STUDY TITLE: Effect of Antimalarial Drugs on the Immune Response to Rabies Vaccine for Post-exposure Prophylaxis. A Randomized, Open Label, Trial in Healthy US Adults Age 18-60 Years

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# Effect of Antimalarial Drugs on the Immune Response to Rabies Vaccine for Post-exposure Prophylaxis

### A Randomized, Open Label Trial in Healthy US Adults Ages 18-60 Years

## Statistical Analysis Plan (SAP)

**Version 1.0, Dated 10 Jan 2017**


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| **Licensed Products:** | RabAvert® Rabies Vaccine<br>Chloroquine<br>Malarone<br>Doxycycline |
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**Statistical Methods**

The analysis will be performed under the responsibility of Upstate Medical University in conjunction with the study partners.

This will be a descriptive study to assess immunogenicity of a licensed rabies vaccine using test dosage schedules in the presence of malaria chemoprophylaxis. No formal statistical hypothesis tests will be conducted. Descriptive analyses will be based on the per-protocol analysis sets using the RFFIT data from blood samples taken samples taken from Day 0, prior to vaccination 3, prior to vaccination 4, 14 and 28 days post 4th vaccination. Separate descriptive analyses will be conducted for each per-protocol data set and group.

Exploratory statistical analyses of final data may be conducted, if indicated by the descriptive results. Parametric, non-parametric and resampling (bootstrapping) methods for statistical inference may be used in exploratory analyses, based on data compliance with assumptions of methods. P -values $\leq 0.05$ will be considered significant and p-values $\leq 0.10$ will be considered a trend. Confidence intervals will be constructed at $\alpha=0.05$ and $\alpha=0.10$. When necessary, p-value corrections for multiple comparisons will be applied.

A descriptive summary of adverse events and serious adverse events that were reported throughout the trial will be produced.

Descriptive and inferential analyses (if any) will be carried out using SAS Version 9.4 (or more recent versions), which is licensed and supplied by SAS Institute, Cary, NC, USA.

**Per-Protocol Analysis Set**

The Per-Protocol analysis set (PPAS) will include all subjects who had no protocol deviations at the time that the data was collected. Two PP analysis sets will be produced for the primary objective that will contain separate data from blood drawn on day 0 and 14 days post 4th vaccination. Descriptive analysis of the secondary endpoint will require three additional per protocol analysis sets for blood drawn prior to 3rd and prior to 4th vaccination and on day 28 post 4th vaccination.

Subjects will be excluded from the PPAS for the following reasons:

1. Subject did not meet all protocol-specified inclusion/exclusion criteria or experienced a definitive contraindication
2. Administration of vaccine was not done per protocol
3. Subject did not receive vaccine in the proper time window as defined in the study procedures
4. Subject did not provide a post-dose serology sample in the proper time window as defined in the study procedures*
5. For the malarone and doxycycline groups, subject missed the three or more of the daily dose of antimalarial in any one week.

6. For the chloroquine group, subject missed their weekly dose by three or more days

*Subjects whose serology sample is outside the defined window for the secondary endpoint will still be included in the primary endpoint analysis.

Subjects will be analyzed by the vaccine group to which they were randomized, subject to the exclusion criteria above

**Handling of Missing Data and Outliers**

For the computation of GMTs, a titer reported as < LLOQ will be converted to a value of 0.5 LLOQ.

For calculating fold-rise and titer ratio (GMTR), < LLOQ will be converted to 0.5 LLOQ for a numerator and < LLOQ will be converted to LLOQ for a denominator

Any titer reported as > ULOQ (upper limit of quantization) will be converted to ULOQ.

Missing data will not be imputed.

Potential outliers will be identified using histograms and modified box plots or normal probability plots, when appropriate. Choice of subsequent tests for outliers (e.g. Grubbs, Tietjen-Moore and ESD) will depend on the number and nature of suspected outliers and may require data transformation. Bootstrapped estimates of standard errors may also be reported. Sensitivity analysis of effect of outliers on descriptive statistics will be conducted, and if necessary descriptive statistics that include and exclude outliers will be reported

**Statistical Methods for Baseline Comparisons**

Mean (SD) and median (IQR) age at baseline will be computed and descriptively compared across the six groups. Results will be presented in tabular format. Baseline mean (SD) and median (IQR) of all other quantitative demographic variables of interest at baseline will be calculated for each group and the results will be presented in a table.

The number and percentage of males and females per group at baseline will be calculated and results will be presented in tabular format. The number and percentage per group at baseline of all other qualitative demographic variables of interest will be calculated for each group and the results will be presented in tabular format.

**Statistical Methods for Subject Disposition**

For each group (three prophylaxis and one control), the number and percentage of subjects who received a total of 0, 1, 2, 3 and 4 rabies vaccinations will be reported in tabular format.

For each group, a line listing of subjects who discontinued the study that includes classification of the most serious reason for termination will be produced.

**Statistical Methods for Primary Immunogenicity Objectives**

*Primary Objective:* Compare GMT at 14 days post completion of four dose PEP with PCECV in each of the malaria prophylaxis groups with control to determine if a fifth dose of PEP at that point would be of any added value.

Immunogenicity against rabies will be assessed descriptively using the following parameters:

Timepoints: At 14 days post-completion of four doses of rabies vaccine

- Geometric mean titer (GMT) against rabies virus for the prophylaxis and control groups at 14 days after completion of four doses of vaccine.

A table that presents the total number of per-protocol subjects and GMT against rabies at 14 days post completion of four doses of vaccine by group will be produced.

**Statistical Methods for Secondary Immunogenicity Objectives**

*Secondary Objective:* To evaluate GMT over protective titer prior to third dose, fourth dose and 28 days post fourth dose of PCECV.

Immunogenicity will be assessed descriptively using the following parameters:

Timepoints: prior to third and fourth dose of rabies vaccine and 28 days after fourth dose of vaccine

A table that presents, by group, the total number of per protocol subjects and the GMT against rabies prior to the third and fourth dose of vaccine and 28 days after fourth dose of vaccine will be produced.

**Statistical Methods for Adverse Events and Serious Adverse Events**

For each treatment group, a line listing by subject that describes adverse events and post-baseline day of occurrence of the AE will be produced.

The number and percent of subjects in each group who reported any AE between Days 0 and 372 will be summarized in tabular format.

A table showing the number and percentage of subjects in each group who reported adverse events by general type (category) of event will be produced.