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 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 will potentially 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 100 countries worldwide - with the United States being a notable exception - and approved for the treatment of Meniere's disease and 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 two or three 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]

[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] *Tighilet B, Trottier S, Lacour M. Dose- and duration-dependent effects of betahistine dihydrochloride treatment on histamine turnover in the cat. Eur J Pharmacol. 2005;523:54-63.*

Key Limitations of Oral Betahistine

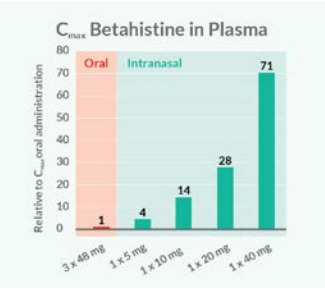
Several pre-clinical and clinical studies have demonstrated or suggested that betahistine's efficacy in the treatment of Meniere's disease and vertigo is dose- and time-dependent.[3] This suggests that higher doses and longer treatment periods could enhance betahistine's efficacy.

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 rapid and extensive metabolism, 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 the achievement of higher concentrations in the bloodstream.

Phase 1 Trial of Intranasal Betahistine

Intranasal betahistine was well tolerated in a randomized, double-blind and placebo-controlled Phase 1 clinical trial with dose escalation. In addition, the trial showed dose-dependent betahistine concentrations in blood plasma with T_{max} about ten minutes post-dose, suggesting rapid onset, and significantly higher plasma concentrations C_{max} than reported with oral dosing. E.g. a single intranasal dose of 20 mg resulted in a maximum plasma concentration that was 28-fold higher than observed after an oral dose 48 mg in another trial (where it was given 3 x daily for 8 days).

Single-dose Phase 1 study with intranasal delivery of betahistine in 40 healthy volunteers vs. multiple dose Phase 1 study with oral betahistine (n=22).



AM-125 Development Program

Auris Medical is planning to initiate a second Phase 1 clinical trial in the first quarter of 2018. The trial will enroll healthy volunteers and 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.