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Cochlear therapies

# Innovative Treatments for Inner Ear Disorders

## KOL Call: Keyzilen® Tinnitus Program

March 5, 2018

NASDAQ: EARS

# Forward-Looking Statements

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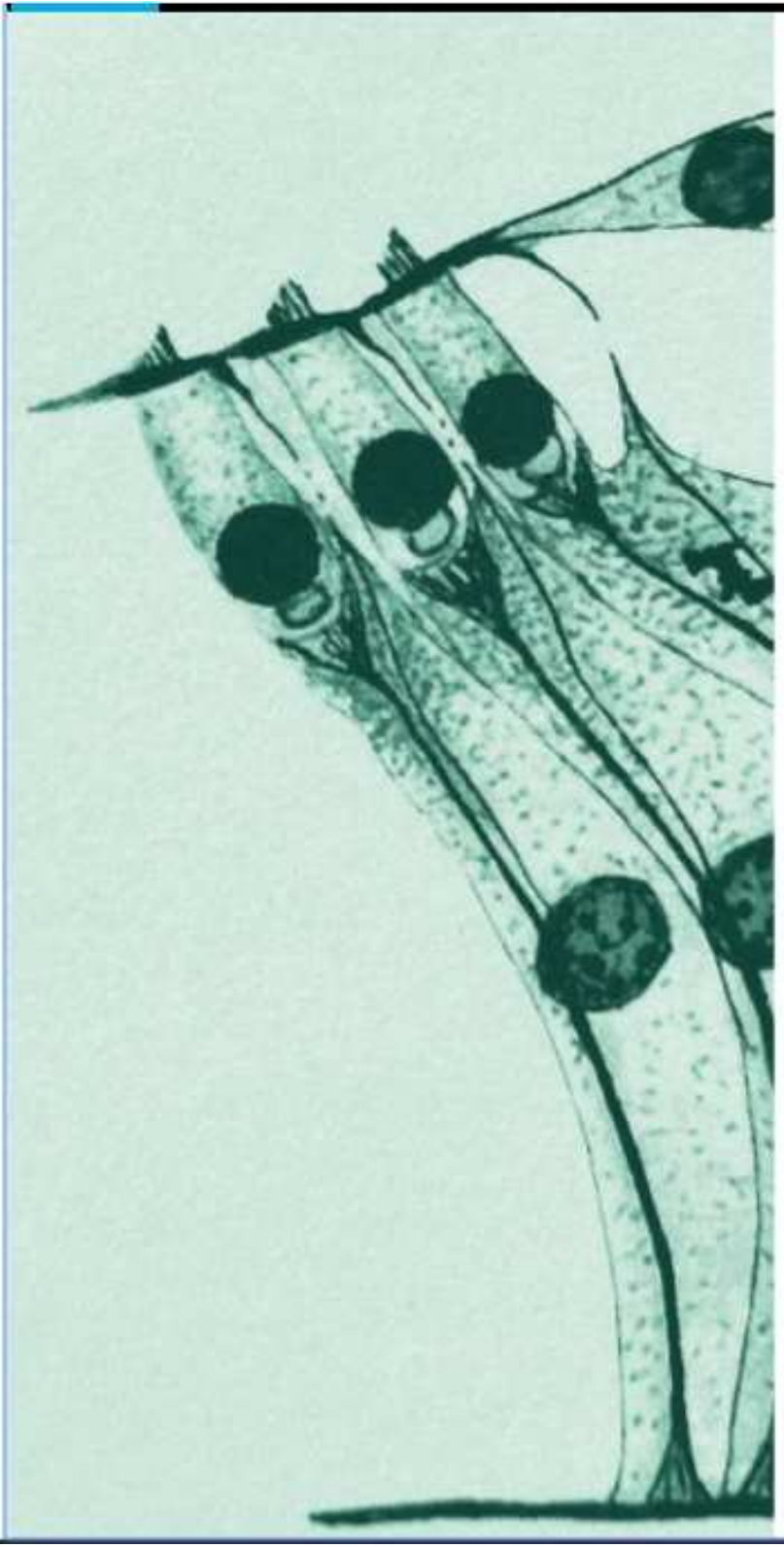
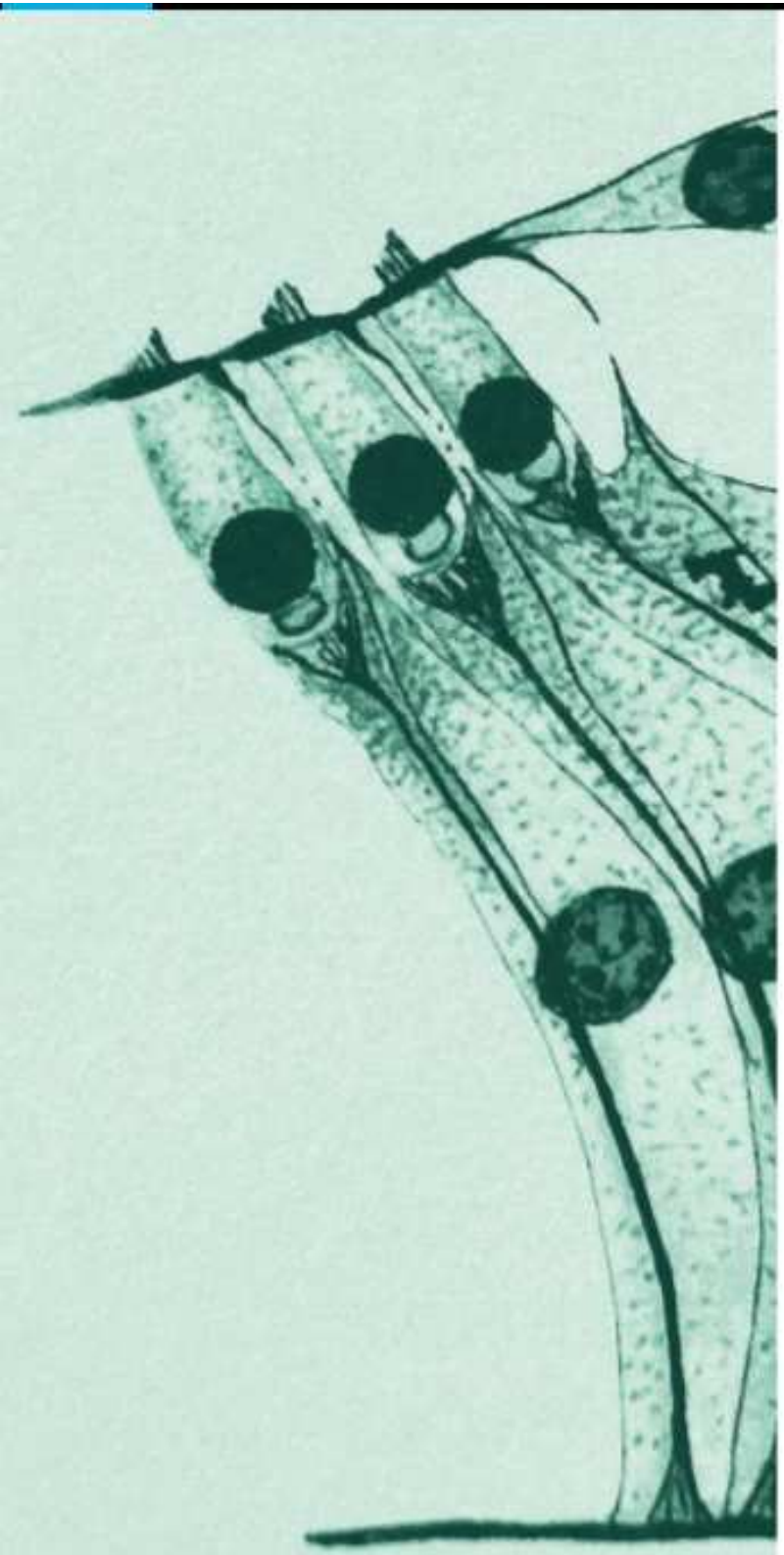


# Agenda

- **Introduction**
  Thomas Meyer
- **Treating Patients with Acute Inner Ear Tinnitus**
  Elias Michaelides
- **Keyzilen® Project Update**
  Thomas Meyer
- **Questions and Answers**



# Introduction

## Thomas Meyer, PhD

Chairman & Chief Executive Officer

# Keyzilen® (AM-101) Product Profile

- Potential to become first-ever drug approved for tinnitus
- Suppress / attenuate symptom of tinnitus following acute inner ear injury
  - Reduce functional impact
  - Reduce risk of life-long burden
- Esketamine 0.87 mg/mL
  - Small-molecule NMDA receptor antagonist
- Otic gel for intratympanic administration
  - Targeted administration with minimal systemic exposure
- Three doses administered over 3-5 days
  - Distributed in kits of three pre-filled syringes

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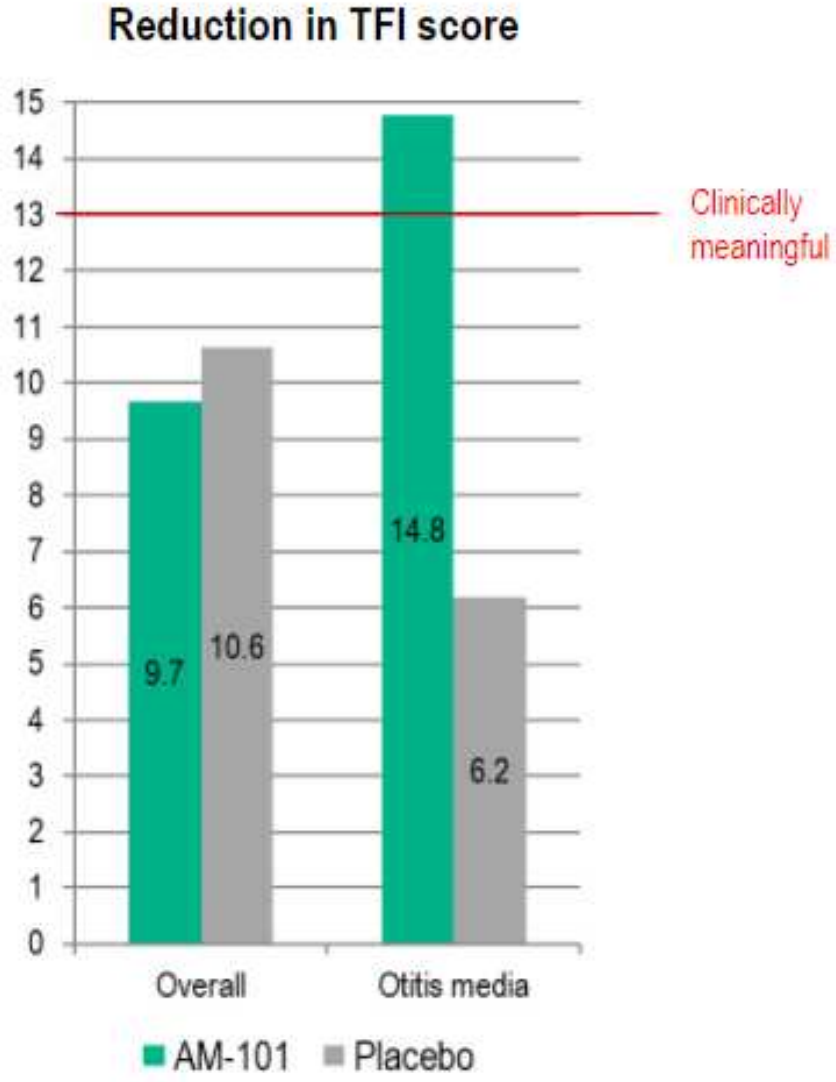
# Keyzilen® Phase 3 Program Overview

| | TACTT2 | TACTT3 | |
|---|---|---|---|
| | *Confirmatory* | Stratum A | Stratum B |
| | | *Confirmatory* | *Exploratory* |
| **Region** | Primarily North America | Europe | |
| **Indication** | Tinnitus following acute traumatic cochlear insults (acute noise trauma, barotrauma, surgery trauma) or otitis media | | |
| **Time from Tinnitus Onset** | Up to 3 months | Up to 3 months | Pre-interim 3-12 months<br>Post-interim 3-6 months |
| **Number of Patients** | 343 | ~370 | ~365<br>*Pre-interim 150, post-interim 215* |
| **Number of Sites** | >60 | >60 | >60 |
| **Treatment** | Keyzilen® 0.87 mg/mL or placebo (ratio 3:2), 3x over 3-5 days | | |
| **Status** | Read-out Aug 2016 | Read-out Mar 2018 | |
| | **AMPACT1** | **AMPACT2** | |
| **Treatment** | Up to three treatment cycles Keyzilen® 0.87 mg/mL, 3x over 3-5 days | | |
| **Status** | Read-out May 2017 | Read-out Apr 2017 | |

# First Phase 3 Did Not Meet Expectations, But…

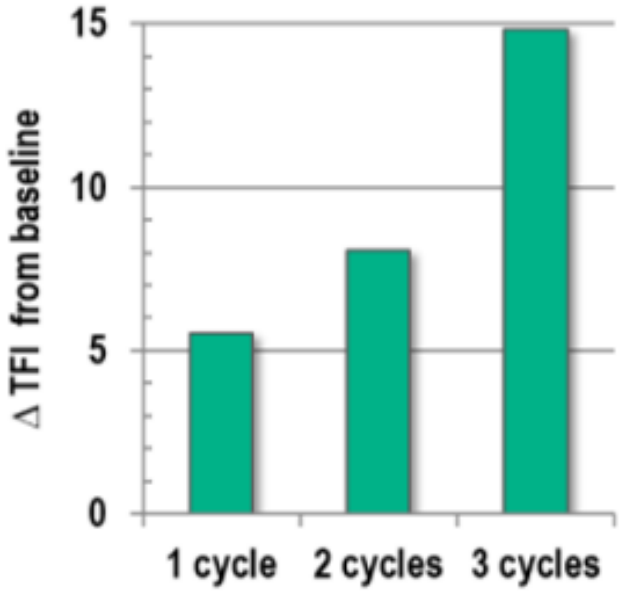
- TACTT2 trial did not meet co-primary endpoints: change in daily rated tinnitus loudness (TLQ) and Tinnitus Functional Index (TFI)
  - Potential design issue related to daily TLQ (patients focusing more on tinnitus, rating fatigue)
  - TFI performing better than TLQ
- Clinically meaningful TFI improvement in pre-specified subgroup of patients with otitis media-related tinnitus
- Keyzilen and intratympanic injection procedure well tolerated



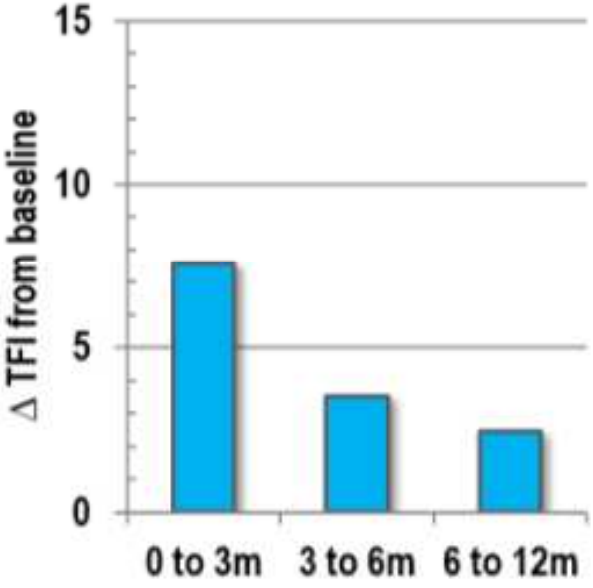

Improvement of TFI score from baseline to Day 84 in whole population (n=326) and patients with tinnitus related to otitis media (n=46); repeated mesures ANCOVA (mITT).

# AMPACT Open-Label Study Outcomes

- >700 patients participated in the two open-label extension studies with ~4,500 intratympanic administrations monitored
- Conducted at request of FDA to generate safety data from chronic intermittent use
- Good safety profile confirmed even with treatment for up to 12 months
- Exploratory efficacy analyses
  - Suggest potential benefits of repeating treatment cycles
  - Support early treatment from onset of inner ear tinnitus



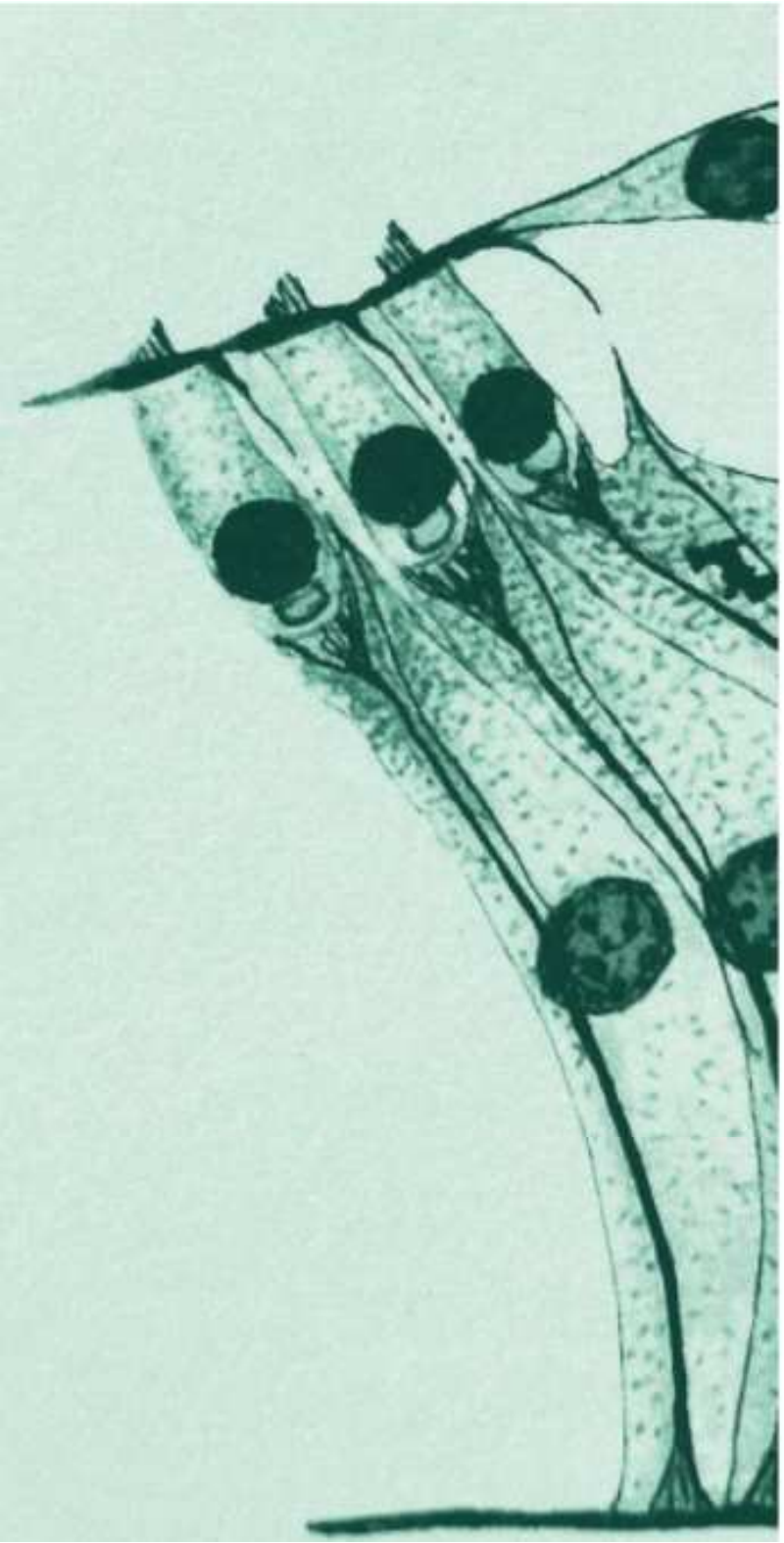

**AMPACT1: repeated treatment**




**AMPACT2: therapeutic time window**

AMPACT1: by number of treatment cycles (n=220). Difference in TFI reduction between 3 cycles and 1 cycles is 7 points (95% confidence interval: 2.3 to 11.8)
AMPACT2: by time from tinnitus onset when enrolling in preceding TACTT1 (n=418)

# TACTT3 Results Are Expected to Be Released Shortly



# Treating Patients with Acute Inner Ear Tinnitus


## Elias Michaelides, MD

Yale School of Medicine

*Associate Professor of Surgery, Otolaryngology*
*Director of the Hearing and Balance Program*

# Disclosure

- Principal Investigator in Auris Medical sponsored trials
  - TACTT2 and ASSENT
- Member of AM-125 scientific advisory board
- Member of additional scientific advisory boards
  - Pfizer
  - Affinimark

# Elias Michaelides, MD

- Personal background:
  - Associate Professor and Vice Chief, Otolaryngology at Yale School of Medicine
  - Director of the Yale Hearing and Balance Center
  - Otolaryngology Residency Program Director
- Clinical and research focus:
  - Medical treatment of hearing loss and tinnitus
  - Novel surgical approaches to Eustachian tube disorders
  - Chemodetection of cerebrospinal fluid

# Tinnitus – the Clinician's Challenge

- Distressing Symptom with No Visible Abnormalities
- Frustrated Patients
- Perception that it is incurable
- Current Treatment options are limited
  - Hearing Aids
  - Psychologic Care
  - Off-label treatment with psychiatric meds

# Types of Tinnitus Patients We Are Seeing

- Majority are chronic
- Systematic review of 891 manuscripts on tinnitus
- Prevalence
  - Between 11.9 and 30.3% of overall population
  - One of the top rated disabilities of VA patients
- Males generally more affected than females
- Age:
  - Prevalence increases with age
  - Plateaus around age 70

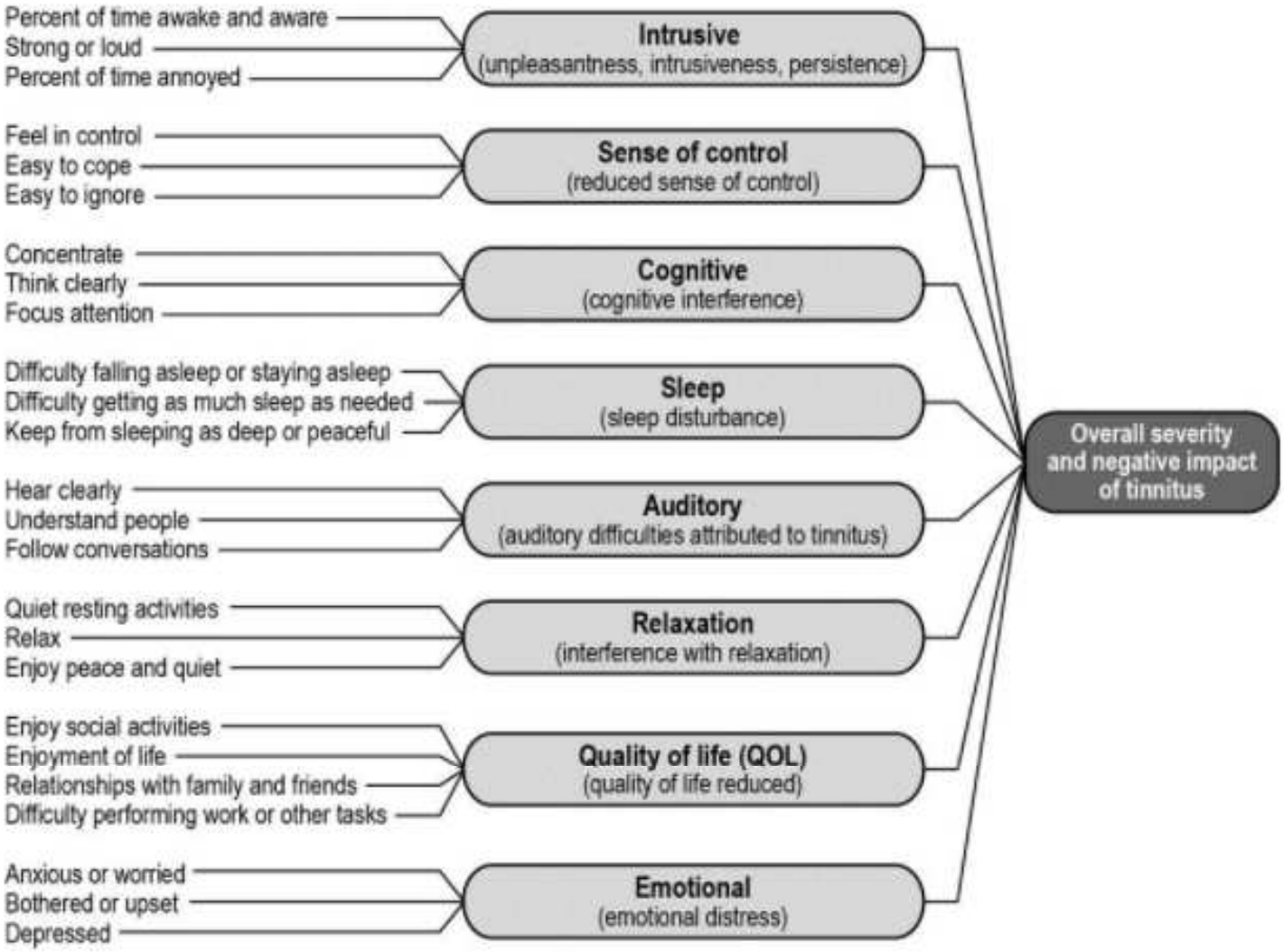
McCormack A et al. (2016) A systematic review of the reporting of tinnitus prevalence and severity. Hear Res. 2016 Jul;337:70-9.

# Etiologies of Tinnitus

- Neural reaction to damage in ear and auditory system
- Acute and chronic
- Transient tinnitus not included

- Causes
  - Age
  - Chronic noise exposure
  - Ototoxic medications
  - Infections
  - Acoustic trauma
  - Traumatic brain injury
  - Metabolic changes

# Assessing Tinnitus Burden with TFI




*Tinnitus Functional Index Domains (25 items, maximum score = 100 points)*

# The Burden of Tinnitus – Sleep Problems

- Poor sleep is most frequent complaint in patients with tinnitus
  - Prevalence rates of 53 to 77% have been reported
  - Significantly higher rates compared to healthy persons
- Patients worry about sleep, have anxiety about falling asleep and experience sleepless nights
- Sleep difficulties include:
  - Sleep latency
  - Sleep duration
  - Sleep continuity
  - Morning fatigue
  - Chronic fatigue

*Crönlein T et al. (2016), Insomnia in patients with chronic tinnitus: Cognitive and emotional distress as moderator variables, J Psychosom Res. 83:65-68.*
*Alster et al. (1993), Sleep disturbance associated with chronic tinnitus, Biol Psychiatry. 34:84-90.*

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# The Burden of Tinnitus – Persistence / Intrusiveness

- Persistence of tinnitus reported as difficulty by 49% of patients in a survey[1]
- Sense of "I cannot escape my tinnitus" and of loss of control
- Intrusiveness may have other functional impacts:
  - Cognitive interferences: *ability to concentrate, think clearly or focus attention on other things*
  - Interferences with relaxation: *ability to relax and enjoy "peace and quiet"*
  - Less enjoyment of social activities or of life in general
  - Impacts relationships with friends, family, and other people
  - Difficulties when performing work or other tasks
  - Auditory difficulties: *hear clearly, understand people who are talking or follow a conversation*

[1] *Tyler RS, Baker LJ (1983), Difficulties experienced by tinnitus sufferers, J Speech Hear Disord.48(2):150-154.*

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# The Burden of Tinnitus – Emotional Distress

- In a survey, 36% of patients reported despair, frustration, or depression[1]
- Prevalence of depression reported as high as >30%[2]
- In a systematic review, 15 out of 16 articles reported a high prevalence of psychiatric disorders in tinnitus-affected patients
  - Nine of the articles reported a high correlation between presence of a psychiatric disorder and tinnitus-related annoyance and severity[3]
- More severe tinnitus associated with poorer health-related quality of life (HRQoL) and more depressive symptoms[4]


[1] *Tyler RS, Baker LJ (1983), Difficulties experienced by tinnitus sufferers, J Speech Hear Disord.48(2):150-154.*
*2 Folmer RL et al. (1999), Tinnitus severity, loudness, and depression, Otolaryngol Head Neck Surg. 121:48-51.*
*3 Pinto PC (2014), Tinnitus and its association with psychiatric disorders: systematic review, J Laryngol Otol. 128(8):660-664.*
*4 Weidt S et al. (2016), Which tinnitus-related characteristics affect current health-related quality of life and depression? A cross-sectional cohort study, Psychiatry Res. 237:114-121.*

# Effectiveness of Current Tinnitus Treatments

- Steroids, while given frequently during the acute stage, have not shown evidence of efficacy[1]
- A systematic review by the HHS Agency for Healthcare Research and Quality found little evidence to suggest that pharmacological interventions or food supplements led to improvements over placebo in the treatment of tinnitus[2]
- To date, the best-established management option for tinnitus seems to be cognitive behavioral therapy (CBT)[3]
- Cochrane meta-analysis of CBT studies[4]:
  - Improves quality of life and reduces depression scores
  - However, does not reduce tinnitus loudness or eliminate the perception


*1 Lavigne P et al. (2015), Intratympanic corticosteroids injections: a systematic review of literature. Eur Arch Otorhinolaryngol. Epub .*
*2 Pichora-Fuller MK et al. (2013), Evaluation and treatment of tinnitus: comparative effectiveness, Comparative Effectiveness, Review No. 122.*
*3 Shore SE et al. (2016), Maladaptive plasticity in tinnitus - triggers, mechanisms and treatment, Nat Rev Neurol. 12(3):150-160.*
*4 Martinez-Devesa P et al. (2010), Cognitive behavioural therapy for tinnitus. Cochrane Database Syst Rev: CD005233.*

# Key Objective: Reduce Tinnitus Burden!

- Patients want to see benefits in their daily life, such as:
  - Improved quality and quantity of sleep
  - Less anxiety and fear
  - Less emotional distress: *"I can do something about it" / "Life can go on"*
  - Better ability to relax
- Best way of preventing tinnitus-related distress is to prevent or cure tinnitus[1]
- Early diagnosis and medical care help to prevent decompensation of tinnitus, development of impact on day-to-day functioning and comorbid conditions such as depression[2]

*1 Malouff JM et al. (2011), Tinnitus-related distress: A review of recent findings, Curr Psychiatry Rep. 13(1):31-36.*
*2 Weidt S (2016), Which tinnitus-related characteristics affect current health-related quality of life and depression? A cross-sectional cohort study. Psychiatry Res. 237:114-121.*

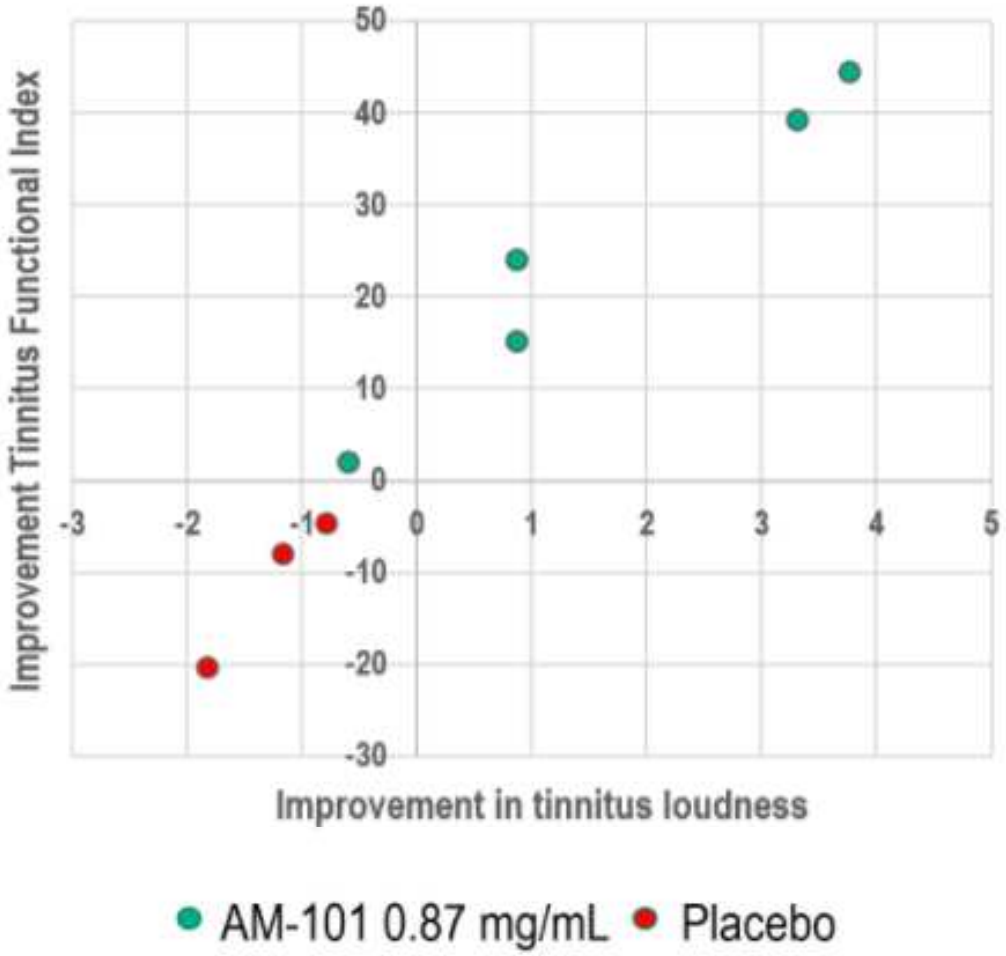
# Where Do Our Patients Come From?

- Local/regional referral network in place
  - General practitioners
  - Private ENT practices (especially cases with previous treatment failures)
- Approximately one third seeking direct access to consultation
- Referals from audiologists and hearing aid dispensers

# Enrolling Patients in TACTT2

- Participated as Principal Investigator
- Screened 20 patients
- Enrolled 8 patients
  - 5 bilateral, 3 unilateral tinnitus
  - 7 acute acoustic trauma, 1 otitis media
- Mean baseline values
  - TFI 49.6 points
  - Tinnitus loudness 6.2 points
- Primary complaints / highest TFI subscores
  - Intrusiveness, unpleasantness, persistence
  - Interference with relaxation
  - Emotional distress

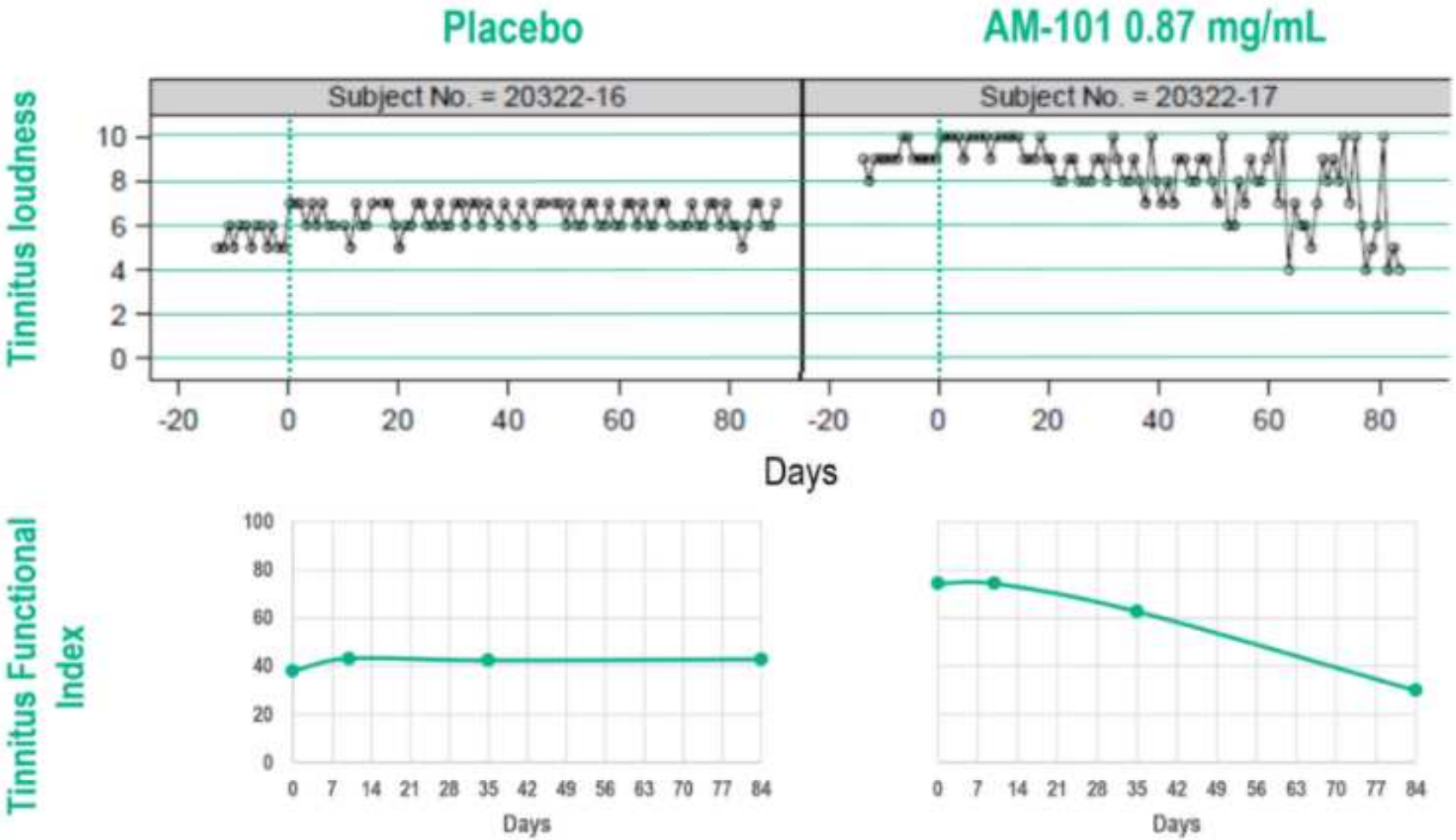
# How Did Patients Perform?



# Daily Tinnitus Ratings

- Daily rating of tinnitus may draw the focus of the patient to tinnitus
- Increasing awareness of symptom and impact
- High frequency of ratings leading to 'study fatigue'
- Less is actually more
- Weekly ratings probably sufficient

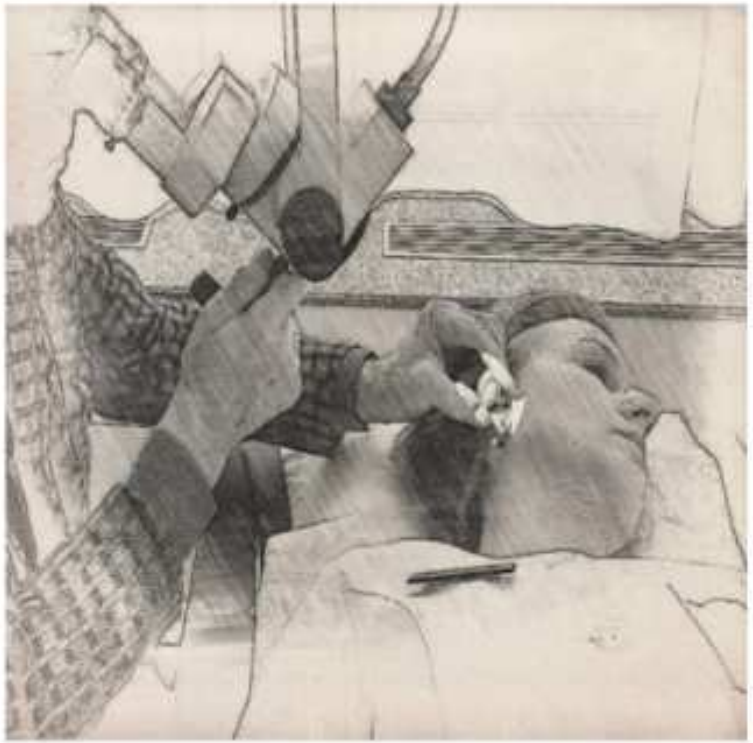
# Two Exemplary Cases




| Δ to Day 84 | Abs. | % | Abs. | % |
|---|---|---|---|---|
| Loudness | +0.8 | +14.3 | -3.8 | -41.0 |
| TFI | +4.8 | +12.6 | -44.4 | -59.7 |

# Acceptance of Intratympanic Administration

- Simple, well tolerated procedure
- Ten-minute application of topical anesthetic
- Painless injection under microscope
- Patient lies flat for 30 minutes
- Puncture site in ear drum may heal as quickly as within 24 hours
- Most are surprised at ease of treatment
- Very well tolerated when process clearly explained to patients



# What Place Could AM-101 Take in Tinnitus Care?

- Acute tinnitus deserves specific attention since there might be a short therapeutic window for specific pharmacological interventions[1]
  - Prevent or reduce long-term suffering from tinnitus
- Tinnitus can have different origins and different treatments may be needed
- AM-101 targets a relatively well-characterized, specific type of tinnitus
- AM-101 has the potential to become the first-in-class treatment for tinnitus and change the way we approach inner ear disorders

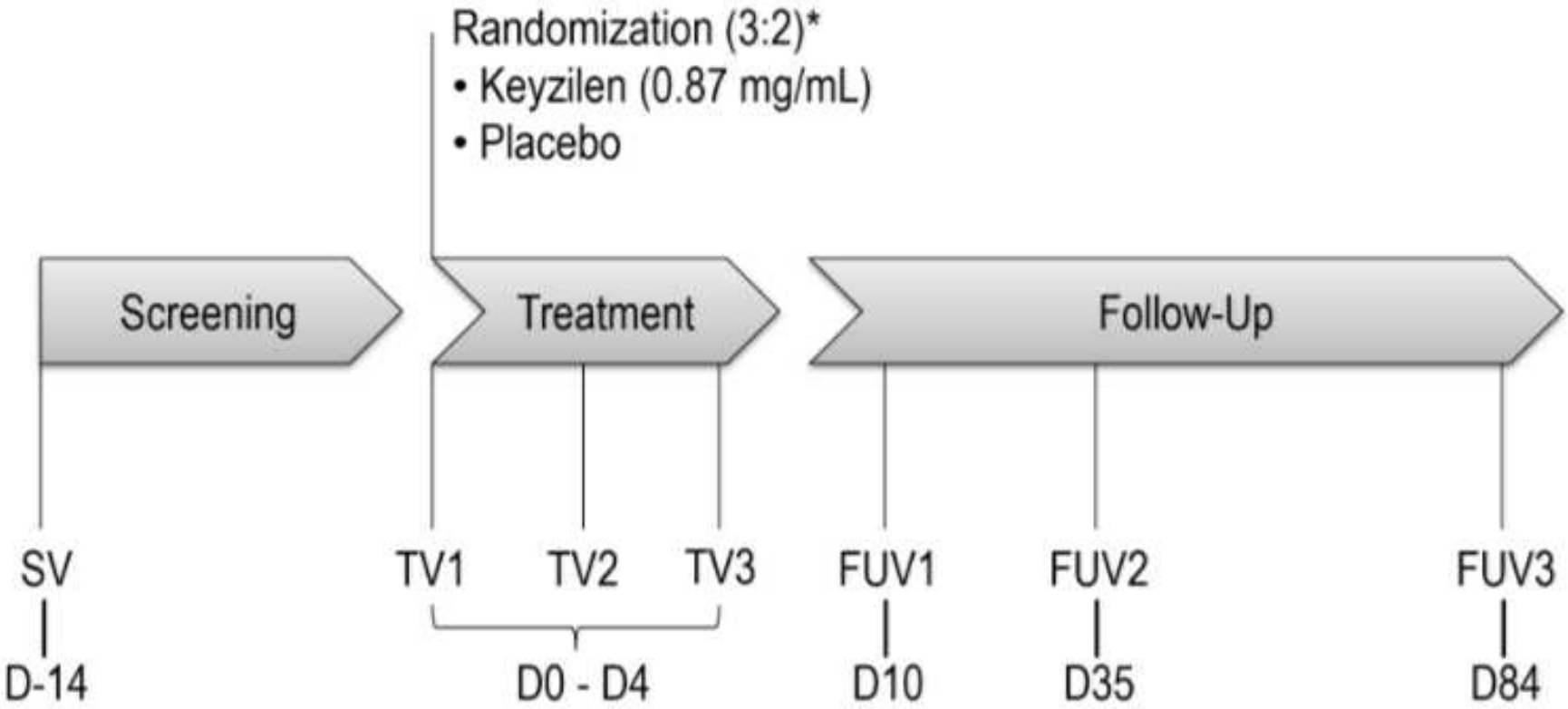
*1 Langguth B, Elgoyhen AB (2012), Current pharmacological treatments for tinnitus. Expert Opin Pharmacother. 13(17):2495-2509.*

# Keyzilen® Project Update

## Thomas Meyer, PhD

Chairman & Chief Executive Officer

# TACTT3 Trial Design Overview




* *Stratified for etiology (traumatic cochlear injury / otitis media) and laterality (uni- / bilateral). SV: screening visit, TV: treatment visit, FUV: follow-up visit*

- Inner ear tinnitus following traumatic cochlear insult or otitis media (up to 3 months)
  - Acute: up to 3 months from onset = Stratum A
  - Post-acute: between 3 and 6 months from onset = Stratum B
- Conducted in 9 European countries

# Comparing TACTT2 With TACTT3

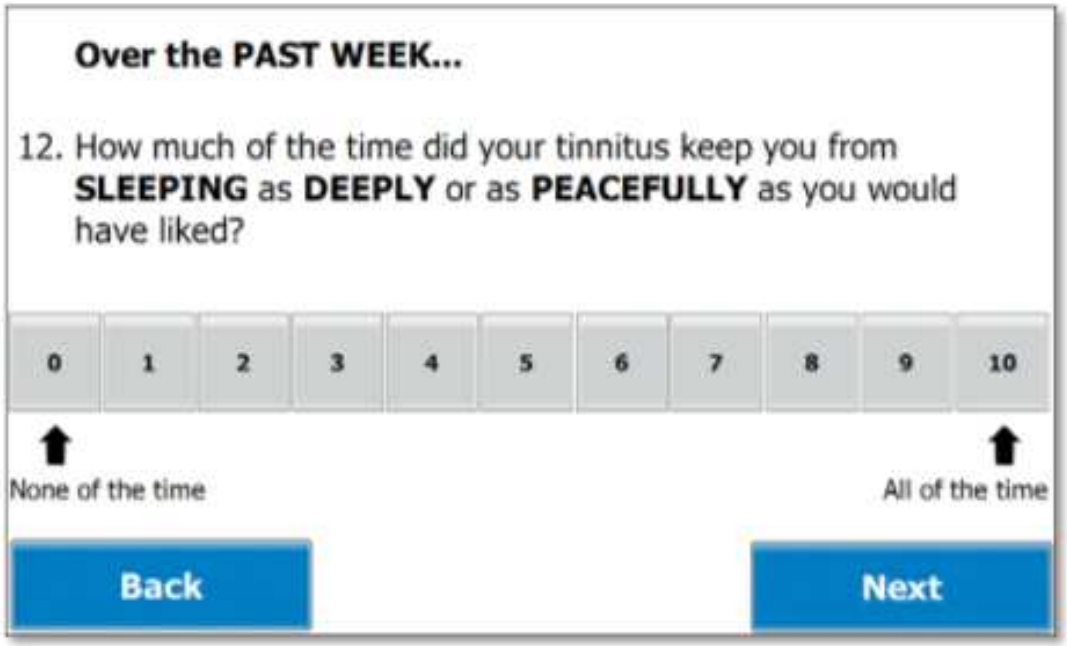
## Same for TACTT3 and TACTT2

- Study design
- Eligibility criteria
- Efficacy and safety outcome variables
- Change in Tinnitus Functional Index as primary efficacy endpoint

## Where TACTT3 Differs

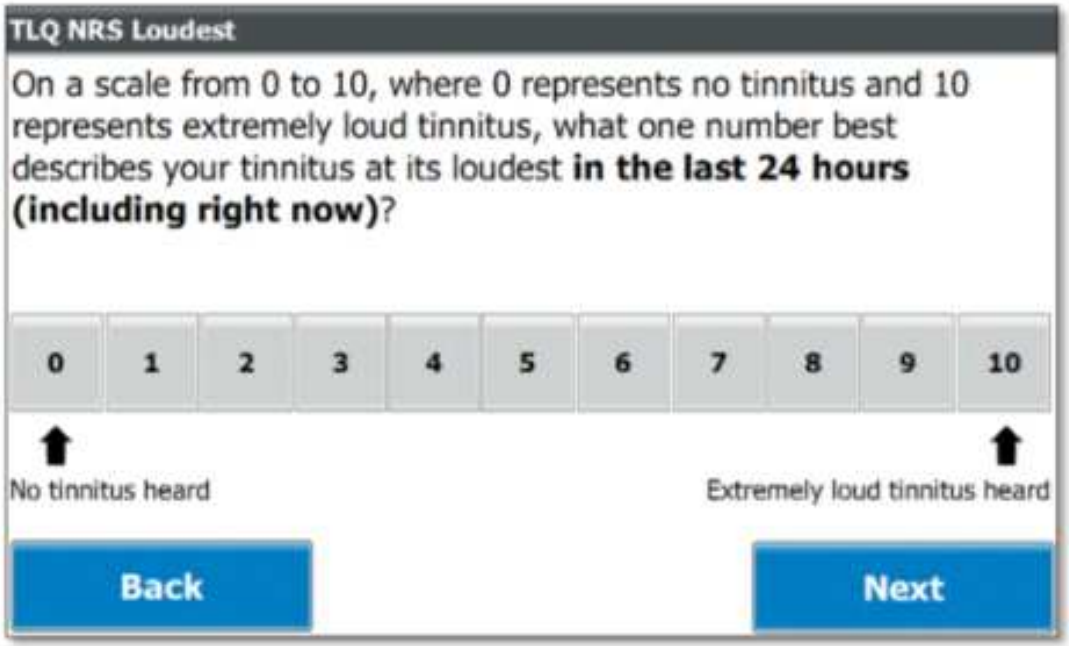
- Confirmatory testing not only for overall population, but also for subpopulation with otitis media related tinnitus
- Reduced rating frequency for tinnitus loudness
- Change in tinnitus loudness no longer primary efficacy endpoint
- Higher share of otitis media tinnitus
- Higher share of unilateral tinnitus
- Inclusion of post-acute tinnitus patients in separate stratum

# Focus on TFI Questionnaire




- Clinically relevant – captures tinnitus impact on day-to-day functioning
- Designed for measuring treatment-related changes
- Only captured during study visits
- More robust in TACTT2 than tinnitus loudness rating

# Tinnitus Loudness as Secondary Efficacy Endpoint

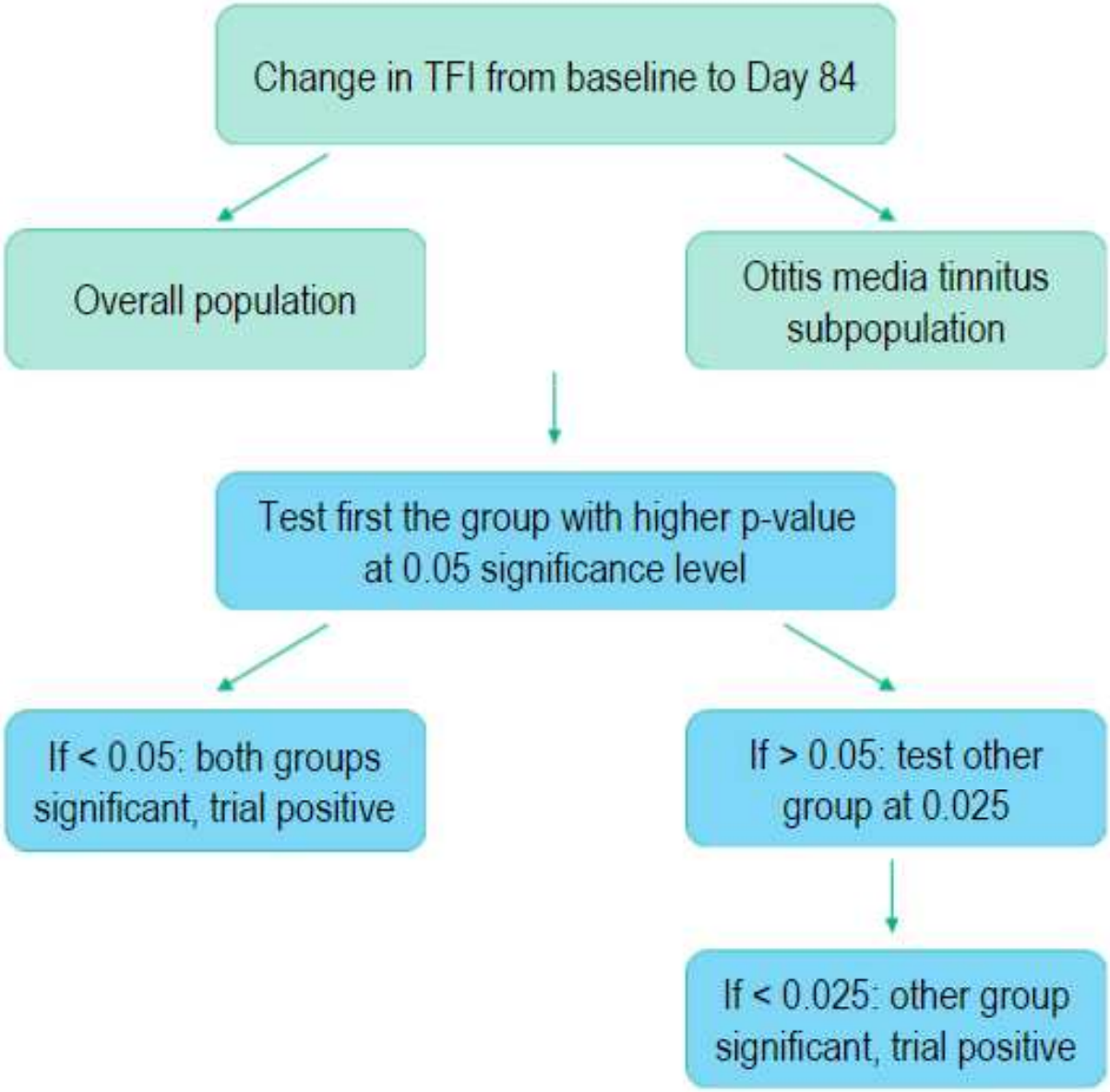



- Rating frequency reduced in TACTT3 to days around study visits
- Downgraded to secondary efficacy outcome given issues with instrument in general and due to change effected during the trial

# TACTT3 Statistics

- Improvement in TFI to be tested by ANCOVA model
- Mixed-effect linear model for repeated measurements
  - No need to replace missing data from dropouts
  - Sensitivity analyses with various pre-specified methods of missing data imputation
- Testing effect in overall population and otitis media subpopulation
  - Control for multiplicity through Hochberg procedure
- ~90% power for treatment effect of
  - 5 points in overall population
  - 7 points in otitis media tinnitus subpopulation (was 8.6 points in TACTT2)
- Various subgroup analyses planned (e.g. traumatic / otitis media, unilateral / bilateral, severity)

# How Testing Works For Primary Endpoint in TACTT3



# What Can We Expect From Stratum B?

- Same analyses as for Stratum A
- Exploratory testing to see how far the therapeutic time window may reach
- Initially enrollment up to 12 months from onset
- Interim analysis for futility following first 150 patients
- Independent data review committee recommended reduction of time window to 6 months as decrease in activity over time was observed
- Results from AMPACT point in same direction
- Testing will be done on patients enrolled after the interim analysis (i.e. ~215 patients)

# Development and Regulatory Path Forward

- Fast tracked by FDA
- Planning to meet with FDA and EMA following TACTT3 read-out
  - Various scenarios as a function of outcomes
  - Unmet medical need
  - Serious condition
  - Safe treatment
- Submission readiness for 2018
  - Validation of manufacturing process completed
  - Working towards completing dossier

# $750 Million US Market Potential

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## Primary Market Research

- 53 US ENT doctors surveyed[1]
  - 41 general ENTs, 12 otologists
- See an average of 44 tinnitus patients per month

**38%**
tinnitus patients seeking treatment in acute stage (up to three months from onset)

**74%**
of respondents expect monthly tinnitus patient volume to increase if an approved IT treatment were available

**43%**
of their tinnitus patients considered candidates for AM-101 type product

## Market Potential

- Target label: *acute peripheral tinnitus following traumatic injury to the cochlea or otitis media*

**~25%**
tinnitus cases caused by traumatic injury or otitis media

**30%**
bilateral patients (both ears affected)

**~250,000**
treatable ears per year

**~$750 Million**
market potential

**Upside Potential:**
- Other onset factors
- Extension of window beyond three months
- GP awareness driving increased referrals

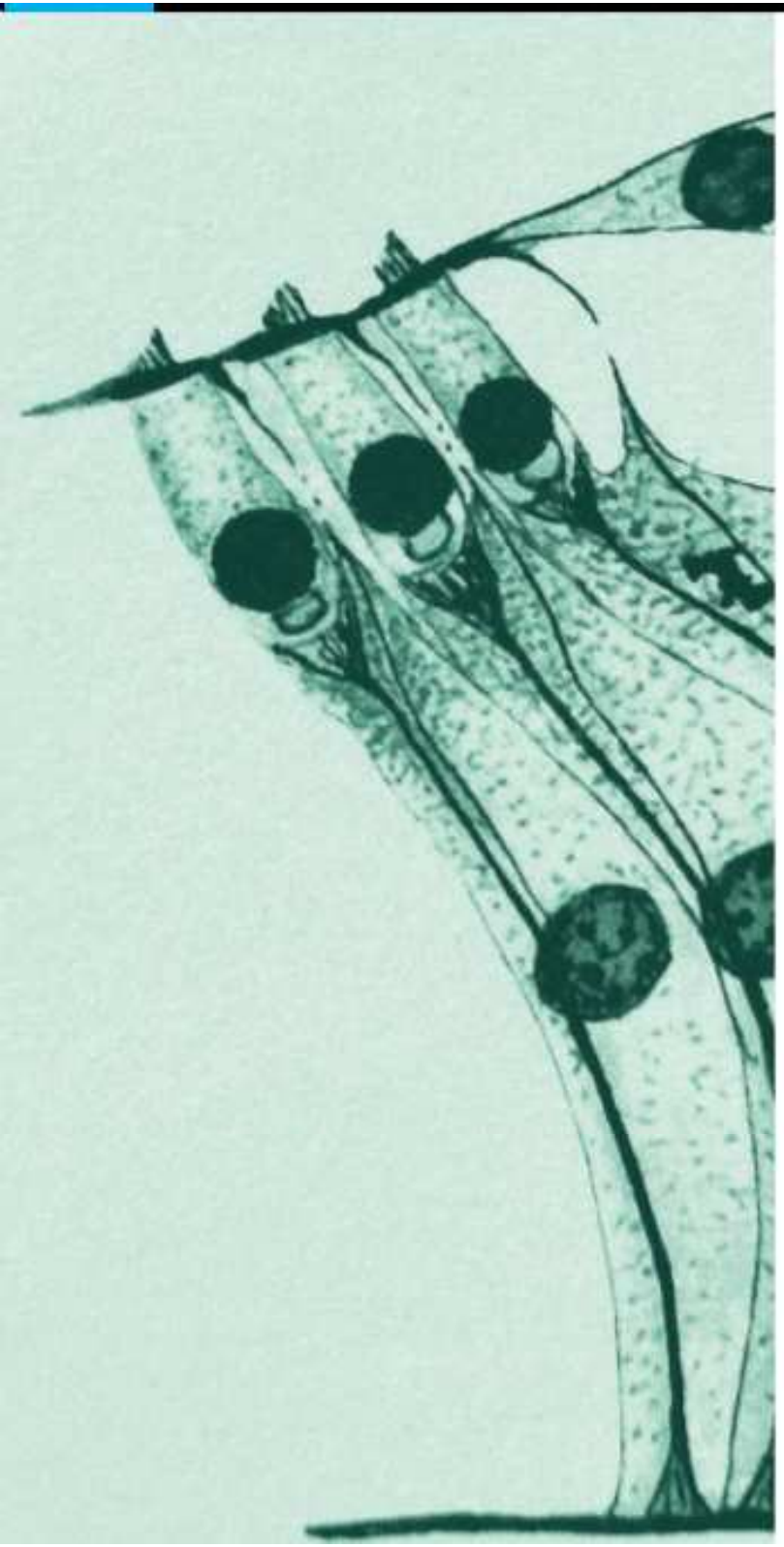
[1] *Survey conducted by MEDACorp, Inc. in April 2014*

# Key Keyzilen® Features

- Efficacy in various animal models
- Favorable safety profile
- Well-known and straightforward office-based procedure
- Reduce day-to-day impact of tinnitus
- Address high unmet medical need

# Key Upcoming Milestones

| | |
|---|---|
| **Q1 2018** | • Announce TACTT3 top-line results<br>• Start second AM-125 Phase 1 trial |
| **Q2 2018** | • Results from ASSENT trial with AM-111<br>• Discussions on AM-111 regulatory pathway |
| **Q3 2018** | • IND for AM-125 |
| **Q4 2018** | • Start AM-125 Phase 2 trial |



# Questions & Answers