Final Analysis
Statistical Analysis Plan (SAP)

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GE Healthcare

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REVISION HISTORY

Version/Date	Version name	Section	Changes implemented
Version 1.0 [redacted]	Final	NA	NA
Version 2.0 [redacted]	Draft	Section 8	Updated for client request to add analyses for prospective and retrospective images/records separately.
Version 2.0 [redacted]	Final	Section 8	Updated for client comments on V 2.0.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

The following abbreviations will be used within this SAP.

Abbreviation or special term	Explanation
AD	Alzheimer's disease
AE	Adverse event
CI	Confidence interval
CSR	Clinical study report
CT	Computed tomography
eCRF	Electronic case report form
FN	False negative
FP	False positive
IA	Interim analysis
ICH	International conference on harmonisation
MedDRA	Medical dictionary for regulatory activities
MRI	Magnetic resonance imaging
NPV	Negative predictive value
PET	Positron emission tomography
PPV	Positive predictive value
PT	Preferred term
SAP	Statistical analysis plan
SD	Standard deviation
SOC	System organ class
SOT	Standard of truth
TEAE	Treatment emergent adverse event
TFLs	Tables, figures and listings
TN	True-negative
TP	True-positive

1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide detailed descriptions of the statistical methods, data derivations and data displays for study protocol GE067-027, 3.0 "A Post-Authorisation Safety Study to Evaluate the Effectiveness of VIZAMYL™ Reader Training in Europe" dated 11Dec2019 for final analysis. The table of contents and templates for the Tables, Figures and Listings (TFLs) will be produced in a separate document.

Any deviations from this SAP will be described and justified in the Clinical Study Report (CSR).

The preparation of this SAP based on International Conference on Harmonization (ICH) E6 and E9 guidelines.

All data analyses and generation of TFLs will be performed using SAS 9.3® or higher.

2 STUDY OBJECTIVES

2.1 Primary objective

The primary study objective is to assess the effectiveness of the VIZAMYL™ reader training programmes (in-person or electronic) in Europe by estimating the diagnostic accuracy, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), of the visual interpretation of VIZAMYL™ images obtained in the course of clinical practice. Diagnostic accuracy is the overall true-interpretation rate for all subjects. One minus the diagnostic accuracy gives the overall image interpretation error rate.

At least 200 VIZAMYL™ images obtained in clinical practice will be reviewed (or will have been reviewed) by clinical readers recruited from European countries where VIZAMYL™ is commercially available [redacted]. The standard of truth (SOT) will be the majority blinded visual image interpretations of the same images by 5 independent expert readers.

2.2 Secondary objectives

Evaluate the impact of demographic and other factors (such as method of training, gap between training and reading, and country) on diagnostic accuracy to try to identify factors that may be associated with image interpretation errors.

Sensitivity is the true-positive (TP) image interpretation rate in subjects with brain amyloid. Specificity is the true-negative (TN) image interpretation rate in subjects without brain amyloid. Positive predictive value (PPV) is the TP image interpretation rate for subjects with positive VIZAMYL™ scans. Negative predictive value (NPV) is the TN image interpretation rate for subjects with negative VIZAMYL™ scans.

3 STUDY DESIGN

3.1 General study design

This is a non-interventional post-authorisation safety study (PASS) with the primary objective of assessing effectiveness of the VIZAMYL™ reader training programmes (in-person or electronic) in Europe by estimating the diagnostic accuracy of the visual interpretation of VIZAMYL™ images by clinical readers recruited from European countries where VIZAMYL™ is commercially available [redacted] (each reader will interpret (or will have interpreted) images collected at his/her institution, for a total of at least 200 images). The diagnostic accuracy of image interpretation will be determined across all images as well as for subsets of images by country and by reader. Sensitivity, specificity, PPV, and NPV will also be determined and will be reported as point estimates along with exact 95% confidence intervals (CIs). The SOT for classifying each image as correct (TP or TN) or incorrect (false positive or false negative) will be the majority blinded visual interpretations of 5 independent expert readers.

Imaging sites will be selected according to the criteria detailed in protocol section 9.2.2. Each imaging site will be assigned a 3-digit identifying number. The VIZAMYL™ images at each participating site will be obtained in clinical practice. Because VIZAMYL™ is approved and no longer investigational, the need for subject informed consent will be decided at each institution by the local independent ethics committee (IEC).

All subjects must satisfy all the inclusion criteria and none of the exclusion criteria as listed in the protocol. When required by the local IEC, signed and dated informed consent must be obtained from all subjects or the subject's legally acceptable representative, if applicable, in accordance with local regulations, prior to collection of any study-specific data. Each subject will be assigned a 7-digit identifying number; the first 3 digits will be the identifying number for the site at which the subject's VIZAMYL™ scan was obtained and the remaining 4 digits will be assigned consecutively at each site. Demographic data will be recorded for each subject.

The images will be de-identified (i.e., subject identifying information will be removed) so that inspection of an image will not reveal the identity of the subject from whom the image was obtained.

If anatomic images are used in the interpretation of the VIZAMYL™ images, they will also be de-identified and transmitted to the core image lab, and will be interpreted with the VIZAMYL™ images by the expert readers.

The clinical reader eligibility criteria are discussed in protocol section 9.2.4. Demographic data will be recorded for each clinical reader. Each clinical reader will be assigned an identifying letter that starts with C (for Clinical): CA, CB, CC, etc.

During the image interpretations, the clinical readers will not be (or were not) blinded to the subjects' clinical information, but will be blinded to the interpretations of the expert readers (which will not be available yet). Each clinical reader will interpret the VIZAMYL™ images

as they are collected at his/her site. VIZAMYL™ images will be interpreted as positive (significant levels of amyloid present) or negative (significant levels of amyloid absent) according to local practices at the institution; these classifications are consistent with the VIZAMYL™ reader training programme, the VIZAMYL™ Summary of Product Characteristics, and the European Association of Nuclear Medicine (EANM) guidelines on interpretation of amyloid positron emission tomography (PET) images. If anatomic images (Magnetic Resonance Imaging [MRI] and/or computed tomography [CT]) are available for a subject, the normal institutional clinical practice regarding use of these images in PET interpretation will be followed. The clinical reader will enter his/her interpretation and other data into an electronic case report form (eCRF). The site will remove identifying information (except for subject number) from the image and transmit the image electronically to the GE Healthcare image core lab.

The image core lab will assign a randomization code to the image and will remove the subject number.

The ≥200 images collected in this study will be interpreted separately by each of 5 expert readers, who will classify each image as positive or negative for brain amyloid. The expert readers will consist of 5 experienced nuclear medicine physicians or radiologists, with extensive experience in PET imaging (including amyloid imaging), who have completed a VIZAMYL™ training programme. The expert readers will be blinded to the subjects' clinical information and to the interpretations of the other expert readers and clinical readers, and will not be permitted to discuss images or interpretations with anyone. The expert read will result in at least 200 x 5 = 1000 expert blinded visual interpretations, which will be analysed by subject to determine the majority blinded visual interpretation, as follows. Each image will have 5 expert interpretations, each of which will be positive or negative. The image interpretation (positive or negative) made by the majority of the 5 expert readers will be taken as the majority interpretation. For example, if 3, 4, or 5 of the expert readers interpreted a specific subject's image as positive, then the majority interpretation for that image will be positive. The result of this analysis will be at least 200 majority interpretations (1 per image). The level of reader certainty will also be recorded on a scale of 1 to 5 (1 = lowest, 5 = highest).

Using subject number, each of the ≥200 clinical image interpretations will be matched to the corresponding expert reader majority interpretation for the subject and the image interpretation will be classified as a TP, TN, false positive (FP) or false negative (FN) using the expert reader majority interpretation as the SOT. For example, if an image interpretation is "positive" and the expert reader majority interpretation is "positive", the image interpretation would be classified a TP. If the expert reader majority interpretation were "negative", however, then the image interpretation would be classified as a FP. The numbers of TP, TN, FP, and FN images among the ≥200 original images will be used to calculate diagnostic accuracy:

Diagnostic accuracy = (nTP + nTN) / (nTP + nTN + nFP + nFN)

Where nTP is the number of true-positive scans, nTN is the number of true-negative scans,

nFP is the number of false-positive scans, and nFN is the number of false-negative scans.

Sensitivity, specificity, PPV, and NPV will also be calculated:

Sensitivity = nTP / (nTP + nFN)

Specificity = nTN / (nTN + nFP)

PPV = nTP / (nTP + nFP)

NPV = nTN / (nTN + nFN)

Treatment-emergent adverse events (AEs) with onset or worsening between the start of VIZAMYL™ injection and subject discharge from the imaging suite will be recorded on an adverse event (AE) eCRF, along with the centre's assessment of relationship to VIZAMYL™, severity, seriousness, timing, need for treatment, and outcome.

Study procedures for prospective data collection are summarised in the Study Schedule of Events for Prospective Data Collection (Table 3-1). For collection of existing data, the activities in the "Subject Enrolment" and "Imaging Visit" columns in Table 3-1 will have occurred in the past and may be obtained from the medical record, including whether or not the patient meets the inclusion and exclusion criteria.

Table 3-1 Study Schedule of Events for Prospective Data Collection

Procedures	Subject Enrolment	Imaging Visit	Post-Imaging	Responsible
Selection of imaging sites				Sponsor
Informed consent obtained from subject (if IEC requires)	X			Centre
Subject inclusion/exclusion criteria assessed	X			Centre
Subject demographic information recorded	X			Centre
VIZAMYL™ administration and PET imaging; AE monitoring from start of injection until discharge from imaging centre		X		Centre
Completion of electronic case report form			X	
De-identification of subject's images			X	Centre
Transmittal of subject's images to Sponsor image core lab			X	Centre
Preparation of images for expert readers			X	Sponsor

The image evaluation by expert readers will be prospective; these activities are summarised in Table 3-2.

Table 3-2 Study Schedule of Events for Image Evaluation by Expert Readers

Procedures	Expert Selection	Expert Image Evaluation	Responsible
Identification of expert reader candidates	X		Sponsor
Informed consent obtained from expert reader candidates	X		Sponsor
Expert reader candidate inclusion/exclusion criteria assessed	X		Sponsor
Selection of 5 expert readers	X		Sponsor
Expert reader demographic information recorded	X		Sponsor
Independent review of images		X	Readers

3.2 Randomization and blinding

The image core lab will assign a randomization code to the image and will remove the subject number. The criteria for blinding are shown below in Table 3-3.

Table 3-3 Blinding of Persons Involved in the Study

Personnel	Blinded To:
Subjects	Expert readers' image interpretations
Imaging Centre Site Personnel	Expert readers' image interpretations
Clinical Readers	Other clinical readers' image interpretations Expert readers' image interpretations
Expert Readers	Clinical readers' image interpretations Other expert readers' image interpretations Subject clinical information

3.3 Study treatments and assessments

Participating subjects will receive (or will have received) VIZAMYL™ intravenously prior to PET imaging, according to clinical practice.

Clinical readers may or may not have completed any training in reading VIZAMYL™ images, and some may have completed 1 or more VIZAMYL™ reader training programmes. They also may or may not have prior experience in reading VIZAMYL™ images.

Expert readers will have been trained in reading VIZAMYL™ images and will have experience in reading amyloid PET images.

4 STUDY ENDPOINTS

4.1 Primary endpoints

The primary endpoints are the diagnostic accuracy, sensitivity, specificity, PPV, and NPV across readers based on all evaluable images.

Using subject number, each of the ≥200 clinical image interpretations will be matched to the corresponding expert reader majority interpretation for the subject and the image interpretation will be classified as a TP, TN, FP or FN using the expert reader majority interpretation as the SOT.

4.2 Secondary endpoints

- The numbers and percentages of images for which 5 expert readers agree, 4 expert readers agree, and 3 expert readers agree.
- Estimates of diagnostic accuracy, sensitivity, specificity, PPV, and NPV by the following variables:
  - Country
  - Time from training to image interpretation (<6 months, ≥6 months)
  - Specialty of the reader
  - Training method (s) used by the clinical reader (in-person, electronic, or both)
  - Number of scans read by the clinical reader in practice prior to the study (<50, ≥50)
  - Reader classification certainty (1 to 5)
- Safety Endpoint:- Adverse events (AEs)

5 SAMPLE SIZE AND POWER

Number of Subjects

This study has no formal hypothesis and no statistical tests will be performed. The endpoints of accuracy, sensitivity, and specificity will be summarised descriptively with point estimates and 95% CIs. Although no formal hypothesis will be tested, the sample size is determined to achieve the desired precision in estimating the primary endpoint of the percentage of subjects whose images are correctly classified as positive or negative (accuracy). Assuming that VIZAMYL™ images from 90% of subjects are read correctly by readers who have taken the VIZAMYL™ training programme, 200 subjects will achieve a 95% CI width of less than 10%.

The endpoints of sensitivity and specificity will also be summarised descriptively. This study aims to characterise reader performance in clinical practice so the number of positive and negative images will not be controlled. However, it is expected that most patients who are referred for a VIZAMYL™ scan will have dementia, and most cases of dementia are Alzheimer's Disease (AD). Since brain amyloid is present in AD, it is expected that the majority of patients in this study will have brain amyloid. It is assumed that the majority blinded interpretation of the expert readers will be SOT-positive for approximately 65% of scans, giving a total of approximately 130 scans for sensitivity, with the remaining 70 scans being SOT-negative and therefore usable for calculating specificity. Assuming a sensitivity of 90% and a specificity of 90%, these sample sizes should give reasonably precise 95% CIs for estimating sensitivity and specificity in this scenario (95% CI width of approximately 15% or less).

Accuracy, sensitivity, and specificity will also be calculated by country where all study images from sites within a given country will be pooled for analysis. No country may contribute more than 25% of the total number of images. Because the number of subjects per country is smaller than the overall number of subjects, the level of precision and the width of the CI will be impacted. Again, since the aim of the study is to characterise reader performance in clinical practice, the exact number of images obtained per country and per site is unknown. Table 5-1 provides examples of 95% CI widths for accuracy assuming a few different sample sizes per country to illustrate the change in precision.

Table 5-1 95% Confidence Interval Width for Different Sample Sizes Assuming 90% Diagnostic Accuracy

Sample Size	Actual 95% CI Width	Lower Confidence Limit	Upper Confidence Limit
30	24.4%	73.5%	97.9%
40	20.9%	76.3%	97.2%
50	18.5%	78.2%	96.7%
60	16.7%	79.5%	96.2%

When calculating sensitivity and specificity per country, precision will again be impacted because the sample size per country will be further divided into SOT-positive and SOT-

negative scans. For example, if a country enrols 40 subjects and 65% of the scans are SOT-positive (n = 26) then the width of the 95% CI for sensitivity would be 26.4% (lower confidence limit = 71.8%) and the width for specificity would be 37% (lower confidence limit = 62.4%).

Accuracy by reader will also be presented in a tabular form, though it may be expected that some institutions will have very few scans per reader.

Number of Clinical Readers

The number of clinical readers (1 to 5 per country) was chosen to allow each European country where VIZAMYL™ is commercially available [redacted].

Number of Expert Readers

The number of expert readers (5) was chosen based on precedent set in prior clinical studies of VIZAMYL™.

6 ANALYSIS POPULATIONS

6.1 Efficacy subject population

The efficacy subject population will consist of all subjects who have an interpretable image that has an available expert majority image interpretation.

6.2 Efficacy clinical reader population

The efficacy clinical reader population will consist of each clinical reader who has interpreted the images included from his/her institution and has had at least one of their image interpretations classified as TP, TN, FP, or FN through comparison with the SOT (the expert reader majority interpretation).

6.3 Safety population (Safety)

The safety population will consist of all subjects who were enrolled in the study and received a dose of VIZAMYL™.

6.4 Exclusions from analysis sets

Subjects who do not meet the definition of the various populations will be determined prior to database freeze and image unblinding.

7 STATISTICAL CONSIDERATIONS AND ANALYSIS

7.1 Derived Variables

Not applicable

7.2 Handling of missing data and outliers

Missing values will not be substituted by estimated values, but treated as missing in the statistical evaluation. All data from all subjects enrolled and imaged in the study will be included in all listings, plots, summary tables, and statistical analyses when appropriate.

7.2.1 Missing data analysis methods

Not Applicable

8 STATISTICAL METHODS

8.1 General statistical conventions

All statistical procedures will be completed using SAS version 9.3 or higher.

Continuous variables will be summarised using descriptive statistics, including number of subjects in the analysis (n), mean, median, standard deviation (SD), and range (minimum and maximum).

For categorical variables, summaries will include counts of subjects and percentages. Percentages will be rounded to one decimal place. Two-sided 95% exact CI will be provided when relevant.

All subject data, including those derived, will be presented in separate data listings showing individual subject values. Unless otherwise stated, unscheduled visit results will be included in date/time chronological order, within patient listings only. All listings will be sorted by investigational site, patient number, date/time and visit. Patient's gender and age will be stated on each listing. Unless otherwise stated, data listings will be based on the safety population.

8.2 Subject disposition

Subject disposition information will be summarised. The disposition summary table will include the following information.

- Number of subjects enrolled (subjects who have signed the informed consent form)
- Number of prospective images
- Number of retrospective images
- Number of subjects in the safety population
- Number of subjects with VIZAMYL™ images included in the efficacy analysis (efficacy subject population)
- Number of subjects who completed the study
- Number of subjects who discontinued the study
- Reasons for withdrawal

The safety population will be used for calculating the percentages.

In addition, a separate table will be provided to summarise the efficacy clinical reader population, the number of clinical readers participating, and number of clinical readers' image interpretations included in the efficacy analysis. Listings will be provided for subject disposition.

8.3 Protocol deviations

Deviations from the protocol will be described and provided in the form of a listing.

8.4 Demographics and baseline characteristics

8.4.1 Subjects-demographic and baseline characteristics

Continuous demographic variable age will be summarised descriptively, and the following categorical variables will be summarised using counts and percentages. Summaries will be provided for prospective and retrospective images along with pooled results based on the safety population.

- Gender
- Race
- Country

Baseline characteristics

- History of renal/hepatic impairment
- Reason for scan
- Type of medical practice of referring physician (primary, secondary, tertiary)
- Type of anatomic images available, if any (MRI and/or CT)

Listings will be provided for each subject's baseline and demographic characteristics.

8.4.2 Clinical Reader - demographic and baseline characteristics

Continuous demographic variable clinical reader's age will be summarised descriptively, and the following categorical demographic and baseline variables will be summarised using counts and percentages. Summaries will be based on the efficacy clinical reader population.

- Gender
- Race
- Country

Baseline characteristics:

- VIZAMYL™ reading training status
- Number of times training done (1, 2, ≥3)
- VIZAMYL™ reading training method (electronic, in-person, or both)
- Training with other amyloid PET imaging agents
- Medical specialty
- Time (month) from last training to the date of image interpretation (<6 months, ≥6 months)
- Number of brain PET scans read in clinical practice (<50, ≥50)
- Type of medical practice (primary, secondary, tertiary)
- Prior experience (clinical or research) with any amyloid PET imaging agent (including VIZAMYL™)

In addition, the following continuous baseline characteristics will be summarised descriptively:

- Duration (months) from last training to the date of image interpretation
- Years of experience reading PET images
- Number of brain PET scans read in clinical practice
- Years of experience reading PET images

- Number of times training done

Listings will be provided for each clinical reader's demographic and baseline characteristics.

8.4.3 Medical history

Not Applicable

8.4.4 Prior and concomitant medications

Not Applicable

8.5 Extent of exposure

8.5.1 Treatment exposure

Subjects will receive (or will have received) VIZAMYL™ intravenously prior to PET imaging, according to clinical practice.

The dose and volume administered will be summarised for prospective and retrospective images along with pooled results. Descriptive statistics will be given for the VIZAMYL™ dose (mBq) and volume administered (mL). VIZAMYL™ dose administration details will be listed.

8.5.2 Treatment compliance

Not applicable

8.6 Efficacy analyses

8.6.1 Analysis methods

All analyses will be provided in descriptive nature, counts and percentages, along with exact 95% CI, wherever applicable. All of the efficacy analyses will be based on the efficacy subject population.

8.6.2 Primary analysis

The endpoints are the diagnostic accuracy, sensitivity, specificity, PPV, and NPV. Each of the clinical image interpretations will be matched to the corresponding expert reader majority interpretation for the subject and the image interpretation will be classified as a TP, TN, FP or FN using the expert reader majority interpretation as the SOT. For example, if an image interpretation is "positive" and the expert reader majority interpretation is "positive", the image interpretation would be classified a TP. If the expert reader majority interpretation were "negative", however, then the image interpretation would be classified as a FP. If any reader interpretation is "probably negative" or "probably positive", this will be considered as "negative" or "positive", respectively in the summary tables. In addition to this primary analysis framework, a sensitivity analysis will be performed for the primary endpoints without considering "probably negative" or "probably positive" clinical image interpretations.

The numbers of TP, TN, FP, and FN images among the ≥200 original images will be used to calculate diagnostic accuracy:

Diagnostic accuracy = $\frac{\text{Number of true positives+number of true negatives}}{\text{Number of true positives+number of true negatives+ Number of false positives+number of false negatives}}$

Diagnostic accuracy will give an indication of the overall image interpretation error rate (1 minus diagnostic accuracy)

The below table provides the details and consideration of TP, TN, FP and FN.

		Expert Reader Interpretation	
		Positive	Negative
Clinical reader Interpretation	Positive	True Positive (TP)	False Positive (FP)
	Negative	False Negative (FN)	True Negative (TN)

Sensitivity, specificity, PPV, and NPV will also be calculated using the below formula:

Sensitivity = $\frac{\text{Number of true positives}}{\text{Number of true positives+number of false negatives}}$

Specificity = $\frac{\text{Number of true negatives}}{\text{Number of true negatives +number of false positives}}$

Positive Predictive Value = $\frac{\text{Number of true positives}}{\text{Number of true positives+number of false positives}}$

Negative Predictive Value = $\frac{\text{Number of true negatives}}{\text{Number of true negatives+number of false negatives}}$

The results from these calculations will be summarised with point estimates and exact 95% CIs for prospective images, retrospective images, and pooled results, separately.

In addition, the clinical reader and expert reader global classification results (positive/ negative) will be summarised separately. Clinical reader and SOT classification certainty ratings (1 = low to 5 = high) will be summarised using counts and percentages for prospective images, retrospective images, and pooled results, separately. For the SOT certainty, the majority of the expert certainty ratings that formed the SOT will be used, and in the case of a tie, the lower level of certainty will be used.

Subject-level listings will be provided for the clinical reader and expert reader image evaluations. PET imaging details will also be provided in the form of listings.

8.6.3 Secondary analysis

Images for which 5 expert readers agree, 4 expert readers agree, and 3 expert readers agree will be summarised using counts and percentages.

In addition, estimates of diagnostic accuracy, sensitivity, specificity, PPV, and NPV, along with exact 95% CIs, will be provided separately for prospective images, retrospective images, and pooled results, separately, using the following variables:

- Country
- Time from training to image interpretation (<6 months, ≥6 months)
- Specialty of the reader
    - Nuclear Medicine
    - Radiology
    - Medical Physics
    - Other
- Training method (s) used by the clinical reader (in-person, electronic, or both)
- Number of scans read by the clinical reader in practice prior to the study (<50, ≥50)
- Clinical reader and SOT classification certainty (1 to 5)

The number of clinical readers in the above subgroups will be provided. The number and percentage of diagnostic accuracy categories <70%, >70% to ≤80%, >80% to ≤90%, and >90% will also be provided by using the above subgroups for prospective images, retrospective images, and pooled results, separately.

8.7 Safety analyses

8.7.1 Adverse events

All AEs will be classified by primary system organ class (SOC) and preferred term (PT) according to the Medical Dictionary for Regulatory Activities (MedDRA).

A treatment-emergent AE (TEAE) is defined as an AE that begins or worsens in severity after at least one dose of study treatment has been administered.

AE summary tables will be presented for TEAEs only and will include the following:

- All TEAEs
- Subject with at least one TEAE
- Related TEAEs
- TEAEs by maximum severity
- Serious TEAEs

An overall summary for the above categories will be presented. All TEAEs categories presented above will also be summarised by SOC and PT using frequency counts and percentages (i.e., number and percentage of subjects with an event). The safety population will be used for these summaries.

If a subject has the same AE, based on PT, reported multiple times in the treatment period, the subject will only be counted once at the PT level in AE frequency tables.

If a subject has multiple AEs within the same SOC in the treatment period, the subject will only be counted once at the SOC level in the AE frequency tables.

When reporting AEs by severity, in addition to providing a summary table based on the event selection criteria detailed above, a summary table will also be provided based on the most intense event during the treatment period, independent of relationship to study treatment.

In the summaries by SOC and PT, AEs will be sorted by decreasing frequency within each SOC and PT within each SOC.

Individual listings will be provided for AEs.

8.7.2 Clinical laboratory evaluations

No laboratory assessment will be done.

8.7.3 Vital signs

No vital assessment will be done.

8.7.4 Physical examinations

No assessment will be done.

8.7.5 Electrocardiograms

No assessment will be done.

8.8 Interim analysis

No formal interim analyses (IA) of the data are planned for this study.

9 CHANGES TO PLANNED ANALYSIS FROM STUDY PROTOCOL

No change in protocol planned analysis.

10 REFERENCES

1. ICH Topic E3: Structure and Content of Clinical Study Reports (CPMP/ICH/137/95-adopted December 1995).
2. ICH Topic E9: Statistical Principles for Clinical Trials (CPMP/ICH/363/96 – adopted March 1998).

11 APPENDICES

Not applicable