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. 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.

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.

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 s evaluated the effects of concomitant administration of olanzapine and oral betahistine at the approved daily dose of 48 mg/day over 16 weeks.[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.

Administering betahistine through the nose results in substantially higher bioavailability. A phase 1 study with intranasal betahistine demonstrated superior bioavailability over a range of four 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-201 Development Program

In 2019, Auris Medical initiated a Phase 1b dose escalation trial with AM-201 in healthy volunteers. Participants received the spray three times a day in parallel with oral olanzapine (10 mg) for four weeks. The study demonstrated in an interim analysis good safety and tolerability of AM-201 and revealed relevant reductions in olanzapine-induced weight gain and daytime sleepiness. In female study participants, who overall showed more pronounced changes than male participants, a reduction in weight gain of 1.1 kg against placebo was observed at the highest tested dose of 20 mg (probability of effectiveness = 90%). The study has since proceed to the next higher and final dose level of 30 mg which is being tested on 30 healthy volunteers.

[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.*