NH004 – Treatment for Sialorrhea

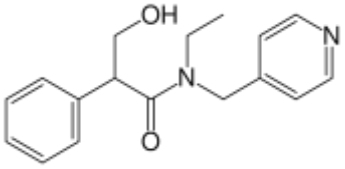
Summary

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 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," 2011), funded by the Michael J Fox Foundation.

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 30-60 minute period.

Listerine® NH004

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Patients would ideally like a safe therapy with the ability to control their problem of sialorrhea and get relief (1) quickly and (2) on a convenient "as needed" basis. Another 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 often described as a disabling, awkward and embarrassing condition in many patients. Depending on its degree, drooling can result in social and medical disability, impaired speech, or serious feeding difficulties. Sialorrhea is usually due to swallowing difficulties rather than excessive production of saliva. Depending on its severity, drooling can result in medical disability, impaired speech or serious eating difficulties. Unable to manage oral secretions, affected persons are at an increased risk of aspiration pneumonia, skin maceration, and infection.

Medications are increasingly being developed and approved to treat symptoms (LID-PD, tremors, walking, psychosis, etc) in Parkinson's and other patients with movement disorders. 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 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.

A marketing study conducted by the Harvard Business School at NeuroHealing's request estimated the U.S. PD market opportunity at $300M in annual revenues and concluded: "PD patients perceive drooling as a major social hurdle. Their families and caregivers are also indirectly affected by it and therefore play an influencing role. Patients are excited about the [NH004] product profile particularly because of its speed of action, ability to use on an 'as needed' basis and the lack of systemic side effects."

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.

Since sialorrhea varies considerably from day to day and during the day, especially in patients with muscle weakness and bending forward of the head, control is a constantly changing need.

NeuroHealing is aware of three current drug approaches for the treatment of sialorrhea: Shionogi received approval for CUVPOSA® glycopyrrolate oral solution in pediatric doses to treat chronic severe drooling in children; Solstice Neurosciences (acquired by 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 (with Orient Pharma) is testing a combination of two off patent drugs (α2 adrenoreceptor agonist and anti-muscarinic agent) to treat sialorrhea.

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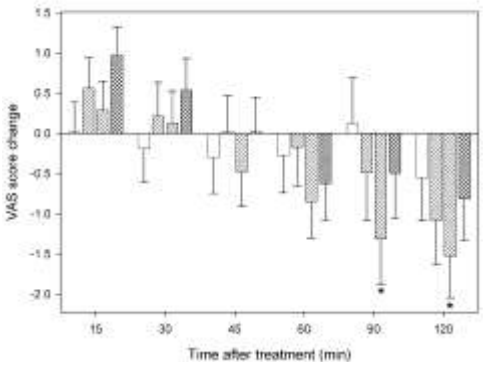
Intellectual Property

NeuroHealing owns patent applications for the NH004 film composition and the use of intra-orally delivered tropicamide and/or anticholinergic agents. Two patents "Methods and Compositions for Decreasing Saliva Production" have issued in the United States: US 9,198,897 (with a PTA to 2032) and US 9,433,616 (expiry 2026). Other patents have issued in Canada (CA2593492), Australia (AU2006206252), and pending in Europe. They include claims for compositions for the treatment of sialorrhea, as well as to provide a dry oral field 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 conducted a phase IIa, dose response, double-blind, placebo-controlled crossover study testing NH004 in PD patients (clinicaltrials.gov identifier 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 have been published ("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 symptoms in Parkinson's disease patients." Lloret SP. Nano G. Carrosella A. Gamzu E. Merello M., Journal of the Neurological Sciences. 310:248-50, 2011).



VAS score change after using placebo, 0.3, 1 and 3 mg tropicamide NH004 thin films. Means ± 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 (clinicaltrials.gov identifier NCT01844648), supported by a second grant from the MJF Foundation, is scheduled to be completed by end of 2015. This study is designed to demonstrate that NH004 provides better short term relief than placebo from sialorrhea symptoms in Parkinson's disease patients when the films are used twice a day, in a home setting, over a period of one week.

A comprehensive review article is available on NH004 entitled "Design and Development of a Novel Supportive Care Product for the Treatment of Sialorrhea in Parkinson's Disease" (Current Topics in Medicinal Chemistry, 15:10, 939-954, 2015).

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