Title: Immunogenicity of a Two vs Three dose, Intradermal (ID) vs Intramuscular (IM) Administration of a Licensed Rabies Vaccine for Pre-Exposure Vaccination

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Immunogenicity of a Two vs Three dose, Intradermal (ID) vs Intramuscular (IM) Administration of a Licensed Rabies Vaccine for Pre-Exposure Vaccination

Randomized, open-label, single center trial in adults aged 18 to 60 years in the US

Statistical Analysis Plan (SAP)

Version 1.1 Dated 05 Dec 2016

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Principle Investigator:	**Mark E Polhemus** Upstate Medical University 725 Irving Ave. Suite 311 Syracuse, NY 13210
Licensed Products:	The RabAvert® Rabies Vaccine
Form /Route:	Intradermal and Intramusclar
Indication For This Study:	Comparison of Dose and Schedule
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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 and routes of administration. No formal statistical hypothesis tests will be conducted Descriptive analyses for the primary endpoints will be based on per-protocol analysis data sets using the data from blood samples taken at baseline (0 days), 28 days, and 365 days after the initial dose and at 7 days after a booster at one year (372 days). 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 ≤ 0.05 will be considered significant and p-values ≤ 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 that were reported throughout the trial will be produced.

Descriptive and inferential analyses (if any) will be carried out using SAS Version 9.2 (or more recent versions), which is licensed and supplied by SAS Institute, Cary, NC, USA.

Per-Protocol Analysis Set

The Per-Protocol (PP) analysis set will include all subjects who had no protocol deviations at the time that the data was collected. Three PP analysis sets will be produced for the primary objective that will contain separate data from blood drawn on day 0, day 28 and day 372, respectively. Descriptive analysis of the secondary endpoint will require a fourth per protocol analysis set for blood drawn on day 365. Subjects will be excluded from the PPAS for the following reasons:

1. Subject did not meet all protocol-specified inclusion/exclusion criteria or definitive contraindications (only for the second and third vaccination)
2. Subject did not receive the correct number of injections
3. Administration of vaccine was not done as per protocol (site and route of administration)
4. Subject did not receive vaccine in the proper time window defined in the tables of the study procedures
5. Subject did not provide a post-dose serology sample in the proper time window defined in the tables of the study procedures

Subjects will remain in this population as long as they do not meet one of the above criteria, except for blood sampling timing and validity of the serology test result*. A PP set will be defined for each injection.

*_Note_: For example, a subject whose time period is outside the defined visit window only between the first injection and the blood sample taken after the first injection will be excluded from PP1 but may be kept in PP2 or PP3.

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

Full Analysis Set

The full analysis set (FAS) is defined as the subjects who received at least one injection of Rabies vaccine and had at least one blood sample drawn and valid post-injection serology result (i.e. a result different from "NR" or missing).

Subjects will be analyzed by the treatment group to which they were randomized.

Populations Used in Analyses

The immunogenicity analysis will be performed on the PP. The kinetic analysis will be performed on the FAS.

Handling of Missing Data and Outliers

Immunogenicity

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.

The number and percentage of males and females per group at baseline will be calculated and results will be presented in tabular format.

Baseline mean (SD) and median (IQR) of all other quantitative demographic variables of interest will be calculated for each group and the results will be presented in a table.

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, 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.

Statistical Methods for Primary Immunogenicity Objectives

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

Timepoints: At baseline, 28 days and 372 days.

- Number and percentage of subjects with a titer ≥ 0.5 IU/ml against rabies virus by treatment group at days 0, 28 and 372.

A table that presents the total number of per-protocol subjects and the number and percent of each treatment group who have a titer ≥ 0.5 IU/ml against rabies virus at days 0, 28 and 372 will be produced.

Statistical Methods for Secondary Immunogenicity Objectives

Immunogenicity will be assessed descriptively using the following parameters:

Timepoints: Days 0, 28 and 365.

A table that presents, by treatment group, the total number of per protocol subjects and the number and percent of each group who have IgG titers ≥ 0.5 IU/ml against rabies virus at days 0, 28 and 365 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.