STATISTICAL ANALYSIS PLAN

ALEGORI: A Randomized Trial of Bevacizumab Nasal Spray vs Placebo as a Treatment for Epistaxis in Hemorrhagic Hereditary Telangectasia (HHT)

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Version 2.0

Sponsor :

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Statistical analysis

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Table of updates

Version	Date	
1.0	May 2015	First version of the document
2.0	June 2015	Second version of the document after intermediate analysis and decision of the Data and Safety Monitoring Board (DSMB).

Compared to the version 1.0, several changes of the analysis plan have been made to take into account the discontinuation of the study as recommended by the DSMB:

- Analysis of the other secondary judgment criteria will focus on the patients included throughout the step 1 of the study in the 4 randomization arms (instead of 2 randomization arms selected after the interim analysis).
- Student test and Mann-Whitney (used in the case of 2 groups) were replaced by ANOVA and Kruskal Wallis test (used in the case of 2 groups).
- Adding a statistical test comparing hemoglobin between visits for each group (ANOVA (or Kruskal Wallis in case of non-normality)) (principal investigator's request)

Statistical analysis plan

The following section includes the main elements of the statistical analysis plan. This plan was revised to make changes in order to adapt to the occurrence of unexpected events in the course of the study and which have an impact on the analysis of the data.
These revisions were carried out before the database is frozen.

The interim analysis with dose selection and re-assessment of the sample size for the second stage was carried out by Dr Raphaël Porcher (Department of Biostatistics and Medical Information Technology, Hôpital Saint Louis, AP-HP), who was blinded and didn't have the randomization codes except the Placebo group.
After interim analysis, the Data and Safety Monitoring Board (DSMB) recommended the definitive discontinuation of the study.

At the end of the study, the data analysis will be carried out by the Clinical Research Unit at the IMER pole (Department of Dr François Chapuis, Hospices Civils de Lyon), who will have the randomization codes, in collaboration with Dr Raphaël Porcher.

Interim analysis by Dr Raphaël Porcher was performed with R.
Final analysis will be performed using SAS software version 9.2 (SAS Institute Inc, Cary, NC, USA). The 0.05 threshold will be considered as statistically significant.

Analysis populations

Intention to treat population

This population will be composed of all the randomized patients who were treated with at least one spray treatment on the three spray treatment provided. Patients will be analyzed as randomized whatever treatment received.

Per protocol population

This population will be composed of all the patients who have received all the spray treatments set out in the protocol. Only patients with correct treatment received will be analyzed.

Safety population

This population will be composed of all the patients who have received at least one spray treatment.

Statistical methods

Populations

All the populations in the study will be presented with their numbers.

Deviation from the protocol

Any deviation from the protocol that may have an impact on the results of the study will be listed.

Initial characteristics

Initial characteristics of the patients will be summarized by means of descriptive statistics (number, average, standard deviation, median, minimum and maximum for the quantitative variables and numbers and percentages for the qualitative variables).
For the interim analysis, these characteristics will be presented on the 4 groups of 20 patients.

For the final analysis, these characteristics will be presented on all the patients in stage 1 (stage 2 will not be realized).

Analyzing the main judgment criterion

Selecting the dose at the end of stage 1 (interim analysis)

The dose that shows the most significant standardized difference (Student test with Simes' correction for multiplicity) with the placebo during the interim analysis will be selected for the second stage of the study. This dose is thus the one for which the degree of signification p_1 is the smallest.
A re-assessment of the number of subjects may occur (*cf* the paragraph, Number of participants).

At the end of this analysis, an interim report will be edited and will present for each group:

- the number of patients studied
- the number of doses effectively received
- the judgment criterion (duration of the nosebleeds before and after treatment)
- the adverse events observed, the date of their occurrence and their resolution

The report will also present the conclusions of the DSMB

Analyzing the secondary judgment criteria

1. On the safety population, for each of the 4 randomization arms (Avastin® 25mg, Avastin® 50mg, Avastin® 75mg and Placebo arms), the following will be presented in the form of a listing:
   - the number of sprays administered,
   - the type of treatment received (bevacizumab/placebo),
   - the dose effectively received,
   - any adverse events observed, their date of onset and of resolution.

2. The clinical efficacy of the bevacizumab sprays will be evaluated by comparing, between the 4 randomization arms, the average monthly duration of the nosebleeds at 6 months after the end of the treatment. The test used will be an ANOVA on independent samples (or a Kruskal Wallis test in case of non-normality).

3. The clinical efficacy of the bevacizumab sprays will be evaluated, between the 4 randomization arms by comparing:

   - the deltas of monthly average duration and average monthly number of nosebleeds between the inclusion values and at 3 months after the end of the treatment then the deltas between the inclusion values and the values at 6 months after the end of the treatment. The test used will be an ANOVA on independent samples (or a Kruskal Wallis test in case of non-normality).

- the trend over time on dimensions of quality of life questionnaire (SF-36) observed at inclusion, 3 months and 6 months after the end of the treatment using a mixed model for repeated measures (time, groupe, time * group).

- the number of red blood cell transfusions at 3 months and 6 months were compared between the 4 randomization arms with an ANOVA on independent samples (or a Kruskal Wallis test in case of non-normality).

4. The biological efficacy of the bevacizumab sprays will be evaluated by comparing, between the 4 randomization arms, the trend over time on hemoglobinemia and serum ferritin observed at inclusion, D14, D28 then 1 month, 3 months and 6 months after the end of the treatment using a mixed model for repeated measures (time, group, time * group).

   Hemoglobinemia by visits will be compared for each group with an ANOVA (or Kruskal Wallis in case of non-normality).

5. The total monthly duration of the nosebleeds will be described in relation to time (3 months before treatment until 6 months after the end of the treatment). Trend over time will be evaluated using a mixed model for repeated measures (time, group, time * group).