



RECOMBINANT HUMAN BUTYRYLCHOLINESTERASE (rBChE) FOR THE PREVENTION AND TREATMENT OF NERVE AGENT TOXICITY

Background

Butyrylcholinesterase (BChE) is a naturally occurring protein found in minute quantities in human 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.

PharmAthene has developed a recombinant form of human butyrylcholinesterase which 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.

rBChE Mechanism of Action

The mechanism of action of rBChE is reversal of the acute toxicity associated with OP agents used in chemical warfare (cholinergic crisis). 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.

Multiple efficacy studies using a broad spectrum of live nerve agents have demonstrated that rBChE is a potent bioscavenger of nerve agents and can act as both a prophylactic as well as a post-exposure therapeutic.

The Market

Both the U.S. Department of Defense (DoD) and the civilian Health and Human services (HHS) have requirements for a broad spectrum pre and post exposure prophylaxis for nerve agent exposure. The current DoD requirement is for full force protection so the stockpile would need to be sufficient to protect all of the branches of the military as well as civilian first-responders.

Development Status

A Phase I human safety trial using a transgenic-derived rBChE product candidate called 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.

A second generation Advanced Expression System (AES) rBChE using a human cell line is now being actively developed with support and funding from the U.S. DoD. This program will allow for the production of a significant number of doses of human-like rBChE at a fraction of the cost of a human plasma derived product. It is believed that this program will move into pre-clinical and clinical development rapidly as a result of the experience gained with the Protexia program.