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Novartis Institutes for BioMedical Research

CGF166

Clinical Trial Protocol CCGF166X2201

# A three-part, multicenter, open label, single dose study to assess the safety, tolerability, and efficacy of intra-labyrinthine (IL) CGF166 in patients with severe-to-profound hearing loss

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| Study phase: | I/II |
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## Notification of serious adverse events

A serious adverse event (SAE) is any event which is fatal or life-threatening, which requires or prolongs hospitalization, which is significantly or permanently disabling or incapacitating, which constitutes a congenital anomaly or a birth defect, or which is medically significant, may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

**Any SAE** occurring in a patient **from consent until 30 days after stopping** study participation (defined as time of last dose of study drug taken or last visit whichever is the later) must be reported either on the paper SAE report form or via the electronic SAE form within the clinical data capture system (where available).

For SAEs reported using the **paper SAE report form**, the investigator will ensure that the form is completed and **faxed** by the **investigator to the local Novartis Chief Medical Office and Patient Safety (CMO & PS) Department within 24 hours** of learning of the occurrence of the SAE even if the SAE does not appear to be drug-related. The original SAE form, together with the fax confirmation sheet, must be kept with the case report forms at the study site.

For SAEs recorded ***electronically*** in the Novartis clinical data capture system, information should be **entered, saved and e-signed within 24 hours of awareness of the SAE**. These data will automatically be submitted to CMO & PS Department.

More details in Section 7 of this protocol.

### Fax numbers of local Novartis Chief Medical Office and Patient Safety (CMO & PS) Departments

| | | |
|---|---|---|
| North America | Fax | (+ 1) 877 778 9739 |
| | | (+ 1) 888 299 4565 (toll free number) |

Any update to the Novartis CMO & PS or personnel information required during the course of the study will be communicated directly to the relevant Investigator site(s); a specific protocol amendment should not be required.

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## List of abbreviations

| | |
|---|---|
| ABR | Auditory brainstem evoked response |
| Ad5 | Adenovirus serotype 5 |
| AE | adverse event |
| AESI | adverse event of special interest |
| ALT | alanine aminotransferase |
| ALP | alkaline phosphatase |
| ANA | anti-nuclear antibody |
| ANCA | anti-neutrophil cytoplasmic antibody |
| ANCOVA | analysis of covariance |
| AST | aspartate aminotransferase |
| ATOH1 | Atonal |
| *Atoh1* | Atonal gene |
| BAER | Brainstem auditory evoked response evaluations |
| BEAP | Brainstem Auditory Evoked Potentials |
| BMI | Body Mass Index |
| BUN | blood urea nitrogen |
| CD-ROM | compact disc – read only memory |
| CFR | Code of Federal Regulation |
| CK | creatinine kinase |
| CRF | Case Report/Record Form (paper or electronic) |
| $CO_2$ | carbon dioxide |
| COWS | Cool – Opposite, Warm – Same |
| CRO | Contract Research Organization |
| CT | Computerized tomography |
| CV | coefficient of variation |
| dB | decibels |



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|---|---|
| DP | Directional preponderance |
| DPT | Distortion product |
| DPOAE | Distortion product otoacoustic emissions |

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| DSMB | Data Safety Monitoring Board |
| EC | Ethics committee |
| ECG | Electrocardiogram |
| EDC | Electronic Data Capture |
| ELISA | Enzyme-linked immunosorbent assay |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| GFAP | Glial fibrillary acidic protein |
| GFP | Green fluorescent protein |
| GV11 | Adenovector backbone used for CGF166 |
| Hath1 | Human atonal Protein |
| h | hour |

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|---|---|
| HINT | Hearing-in-noise test |
| HIV | human immunodeficiency virus |
| HL | Hearing Loss |
| ICH | International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| IDPN | 3', 3'-iminodipropionitrile |
| IEC | Independent Ethics Committee |
| IL | Intra-labyrinthine |
| i.v. | intravenous |
| IRB | Institutional Review Board |
| kHz | Kilohertz |
| LDH | lactate dehydrogenase |
| LLQ | lower limit of quantification |
| LLN | lower limit of normal |
| LO | Labyrinthitis Ossificans |

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|---|---|
| mg | milligram(s) |
| mL | milliliter(s) |
| MRI | Magnetic resonance imaging |

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| PD | pharmacodynamic(s) |
| PK | pharmacokinetic(s) |

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| PTA | Pure tone average |
| RBC | red blood cell(s) |
| REB | Research Ethics Board |
| SAE | serious adverse event |
| SCM | sternocleidomastoid muscle |
| SGOT | serum glutamic oxaloacetic transaminase |
| SGPT | serum glutamic pyruvic transaminase |
| SD | standard deviation |
| SPV | slow phase velocity |

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| TBL | total bilirubin |
| TRQ | Tinnitus reaction questionnaire |
| ULN | upper limit of normal |
| ULQ | upper limit of quantification |
| VCR | vestibulocollic reflex |

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| vHIT | video Head Impulse Test |
| VOR | Vestibulo-ocular reflex |
| vp | Viral particles |
| WBC | white blood cell(s) |

## Glossary of terms

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| Assessment | A procedure used to generate data required by the study. |
| Enrollment | Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e., prior to starting any of the procedures described in the protocol). |
| Investigational drug | The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug" or "investigational medicinal product". |
| Investigational treatment | All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls.<br><br>This includes any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination.<br><br>Investigational treatment generally does not include other treatments administered as concomitant background therapy required or allowed by the protocol when used within approved indication/dosage. |
| Part | A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc. |
| Patient | An individual who has consented to participate in this study. The term Patient may be used to describe either a healthy volunteer or a patient. |
| Patient number | A number assigned to each patient who enrolls in the study. When combined with the center number, a unique identifier is created for each patient in the study. |
| Period | A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration, washout, etc. |
| Personal Data | Subject information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples. |
| Premature patient withdrawal | Point/time when the patient exits from the study prior to the planned completion of all study drug administration and assessments; at this time all study drug administration is discontinued and no further assessments are planned. |

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| Study completion | Point/time at which the patient came in for a final evaluation visit or when study drug was discontinued whichever is later. |
| Study drug discontinuation | Point/time when patient permanently stops taking study drug for any reason; may or may not also be the point/time of premature patient withdrawal. |
| Study drug/treatment | Any drug (or combination of drugs) administered to the patient as part of the required study procedures; includes investigational drug, active drug run-ins or background therapy. |
| Treatment number | A unique identifier assigned to each treated patient, corresponding to a specific treatment arm assignment. |
| Variable | Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints. |
| Withdrawal of consent (WoC) | Withdrawal of consent from the study occurs only when a subject does not want to participate in the study any longer, and does not allow any further collection of personal data |

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## Protocol synopsis

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| **Protocol number** | CCGF166X2201 |
| **Title** | A three-part, multicenter, open label, single dose study to assess the safety, tolerability, and efficacy of intra-labyrinthine (IL) CGF166 in patients with severe-to-profound hearing loss |
| **Brief title** | A study of the gene therapy CGF166 in patients with severe-to-profound hearing loss |
| **Sponsor and Clinical Phase** | Novartis<br>Phase 1/2 |
| **Investigation type** | Gene therapy |
| **Study type** | Interventional |
| **Purpose and rationale** | The current study is to evaluate the safety, tolerability, and the potential ability of CGF166 delivered through IL-infusion to improve hearing and vestibular function. CGF166 is recombinant adenovirus 5 (Ad5) vector containing the human Atonal transcription factor (Hath1) cDNA |
| **Primary Objective(s) and Key Secondary Objective** | • To assess the safety and tolerability of IL CGF166<br>• To assess the efficacy of IL CGF166 as determined by the change in pure tone audiometry compared to pretreatment values |
| **Secondary Objectives** | • To assess the efficacy of CGF166 as determined by the change in brainstem auditory evoked responses (BAER) compared to pretreatment values<br>• To evaluate the effects of CGF166 on various assessments of vestibular function compared to pretreatment values<br>• To compare the changes in auditory functions (speech recognition) and vestibular functions before and after IL infusion of CGF166 into the study ear |

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| **Study design** | The current three part study utilizes an open label, single dose design for the investigation of CGF166 and will be conducted in multiple centers. Part A, B, and C will be conducted in a sequential manner.<br>The current study will evaluate the safety, tolerability, and potential efficacy of CGF166 and the associated delivery procedures in patients with severe-to-profound bilateral or unilateral hearing loss with intact vestibular function in the non-operative ear. Patients are required to have documented non-fluctuating hearing loss.<br>**Part A**<br>Part A will include a safety and tolerability cohort (N=3). Patient dosing will be staggered; dosing the next patient in a cohort will be based on a safety data review including all data available through 4 weeks post-dose of the previously dosed patient(s).<br>**Part B**<br>Part B will include a volumetric escalation design to evaluate infusion volumes of the same CGF166 concentration Commercially Confidential Information in 3 cohorts of patients (n=3/cohort; total of 9 patients).<br>Each subsequent cohort will be dosed only after the volume delivered in the prior cohort is deemed to be safe and tolerable as determined by the dose safety review meeting based on safety data review of the complete previous cohort including all data through 4 weeks post-dose.<br>Safety review meetings will be organized to evaluate available safety data and to determine if it is appropriate to escalate to the next infusion volume.<br>**Part C**<br>Based on the DSMB review of data from Part A and Part B of the study, Part C of the study will administer a dose volume of 30 µL at the rate of 10 µL/min. A total of 10 patients will be enrolled in Part C of the study. |
| **Population** | • Patients with severe-to-profound bilateral or unilateral hearing loss with intact vestibular function in the non-operative ear<br>• Adult patients who are candidates for a cochlear implant |

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| **Inclusion criteria** | • For all Parts A, B and C of the study, male or female patients, 18 to 75 years old, inclusive, with severe-to-profound bilateral hearing loss or unilateral hearing loss with intact vestibular function in the non-operative ear. Non-fluctuating severe-to-profound hearing loss is required for the study ear and is defined as:<br>  • Pure-tone average (PTA) within 10 dB of the PTA obtained at least 11 months previously<br>  • Word recognition within 20% of previous test at least 11 months previously<br>• Candidate ear (“study ear”): Minimal residual hearing based on the pure tone average of 0.5, 1, 2, and 4 kHz thresholds of ≤110 dB HL.<br>• Candidate ear (“study ear”): pure tone audiometric thresholds of ≥50 dB HL for each testable octave frequency of 0.125 and 0.250 kHz, ≥70 dB for each testable octave frequency from 0.5 through 8 kHz, and sentence recognition ≤50% at screening.<br>• Patients with intact vestibular function in at least one ear (non-study ear) as measured by vestibular evoked myogenic potential (VEMP)<br>• MRI scan within 6 months or at screening to confirm suitability for inner ear surgery<br>• Ability to understand the study and provide informed consent; willingness to comply with the protocol |
| **Exclusion criteria** | • Patients with hearing loss caused by genetic/developmental disorders, e.g., cochlea aplasia or autoimmune ear disease<br>• Patients with existing conductive hearing loss or mixed hearing loss as judged by the Principal Investigator following a thorough review of all of the trial hearing assessments and MRI scan<br>• Patients with cochlear implants or past cochlear implant in the candidate study ear<br>• Hearing loss due to any other cause that would not be expected to respond to hair cell regeneration, for example trauma or central auditory lesions or lack of an auditory nerve<br>• Patients who will require ototoxic drugs as routine therapy over the course of the study, such as cystic fibrosis patients<br>• Any contraindication to the planned surgery or anesthesia as determined by the surgeon, anesthesiologist, or designee<br>• Previous surgery in the study ear<br>• Any otological history, such as chronic otitis, cholesteatoma, tympanic membrane perforation, that suggests poor candidacy for cochlear implant or inner ear surgery or suggests potential interference with study auditory or vestibular function tests<br>• Pregnant women<br>• Abnormal vital signs and/or ECG that suggest potential contraindication for planned study anesthesia<br>• Past serious adverse reaction to anesthesia<br>• Meniere’s Disease<br>• History of radiation therapy to the head and neck<br>• Participation in a clinical trial within the last 30 days |

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| **Investigational and reference therapy** | • CGF166 is recombinant adenovirus 5 (Ad5) vector containing the human Atonal transcription factor (Hath1) cDNA. CGF166 will be provided in a septum vial, containing 0.5 mL Commercially Confidential Information of opalescent liquid viral vector.<br>• In Part A and Part B all investigational infusion volume was infused at a rate of 10 µL/min except 1 patient where in fusion volume was infused at a rate of 20 µL/min. In Part C all following protocol amendment 5 all investigational infusion volumes will be infused at a rate of up to 10 µL/min in to the perilymphatic space |
| **Efficacy assessments** | **Auditory assessments**<br>• Pure tone audiometry, including immittance testing<br>• Speech audiometry<br>• Brainstem auditory evoked response evaluations (BAER)<br>**Vestibular assessments**<br>• Head Impulse test<br>Commercially Confidential Information |
| **Safety assessments** | • Physical examination<br>• Otoscopy<br>• Neurological exam<br>• FSH verification and Pregnancy test (serum at screening and urine at subsequent visits)<br>• Vitals and body measurements (height, weight, temperature, blood pressure, and pulse rate)<br>• ECG<br>• Clinical laboratory tests (hematology, chemistry, and urinalysis)<br>• MRI with gadolinium (within 3 months or performed at screening)<br>• Adverse events |
| **Other assessments** | Commercially Confidential Information |

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| **Data analysis** | • Tone thresholds will be analyzed for each frequency tested separately.<br>• Pure tone audiometry air conduction threshold data will be listed and graphically displayed by patient, infusion volume, frequency, and visit/time.<br>• Summary statistics will be provided by infusion volume, frequency, ear and visit/time.<br>• Change from baseline of the thresholds (mean of screening and baseline visit) will also be summarized by infusion volume, frequency, ear and visit/time |
| **Key words** | Hearing loss, cochlear implant, gene therapy |

## Assessment schedule

| Study Phase | Screening visit | Baseline | Treatment day | Post-op Observation period | | | | | Follow-up Period | | | | | End of Study[5] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Day -63 to -4 | Day -3 to -1 | Day 1 | | | Day 2 | Day 4 | Day 6 | Day 15 | Day 29 | Day 57 | Day 113 | Day 169 | |
| Visit Numbers | 1 | 2 | 3 | | | 4 | 5 | 6 | 7 | 8 | 9 | 11 | 13 / 777 | 777 |
| Time (h) | | | pre-infusion | Post-infustion | 4 hr | | | | | | | | | |
| Inclusion/Exclusion | x | x | | | | | | | | | | | | |
| Relevant medical history/Current medical conditions | x | x | as needed | | | | | | | | | | | |
| Demography | x | | | | | | | | | | | | | |
| Auditory and vestibular function assessments | x | x | | | | | | | | x | x | x | x | x |
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| History of alcohol and drug dependence | x | | | | | | | | | x | | | | |
| General Physical exam | x | x | | | | | | | | | | | | |
| Otoscopy | x | x | | | | | | | x | x | x | x | x | x |
| Neurological evaluation | x | x | | | | x | x | x | x | x | x | x | x | x |
| Pregnancy test | x (serum) | x | | | | | | | | | | | x[6] | x |
| HIV and Hepatitis | x | | | | | | | | | | | | | |
| Vitals Signs and body measurements | | | | | | | | | | | | | | |
| Body Height | x | | | | | | | | | | | | | |
| Body Weight | x | x | | | | | | | | | x | x | x | x |
| Body Temperature | x | x | | | | x | x | x | x | x | x | x | x | x |
| Blood pressure / Pulse rate | x | x | | | | x | x | x | x | x | x | x | x | x |
| ECG | x | x | | | | x | | | | | x | x | x | x |
| Hematology, Blood chemistry, Urinalysis | x | x | | | | x | x | | x | | x | x | x | x |
| [1] Commercially Confidential Information | | | | | | | | | | | | | | |
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[5] - Pts. Who have completed Day 169 in the study will return to site as soon as possbile and complete end of study visit 777; Patients who have not completed Day 169 in the study will complete end of study (visit 777) assessment on Day 169

[6] - assessment done if it is end of study assessment.

| Study Phase | Screening visit | Baseline | Treatment day | Post-op Observation period | | | Follow-up Period | | | | | End of Study[5] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Day -63 to -4 | Day -3 to -1 | Day 1 | Day 2 | Day 4 | Day 6 | Day 15 | Day 29 | Day 57 | Day 113 | Day 169 | |
| Visit Numbers | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 11 | 13 / 777 | 777 |
| MRI with gadolinium | x | | | | | | | | x[3] | x[3] | x[3] | x |
| C-SSRS | | x | | | | | | x | x | x | x | x |
| Comments | as needed | | | | | | | | | | | |
| Adverse events | | | as needed | | | | | | | | | |
| Concomitant meds/Therapies | as needed | | | | | | | | | | | |
| Study Surgery | | | x | | | | | | | | | |
| Dose administration | | | x | | | | | | | | | |
| Study Completion | | | | | | | | | | | x[6] | x |

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C-SSRS- Columbia Suicide Severity Rating Scale; Commercially Confidential Information

[3] MRI may be performed if the audiometery meets one of the stopping criteria

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[5] - Pts. Who have completed Day 169 in the study will return to site as soon as possbile and complete end of study visit 777; Patients who have not completed Day 169 in the study will complete end of study (visit 777) assessment on Day 169

[6] - assessment done if it is end of study assessment.

# 1 Introduction

## 1.1 Background

Sensorineural hearing loss and vestibular dysfunction may result from destruction of inner ear sensory hair cells and/or auditory nerves. Humans are born with ~30,000 sensory hair cells. Sensory hair cells in the organ of Corti, located within the mammalian cochlea, are critical for auditory function while vestibular sensory hair cells located in the vestibular canals and the utricle and saccule provide the basis for vestibular function. Sensory cells can be damaged or destroyed by pharmacological agents (chemotherapy and aminoglycosides), loud noises, infections or simply aging and loss of these cells is permanent as they do no regenerate. Hearing loss is currently treated with a hearing aid or a cochlear implant in patients with severe impairment; patients are eligible for a cochlear implant when they have severe to profound hearing loss with the inability to discriminate 40% of speech. No pharmacologic agents exist to restore hearing function. More than 300,000 people worldwide have received cochlear implants. Cochlear implants improve auditory function but require invasive surgery, require ongoing maintenance and patient training; they also are expensive. Severe vestibular dysfunction patients may experience debilitating vertigo and nausea. There is no therapy other than rehabilitation to acquire environmental signals to compensate for vestibular dysfunction. There are no therapeutic options available to regenerate sensory hair cells to restore auditory or balance function and as such this represents a significant medical need.

The atonal gene, *Atoh1*, is a basic helix-loop-helix (bHLH) transcription factor that is required for initiation of the required gene regulatory pathway for differentiation of hair cells from progenitors during prenatal development. The ATOH1 protein is called Hath1 in humans

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Moreover, ATOH1 expression can force the supporting cells, which normally surround the sensory hair cells and lack sensory function, to transdifferentiate into new sensory hair cells.

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### 1.1.1 Relevant data summary

CGF166 is a replication-incompetent Adenovirus 5 (Ad5) vector engineered to deliver Hath1 expressed under the control of the GFAP (glial fibrillary acidic protein) promoter. CGF166 is provided as a solution in single-use septum vials that are stored frozen at -20°C and thawed prior to use.

## Pharmacology

**The GFAP promoter will provide for low level expression restricted to supporting and neuronal cells.**

CGF166 contains the GFAP promoter, which will limit the Hath1 transgene expression to cells that have endogenous GFAP protein expression. Studies by (Rio et al 2002) and (Schlecker et al 2011) show endogenous GFAP protein expression by immunohistochemistry in the normal inner ear: cochlear supporting cells, organ of corti, vestibular supporting cells, and glial cells in the spiral ganglion. Sensory hair cells did not show positive GFAP staining.

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FAP protein positive cells included the supporting cells in the organ of Corti and in the macular organ ampulla as well as in the glial cells of the spiral ganglion. Additionally, (Staecker et al 2011) report a similar distribution pattern obtained using an adenoviral vector expressing GFP under the control of the GFAP promoter. These studies taken together support that the GFAP promoter contained in CGF166 will limit expression of Hath1 to the supporting cells in the normal and injured ear.

The GFAP promoter was chosen for its selectivity to limit transgene expression to supporting cells and also for its ability to promote the generation of sensory hair cells.

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**CGF166 regenerates sensory hair cells in human vestibular explants *ex vivo***

Human vestibular explants, harvested from mature human vestibular end organs at the time of labyrinthectomy, provide a unique opportunity to study gene transfer agents designed to treat inner ear disorders. CGF166-mediated Hath1 expression has been shown to regenerate sensory hair cells was evaluated in human macular organ cultures. These studies demonstrated that CGF166 mediated Hath1 expression effectively regenerated sensory hair cells in human explants cultures compared with the neomycin-treated control sample.

**Development of IL delivery for inner ear exposure**

IL delivery is the intended clinical route of administration for inner ear gene delivery of CGF166. This route of delivery is expected to distribute the vector throughout the cochlea and vestibular fluid space to allow access to the target supporting cells in the organ of Corti and vestibular organs. While IL delivery was successfully developed for clinical and non-clinical use, the point of access varied between species due to anatomical variations of the external auditory canal (EAC), middle ear, and skull. The clinical access point is via the stapes footplate/oval window and will deliver CGF166 into the scala vestibuli perilymph.

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Also, human temporal bone studies were conducted to optimize the IL delivery method via the stapes footplate for clinical studies (Investigator's Brochure).

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#### 1.1.1.5 Human pharmacokinetic data

Not applicable.

#### 1.1.1.6 Human pharmacodynamic data

Not applicable.

## 1.2 Study purpose

The current study is to evaluate the safety, tolerability, and the potential ability of CGF166 delivered through IL-infusion to improve hearing and vestibular function. CGF166 is recombinant adenovirus 5 (Ad5) vector containing the human Atonal transcription factor (Hath1) cDNA.

# 2 Study objectives

## 2.1 Primary objective(s)

- To assess the safety and tolerability of IL CGF166
- To assess the efficacy of IL CGF166 as determined by the change in pure tone audiometry compared to pretreatment values

## 2.2 Secondary objective(s)

- To assess the efficacy of CGF166 as determined by the change in brainstem auditory evoked responses (BAER) compared to pretreatment values
- To assess the efficacy of CGF166 in regenerating vestibular function as determined by the change in phase compared to pretreatment values
- To compare the changes in auditory functions (speech recognition) and vestibular functions before and after IL infusion of CGF166 between the study ear

## 2.3 Exploratory objective(s)

# 3 Investigational plan

## 3.1 Study design

This non-confirmatory three part study utilizes an open label, single dose, sequential cohort design for the investigation of CGF166 and will be conducted in multiple centers.

The current study will evaluate the safety, tolerability, and potential efficacy of CGF166 and the associated delivery procedures in patients with severe-to-profound bilateral or unilateral hearing loss with intact vestibular function in the non-operative ear. Patients are required to have documented non-fluctuating severe-to-profound bilateral or unilateral hearing loss prior to enrollment. A maximum of 22 patients will be enrolled in this 3 Part, 5 cohort trial (Figure 3-1).

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### Part A

Part A will assess the safety and tolerability as well as potential efficacy following a single IL dose of 20 uL of CGF166 concentration Commercially Confidential Information. Patient enrollment will be staggered so that a safety data review can be done after each treated patient (~4 weeks after treatment) prior to dosing each subsequent patient.

### Part B

Part B will include a volumetric escalation design to evaluate up to 3 infusion volumes (between 20 and 60 µL) of the same CGF166 concentration Commercially Confidential Information in 3 cohorts of patients (n=3/cohort; total of 9 patients). All dose volumes are subject to change based on trial safety data.

Each subsequent cohort will be dosed only after the volume delivered in the prior cohort is deemed to be safe and tolerable as determined by the Drug Safety Monitoring board (DSMB). The DSMB will consist of internal Novartis personnel as well as at least one external subject matter expert who is not serving as an investigator or otherwise privy to trial data. The membership and workings of the DSMB will be detailed in the DSMB Charter. In addition, the scheduling and dosing of the first patient in each cohort will be staggered to allow at least a four week interval in between treating the remaining 2 patients in each cohort.

### Part C

Considering the preliminary overall review of the data including changes observed in audiometry for patients from Cohort 1 through Cohort 4, the DSMB endorsed the team's proposal that 30 µL is the maximum tolerated dose (volume) observed in the study.

The highest safe and tolerable volume determined in Part B will be used for IL-infusion in Part C patients. A total of 10 patients will be required for Part C of the current study. A safety review analogous to that described for parts A and B will take place whenever a block of five patients completes the first 4 weeks of study assessments.

### Part A-C

Patients will undergo the same protocol-required assessments and visit schedule in all Parts of the trial (A-C). Part C of the study will only commence once preliminary safety and tolerability has been established for CGF166 and the associated delivery methods in patients in Part A and B.

The trial duration will consist of 63 day screening period followed by a 1-3 day baseline assessment period and in house surgical dose/post operation assessment period (~6-14 days) followed by a 6 month post-dose assessment period. In addition, all dosed patients in all Parts A-C will be advised of the opportunity to enroll in a separate protocol

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During the screening period, eligibility of potential patients will be verified at the study centers.

Potential patients will be evaluated for fitness to undergoing protocol-required surgery and for the planned therapy based on physical exam, MRI, past/current medical history, and laboratory testing. During the screening period, potential patients will also undergo pre-treatment Commercially Confidential Information, auditory and vestibular function tests.

At least two outpatient visits during the screening period are anticipated in order to complete the required verification and assessments. If all screening assessments can be completed in one visit, that is allowed. Additional outpatient screening visits (i.e., more than 2 visits) are permitted pending patients' and clinic schedule and the need for re-verifications and potential re-testing.

Based on the screening assessments, one ear will be selected as the study ear and will undergo the study required surgery; criteria for the selection of the study ear are described as follow:

- The ear with more severe hearing loss as determined by pure tone audiometry and speech recognition score
- If both ears have equal severity in hearing loss, then the study ear will be selected by the investigator's preference

Upon completing the screening visits, eligible patients will be scheduled for a baseline visit and surgery.

### Baseline (Day -3 to -1)

Eligible patients will return to the study center at baseline (Day –3 to -1) and undergo pre-operative preparation as well as pre-treatment functional assessments.

### Day 1 visit

On Day 1, study patients will undergo the required protocol assessments and the stapedotomy for delivery of the study drug to the scala vestibuli perilymphatic space of the inner ear. At the completion of the surgery and study drug infusion, study patients will recover in the surgical center's post-op facility and undergo post-surgery evaluations and assessments. Study patients may be transitioned to either the inpatient unit of the surgical center or pre-arranged temporary housing close to the surgical center.

### Day 2 to Day 6 visits

Study patients will be followed up for the next 5 post surgery days (Day 2 to Day 6) and will undergo the protocol-required safety follow up evaluations. Study patients will be discharged home if there are no significant adverse events requiring prolonged monitoring. Patients will have the option to remain in the provided housing until the completion of the Day 14 visit.

Subsequent visits will be scheduled with the study patients prior to being discharged.

### Day 15 visit

Study patients will return to the study center to have surgical packing removed from their ear and will also undergo study required assessments. Patients will be discharged home or to their local housing at the end of all study required evaluations. Patients will be reminded of their next scheduled visit.

### Follow up and end of study visits

Total follow-up period in the trial will be 6 months after administration of CGF166. The follow-up visits will be at 2, 4, and 6 months/EOS.

Patient who have already completed Day 169 assessment (~ 6 month) will return to site to complete end of study visit (visit 777) as soon as practically possible. Patients who have not completed Day 169 will complete end of study visit (visit 777) on Day 169.

During each visit to the study center, post-operative recovery of the study ear will be monitored and evaluated. Study patients will also undergo the study-required safety, Commercially Confidential Information auditory, and vestibular function tests during each visit. Bio-distribution blood samples will also be collected during each visit. Samples for immunogenicity testing will be collected as per the blood log. At completion of the 6 month post-surgery visit (end of study visit), if there are no significant adverse events requiring prolonged monitoring, study patients will be considered to have completed the study and will be discharged from the study.

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Detail on the pre-surgery preparation, the surgical procedure, and the preparation of study drug as well as infusion procedure can be found in the study surgical and pharmacy and drug delivery manual.

Detail on performing the study auditory and vestibular assessments can be found in the study auditory and vestibular evaluation manual.

### Safety Data Reviews:

Prior to dosing each patient in Part A (cohort 1) and prior to dosing the 2 remaining patients in Part B (cohorts 2-4), a review of all safety and tolerability data as well as a review of selected auditory and vestibular function data will be conducted. Data considered for review will be those available up to 4 weeks post-dose, as outlined in the DSMB Charter. Safety and tolerability must be assessed as satisfactory in order to proceed with the remaining patients in the cohort. For cohorts 2-4, the decision to dose the remaining 2 patients will be made by the DSMB. If notable adverse events or safety concerns are found at one of the planned dose levels, the next planned dose level may be changed, as summarized in Section 5.5.5.

After completion of one cohort and prior to proceeding to the next cohort, a review of all safety and tolerability data, as well as limited auditory and vestibular data will be performed for all patients who received a dose of CGF166 and have completed at least 4 weeks of study

assessments. Safety and tolerability must be assessed as satisfactory in order to proceed to the next cohort. This decision will be made by the DSMB. Should notable adverse events or safety concerns be found at one of the planned dose levels, the next planned dose level may be changed, as summarized in Section 5.5.5.

For Part C, the safety review described above will be performed as each 5 patients complete their first 4 weeks of study assessments.

## 3.2 Rationale of study design

The open label, adaptive gene therapy trial design is intended to assess the safety, tolerability and efficacy of a single dose of CGF166. The trial design uses a staggered patient enrollment with continuous data reviews to limit as much unforeseen risk as possible prior to enrolling each patient in Part A or initiating another cohort in Part B, while also allowing for a potential clinical benefit. In addition, the trial design uses a sequential three Part design (Part A - Safety; Part B - Volume escalation; Part C - Efficacy) with cohort safety data reviews as described above. Based on the preliminary review of the data including changes observed in audiometry for patients from Cohort 1 through Cohort 4, the DSMB endorsed the team's proposal that 30 µL is the maximum tolerated dose (volume) and start the Part C of the study.

## 3.3 Rationale of dose/regimen, duration of treatment

As a gene therapy that requires surgical administration, this will be a single dose study to assess the safety and tolerability as well as efficacy of CGF166.

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## 3.4 Rationale for choice of comparator

Not applicable.

## 3.5 Purpose and timing of interim analyses / design adaptations

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## 3.6 Risks and benefits

### 3.6.1 Risks of clinical assessments

Magnetic resonance imaging with contrast will be performed during the course of this study. Common risks associated with MRI include interference with implanted metallic objects and there is a risk nephrogenic systemic fibrosis in patients with severe renal impairment who receive gadolinium. Accordingly, these patients must be excluded from this study. Some of the vestibular assessments may provoke nausea, vomiting and disequilibrium; these symptoms should be anticipated and managed expectantly.

### 3.6.2 Risks of general anesthesia and stapedotomy surgery

Foreseeable risks for the administration of CGF166 are largely those known for general anesthesia, which are uncommon, and those associated with modern stapedotomy.

In published series that describe stapedotomy outcomes, many patients experience transient vestibular symptoms that are procedure-related including dizziness and nausea. Post-operatively, it is possible that symptoms and signs of vestibular dysfunction may be more frequent or more severe than are usually observed after stapedotomy, or may persist for a longer period of time. Strategies to avoid patient Valsalva maneuvers and possible effects on the stapedotomy plug or the re-positioned tympanic membrane are important. Such preemptive approaches might include treatment with dexamethasone and anti-histamines, for example.

Known surgical risks of mild to moderate severity include persistent alteration of taste due to injury of the chorda tympani, infectious otitis media, perilymph fistula, reparative granuloma and perforation of the tympanic membrane, and worsened hearing. Each of the foregoing items carries a risk of 5% or less. Rare, but more serious adverse effects include facial nerve palsy, infective labyrinthitis or meningitis.

### 3.6.3 Risks of administering volume and CGF166 into the inner ear

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### 3.6.4 Potential benefits of CGF166 administration

Potential clinical benefits envisioned include improved hearing that may manifest as improved speech recognition and the ability to benefit from a hearing aid and avoid the need for a cochlear implant. Hearing correction achieved by the stapedotomy procedure often improves tinnitus in otosclerosis patients who have a post-operative improvement in their air-bone gap, so for those patients with tinnitus, it's possible that CGF166 therapy could improve the severity of their tinnitus too.

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For more details please refer to the Investigator Brochure.

## 4 Population

The study population will be comprise of patients who have severe-to-profound bilateral hearing loss or unilateral hearing loss with intact vestibular function in the non-operative ear. Patients are required to have documented non-fluctuating severe-to-profound hearing loss prior to enrollment. Up to 22 patients will be enrolled in the trial.

The investigator must ensure that all patients being considered for the study meet the following eligibility criteria. No additional criteria should be applied by the investigator, in order that the study population will be representative of all eligible patients.

Patient selection is to be established by checking through all inclusion/exclusion criteria at screening and baseline. A relevant record (e.g., checklist) of the eligibility criteria must be stored with the source documentation at the study site.

Deviation from **any** entry criterion excludes a patient from enrollment into the study.

## 4.1 Inclusion criteria

Patients eligible for inclusion in this study have to fulfill **all** of the following criteria:

1. Written informed consent must be obtained before any assessment is performed.
2. For all Parts (A, B and C) of the study, male or female patients, 18 to 75 years old, inclusive, with severe-to-profound bilateral or unilateral hearing loss with intact vestibular function. Non-fluctuating severe-to-profound hearing loss is required for the study ear and is defined as:
   - PTA within 10 dB of the PTA obtained at least 11 months previously.
   - Word recognition within 20% of previous test at least 11 months previously [AAO-HNS Hearing Classification System]
3. Candidate ear ("study ear"): Minimal residual hearing based on the pure tone average of 0.5, 1, 2, and 4 kHz thresholds of ≤110 dB HL
4. Candidate ear ("study ear"): Pure tone audiometric thresholds of ≥50 dB HL for each testable octave frequency of 0.125 and 0.250 kHz, ≥ 70 dB HL for each testable octave frequency from 0.5 through 8 kHz and sentence recognition scores ≤50% at screening. Subject responses will be monitored for vibrotactile sensation, particularly for the low-frequency stimuli (e.g., 125 and 250 Hz). A frequency that elicits vibrotactile responses at levels below 70 dB HL will be considered "not testable" for hearing threshold and only those frequencies that are testable for hearing threshold will be considered for patient inclusion/exclusion in the study.
5. Patients with intact vestibular function in at least one ear (non-study ear) as measured by vestibular evoked myogenic potential (VEMP)
6. Able to communicate well with the investigator, to understand and comply with the requirements of the study
7. Meet surgical requirements/eligibility (including MRI scan within 3 months or at screening to confirm suitability for inner ear surgery)
8. Patients must weigh at least 40 kg to participate in the study, and must have a body mass index (BMI) <45 $kg/m^2$. BMI = Body weight (kg) / $[Height (m)]^2$

## 4.2 Exclusion criteria

Patients fulfilling **any** of the following criteria are not eligible for inclusion in this study:

1. Use of other investigational drugs at the time of enrollment, or within 5 half-lives of enrollment, or until the expected PD effect has returned to baseline, whichever is longer; or longer if required by local regulations.
2. History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes.
3. Patients with hearing loss caused by genetic/developmental disorders, e.g., cochlea aplasia.
4. Patients with existing conductive hearing loss or mixed hearing loss as judged by the Principal Investigator following a thorough review of all of the trial hearing assessments, air-bone gap assessment based on air and bone pure tone audiometry and MRI scan.
5. Patients with a history of cochlear implant in the study ear.

6. Hearing loss due to any other cause that would not be expected to respond to hair cell regeneration, for example trauma or central auditory lesions or lack of an auditory nerve
7. Patients who will require ototoxic drugs as routine therapy over the course of the study, for example cystic fibrosis patients.
8. Any contraindication to the planned surgery or anesthesia as determined by the surgeon, anesthesiologist, or designee.
9. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 6 months following treatment period of the investigational medication. ***Highly effective contraception methods include:***
   - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
   - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
   - Male sterilization (at least 6 months prior to screening). For female subjects on the study the vasectomized male partner should be the sole partner for that subject.
   - Combination of any two of the following (a+b or a+c, or b+c):
     a. Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception.
     b. Placement of an intrauterine device (IUD) or intrauterine system (IUS).
     c. Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository.

     In case of use of oral contraception women should have been stabile on the same pill for a minimum of 3 months before taking study treatment.
10. Sexually active males must use a condom during intercourse after investigational drug treatment and for 6 months after stopping investigational medication and should not father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid.
11. Bilateral cochlear implants or a past attempt for cochlear implant in the study ear or any other inner ear surgery that could interfere with drug efficacy.
12. Any other otologic history, including but not limited to chronic otitis, cholesteatoma, tympanic membrane perforation, head and neck radiation or Meniere's disease, that suggests poor candidacy for cochlear implant or inner ear surgery or suggests potential interference with study auditory or vestibular function tests.
13. Abnormal vital signs and/or ECG that suggest potential contraindication for planned study anesthesia or past serious adverse reaction to anesthesia.
14. Patients with estimated glomerular filtration rate (GFR) < 30 ml/min (MDRD formula) at screening.
15. Patients with heart failure NYHA class III or IV.

16. Patients with Child-Pugh class C cirrhosis.
17. History of myocardial infarction, coronary bypass surgery, or any percutaneous coronary intervention (PCI) within 6 months prior to screening.
18. Patients who require chronic anticoagulation, except daily aspirin.
19. A psychiatric disease or substance abuse history likely to interfere with protocol compliance.
20. Any medical condition, judged by the investigator, that is likely to interfere with the patient's participation in the study, or likely to cause serious adverse events during the study.
21. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.
22. Immunocompromised patients, as judged by the investigators based on patient history, physical exam and CBC

No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

# 5 Treatment

## 5.1 Protocol requested treatment

### 5.1.1 Investigational treatment

CGF166 is a recombinant adenovirus 5 (Ad5) vector containing the human Atonal transcription factor (Hath1) cDNA.

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CGF166 will be delivered using an infusion pump system with a blunt needle cannula (as per the Surgical and Pharmacy/Drug Delivery Manuals details provided separately).

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### 5.1.2 Additional study treatment

No additional treatment beyond investigational treatment is requested for this trial.

## 5.2 Treatment arms

Patients will be assigned to one of the 5 cohorts. Part A and Part B of the study have been completed; dose volumes administered reflect the study treatment for each cohort including planned dose volume for Part C of the study (see Table 5-1 for estimated viral particle delivery quantity and normalized doses estimates).

Study treatments are defined as:

- Part A:
  - Cohort 1: single dose of 20 µL CGF166
- Part B:
  - Cohort 2: single dose of 40 or 30 µL CGF166
  - Cohort 3: single dose of 40 µL CGF166
  - Cohort 4: single dose of 60 µL CGF166
- Part C:
  - Cohort 5: single dose of 30 µL @ 10 µL/minCGF166

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## 5.3 Treatment assignment

Treatment numbers will be assigned in ascending, sequential order to eligible patients (see Section 5.5.1 for details). The investigator will enter the Treatment number on the CRF.

## 5.4 Treatment blinding

This is an open label trial.

## 5.5 Treating the patient

### 5.5.1 Treatment / Patient numbering

#### Screening number

Each patient screened is assigned a unique screening number. The screening number is a combination of the center number, that is provided by Novartis, and a three digit number starting with 001 for each patient which is assigned by the Investigator. Therefore, if the center number is 1 (any leading 0's in the center number are dropped) the screening numbers will be assigned such as 1001001, 1001002, 1001003 in ascending order. If the center number is 2 (or 0002), the screening numbers will be 1002001, 1002002, 1002003 in an ascending order.

### Treatment number

If the patient is deemed eligible for the study and will commence dosing, a treatment number will be assigned. Once assigned to a patient, a treatment number will not be reused.

The treatment number becomes the definitive patient number as soon as a patient receives the first dose of the respective study treatment.

There should be a source document maintained at the site which links the screening number to the treatment assignment number (once assigned). This source document should be provided to all appropriate parties (i.e., Central Laboratory, ECG Laboratory) as soon as this is available.

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## 5.5.2 Dispensing the study treatment

The investigational drug, CGF166 will be prepared by Novartis and supplied to the Investigator site as open labeled bulk medication in single dose septum vials.

For preparation of the study medication, please refer to the separate Pharmacy/Drug Delivery manual.

Appropriate documentation of the patient specific dispensing process must be maintained.

The medication labels will be in the local language, will comply with the legal requirements of each country, and will include storage conditions for the drug but no information about the patient.

## 5.5.3 Handling of study treatment

### 5.5.3.1 Handling of investigational treatment

Investigational treatment must be received at the study site by a designated person, handled and stored safely and properly, and kept in a secured location to which only the Investigator and designated staff have access. Upon receipt, the study drugs should be stored according to the instructions specified on the labels and in the Pharmacy/Drug Delivery Manual provided separately.

Storage conditions must be adequately monitored and appropriate temperature/humidity logs maintained as Source data.

The Investigator must maintain an accurate record of the shipment and dispensing of study drug in a drug accountability ledger. Drug accountability will be noted by the Monitor during site visits and/or at the completion of the trial.

All drug supplies are to be used only for this protocol and not for any other purpose. Unless specifically instructed by Novartis, the Investigator must not destroy any drug labels, or any partly used or unused drug supply.

At the conclusion of the study, and, if allowed during the course of the study (e.g., an open label study), the Investigator will provide a copy of the drug accountability ledger to the Monitor.

Only after receiving a written authorization by Novartis, the Investigator/designee will send all the unused and partly used drug supplies as well as the empty containers to the address provided at the time of authorization for destruction or have the unused and partly used drug supplies as well as the empty containers destroyed by the site's pharmacist, providing a drug destruction certificate.

#### 5.5.3.2 Handling of other study treatment

Not applicable.

### 5.5.4 Instructions for prescribing and taking study treatment

The dose prescribed and dispensed to the patient must be recorded on the Dosage Administration Record CRF including any observed leaking from the ear canal during dosing.

### 5.5.5 Permitted dose adjustments and interruptions of study treatment

Study drug dose adjustments and/or interruptions are not permitted, unless during surgical procedure the surgeon deems the patient ineligible or is unable to dose the patient.

In case of notable adverse events and safety concerns during dose escalation of the study, the following changes to the next planned dose level may be considered:

- Administration of a dose below the starting dose
- Administration of an intermediate dose between the current and preceding dose
- Administration of an intermediate dose between the current and next planned dose
- Repeated administration of the current dose
- Termination of any further dose escalation

These changes must be recorded on the Dosage Administration Record CRF.

### 5.5.6 Recommended treatment of adverse events

Medication used to treat AEs must be recorded on the Concomitant medications/Significant non-drug therapies CRF.

### 5.5.7 Rescue medication

Not applicable.

### 5.5.8 Concomitant treatment

All prescription medications, over-the-counter drugs and significant non-drug therapies (including physical therapy and blood transfusions) administered or taken within the timeframe defined in the entry criteria prior to the start of the study and during the study, must be recorded on the Concomitant medications/ Significant non-drug therapies section of the CRF.

Medication entries should be specific to trade name, the single dose and unit, the frequency and route of administration, the start and discontinuation date and the reason for therapy.

### 5.5.9 Prohibited treatment

Use of known ototoxins, for example systemic aminoglycoside antibiotics, should be avoided if possible following dose administration through study completions. If a known, potent ototoxin should be required, for example cisplatin, then the patient may remain in the study but should be excluded from the efficacy analysis.

### 5.5.10 Discontinuation of study treatment and premature patient withdrawal

#### Study and cohort "Stopping rules"

The study will be put on hold and no new patients dosed pending a full safety review if any of the following criteria should be met:

- 3 or more patients with study drug-related or surgical procedure-related SAEs are reported
- At least 2 patients in the same cohort experience a similar AE which is assessed as severe in intensity, and is related to the study drug or surgical procedure
- Clinical evidence of post-operative vestibular dysfunction of moderate severity (impairs instrumental activities of daily living, such as preparing meals or housework) that persists longer than 4 weeks in 2 patients.
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- 1 patient develops a severe systemic immune response attributed to study drug
- 1 patient develops a severe infection consistent with those caused by adenovirus (if confirmed to be related to study drug).

### Individual patient withdrawal

Patients may voluntarily withdraw from the study for any reason at any time. They may be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason.

If a patient withdrawal occurs for any reason, the investigator must make every effort to determine the primary reason for a patient's withdrawal from the study and record this information on the CRF.

The investigator should withdraw the patient from study if, on balance, he/she believes that continuation would be detrimental to the patient's well-being. A patient may withdraw consent from the study at any time.

A decision to not administer the single dose study treatment and patient withdrawal will be at the discretion of the Investigator, under the following circumstances:

- Complication during surgery or patient ear anatomy does not allow the surgeon to properly administer the dose infusion
- Use of prohibited treatment
- Any other protocol deviation that results in a significant risk to the patient's safety

Patients who discontinue study treatment should NOT automatically be considered withdrawn from the study. As single dose gene therapy, every effort will be to follow up with all treated patients whom have discontinued for whatever reason. See Section 6 for the required assessments of these patients after discontinuation of study treatment.

For patients who are lost to follow-up (i.e., those patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), the investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

Patients who are withdrawn from the study for reasons other than safety or lack of efficacy will not be replaced by an equal number of newly enrolled patients.

## 5.5.11 Withdrawal of informed consent

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a subject:

- Does not want to participate in the study anymore, and
- Does not allow further collection of personal data

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the subject's decision to withdraw his/her consent and record this information.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the subject are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the subject's study withdrawal should be made as detailed in the assessment table.

Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a subject's samples until their time of withdrawal) according to applicable law.

All biological samples not yet analyzed at the time of withdrawal may still be used for further testing/analysis in accordance with the terms of this protocol and of the informed consent form.

### 5.5.12 Study completion and post-study treatment

Each patient will be required to complete the study in its entirety and thereafter no further study treatment will be made available to them. The study will complete when the last patient completes their Study Completion visit, and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator. After completion of the trial, each patient will be offered the opportunity to participate in a separate follow-up trial.

The investigator must provide follow-up medical care for all patients who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care.

All patients will be expected to participate in a separate long term follow-up observational study.

### 5.5.13 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible and treated as a prematurely withdrawn patient. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing IRBs and/or ECs of the early termination of the trial.

## 6 Visit assessments

The full Assessment schedule is presented at the end of the synoptic section, above.

Patients should be seen for all visits on the designated day or as close to it as possible.

Patients who discontinue study before completing the study, and those who prematurely withdraw from the study for any reason, should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed.

Acceptable deviations ranges from assessment times based on logistical and operational considerations are detailed in separate data management module documents.

## 6.1 Dietary, fluid and other restrictions

During recruitment, screening/informed consent review, and baseline visit, the patients will be informed and reminded of the following restrictions:

- Avoid strenuous physical exercise (e.g., weight training, aerobics, football) before each visit and until after Study Completion evaluation.
- Avoid alcohol for 48 hours before each visit until after Study Completion evaluation.
- Patients should avoid getting water into their external auditory canal for 2 weeks after surgery.
- Patients may not swim for 4 weeks after surgery.
- Patients may not be passengers in airplanes for 2 weeks after surgery.

All patients will fast prior to surgery as instructed in the surgical procedure manual and continue to fast for at least 4 hours thereafter.

## 6.2 Patient demographics / other baseline characteristics

Patient demographic and baseline characteristic data to be collected on all patients include: date of birth, age, sex, race, predominant ethnicity.

Relevant medical history/current medical conditions data includes data until signature of informed consent. Where possible, diagnoses and not symptoms will be recorded.

## 6.3 Treatment exposure and compliance

Not required.

## 6.4 Efficacy assessments

Efficacy/Pharmacodynamics will be measured in this clinical study by the following assessments:

**Auditory assessments**

- Pure tone audiometry
- Speech audiometry
- Brainstem auditory evoked response evaluations (BAER)

**Vestibular assessments**

- Head Impulse Test

### 6.4.1 Auditory assessments

#### 6.4.1.1 Pure tone audiometry

Hearing sensitivity to frequency-specific pure tone stimuli will be determined by measuring audiometric thresholds through earphones (air conduction) and bone-conduction vibrator (bone conduction) using a standard loudness bracketing procedure. The patient will be asked to respond when s/he hears the tone, and the softest sound detected will be defined as threshold for that tone. Immittance testing is completed as part of standard audiometric assessment.

- Air conduction thresholds will be measured for standard-frequency and extended-frequency ranges: 0.125, 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, 12.5, 14, 16 kHz.
- Bone conduction will be measured for frequencies 0.25 -4 kHz. Masking to determine ear-specific bone conduction thresholds will be performed when necessary.

#### 6.4.1.2 Speech audiometry

For all speech perception tests, the patient repeats the words and/or sentences after they are presented. Speech perception is scored in percent of words correctly repeated.

- Ear-specific speech recognition threshold (SRT) will be measured using two-syllable spondee words via monitored live voice through headphones. SRT is defined as the lowest stimulation level at which speech perception is 50% correct.
- Ear-specific word recognition at 40 dB sensation level (SL), or maximum comfortable level if 40 dB SL not possible, will be tested using NU-6 words via monitored live voice through headphones.
- Aided word recognition testing for individual ears using consonant-nucleus-consonant (CNC) words (Peterson and Lehiste 1962) will be presented at 60 dB SPL-A in the sound field. The CNC is a test of 50 monosyllable words, and the stimuli are a pre-recorded test of 50 monosyllabic words.

#### 6.4.1.3 AzBio Sentence test

The Minimum Speech Test Battery (MSTB) for cochlear implant evaluation was updated in 2011 to include more challenging sentence test materials, such as the AzBio Sentences Test (Spahr and Dorman 2004), due to ceiling effects in performance observed with the Hearing in Noise Test (Gifford et al 2008). The AzBio Sentences Test consists of 15 sentence lists, with the MSTB including 8 additional lists, and is scored in percent of words correctly repeated. The AzBio sentence test presented at 60 dB SPL-A, both in quiet and with background 10-talker speech babble noise presented at +5 dB signal-to-noise-ratio (SNR). Presentation is in the soundfield in an individual-ear aided condition.

#### 6.4.1.4 Hearing-in-Noise-Test (HINT)

The Hearing in Noise Test (HINT) (Nilsson et al 1994) consists of 25 lists of recorded sentences presented at 60 dB SPL-A in quiet and in speech-weighted noise at +8 SNR. The HINT sentences are relatively easy to understand and often show ceiling effects of performance with cochlear implant testing. For this reason, the cochlear implant test battery

has recently been updated to replace the HINT with the AzBio Sentences Test. However, the HINT can also be administered adaptively, with the sentences remaining at a fixed stimulation level and the noise level adapted until the patient scores 50% correct understanding. Performance is quantified as signal-to-noise ratio (SNR) in dB. This adaptive testing method avoids ceiling effects observed when using fixed stimulation levels; however, this method is not routinely used clinically in the US. One potential future benefit is it resembles adaptive sentence in noise testing in other languages, such as the German Oldenburger Satztest/Oldenburg Sentence Test (OLSA). Presentation is in the sound field in an individual-ear aided condition.

#### 6.4.1.5 Brainstem auditory evoked response evaluations (BAER)

The BAER provides electrophysiologic information on the status of the auditory pathway from the periphery up through the brainstem. The BAER waveform reflects responses from different neural generators, with the most robust neural response arising from the inferior colliculus, observed as wave V. The BAER can be elicited by click or tone-burst stimuli, the latter providing more frequency-specific information.

Surface electrodes are placed as non-inverting on the vertex, inverting on lobe or mastoid of the test ear, and ground on the forehead. The patient is at rest, and the click or toneburst stimuli are presented through insert earphones at a high level (starting level depends on degree of hearing loss), and the stimulation level is decreased until BAER threshold is obtained, defined as the lowest stimulation level at which a repeatable wave V is observed.

### 6.4.2 Vestibular assessments

#### 6.4.2.1 Head Impulse Testing

The head impulse test (HIT) is a clinical maneuver used to assess the vestibulo-ocular reflex (VOR) during quick head rotations. The examiner delivers small-amplitude (<20 degree) head rotations with high peak velocities in the planes corresponding to each of the six semicircular canals. (Halmagyi and Curthoys 1988, Cremer 1998). A normal VOR results in a smooth eye movement equal and opposite direction to the head movement, thus achieving gaze stabilization without the need of a compensatory eye saccade. A patient with a deficient VOR fails to keep his/her eyes on target and subsequently makes a corrective, quick eye movement (a corrective/catch-up saccade) to refixate the target. When this refixation saccade occurs after the head has come to rest at the end of the head movement, it is visible to an examiner and serves as an indicator of hypofunctional sensation in the semicircular canal predominantly excited by the head motion. Head impulses can be directed in each of 6 directions, thereby selectively testing the function of each of the 3 semicircular canals in each of the two labyrinths.

Over time, a patient with a hypofunctional semicircular canal may develop an ability to make corrective saccades that begin and end during the head rotation. While this improves the patient's ability to maintain visual fixation of a target during head movements, it also degrades the examiner's ability to detect hypofunction of the semicircular canal. In such cases, a video Head Impulse Test (vHIT) is useful to identify VOR abnormalities that are not obvious to the examiner. A vHIT system comprises an eye-tracking camera and motion sensor

mounted on light, securely fit, head-worn goggles. Because the vHIT system's camera travels with the head, it is less susceptible to missing corrective saccades that occur during the head movement. Because the vHIT quantitatively measures head and eye angular velocities throughout a head movement, it provides a numerical estimation of VOR gain, which is calculated as the ratio of slow phase (VOR-driven) eye velocity divided by head velocity. The vHIT has been well validated against the magnetic field scleral search coil technique, which is the gold standard for HIT measurements (MacDougall et al 2013, Agrawal et al 2013).

## 6.5 Safety

### 6.5.1 Physical examination

A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and/or pelvic exams may be performed.

Information for all physical examinations must be included in the source documentation at the study site and will not be recorded the CRF. Significant findings that are present prior to informed consent are included in the Relevant Medical History CRF. Significant findings observed after informed consent signature which meet the definition of an Adverse Event must be appropriately recorded on the Adverse Event CRF.

### 6.5.2 Vital signs

Vital signs include blood pressure (BP) and pulse measurements. After the patient has been sitting for 3 minutes, with back supported and both feet placed on the floor, systolic and diastolic BP will be measured using an automated validated device, with an appropriately sized cuff. In case the cuff sizes available are not large enough for the patient's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used.

If vital signs are out-of-range at screening and baseline, the Investigator may obtain two additional readings, so that a total of up to three consecutive assessments are made, with the patient seated quietly for approximately five minutes preceding each repeat assessment.

### 6.5.3 Height and weight

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured.

Body mass index (BMI) will be calculated using the following formula:

- BMI = Body weight (kg) / [Height (m)]$^2$

### 6.5.4 Laboratory evaluations

In the case where a laboratory assessment that is listed in the inclusion/exclusion criteria is outside of a **protocol-specified range** at screening and/or at the initial baseline, the assessment may be repeated once prior to randomization. If the repeat value remains outside of protocol-specified ranges, the patient is excluded from the study.

In the case where a laboratory range is **not specified by the protocol**, but is outside the reference range for the laboratory at screening and/or initial baseline, a decision regarding whether the result is of clinical significance or not shall be made by the Investigator and shall be based, in part, upon the nature and degree of the observed abnormality. The assessment may be repeated once prior to randomization.

Further retests at screening or baseline could be permitted if deemed necessary by the investigator; however, each case must be discussed and agreed with the Sponsor on a case-by-case basis.

In all cases, the Investigator must document in the source documents, the clinical considerations (i.e., result was/was not clinically significant and/or medically relevant) in allowing or disallowing the patient to continue in the study.

Clinically relevant deviations of laboratory test results occurring during or at completion of the study must be reported and discussed with Novartis personnel. The results should be evaluated for criteria defining an adverse event and reported as such if the criteria are met. Repeated evaluations are mandatory until normalization of the result(s) or until the change is no longer clinically relevant. In case of doubt, Novartis personnel should again be contacted.

#### 6.5.4.1 Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential (e.g., neutrophils, basophils, eosinophils, monocytes, lymphocytes) and platelet count will be measured.

#### 6.5.4.2 Clinical chemistry

Albumin, alkaline phosphatase, total bilirubin, bicarbonate/$CO_2$, calcium, cholesterol, chloride, creatinine, CK, γ-GT, glucose, LDH, inorganic phosphorus, lipase, amylase, magnesium, potassium, total protein, AST, ALT, sodium, triglycerides, BUN, and uric acid (for all laboratory assessments). Anti-Nuclear Antibody (ANA), anti-neutrophil cytoplasmic antibody (ANCA), rheumatoid factor, and anti-cyclic citrullinated peptides will be measured at screening only.

If the total bilirubin concentration is increased above 1.5 times the upper limit of normal, direct and indirect reacting bilirubin should be differentiated.

#### 6.5.4.3 Urinalysis

A midstream urine sample (approx. 30 mL) will be obtained, in order to avoid contamination with epithelial cells and sediments, and allow proper assessments.

A semi-quantitative “dipstick” evaluation for the following parameters will be performed: specific gravity, pH, glucose, protein, bilirubin, ketones, nitrite, leukocytes and blood.

If the dipstick result is positive for protein, nitrite, leucocytes and/or blood, the sample will be sent for microscopic analysis of WBC, RBC and casts.

#### 6.5.4.4 Special clinical laboratory evaluations

Not applicable.

### 6.5.5 Electrocardiogram (ECG)

A standard 12 lead ECG will be performed seated. Interpretation of the tracing must be made by a qualified physician and documented on the ECG / in the ECG section of the CRF. Each ECG tracing should be labeled with the

- study number
- patient / patient initials
- patient / patient number
- date

and kept in the source documents at the study site. Clinically significant abnormalities should be recorded on the relevant medical history/Current medical conditions CRF page prior to informed consent signature and on the Adverse Events page thereafter. Clinically significant findings must be discussed with the sponsor.

The CRF will contain:

- date and time of ECG
- heart rate
- PR interval
- QT interval
- QTcF
- QRS duration

Original ECG tracings, appropriately signed, will be archived at study site.

### 6.5.6 Hearing and balance assessments

The assessments for efficacy outlined in Section 6.4 will also serve as safety assessments.

### 6.5.7 Magnetic resonance Imaging (MRI)

Magnetic resonance imaging with gadolinium (MRI) will be used to assess the structural integrity of the inner to determine if the patients study ear is suitable for enrolling the trial as well as following treatment to assess the inner ear structural integrity and evaluate for other potential complications of treatment, including labyrinthitis ossificans. The imaging acquisition will follow the local facility procedures indicating the specific hardware and software settings for acquisition of all inner ear structural parameters.

## 6.6 Pharmacokinetic assessments

Not applicable.

## 6.7 Other assessments

Not applicable.

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# 7 Safety monitoring

## 7.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (i.e., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a patient or clinical investigation patient *after providing written informed consent* for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product. Pre-existing medical conditions/diseases (i.e., Medical History(ies)) are considered AEs if they worsen after providing written informed consent. Abnormal laboratory values or test results constitute AEs only if they induce clinical signs or symptoms, or are considered clinically significant, or they require therapy.

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments.

Adverse events must be recorded on the Adverse Events CRF under the signs, symptoms or diagnosis associated with them, and accompanied by the following information:

1. the severity grade:
   - mild: usually transient in nature and generally not interfering with normal activities
   - moderate: sufficiently discomforting to interfere with normal activities
   - severe: prevents normal activities
2. its relationship to study treatment
3. its duration (e.g., start and end date)
4. whether it constitutes a serious adverse event (SAE)
5. action taken regarding study treatment
6. whether other medication or therapies have been taken (concomitant medication / non-drug therapy)
7. its outcome

An SAE is defined as any AE which meets any one of the following criteria:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent form
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
  - social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above.

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

**Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements; see Section 7.2.**

All adverse events should be treated appropriately. Treatment may include one or more of the following: no action taken (i.e., further observation only); study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication given; non-drug therapy given. The action taken to treat the adverse event should be recorded on the Adverse Event CRF.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug can be found in the Investigator Brochure (IB) or will be communicated between IB updates in the form of Investigator Notifications. This information will be included in the informed consent and should be discussed with the patient during the study as needed.

## 7.2 Serious adverse event reporting

### Screen Failures

Note the following requirement for Screen Failures: SAEs occurring after the subject has provided informed consent until the time the subject is deemed a Screen Failure must be reported to Novartis.

### Treated subjects

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until 30 days after the patient has stopped study participation (defined as time of last dose of study drug taken or last visit whichever is the later) must be reported to Novartis within 24 hours of learning of its occurrence.

Any SAEs experienced after this 30 day period should only be reported to Novartis if the investigator suspects a causal relationship to the study drug.

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until 30 days after the last study visit if there are post-treatment follow-up visits with no required procedures must be reported to Novartis within 24 hours of learning of its occurrence. Any SAEs experienced after the 30 day period should only be reported to Novartis if the investigator suspects a causal relationship to study treatment.

Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted within 24 hours of the investigator receiving the follow-up information. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs (either initial or follow-up information) is collected and recorded on the Serious Adverse Event Report Form. The investigator must assess the relationship of any SAE to each specific component of the study treatment (if the study treatment consists of several components), complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours of the awareness of the SAE to the local CMO & PS Department and also a copy to the Novartis Medical Expert and/or Clinical Trial Leader (according to page 2). The telephone and fax numbers of the contact persons in the local Drug Safety and Epidemiology department, specific to the site, are listed on page 2 of this protocol and/or in the investigator folder provided to each site. The original copy of the SAE Report

Form and the fax confirmation sheet must be kept with the case report form documentation at the study site. Follow-up information should be provided using a new paper SAE Report Form stating that this is a follow-up to a previously reported SAE.

Follow-up information provided should describe whether the event has resolved or continues, if and how it was treated, whether the treatment code was broken or not and whether the patient continued or withdrew from study participation. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the investigational treatment a Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same investigational treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities, relevant ethics committees and additional regulatory bodies as required for Gene Therapy studies (e.g the NIH in the United States) in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

## 7.3 Liver safety monitoring

To ensure patient safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

Liver events are divided into two categories:

- Liver events of special interest (AESI) which consist of LFTs elevations
- Medically significant liver events which are considered as serious adverse events (SAEs) and which consist of marked elevations of LFTs and / or pre-specified adverse events.

Please refer to Table 15-1-Appendix 3 for complete definitions of liver events.

Any liver event which meets the criteria for a "**medically significant**" event should follow the **standard procedures for SAE reporting** as described in Section 7.2.

Every liver event as defined in Table 15-1-Appendix 3 should be followed up by the investigator or designated personal at the trial site, as summarized below and detailed in Table 15-2-Appendix 3.

- Repeating the LFT to confirm elevation as appropriate
- Discontinuation of the investigational drug if appropriate
- Hospitalization of the patient if appropriate
- A causality assessment of the liver event via exclusion of alternative causes (e.g., disease, co-medications)
- An investigation of the liver event which needs to be followed until resolution

These investigations can include serology tests, imaging and pathology assessments, hepatologist's consultancy, based on investigator's discretion. All follow-up information, and the procedures performed should be recorded as appropriate in the CRF.

## 7.4 Pregnancy reporting

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the local CMO & PS Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the investigational/study treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

## 7.5 Prospective suicidality assessment

The Columbia-Suicide Severity Rating Scale (C-SSRS), a questionnaire that prospectively assesses Suicidal Ideation and Suicidal Behavior using a semi-structured interview to probe patient responses, has to be administered.

If at any assessment after screening and/or baseline the score is 4 or above on the Suicidal Ideation item or any "yes" on the Suicidal Behavior item, the patient **must** be referred to a health care professional for further assessment and/or treatment. The decision on whether the study treatment should be discontinued is to be taken by the health care professional to whom the patient is referred.

## 7.6 Early phase safety monitoring

The Investigator will monitor adverse events in an ongoing manner and inform the Sponsor of any clinically relevant observations. Any required s will be made jointly between medically qualified personnel representing the Sponsor and Investigator. Such evaluations may occur verbally, but the outcome and key discussion points will be summarized in writing (e-mail) and made available to both Sponsor and all Investigator(s). Criteria pertaining to stopping the study/treatment or adapting the study design are presented above.

When two or more clinical site(s) are participating in the clinical study, the Sponsor will advise the Investigator(s) at all sites in writing (e-mail) (and by telephone if possible) of any new, clinically relevant safety information reported from another site during the conduct of the study in a timely manner.

# 8 Data review and database management

## 8.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and CRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the CRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study drug is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the patient's file. The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the patients will be disclosed.

## 8.2 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms using fully validated software that conforms to 21 CFR Part 11 requirements. Designated investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer of the data to Novartis or the CRO working on behalf of Novartis. The Investigator must certify that the data entered into the Electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive a CD-ROM or paper copies of the patient data for archiving at the investigational site.

All data captured for this study will have an external originating source (either written or electronic). The CRF is not considered as source.

## 8.3 Database management and quality control

All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification.

Novartis staff or CRO working on Novartis's behalf will review the data entered into the eCRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data. If the electronic query system is not used, a paper Data Query Form will be sent (e.g., fax, e-mail) to the site. Site personnel will complete and sign the copy, then send it (with original signature) back to Novartis staff who will make the correction to the database.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Laboratory samples will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).



## 8.4 Data Safety Monitoring Board

A Data Safety Monitoring Board (DSMB) has been assembled for this compound to monitor safety data for the combined First In Man and Proof of Concept study. This committee is autonomous and comprises one external expert as well as selected Novartis associates who have subject matter expertise in auditory and vestibular clinical diagnosis, as well as general expertise in safety monitoring, monitoring of clinical trials, and statistical analysis and data visualization.

The DSMB will convene as outlined in the DSMB Charter to review adverse events, including clinical laboratory data, pure tone audiometry assessment and vestibular safety assessment will be continuously reviewed.

## 8.5 Adjudication Committee

Not required.

# 9 Data analysis

## 9.1 Analysis sets

For all analysis sets, patients will be analyzed according to the study treatment(s) received.

The safety analysis set will include all patients that received any study drug.

The PD analysis set will include all patients with available PD data and no protocol deviations with relevant impact on PD data.

## 9.2 Patient demographics and other baseline characteristics

All data for background and demographic variables will be listed by treatment group and patient. Summary statistics will be provided.by treatment group.

Relevant medical history, current medical conditions, results of laboratory screens, drug tests and any other relevant information will be listed by treatment group and patient.

## 9.3 Treatments (study drug, rescue medication, other concomitant therapies, compliance)

Data for study drug administration (rescue medication) and concomitant therapies will be listed by treatment group and patient.

## 9.4 Analysis of the primary variable(s)

The primary aim of this study is to determine the effect of a single injection of CGF166 on pure tone audiometry measured at 4 week intervals from month 1 to month 6 after surgery. The second primary objective is to assess the safety and tolerability of IL CGF166.

### 9.4.1 Variable(s)

The primary analysis variable is the audiometric threshold measured on a dB HL (hearing loss) scale at these frequencies: 0.125, 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, 12.5, 14, 16 kHz.

### 9.4.2 Statistical model, hypothesis, and method of analysis

Tone thresholds will be analyzed for each frequency tested separately.

For pure tone audiometry, a measure that depends on a patient being able to hear a tone, the following imputation will be done: If a patient is unable to hear the tone at a specific frequency it can be inferred that the threshold value exceeds the upper limit of the machine. In this case the value will be imputed to 5dB above the upper limit of the machine.

All pure tone audiometry air conduction threshold data will be listed and graphically displayed by patient, infusion volume, frequency, and visit/time. Summary statistics will be provided by infusion volume, frequency, ear and visit/time. Change from baseline of the thresholds (mean of screening and baseline visit) will also be summarized by infusion volume, frequency, ear and visit/time.

In addition, safety and tolerability is a co-primary endpoint, and will be analyzed as in Section 9.5.2 (Safety).

### 9.4.3 Handling of missing values/censoring/discontinuations

All missing data, which are missing due to an assessment not having been made, will be treated as "missing at random". Patients with partial data will be included in the primary analysis. Where a missing data value occurs, this will be set to missing in the analysis. For the combined baseline of screening and baseline data, where only screening or baseline data is available, this value will be taken as the baseline. If no pre-treatment data is available, the subject will be excluded from the analysis when comparing the change to pre-treatment values.

Pure tone audiometry values which are missing because the hearing threshold exceeded the upper limit of the machine will be imputed with the value of 5dB above the upper limit of the machine.

### 9.4.4 Supportive analyses

Not applicable.

## 9.5 Analysis of secondary Commercially Confidential Information variables

Secondary variables will be analyzed descriptively.

### 9.5.1 Efficacy

Secondary efficacy variables will be reported descriptively.

### 9.5.2 Safety

#### Vital signs

All vital signs data will be listed by treatment, patient, and visit/time and if ranges are available abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by treatment and visit/time.

#### ECG evaluations

All ECG data will be listed by treatment, patient and visit/time, abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

#### Clinical laboratory evaluations

All laboratory data will be listed by treatment, patient, and visit/time and if normal ranges are available abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

#### Adverse events

All information obtained on adverse events will be displayed by treatment and patient.

The number and percentage of patients with adverse events will be tabulated by body system and preferred term with a breakdown by treatment. A patient with multiple adverse events within a body system is only counted once towards the total of this body system. Exact 95% binomial confidence intervals may be provided for AE rates. If a dose-related safety signal is suspected, this may be confirmed by a permutation contrast test t using the nominal dose level as contrast.

### Other safety evaluations

Not applicable.

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## 9.6 Sample size calculation

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### 9.7 Power for analysis of key secondary variables

Not applicable.

### 9.8 Interim analyses

No interim analyses are planned in the study.

## 10 Ethical consideration

### 10.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

### 10.2 Informed consent procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent, or, if incapable of doing

so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (i.e., all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC approval.

Women of child bearing potential should be informed that taking the study drug may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

The study includes an optional pharmacogenetic component which requires a separate signature if the patient agrees to participate. It is required as part of this protocol that the Investigator presents this option to the patient. The process for obtaining consent should be exactly the same as described above for the main informed consent.

Declining to participate in these pharmacogenetic assessments will in no way affect the patient's ability to participate in the main research study.

In the event that Novartis wants to perform testing on the samples that are not described in this protocol, additional Institutional Review Board and/or Ethics Committee approval will be obtained.

## 10.3 Responsibilities of the investigator and IRB/IEC

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee / Research Ethics Board (IRB/IEC/REB) before study start. A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC/REB must be given to Novartis before study initiation. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs/REBs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

## 10.4 Publication of study protocol and results

Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and

finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

# 11 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the trial to request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

## 11.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC/REB. Only amendments that are required for patient safety may be implemented prior to IRB/IEC/REB approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the Health Authorities (where required) and the IRB/IEC/REB at the study site should be informed within 10 working days or less, if required by local regulation.

# 12 References

Available upon request.

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# 13 Appendix 1: Sample Log table – all matrices

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# 15 Appendix 3: Liver event definitions and follow-up requirements

**Table 15-1 Liver Event Definitions**

| | **Definition / threshold** |
|---|---|
| **Adverse event of special interest** | |
| Laboratory values | ALT or AST > 3 x ULN |
| | ALP > 2 x ULN |
| | TBL > 1.5 x ULN |
| **Medically significant event (SAE)** | |
| Laboratory values | ALT or AST > 5 x ULN (with or without TBL > 2 x ULN [mainly conjugated fraction]) |
| | ALP > 5 x ULN (with or without TBL > 2 x ULN [mainly conjugated fraction]) |
| | TBL > 3 x ULN |
| | Potential Hy's Law cases (defined as ALT/AST > 3 x ULN and TBL > 2 x ULN [mainly conjugated fraction] without notable increase in ALP to > 2 x ULN) |
| Adverse events | Any clinical event of jaundice (or equivalent term) |
| | ALT or AST > 3 x ULN accompanied by general malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia |
| | Any event that links to a preferred term (PT) in the MedDRA dictionary falling under the SMQ sub-module "Drug-related hepatic disorders – severe events only"* or any "Hy's law case" PT |

*These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms

**Table 15-2 Liver Event Follow Up Requirements**

| Criteria | Event type | Actions required | Follow-up monitoring |
|---|---|---|---|
| Potential Hy's Law case[a] | Medically significant | Hospitalize, if clinically appropriate<br>Report to Novartis as an SAE<br>Establish causality | ALT, AST, TBL, Alb, PT, ALP and γGT until resolution[c] (frequency at investigator discretion) |
| **ALT or AST** | | | |
| > 8 x ULN | Medically significant | Repeat LFT within 48 hours<br>Hospitalize if clinically appropriate<br>Report to Novartis as an SAE<br>Establish causality | ALT, AST, TBL, Alb, PT, ALP and γGT until resolution[c] (frequency at investigator discretion) |
| > 5 to ≤ 8 x ULN | Medically significant | Repeat LFT within 48 hours<br>If elevation persists for *more than 2 weeks*, discontinue the study drug<br>Report to Novartis as an SAE<br>Establish causality | ALT, AST, TBL, Alb, PT, ALP and γGT until resolution[c] (frequency at investigator discretion) |
| > 3 x ULN accompanied by symptoms[b] | Medically significant | Hospitalize if clinically appropriate<br>Report to Novartis as an SAE<br>Establish causality | ALT, AST, TBL, Alb, PT, ALP and γGT until resolution[c] (frequency at investigator discretion) |
| > 3 to ≤ 5 x ULN<br>(patient is asymptomatic) | AESI | Central laboratory to report to Investigator & Novartis<br>Repeat LFT once or twice in the week<br>If elevation persists, establish causality | Investigator discretion<br>Monitor LFT within 1 to 4 weeks or at next visit |
| ≤ 3 x ULN<br>(patient is asymptomatic) | N/A | Repeat LFT at next visit | |
| **ALP (isolated)** | | | |
| > 5 x ULN | Medically significant | Repeat LFT within 48 hours<br>If elevation persists, report to Novartis as an SAE<br>Establish causality | Investigator discretion<br>Monitor LFT within 1 to 4 weeks or at next visit |
| > 2 to ≤5 x ULN<br>(patient is asymptomatic) | AESI | Central laboratory to report to Investigator & Novartis<br>Repeat LFT once or twice in the week<br>If elevation persists, establish causality | Investigator discretion<br>Monitor LFT within 1 to 4 weeks or at next visit |
| ≤ 2 x ULN<br>(patient is asymptomatic) | N/A | Repeat LFT at next visit | |

| Criteria | Event type | Actions required | Follow-up monitoring |
|---|---|---|---|
| **TBL (isolated)** | | | |
| > 3 x ULN | Medically significant | Repeat LFT within 48 hours<br>Hospitalize if clinically appropriate<br>Report to Novartis as an SAE<br>Establish causality | ALT, AST, TBL, Alb, PT, ALP and γGT until resolution[c] (frequency at investigator discretion)<br>Test for hemolysis (e.g., reticulocytes, haptoglobin, unconjugated [indirect] bilirubin) |
| > 1.5 to ≤ 3 x ULN (patient is asymptomatic) | AESI | Central laboratory to report to Novartis<br>Repeat LFT once or twice in the week<br>If elevation persists, establish causality | investigator discretion<br>Monitor LFT within 1 to 4 weeks or at next visit |
| ≤ 1.5 x ULN (patient is asymptomatic) | N/A | Repeat LFT at next visit | |
| **Preferred terms** | | | |
| Jaundice | Medically significant | Hospitalize the patient<br>Report to Novartis as an SAE<br>Establish causality | ALT, AST, TBL, Alb, PT, ALP and γGT until resolution[c] (frequency at investigator discretion) |
| "Drug-related hepatic disorders - severe events only" SMQ AE | Medically significant | hospitalization if clinically appropriate<br>Report to Novartis as an SAE<br>Establish causality | Investigator discretion |

[a] Elevated ALT/AST > 3 x ULN and TBL > 2 x ULN but with no notable increase in ALP to > 2 x ULN

[b] General malaise, fatigue, abdominal pain, nausea, or vomiting, rash with eosinophilia

[c] Resolution is defined as an outcome of one of the following: return to baseline values, stable values at three subsequent monitoring visits at least 2 weeks apart, remain at elevated level after a maximum of 6 months, liver transplantation, and death.