Institute of Biostatistics and Analyses

MYRISK
Statistical Analyses Plan

Sponsor:	**Helsinn Healthcare SA, Via Pian Scairolo 9, 6912 Pazzallo-Lugano, Switzerland**
Protocol:	IBA1160
Study name:	**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.
EudraCT Number:	2019-004686-41
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Signature Page

Sponsor project team review and approval

Name	Title/role	Date and Signature
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Content

Table of Changes

Version	Supersedes	Change description	Valid from	Revised by
1.0	-		02.04.2020	
2.0	1.0	Changes integrated from new version (v2.0) of Protocol	02.02.2021	Markéta Wiesnerová
3.0	2.0	Detailed specification of the Protocol – acceptable percentage of carboplatin usage per country, updated list of chemotherapy treatment in chapter 7.3	01.09.2021	Markéta Wiesnerová
4.0	3.0	Acceptable percentage of carboplatin, omitting country limit. Specification of data sources for analyses. Sample size update adopted from new version of protocol (version 5.1). Multiple Imputations and Last Observation Carried Forward approach added for the efficacy endpoints adopted from the new protocol (version 5.1). Information of pre-global country-specific summary added at section 9.9.	31.01.2024	Jiří Šilar

List of Abbreviations

ADL	Activities of Daily Living
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
ISO	International Organization for Standardization
ICER	Incremental Cost-Efficacy Ratio
ICF	Informed Consent Form
ICH	International Council for Harmonization
IV	Intravenous
LEC	Low Emetogenic Chemotherapy
LOCF	Last Observation Carried Forward
MASCC	Multinational Association of Supportive Care in Cancer
MAT	MASCC Antiemesis Tool
MAH	Marketing Authorization Holder
MAR	Missing at Random
MCAR	Missing Completely at Random
MEC	Moderately Emetogenic Chemotherapy
MiE	Minimal Emetogenic Chemotherapy
MVTF	Missing Value Treated as Failure
NEPA	netupitant and palonosetron
NIMP	Non-Investigational Medicinal Product
NRI	Net Reclassification Improvement
PS	Performance Status
RA	Receptor Antagonist
RPN	Risk Priority Number
QOL	Quality of Life
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics

VAS	Visual Analogue Scales

1. Introduction

The Statistical analysis plan (SAP) describes the statistical analyses to be undertaken in the study. This involves the definition of analysis sets and protocol deviations, the specification of the primary, secondary and health economic endpoints to be analyzed and the outline of outputs (tables, listings and figures) to be compiled in the Clinical study report (CSR).

The SAP is created in accordance with the v5.1 of Study Protocol (version from the 05-FEB-2024) and (e-)CRF (version 2.0 from the 25-05-2020). The analyses and outputs closely follow the ICH guidelines for industry on topic E3 (Structure and Content of Clinical Study Reports) [1] and E9 (Statistical Principles for Clinical Trials) [2].

Activities to be performed before analysis are described and confirmed in the F70 Checklist for activities to be done before analysis.

The SAP has to be completed and approved before execution of study analysis. This is accompanied also by approval of definitions of the protocol deviations and the disposition of subjects into analysis sets before compilation of final SAP. Critical dates and times (e.g. of and adverse events) have to be cleaned before DB lock.

2. Changes from the Study Protocol

There are no changes from the Study protocol v5.1 (version from the 05-FEB-2024).

3. Activities to Be Done before Execution of Final Analyses

- The following tasks have to be done before final execution of analysis: Study database have to be locked (Status “read only”). All relevant data-management processes are finalized (approval by Project data manager or Project Manager).
- Disposition of patients in analysis sets and list of protocol deviations have to be approved.
- Assignment of adverse events to study treatment has to be approved.
- Coding of Adverse events and medical history have to be finalized and approved.
- A reconciliation of serious adverse events (SAEs), i.e. a comparison of SAEs in the clinical database and SAEs reported to the sponsor must be performed.
- Data from the Patient´s diary, MAT questionnaire and FLIE questionnaire have to be digitalized, included in the clinical database and checked for discrepancies.

4. Study Objectives

4.1. Primary Objective

The primary objective is:

- 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 over three cycles of chemotherapy

4.2. Secondary Objectives

The secondary objectives are:

- To evaluate acute (0 to 24 hours), delayed (>24 to 120 hours), and overall (0 to 120 hours) CINV indicators in each cycle of chemotherapy
- To evaluate the predictive role of potential risk factors in the development of CINV over three cycles of chemotherapy
- To evaluate the safety profile of the antiemetic drug over three cycles of chemotherapy
- To explore the effect of CINV on daily activities and quality of life in patients receiving moderately-emetogenic chemotherapy over thee cycles of chemotherapy
- To evaluate resource utilization and health economic outcome

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.

Information on CINV indicators during acute and delayed phase will be taken from MAT questionnaires. Daily information (apart from Day 1) will be taken from Patient's Diary.

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

5. Study Design

5.1. Brief Summary

This is a phase IV, interventional, open-label, randomized, active controlled, parallel arms, multicentre and multinational study, designed to assess the effect NEPA in preventing CINV among MEC-treated cancer patients with high risk of CINV and to compare it to the standard of care.

The planned number of patients is 410, from 22 participating sites. These cancer patients, aged ≥ 18 years, can be both naïve and non-naïve to chemotherapy. Enrolled patients will be treated with three consecutive cycles with a single dose of any IV MEC regimen, including carboplatin, and then divided into two arms.

Patients in ARM A will receive 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.

Patients in ARM B will receive 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 (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.

The received 5-HT3-RA may change between cycles in ARM B, as long as it complies with the above-mentioned list of 5-HT3-RAs.

In order to assess CINV, each patient will complete a MASCC Antiemesis Tool (MAT) questionnaire during each chemotherapy treatment cycle. The effect of CINV on daily activities and quality of life will be measured by using the

Functional Living Index-Emesis (FLIE) questionnaire, a validated, nausea and vomiting specific, patient-reported outcome instrument. The frequency and intensity of acute and delayed nausea and vomiting will be measured via MAT. Rescue medication will be allowed at any time, during every cycle. The choice will be left at the discretion of the Investigators. The intake of rescue medications, either prescribed or non-prescribed, must be recorded in the Patient´s diary and in the eCRF.

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 on the basis of 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

The planned study enrolment time will be 12–18 months, with each patient making maximum of 5 visits in total.

5.2. Randomization and Blinding

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 and will be performed using permuted blocks. The randomization process will be managed centrally through the eCRF.

Once assigned to a treatment group before the start of cycle 1, patients will stay in the same treatment group until study completion. Changes of treatment, such as switching from one standard of care product to another, are allowed.

The criteria for randomization will be evaluated only once, at the beginning of the study. Any subsequent changes in patient’s chemotherapy treatment (e.g. switching to carboplatin use) will not have any effect on their treatment arm.

6. 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.

6.1. Primary Endpoint

The primary endpoint will be the proportion of complete responses (no emetic episode and no rescue medication) over three cycles of chemotherapy after the start of the MEC administration. The endpoint will be analyzed for the overall period, including all three cycles.

6.2. Secondary Endpoints

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 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)

6.3. Health economic endpoints

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 (more details below)
- 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

The grade 2 vomiting is characterized in CTCAE version 5 as vomiting requiring intervention in the form of IV hydration. In this study, we will consider 2-5 vomiting episodes in 24 hours after chemotherapy administration as grade 2.

7. Definitions

7.1. Study Database and External Data

Data collected and validated in the clinical study database will be analyzed. Data from the Patient´s diary, MAT and FLIE questionnaires will be digitalized to become a part of the clinical database. No other external data are planned to be used for the analysis.

7.2. Labels and Tags used in SAP and/or Outputs

The following labels will be used for the treatment groups:

- NEPA– the test arm (Akynzeo® (netupitant 300 mg /palonosetron 0.50 mg) + dexamethasone 8 mg)
- SoC– the control arm (one standard oral dose of one of the available 5-HT3 RA + dexamethasone 8 mg)

Notation of time points during the study should include the cycle and day number, e.g. „C2D1“or „Cycle 2 day 1“.

Visits should be referred to as Visit 0/V0 for screening visit, Visit 1/V1 for visit at the start at Cycle 1 (correspondently for Visit 2 and Visit 3), and Visit 4/V4 for follow/up visit at the end of cycle 3.

7.3. General definitions

Treatment Start date is defined as the date (time) when a dose of antiemetic drug is administered.

Treatment end date is defined as the last day of Cycle 3.

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.

IMP in this study is 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).

The non-IMP (NIMP) is defined as any medicinal products intended for research and development trials, which does not fall within the definition of an IMP.

Standard of care (dexamethasone, granisetron, palonosetron, ondansetron) used in Arm SoC and dexamethasone used in Arm NEPA is not fixed to a particular product. It is current standard treatment, based on national and international consensus, given according to local clinical practice for the CINV indication which is used regardless of whether the patient is being treated in the study or not. It is prescribed depending on patient´s needs, according to the doctor's judgement and according to the availability in site. The patient may already be taking the standard care medicine(s) when entered into the study.

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 [7]. The dosages are perfectly in the range of dosages specified in SPC 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, trabectedina) in both arms NEPA and SoC 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.

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 if the final visit of the study.

After participation in the study, the patient will be treated according to the common clinical practice based on the physician´s discretion.

7.4. Baseline Values

A baseline is defined as the assessment collected at the baseline (screening, V0) visit. If there is no such value, the baseline will be missing.

7.5. Coded Terms and Used Dictionaries

Medical history and AEs will be coded using the Medical dictionary for regulatory activities (MedDRA).

7.6. Handling/Classification of Adverse Events

AEs will be classified with regard to their 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.

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 non-invasive 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

The causal relationship of an AE with the study drug will be classified as:

- Related
- Not related

If the Investigator's causality assessment is missing or unknown, the AE must be considered as related to the product.

7.7. Methods for Handling of Incomplete dates/times

No general imputation of dates/times will be performed except for the cases below.

7.6.1. AEs

If the time of the AE onset is missing and the date is the same as the start of treatment, the AE will be considered as starting after the beginning of the treatment.

If the day part of the date is missing and the month of the AE is the same as the month of the start of the treatment, the date of the first day of treatment will be imputed. If the AE occurs in a different month, the 1st of the month will be imputed, or if it is possible to determine a possible range of dates, the earliest date from this range.

If the month and/or year is missing from a date, and the month/year is the same as the month/year at the start of treatment, the date of start of treatment will be imputed. If the month/year is greater than the month/year at the start of treatment, the 1st of month/year will be imputed.

If the date is missing altogether, the treatment start date will be imputed.

7.6.2. Medical history

If the day/month is missing in the start date of the medical history issue, the 1st of the month/1st of the year will be imputed. If the day/month is missing in the stop date, the last day of month/last day of year will be imputed. If the stop date is missing completely, the issue will be considered as on-going. In case of the imputation of a stop date resulting in a date that is in future, the last day before the start of treatment will be imputed instead.

7.7.1. Concomitant medication

If the day and/or month is missing in the start date, the start of treatment will be imputed. If the day is missing in the stop date, the earlier date from last day of month/treatment end date will be imputed. If the month is missing in the stop date, the earlier date last day of the year/treatment end date will be imputed. If the stop date is missing completely, treatment with concomitant medication will be considered as on-going. In case of the imputation of a stop date resulting in a date that is in future, the last day before the start of treatment will be imputed instead.

7.8. Unscheduled/Repeated Assessments

In this study, the patients are followed for three consecutive cycles of chemotherapy. That is why the endpoint and secondary analysis will take into account a correlation between observations from one patient.

Unscheduled assessment should not occur and are not included in the CRF.

7.9. Rules and Formulas for Derived Variables

The CINV score will be calculated and used to identify patients with high risk of CINV. The calculation of CINV score will be done using following rules:

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

Since only the year of birth is available, the age of the patients will be calculated as the difference between the date of the screening and the first of January of the recorded year of birth.

The FLIE total score will be calculated from the corresponding questionnaire. The total score is the result of summing the responses to the 18 questions as the sum of the nausea and vomiting domain scores [5]. At least 12 of the 18 FLIE items (i.e., ≥66% overall item response rate) must be non-missing, and both the vomiting and nausea domains must be non-missing, to calculate a FLIE total score. The score for domains (Nausea, Vomiting) will be also presented. At least 5 of the 9 FLIE domain items (i.e., >50% overall item response rate) must be non-missing to calculate a FLIE nausea / vomiting domain score. Because the scale anchors are in the opposite direction on items 3, 6, 11, 15, and 18, the sensitivity analysis will be performed to assess the impact of incorrect responses. To assess the impact of these errors, the invalid item(s) will be set to missing before calculating the domain and total scores.

- Invalid nausea response: Set item 3 and/or 6 to missing if the item(s)are ±50mm or more from the mean of items 1, 2, 4, 5, 7, 8, and 9.
- Invalid vomiting response: Set item 11, 15, and/or 18 to missing if the item(s) are ±50mm or more from the mean of items 10, 12, 13, 14, 16, and 17.

The MAT scale for overall phase will be created by pooling the data from acute and delayed phases.

8. Flow of Patients and Specifications for analysed Populations

The flow of patients will be based primarily on analysis sets and if appropriate any other conditions which lead to exclusion of patients from total set of patients should be also included.

The following analysis sets are defined by the Study protocol.

8.1. Analysis Sets

8.1.1. Total Set

The Total Set will consist of all patients who were enrolled into the study.

8.1.2. Full Analysis Set

The Full Analysis Set (FAS) will consist of all randomized patients to whom study 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.

8.1.3. Per Protocol Set

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 actually received. Efficacy analyses based on the PP population will be considered supportive.

8.1.4. Safety Set

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 analysed according to the treatment they actually received.

8.2. Protocol Deviations

List of protocol deviations (list of subjects to be excluded from the Per Protocol set) will be created and agreed before database lock and execution of statistical analysis.

For the Per Protocol set major protocol deviations will be reasons for exclusion. Minor protocol deviations do not lead to exclusion from Per Protocol set.

Following deviations will be monitored, but other deviations might also be considered after discussion:

- Any inclusion criterion not fulfilled.
- Any exclusion criterion violated.
- Study visits not corresponding to study design

9. Statistical Methodology and Specification of Sample Size

This section describes the data analysis in details. The statistical methods are planned in accordance with the study protocol and in accordance with ICH Topic E9 Statistical Principles for Clinical Trials.

9.1. General Principles

The SOP.111 Statistical analysis of clinical data describes generally the procedure for carrying out statistical analysis of clinical data and has to be followed during inspection of data and analyses as well as instruction in this SAP.

Statistical software SAS (version 9.4 or higher)[3] will be used for analysis and for generation of tables, figures and listings (TFL).

All tables and listings will be presented by treatment groups. The tables related to a baseline will include a 'Total' column. The listings will present data from the eCRFs by patient. The listings will be created only when summaries are not sufficient for a given type of data.

9.1.1. Descriptive Statistics

Standard descriptive statistics are used in the analysis; all results are described by number of samples in the base for given computation; valid N is also reported in case of missing values in continuous variables. Median supplemented by 5th – 95th percentile range (or alternatively min-max or interquartile range) are used for continuous variables. Mean supplemented by standard deviation or 95% confidence interval is adopted for continuous variables (geometric mean and its 95% confidence interval can be presented for log-normally distributed data).

Categorical data are described using absolute and relative prevalence (frequencies) of categories; missing values can be included in the computation of categories percentages when necessary.

Results will be presented overall or if appropriate by study arms.

Figures used to illustrate selected summary tables will always refer to the number of patients included in the analysis set.

9.1.2. Rounding

The protocol does not specify any rules for rounding, therefore, following rules will be used:

- Mean (geom. mean) +1; standard deviation +2, median +1, min/max +0, confidence intervals (CIs) +1
- Percentages in frequency tables will be displayed to one decimal place
- All p-values will be rounded to three decimal places

9.1.3. Missing Data

Missing data on the primary and secondary efficacy endpoints will be imputed by multiple imputation (MI) procedure and using last observation carried forward (LOCF), as described in Section 9.4.1. Other missing data will not be imputed, except for missing times and dates, as described in Section 7.7.

9.1.4. Validation of Data

The data will be controlled in the context of other recorded data. The statistical monitoring will include evaluation of the consistence and variability of data, systematic or serious mistakes within the particular centres and between centres. Effort will be taken to identify mistakes resulting in records with non-sensical or impossible values, incorrect continuity of dates or systemic errors resulting in incorrect or missing values. This will include, among others, dates of

visits, starting/ending dates of treatment or dates of AEs, whose inaccuracy would significantly lower the reliability of results. Data from FLIE, MAT and HEOR questionnaires and Patient's Diary, are crucial for endpoint analyses and their correctness is of great importance. Data from digitalized sources (FLIE and MAT questionnaires, Patient's Diary) will also be paid close attention to, as the digitalization process is another potential source of errors. Errors will be analyzed to determine whether they occur at random or if there is any systematic failure. If a systematic failure is suspected, effort will be taken to find its source (e.g. a particular centre).

Quantitative endpoint variables used for statistical testing will be checked for their distribution using visual inspection of histograms and tested by Shapiro-Wilk test. Presence of outliers should be discussed.

9.1.5. Validation of Statistical Programming

There are three levels of validation defined (described in detail in internal IBA SOP.114 Statistical Programming):

- Level 1: Validation by a programmer (author of the program)
- Level 2: Validation by an independent programmer
- Level 3: Reprogramming by an independent programmer

Each statistical program will be validated at Level 1 at minimum. The most important analyses (primary and secondary endpoints) will be validated at level 2 or 3. If there are any figures produced in R, they must be compared visually by the analogous figures produced in SAS.

The second statistician or data analyst will check the final results. The check will include following:

- The double programming of the primary and secondary efficacy analyses and of frequency tables of adverse events
- Check of disposition of subjects in analysis sets
- Review of other outputs
- Check of errors and unexpected warnings in logs of all programs used for analysis and data preparation

In statistical programs (scripts), any corrections or updating of study data has to be documented in statistical report if the modification in clinical DB or source data was not done till the DB lock. Namely, this refers to the cases when subjects or the data are added/changed using a script rather than updating the DB. This kind of hard coding is usually proposed to correct deficiencies in the DB (missing values, wrong values, and wrong measurement units).

The hard coding may not be done in any programs used for the creation of analysis data sets, tables, listings, or analyses that are intended for external reporting after DB lock (i.e. clinical study reports/all phases/, publications, abstracts, etc.).

Since no changes are made to the study data without appropriate documentation from the investigator sites and appropriate audit trails within the clinical trial DB, this process ensures integrity of clinical data.

In very exceptional situations, when there is no other way how to correct deficiencies in the database, the hard coding may be allowed, if approved by the Sponsor. It has to be appropriately documented, at minimum in the CSR.

9.2. Determination of Sample Size

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.

9.3. Description of Baseline Characteristics

Demographic, physical characteristics and medical history data will be tabulated, using the standard sets of summary statistics as defined in Section 9.1.1.

All demographic and other baseline characteristics will be presented for the FAS and the data will be presented by treatment groups and overall. All details will be listed.

9.4. Analysis of Efficacy

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.

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 to 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.

Information on nausea and vomiting during the acute and delayed phase and overall from MAT will be considered for analysis. For analysis of daily occurrences, MAT information will be used for Day 1 (identical to acute phase), otherwise data from Patient's Diary will be used.

9.4.1. Imputation of endpoints data

To achieve the largest possible sample, imputation techniques will be used to impute missing data for the FAS population. 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.

The following MI procedure code will be used to perform MI with 5 imputations.

```
PROC MI data = dataset seed=s out = MIdataset nimpute = 5;
VAR study_treatment carboplatin country vis1_event – vis3_event;
CLASS study_treatment carboplatin country vis1_event – vis3_event;
monotone logistic;
RUN;
```

The exact names of the variables may differ.

9.4.2. Missing data within the FAS population on secondary efficacy endpoints will be imputed using the last observation carried forward (LOCF). Primary Efficacy Endpoint

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, using data from the overall period of three cycles.

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 results will be obtained via the GENMOD procedure, using following code:

```
PROC GENMOD data = dataset;
CLASS id study_treatment carboplatin country;
MODEL complete_response = study_treatment carboplatin country / dist = bin
                                                                link = logit;
REPEATED subject = id / type = exch covb corrw;
LSMEANS study_treatment / diff exp ilink cl;
RUN;
```

The exact names of the variables may differ.

With MI the code will be modified to:

```
PROC GENMOD data = dataset;
CLASS id study_treatment carboplatin country;
MODEL complete_response = study_treatment carboplatin country / dist = bin
                                                                link = logit;
REPEATED subject = id / type = exch ecovb;
LSMEANS study_treatment / diff exp ilink cl;
ODS OUTPUT GEEEmpPEst=parms_est;
RUN;

PROC MIANALYZE parms(classvar = LEVEL)=parms_est;
```

```
CLASS study_treatment carboplatin country;
MODELEFFECTS Intercept study_treatment carboplatin country;
ODS OUTPUT ParameterEstimates = combined_parms;
RUN;
```

The exact names of the variables may differ.

9.4.3. Secondary Efficacy Endpoint

The same statistical approach as for the primary endpoint (GLIM) will be used for all the secondary efficacy endpoints with the exception of 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, using following code (*delay_length* can be replaced with *amount_reduction*):

```
PROC NPAR1WAY data=dataset wilcoxon;
CLASS study_treatment;
VAR delay_length;
STRATA country carboplatin;
EXACT wilcoxon;
RUN;
```

The exact names of the variables may differ.

The code will be equivalent to the one used in the analysis of primary endpoint, only changing variable from *complete_response* to variables describing the secondary endpoints:

- Complete response during the acute (0-24h), delayed phase (25-120h), 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 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)

9.5. Analysis of Safety

All the safety analyses will be performed on the Safety Set.

9.5.1. Adverse Events

Detailed definitions and classification of AEs are specified in Study Protocol, Section 10.

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. The rules for recording AEs and their follow-up are described in Study protocol, Section 10.3.

Serious Adverse Events either related and not related to Akynzeo® will be collected and communicated as per law requirements. A patient with multiple occurrences of a given AE will be counted only once in the AE category.

A reconciliation of serious adverse events (i.e. a comparison of the number of SAEs in the clinical database and the number of SAEs reported to sponsor) will be performed before DB lock. Assignment of treatment period and/or study period to AEs and coding should be done and approved by the sponsor before DB lock, as well.

All AEs will be summarized by their:

- Severity
- Seriousness
- Relationship to a drug

The number (%) of subjects reporting each treatment emergent AE (TEAE) will also be summarized by:

- Primary System Organ Class (SOC)
- Preferred Term (PT)

Subjects with more than one TEAE within a particular SOC and PT are counted only once for that SOC and PT. Percentages are based on the number of subjects actually receiving a given treatment (based on the safety population) within each treatment group.

An overall summary of AEs will be presented, including the frequency and percentage of patients with:

- Any treatment-emergent adverse event
- Any treatment-emergent adverse event related to a study drug
- Any treatment-emergent adverse event leading to chemotherapy dose reductions or interruptions
- Discontinuations Due to Adverse Event
- Any treatment-emergent serious adverse event
- On treatment deaths due to adverse event

In addition, following listings will be presented:

- All AEs (including pre-treatment AEs)
- Serious adverse events
- Adverse events resulting in withdrawn of study drug

No formal statistical tests will be performed.

9.6. Health Economic Analysis

The analytical approach will be a cost-efficacy analysis. This approach combines measures of costs over time with efficacy measures. The analyses will be performed on the Full Analysis Set.

9.6.1. Resource Utilisation

The analysis of medical consumption will be performed by comparing the amount of resources consumed per treatment group. Health care resource consumption will be expressed in units for each selected resource:

- Number of days and daily doses of rescue medication administered for the treatment of CINV
- Number of days of unplanned hospitalisation due to CINV
- Department of hospitalization
- Number of physicians' consultations due to CINV
- Number of re-hydration bags for at least grade 2 vomiting
- Number of unplanned laboratory tests
- Discontinuation from chemotherapy due to CINV
- Delay of chemotherapy administration due to CINV
- Days of absence from work

For each selected resource unit, both the frequency of use (i.e., % patient usage) and intensity of use (i.e., average amount used) will be presented.

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

9.6.2. 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. The cost data will be collected outside of the study and then provided for analysis.

9.6.3. Cost-efficacy Analysis

The economic data will be collected primarily in physical units of health care resource used per patient and per event (efficacy / safety).

The incremental cost-efficacy ratio (ICER) is defined as the difference in cost between the study arms, divided by the difference in efficacy. It 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.

9.7. Interim Analysis

No interim analysis is planned for this study.

9.8. Secondary Analysis

An analysis with development of CINV as a dependent variable will be performed to identify additional potential risk factors of CINV. The analysis will be performed using the Per Protocol population. Data on 16 risk factors will be collected before each chemotherapy cycle:

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

The first 7 factors are used throughout this study to identify patients with high risk of CINV. The CINV score is recalculated for each of patient's cycles and has no impact on patient´s participation in the study and the randomized group.

The purpose of secondary analysis is to identify other, potentially predictive factors among the 9 additional ones.

A simple logistic regression model with the development of CINV over three cycles of chemotherapy 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 used to determine the final set of additional risk factors.

By using reclassification analysis 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, by presenting NRI_e and NRI_{ne}, the event- and non-event reclassification index.

These indices can be interpreted as a change in True Positive Rate and the negative of change of False Positive Rate, when using a new model and comparing it to the previously used one.

The calculation will be performed in SAS, the NRI analysis will be done using a macro developed for this purpose. The code can be found at [6].

9.9. Pre-global country-specific summary

Each country can process its own data before the final analysis is performed. The pre-global country-specific summary will have descriptive character and no study endpoint hypothesis will be tested, focusing only on frequencies. The pre-global summary will describe population size, demography, treatment details, occurrence of the events, and also will present incidence of adverse events. The full country-specific analysis will be conducted after the global data analysis.

Data to be presented in pre-global country-specific analysis:

- Disposition of patients and analysis sets
- Demography, Disease characteristics data and therapy history (by total and arm)
- Treatment pattern at each visit (by total and arm)
    - Visit details
    - Chemotherapy administration
    - Antiemetic treatment and corticosteroids administration
- Frequency of the endpoint events occurrence (by arm)
- Health economic data (by arm)
- Number of patients with AE occurrence (by arm)

No statistical modelling or testing will be performed. All endpoint events in the pre-global analysis will be presented for the FAS population only, the PP population will be omitted, and imputation of endpoint data will not be performed. Since no imputation will be done, the primary endpoint, proportion of patients with complete response in the overall phase (0-120 hours) over three cycles of chemotherapy, will be analysed only for patient with complete information. They must be treated in all three cycles of treatment with complete CINV information and rescue medication on MAT and PD questionnaires.

Coding of adverse events will be done after all data collection and will not be available for pre-global analysis. Therefore, only the summary of the number of patients with AE will be presented here.

For the pre-global country specific analysis a separate layout of tables will be created, details in Appendix 2.

10. List of Tables, Figures and Listings

The table below presents a preliminary list of tables, figures and listings which will be included in study report. The numbering and structure are proposed according to the ICH guidelines - E3: Structure and Content of Clinical Study Reports.

10.1. Tables and Figures

Output	Numbering	Title	Analysis Set
	14.1	**Demographic data**	
Table	14.1-1	Disposition of patients and analysis sets	Total Set
Figure	14.1-2	Flow of patients in analysis sets	Total Set
Table	14.1-3	Total number of patients enrolled by centre	Total Set
Table	14.1-4	Reasons for exclusion from analysis sets and protocol deviations	Randomized Set
Table	14.1-5	Study Enrolment by Site	Total Set
Table	14.1-6	Treatment Disposition	Full Analysis Set
Table	14.1-7	Demographic and baseline characteristics	Full Analysis Set
Table	14.1-8	CINV risk parameters at screening	Full Analysis Set
Table	14.1-9	Disease characteristics	Full Analysis Set
Table	14.1-10	Previous therapy history	Full Analysis Set
Table	14.1-11	Visits details	Full Analysis Set
Table	14.1-12	Chemotherapy	Full Analysis Set
Table	14.1-13	Prophylactic antiemetic regimen	Full Analysis Set
	14.2	**Efficacy data**	
Table	14.2-1	Proportion of patients with complete responses in the overall phase (0-120 hours) over three cycles of chemotherapy	Full Analysis Set, Per Protocol
Figure	14.2-1	Complete response – Logistic Regression	Full Analysis Set, Per Protocol
Table	14.2-2	Patients with Complete response during the acute/delayed/overall phase and daily	Full Analysis Set, Per Protocol
Figure	14.2-2	Complete response during the acute/delayed/overall phase and daily – Logistic Regression	Full Analysis Set, Per Protocol
Table	14.2-3	Number and Percentage of Patients with No Emesis	Full Analysis Set, Per Protocol

Output	Numbering	Title	Analysis Set
Figure	14.2-3	Emetic episodes during the acute/delayed/overall phase and daily – Logistic Regression	Full Analysis Set, Per Protocol
Table	14.2-4	Number of vomiting episodes per patient	Full Analysis Set, Per Protocol
Figure	14.2-4	Vomiting episodes during the acute/delayed/overall phase and daily –Regression	Full Analysis Set, Per Protocol
Table	14.2-5	Number and Percentage of Patients with No Rescue Medication	Full Analysis Set, Per Protocol
Figure	14.2-5	Rescue medication during the acute/delayed/overall phase and daily – Logistic Regression	Full Analysis Set, Per Protocol
Table	14.2-6	Number and percentage of patients with No Significant nausea	Full Analysis Set, Per Protocol
Figure	14.2-6	Significant nausea during the acute/delayed/overall phase and daily – Logistic Regression	Full Analysis Set, Per Protocol
Table	14.2-7	Number and percentage of patients with No Nausea	Full Analysis Set, Per Protocol
Figure	14.2-7	No nausea during the acute/delayed/overall phase and daily – Logistic Regression	Full Analysis Set, Per Protocol
Table	14.2-8	Number and Percentage of patients with Complete protection	Full Analysis Set, Per Protocol
Figure	14.2-8	Complete protection during the acute/delayed/overall phase and daily – Logistic Regression	Full Analysis Set, Per Protocol
Table	14.2-9	Quality of life indicators	Full Analysis Set, Per Protocol
Figure	14.2-9	Quality of life indicators – FLIE	Full Analysis Set, Per Protocol
Table	14.2-10	Chemotherapy delay	Full Analysis Set, Per Protocol
Table	14.2-11	Chemotherapy reduction	Full Analysis Set, Per Protocol
	14.3	**Safety Data**	
Table	14.3-1	Drug Exposure	Safety Set
Table	14.3-2	Overall summary of AE	Safety Set
Table	14.3-3	Treatment emergent AEs by System Organ Class and Preferred Term	Safety Set
	14.4	**Health Economy Data**	
Table	14.4-1	Number of days and daily doses of rescue medication administered for the treatment of CINV	Full Analysis Set

Output	Numbering	Title	Analysis Set
Table	14.4-2	Number of re-hydration bags given for at least grade 2 vomiting (CTCAE grade 5)	Full Analysis Set
Table	14.4-3	Unplanned hospitalisation related to CINV	Full Analysis Set
Table	14.4-4	Outpatient visits and health care consultations due to CINV	Full Analysis Set
Table	14.4-5	Unplanned laboratory tests including those at unplanned hospitalisation due to CINV	Full Analysis Set
Table	14.4-6	Discontinuation of chemotherapy treatment due to CINV	Full Analysis Set
Table	14.4-7	Days of absence from work	Full Analysis Set

10.2. Patient Data Listings

Numbering	Title
16.2.1	**Discontinued patients**
16.2.1-1	Discontinued subjects
16.2.2	**Protocol deviations**
16.2.2-1	Protocol deviations
16.2.7	**Adverse event listings**
16.2.7-1	Adverse events (including pre-treatment)
16.2.7-2	Serious adverse events
16.2.7-3	Adverse events resulting in withdrawal of study drug
16.2.7-4	Deaths

11. Layout of TFLs

Details in Appendix 1.

12. References

[1] ICH guidelines - E9: Statistical Principles for Clinical Trials, Adopted in EU by CPMP, March 1998, issued as CPMP/ICH/363/96

[2] ICH guidelines - E3: Structure and Content of Clinical Study Reports, Adopted in EU by CPMP, December 95, issued as CPMP/ICH/137/95

[3] SAS 9.4; © SAS Institute Inc., Cary, NC, USA; OnLine Doc.

[4] Dranitsaris G, Molassiotis A, Clemons M, et al. The development of a prediction tool to identify cancer patients at high risk for chemotherapy-induced nausea and vomiting. Annals of Oncology. 2017;28(6):1260-1267.

[5] Lindley, C. M., Hirsch, J. D., O'Neill, C. V., Transau, M. C., Gilbert, C. S., & Osterhaus, J. T. (1992). Quality of life consequences of chemotherapy-induced emesis. *Quality of Life Research*, *1*(5), 331-340.

[6] Cook, N., Reclassification Statistics Retrieved from http://ncook.bwh.harvard.edu/sas-macros.html

[7] Aapro M, Gralla RJ, Herrstedt J, Molasiotis A, Roila F., MASCC and ESMO antiemetic guideline 2016, with updates in 2019.