

## About AM-101

AM-101 contains the N-Methyl-D-Aspartate (NMDA) receptor antagonist Esketamine formulated in a biocompatible and fully biodegradable gel. It targets NMDA receptor mediated aberrant excitation of the auditory nerve which is at the origin of certain types of tinnitus.

Auris Medical is developing AM-101 for the treatment of acute peripheral tinnitus following traumatic cochlear injury or otitis media.

AM-101 is administered by intratympanic injection (3x over 3 to 5 days).

In Phase 2 clinical trials, AM-101 was well tolerated and showed a dose dependent and persistent improvement in tinnitus loudness and other outcomes (see below).

## Phase 3 Clinical Trials

In Q1/2014 Auris Medical initiated two Phase 3 clinical trials with AM-101: TACTT2 in North America and selected European and Asian countries and TACTT3 in Europe. AM-101 0.87 mg/mL or placebo is administered 3x over 3 to 5 days.

Auris Medical plans to enroll 960 patients in total: 630 in the acute stage (i.e. up to three months from tinnitus onset) for confirmatory testing and 330 in the post-acute stage for exploratory testing (TACTT3 only).

The Phase 3 design builds on the Phase 2 program as well as regulatory feed-back from the FDA (through a “Special Protocol Assessment”) and the EMA. The primary endpoint, mean improvement in subjective tinnitus loudness, was used as co-primary or primary endpoint in Phase 2. Improvement in the Tinnitus Functional Index will be tested as co-primary endpoint in TACTT2 and as a secondary endpoint in TACTT3.

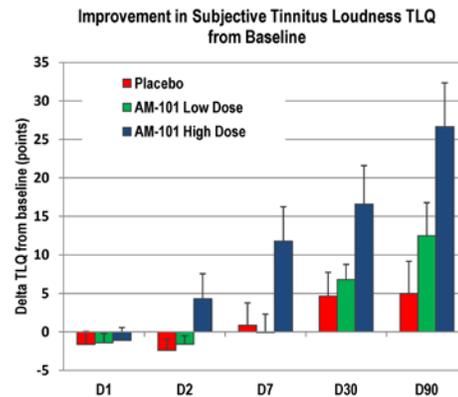
An interim analysis by an Independent Data Review Committee after enrollment of 150 patients with post-acute tinnitus suggested that AM-101 might be effective also in tinnitus older than three months. Since higher levels of drug activity were observed in the early post-acute stage than at a later stage, enrollment has since been limited to patients with tinnitus onset between 3 to 6 months prior.

Participants completing the TACTT trials have the option to roll over into open-label studies (AMPACT1/AMPACT2) and receive up to three AM-101 treatment cycles.

For further information please visit [www.tinnitus-study.info](http://www.tinnitus-study.info).

## Phase 2 Clinical Trials

Auris Medical conducted two randomized, placebo-controlled Phase 2 trials enrolling 248 (TACTT0) and 85 (TACTT1) patients with acute inner ear tinnitus.



Mean absolute improvement of subjective tinnitus loudness (TLQ) from baseline in patients with unilateral tinnitus following acute acoustic trauma or otitis media (n = 84). TLQ was rated on a scale from 0 (no tinnitus heard) to 100 (extremely loud tinnitus). Study participants received three injections of AM-101 or placebo on Day 0, Day 1 and Day 2. Whiskers: standard error mean. Van de Heyning et al., 2014.

In TACTT0 AM-101 0.27 or 0.81 mg/mL or placebo was administered 3x over 3 consecutive days.

In TACTT1 AM-101 0.81 mg/mL or placebo was administered in a single dose or 3x over 2 weeks.

## Principal Phase 2 Results

**TACTT0 – Efficacy:** Patients with tinnitus following acute acoustic trauma or otitis media treated with AM-101 0.81 mg/mL showed a gradual and statistically significant improvement to Day 90 in patient reported outcomes (PROs) such as tinnitus loudness (co-primary endpoint), sleep difficulties and overall tinnitus impact over placebo.

At Day 90, mean tinnitus loudness improvement was 48%; 62% of patients (unilaterally affected and treated) reported much or very much improved tinnitus severity.

**TACTT1 – Efficacy:** AM-101 treated patients showed the same type of gradual improvement in tinnitus loudness (primary endpoint) and other PROs over placebo as in TACTT0. Trends for 1xAM-101 and 3xAM-101 were similar.

The effect size for AM-101 was largest in TACTT0, suggesting that repeated treatment concentrated in time provides the best treatment benefit.

**Safety:** AM-101 was well tolerated and had no negative impact on hearing. Adverse events were mostly local and procedure-related, as expected. Following i.t. injections, a number of patients experienced a transient increase in tinnitus loudness and muffled hearing. These effects usually resolved with closure of the ear drum (typically a few days post injection).