

A Supportive Care Product for Parkinson's Disease Patients

NH004 – Treatment for Sialorrhea

Summary

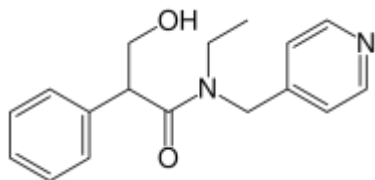
NH004 is a novel treatment to control the symptoms of sialorrhea (excessive drooling) in patients suffering from Parkinson's disease and other motor disorders. NH004's active ingredient is the anticholinergic drug tropicamide, delivered in a thin film designed to adhere and slowly dissolve within the oral cavity to allow the drug to reach the underlying salivary gland, thereby reducing saliva secretions. The advantages of NH004 include local bioavailability with low systemic exposure, rapid onset of action and, importantly, convenience of use for patients. The active agent has a long history of safe topical ophthalmologic use in humans.

A double-blind phase IIa clinical study testing NH004 in Parkinson's disease (PD) patients has been completed, demonstrating a difference in reducing sialorrhea between the NH004 treated and placebo groups (Lloret SP, et al, "A double-blind, placebo-controlled, randomized, crossover pilot study of the safety and efficacy of multiple doses of intra-oral tropicamide films for the short-term relief of sialorrhea", J Neurol Sci 2011), funded by the Michael J Fox Foundation.

According to IMS, 2009 sales of PD therapies in the U.S., European Union and Japan totaled approximately \$3.6 billion. Currently, there are no approved therapies to treat sialorrhea for these patients.

Mechanism of Action

The active pharmaceutical ingredient in NH004 is tropicamide, a synthetic tertiary amine anticholinergic agent acting as a non-selective blockage to muscarinic receptors. Tropicamide is currently FDA approved as an ophthalmic solution for diagnostic procedures and surgeries. In sialorrhea, tropicamide acts by blocking the acetylcholine receptors of the salivary glands. A short-acting anticholinergic agent, tropicamide (plasma half-life of 30 min) has the potential to reduce saliva secretion without the side effects associated with long-acting cholinergic blockers.



Active Ingredient: Tropicamide

N-ethyl-alpha-(hydroxymethyl)-N-(4-pyridinylmethyl)-benzeneacetamide

CAS number: 1508-75-4

NH004 Delivery System

NH004 contains tropicamide formulated in a novel and convenient drug delivery means known as thin films or “thin strips,” modeled on Listerine PocketPaks® breath strips, with two significant modifications: the film used in NH004 is formulated with a **muco-adhesive property** to adhere to the oral mucosa and allow the drug to be absorbed locally near the submandibular salivary gland. After placement in the mouth, the film **dissolves slowly** over a 60-90 minute period.



Listerine®

NH004

An attractive feature of NH004 films is the ability to readily modify the amount of the drug and excipients (such as flavors) or change the dissolution rate, and thereby differentiate a spectrum of marketable products.

Market Segments and Size

Sialorrhea is one of the major non-motor complaints in patients suffering from various neurological impairments, including Parkinson’s disease, cerebral palsy, ALS, Huntington’s, stroke and traumatic brain injury. Sialorrhea is often described by these patients as one of the most significant disabling social problems of their disease and not discussed due to the embarrassing nature of the condition. Depending on its severity, drooling can result in medical disability, impaired speech or serious eating difficulties.

Sialorrhea may affect up to a million patients with diverse neurological diseases. It affects a large proportion of Parkinson’s disease (PD) patients, ranging up to 78% in advanced stages, with many PD patients considering drooling as their worst non-motor symptom. PD prevalence in the US is estimated at 1.2 million. Sialorrhea also affects up to 37% of patients with cerebral palsy, the US prevalence of which is estimated at 500,000. Other large target populations include millions of survivors of stroke and severe traumatic brain injury.

Existing approaches to treating sialorrhea are not satisfactory. These include surgical procedures, prosthetic devices, botulinum toxin injections, systemic anticholinergic drugs, and speech and behavioral therapy. No single therapy satisfactorily resolves sialorrhea in all patients. There are also several ‘off label’ drug approaches to treat sialorrhea, including atropine, glycopyrrolate and ipratropium bromide spray. Each of these treatments has several shortcomings impeding their use and they have not gained any general acceptance.

NeuroHealing is aware of three current drug approaches for the treatment of sialorrhea: Sciele (now Shionogi) received approval in 2010 for glycopyrrolate oral solution in pediatric doses to treat chronic severe drooling in children; Solstice Neurosciences (now USWorld Meds) is sponsoring a trial of intra-glandular injections of botulinum toxin type B (Myobloc™) for the treatment of sialorrhea in adult PD patients; and Summit (now Orient Pharma) is testing a combination of two off patent drugs ($\alpha 2$ adrenoreceptor agonist and anti-muscarinic agent) to treat sialorrhea, with a focus on developing a buccal formulation of these agents.

NeuroHealing estimates the potential market size at \$400 million for PD patients and that the initial marketing would be to neurologists and movement disorders specialists.

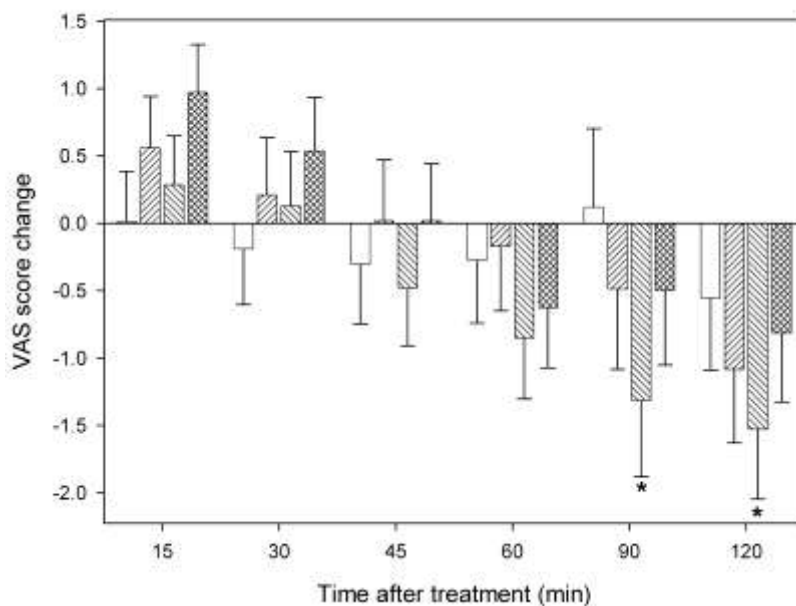
Intellectual Property

NeuroHealing owns multiple patent applications for the NH004 film composition and the use of intra-orally delivered tropicamide and/or anticholinergic agents. The first issued patent (2006206252AU) in this family “Methods and Compositions for Decreasing Saliva Production” includes claims for compositions for the treatment of sialorrhea, as well as to provide a dry oral field, such as during dental procedures, in otherwise healthy individuals. In addition, the company has proprietary know-how related to the manufacture and delivery of muco-adhesive slow-dissolving thin strips containing anticholinergic agents.

Development Status

NeuroHealing’s clinical studies have demonstrated encouraging results in reducing sialorrhea. In Parkinson’s patients complaining of sialorrhea, a clinically effective reduction of saliva was observed with no side effects or complications.

NeuroHealing has conducted a phase IIa, dose response, double-blind, placebo-controlled crossover study testing NH004 in PD patients (www.clinicaltrials.gov/show/NCT00761137). PD patients complaining of sialorrhea were randomized to receive treatment with three doses of NH004 and placebo. Results of this study showed that NH004 produced a reduction in drooling, as determined by two outcomes measurements. No adverse events were detected in any of the treatment sequences. Results were presented December 2010 at the International Congress on Mental Dysfunctions & Other Non-Motor Features in Parkinson’s Disease (Barcelona, Spain).



VAS score change after using placebo, 0.3, 1 and 3 mg tropicamide NH004 thin films. Means \pm standard errors of the mean are shown. The primary efficacy measure is the difference from 120 min to baseline. Time effect: $p < 0.001$. * 95% confidence interval of VAS difference excludes 0.

Based on the findings of this single-administration dose-finding study, another Parkinson’s study is about to begin to demonstrate that NH004 films provide better relief from sialorrhea than placebo when taken ‘as needed’ over a period of one week.