Raxibacumab (ABthrax) is a human IgG1 monoclonal antibody against Bacillus anthracis protective antigen. HGS is currently providing stockpiles of the agent to the US government for use in the prevention and treatment of inhalation anthrax. As of May 2009, the candidate was undergoing review by the US Food and Drug Administration. The availability of bioterrorism countermeasures has become more important since the September 2001 anthrax attacks, and development of raxibacumab is a significant advance in this area.

**Introduction**

Since their entry into clinical studies in the 1980s, monoclonal antibodies (mAbs) have primarily been designed to target cancer and diseases of the immune system. Relatively few mAb candidates have entered clinical study for the prevention or treatment of infectious diseases. However, motivation to change this situation occurred as a consequence of the September 2001 bioterrorism incident involving anthrax.

The causative agent of anthrax is a spore forming bacterium, Bacillus anthracis, and the disease manifests in three forms depending on the route of infection-cutaneous, gastrointestinal and inhalation anthrax. As the bacteria can exist in a dormant state as spores, cutaneous anthrax is the most common form of infection and develops after spores contact an open wound, cut or abrasion. Gastrointestinal anthrax results from ingestion of large numbers of vegetative bacilli in poorly cooked, infected meat. Inhalation anthrax is the most commonly fatal form because bacteria can multiply in the lungs and produce toxins before onset of symptoms, thereby making the disease more difficult to treat. In the 2001 anthrax incident, B. anthracis was mailed out via the US Postal Service in a powdered form and a powdered or aerosolized version would be the most deadly in a bioterrorism attack.

Inhalation anthrax manifests initially with fever and chills, fatigue, nausea and chest discomfort. Most patients show hemorrhagic thoracic lymphadenitis, pleural effusions and in some cases hemorrhagic meningitis. During infection, B. anthracis spores are deposited in the alveolar spaces of the lungs, and these spores then germinate over the course of 2 to 43 days. Clinical symptoms develop rapidly after germination. Actively dividing bacilli produce protective antigen (PA), lethal factor (LF) and edema factor (EF). PA facilitates binding of LF and EF to anthrax toxin receptor (ATR) or capillary morphogenesis protein 2 (CMG2) on mammalian cell surfaces, resulting in a protein-receptor complex that enables the lethal and edema factors to enter cells. The toxins inhibit normal immune system functioning, interfere with signal transduction pathways and ultimately cause cell death.

Current countermeasures for anthrax are antibiotics and vaccines. They are an integral part of medical care, but both have limitations. Antibiotics might control the bacterial infection, but they fail to clear released toxins from the bloodstream, and anti-biotic-resistant strains may not be effectively thwarted. Vaccines can be more effective in the long term, but they are slow-acting initially, and require booster doses to maintain immunity.

Raxibacumab is an anti-PA human recombinant, IgG1κ mAb. By binding PA, the mAb prevents LF and EF from entering cells, and thus prevents progression of the disease. The mAb was developed by Human Genome Sciences (HGS), and has been evaluated in safety and efficacy studies in animals, and safety studies in humans. Raxibacumab received fast track designation from the US Food and Drug Administration (FDA), which enables expedited development of the drug as a prophylactic and a potential countermeasure to natural and artificial infection with B. anthracis. Animal studies suggest that a single dose of the drug can protect against infection. A marketing application has been filed with FDA, although the US government is already purchasing supplies of the drug. Because the study of efficacy in humans was not ethical or feasible, FDA will apply ‘animal rule’ regulations to the review of the application.

**Genesis of the Animal Rule**

In September 2001, the United States was subjected to biological terrorism that affected the lives of civilians throughout the country. B. anthracis spores were sent through the US Postal Service to several locations. Twenty-two people developed anthrax infections as a result of the exposure; 11 cases were the inhalation form of the disease. A total of five people with pulmonary infections ultimately died. Since bioterrorist attacks cannot be predicted, easily detected, or defended against without appropriate countermeasures, the US government encouraged development of countermeasures by crafting the ‘animal rule’ regulations in 2002, and enacted the Project BioShield Act in 2004.

The animal rule regulations allow FDA to approve drugs that demonstrate efficacy only in animal models, provided the drug would have a reasonable health benefit in humans and the drug...
is deemed safe for human use. The animal rule can be applied in case of infections that usually have a low incidence such as anthrax. The Project Bioshield Act specifically encouraged and appropriated funding for development of “countermeasures against agents that may be used in terrorist attacks against the United States.” Project Bioshield also established the Strategic National Stockpile (SNS), which stores substantial amounts of drugs and medical supplies to protect the US population in case of a public health crisis, as part of the US Department of Health and Human Services.

Outbreaks of infectious diseases due to either natural or intentional causes, e.g., bioterrorist attacks, can be sufficiently acute causing local medical supplies to be exhausted. After the September 2001 anthrax attacks, the SNS contracted HGS to supply raxibacumab for treatment of inhalation anthrax. The company began delivery of the first 20,000 doses in April 2009. In July 2009, HGS was assigned another order for 45,000 doses to be delivered over a period of three years, starting at the end of 2009. The contract awards HGS $151 million at the completion of the deliveries.

### Origin and in vitro Evaluation

Raxibacumab was derived from a phage display library licensed by HGS from Cambridge Antibody Technology. Recombinant PA was used to pan the library and selected candidates were screened for PA-neutralizing activity as assessed by inhibition of ATR and CMG2 binding, inhibition of pore formation in CHO-K1 cells, and inhibition of lethal toxin-mediated killing of murine macrophage J774A.1 cells.

In the receptor-binding assay, the PA concentration was 300 ng/mL, ATR concentration was 150 ng/mL and raxibacumab was tested at concentrations in the range of 0.0156 ng/mL to 25 μg/mL. Antibody-mediated inhibition of PA binding to ATR was found to be dose-dependent; the IC50 was 503 pM. In the macrophage cell killing assay, 100 ng/mL PA was pre-incubated with antibody, and the mixture was added to 50 ng/mL LF to the cells. Raxibacumab inhibited lethal toxin-mediated cell death with an IC50 of 0.21 nM. In addition, binding kinetics of raxibacumab to PA were determined using BIAcore studies; the equilibrium binding constant (Kd) was 2.78 nM.

### Bioprocessing Parameters

Raxibacumab comprises a human IgG1 with a λ light chain, and one N-linked glycosylation site per heavy chain. The isoelectric point is approximately 9.0, and the antibody has a molecular weight of approximately 150 kilodalton. Raxibacumab produced for Phase 1 studies was expressed in the N50 murine myeloma cell line, secreted into the extracellular culture media, and harvested by filtration. The purification process included a series of three chromatography steps, virus filtration, a fourth chromatography step, and then ultrafiltration/diafiltration (UF/DF). The overall yields for the purification process for six runs were in the range of 66 to 76%, which was considered very consistent.

The bulk purity of the Phase 1 study agent, as assessed by size-exclusion chromatography, was consistent. A design of experiments approach to process characterization was used to assess various parameters. The load pH, NaCl concentration, bed height, flow rate and resin capacity were varied in the experiments: pH varied from 6.5 to 8.5, salt concentration varied from 50 to 150 mM, bed height varied from 13 to 28 cm, flow rate varied from 100 to 300 cm/hr, and resin capacity varied from 15 to 40 g/L. Load pH and conductivity were identified as critical parameters in the process; there was also evidence for interactions between the load pH, conductivity and resin capacity.

Concentrated antibody formulations needed for the subcutaneous (SC) injections could be prepared using an optimized UF/DF step. The process required initial concentration, diafiltration into the formulation buffer, and concentration to the final desired concentration. Prior to the UF/DF step, the antibody concentration was 6 mg/mL; final concentrations of up to 183 mg/mL were achieved. Product recovery was 100, 92 and 80% at final antibody concentrations of 106.5, 167 and 183 mg/mL, respectively, and the total processing time was 2 h for a 250 g/m² load.

### Preclinical Studies in Animals

Studies assessing the efficacy of raxibacumab in both pre-exposure and post-exposure settings have been conducted in a number of animal models. Study of pre-exposure prophylaxis was important because raxibacumab may need to be administered to individuals in high risk groups even in the absence of exposure to anthrax. Post-exposure studies were crucial in determining the therapeutic window of time in which the drug can be administered and still be effective. Current treatment options have a very narrow therapeutic window which makes anthrax hard to treat once time since exposure crosses a certain threshold. Studies of pre-exposure prophylaxis and post-exposure treatment were conducted in rats (2 post exposure, 1 pre exposure; Table 1), rabbits (3 post exposure, 1 pre exposure; Table 2) and cynomolgus monkeys (1 post exposure, 1 pre exposure; Table 3). In addition, four safety studies were conducted in humans (Table 4).

### Studies in Rats

Initial studies in rats focused on post-exposure treatment regimens. Raxibacumab was evaluated for its ability to increase survival of rats infused with lethal factor and PA. In one study, toxin was administered as an IV bolus; however the mean time to death was only 1.5 hours. Raxibacumab improved survival if administered prior to, or within 30 minutes of, toxin injection, but not when administered later.

A second study utilized a 24 hour infusion of toxin, which extended the time to first death to 9 hours. A total of 324 Sprague-Dawley rats were included in the study. To mimic anthrax exposure, animals were treated over 24 hours with infusions containing total doses of 150 μg/kg lethal factor and 300 μg/kg PA in phosphate-buffered saline; the mixture was administered at a rate of 0.5 mL per hour. Administration of a single concentration of raxibacumab at different time points, and administration of
Pre-exposure prophylaxis was also studied in rats. In a study of the route of administration, three groups of five Fisher 344 rats received SC, IM or IV administration of 1.5 mg/kg raxibacumab 24 h prior to injection of lethal toxin (8 μg lethal factor and 22.5 μg PA per rat). An additional three groups of five rats received SC, IM or IV administration of control IgG. All rats that received raxibacumab survived throughout the observation period (24 h). In contrast, all rats in the control groups died within 90 minutes.5

Studies in Rabbits

In a study of New Zealand white rabbits, six cohorts of 12 animals each were administered a single SC dose of placebo or raxibacumab at 1, 5, 10 or 20 mg/kg 48 hours prior to exposure, or an IV dose of raxibacumab at 40 mg/kg immediately after exposure. All animals were exposed to anthrax spores (Ames strain) on day 0 at an actual mean value of 202.5 times the median lethal dose (LD<sub>50</sub>; 1x value for rabbits defined as 105,000 for rabbits). The primary efficacy end point of the study was survival.
In the time course experiment, five groups of 12 New Zealand white rabbits were exposed to *B. anthracis* spores at 103x (actual mean value) the LD50, and then administered IV raxibacumab at 40 mg/kg at time 0, 12, 24 or 36 h post-exposure. Rabbits in the control cohort were administered placebo at time 0. After 14 days, all rabbits that received raxibacumab at the 0 and 12 h time points had survived. Of those in the 24 and 36 h cohorts, 50%, and 41.7%, respectively, survived. One rabbit (8.3%) in the placebo cohort survived. None of the rabbits that received raxibacumab and survived to day 14 developed bacteremia.14

The 10, 20 and 40 mg/kg doses of drug were significant in increasing survival at day 14 in a dose dependent manner (83–100% survival) compared to placebo; one rabbit of 36 in the three cohorts developed terminal bacteremia.13 Since raxibacumab had provided complete protection when administered as a prophylactic measure, the mAb was then studied for its post-exposure therapeutic potential.14 Two methods were investigated—a time course experiment after the animals received administration of a single dose, and a dose-response study.

**Table 2. Studies in rabbits**

| Study objective | Species | Dose, number of subjects | Results | Reference |
|-----------------|---------|--------------------------|---------|-----------|
| Pre-exposure prophylaxis and post-exposure treatment | Rabbit, New Zealand white | A single SC dose of placebo or raxibacumab at 1, 5, 10 or 20 mg/kg 48 h prior to exposure, or an IV dose of raxibacumab at 40 mg/kg immediately after exposure (6 cohorts of 12). Animals were exposed to anthrax spores (Ames strain) on day 0 at an actual mean value of 202.5 times the median lethal dose (LD50: 1x value for rabbits defined as 105,000 for rabbits). | The primary end point of the study was survival at day 14. Placebo-0% survival; all 12 animals developed bacteremia | 13 |
| | | | Dose mg/kg | Number of survivors (%) | p value |
| | | | 10, SC | 10 (83%) | <0.0001 |
| | | | 20, SC | 10 (83%) | <0.0001 |
| | | | 40, IV | 12 (100%) | <0.0001 |
| Post-exposure treatment | Rabbit, New Zealand white | Animals were exposed to *B. anthracis* spores at 103x (actual mean value) the LD50, and then administered IV raxibacumab at 40 mg/kg at time 0, 12, 24 or 36 h post-exposure (5 cohorts of 12). Placebo was administered at time 0. | No surviving animals receiving raxibacumab at day 14 developed bacteremia |
| | | | Treatment/Time after exposure (hrs) | Number of survivors (%) | p value |
| | | | Vehicle | 1 (8.3%) | - |
| | | | Drug-0 h | 12 (100%) | <0.0001 |
| | | | Drug-12 h | 12 (100%) | <0.0001 |
| | | | Drug-24 h | 6 (50%) | 0.0687 |
| | | | Drug-36 h | 5 (41.7%) | 0.1550 |
| Post-exposure treatment | Rabbit, New Zealand white | Five cohorts of 12 animals (0, 5, 10, 20 and 40 mg/kg) were exposed to *B. anthracis* spores at 128x (actual mean value) the LD50, and then administered IV raxibacumab 24 h later. A 6th group was administered IV 20 mg/kg raxibacumab 36 h after exposure to the spores. | The primary efficacy end point of the study was survival at day 14. No placebo animals or those treated with 20 mg/kg drug 36 h after exposure, survived until day 14. | 14 |
| | | | Treatment mg/kg | % of survivors | p value |
| | | | Vehicle | 0 (0%) | - |
| | | | 5, 24 h | 3 (25%) | 0.2174 |
| | | | 10, 24 h | 4 (33.3%) | 0.0932 |
| | | | 20, 24 h | 5 (41.7%) | 0.0373 |
| | | | 40, 24 h | 4 (33.3%) | 0.0932 |
| | | | 20, 36 h | 0 (0%) | 1.0 |
| Post-exposure treatment | Rabbit, New Zealand white | Fifty-four rabbits were divided into three groups (Placebo, 17; 40 mg/kg raxi, 18, and 20 mg/kg raxibacumab, 18) and exposed to anthrax spores on day 0. Animals were monitored for onset of symptoms including fever. On increase in body temperature by 2°F or presence of protective antigen in the blood stream, a single IV dose of raxibacumab (20 or 40 mg/kg) or placebo was administered. | No placebo animals or those treated with 20 mg/kg drug 36 h after exposure, survived until day 14. | 5 |
| | | | Treatment | % of survivors | p value |
| | | | Placebo | 0 | - |
| | | | 20 mg/kg | 28 | 0.02 |
| | | | 40 mg/kg | 44 | 0.003 |
then performed. Fifty-four rabbits were divided into three groups to treat exposure to spores at a targeted value of 200x the LD50 was determined. Results from the studies demonstrated that the survival rate at 28 days, and bacterial levels in the blood at different time points were determined. The primary efficacy end point of the studies was survival at day 28. A total of 22 macaques that received drug survived until day 28. All animals that received placebo died prior to day 7. None of the drug-treated animals developed bacteremia, as assessed at days 7, 14, 21 and 28. The primary end point of the studies was survival at day 28. Median survival for placebo animals was 3.3 days and was greater than 28 days for all animals that received raxibacumab at either dose. To assess the ability of the immune response to protect against re-exposure, 21 of the 22 surviving macaques were then subjected to a second challenge with a lethal dose of B. anthracis spores approximately 11 months after the initial challenge. Six control animals were also exposed to the anthrax spores. All 21 of the animals originally treated with raxibacumab survived the re-challenge, while all the control animals died. Post-exposure efficacy was also studied in cynomolgus macaques. This study involved 40 animals with no prior exposure that were assigned to 2 groups of 14 monkeys each, with one control group of 12 macaques. The animals were exposed to a target dose of anthrax spores at 200x the LD50. Single bolus IV doses of raxibacumab (20 or 40 mg/kg) or placebo were administered when PA was detected in the serum of the animals. A total of 22 macaques that received drug survived until day 28. All animals that received placebo died prior to day 7. None of the drug-treated animals developed bacteremia, as assessed at days 7, 14, 21 and 28. The primary end point of the studies was survival at day 28. Median survival for placebo animals was 3.3 days and was greater than 28 days for all animals that received raxibacumab at either dose. To assess the ability of the immune response to protect against re-exposure, 21 of the 22 surviving macaques were then subjected to a second challenge with a lethal dose of B. anthracis spores approximately 11 months after the initial challenge. Six control animals were also exposed to the anthrax spores. All 21 of the animals originally treated with raxibacumab survived the re-challenge, while all the control animals died.

Post-exposure efficacy was also studied in cynomolgus macaques. This study involved 40 animals with no prior exposure that were assigned to 2 groups of 14 monkeys each, with one control group of 12 macaques. The animals were exposed to a target dose of anthrax spores at 200x the LD50. Single bolus IV doses of raxibacumab (20 or 40 mg/kg) or placebo were administered when PA was detected in the serum of the animals. The primary end point of the studies was survival at day 28. Median survival for placebo animals was 3.3 days and all animals that received raxibacumab at either dose survived more than 28 days.

The dose-response study was performed in 5 cohorts of 12 New Zealand white rabbits that were exposed to B. anthracis spores at 128x (actual mean value) the LD50, and then administered IV raxibacumab 24 h later. The mAb was dosed at 0, 5, 10, 20 and 40 mg/kg. A sixth cohort was administered IV 20 mg/kg raxibacumab 36 h after exposure to the spores. The primary efficacy end point of the study was survival at day 14. Of the rabbits treated with 5, 10, 20 or 40 mg/kg raxibacumab 24 h after exposure to B. anthracis, 25%, 33.3%, 41.7% or 33.3% survived. None of the animals treated with placebo, or those treated with 20 mg/kg raxibacumab 36 h after exposure, survived until day 14.

An additional study that evaluated the ability of raxibacumab to treat exposure to spores at a targeted value of 200x the LD50 was then performed. Fifty-four rabbits were divided into three groups and exposed to anthrax spores on day 0. Animals were monitored for onset of symptoms of anthrax that correlated with levels of anthrax PA in the blood, including fever. On detection of 2°F elevation in body temperature or detection of PA in the blood stream, a single IV dose of raxibacumab (20 or 40 mg/kg) or placebo was administered when PA was detected in the serum of the animals. A total of 22 macaques that received drug survived until day 28. All animals that received placebo died prior to day 7. None of the drug-treated animals developed bacteremia, as assessed at days 7, 14, 21 and 28. The immune response of the surviving animals was assessed six months after raxibacumab administration. As detected by a cAMP-induction bioassay of serum, 16 of the surviving 22 macaques had generated a significant PA-neutralizing response.

Studies in Cynomolgus Macaques

In a study of macaques, four groups of ten animals each received either a single SC dose of placebo or raxibacumab at 10, 20 or 40 mg/kg 48 hours prior to exposure. All animals were exposed to B. anthracis spores (Ames strain) on day 0 at 185x (actual mean value) the LD50 (1x defined as 61,800 spores). The study evaluated survival at 28 days, and bacterial levels in the blood at different time points. A total of 22 macaques that received raxibacumab survived until day 28 (60%, 70% and 90% in the 10, 20 and 40 mg/kg dosage groups, respectively), while all those that received placebo died prior to day 7. None of the raxibacumab-treated animals developed bacteremia, as assessed at days 7, 14, 21 and 28. The immune response of the surviving animals was assessed six months after raxibacumab administration. As detected by a cAMP-induction bioassay of serum, 16 of the surviving 22 macaques had generated a significant PA-neutralizing response.

To assess the ability of the immune response to protect against re-exposure, 21 of the 22 surviving macaques were then subjected to a second challenge with a lethal dose of B. anthracis spores approximately 11 months after the initial challenge. Six control animals were also exposed to the anthrax spores. All 21 of the animals originally treated with raxibacumab survived the re-challenge, while all the control animals died.

Studies in Cynomolgus Macaques

| Study objective | Species | Dose, number of subjects | Results | Reference |
|----------------|---------|--------------------------|---------|-----------|
| Pre-exposure prophylaxis | Cynomolgus macaque | Four groups of ten animals each received either a single SC dose of placebo or raxibacumab at 10, 20 or 40 mg/kg 48 hours prior to exposure. Survival at day 28 was evaluated, and bacterial levels in the blood at different time points were determined. | A total of 22 macaques that received drug survived until day 28. All animals that received placebo died prior to day 7. None of the drug-treated animals developed bacteremia, as assessed at days 7, 14, 21 and 28. | 13 |
| Treatment (mg/kg) | % of survivors | | |
| Placebo | - |
| 10 | 60% |
| 20 | 70% |
| 40 | 90% |
| Post-exposure treatment | Cynomolgus macaque | 40 animals with no prior exposure were assigned to two groups of 14 monkeys each (20 and 40 mg/kg raxibacumab) and a control group of 12 animals. Animals were exposed to a target dose of anthrax spores at 200x the LD50. A single bolus IV dose of raxibacumab (20 or 40 mg/kg) or placebo was administered when PA was detected in the serum of the animals. | The primary end point of the studies was survival at day 28. | 5 |
| Treatment | % of survivors | p value | |
| Placebo | 0 | - |
| 20 mg/kg | 50% | 0.003 |
| 40 mg/kg | 64% | <0.001 |

Table 3. Studies in cynomolgus macaques
HGS received FDA clearance to initiate human trials with raxibacumab in 2003, and began enrolling healthy individuals into this Phase 1 placebo-controlled, dose-escalation clinical study to assess the safety, tolerability and pharmacokinetics (PK) of the mAb. PK parameters were linear within the route and site administrations; however, a number of parameters varied significantly between the 2 IM route groups. Bioavailability was higher in the subjects who received doses to the vastus lateralis (71–85%) compared to those who received doses to the gluteus maximus (50–54%).

A total of four studies to assess safety, tolerability and pharmacokinetic parameters in healthy humans were completed. Some of the studies were designed to evaluate the utility of raxibacumab under realistic conditions. In the case of potential exposure to anthrax, raxibacumab use by military and healthcare personnel would be more convenient as intramuscular (IM) administration rather than IV, and the product would likely be co-administered with an antibiotic. Two of the Phase 1 studies thus included subjects who received IM injections to the gluteus maximus or vastus lateralis, and subjects who received ciprofloxacin in addition to raxibacumab. The study designations were PAM-NH-01, NCT00639678 (also referred to as HGS1021-C1063), HGS1021-C1064 and HGS1021-C1069.
The safety and PK parameters of IV-administered, 40 mg/kg raxibacumab given in combination with ciprofloxacin were evaluated in this Phase 1 study. A total of 88 subjects were included in three treatment groups that received raxibacumab and ciprofloxacin, raxibacumab only or ciprofloxacin only. Raxibacumab and ciprofloxacin were administered as follows: 500 mg doses of ciprofloxacin were given by mouth every 12 hours for 6 days (total of 13 doses). On day 5, a single IV, 40 mg/mL dose of raxibacumab was administered. In the raxibacumab only control arm of the study, a single IV, 40 mg/mL dose of agent was administered at day 0. The ciprofloxacin only control arm comprised two subjects who received two IV-administered 400 mg doses at 12 h intervals on day 0, then 500 mg doses of ciprofloxacin by mouth every 12 hours for six days (total of 13 oral doses). Serum concentrations of either ciprofloxacin or raxibacumab were not altered by co-administration of the agents, indicating that co-administration does not adversely affect the pharmacokinetics of either drug.

**NCT00639678 (HGS1021-C1063)**

This randomized, placebo-controlled study assessed the safety and tolerability of IV-administered, 40 mg/kg doses of raxibacumab in healthy subjects. A total of 320 participants were assigned to receive either one or two doses of raxibacumab administered as an intravenous infusion for a period of two hours, or placebo. Subjects in the two dose group received a dose on day 0 and day 14 of the study. The primary outcome measure was a safety assessment, including immunogenicity. The secondary outcome measure was PK analysis. The majority of subjects (68%, 217/320) were assigned to the raxibacumab single dose cohort; an additional 23 subjects received two doses. A total of 23 subjects were assigned to receive two doses of the study agent.

Study results were combined with those of PAM-NH-01 and HGS1021-C1064 for publication. In these studies, a total of 333 subjects received one or two doses of IV-administered, 40 mg/mL raxibacumab. The half-life of the mAb was in the range of 20–22 days, and serum levels were maintained for 28 days at a concentration equal to or greater than the highest concentration of PA in the serum of monkeys exposed to lethal doses of *B. anthracis*. Adverse events were transient and mild to moderate in severity, and no significant difference was noted in adverse events observed in experimental and control groups. The most common adverse event was headache in subjects who received either raxibacumab or placebo (9.9% or 13.3%, respectively).

**HGS1021-C1069**

This study was designed to further assess safety and immunogenicity of a ‘booster’ dose of IV-administered, 40 mg/kg raxibacumab in 20 healthy subjects who had already received one similar dose in study HGS1021-C1064. The interval between the first and second dose was four months or greater. Results from this study have not been published as of September 2009.

**Future Prospects**

The intentional and deliberate discharge of anthrax spores in 2001 prompted the development of safety measures and preparedness in case of a future attack. As a result, pre-exposure prophylactic agents or post-exposure treatments for inhalation anthrax, including raxibacumab, have been studied for efficacy in animals and safety in humans. In addition to raxibacumab, Anthim (Elusys Therapeutics), a humanized, affinity-enhanced anti-PA mAb, and Valortim (PharmAthene/Medarex), a human anti-PA mAb, are being tested for prophylaxis and treatment of anthrax.

Raxibacumab has demonstrated efficacy in a post-exposure setting even after toxins were released into the bloodstream. However, 3 of 4 safety studies were conducted using an IV dosing, whereas a bioterrorism countermeasure would be more useful with an IM or SC route of administration. There is thus opportunity for development of an improved version, i.e., a more potent antibody that would be equally effective at a lower dose, and so could be formulated for IM or SC administration. Nevertheless, the availability of raxibacumab in the Strategic National Stockpile, and potentially on the market, represents a significant advance in safeguarding citizens against anthrax.
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