NH004 – Treatment for Sialorrhea

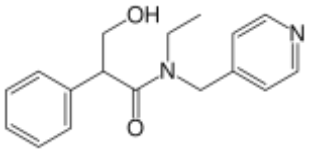
Summary

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 demonstrated 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 for Parkinson's Research (USA).

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 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.

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

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films is the ability to readily modify the amount of the drug and excipients (such as flavors) or change the dissolution rate.

Sialorrhea and Treatments

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. Sialorrhea also affects up to 37% of patients with cerebral palsy. 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 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.

Glycopyrrolate has been used off-label for many years for treatment of excessive drooling in PD. It was approved in 2010 by the U.S. FDA as Cuvposa for use specifically in children 3-16 years old with severe chronic drooling due to a neurologic condition, such as cerebral palsy. The FDA has also approved intra-glandular injections of incobotulinumtoxinA for the treatment of chronic sialorrhea in patients with neurological disorders, such as PD, ALS, CP or Alzheimer's.

Development Status

A phase IIa, dose response, double-blind, placebo-controlled crossover study testing NH004 in PD patients (clinicaltrials.gov identifier NCT00761137) has been conducted. PD patients complaining of sialorrhea were randomized to receive a single administration 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

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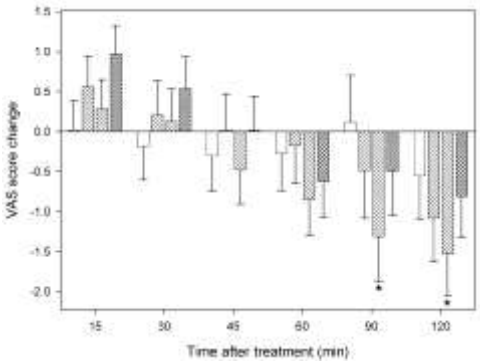
sialorrhea symptoms in Parkinson's disease patients." Lloret SP. Nano G. Carrosella A. Gamzu E. Merello M., Journal of the Neurological Sciences. 310:248-50, 2011).



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.

Another study, supported by a second grant from the MJ Fox Foundation and out-sourced to a CRO in Europe, was conducted to demonstrate the safety and efficacy of a 1 mg dose of NH004 to provide short term relief from sialorrhea symptoms in PD patients when the films are used twice a day, in a home setting, over a period of one week. The safety of the NH004 films was acceptable, with relatively few, and no serious, side effects. The use of intra-orally dissolving thin films appears to be an acceptable drug delivery means for Parkinson's patients. However, while the hypothesis is still valid, the results did not confirm that NH004 thin films reduce sialorrhea over placebo films. Part of the reason may have been the unanticipated considerable variability in the outcome measures at baseline or the chosen test dose, both directions for further investigation.

Further Details

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).

NeuroHealing Pharmaceuticals

NeuroHealing Pharmaceuticals, Inc. is a private, clinical stage company in Boston (USA) developing innovative treatments for specialty indications based on repositioning neurologically active compounds. Programs include NH001 (phase II), a dopaminergic agent to help post traumatic brain injury patients to emerge from a coma, vegetative or minimally consciousness state, and NH004 (phase II), an anticholinergic agent in a convenient intra-orally muco-adhesive dissolving film to help treat motor neuron disease patients who suffer from sialorrhea (drooling).

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