DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
1401 Rockville Pike
Rockville, MD 20852-1448

Our STN: 125335/0
Rare Disease Therapeutics, Inc.
Attention: Ms. Jennifer Spinella
July 1, 2011
By email

Dear Ms. Spinella:

We are reviewing your resubmission to your biologics license application for Centruroides (Scorpion) Immune F(ab')2 Intravenous (Equine). We are providing the following comments:

We are reviewing your resubmission to your biologics license application for Centruroides (Scorpion) Immune F(ab')2 Intravenous (Equine). We are providing the following comments:

1. Your response to item 67.b. of the CR Letter does not explain the choice of 0.2 as a clinically meaningful difference. As stated in the CR item, while it may be acceptable to have a difference of 0.2 for treatment of a serious and life-threatening condition, if "the endpoint is vague and the venom toxicities exhibited by the subjects under study are not life-threatening, such as agitation in the absence of respiratory or other serious manifestations, there should be a much bigger difference in order to be certain of a meaningful therapeutic benefit." Please address your choice of clinically meaningful difference in light of the severity of envenomation in the subjects studied in your pivotal trial, AL-02/03.

2. CR Letter item 71 asks for addressing the serum antivenom assay which is an -(b)(4)- but not measuring neutralizing activity in serum, whereas your response explains the potency testing for Anascorp. Please support your serum antivenom assay by providing its correlation with neutralization activity.

3. In your response to CR Letter item 73, you describe the evolution of the designing of Studies AL-03/06, AL-02/04, AL-02/05, and AL-02/06. You have not addressed the CR item issue about lack of pre-specified hypotheses-testing in these "controlled" studies based on AL-03/06 historical data, which showed *success rate without antivenom treatment in the order of around 0.4*, as 58.8% of subjects in AL-03/06 still had clinical signs at the end of 4 hours, whereas protocols AL-02/04, AL-02/05, and AL-02/06 *assumed historical control success rate of 0.7 to 0.8*. Please address the CR item.

4. Table 5.4.3 of the Integrated Summary of Safety lists 48 serious adverse events (SAEs) in 41 subjects (41/1534, or 2.7%; with 5 adults [5/330, or 1.5%], and 36 pediatric patients [36/1204, or 3.0%]). However, section 5.1 of the report also states: "Thirty-four (2.2%; 34/1534) patients experienced a total of 39 serious adverse events. The incidence of patients experiencing SAEs in the adult and pediatric populations are 1.2%; 4/330 and 2.5%; 30/1204, respectively." Please resolve this discrepancy.

5. Although we shall be conveying to you more comprehensive comments to your draft package insert, the following are labeling and promotional issues arising from your responses to the CR Letter items:

- In your response to CR Letter item 62, you state that the WARNINGS AND PRECAUTIONS section in the draft label has been revised to mention 3 patients exhibited symptoms suggestive of an acute hypersensitivity reaction and eight patients exhibited symptoms suggestive of a Type III immune response; no patient manifested the full serum sickness syndrome. These may be underestimates because of the use of premedications and concomitant medications, as well as the suboptimal follow-up procedures for serum sickness. Please include such information to provide perspective to the prescriber.

- In your response to CR Letter item 63, you have provided language for the DRUG INTERACTIONS section of the package insert concerning adverse event rates with benzodiazepines and opiates or phenylpiperidines. The wording has been revised in your latest draft package insert submitted on 3/18/11, which states in bold: "**It is not necessary to administer concomitant sedation for the treatment of scorpion envenomation, and the use of sedatives may increase the risk of adverse events.**" As the patients who require concomitant sedation may be sicker than those who do not, it may be premature to conclude that use of sedation may increase the risk of adverse events. Moreover, the focus of the CR Letter item is on antihistamines and corticosteroids which may mask acute hypersensitivity reactions to the equine product. Please address their effects in labeling.

- In your response to CR Letter item 66.b., you propose to have the Indications and Usage section to be revised to: "*Anascorp is an equine-derived F(ab)2 antivenin indicated for the management of patients with clinically important signs, primarily driven by data on pathological agitation, of scorpion envenomation*". You also recognize the Agency's position concerning the nonverifiability of "respiratory compromise" in the subjects enrolled in your pivotal trial, and our request to have more specific language in the Indications and Usage section. Because of the fact that your pivotal study data on reversal of clinical signs are purely based on pathological agitation, labeling should be revised to that effect: "*Anascorp is an equine-derived F(ab)2 antivenin indicated for the management of pathological agitation in patients with scorpion envenomation.*"

- CR Letter item 66.c. asserts that the pivotal clinical trial did not enroll subjects with sufficient disease severity to support a claim for the product to be a treatment of a serious and life-threatening condition, and no benefit for mortality or major morbidity has been demonstrated. Efficacy, if demonstrated in this study, is limited to subjects not showing life-threatening manifestations of envenomation. Although there may be a potential for the product to be a treatment for a serious and life-threatening condition, please be reminded that because the pivotal study did not include subjects showing life-threatening manifestations of envenomation, ***promotional claims to the effect that efficacy has been established for the product to be intended for a serious and life-threatening condition would be inappropriate***. In fact, your response to CR Letter item 72 recognizes that the product may have a role in preventing "prolonged ICU admissions during which most of the severe manifestations of envenomation would have manifested" instead of ***treating*** a serious and life-threatening condition. As such, you are actually agreeing with the CR Letter item for "the ***potential*** role of antivenom in scorpion envenomation as being primarily in the shortening of the neuromuscular effects of envenomation or reduction in the use of concomitant medications, rather than providing benefit on mortality or irreversible morbidity."

- In addition, the Clinical Studies section contains data from chart review (AL-03/06) as "historical control". Labeling should be based on data from adequate and well-controlled trials, and the use of AL-03/06 data should be avoided. Similarly, data from uncontrolled studies AL-02/04, AL-02/05, AL-02/06, and AL-03/07 should be removed from Figure 1 of the draft label, because the studies are not blinded and subject to bias. As well, the Clinical Studies section contains a paragraph and a Table (Table 4) on serum levels of venom. Because of issues relating to the validity of the binding assay for serum venom levels (CR Letter item 64), e.g., interference by antibodies and correlation with activity, these venom level data may be misleading and should not be included in labeling.

The review of this submission is on-going and issues may be added, expanded upon, or modified as we continue to review this submission. Please submit your revised labels, in electronic format, as an amendment to this file no later than July 6, 2011.. If you anticipate you will not be able to respond by this date, please contact the Agency immediately so a new response date can be identified.

If we determine that your response to this information request constitutes a major amendment, we will notify you in writing.

The action due date for this file is August 3, 2011.

If you have any questions, please contact me at (301)827-6157.

Sincerely,

Debbie Cordaro
RPM
FDA/CBER/OBRR