About AM-125

AM-125 is a spray formulation of betahistine dihydrochloride. Betahistine is a small molecule drug that acts as a partial H_1 histamine receptor agonist and a H_3 receptor antagonist. The compound increases inner ear and cerebral blood flow, histamine turnover and histamine release in the brain, and also the release of acetylcholine, dopamine and norepinephrine. Further, it leads to general brain arousal.

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.

Treatment Effects of Betahistine

Betahistine for oral administration is marketed today in 115 countries worldwide - with the United States being a notable exception - and approved for the treatment of Meniere's disease and vertigo. The recommended daily dose is 24-48 mg, divided in two or three single doses.

Betahistine has been shown to increase cochlear, vestibular and cerebral blood flow, facilitate vestibular compensation and inhibit neuronal firing in the vestibular nuclei. 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]

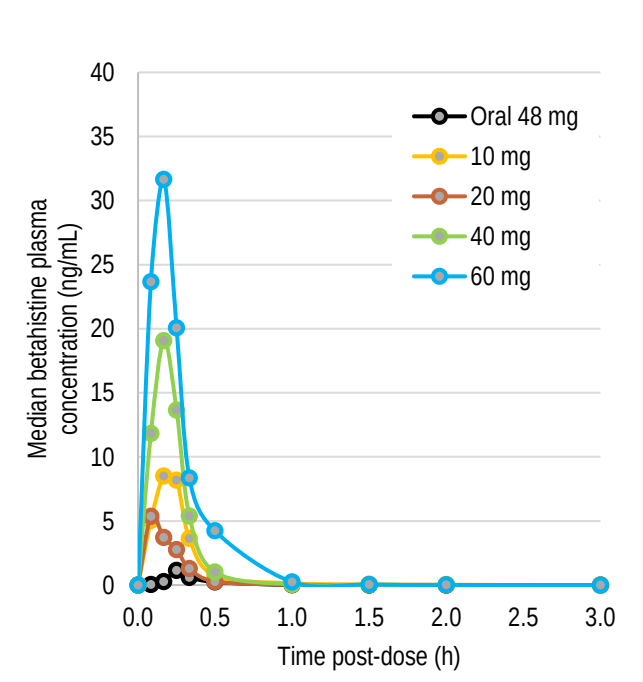
Key Limitations of Oral Betahistine

When administered orally, 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 very low in humans, which limits the treatment's clinical utility.

Several pre-clinical and clinical studies have demonstrated or suggested that betahistine's efficacy is dose- and time-dependent[3] and that higher bioavailability results in better therapeutic outcomes.[4] Indeed, it could be shown in a study in cats that higher plasma concentrations of betahistine both reduced the acute symptoms of vertigo following resection of the vestibular nerve and accelerated the recovery of the animal's balance in a statistically significant way compared to controls.

Improving Betahistine's Bioavailability

Administering betahistine through the nose results in substantially higher bioavailability. A phase 1 study with AM-125 demonstrated superior bioavailability over a range of four intranasal betahistine doses compared to oral betahistine 48 mg, with plasma exposure being 6 to 29 times higher (p-value between 0.056 and p<0.0001).



AM-125 Development Program

Auris Medical plans to initiate a randomized double blind placebo controlled proof-of-concept study with AM-125 in the first quarter of 2019. The Phase 2 "TRAVERS" clinical trial will enroll patients suffering from acute vertigo following vestibular schwannoma resection.

[1] *James A, Burton M.J. 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.
[4] Tighilet B, Léonard J, Watabe I, Bernard-Demanze L, Lacour M (2018). Betahistine treatment in a cat model of vestibular pathology: pharmacokinetic and pharmacodynamic approaches. Front Neurol. 11(9):431