NOVARTIS

Clinical Development

CGF166

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

TSc RAP Module 3: Detailed Statistical Methodology

Author(s):	Personal Protected Data

Document type:	Amendment 2 TSc RAP Module 3: Detailed Statistical Methodology
Document status:	Final
Release date:	17-Aug-2018

Table of contents

List of tables

Commercially Confidential Information

1 Introduction to RAP documentation

1.1 Scope

The RAP documents contain detailed information to aid the production of Statistics & Programming input into the Clinical Study Report (CSR) for trial ***"CCGF166X2201".***

Module 3 (M3) provides the description of the statistical methodology used to analyze the data, **Module 7** (M7) details the presentation of the data, including shells of summary tables, figures and listings, and **Module 8 (**M8) contains programming specifications e.g. for derived variables and derived datasets, to support the creation of CSR outputs.

1.2 Changes to RAP documentation (M3)

Refer to corresponding guidances and Translational Sciences (TSc) RAP Addendum template for detailed information on the requirements of documenting changes to RAP documentation.

For the statistical methodology (M3), any major changes occurring before database lock to the statistical methodology should be reflected in the RAP M3 documentation via version control (new document version to be approved by the trial team as the original module.

Major changes include, but are not limited to, changes in protocol that affect study design and statistical methodology.

Minor changes to the RAP M3 documentation can be captured e.g. by a study note to file / note in RAP Addendum or within the CSR itself. Minor changes include, but are not limited to, change in statistical model. Corrections of typographical errors or modification of spelling (from English to American, for example) do not need to be incorporated into the RAP M3 documentation.

2 Study objectives and design

2.1 Study objectives

2.1.1 Primary objectives

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

2.1.2 Secondary objectives

- To assess the efficacy of CGF166 as determined by the change in otoacoustic emission testing compared to pretreatment values
- 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 caloric nystagmography and vestibulo-ocular reflex (VOR) 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 and the contralateral ear

2.1.3 Exploratory objectives

Commercially Confidential Information

2.2 Study design and treatment

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.

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 hearing loss with intact vestibular function in the non-operative ear. Patients are required to have documented non-fluctuating hearing loss.

Commercially Confidential Information

Part A

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).

Part B

Part B will include a volumetric escalation design to evaluate infusion volumes of the same CGF166 concentration Commercially Confidential Information in 4 cohorts of patients (N=3/cohort; total of 12 patients).

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.

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.

Part C

Once the highest safe and tolerable volume is determined in previous cohorts, it will be used for IL-infusion in Part C patients. A total of 20 patients, possibly increasing to 30 based on a sample size re-estimation after a data review of the Part A and B (cohorts 1-5), will be required for Part C of the current study.

3 First interpretable results (FIR)

Commercially Confidential Information

4 Interim analyses

Commercially Confidential Information

5 Statistical methods: Analysis sets

All patients that received study drug and with no protocol deviations with relevant impact on safety will be included in the safety analysis set.

Commercially Confidential Information

Commercially Confidential Information

6 Statistical methods for Pharmacokinetic (PK) parameters

Not applicable.

7 Statistical methods for Pharmacodynamic (PD) parameters

7.1 Analysis of the primary variable

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.

7.1.1 Variable

The primary variable is the audiometric threshold (air conduction) 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.

7.1.2 Statistical model, hypothesis, and method of analysis

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.

7.1.3 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.

7.2 Analysis of secondary Commercially Confidential Information variables

Unless stated specifically, the baseline result will be the result measured at Baseline (Visit 2). Where a patient has missing data at Visit 2, Screening (Visit 1) data may be used as their baseline.

7.2.1 Auditory assessments

7.2.1.1 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). Air conduction thresholds will be reported as described in Section 7.1.

Bone conduction will be measured for frequencies 0.25 – 4 kHz. All bone conduction threshold data will be listed by infusion volume, patient, frequency, and visit/time.

7.2.1.2 Speech audiometry

For all speech recognition tests (ear-specific speech recognition threshold [SRT], ear-specific word recognition at 40 dB sensation level [SL], aided word recognition) the data will be listed by infusion volume, patient and visit/time.

7.2.1.3 AzBio Sentence test

The Minimum Speech Test Battery (MSTB) and AzBio Sentences Test data will be listed by infusion volume, patient and visit/time.

7.2.1.4 Hearing-in-Noise-Test (HINT)

The data from the HINT will be listed by infusion volume, patient and visit/time.

7.2.1.5 Brainstem auditory evoked response evaluations (BAER)

The BAER data will be listed by infusion volume, patient and visit/time.

7.2.1.6 Distortion Product Otoacoustic emission testing (DPOAE)

The DPOAE data will be listed by infusion volume, patient and visit/time.

7.2.2 Vestibular assessments

7.2.2.1 Rotary Chair

Rotational chair tests assess the component of the vestibule-ocular reflex (VOR) mediated by the horizontal semicircular canals. The VOR responses are quantified and analyzed as gain, phase, and asymmetry. The rotary chair response data will be listed by infusion volume, frequency, patient and visit/time.

7.2.2.2 Head Impulse Testing

The head impulse testing data will be listed by infusion volume, patient and visit/time.

Commercially Confidential Information

8 Statistical methods for safety and tolerability data

Patient demographics and other baseline characteristics

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

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

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

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

8.1 Safety

The second primary objective is to assess the safety and tolerability of IL CGF166.

Vital signs

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

ECG evaluations

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

Clinical laboratory evaluations

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

Adverse events

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

The number and percentage of patients with adverse events will be tabulated by body system and preferred term with a breakdown by infusion volume where applicable. A patient with multiple adverse events within a body system is only counted towards the total of this body system.

Magnetic Resonance Imaging (MRI)

An MRI will be used to assess the structural integrity of the inner ear at screening and following treatment. The MRI data will be listed by infusion volume, patient and visit.

Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS data will be listed by infusion volume, patient and visit/time.