



PROTEXIA[®] – RECOMBINANT HUMAN BUTYRYLCHOLINESTERASE FOR THE PREVENTION AND TREATMENT OF NERVE AGENT TOXICITY

Background

Protexia[®] is a recombinant version of human butyrylcholinesterase (BChE), a naturally occurring protein found in minute quantities in blood (2 mg/liter). BChE functions as a natural bioscavenger, like a sponge, to absorb and degrade organophosphate poisons (e.g. nerve agents) before they cause neurological damage. Protexia[®] is being developed as a pre- and post-exposure therapy for casualties on the battlefield or civilian victims of nerve agent attacks. Nerve agents belong to a class of compounds known as organophosphate (OP) agents. OP nerve agents, such as sarin gas, soman, tabun or VX, enter the blood stream via inhalation or absorption through the skin. The nerve agents travel in the circulatory system to the brain and muscles causing the nerves to become over-stimulated which lead to massive convulsions and death in severe cases.

Pyridostigmine bromide (PB) is the only FDA approved product for use as a "pre-treatment adjunct" only for poisoning by the nerve agent, soman. It confers no protection on its own but enhances the protection conferred by post-exposure treatment. The current standard of care for post-exposure treatment involves repeated doses of a cocktail of drugs including atropine, oxime reactivators (2PAM) and anti-convulsants. Available pre-and post-treatment options are inadequate and there is a clear need for more efficacious countermeasures.

The Nerve Agent Threat

The potency of OP agents was recognized during World War II, when they were developed as nerve agents for use in chemical weapons. In recent history, terrorists have deployed nerve agents as weapons of mass destruction. The sarin nerve gas attack in the Tokyo subway system in 1995 exposed the vulnerability of North American and European cities to chemical weapons. Following 9/11, the U.S. government embarked upon an intensive anti-terrorism campaign and has allocated unprecedented financial resources through Project BioShield to develop new technologies and products to address these threats.

Development Status

A Phase I human safety trial of Protexia[®] was completed in 2009. The Phase I clinical study was a randomized, placebo-controlled, third-party double-blind, dose-escalating study conducted to assess the safety and tolerability of Protexia[®] administered intramuscularly at one or two time points in healthy human volunteers.

Under the study protocol, either Protexia[®] or a saline placebo was administered in escalating doses to six groups of volunteers. A total of 33 subjects participated in the

study; 22 of these subjects were treated with Protexia[®] and 11 were treated with saline placebo. Five of the six dose groups (15 volunteers) received a single intramuscular (IM) dose of Protexia[®] ranging from 50 to 750 mg. Subjects in the 250mg dose cohort (7 volunteers) received a second dose of Protexia[®] 72 days following the first dose.

Government Funding

In September 2006 PharmAthene was awarded a multi-year contract valued at up to \$219 million from the Department of Defense (DoD) U.S. Army Space and Missile Command, for advanced development of Protexia[®]. Additional contract modifications implemented since 2006 have increased the total potential value of the contract up to \$223.5 million.

Under the contract, PharmAthene is responsible for the conduct and oversight of all product development activities for Protexia[®]. The initial stage of development, for which approximately \$41 million was initially allocated, included manufacturing process development, preclinical safety and toxicity testing, submission of an Investigational New Drug (IND) Application with the United States Food and Drug Administration (FDA), and initiation and completion of a Phase I clinical trial, which was completed in 2009.

Following the successful completion of the Phase I clinical trial, the Department of Defense has an option to fund additional development activities leading to FDA licensure of Protexia[®]. PharmAthene anticipates that the DoD will make a decision regarding this option sometime in the first half of 2010. The contract also provides the Department of Defense with the option to procure an initial 90,000 doses of Protexia[®].

Protexia[®] Mechanism of Action

The mechanism of action of Protexia[®] is reversal of the acute toxicity associated with OP agents used in chemical warfare (cholinergic crisis). Protexia[®] rescue therapy removes nerve agents directly from the bloodstream by breaking them down into inactive components, rather than just treating the neurotoxic symptoms, as is the case with existing therapies.

In-vitro and *in-vivo* studies demonstrate that Protexia[®] serves as a safe and potent scavenger for nerve agents. Of the cholinesterases evaluated so far, human serum BChE (purified from plasma) has advanced the furthest in terms of preclinical development. However, human serum BChE is not a viable commercial option because it is only expressed in minute quantities in human plasma and production of large quantities needed for civilian and military stockpiles is not possible.

Protexia's[®] capability as a medical countermeasure has been demonstrated *in-vivo* to protect animals from multiple lethal doses of a broad spectrum of nerve agent chemical weapons, including sarin, soman, tabun and VX. Protexia[®] has several likely advantages, including providing protection both pre- and post-exposure, detoxification of OP nerve agents with full spectrum protection and a very acceptable safety profile.

Protexia[®] is being developed for two indications—pre-exposure prophylaxis and as a post-exposure therapy.

