RECORD OF TELEPHONE CONVERSATION

Submission Type: BLA   Submission ID: 125488/0   Office: OBRR

Product: Crotalidae (pit viper) Immune F(ab')2 (Equine) Injection

Applicant: Instituto Bioclon, S.A. de C.V.

Telecon Date/Time: 24-Jun-2013 04:00 PM   Initiated by FDA? Yes

Communication Category: 1. Advice

Drafted: Edward Thompson/ June 24, 2013
Revised: Mitchell Frost /June 26, 2013

Telecon Summary: Discuss outcomes of clinical studies and regulatory implications.

FDA Participants:
Michael Kennedy, PhD, CBER/OBRR/DH/LPD
Nisha Jain, MD, Chief, CBER/OBRR/DH/CRB
Mitchell Frost, MD, CBER/OBRR/DH/CRB
Mary Lin, PhD, CBER/OBE/DB
Renee Rees, PhD, CBER/OBE/DB
Edward Thompson, CBER/OBRR/DBA/RPMB

Non-FDA Participants:
Instituto Bioclon
Walter Garcia, MD – Medical Director, Instituto Bioclon
Milton Ellis – President and CEO, Rare Disease Therapeutics, Inc.
Jude McNally, RPh, DABAT-VP, Medical Science Liaison, Rare Disease Therapeutics, Inc.
Jennifer Spinella, MT(ASCP), RAC- VP, Regulatory Affairs & Quality Assurance, Rare Disease Therapeutics, Inc, (US Agent for Instituto Bioclon)
(b) (4)   (Statistician consultant)

Telecon Body:
FDA initiated the teleconference with Instituto Bioclon to discuss the clinical data submitted by the applicant for the Crotalidae Immune Fab2 Equine product.   FDA informed Bioclon that the submitted data failed to demonstrate statistical significance for the pre-specified primary efficacy endpoint,, i.e. superiority over CroFab for the incidence of recurrent coagulopathy.

FDA understands that the product is intended for use to treat a rare disease and represents an unmet medical need because of its improved safety profile based on the manufacturing process.

FDA requested the submission of additional data to aid in the review of the application for evaluation of the products effectiveness. The following data was requested:

1. Historical data that describes the natural history (e.g., coagulopathy, bleeding, myolysis, etc.) of patients with North American Crotalidae envenomation and untreated with antivenin.

2. Pharmacovigilance data from the Mexican market.

3. Snake Bite Severity Scores calculated at multiple time points beyond baseline, at least through the end of maintenance, and at Days 5 and 8 if possible. Use descriptive statistics to tabulate and graph the data for all 3 Groups.

4. For all 3 Groups graph vital signs, PT, PTT and INR over time (Mean ±SD).

5. For all 3 Groups, graph over time each individual patient whose platelet count at baseline was < 100K and graph the composite for each Group (Mean ±SD). Please construct one graph with the individual patients (i.e., all patients on one graph not an individual graph for each patient) and another with the composites.

6. For all 3 Groups, graph over time each individual patient whose fibrinogen at baseline was < 100 mg/dL and graph the composite for each Group (Mean ±SD). Please construct one graph with the individual patients (i.e., all patients on one graph not an individual graph for each patient) and another with the composites.

Instituto Bioclon acknowledged the request and agreed to provide the requested data.

The FDA Statistician requested clarification on the analysis of the primary endpoint using the multiple imputation method the sponsor submitted on June 22, 2013. The sponsor confirmed that they used standard logistic regression in the analysis as opposed to exact logistic regression. The FDA statistician requested that the sponsor perform the analysis using exact logistic regression, since it is the primary analysis method pre-specified in the SAP. The sponsor stated that SAS MI procedure only supports standard logistic regression. The sponsor stated that they will research the topic and submit the correct analysis.

Instituto Bioclon acknowledged the request and will perform the calculation and wil submit the data.