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ETOP 12-17 ALERT-lung

A single arm phase II trial evaluating the activity of alectinib for the treatment of pretreated RET-rearranged advanced NSCLC

Statistical Analysis Plan (SAP) for Final analysis

A clinical trial of ETOP

SAP VERSION	V1.1
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Contents

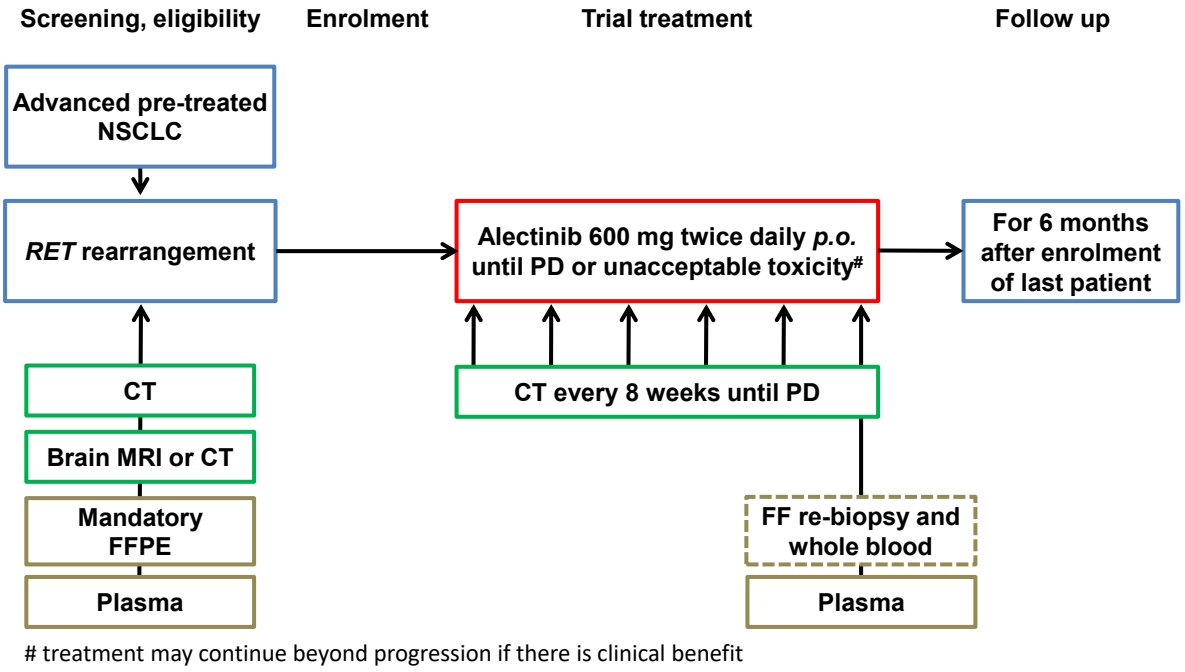
INTRODUCTION

The aim of this Statistical Analysis Plan (SAP) is to describe an analytic and solid framework that will be followed in order the final efficacy analysis of the ALERT-lung trial to be implemented. A short description of the contents of this statistical analysis plan is provided below:

1. **Trial oversight**: trial's schema, objectives and trial endpoints, eligibility criteria, study treatment, statistical design (sample size and power), trial duration
2. **Statistical considerations for final analysis**: analysis timing, definition of primary and secondary endpoints, (serious) adverse events definition, analysis populations
3. **Primary efficacy analysis of alectinib in terms of best overall response (OR) assessed by RECIST v1.1**
4. **Additional secondary analysis:** accrual and baseline characteristics, follow-up and treatment administration, secondary analysis (including analysis of biomarkers available)
5. **Technical issues**: data retrieval, testing, handling of missing data, reporting conventions

1 Trial oversight (according to trial protocol)

ALERT-lung is a single arm, multicentre phase II trial evaluating the activity of alectinib as second-line treatment of pretreated RET-rearranged advanced NSCLC.



SCHEMA 1. Trial design

1.1 Objectives

Primary objective

The **primary objective** is to assess the efficacy of alectinib in terms of best overall response (OR) assessed by RECIST 1.1., from the start of trial treatment across all time points until the end of trial treatment.

Secondary objectives

The **secondary objectives** of the study include:

- To evaluate secondary measures of clinical efficacy including disease control, progression-free survival (PFS), and overall survival (OS).
- To assess the safety and tolerability of the treatment.

Correlative studies

Further exploratory analyses include description of primary and secondary outcomes for patient subgroups of interest, as defined by patient or tumour characteristics or different levels of biomarkers examined.

1.2 Endpoints

Primary endpoint:

• Best overall response (OR = CR or PR), per investigator assessment, according to RECIST 1.1.

Secondary endpoints:

- Best overall response per independent review.
- Disease control at 24-weeks: best overall response of CR or PR, or SD (or non-CR/non-PD in the case of non-measurable disease only)
- PFS defined as the time from the date of enrolment until documented progression or death, if progression is not documented
- OS defined as time from the date of enrolment until death from any cause
- Safety and tolerability

1.3 Most important eligibility criteria

Inclusion criteria:

- Histologically or cytologically documented non-small cell lung carcinoma.
- Advanced disease defined as recurrent stage IV (according to 8th TNM classification) or recurrent or progressive disease following multimodal therapy (radiation therapy, surgical resection, or definitive chemo-radiation therapy for locally advanced disease).
- At least one prior platinum-based systemic regimen: Adjuvant or neoadjuvant or definitive platinum-based chemo-radiotherapy treatments are considered as a line of treatment only if completed less than 6 months before enrolment. Maintenance therapy following platinum doublet-based chemotherapy is not considered a separate regimen of therapy.
- RET rearrangement detected by FISH, Nanostring or by parallel-sequencing on FFPE tumour tissue assessed locally.
- Availability of FFPE tumour material for central confirmation of RET-rearrangement.
- Measurable or non-measurable, but radiologically evaluable (except for skin lesions) disease according to RECIST v1.1 criteria.

- Age ≥18 years.
- Eastern Cooperative Oncology Group (ECOG) Performance Status 0-2.
- Life expectancy >3 months.

Exclusion criteria:

- Untreated, active CNS metastases.
- Carcinomatous meningitis.
- Any previous (in the past 3 years) or concomitant malignancy EXCEPT adequately treated basal or squamous cell carcinoma of the skin, in situ carcinoma of the cervix or bladder, in situ ductal carcinoma of the breast.
- Any serious diseases or clinical conditions, including but not limited to uncontrolled active infection and any other serious underlying medical processes, that could affect the patient's capacity to participate in the trial.
- Previous treatment with any RET TKI or RET targeted therapy.
- Patient with locally detected EGFR, ROS or ALK mutation (in addition to RET rearrangement).
- Any concurrent systemic anticancer therapy.
- Women who are pregnant or in the period of lactation.

1.4 Trial treatment

Alectinib is administered orally, 600 mg, twice per day (1200 mg per day) until progression, refusal or unacceptable toxicity. Trial treatment may also continue beyond progression, with physician and patient agreement, for as long as the patient may still derive clinical benefit as per investigator decision. Treatment has to start as soon as possible after enrolment, ideally within 7 days. Treatment visits are planned at treatment start (week 0) and then every 2 weeks (±3 days) for the first 12 weeks and every 4 weeks (±3 days) thereafter.

1.5 Statistical design, sample size & power

According to the protocol, the trial targets a best OR rate of 35% and considers an OR rate of 15% as too low.

Based on a one-sided exact test for proportions, the trial is designed to test the following hypotheses: **H_0: $p_0 \leq 0.15$ vs H_A: $p_A > 0.35$, where p is the rate of best OR (ORR) at a one-sided significance level of 0.025 and a power of at least 0.80.**

A significance level of 0.015 and power of 0.82 are achieved with a sample size of 41 evaluable patients. The null hypothesis will be rejected and the alternative hypothesis accepted if at least 12 patients achieve OR.

The total sample size of **44 patients** allows for up to 3 patients to be replaced if a patient is ineligible (retrospective review), has not started the experimental treatment or is lost to follow-up before evaluation of response.

1.6 Total trial duration

Clinical visits are expected to span approximately **44 months** after enrolment of the first patient. Assuming an accrual rate of approximately 1 patient per month and a start-up period of 6 months as the trial is activated by participating centres, the final trial report is expected to be available approximately 5 years after the enrolment of the first patient.

2 Statistical considerations for final analysis

2.1 Premature trial closure

Since the activation of the ALERT-lung trial in April 2018, promising new agents for the treatment of RET-rearranged NSCLC have been introduced. At the same time, in a Japanese study, alectinib has shown only moderate activity in this indication.

For both the aforementioned reasons, **ETOP decided to prematurely close the ALERT-lung trial, by March 31, 2021.** Follow-up and safety information will be updated until 31 March 2021.

A final analysis will be performed based on all enrolled patients and respective available information collected up to trial's premature closure.

2.2 Study's endpoints

2.2.1 Primary endpoint

Overall response (OR) is defined as best overall response (complete response (CR) or partial response (PR) according to RECIST criteria v1.1 from the start of trial treatment across all time points until the end of trial treatment.

Objective response rate (ORR) will be calculated as the rate of patients achieving CR or PR over the total number of patients in the analysis cohort.

2.2.2 Secondary endpoints

Secondary endpoints, according to the protocol, include disease control at 24-weeks, PFS, OS, safety and tolerability. More specifically:

- Disease control (DC) is defined as complete or partial response, or disease stabilisation at 24 weeks. Accordingly, disease control rate (DCR) will be calculated as the rate of patients achieving DC over the total number of patients in the analysis cohort.
- PFS is defined as the time from the date of enrolment until documented progression (based on RECIST 1.1 criteria) or death, if progression is not documented. Censoring (for patients without a PFS/death event) will occur at the date of last tumour assessment if patient is lost to follow-up or refuses further documentation of follow-up.
- OS is defined as time from the date of enrolment until death from any cause. Censoring will occur at the last follow-up date.

All safety parameters will be summarised in tables to evaluate the safety profile of patients treated with alectinib in terms of:

- Adverse events including adverse events leading to dose modifications or interruptions, study drug withdrawal, and death
- Any cause adverse events; Treatment-related adverse events
- Severe, serious, and selected adverse events
- Deaths
- Laboratory parameters and abnormalities, vital signs and ECGs

2.2.3 Exploratory endpoints

Other endpoints that will be presented, in an exploratory frame, include:

- Time to treatment failure (TTF) is defined as time from the date of enrolment until discontinuation of protocol treatment for any reason (including progression of disease, death, treatment discontinuation due to any reason, such as treatment toxicity or investigator's decision, withdrawal/lost to follow-up (LFU)). Censoring for TTF (patients on treatment) will occur at the last follow-up date.

Correlative endpoints include:

- Type of RET fusion and other transcripts

Co-mutations detected with either Next Generation Sequencing (NGS), or Copy Number Variations. Correlative endpoints will be used in the subgroup analysis.

(Serious) Adverse Events

Adverse events (AE)

The main criterion for treatment tolerability is the occurrence of toxicities and adverse events. The severity and causality will be classified according to the NCI CTCAE v4.0. The CTCAE v4.0 is available for downloading (http://evs.nci.nih.gov/ftp1/CTCAE/About.html).

An AE is defined as any untoward medical occurrence that occurs from the date of signature of inform consent until 30 days after all trial treatment discontinuation, regardless of whether it is considered related to a medication.

Serious Adverse Events (SAE)

A SAE is defined in general as any undesirable medical occurrence/adverse drug experience that, at any dose:

- results in death (any cause, except progression of cancer under study)
- is life-threatening
- requires or prolongs inpatient hospitalization (>24 hours)
- results in persistent or significant disability/incapacity
- constitutes an important medical event
- is a congenital anomaly or birth defect (including neonatal deaths and abortions)
- is a secondary malignancy/second primary malignancy

Adverse events of special interest (AESI)

AEs of special interest for this trial are the following:

- **Drug-induced liver injury.** Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law.
- **Suspected transmission of an infectious agent by the IMP.** Any organism, virus, or infectious particle (e.g., prion protein transmitting spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

- **Adverse events associated with an overdose.** An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of IMP is not itself an AE, but it may result in an AE.

Severity Grade of (serious) adverse event

The (serious) AE severity grade provides a qualitative assessment of the extent or intensity of a specific event, as determined by the investigator or as reported by the patient. *The severity grade does not reflect the clinical seriousness of the event*, only the degree or extent of the affliction or occurrence (e.g. severe nausea, mild seizure), and does not reflect the relationship to trial drug. Severity grade for other adverse events not covered in the toxicity grading scale:

Grade 1	Mild- transient or mild discomfort; no limitation in activity; no medical intervention/therapy required
Grade 2	Moderate- mild to tolerate limitation in activity; some assistance may be needed; no or minimal medical intervention/therapy required
Grade 3	Severe- marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization is possible
Grade 4	Life-threatening- extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable
Grade 5	Fatal- the event results in death

Causality of (serious) adverse event

The investigator must determine the relationship between the administration of trial drug(s) and the occurrence of an AE/SAE following the definitions indicated below:

- Not suspected (unrelated/unlikely): The temporal relationship of the adverse event to trial drug(s) administration makes a causal relationship unlikely or remote, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.
- Suspected (possible/probable/definite): The temporal relationship of the adverse event to trial drug(s) administration makes a causal relationship possible, and other medications, therapeutic interventions, or underlying conditions do not provide a sufficient explanation for the observed event.

2.3 Analysis populations

Intention-To-Treat Cohort: The Intention-To-Treat (ITT) cohort will include all patients enrolled in the trial.

Efficacy Cohort: The efficacy cohort will encompass all evaluable patients, i.e., all enrolled patients excluding patients that were found to be ineligible (in retrospective review), patients that have never started the trial treatment and patients that are lost to follow-up before their first response evaluation (by RECIST 1.1).

Safety Cohort: The safety cohort will include all enrolled patients that have received at least one dose of trial treatment.

3 Primary efficacy analysis of OR

The **primary analysis of OR** will be performed on all the patients included in the **efficacy cohort**. OR rate (ORR) will be estimated as the rate of patients achieving CR or PR over the total number of patients in the efficacy cohort, along with the corresponding 95% exact binomial confidence interval (CI).

Formal hypothesis testing

According to the protocol, the trial has been designed to test the null hypothesis **H_0: ORR_0 ≤0.15 versus the alternative H_A: ORR_A >0.15 evaluated at 0.35**, using a one-sided exact test for proportions, at a one-sided significance level of 0.025 and a power of at least 0.80. The attained alpha of 0.**015** and **power of 82%** will be achieved with a sample size of **41 evaluable patients**. The null hypothesis H_0 would be rejected and the alternative hypothesis H_A accepted **if at least 12 patients achieve OR.**

Due to trial's premature closure, the target sample size has not been reached and, thus the above formal testing cannot be performed. However, an adhoc hypothesis testing (based again on binomial distribution) will be performed using the available data.

OR analysis will also include:

- A waterfall plot to graphically depict the best percent change in tumor size (sum of target lesions diameter) from the baseline tumor assessment before enrolment.
- A spider plot to graphically depict the percent changes in tumor size (sum of target lesions diameter) from the baseline tumor assessment before enrolment, over time.
- Depending on the number of available responses (i.e., if at least 5), the use of univariate and multivariate logistic regression models will be explored to investigate the effect of the clinicopathological variables of interest (gender, age category, smoking history, ECOG performance status at enrolment, and stage at enrolment) on ORR.

4 Additional secondary analyses

In this section, detailed information about the additional analyses that will be performed in the frame of the final efficacy analysis for ALERT-lung trial is presented.

4.1 Patient accrual and baseline characteristics

- Patient accrual by centre and by country will be presented in tabular format.
- In addition, expected vs. observed accrual will be graphically displayed.
- For patients deemed ineligible (patients registered in the online database but eventually not enrolled), a table summarizing the reasons for non-enrolment will be provided.
- Patient & tumor baseline characteristics (categorical variables: ethnicity, gender, smoking history, ECOG performance status at enrolment, tumor stage at enrolment, and continuous variables: age at enrolment) will be presented. Frequencies and corresponding percentages will be presented for categorical variables (if missing cases exist, a separate category named "*Missing*" will be created), while the following descriptive measures will be considered for the continuous variables: n (non-missing sample size), mean, 95% CI for the mean, median, maximum and minimum value.
- Also available information on medical history and prior treatment will be summarised.
- Molecular characteristics at baseline (enrolment): Type of RET fusion and other transcripts; Co-mutations detected with either Next Generation Sequencing (NGS), or Copy Number Variations. Comparisons will also be performed with assessments at subsequent time points (PD) whenever available.

Note: For the efficacy analysis (e.g. subgroup analysis, logistic regression models) age will be categorised according to the observed median.

4.2 Follow-up information and treatment administration

Firstly, a consort flow diagram will be created.

Median follow-up (FU) of the patients along with the respective interquartile range (IQR) and the number (%) of patients that are still alive, will be summarized in a table. Median follow-up time will be estimated based on the method of reverse censoring of OS. A Kaplan-Meier plot will be provided for illustrative reason.

Treatment information will be summarized and presented in a tabular format. More specifically:

- The number of patients that started treatment will be reported. For those patients enrolled, progressed but with physician's and their own agreement continued receiving treatment, information on treatment failure after first progression will be additionally provided.
- The number of patients that did not receive any dose of trial treatment, along with reasons for not doing so will also be presented.
- Number of treatment failures, the 6-month TTF estimate and median TTF time along with the corresponding 95% CIs and the reasons for treatment failure/discontinuation will be presented.
- TTF will be graphically depicted via a Kaplan Meier plot.
- For patients with treatment failure, information for further lines of treatment will also be provided.

4.3 Secondary and exploratory efficacy endpoints

4.3.1 Disease control rate

Clinical efficacy will be further explored by the estimation of **disease control rate (DCR) in the efficacy cohort**.

- Disease control rate (DCR) at 24 weeks will be presented along with its 95% exact binomial CI.
- The use of univariate and multivariate logistic regression models will be considered (if possible, taking into account the limited number of enrolled patients) to investigate the effect of the clinicopathological variables of interest (gender, age category, smoking history, ECOG performance status at enrolment, and stage at enrolment) on DCR.

4.3.2 Progression-free survival

PFS will be evaluated in the **efficacy cohort** by the Kaplan-Meier method. Specifically, the PFS analysis will include:

- The total number (%) of PFS events observed, the 6-month estimate, median and respective 95% CIs.

- Graphical representation of PFS via Kaplan-Meir plots, overall and separately by each clinicopathological variable of interest (if possible due to the limited number of enrolled patients).
- A table with information about the sites of progression.

4.3.3 Overall survival

Similar to PFS, **OS** will be evaluated in the **efficacy cohort**. OS analysis will include:

- The total number (%) of OS events observed, the 12-month estimate, median and respective 95% CIs.
- Graphical representation of OS via Kaplan-Meir plots, overall and separately by each clinicopathological variable of interest (if possible due to the limited number of enrolled patients).
- Summary table of the death causes.

4.3.4 Sensitivity efficacy analysis

A secondary analysis of all efficacy endpoints evaluated in the **ITT cohort** (if different than the efficacy cohort) will also be performed. Efficacy endpoints to be re-assessed include overall response rate (ORR), disease control rate (DCR) at 24 weeks, progression-free survival (PFS), overall survival (OS).

4.3.5 Safety and tolerability

The **safety and the tolerability** of the trial treatment will be evaluated by the **occurrence of AEs** on all patients that have received at least one dose of trial treatment **(safety cohort)**. Classification of severity and causality will be performed according to CTCAE v4.0 and will be presented using tables and bar charts. For each subject, each AE will be analysed according to the worst grade of toxicity observed over the whole treatment period.

Safety and tolerability assessment will include the following:

- Overview of the number of patients who experienced an AE/SAE, as well as the number of patients in the safety cohort who did not experience an event, along with respective percentages.
- Number of AEs/SAEs/AESIs (any cause or treatment-related) and rate of occurrence per month of follow-up.
- Number of patients experiencing a specific number of AEs/SAEs.

- Distribution of AEs/SAEs by grade and CTCAE category. Six columns, one for each grade and one for all (any) grades, will be shown. An additional column indicating which events were SAEs -or started as AEs and became SAEs later on- will be also available. In this column, the frequency of the SAEs and the severity grade will be given. The percentages that will accompany the frequencies will be based on the respective frequency of an event over the total number of patients in the safety cohort. This table will include all AEs/SAEs irrespective of their relation to the trial treatment.
- Analogous table focusing only on the treatment related AEs/SAEs.
- A bar plot illustrating frequencies of AEs/SAEs (only AEs/SAEs with frequency >2% (or any other relevant %) will be presented). A similar plot by CTCAE category will be produced.
- A bar plot illustrating frequencies of treatment related AEs/SAEs.
- Number and corresponding percentages of treatment related AEs/SAEs, leading either to treatment discontinuation or death.
- Maximum severity of AEs/SAEs per patient.
- Number of SAEs by centre.
- For all fatal SAEs, cause of death will be provided.

4.3.6 Subgroup analysis

Further exploratory analyses include description of primary (ORR) and secondary (DCR, PFS, OS) outcomes for patient subgroups of interest, as defined by the following patient or tumour characteristics:

- Smoking status (Current/Former vs Never)
- Gender
- Age group
- ECOG PS
- Stage
- Type of prior treatments

Additional subgroup analysis will be performed by molecular characteristics (at enrolment):

- Type of RET fusion
- Co-mutations detected

Of note, due to the small number of patients, these analyses will be mainly of exploratory nature. Depending on data, Fisher's exact test will be used for comparing ORR, DCR and log-rank test for comparing PFS, OS between different subgroups of patients.

5 Technical details

Data will be primarily analysed using the SAS software package (version 9.4), while the R statistical software will be also used for specific analyses and plots.

All final analysis and reviews will be performed according to the Standard Operating Procedures (SOPs) of the Frontier-Science Foundation Hellas (FSFH) statistical team. A second statistician, the reviewing statistician, will independently reproduce all analyses and summary statistics. The reviewing statistician will have an overview of the entire analysis and will explicitly check the code producing tables and figures, as well as any other pieces of code as desired.

5.1 Data Retrieval Information

On February 8, 2021, ETOP announced the premature closure of the ALERT-lung trial (ETOP 12-17 ALERT-lung Trial Closure Guidance Letter). **Trial will be terminated by March 31, 2021. Follow-up and safety information will be updated until March 31. All outstanding data and query replies will be submitted by 28 February 2021. Final database lock and trial closure date will be on 31 March 2021.**

5.2 Missing Data

Baseline characteristics

For categorical baseline characteristics if missing cases exist, a separate category named 'Missing' will be created. As far as continuous values, missing cases will not be replaced by any statistics calculated over non-missing data.

Dates

If the day of the month is missing for any date used in the analysis, the 15th of the month will be used to replace the missing date unless the calculation results in a negative time duration (eg, onset date cannot be prior to day one). In this case, the date resulting in one day of duration will be used. If the day of the month and the month are missing for any date used in a calculation, January 1 will be used to replace the missing date. Missing dates for adverse events will be imputed based on the similar principle.

Incomplete tumor assessment information

In patients who have no on-study assessments:

- If death is recorded prior to the first planned tumor assessment, the death date will be considered as the date of the PFS event.
- If clinical progression is recorded prior to the first planned tumor assessment, the date of the reported clinical progression will be considered as the date of the PFS event.
- In any other case, the patient will be censored at the date of enrolment plus 1 day.

5.3 Reporting conventions

Regarding the estimates presented in the report, the following rules will be adopted:

- P-values ≥0.001 will be reported with three decimal places
- P-values >0.010 will be reported with two significant decimal digits
- P-values less than 0.001 will be reported as '<0.001'
- Means, medians, 95% confidence intervals (CIs), quantiles, and any other statistics, will be reported with one decimal digit
- Hazard ratios (HRs) and their 95% CIs will be reported with two decimals
- Estimated parameters, not on the same scale as raw observations (e.g., regression coefficients) will be reported with three significant figures

5.4 Multiple recordings of an event for the same patient

There are some cases where a patient may experience the same event (AE/SAE) more than one time. In such cases, the event will be count only once (with the highest grade) for the calculation of the total number of events.

5.5 Presentation of results

The results will be presented through tables and figures. A summary of the results will also accompany the main report. First, a short synopsis of the results will be presented through bullets, where only the most important findings will be shown. Following that, a more detailed description of the results will be provided, sectioned in the following order:

I. Patient accrual and baseline characteristics
II. Follow-up and treatment administration
III. Efficacy analysis
IV. Safety analysis