UNIVERSITY of KANSAS
Department of
Otolaryngology
Head & Neck Surgery

Safety of Repeated Intratympanic AM-101 in Acute Inner Ear Tinnitus

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Hinrich Staecker, Department Otolaryngology Head and Neck Surgery, University of Kansas

Pavel Chrbolka, MediORL s.r.o, Prague, Czech Republic

Joong Ho Ahn, Asan Medical Center, Seoul, Korea

Thomas Meyer, Auris Medical AG, Basel, Switzerland

Michael Morelock, Alliance Clinical Research, Escondido, CA

Timothy Kramer, The Medical Arts Health Research Group, Kelowna, BC, Canada

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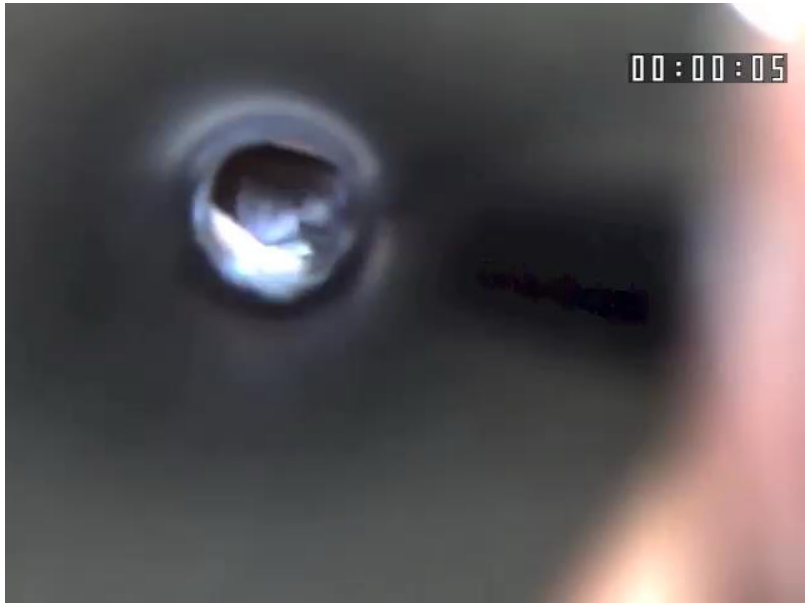
What is the safety profile of Intratympanic Injections?

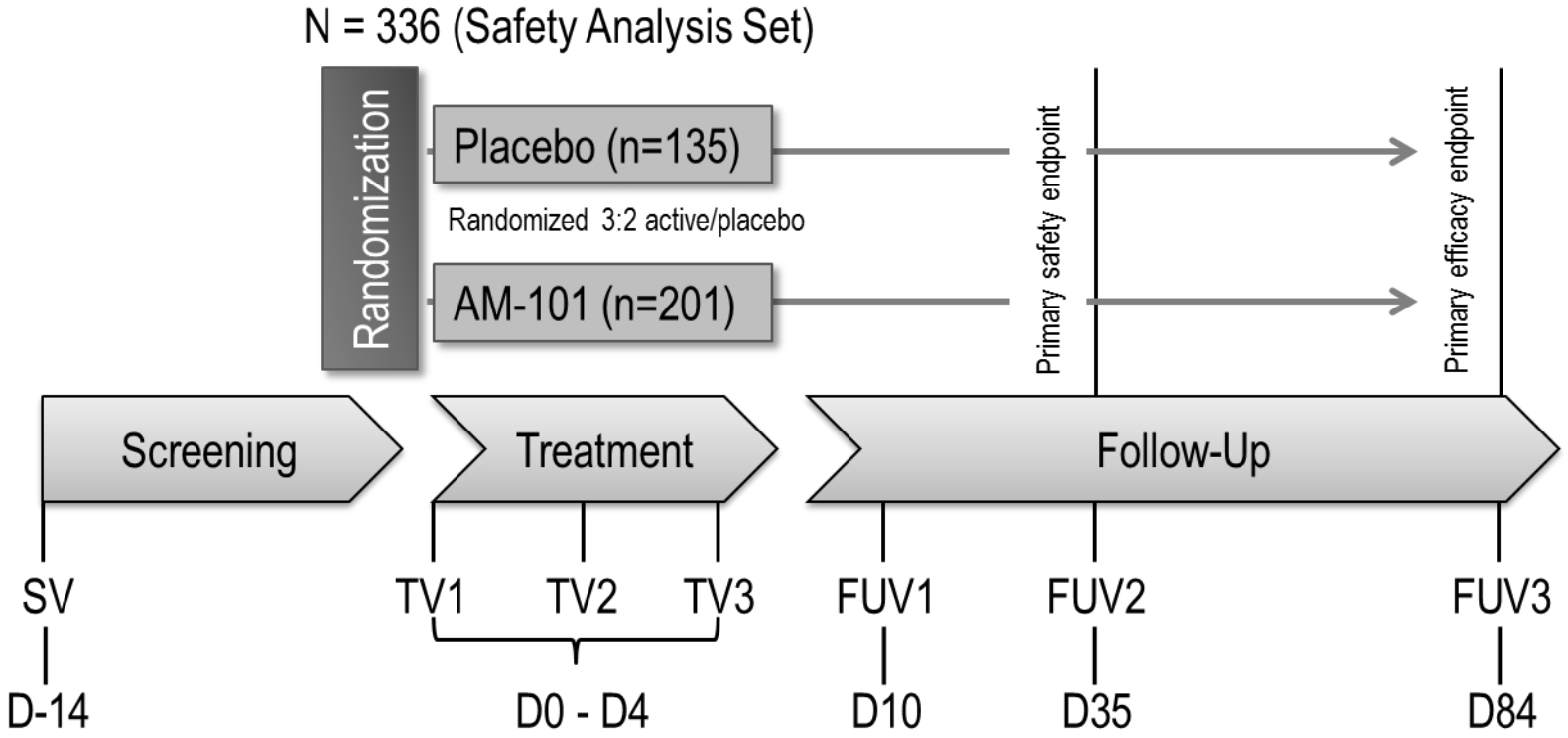
- Common procedure in ENT offices
- Procedure is generally considered safe and routine; Some old literature suggests increased risk of TM perforation
- Commonly used for local, off-label administration of corticosteroids or gentamicin
- Until recently, no drug approved for this route of administration
- Limited data on safety available especially when repeat administrations are performed



Safety Data Collected in TACTT2 Trial

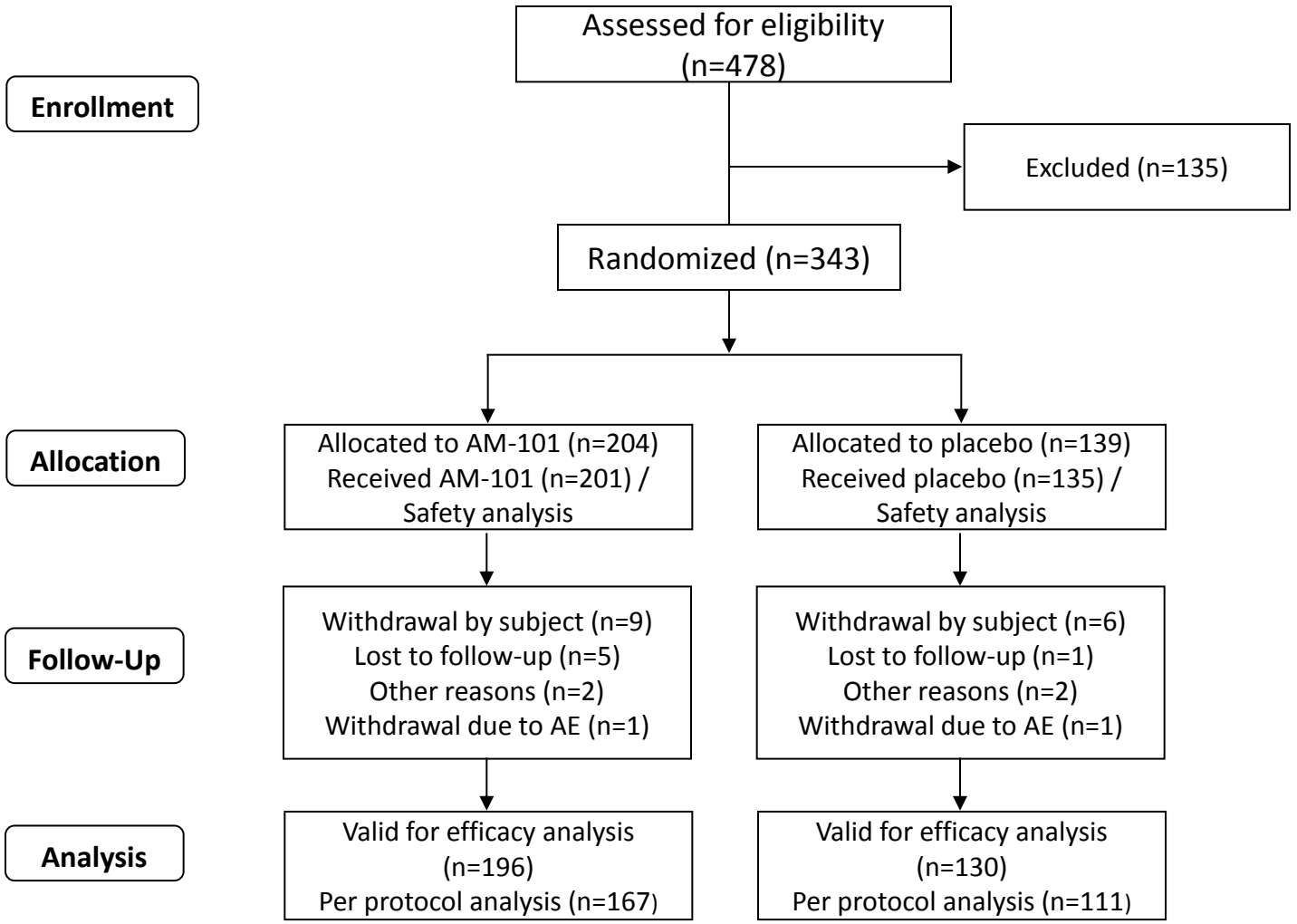
- Efficacy and Safety of AM-101 in the **T**reatment of **Ac**ute Peripheral **T**inni**t**us **2** (TACTT2)
  - AM-101 is a small molecule NMDA receptor antagonist formulated in hyaluronic acid and delivered via an intratympanic injection
- Systematic collection of safety data on repeated intratympanic injections
  - Approximately 1,000 intratympanic injection procedures
  - >60 secondary and tertiary sites in six countries
    - US, Canada, Czech Republic, South Korea, Turkey, Israel
  - Enrollment phase between March 2014 and March 2016

TACTT2 Trial Design Overview



- Acute peripheral tinnitus following traumatic cochlear insult (acute noise trauma, barotrauma, surgery trauma) or otitis media
- Up to 3 months from onset
- Documented tinnitus history

Patient Enrollment



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Demographics and Baseline Characteristics

Safety Population	AM-101 (n=201)	Placebo (n=135)	Total (n=336)
Age (mean)	43.4	44.2	43.7
Age (range)	18 to 74	20 to 73	18 to 74
Time from tinnitus onset (mean in days)	64.8	64.6	64.7
Average hearing threshold (4, 6 and 8 kHz)	27.4	28.7	28.0
Tinnitus treatment laterality			
Unilateral	119	76	195
Bilateral	82	59	141

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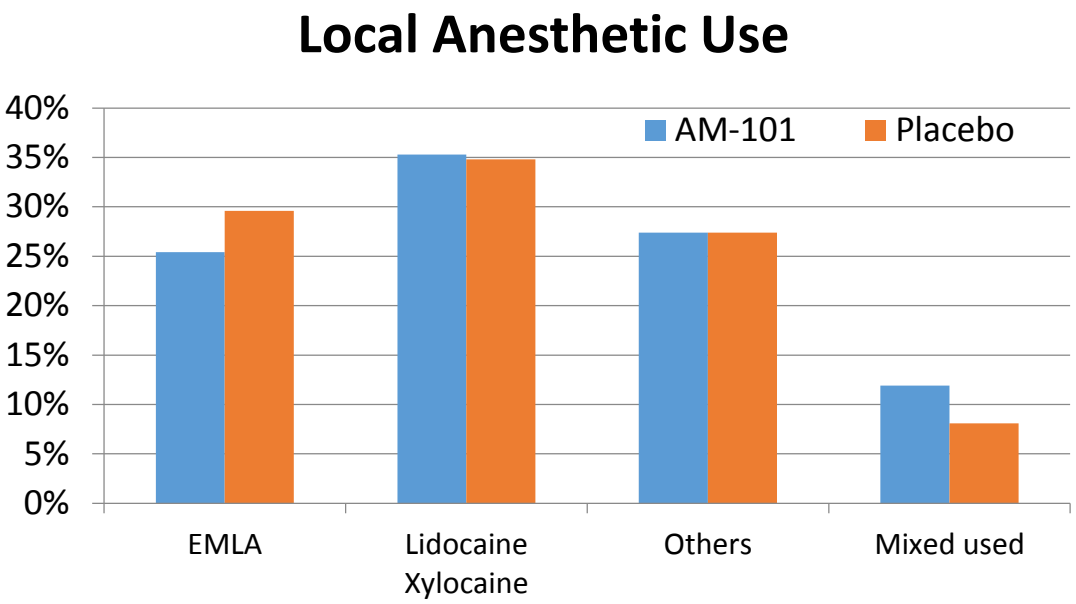
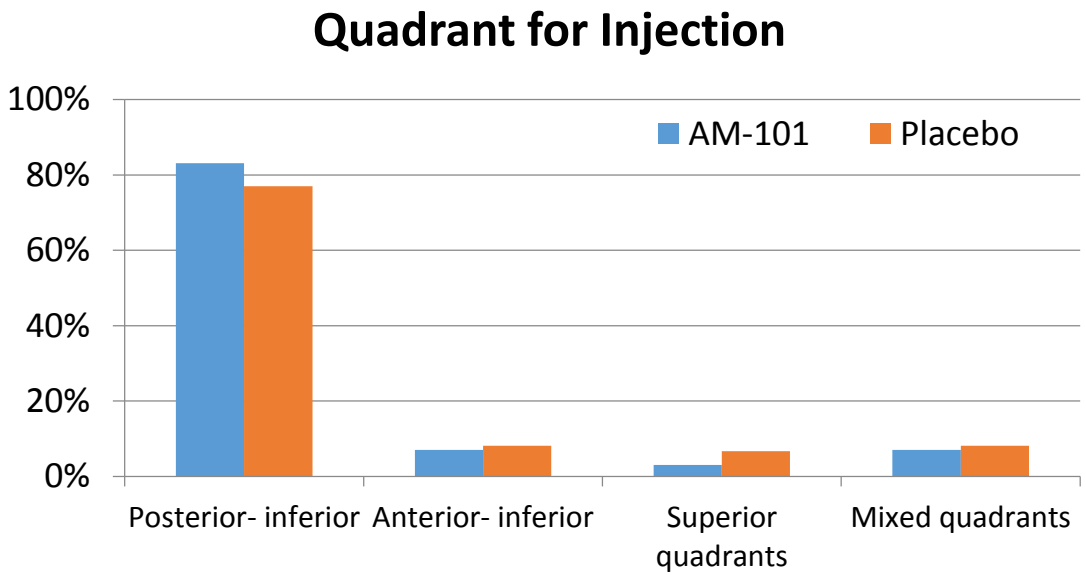
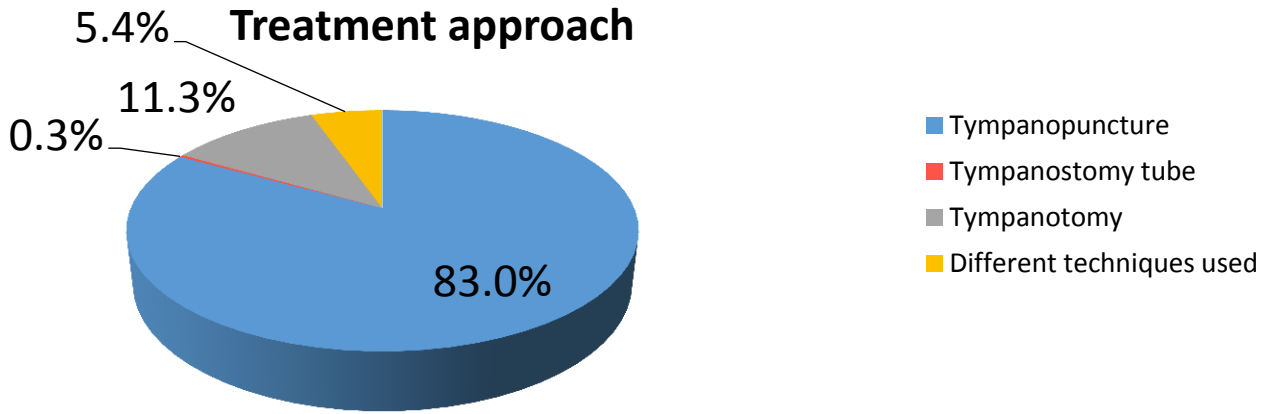
Safety Endpoints

- Primary: Average hearing deterioration of ≥15 dB from baseline to Day 35 in two contiguous frequencies
  - 15 dB considered as clinically relevant
  - Permanent threshold shift from intervention, if any, expected to show at Day 35
- Secondary:
  - Clinically relevant hearing deterioration from baseline to Day 10 and Day 84
  - Difference in occurrence of clinically relevant hearing deterioration from baseline to all post-baseline visits between treated and untreated contralateral ear (unilaterally treated patients only)
  - Adverse events
- Exploratory:
  - Hematology and biochemistry
  - Vital signs

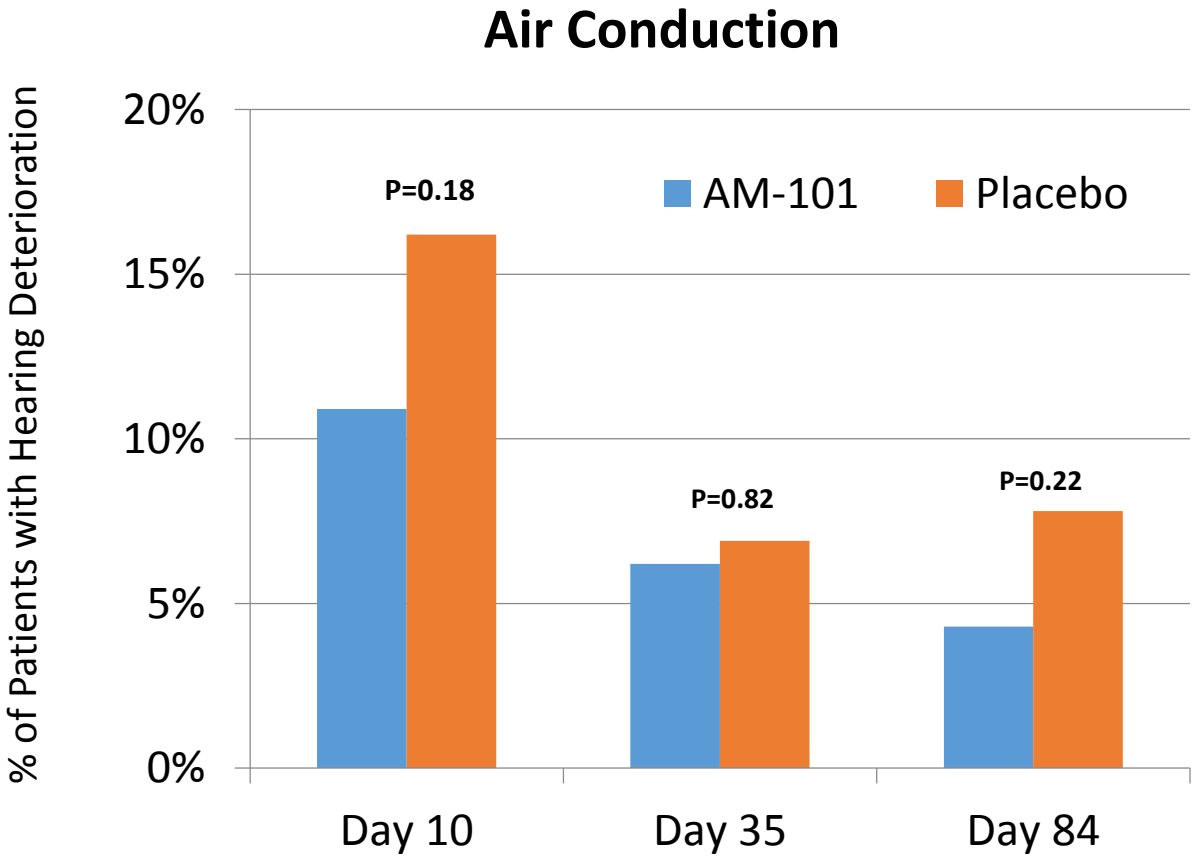
Injection Procedure (Safety Population)

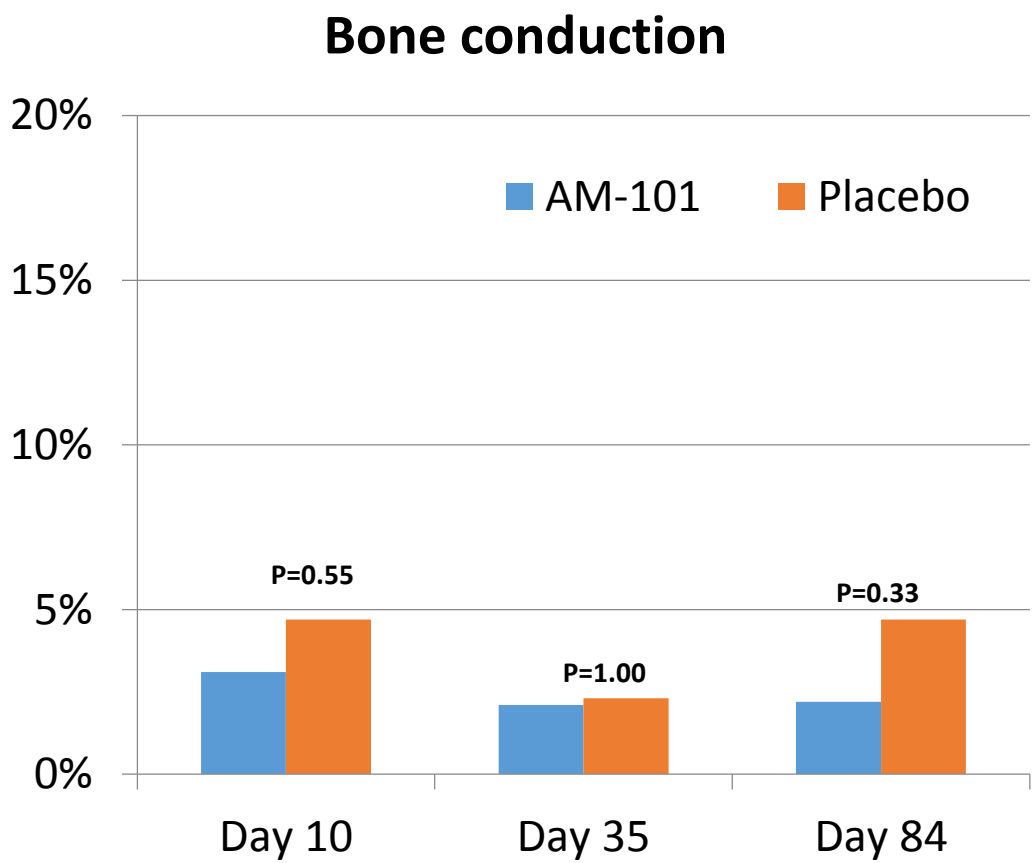






Clinically Relevant Hearing Deterioration





- No difference between treated and untreated ear in unilateral cases, except for placebo at Day 10
- Essentially no change from baseline to Day 84 at average of 4, 6 and 8 kHz:
  - +0.56 dB for AM-101 and +0.23 dB for placebo

Adverse Events

Number of Patients n(%)	AM-101 (n=201)	Placebo (n=135)	Total (n=336)
Any AEs	97 (48.3%)	50 (37.0%)	147 (43.8%)
TEAEs	90 (44.8%)	46 (34.1%)	136 (40.5%)
Drug-related AEs	14 (7.0%)	6 (4.4%)	20 (6.0%)
Procedure-related AEs	34 (16.9%)	22 (16.3%)	56 (16.7%)
SAEs	5 (2.5%)	1 (0.7%)	6 (1.8%)
AEs leading to withdrawal	1 (0.5%)	1 (0.7%)	2 (0.6%)
AEs leading to death	0	0	0

- All drug-related AEs were mild to moderate
- Procedure-related AEs were predominantly transient and mild to moderate
- All SAEs were isolated cases and not related to study drug or procedure
- Low rate of procedure-related infections
- AEs leading to withdrawal:
  - AM-101: Subjective worsening of hearing (procedure related)
  - Placebo: Blockage and discomfort (drug related)

Tympanic Membrane Closure

- Rapid closure of tympanic membrane perforation following injection
- Data confirmed results from previous Phase 2 trial

Closure observed at follow-up visit on:	**AM-101**	**Placebo**
Day 10	91.7%	93.1%
Day 35	99.0%	99.2%
Day 84	100.0%	100.0%

Summary of TACTT2 Safety Results

- AM-101 and intratympanic injection procedure were well tolerated
  - Over course of ~1,000 injections, no drug or procedure-related SAEs observed
  - Comparable drug- and procedure-related AE rate between AM-101 and placebo
  - Low occurence of transient procedure-related effects
  - Closure of tympanic membrane within one week in almost all patients

- Primary safety endpoint at Day 35 achieved
  - Occurrence of clinically relevant hearing deterioration low and not different between treatment groups
  - Normal variation since no difference to untreated contralateral ear

- Repeated intratympanic injections with AM-101 over 3-5 day period are safe and well tolerated

Acknowledgements

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