

MIRS Exercise

Example:

Raxibacumab 2009
Advisory Committee
Briefing Package

Adapted from the 2015 RAPS Regulatory Convergence session presented by Frank Carillo of ECG, Inc. and Robin Conrad of Elusys Therapeutics, Inc.

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11 Benefit:Risk

Raxibacumab has a favorable benefit:risk profile in the treatment of inhalation anthrax. It fills an important gap in the available treatment options by delivering a potent and specific anti-toxin that acts directly on the primary driver of anthrax pathogenesis. A single 40 mg/kg dose of raxibacumab provides immediate and durable inhibition of anthrax toxin until natural anti-toxin immunity can develop.

Anthrax is a significant bioterrorism threat facing the United States. The attack involving the postal service in 2001 resulted in 11 symptomatic cases of inhalation anthrax. All of these patients suffered serious morbidity requiring prolonged hospitalization and 5 of them died. The US Government has simulated mass anthrax exposures in terror attacks, and the death tolls were of much greater magnitude than sustained in the 2001 attacks.

In response to this danger, the US Government has made the development of a direct anti-toxin a priority for civilian defense. Raxibacumab has met the governmental requirements for inclusion of the SNS and CDC has accepted 20,000 doses and contracted an additional 45,000. With this submission, raxibacumab is the first product developed since the terror attacks to be considered for approval under the Animal Rule. The proposed indication for raxibacumab is for the treatment of patients with anthrax infection. Raxibacumab should be used to treat infections that are proven or strongly suspected to be caused by *B. anthracis* bacteria. When used in combination with antibiotics, raxibacumab is not expected to interfere with antibiotic efficacy. Raxibacumab is recommended for use in combination with antibiotics, but it can be used as monotherapy for patients in whom antibiotics are contraindicated or in whom anthrax disease is due to antibiotic-resistant strains of *B. anthracis*.

The demonstration of efficacy of raxibacumab followed the requirements of the Animal Rule. The design, conduct, and results of the raxibacumab development program met or exceeded each of the 4 requirements of the Animal Rule. In addition, the studies met GLP and statistical requirements typically applied to human trials. Both the 20 mg/kg and 40 mg/kg doses achieved a statistically significant and clinically meaningful difference over placebo, meeting the prespecified primary endpoint of the trials. The statistical analysis plan included prespecified adjustments for multiple comparisons. All of post-hoc sensitivity analyses supported the conclusions of the primary analyses. The 40 mg/kg dose demonstrated statistically significant benefit in every sensitivity analysis. Both the magnitude and the robustness of the results for the 40 mg/kg raxibacumab dose were greater than those for the 20 mg/kg, supporting the selection of the 40 mg/kg raxibacumab dose.

The pivotal studies demonstrated that raxibacumab provides a significant survival benefit over placebo in animals with symptomatic systemic anthrax disease, achieving the primary endpoint. The secondary endpoint of the pivotal studies, demonstration of longer survival time, was also positive. The raxibacumab/antibiotic combination studies also achieved positive results for all of the primary and secondary efficacy endpoints. In addition, the combination studies demonstrated that concomitant treatment with raxibacumab does not block the effect of antibiotics. Additional studies with raxibacumab in pre-exposure

Example of Main Messages

11. Benefit:Risk

Raxibacumab has a favorable benefit:risk profile in the treatment of inhalation anthrax. It fills an important gap in the available treatment options by delivering a potent and specific anti-toxin that acts directly on the primary driver of anthrax pathogenesis.

A single 40 mg/kg dose of raxibacumab provides immediate and durable inhibition of anthrax toxin until natural anti-toxin immunity can develop.

Example of Messages & Issues

The demonstration of efficacy of raxibacumab followed the requirements of the Animal Rule. The design, conduct, and results of the raxibacumab development program met or exceeded each of the 4 requirements of the Animal Rule [**MESSAGE**].

In addition, the studies met GLP and statistical requirements typically applied to human trials. Both the 20 mg/kg and 40 mg/kg doses achieved a statistically significant and clinically meaningful difference over placebo [**ISSUE**], meeting the prespecified primary endpoint of the trials.

The statistical analysis plan included prespecified adjustments for multiple comparisons [**ISSUE**]. All of post-hoc sensitivity analyses supported the conclusions of the primary analyses. The 40 mg/kg dose demonstrated statistically significant benefit in every sensitivity analysis.

Example of an Issue and Response

The demonstration of the safety of raxibacumab includes human as well as animal data. The only treatment-emergent adverse event that occurred at a greater rate in healthy human volunteers was a mild to moderate transient rash that was successfully managed with oral Antihistamines [**ISSUE**].

In patients who received oral antihistamine prior to raxibacumab infusion, there was no increased incidence of rash compared with placebo treatment. Oral antihistamine prophylaxis is recommended for all patients receiving raxibacumab. Importantly, there was no evidence of immunogenicity associated with raxibacumab administration [**RESPONSE**] either as a single dose or with repeat administration.

Example of an Issue, Response, & Support

There was a potential risk identified only in raxibacumab [**ISSUE**] monotherapy-treated non-surviving animals. Compared with placebo animals, in rabbits and monkeys that succumbed to inhalation anthrax despite raxibacumab treatment, histological examination of tissues shows fewer bacteria and less tissue damage in visceral organs and a higher incidence of meningeal findings associated with anthrax infection.

This may be a reflection of the inability of raxibacumab to cross the blood brain barrier and neutralize the damaging effects of toxins produced by bacteria that reach the brain [**RESPONSE**].

No adverse neurological effects were observed in any surviving animal and there was no increase in the incidence of adverse effects observed in healthy subjects receiving raxibacumab [**SUPPORT**].