AM-125 for Meniere's Disease & Vestibular Vertigo

Betahistine spray for intranasal use

Auris Medical
Cochlear therapies

About AM-125

AM-125 is a spray formulation of betahistine dihydrochloride. Betahistine is a small molecule drug that acts as a partial histamine H1-receptor agonist and a H3-receptor antagonist. The compound has been shown to increase cochlear, vestibular and cerebral blood flow, facilitate vestibular compensation and inhibit neuronal firing in the vestibular nuclei.

AM-125 is being developed for the intranasal treatment of Meniere's disease and vestibular vertigo. The drug is administered with a metered dose spray pump. AM-125 is expected to become the first product for intranasal administration of betahistine. It has the potential to offer higher efficacy, a more rapid onset of action and better tolerability compared to oral betahistine.

In a Phase 1 clinical trial, intranasal betahistine was well tolerated and showed substantially higher plasma concentrations than known from oral administration.

How Betahistine Is Used Today

Betahistine for oral administration is marketed today in more than 80 countries worldwide - with the United States being a notable exception - and approved for the treatment of Meniere's disease and vestibular vertigo. Since its introduction in the 1960s, more than 130 million patients have been treated with oral betahistine. The recommended daily dose is 24-48 mg, divided in 2 or 3 single doses.

Treatment Effects of Betahistine

Most clinical trials with betahistine for Meniere's disease report a reduction in vertigo. However, others could not confirm these data resulting in some uncertainty about the drug's objective efficacy. Various studies and meta-analyses have demonstrated therapeutic benefits of betahistine in both the treatment of vertigo[1] as well as in supporting vestibular rehabilitation.[2]

Key Limitations of Oral Betahistine

Several pre-clinical and clinical studies have demonstrated or suggested that betahistine's efficacy in the treatment of Meniere's disease and vestibular vertigo is dose- and time-dependent. This suggests that higher doses and longer treatment periods could enhance betahistine's efficacy.

However, when orally administered, betahistine is rapidly and almost completely metabolized into 2-pyridylacetic acid, also known as 2-PAA, which lacks pharmacological activity. Due to a very high hepatic first-pass effect, the bioavailability of oral betahistine is estimated to be only about 1%. Not surprisingly, the plasma levels of betahistine were shown in a study to be less than 0.5 ng/mL following oral intake of 24 mg. Intranasal delivery allows for avoiding the first-pass effect and achieving higher concentrations in the bloodstream.[3]

Phase 1 Trial of Intranasal Betahistine

Intranasal betahistine was tested in a randomized, double-blind and placebo-controlled Phase 1 clinical trial with dose escalation. A total of 40 healthy volunteers received a single dose of intranasal betahistine of up to 40 mg. Intranasal betahistine was well tolerated. In addition, betahistine plasma concentrations were significantly higher than ever reported for oral betahistine administration and increased with dose.

AM-125 Development Program

Auris Medical is planning to conduct a second Phase 1 clinical trial in healthy volunteers to test repeated dosing over an extended period of time. This shall be followed by a Phase 2 dose-ranging trial to establish proof-of-concept.

[1] *James A, Burton MJ. Betahistine for Ménière's disease or syndrome. Cochrane Database of Systematic Reviews 2001;1:CD001873.*

[2] *Karapolat H, Celebisoy N, Kirazli Y, Bilgen C, Eyigor S, Gode S, Akyuz A, Kirazli T. Does betahistine treatment have additional benefits to vestibular rehabilitation? Eur Arch Otorhinolaryngol. 2010;267(8):1207-12.*

[3] *Otifex Therapeutics single-dose toxicology study with intranasal delivery in healthy volunteers*