AM-111 for Acute Inner Ear Hearing Loss

Brimapitide otic gel for intratympanic use

Auris Medical
Cochlear therapies

About AM-111

AM-111 contains brimapitide, or D-JNKI-1, an inhibitor of the JNK stress kinase coupled to an intracellular transporter. AM-111 is formulated in a biocompatible and fully biodegradable gel and administered in a single dose via intratympanic administration locally into the middle ear by an otolaryngologist (ear, nose, throat physician). AM-111 blocks cell death (apoptosis) in stress-injured sensory cells and attenuates inflammation after acute inner ear injury.

AM-111 has orphan drug designation from both the US Food & Drug Administration and the European Medicines Agency for the treatment of acute sensorineural hearing loss (ASNHL): hearing loss from acoustic trauma, sudden deafness (idiopathic sudden sensorineural hearing loss; ISSNHL) and surgery-induced acoustic trauma. In addition, the FDA has granted AM-111 fast track designation.

In a Phase 2 clinical trial, AM-111 was well tolerated and showed a clinically relevant and statistically significant improvement in hearing and tinnitus.

Phase 3 Clinical Trials

The Phase 3 clinical development program for AM-111 includes two trials. The HEALOS trial, initiated in late 2015, is being conducted in Europe and Asia and is set to enroll ~255 patients. Completed enrollment for HEALOS is expected in the summer of 2017 with top-line results expected in the fall of 2017. The ASSENT trial, initiated in June 2016, is being conducted in North America, South Korea and Europe and is set to enroll ~300 patients. In these trials, patients suffering from acute severe to profound hearing loss within 72 hours of ISSNHL onset receive a single dose of AM-111 0.4 mg/mL, 0.8 mg/mL or placebo. Oral corticosteroids may be taken as reserve or background therapy.

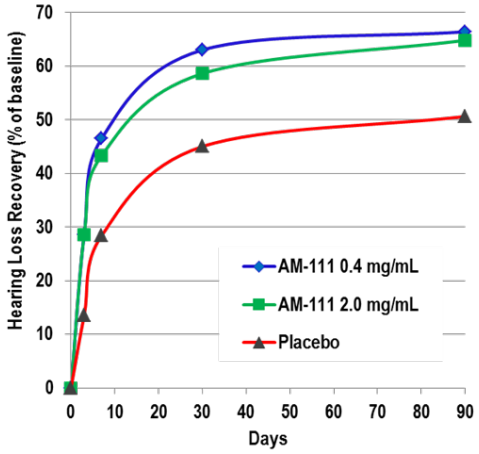
The primary endpoint of the Phase 3 trials is the mean hearing improvement at the three worst affected contiguous test frequencies as measured by the change in pure tone average to Day 28 in the HEALOS trial and to Day 91 in the ASSENT trial. Additional endpoints include the frequency of complete hearing recovery, complete tinnitus remission and improvement in speech discrimination.

Phase 2 Clinical Trials

In a randomized, placebo-controlled Phase 2 trial of 210 patients who suffered from either ASNHL following acute noise trauma or ISSNHL, patients were treated within 48 hours post-onset with a single dose of AM-111 0.4 mg/mL, 2.0 mg/mL or placebo. The primary endpoint of the trial was the change in hearing between baseline and Day 7.

AM-111 Efficacy: Patients with severe to profound hearing loss (i.e. hearing thresholds $\geq$ 60 dB at the three worst affected test frequencies) who were treated with AM-111 0.4 mg/mL showed a clinically relevant improvement in hearing threshold and speech discrimination and a higher rate of complete tinnitus remission compared with placebo. Hearing thresholds improved by 29.9 dB at Day 7 and 44.3 dB at Day 90 in the active group compared with 17.9 dB and 33.5 dB in the placebo group, respectively. Improvement in the AM-111 2.0 mg/mL group tended to be lower and failed to reach significance. In patients who were treated more than 24 hours after ASNHL onset, the effect of AM-111 increased as the rate of spontaneous recovery decreased.

Safety: AM-111 was well tolerated with no negative impact on hearing, balance or tinnitus. Adverse events were mostly local, transient and procedure-related, such as ear discomfort, incision-site complications, or middle ear infection in less than 5% of patients.



Patients with severe to profound hearing loss, n = 92 (n = 76 for tinnitus data). Mean baseline hearing loss at three most affected contiguous test frequencies = 67 decibels (dB), hearing threshold (PTA) = 82.9 dB. Mean word recognition score @ 80 dB = 27.6%. Mean time from onset = 30 hours.