About AM-201

AM-201 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 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-201 is being developed for the intranasal treatment / prevention of antipsychotic-induced weight gain and drowsiness (somnolence). The drug is administered with a metered dose spray pump. AM-201 is expected to become the first product for mental health supportive care, addressing major side effects of several widely-used antipsychotic drugs in the treatment of schizophrenia or bipolar disorder.

Previous preclinical and clinical work by other parties have shown that oral betahistine reduces weight gain related to the use of olanzapine, one of the most effective and frequently used antipsychotic drugs. It is expected that intranasal betahistine, thanks to superior bioavailability, will provide even more pronounced treatment effects.

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

In a rat model, betahistine attenuated olanzapine induced weight gain by counteracting increased expression of the H1 histamine receptor, pAMPK, orexigenic neuropeptide Y and decreased expression of the anorexigenic neuropeptide pro-opiomelanocortin.[1,2] In humans, a pilot study in 36 patients with a diagnosis of schizophrenia or schizoaffective disorder who were treated with olanzapine for 16 weeks evaluated the effects of concomitant administration of oral betahistine at the approved daily dose of 48 mg/day.[3] The study showed no interference of betahistine with the antipsychotic effect of olanzapine, and a trend for reduction in weight gain against placebo (+5.6 vs. +6.9 kg). In a subsequent study with a threefold higher betahistine dose (144 mg/day) administered concomitantly with olanzapine for three weeks to healthy volunteers (n=48), significant reductions in weight gain and somnolence were observed compared against placebo: +1.2 kg vs. +1.9 kg (p=.049) and +1.8 vs. +3.6 units in the daytime Epworth sleepiness score (p=.042).[4]

Key Limitations of Oral Betahistine

Several pre-clinical and clinical studies have demonstrated or suggested that betahistine's efficacy is dose- and time-dependent. Therefore higher doses and longer treatment periods are expected to enhance betahistine's effects.

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% in humans. In contrast, intranasal delivery allows for substantially higher betahistine concentrations in the bloodstream.

AM-201 Development Program

In a first Phase 1 clinical trial in healthy volunteers receiving one single dose of intranasal betahistine up to 40 mg, a dose-dependent increase of betahistine concentrations was observed in blood plasma. Overall, these levels were much higher than when compared with those observed following oral betahistine. Relative bioavailability was about 20 to 40 times higher than with intranasal betahistine.

Auris Medical initiated a second Phase 1 clinical trial in the first quarter of 2018. The trial is enrolling healthy volunteers to obtain additional pharmacokinetic data and also test repeated dosing over several days. In a next step, AM-201 shall be tested concomitantly with an antipsychotic drug such as olanzapine.

[1] *Deng C et al. (2012). Reducing olanzapine-induced weight gain side effect by using betahistine: a study in the rat model. J Psychopharmacol. 26(9):1271-9.*
[2] *Lian J et al. (2014). Preventing olanzapine-induced weight gain using betahistine: a study in a rat model with chronic olanzapine treatment. PLoS One 9(8):e104160.*
[3] *Barak N et al. (2016). Betahistine decreases olanzapine-induced weight gain and somnolence in humans. J Clin Psychopharmacol 30(3): 237-41.*
[4] *Barak N et al. (2016). A randomized, double-blind, placebo-controlled pilot study of betahistine to counteract olanzapine-associated weight gain. J Clin Psychopharmacol. 36(3):253-6.*