Sensorion

Hearing Loss Innovation: Expanding Frontiers in Protection & Restoration

Symposium

April 26, 2025

Hearing Loss Innovation: Expanding Frontiers in Protection & Restoration

April 26, 2025 - 11:30 am to 12:15 pm (UTC+1)

Moderator: Nawal Ouzren, Chief Executive Officer, Sensorion

- **Protecting Hair Cells, Preserving Hearing: The Potential of SENS-401**
  Prof. Yann Nguyen, Department of Otolaryngology-Head & Neck Surgery, Pitié-Salpêtrière Hospital, Paris, France
- **From Bench to Bedside: The Journey of GJB2 & OTOF Gene Therapies for Children with Severe to Profound Hearing Loss**
  - Advancing Gene Therapy for OTOF-Related Hearing Loss in Young Children
    Prof. Natalie Loundon, Pediatric Department of Otolaryngology-Head & Neck Surgery, Necker Enfants Malades Hospital, Paris, France
  - Developing Novel Gene Therapy for Hereditary Hearing Loss in Patients with GJB2 Mutations
    Laurent Désiré, PhD, Head of Preclinical Development, Sensorion
- **Q&A Session & Conclusion:** Nawal Ouzren, Chief Executive Officer, Sensorion

Sensorion

Protecting Hair Cells, Preserving Hearing: The Potential of SENS-401

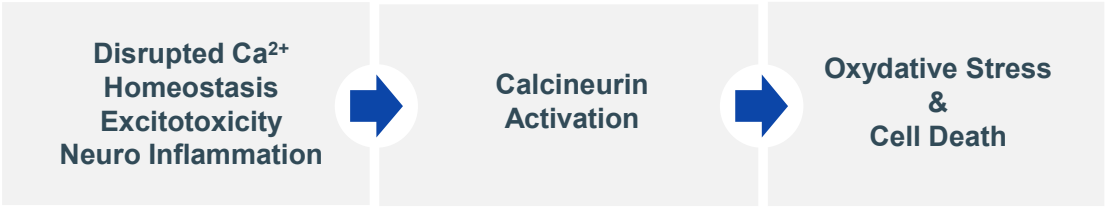
Yann Nguyen

AP-HP, GHU « Sorbonne Université » ; site Pitié Salpêtrière ; DMU « ChIR » Chirurgie Innovation et recherche, Service ORL, Paris.
IHU Institut Reconnect, équipe TI2S « Technologies innovantes et thérapies translationnelles de la surdité ».

SENS-401 AS A POTENTIAL OTOPROTECTIVE AGENT

SENS-401 Acts as A Specific Antioxydant Agent in the Cochlea Through A Dual Mechanism

	SENS-401 (® Azasetron)
Therapeutic Class	Selective 5-HT3 receptor antagonist
Molecular Structure & Weight	$C_{23}H_{26}ClN_3O_6S$ 507.98
Biodistribution	Longer and higher inner ear tissue exposure compared to other setrons
PK Interactions	No impact on cisplatin activity *in vivo* (animal models) & *in vitro* (cells lines) Not a substrate of CYP450
Half-Life Ranges	12 to 14h
Route of Administration	Oral, BID
MOA	Selective 5-HT3 receptor antagonist & calcineurin antagonist
Animal Model	Significantly reduces ciplatin hearing loss & enhances OHC survival in rats



Petremann et al. Otol Neurotol: Oral Administration of Clinical Stage Drug Candidate SENS-401 Effectively Reduces Cisplatin-induced Hearing Loss in Rats. 2017.
Data on file.

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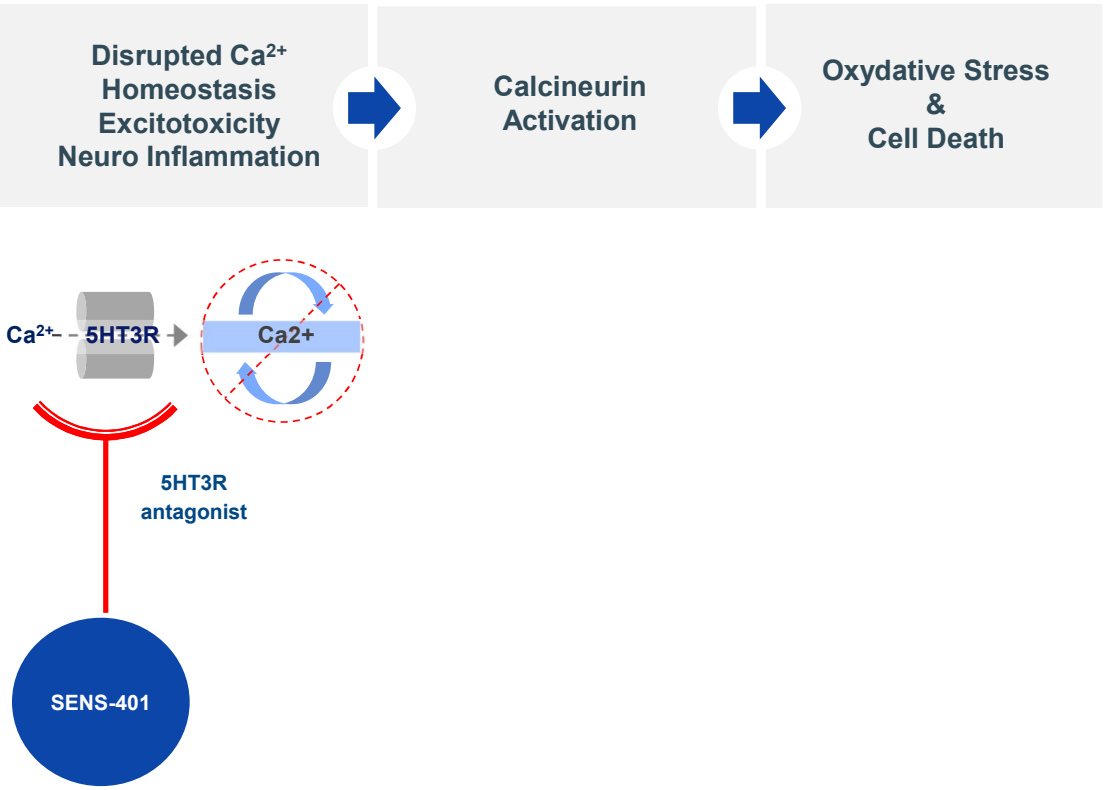

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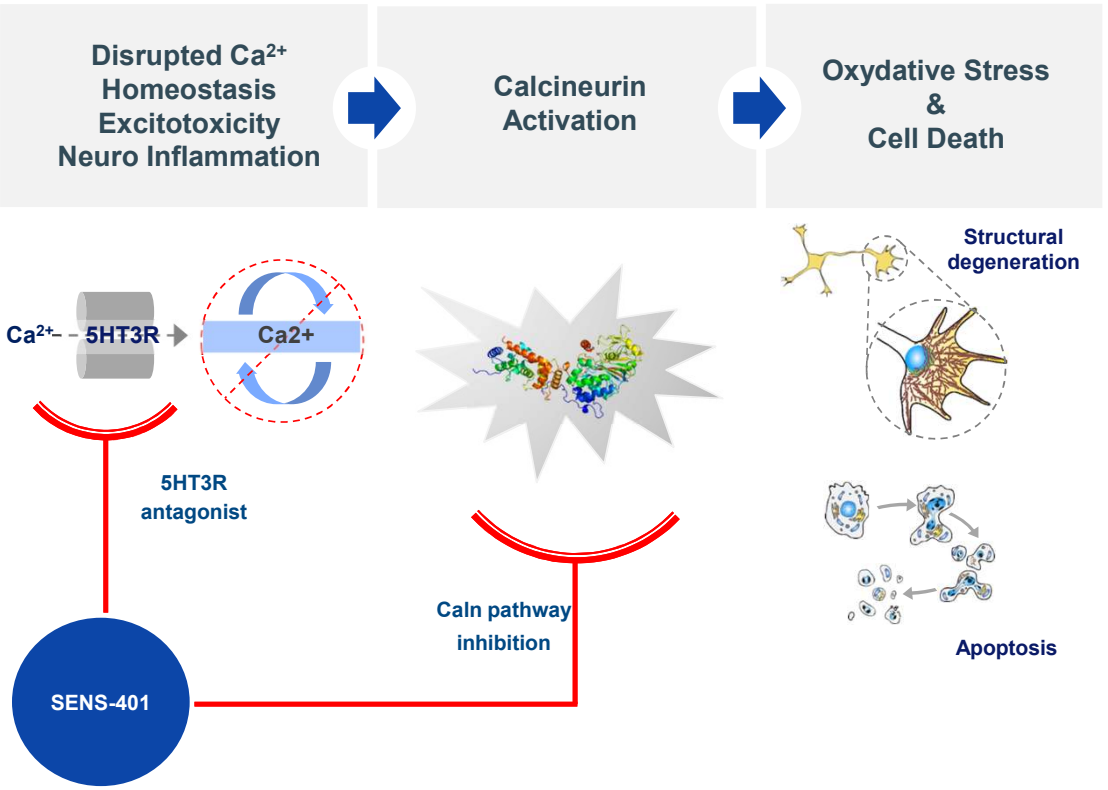

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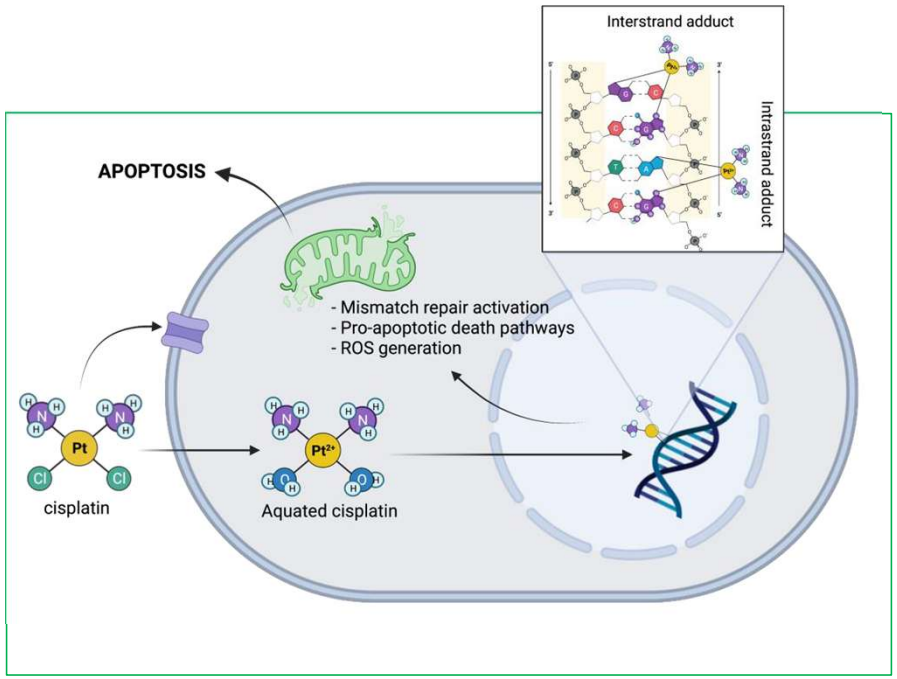
CISPLATIN-INDUCED OTOTOXICITY MECHANISM OF ACTION

NOTOXIS

Cisplatin-Induced Cochlear Inflammation & Oxydative Stress



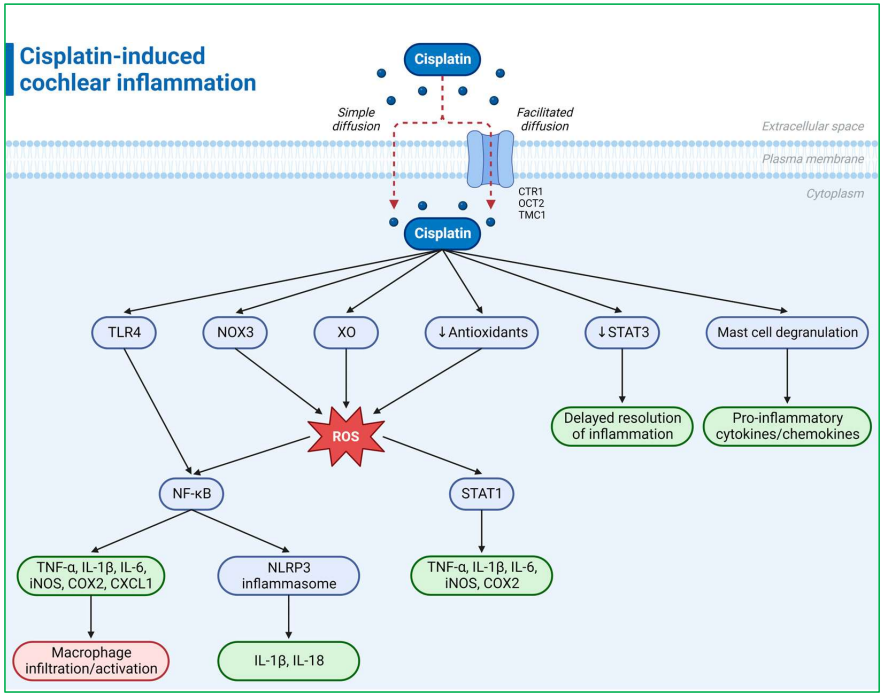
Uptake

Accumulation

Overload ROS

Damage to cellular DNA, lipids & proteins

Inflammation & apoptosis



Cisplatin-induced inflammation & oxydative stress lead to hair cell death

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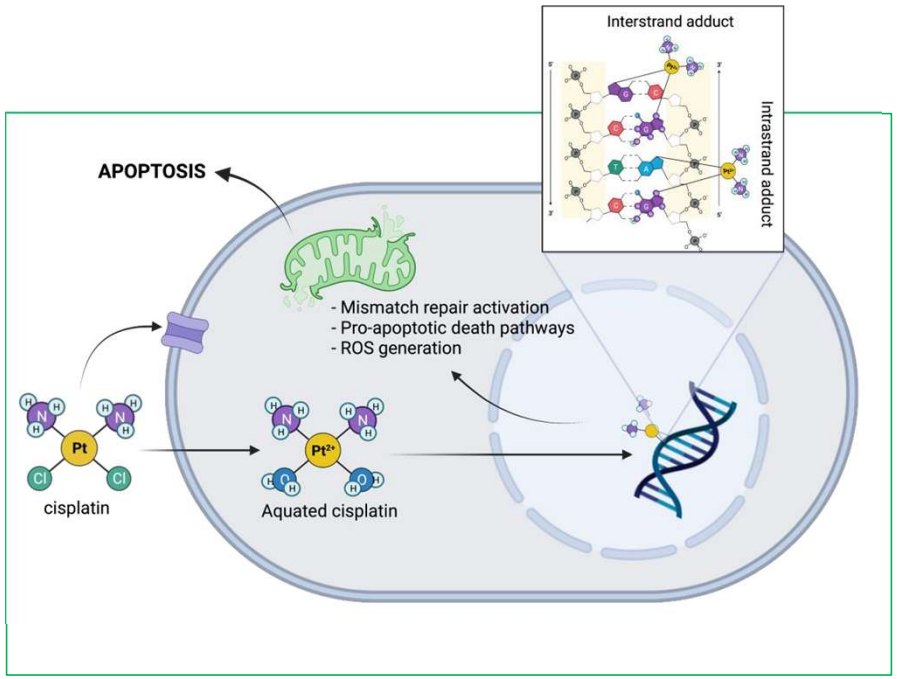

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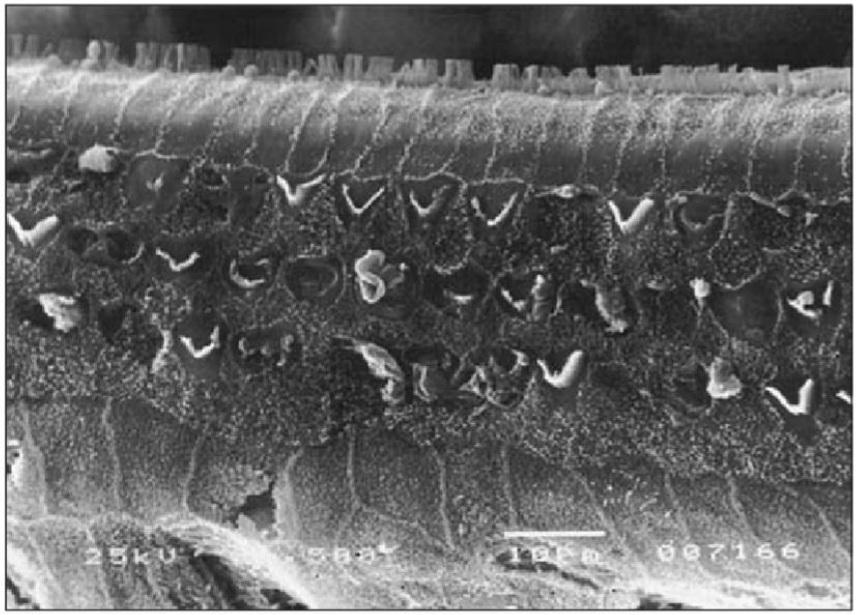

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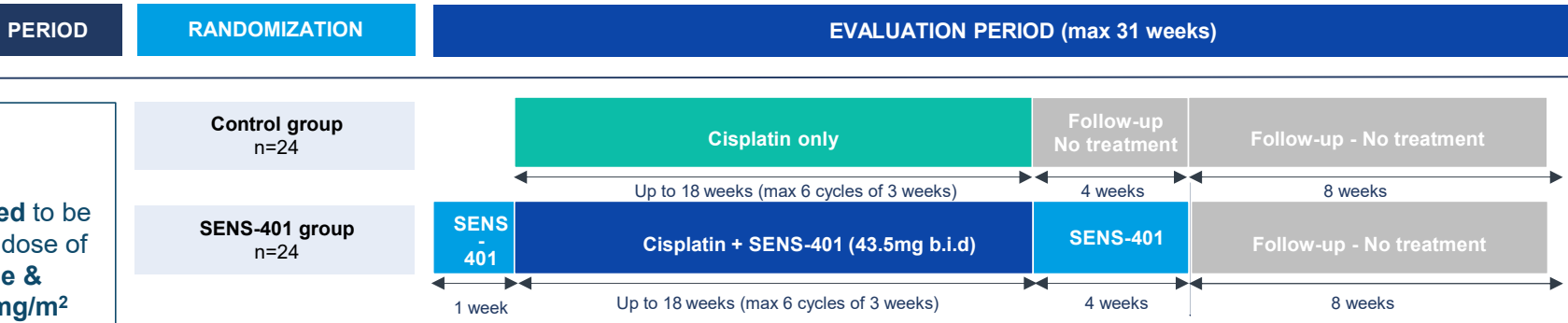
STUDY DESIGN & OBJECTIVES

NOTOXIS

A Phase IIa, Multicenter, Randomized, Controlled, Open-label Study to Evaluate the Efficacy of SENS-401 to Prevent the Ototoxicity Induced by Cisplatin in Adult Subjects with a Neoplastic Disease

- **Adults ≥** 18 years
- **Adequate hearing levels**
- **Neoplastic disease planned** to be treated with cisplatin with a dose of **at least 70 mg/m² per cycle & a cumulative dose ≥ 210 mg/m²**



Primary Endpoint (4 weeks after the last cisplatin dose)

- Maximum change from baseline in Pure Tone Audiometry (PTA) across three consecutive frequencies within the 0.5-12.5 KHz range

Secondary Endpoints (4 and 12 weeks after the last cisplatin dose)

- Maximum change from baseline in Pure Tone Audiometry (PTA) across three consecutive frequencies within the 0.5-12.5 KHz range
- CTCAE grading
- Change from baseline of speech discrimination score (noise & quiet)
- Change from baseline in THI questionnaires

Clinicaltrials.gov ID: NCT05628233- Protocol SENS-401-202 –EudraCT number : 2021-002705-10

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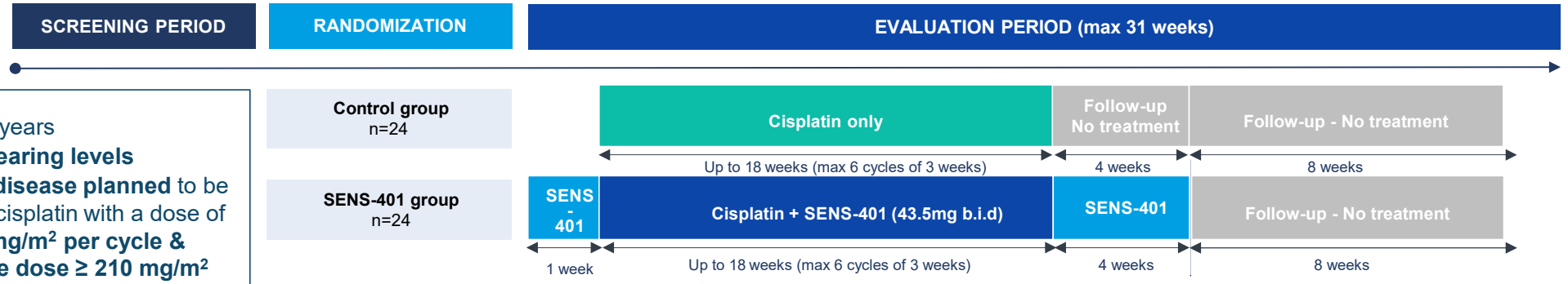

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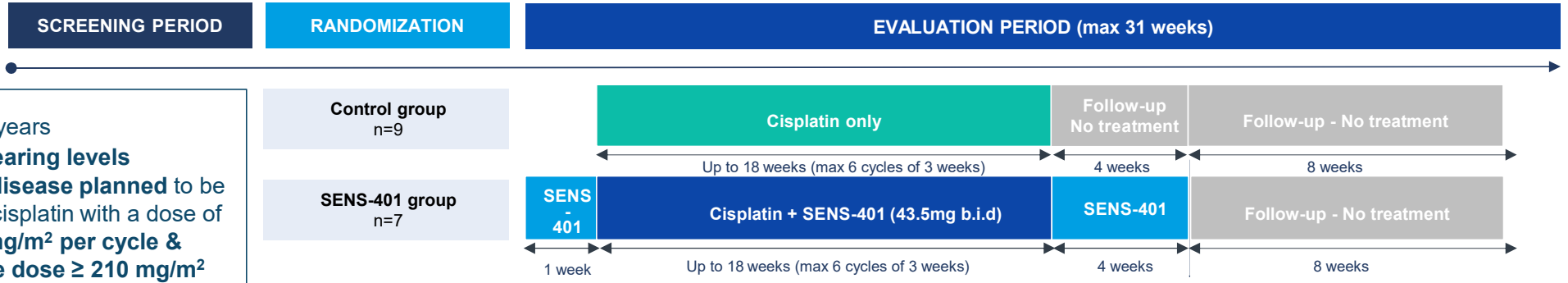

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Preliminary analysis on 16 patients (4 weeks after last cisplatin dose)

Clinicaltrials.gov ID: NCT05628233- Protocol SENS-401-202 –EudraCT number : 2021-002705-10

PATIENT CHARACTERISTICS

Demographic Characteristics at Baseline

Demographic Data		SENS-401 Group (n=7)	Control Group (n=9)	Total Patients (n=16)
Gender	Male (n)	7	7	14 (87.5%)
	Female (n)	0	2	2 (12.5%)
Mean Age (years)		57.3	56.1	56.6

(Extraction date 31 July 2024)

Mainly urological and head & neck cancers,
with a similar distribution between the two groups

Majority of male, representing 88% of the total population
Mean age is comparable between the 2 groups

PATIENT CHARACTERISTICS

NOTOXIS

Demographic Characteristics at Baseline & Cisplatin Exposure

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Group	n	Average Cis. Cumulative Dose (mg/m^2)	Number of Cycles
Control	9	305.6	3.3
SENS-401	7	342.2	4.0

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Mainly urological and head & neck cancers,
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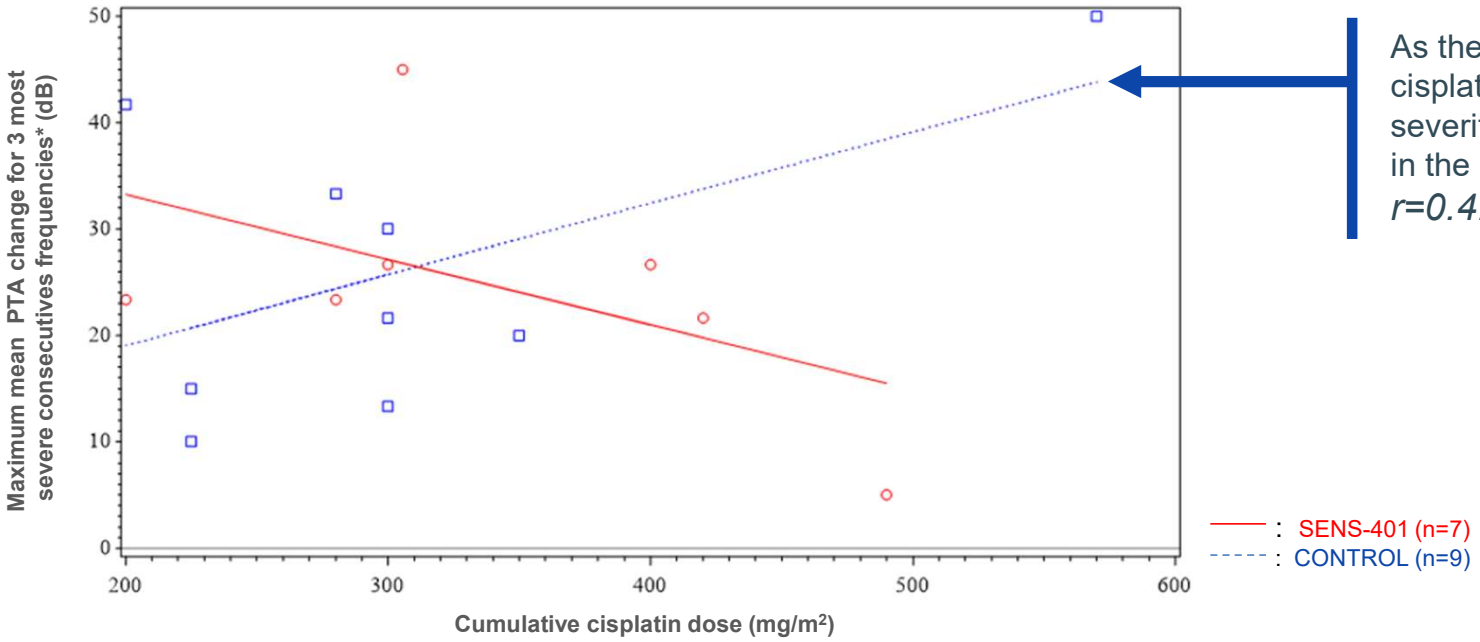
Mainly urological and head & neck cancers,
with a similar distribution between the two groups

Higher doses of cisplatin in the SENS-401 group compared to control

STUDY DESIGN & OBJECTIVES

NOTOXIS

Maximum Change From Baseline in PTA 4 Weeks After the Last Cisplatin Dose



As the cumulative dose of cisplatin increases, severity of ototoxicity observed in the control group escalates
r=0.42

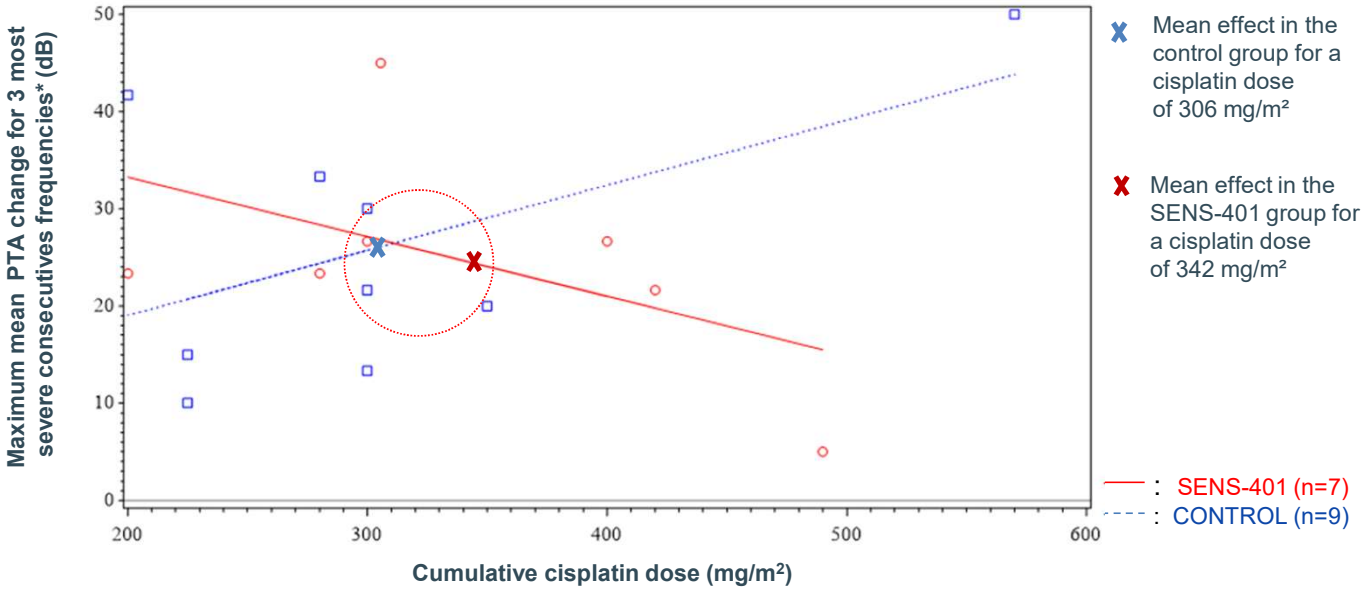
Cumulative dose of cisplatin is a key factor of ototoxicity severity

** frequencies within the 0.5-12.5 KHz range*

STUDY DESIGN & OBJECTIVES

NOTOXIS

Maximum Change From Baseline In PTA 4 Weeks After the Last Cisplatin Dose (Primary Endpoint)



Groups	n	Variables	Mean	SD
Control	9	Cisplatin dose	**305.6**	110.0
		PTA change	**26.1**	13.6
SENS-401	7	Cisplatin dose	**342.2**	98.7
		PTA change	**24.5**	11.7

Mean PTA change is similar between the SENS-401 and control group
However, the cisplatin exposure levels were different

** frequencies within the 0.5-12.5 KHz range*

CONCLUSIONS

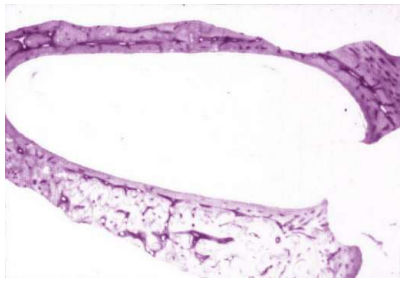
NOTOXIS

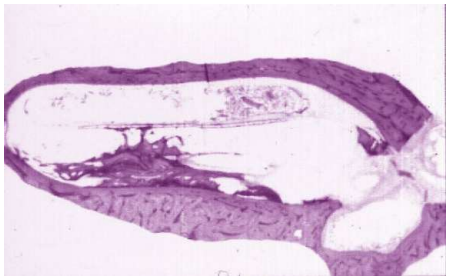
- **Cumulative dose** of cisplatin is a **key factor** of ototoxicity severity
- Based on preliminary data, **no significant difference** observed on ototoxicity measured by **PTA change** or CTCAE grading, **however SENS-401 treated group received higher cumulative dose of cisplatin compared to control**
- Patients with **higher exposure** to cisplatin **may benefit the most** from **SENS-401's otoprotective effect**
- **Good safety profile of SENS-401** is confirmed, with the drug being administered for a duration of up to **23 weeks**
- Additional analysis will be conducted with more patients at the end of the study

VARIOUS MECHANISMS RESULT IN RESIDUAL HEARING LOSS

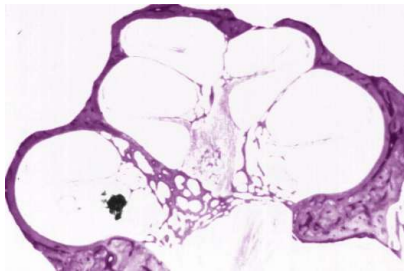
- **Mechanical disruption of intracochlear structures** *(basilar membrane, spiral ligament, modiolar wall,spiral osseous lamina)*
- **Inflammatory process** *(fibrosis in perilymphatic space)* and secondary apoptosis
- **Disturbance of fluid balance** *(endolymphatic or perilymphatic)*
- **Acute or chronic bacterial infection**
- **Cochlear mechanism dysfunction**

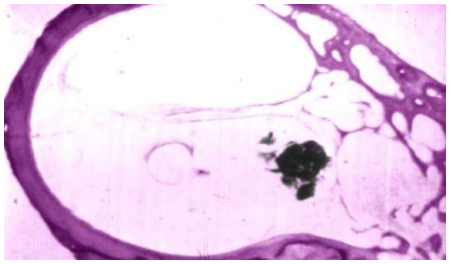
Mechanical disruption of intracochlear structures





Inflammatory process and secondary apoptosis





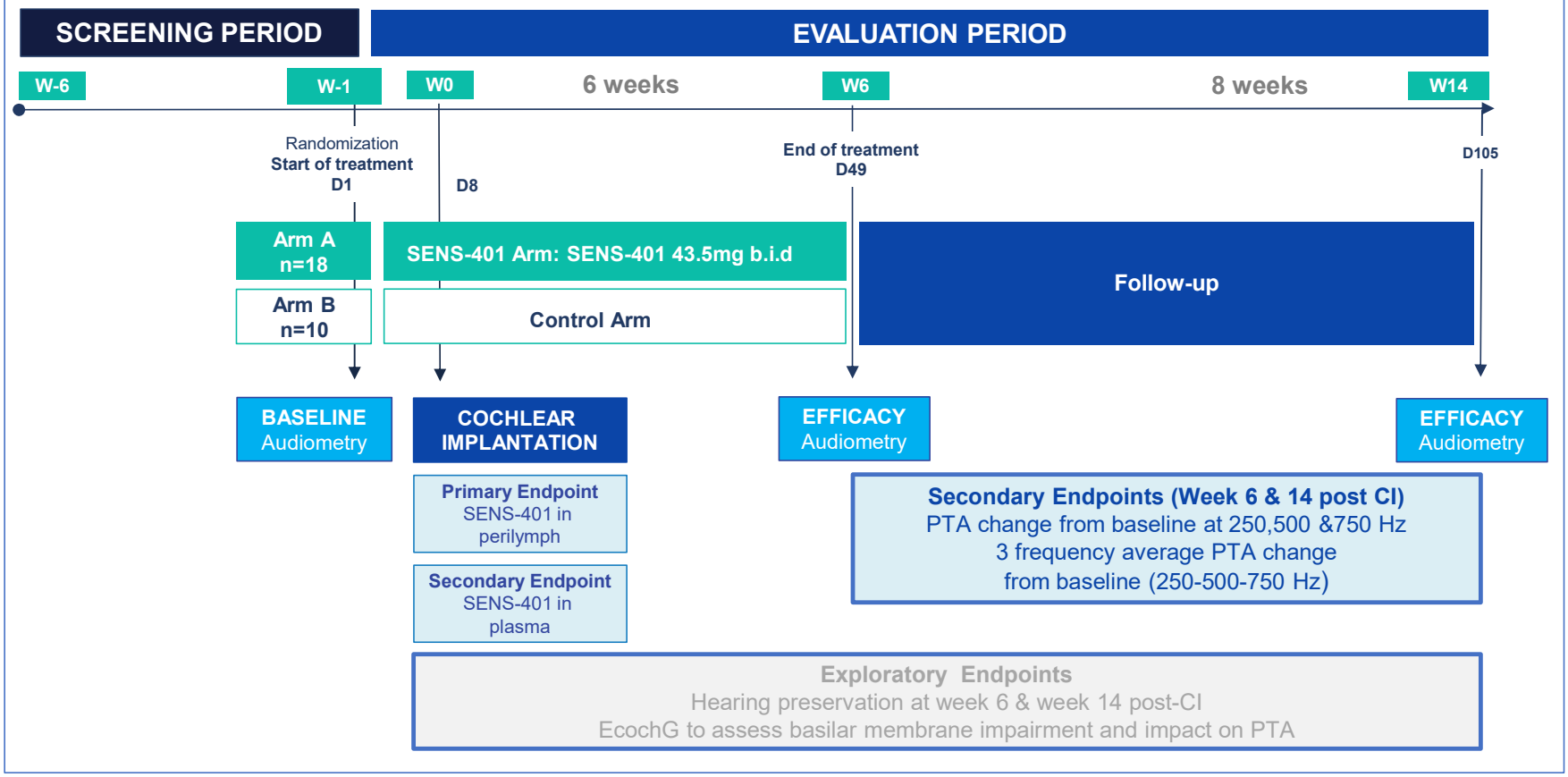
RESIDUAL HEARING PRESERVATION IN ADULTS

Study Design & Objectives

- **Adults** ≥18 yrs
- **Residual Hearing** (≥80 dB at 500 Hz)
- **Cochlear Implant Indication** with Cochlear's Slim Straight Electrode (CI 622)

- **Exclusion**: Moderate to severe renal impairment (creatinine clearance ≤60 ml/min)

A Phase 2a, Multicenter, Randomized, Controlled, Open-label Study to Evaluate the Presence of SENS-401 in the Perilymph after 7 days of Repeated Oral Administration in Adult Participants Scheduled for Cochlear Implantation



Clinicaltrials.gov ID: NCT05258773 - Protocol SENS-401-203 -EudraCT Number - 2021-006615-28.

RESIDUAL HEARING PRESERVATION IN ADULTS

Patient Characteristics at Baseline

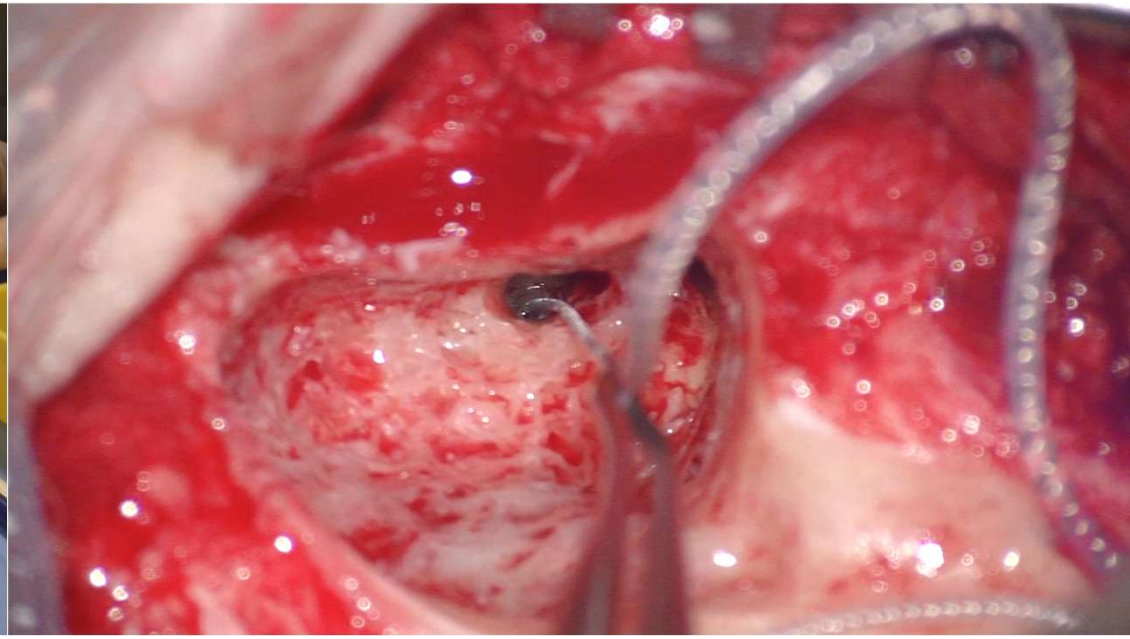
		Treated Group (n=17)	Control Group (n=10)
Age (mean)			
Gender (n) (%)	Female	11 (65%)	6 (60%)
	Male	6 (35%)	4 (40%)
Mean PTA Hearing Threshold (dB HL) at 500 Hz		67	61

Cochlear implant indications were genetic/hereditary (n=5, 18%), infection related (n=2, 7%), noise exposure (n=3, 11%), other diseases including autoimmune, neuropathy, Ménière's disease (n=3, 11%) and 14.5% of unknow causes (including age-related)

Patient baseline characteristics are well-balanced across the two groups

PERILYMPH SAMPLING PROTOCOL

Perilymph sampling technique with the courtesy of Pr Steven O'Leary



Cochlear CI622 array insertion (CHU Pitié Salpêtrière, AP-HP)

RESIDUAL HEARING PRESERVATION IN ADULTS

Primary Endpoint: Presence of SENS-401 in the Perilymph

	Treated with SENS-401 (n=16) n (%)
SENS-401 levels ≤ LLOQ	0
SENS-401 levels > LLOQ	14*(100)

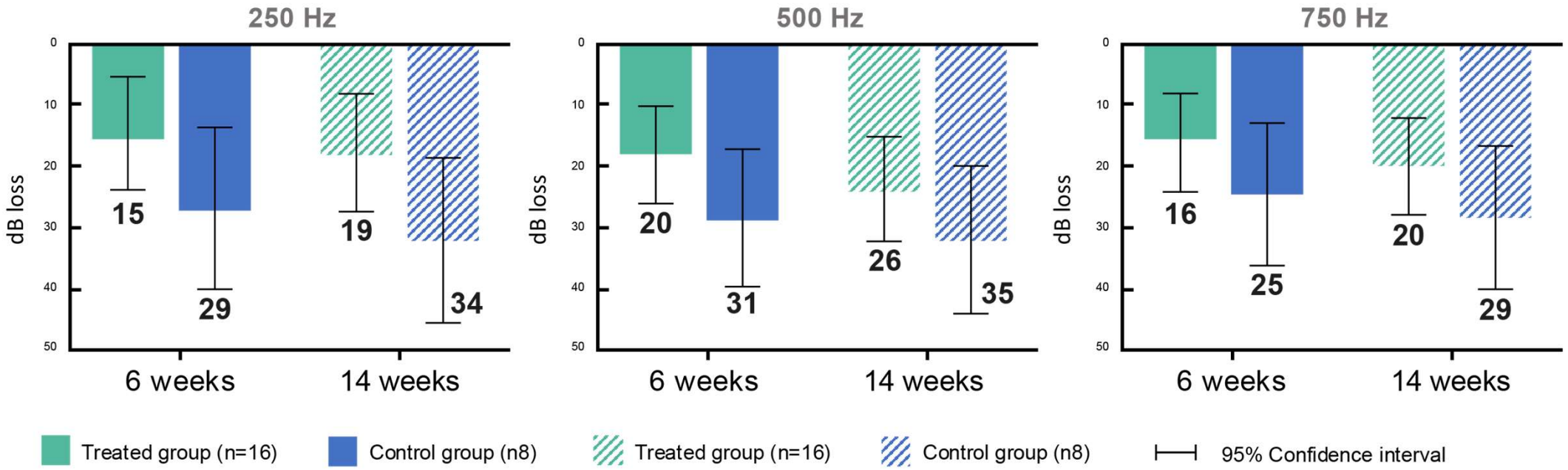
**Among the 16 participants who underwent surgery, 15 have a perilymph samples and 14 samples were analyzable*
**LLOQ define by a specific method developed for SENS-401*
***The sampling times for SENS-401 levels in the perilymph were standardized in relation to the last oral dose of treatment*

- **SENS-401 presence in 100% of the analyzable perilymph samples & above the lower limit of quantification (LLOQ)**
- **Ability of SENS-401 to cross labyrinthine barrier demonstrated**

Clinicaltrials.gov ID: NCT05258773 - Protocol SENS-401-203 -EudraCT Number - 2021-006615-28.

RESIDUAL HEARING PRESERVATION IN ADULTS

Secondary Endpoint: PTA Change at Week 6 & 14 Post-CI



- After 7 weeks of SENS-401 treatment (6 weeks post-CI), reduction in residual hearing loss is consistently better across all frequencies in the SENS-401 treated group
- This protective effect is maintained 8 weeks after SENS-401 discontinuation (14 weeks post-CI)

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RESIDUAL HEARING PRESERVATION IN ADULTS

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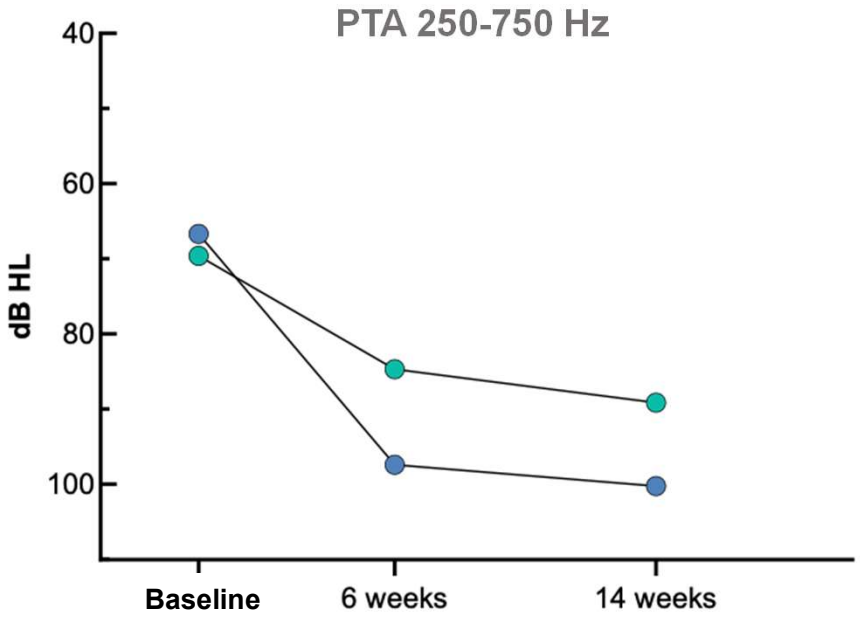

Treated Group (n=15)

Control Group (n=7)

ANCOVA analysis and descriptive statistics
p-value of 0.0567
(LS mean difference of -14.40 between Arm A and Arm B change from baseline suggested a trend towards statistical significance)

- **Residual hearing loss is lower in patients treated with SENS-401 at 6 weeks post-CI and 8 weeks after SENS-401 discontinuation (14 weeks post-CI)**
- **Resulting in a preservation of 14dB for the three-frequency average (250-750 Hz)**

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RESIDUAL HEARING PRESERVATION IN ADULTS

Conclusions

- Primary objective achieved: SENS-401 crosses the labyrinthine barrier **and reaches the perilymph fluid**
- **Clinically relevant reduction of residual hearing loss in SENS-401 treated group** compared to the control group at 6 weeks after cochlear implantation
- Complete hearing preservation is exclusively observed in the patients treated with SENS-401 at **6 weeks post-CI**
- Eight weeks after discontinuation of SENS-401, the **hearing protective effect is maintained**
- The 7-week SENS-401 exposure confirmed a favorable safety profile **consistent with other studies**
- These results support the continued clinical development of SENS-401 for hearing preservation in patients who will receive a cochlear implant

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Hearing Loss Innovation: Expanding Frontiers in Protection & Restoration

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Moderator: Nawal Ouzren, Chief Executive Officer, Sensorion

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- **Q&A Session & Conclusion:** Nawal Ouzren, Chief Executive Officer, Sensorion

Sensorion

Advancing Gene Therapy for OTOF- Related Hearing Loss in Young Children

Natalie LOUNDON
ENT Department Necker Enfants malades Hospital,
Paris, France

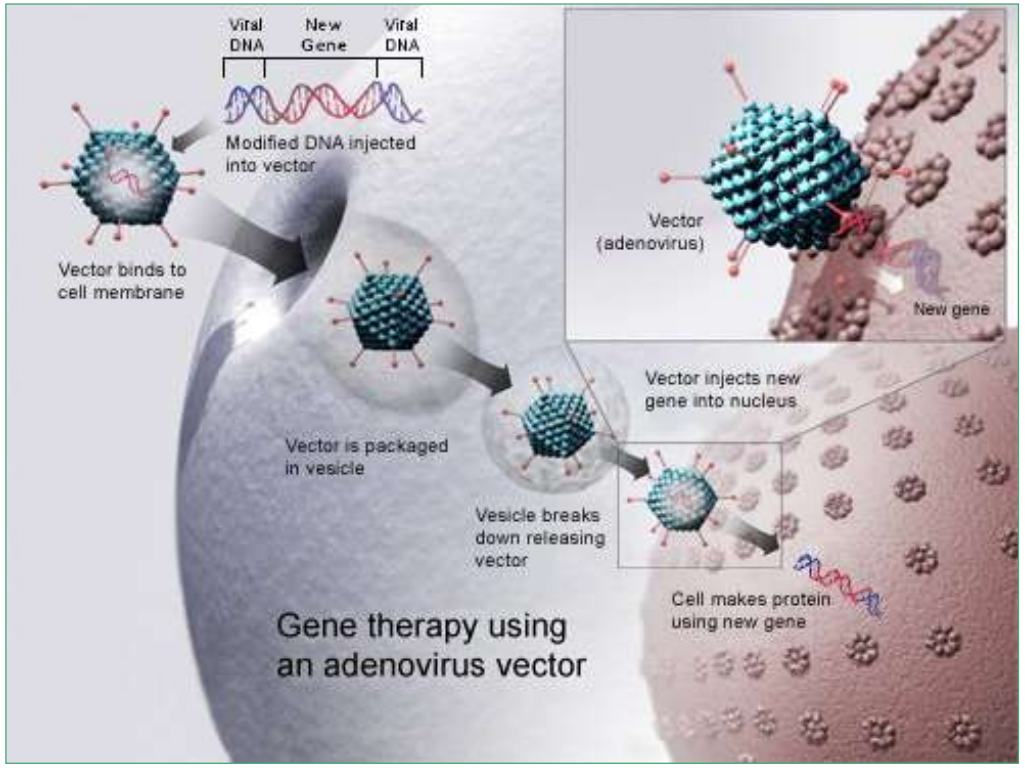
Audinnove project

Consultant for Sensorion

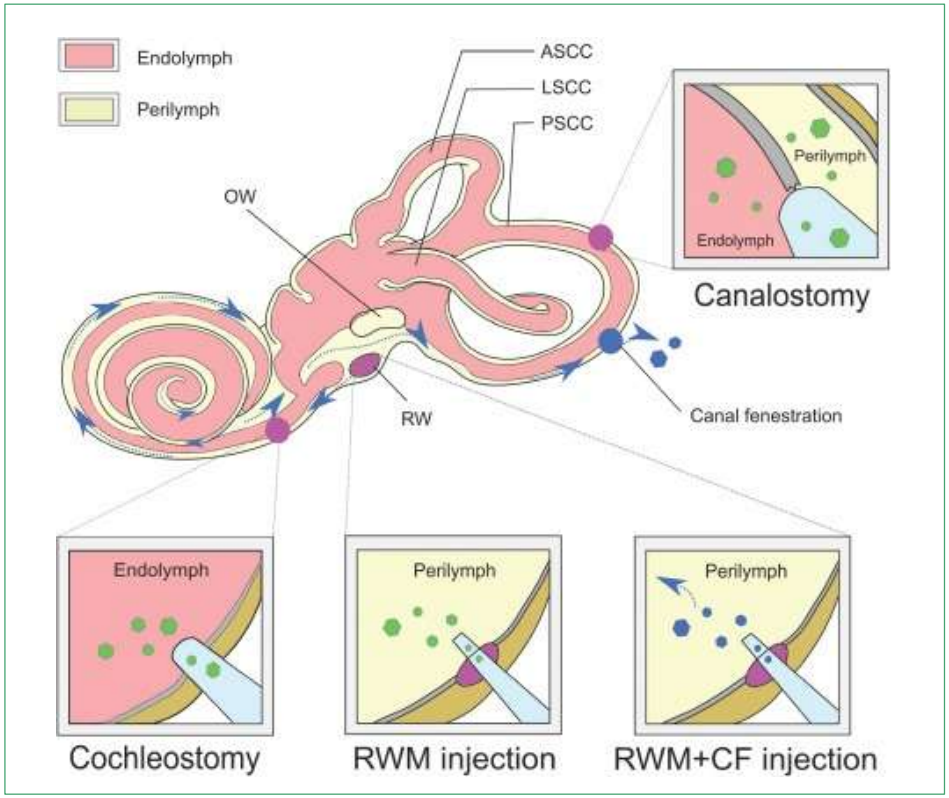
Gene Therapy in Human

- ***In Vivo* or *Ex Vivo***
  - ***In Vivo*:** The vector carrying the therapeutic DNA is directly injected into the subject
  - ***Ex Vivo*:** The cells to be treated are extracted and reinjected once treated (onco-hematology)

- **Pathologies treated with GT using Associated Adenovirus (AAV) as vector**
  - Beta-thalassemia, Haemophilia
  - AMD, Retinitis
  - Infantile Spinal Atrophy
  - Achondroplasia



Gene Therapy for the Inner Ear



Omichi *et al.*, Hum Mol Genet., 2019.

The inner ear is a good target for GT

- Isolated organ
  - *Limited diffusion*
  - *Limited off target effect*
- Surgical routes

The approaches

- Cochleostomy/Round, Oval window/Canalostomy
- Combined routes

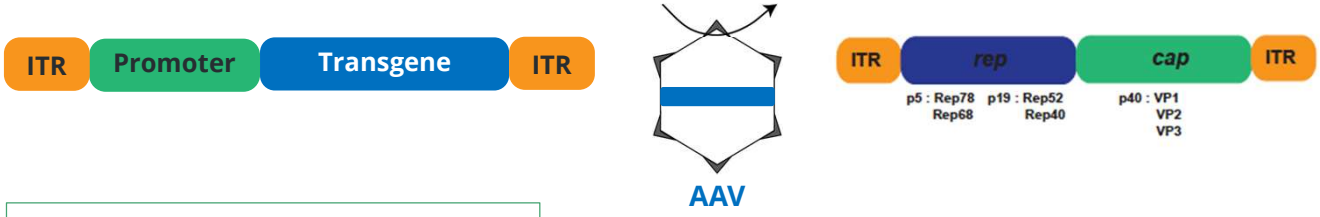
Volume

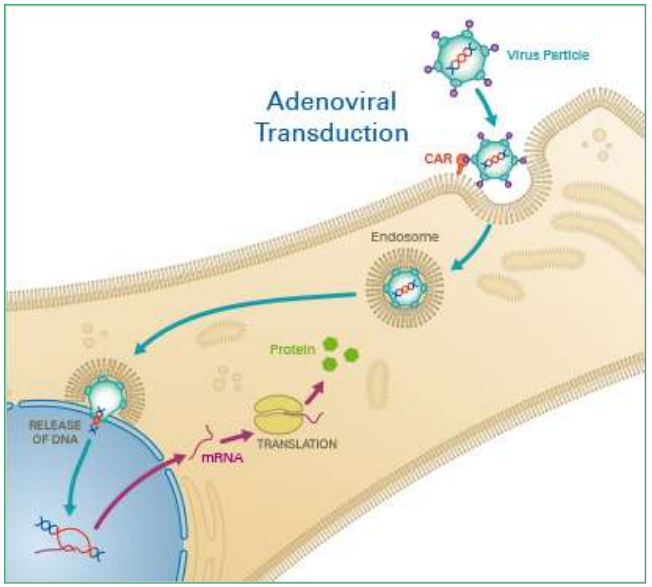
- 40-150µl (15 drops)

Associated Adenovirus (AAV)

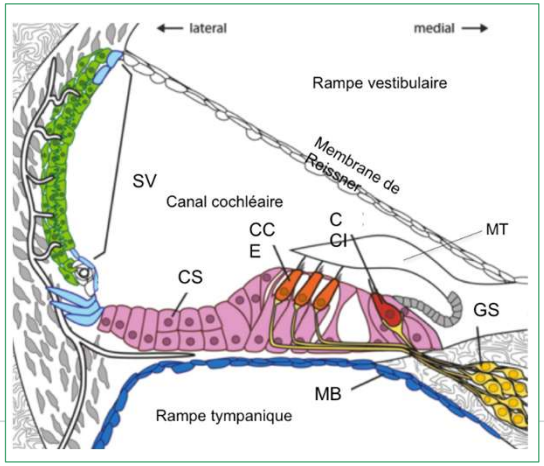
Vector

- Non-pathogenic
- Low immunogenicity
- 12 serotypes & combinations ➔ Target cells, tolerance





AAV gene therapy principle



Hair Cells (CC)

- Usher, Otoferlin, Stereocilin

Stria Vascularis Cells (SV)

- Waardenburg

Supportive Cells (CS)

- Connexin 26

➔ Work on mice models

Towards the Clinical Application of Gene Therapy for Genetic Inner Ear Diseases.
J. Clin. Med. 2023, Institut Pasteur, Institut Audition

Fondation pour l'audition
INSTITUT PASTEUR
Sensorion
Investir l'avenir
Hôpital Necker Enfants malades AP-HP

Auditory Neuropathy Spectrum Disorder

Clinical aspects

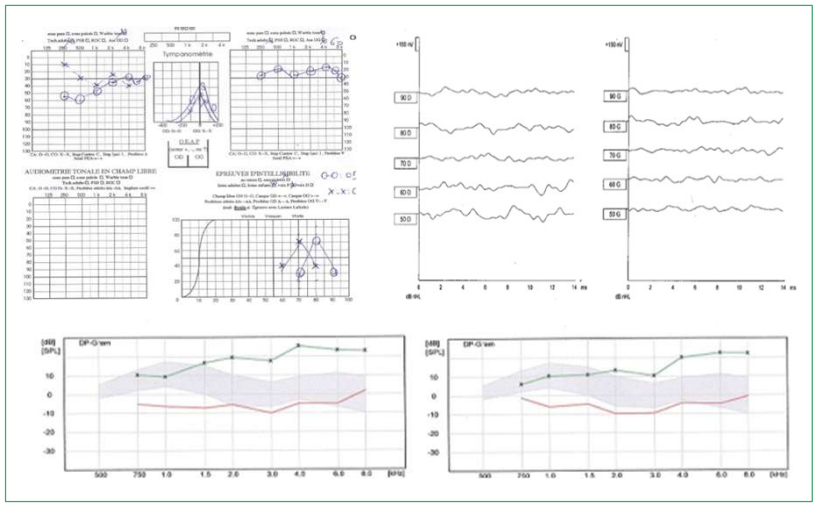
- 2-10% Sensorineural Hearing loss (Berlin *et al.* 2010)
- **Mild to profound hearing loss** (Pure Tone Audiometry)
- Poor speech intelligibility rate
- **Desynchronized** Auditory Brainstem Responses
- **Preserved** Oto-Acoustic Emissions (30-83%)

Standard care

- Hearing aids/Cochlear implants

Etiology

- Central: Hyperbilirubinemia, mitochondrial
- Nerve: Hereditary Sensory-motor, late onset (10-15 years), abnormal VIIIc



OTOF

- Otoferlin, DFNB9
- 3-5% profound SNHL
- IHC, Vestibular Cells type 1
- Calcium-dependent fusion synaptic vesicles

Synapse: Otoferlin (DFNB9), non syndromic & recessive, Incidence: ~1,080/year (USA + EU + Japan)

DFNB9: Current Candidate for GT Treatment

- **Isolated synaptic** dysfunction
- **Preserved inner ear** fine structures
- Relevant mouse model
- **Effective GT** in **mature** mice

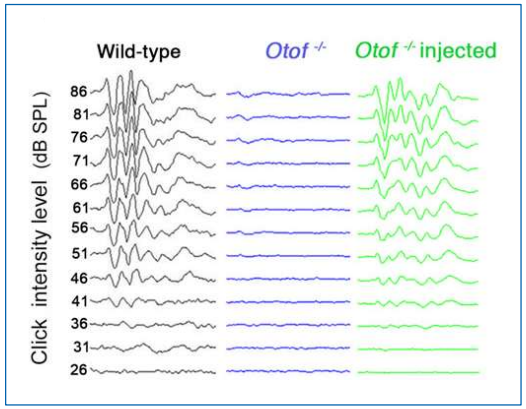
PNAS

Dual AAV-mediated gene therapy restores hearing in a DFNB9 mouse model

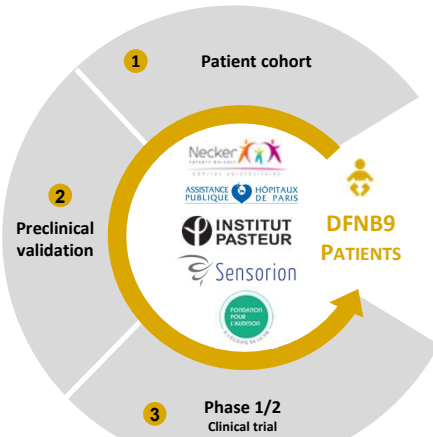
Omar Akil[a], Frank Dyka[b], Charlotte Calvet[c,d,e], Alice Emptoz[c,d,e], Ghizlene Lahlou[c,d,e], Sylvie Nouaille[c,d,e], Jacques Boutet de Monvel[c,d,e], Jean-Pierre Hardelin[c,d,e], William W. Hauswirth[b], Paul Avan[f], Christine Petit[c,d,e,g,1], Saaid Safieddine[c,d,e,h,1], and Lawrence R. Lustig[i]

[a]Department of Otolaryngology–Head and Neck Surgery, University of California, San Francisco, CA; [b]Department of Ophthalmology, College of Medicine, University of Florida, Gainesville, FL 32610; [c]Genetics and Physiology of Hearing Laboratory, Institut Pasteur, 75015 Paris, France; [d]Inserm Unité Mixte de Recherche en Santé 1120, Institut National de la Santé et de la Recherche Médicale, 75015 Paris, France; [e]Complexité du Vivant, Sorbonne Universités, F-75005 Paris, France; [f]Laboratoire de Biophysique Sensorielle, Faculté de Médecine, Centre Jean Perrin, Université d'Auvergne, 63000 Clermont-Ferrand, France; [g]Collège de France, 7505 Paris, France; [h]Centre National de la Recherche Scientifique, 75794 Paris, France; and [i]Department of Otolaryngology–Head and Neck Surgery, Columbia University Medical Center and New York Presbyterian Hospital, New York, NY 10032

2019/ S. Safieddine



Audinnove project



Audinnove project

Hôpital Necker Enfants malades AP-HP

Audiogene Clinical Trial (Sensorion)

April 2024 (Europe and Australia)

- Clinical trial accepted in Europe (France first center) and Australia

Candidates and study

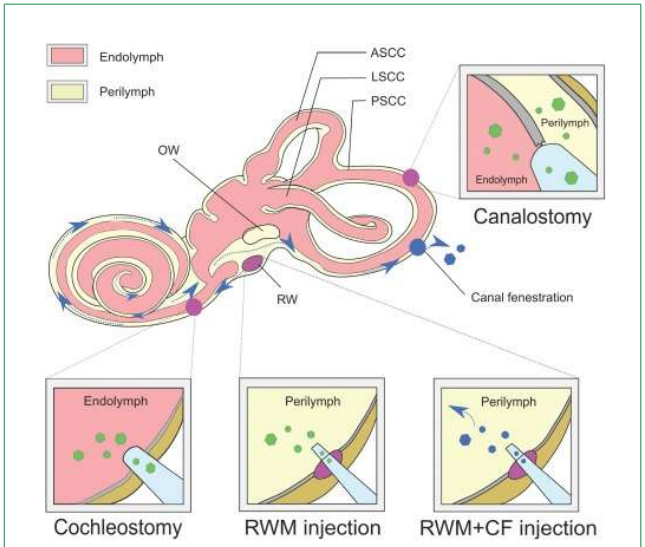
- Infants aged **6 to 31 months with DFNB9 confirmed** (bi-allelic otoferlin mutation)
- Severe to profound bilateral HL
- No cochlear implant

Injection

- Unilateral intra-cochlear injection
- Round Window (RW)+Oval Window (OW) with specific injection system

Primary Objectives

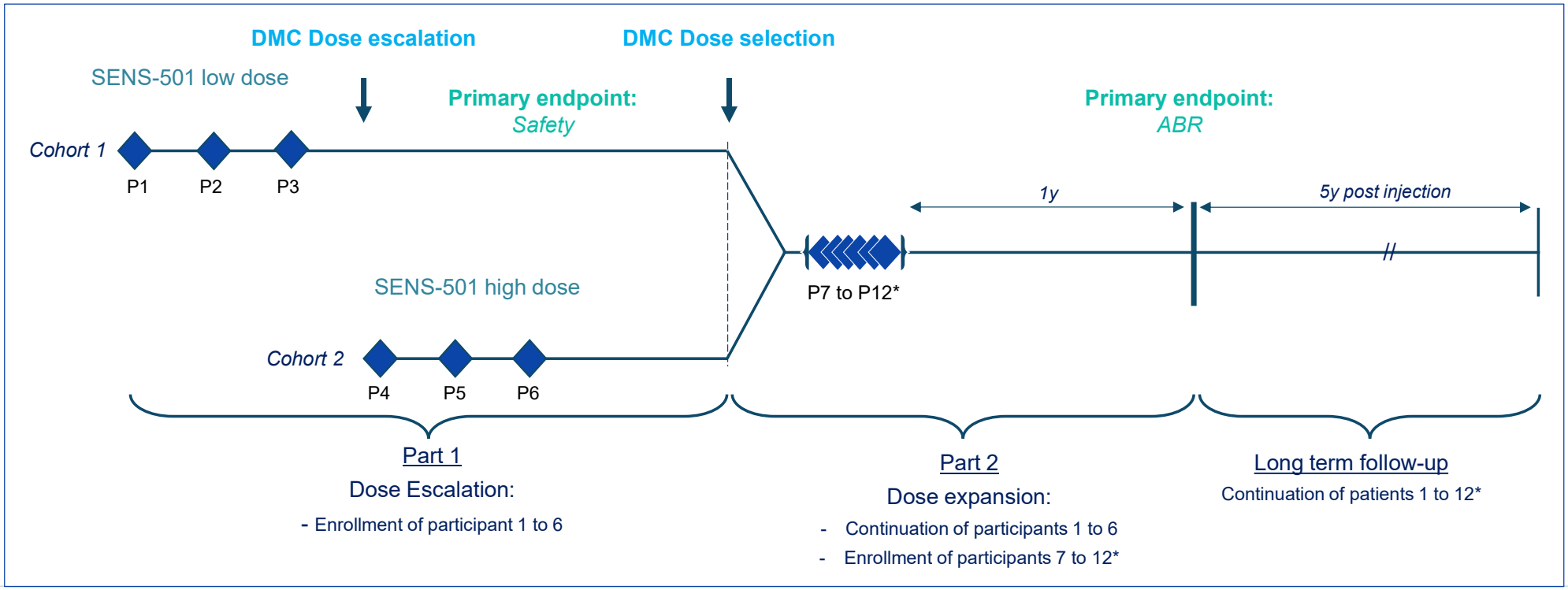
- Part 1 (escalation): Safety
- Part 2 (expansion): Efficacy



Omichi *et al.*, Hum Mol Genet., 2019.

Audiogene Clinical Trial (Sensorion)

Audiogene, a Phase 1/2 clinical trial in homogenous population of infants and toddlers, aged 6 to 31 months, naive of cochlear implants, to assess safety, tolerability, and efficacy of SENS-501 following unilateral injection into the cochlea



*Further participants may be recruited if required

Audiogene Clinical Trial (Sensorion)

Cohort 1 demographics and clinical characteristics of enrolled patients (SENS-501 low dose)

	Patient 1	Patient 2	Patient 3
Site Location	Sydney Cochlear Implant Centre, Australia	Paris Necker Hospital, France	Sydney Cochlear Implant Centre, Australia
Age of Dosing (months)	14	11	11
Cochlear Implant History	None	None	None
Administration	Right	Left	Right
DPOAE Status at Baseline	Present	Present	Present
Pathogenic OTOF Variant	c.2887C>T p.(Arg963*) / c.2957G>C p.(Arg986Pro) / c.3400C>T p.(Arg1134*)	c.1622G>A p.(Gly541Asp) / c.1768G>T p.(Glu590*)	Homozygote c.5567G>A p. (Arg1856Gln)
Dose Received (vg/ear)	1.5 10E11	1.5 10E11	1.5 10E11
Surgical Delivery	Uneventful	Uneventful	Uneventful

Audiogene Clinical Trial Status

FIRST COHORT INJECTED

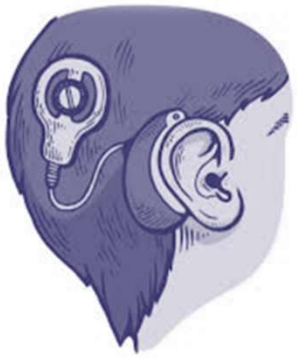
- **Patient recruitment as planned: first cohort of 3 infants and toddlers injected in H2 - 2024**
- **In the first 3 patients, good initial safety:**
  - No dose-limiting toxicities, no Serious Adverse Events
  - Vestibular function and Otoacoustic Emissions (OAEs) remained unchanged from baseline
  - Surgical administration and procedure well tolerated
- **Efficacy data set being collected**

SECOND COHORT RECRUITING

- **Data Monitoring Committee provided positive recommendation to move to the second dose**
- **Ongoing Natural History Study (OTOCONEX) supports eligible patients' identification**

INSTITUT PASTEUR Sensorion INVESTIR L'AVENIR Hôpital Necker Enfants malades AP-HP

Impact on our Practice



Pediatrician, ENT Specialist, Speech Therapist, Audiologists

INSTITUT PASTEUR Sensorion INVESTIR L'AVENIR Hôpital Necker Enfants malades AP-HP

How does those GT trials impact our practice?

- **Counselling: Hearing loss due to OTOF mutations**
  - GT described as an **alternative to cochlear implantation in infants and toddlers**
  - *Early parental **counselling**: algorithm rehabilitation program (ENT/Audiologists)*
- **Setting a specific screening program for OTOF**
  - **Hearing tests**: New Born hearing screening using **ABR**
  - **Genetics**: enlarging screening to **OTOF mutations**

What should we get prepared for in a near future?

Patients with DFNB9

- Babies with profound HL: discuss GT rather than CI
- Older children/ Adults with congenital profound HL and unilateral CI: wait for future GT indications
- Progressive HL forms: GT could be an alternative to CI

What should we get prepared for in a near future?

- **Other causes of Hearing loss: possible GT trial in few years from now?**
  - GJB2
  - USH2
  - STRC

Rehabilitation VS Restoration

Are we here Yet?

Life-changing advances

Hope for natural hearing restoration

Thank you for your attention!

Hearing Loss Innovation: Expanding Frontiers in Protection & Restoration

April 26, 2025 - 11:30 am to 12:15 pm (UTC+1)

Moderator: Nawal Ouzren, Chief Executive Officer, Sensorion

- **Protecting Hair Cells, Preserving Hearing: The Potential of SENS-401**
  Prof. Yann Nguyen, Department of Otolaryngology-Head & Neck Surgery, Pitié-Salpêtrière Hospital, Paris, France
- **From Bench to Bedside: The Journey of GJB2 & OTOF Gene Therapies for Children with Severe to Profound Hearing Loss**
  - Advancing Gene Therapy for OTOF-Related Hearing Loss in Young Children
    Prof. Natalie Loundon, Pediatric Department of Otolaryngology-Head & Neck Surgery, Necker Enfants Malades Hospital, Paris, France
  - Developing Novel Gene Therapy for Hereditary Hearing Loss in Patients with GJB2 Mutations
    Laurent Désiré, PhD, Head of Preclinical Development, Sensorion
- **Q&A Session & Conclusion:** Nawal Ouzren, Chief Executive Officer, Sensorion

Sensorion

Developing Novel Gene Therapy for Hereditary Hearing Loss in Patients with GJB2 Mutations Presentation

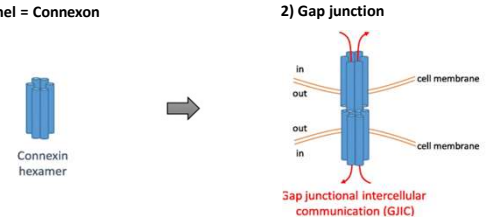
Laurent DÉSIRÉ, Ph.D,
Head of Preclinical Development,
Sensorion

GJB2-GT For DFNB1A

Connexin 26 is Encoded by *GJB2* Gene and is Responsible for Tissue Homeostasis

Mutations in the *GJB2* Gene Lead to Deafness

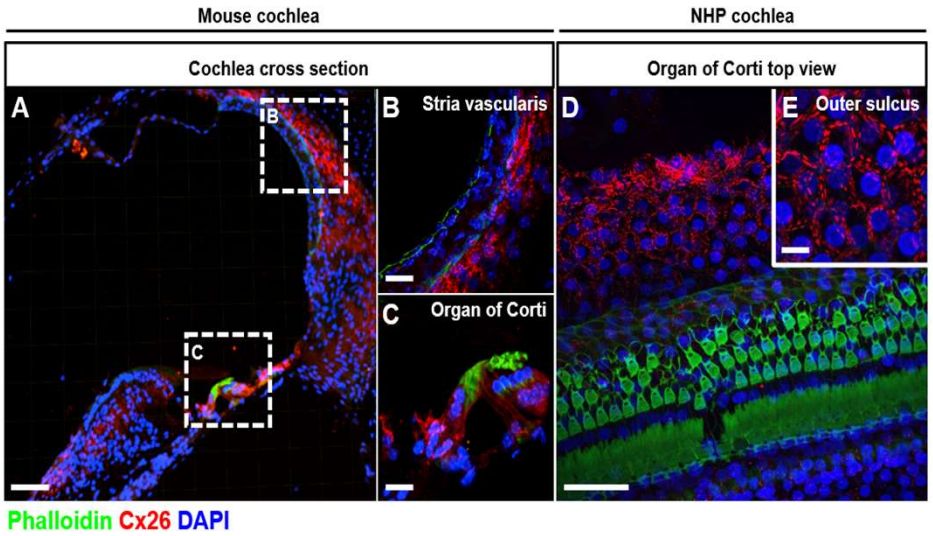
- Biggest cause of congenital deafness, around 50% of autosomal recessive non syndromic hearing loss cases are thought to result from GJB2 mutations.
- Connexin 26 and Connexin 30 proteins are the dominating connexins in the cochlea; heteromeric or heterotypic hexamers forming Gap Junctions.
- Gap Junctions are key for the intercellular exchange of molecules (miRNA, glucose, ions, etc.) hence responsible for tissue homeostasis.



Schematic representation of a gap junction

- More than 100 recessive mutations origin Cx26 truncation/ deletion leading to non-syndromic hearing loss and deafness, most are addressable via gene replacement.
- Severity of hearing loss correlates with degree of loss of *GJB2* function.

GJB2 Expression in the Cochlea



- Supporting cells of the organ of Corti
- Fibrocytes of the spiral limbus and the lateral wall
- Intermediate and basal cells of the stria vascularis
- Not expressed in hair cells

GJB2-GT

Lead Candidate was Selected to Answer Specific Development Criteria

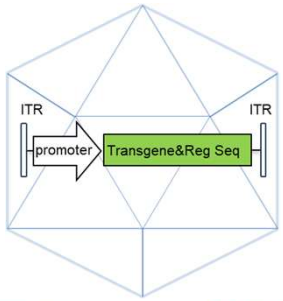
CRITERIA	LEAD CANDIDATE
Natural and synthetic AAV capsid libraries screening for broad coverage of target cells.	✓
Expression cassette design for high-level of target cells transduction, correct cellular localization.	✓
Avoiding off-target expression (i.e. hair cells): promoter and regulatory sequences design.	✓
Limited off-target tissue biodistribution.	✓
Surgical approach developed and mastered by ENT surgeons.	✓

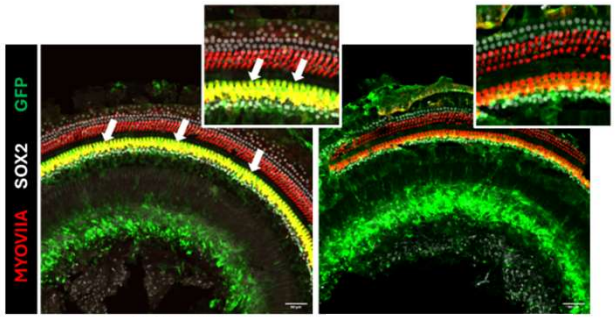
Our Lead Candidate was Designed to Ensure Broad Coverage of Relevant Cochlear Cells While Detargeting Hair Cells

GJB2-GT

Sensorion's Proprietary GJB2-GT Candidate

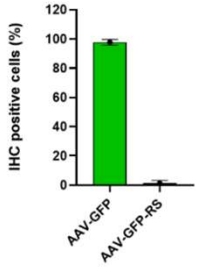
AAV capsid





Control vector

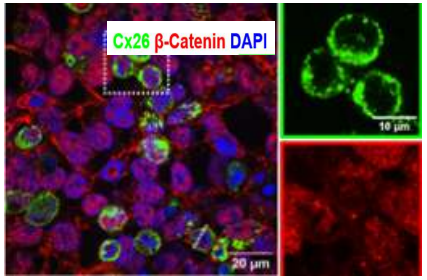
GFP candidate (+ Reg S1)



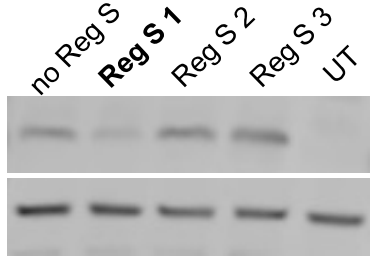
- Synthetic AAV capsid with broad tropism for support cells
- Correctly adresses Cx26 at the cell membrane
- Creates functional gap junctions *in vitro* (dye transfer)
- Regulatory sequence Reg S1 to detarget hair cells

Expression Assay

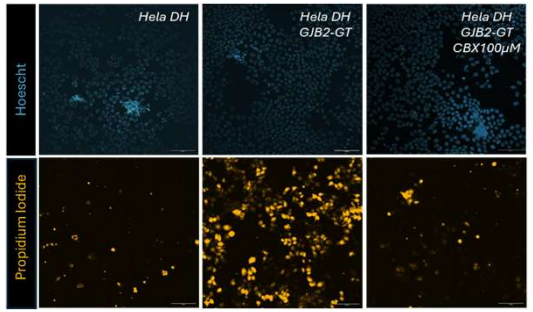
HEK293



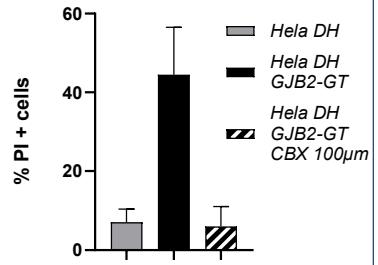
HeLa DH



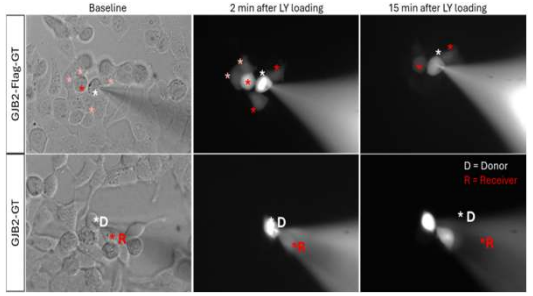
Hemichannel Assay



HeLa DH



Gap Junction Assay



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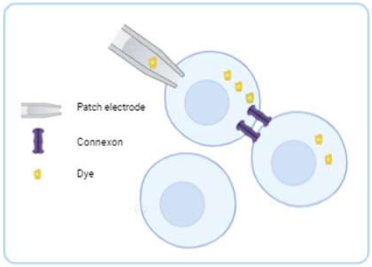
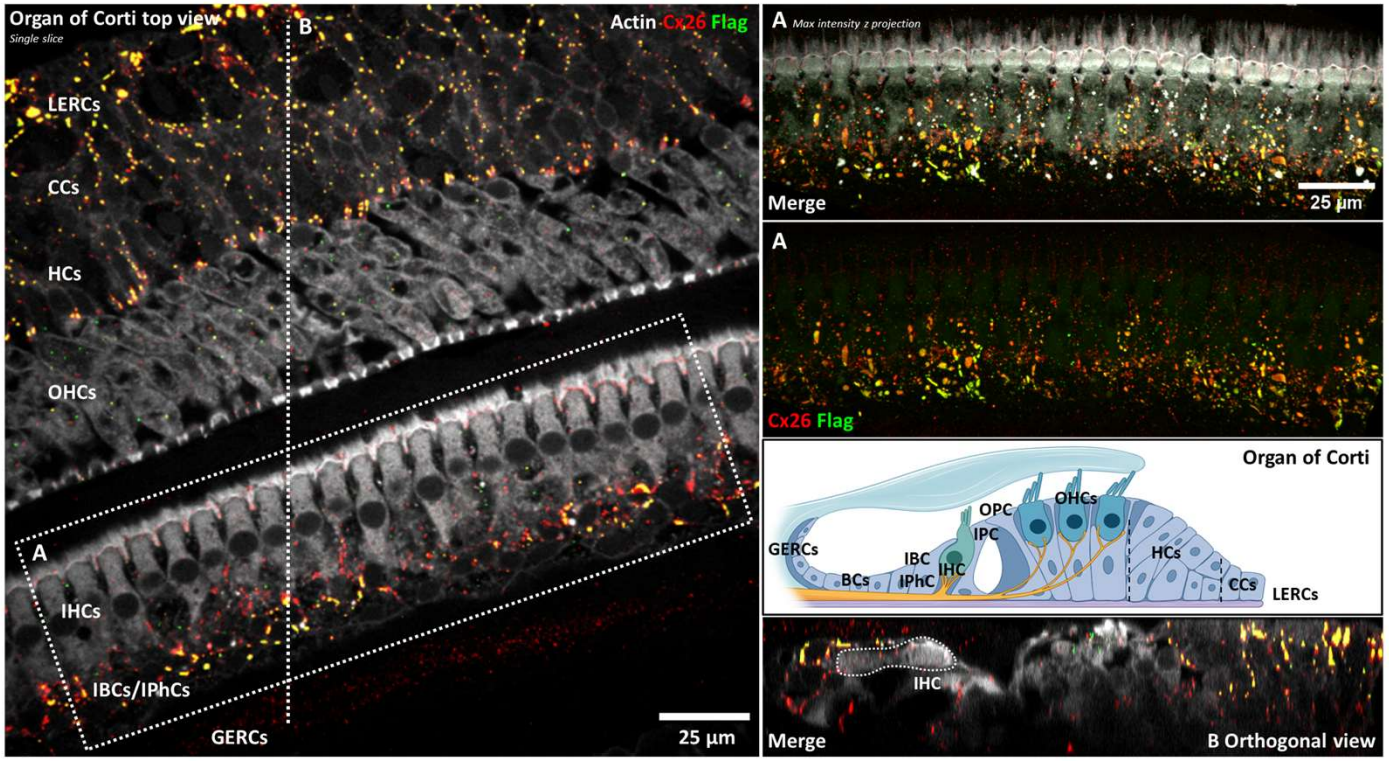


GJB2-GT

Lead Candidate can Deliver Connexin 26 in the Appropriate Target Cells

Correct Delivery Of Connexin 26 Using Lead Candidate Flag In Non-Human Primate Cochlea



Cell Types

Claudius Cells	✓
Deiters Cells	✓
Great Epithelial Ridge Cells	✓
Hensen Cells	✓
Inner Border Cells	✓
Inner Hair Cells	–
Inner Phalangeal Cells	✓
Pilar Cells	✓
Lateral Epithelial Ridge Cells	✓
Outer Hair Cells	–
Fibrocytes	✓
Stria Vascularis	✓

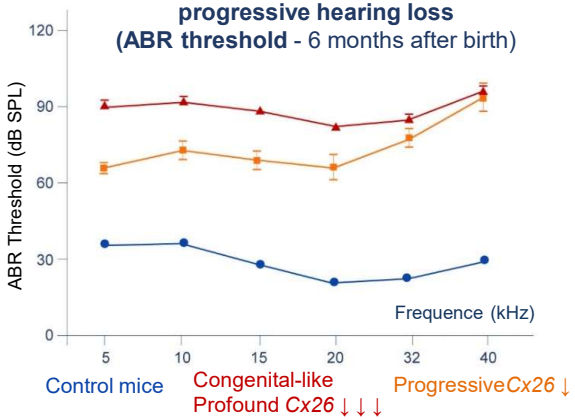
- No expression in Hair Cells confirmed.
- No morphological defects observed 3 and 9 weeks after intracochlear administration.

GJB2-GT

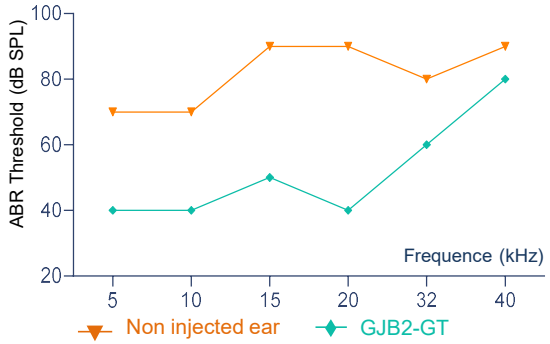
Lead Candidate Prevents Hearing Loss in DFNB1A cKO Mouse Model

Proof Of Concept in Mice with Progressive Hearing Loss

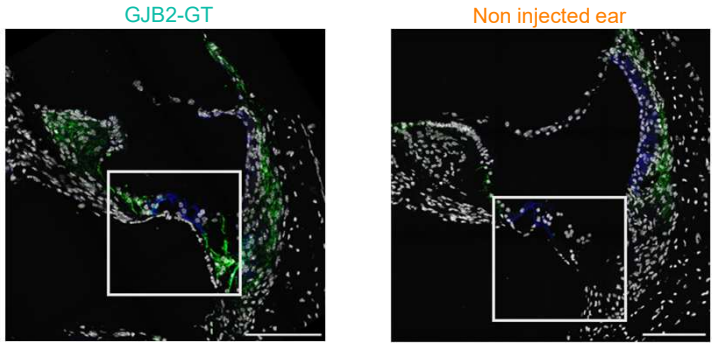
Mouse model provides congenital and progressive hearing loss
(ABR threshold - 6 months after birth)



Progressive Model
Injected After Hearing Onset
ABR threshold - 10 weeks post-injection



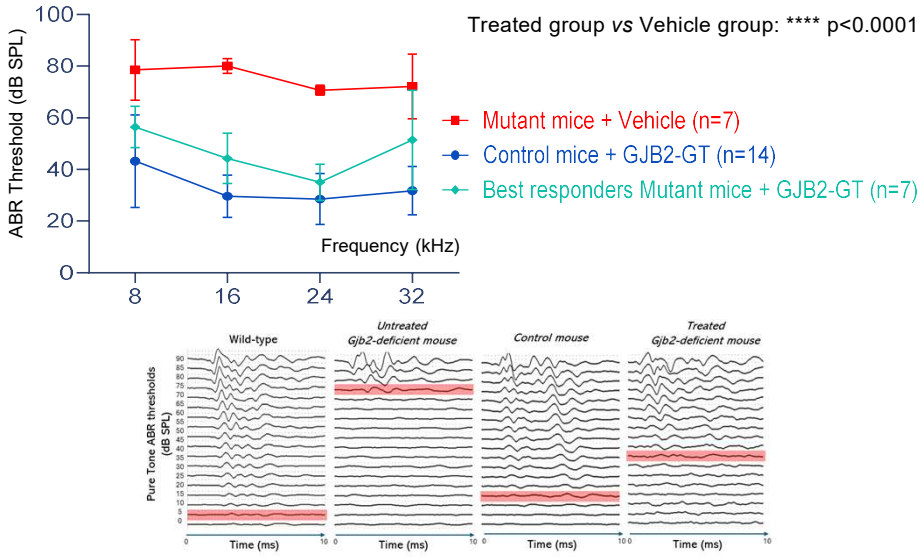
Hearing Loss Prevention Correlates With Connexin 26 Expression



Left: Green staining demonstrates efficient Cx26 re-expression in target cells, which are otherwise depleted (right) in Cx26 in the *GJB2* deficient model

Proof of Concept in Mice with Congenital Hearing Loss

Congenital model
ABR threshold - 7 weeks post-injection



- In **progressive model**: hearing loss prevention correlates with Connexin 26 re-expression in target cells.
- In **congenital model**: GJB2-GT induced a statistically significant hearing recovery:
  - as early as 3 weeks after injection
  - dose-response effect

Tran Van Ba *et al.*, ESGCT 2024 (link), ARO 2025 (link)

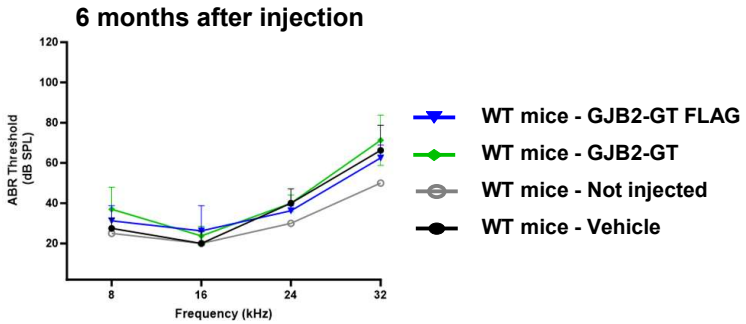
GJB2-GT

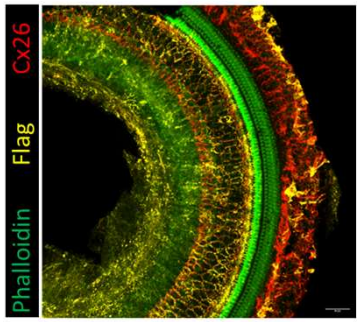
Adequate Safety and Biodistribution Profile Including Long-term Local Tolerability in Mice and NHP

Acute toxicity in WT Mice - High dose IV injection

- Study performed in preparation of upcoming GLP-toxicity in mice after IV injection.
- GJB2-GT does not interfere with normal growth and don't elicit elevated transaminase levels 4 and 8 weeks after injection.
- Behavioral evaluation (Functional Observation Battery, exploratory behavior 3 and 7 weeks after injection: no findings.

6-Month Exploratory Safety and Transgene Expression in WT Mice – Intracochlear injection





GT-GJB2-Flag imaging – 6 months post intracochlear injection in mice

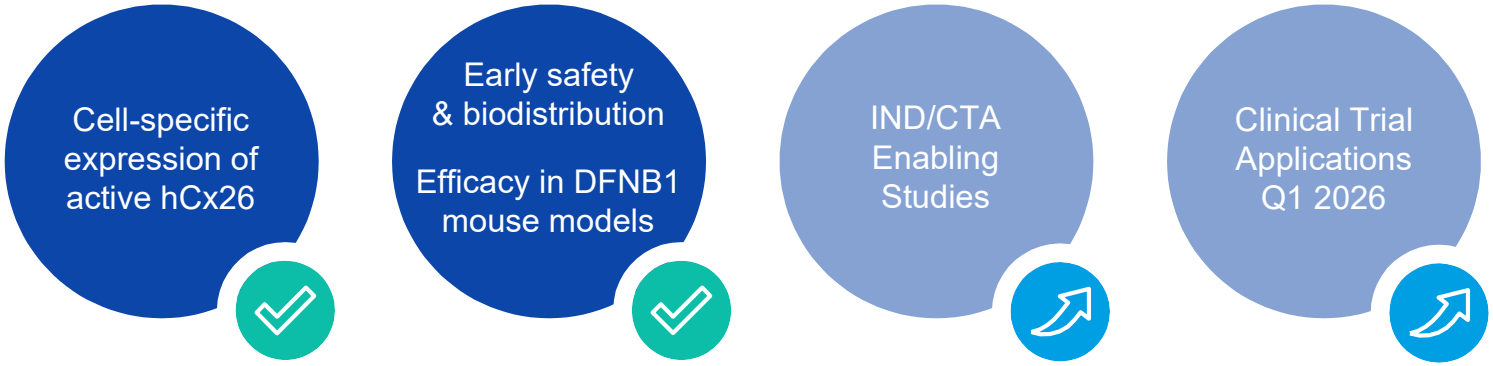
- No impact on ABR up to 6 months.
- Normal histology maintained.
- Transgene expression persistence.
- Hair cells detargeted.
- Clinical pathology: no findings.

3-Month Exploratory Toxicity and Biodistribution in Non-Human Primate – Intracochlear injection

- GJB2-GT is well tolerated and did not induce any macroscopic/organ weight changes or local/systemic microscopic findings.
- Normal cochlear histology.
- No lab and clinical findings.
- Biodistribution: the vast majority of the vector remains in injected ears, no dissemination observed in gonads, main organs, dorsal root ganglion (DRG).

Summary

GJB2-GT is Now in IND/CTA Enabling Studies



THANK YOU

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Hearing Loss Innovation: Expanding Frontiers in Protection & Restoration

April 26, 2025 - 11:30 am to 12:15 pm (UTC+1)

Moderator: Nawal Ouzren, Chief Executive Officer, Sensorion

- **Protecting Hair Cells, Preserving Hearing: The Potential of SENS-401**
  Prof. Yann Nguyen, Department of Otolaryngology-Head & Neck Surgery, Pitié-Salpêtrière Hospital, Paris, France
- **From Bench to Bedside: The Journey of GJB2 & OTOF Gene Therapies for Children with Severe to Profound Hearing Loss**
  - Advancing Gene Therapy for OTOF-Related Hearing Loss in Young Children
    Prof. Natalie Loundon, Pediatric Department of Otolaryngology-Head & Neck Surgery, Necker Enfants Malades Hospital, Paris, France
  - Developing Novel Gene Therapy for Hereditary Hearing Loss in Patients with GJB2 Mutations
    Laurent Désiré, PhD, Head of Preclinical Development, Sensorion
- **Q&A Session & Conclusion:** Nawal Ouzren, Chief Executive Officer, Sensorion

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