

AZASETRON FOR THE PRESERVATION OF RESIDUAL HEARING FOLLOWING COCHLEAR IMPLANTATION

FIELD OF INVENTION

- 5 [0001] The present invention relates to the preservation of residual hearing following insertion of a cochlear implant in a subject in need thereof.

BACKGROUND OF INVENTION

- [0002] 466 million people worldwide have disabling hearing loss, with 900 million people worldwide expected to have disabling hearing loss by 2050 (World Health
10 Organization (WHO) 2020). There are currently no medications approved by any regulatory agency to improve or treat hearing loss, and use of hearing aids and hearing implants, in particular cochlear implants, are the main treatment options.

- [0003] Cochlear implants started to be developed in the 1960s. Since that time, rapid
15 advances in digital technology have led to the development of highly sophisticated devices that can deliver patterned auditory information at rapid rates to surviving auditory neurons. Their basic principle is based on the transformation of sound waves into an electrical signal by a processor. Equipped with an electrode, cochlear implants thus directly stimulate the intact auditory nerve in the cochlea.

- [0004] Originally, cochlear implants were only indicated for total congenital bilateral
20 deafness in newborns and for profound acquired deafness in adults who could not achieve sufficient gain with conventional hearing aids. However, due to the improved performance and low complication rate of this technology, the indications for cochlear implants now extend to profound single ear hearing loss and severe high frequency hearing loss with residual hearing at low frequencies.

- 25 [0005] Cochlear implantation is thus currently considered the "gold standard" treatment for severe to profound sensorineural hearing loss. However, one of the complications

following the insertion of a cochlear implant is the loss of the residual hearing at low frequencies. Apart from purely surgical technical considerations that can reduce this risk, there are non-surgical factors that can help to improve rates of residual hearing preservation after cochlear implant surgery. Such non-surgical factors include the choice
5 of electrode design and the use of corticosteroids, such as dexamethasone, for anti-inflammatory action.

[0006] Azasetron (also known as arazasetron) is a small molecule which is currently being investigated as a therapeutic and prophylactic treatment for sensorineural hearing loss (WO2016/184900). In particular, azasetron is thought to be able to protect and
10 preserve inner ear tissue from damage responsible for hearing impairment. Azasetron may thus be able to preserve residual hearing following insertion of a cochlear implant. It would be helpful to identify the subjects, recipients of a cochlear implant, most likely to benefit from the administration of azasetron.

[0007] The Inventors have now obtained data indicating that azasetron preserves
15 residual hearing in subjects being the recipient of a cochlear implant. In particular, the data indicate that subjects having a hearing threshold at baseline in at least one ear corresponding to an unaided audiometric threshold at baseline greater than 65 dB are more likely to benefit from the administration of azasetron.

[0008] The present invention thus relates to azasetron or an analog of azasetron, or a
20 pharmaceutically acceptable salt and/or solvate thereof, for use in the preservation of residual hearing following insertion of a cochlear implant in a subject in need thereof, in particular in a subject most likely to benefit from the administration of azasetron or an analog of azasetron, or a pharmaceutically acceptable salt and/or solvate thereof, such as a subject having a hearing threshold at baseline in at least one ear corresponding to an
25 unaided audiometric threshold at baseline greater than 65 dB, the unaided audiometric threshold being preferably expressed as the average of at least 3 values each determined at a different frequency within the range from 0.25 kHz to 0.75 kHz.

SUMMARY

[0009] The present invention relates to azasetron or an analog of azasetron, or a pharmaceutically acceptable salt and/or solvate thereof, for use in the preservation of residual hearing following insertion of a cochlear implant in a subject in need thereof, wherein the subject has a hearing threshold at baseline in at least one ear corresponding to an unaided audiometric threshold at baseline greater than 65 dB, the unaided audiometric threshold being expressed as the average of at least 3 values each determined at a different frequency within the range from 0.25 kHz to 0.75 kHz.

[0010] In some embodiments, the unaided audiometric threshold is expressed as the average of the values determined at 0.25 kHz, 0.5 kHz and 0.75 kHz. In some embodiments, the unaided audiometric threshold is unaided pure-tone average (PTA).

[0011] In some embodiments, the pharmaceutically acceptable salt of azasetron or an analog thereof is selected from a besylate salt, a malate salt, and a hydrochloride salt.

[0012] In some embodiments, azasetron is (*R*)-azasetron, (*S*)-azasetron, a mixture thereof, or a pharmaceutically acceptable salt and/or solvate thereof. In some embodiments, azasetron is (*R*)-azasetron or a pharmaceutically acceptable salt and/or solvate thereof. In some embodiments, the pharmaceutically acceptable salt of azasetron is (*R*)-azasetron besylate.

[0013] In some embodiments, the analog of azasetron is a benzoxazine compound or a pharmaceutically acceptable salt and/or solvate thereof, preferably selected from 6-chloro-3,4-dihydro-2-methyl-3-oxo-N-(3-quinuclidinyl)-2H-1,4-benzoxazine-8-carboxamide, 6-chloro-3,4-dihydro-2,4-dimethyl-3-oxo-N-(3-quinuclidinyl)-2H-benzoxazine-8-carboxamide, 6-chloro-2-ethyl-3,4-dihydro-4-methyl-3-oxo-N-(3-quinuclidinyl)-2H-1,4-benzoxazine-8-carboxamide, 6-bromo-3,4-dihydro-2,4-dimethyl-3-oxo-N-(3-quinuclidinyl)-2H-1,4-benzoxazine-8-carboxamide, 6-chloro-3,4-dihydro-2,2,4-trimethyl-3-oxo-N-(3-quinuclidinyl)-2H-1,4-benzoxazine-8-carboxamide, and pharmaceutically acceptable salts and/or solvates thereof.

[0014] In some embodiments, azasetron or the analog of azasetron, or the pharmaceutically acceptable salt and/or solvate thereof, is for administration at a daily dose ranging from about 20 mg to about 200 mg. In some embodiments, azasetron or the analog of azasetron, or the pharmaceutically acceptable salt and/or solvate thereof, is for administration at a daily free base equivalent dose of about 40 mg or of about 60 mg.

[0015] In some embodiments, azasetron or the analog of azasetron, or the pharmaceutically acceptable salt and/or solvate thereof, is for oral administration. In some embodiments, azasetron or the analog of azasetron, or the pharmaceutically acceptable salt and/or solvate thereof, is for local administration.

[0016] In some embodiments, azasetron or the analog of azasetron, or the pharmaceutically acceptable salt and/or solvate thereof, is for administration from at least 3 days prior to insertion of the cochlear implant.

DEFINITIONS

[0017] In the present invention, the following terms have the following meanings:

[0018] The terms “**a**” and “**an**” refer to one or to more than one (*i.e.*, to at least one) of the grammatical object of the article. By way of example, “an element” means one element or more than one element.

[0019] “**About**”, when preceding a figure, encompasses plus or minus 10%, or less, of the value of said figure. It is to be understood that the value to which the term “about” refers is itself also specifically, and preferably, disclosed.

[0020] “**Baseline**”, when qualifying a parameter observed in the subject, refers to the time preceding the start of administration to the subject of azasetron or an analog of azasetron, or a pharmaceutically acceptable salt and/or solvate thereof, as described herein. For example, for a given subject, the hearing threshold or pure-tone average (PTA) at baseline is the hearing threshold or PTA of the subject prior to the first administration to the subject of azasetron or an analog of azasetron, or a pharmaceutically acceptable salt and/or solvate thereof, as described herein.

[0021] As used herein, “**PTA**” refers to pure-tone average and corresponds to the average of hearing thresholds determined at a set of fixed frequencies. For example, the pure-tone average may correspond to the average of the hearing thresholds determined with pure tone audiometry at 0.250 kHz, 0.5 kHz and 0.75 kHz.

5 [0022] “**Pharmaceutically acceptable excipient**” or “**pharmaceutically acceptable carrier**” refers to an excipient or carrier that does not produce an adverse, allergic or other untoward reaction when administered to a subject. It includes any and all solvents, such as, for example, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents. A pharmaceutically acceptable excipient or
10 carrier refers to a non-toxic solid, semi-solid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. For human administration, preparations should meet sterility, pyrogenicity, general safety and purity standards as required by the regulatory offices such as the FDA (U.S. food and drug administration) or EMA (European medicines agency).

15 [0023] “**Subject**” refers to a mammal, preferably a human. The mammal may be selected from cats, dogs, cows, pigs, horses, monkeys, apes and humans. In particular, the mammal may be selected from cats, dogs and humans. The mammal may be a primate, in particular a human. The subject may be a “**patient**”, *i.e.*, a mammal, preferably a human, who/which is awaiting the receipt of, or is receiving medical care or was/is/will
20 be the object of a medical procedure, or is monitored for hearing loss. A “**subject in need of treatment**” may be a subject who is awaiting the receipt of, or is receiving medical care, or was/is/will be the object of a medical procedure, or is monitored for hearing loss.

[0024] “**Therapeutically effective amount**” or “**therapeutically effective dose**” refers to the amount or dose of azasetron or an analog of azasetron, or a pharmaceutically
25 acceptable salt and/or solvate thereof, that is aimed at, without causing significant negative or adverse side effects to the subject in need of treatment, (i) preserving residual hearing following insertion of a cochlear implant or (ii) preventing or slowing down or attenuating residual hearing loss following insertion of a cochlear implant.

[0025] “**Treating**” or “**Treatment**” refers to a therapeutic treatment, to a prophylactic
30 (or preventative) treatment, or to both a therapeutic treatment and a prophylactic (or

preventative) treatment, wherein the object is to prevent, reduce, or slow down (lessen) residual hearing loss following insertion of a cochlear implant. A subject being a cochlear implant recipient may thus be successfully "treated", if, after receiving a therapeutically effective amount or dose of azasetron or an analog of azasetron, or a pharmaceutically acceptable salt and/or solvate thereof, the subject shows a preserved residual hearing and/or a reduced or lessened or minimized residual hearing loss. Parameters for assessing successful treatment are readily measurable by routine procedures familiar to a physician. In particular, examples of methods for assessing residual hearing are mentioned hereinafter.

10 DETAILED DESCRIPTION

- [0026] The present invention relates to azasetron or an analog of azasetron, or a pharmaceutically acceptable salt and/or solvate thereof, for use in the preservation of residual hearing following insertion of a cochlear implant in a subject in need thereof as described herein.
- 15 [0027] As used herein, "insertion of a cochlear implant" may also be referred to as "cochlear implantation". Thus, in other words, the present invention relates to azasetron or an analog of azasetron, or a pharmaceutically acceptable salt and/or solvate thereof, for use in the preservation of residual hearing following cochlear implantation in a subject in need thereof as described herein.
- 20 [0028] As used herein, subjects undergoing or having undergone insertion of a cochlear implant may be referred to as "cochlear implant recipients". Thus, in other words, the present invention relates to azasetron or an analog of azasetron, or a pharmaceutically acceptable salt and/or solvate thereof, for use in the preservation of residual hearing in a subject being a cochlear implant recipient as described herein.
- 25 [0029] As used herein, "preservation of residual hearing" may also be referred to as treatment (in particular prophylactic treatment or prevention) of residual hearing loss. Thus, in other words, the present invention relates to azasetron or an analog of azasetron, or a pharmaceutically acceptable salt and/or solvate thereof, for use in the treatment (in

particular the prophylactic treatment or prevention) of residual hearing loss following insertion of a cochlear implant in a subject in need thereof as described herein.

[0030] As used herein “subject to be treated” or “subject in need of treatment” refers to a cochlear implant recipient (*i.e.*, a subject inserted or to be inserted with a cochlear
5 implant) in whom residual hearing is to be preserved (that is to say in whom residual hearing loss is to be prevented or minimized).

[0031] As used herein, “residual hearing” refers to the remaining hearing assessed in the impaired ear (*i.e.*, in the ear affected by hearing loss). In other words, residual hearing refers to the hearing acuity that can be assessed in the impaired ear, *i.e.*, in the ear affected
10 by hearing loss. Accordingly, “residual hearing loss” refers to the loss of residual hearing that may occur, in particular after insertion of a cochlear implant.

[0032] Methods for assessing hearing acuity are well-known by the skilled artisan. Examples of such methods include audiometric testing, in particular pure tone audiometry corresponding to pure tone audiometric air conduction test and/or pure tone audiometric
15 bone conduction test, speech audiometry, behavioral observation audiometry, visual reinforcement audiometry, conditioned play audiometry. Methods for assessing hearing acuity also include ABR (auditory brainstem responses) measurement, DPOAE (distortion product otoacoustic emissions) measurement, TEOAE (transiently evoked otoacoustic emissions) measurement, speech-in-noise test, word comprehension test,
20 tympanometry, acoustic reflex tests, and tuning fork test.

[0033] In particular, residual hearing may be assessed using audiometry or audiometric testing, preferably pure tone audiometry. Pure tone audiometry is considered a gold standard test for assessing hearing acuity. Pure tone audiometry is a standardized subjective hearing test determining air-conduction and/or bone-conduction hearing
25 thresholds (expressed in dB) at a given frequency or at a set of fixed frequencies, usually selected in the range from 0.125 kHz to 8 kHz. The hearing thresholds determined at a given frequency may be plotted on an audiogram for each ear independently. For example, the hearing threshold (at a given frequency or expressed as the average of hearing thresholds at a set of fixed frequencies) may be defined as the lowest audible

level, measured twice out of three presentations to the subject.

[0034] A hearing threshold, in particular a hearing threshold determined with pure tone audiometry, may be referred to as pure-tone average (PTA), which corresponds to the average of hearing thresholds determined at a set of fixed frequencies. For example, a
5 pure-tone average may correspond to the average of 2, 3, 4 or more hearing thresholds each determined at a different frequency. The frequencies may be selected from 0.125, 0.25, 0.5, 0.75, 1, 2, 3, 4, and 8 kHz. In particular, the frequencies may be consecutive frequencies. Example of consecutive frequencies selected from 0.125, 0.25, 0.5, 0.75, 1, 2, 3, 4, and 8 kHz include 0.125, 0.25, and 0.75 kHz; or 0.25, 0.5, and 0.75 kHz; or 0.5,
10 0.75, and 1 kHz.

[0035] Residual hearing is assessed unaided, that is to say without any hearing device such as a hearing aid aiming at amplifying sounds (*e.g.*, behind-the-ear (BTE) aids, receiver-in-the-canal (RIC) aids, in-the-ear (ITE) aids, or in-the-canal (ITC) aids, or completely-in-the-canal (CIC) aids). In cochlear implant recipients, residual hearing is
15 assessed without the aid of the cochlear implant (for example after turning off the device or after removing the external part of the device).

[0036] Residual hearing preservation may be assessed by conducting audiometric testing over time in the impaired ear(s), in particular before and after insertion of the cochlear implant. When assessed after insertion of the cochlear implant, residual hearing may be
20 assessed prior to the initial activation of the cochlear implant, which usually occurs about 2 to 4 weeks after cochlear implant surgery. For example, residual hearing may be assessed about 1, 2, 3, or 4 week(s) after insertion of the cochlear implant. Alternatively or additionally, when assessed after insertion of the cochlear implant, residual hearing may be assessed after the initial activation of the cochlear implant, which as indicated
25 above usually occurs about 2 to 4 weeks after cochlear implant surgery. For example, residual hearing may be assessed about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 month(s) after insertion of the cochlear implant.

[0037] Residual hearing preservation may thus be assessed by determining the hearing threshold or audiometric threshold (*e.g.*, pure-tone average or PTA) over time, in

particular before and after insertion of the cochlear implant as described above. Low frequencies (*e.g.*, 0.125, 0.25, 0.5, 0.75 and 1 kHz) are of particular importance for assessing residual hearing because cochlear implants are typically proposed to subjects experiencing hearing loss at higher frequencies (for example frequencies higher than 1 kHz). Therefore, at the time of cochlear implantation, some cochlear implant recipients typically retain some level of hearing at the lower frequencies (for example frequencies equal to or lower than 1 kHz). Accordingly, residual hearing preservation may in particular be assessed by determining the hearing threshold or audiometric threshold (*e.g.*, pure-tone average or PTA) at low frequencies such as 0.125, 0.25, 0.5, 0.75 and/or 1 kHz.

[0038] For example, it may be considered that, for a subject, residual hearing is preserved if, after insertion of the cochlear implant, the unaided hearing threshold or unaided audiometric threshold of said subject does not increase by 10 dB or more, in particular as compared to the unaided hearing threshold or unaided audiometric threshold at baseline.

[0039] As used herein, the expression “does not increase by 10 dB or more”, encompasses any increase of less than 10 dB, any decrease and any absence of variation. In accordance with such definition, it would thus be considered that residual hearing is preserved for a subject if, after insertion of the cochlear implant, the unaided hearing threshold or unaided audiometric threshold of said subject does not vary, or decreases, or increases by less than 10 dB, in particular as compared to the unaided hearing threshold or unaided audiometric threshold at baseline.

[0040] Hearing preservation may also be assessed through the calculation of a hearing preservation percentage (HP %), as follows:

$$\text{HP \%} = [1 - (\text{PTA post-implantation} - \text{PTA pre-implantation} / (\text{PTA max} - \text{PTA pre-implantation}))] * 100,$$

with PTA standing for pure-tone average, as described in Skarzynski *et al.* Towards a consensus on a hearing preservation classification system. *Acta Otolaryngol Suppl.* 2013;(564):3-13.

From the calculated hearing preservation percentage (HP %), a classification may be established, wherein: a hearing preservation percentage greater than 75% corresponds to

a complete or near-complete preservation (HP1); a hearing preservation percentage greater than 25% and equal to or lower than 75% corresponds to a partial preservation (HP2); a hearing preservation percentage ranging from 0 to 25% corresponds to a minimal preservation (HP3); and no measurable hearing corresponds to
5 loss of hearing or no hearing (HP4).

[0041] It may alternatively be considered that, for a subject, residual hearing is preserved if, after cochlear implantation, the unaided hearing threshold or unaided audiometric threshold of said subject is lower than 85 dB, in particular at 0.125 kHz, 0.25 kHz and/or 500 kHz.

10 [0042] As used herein, “cochlear implant” refers to an electronic hearing device that stimulates the auditory nerve through electrode(s) placed in the cochlea of the inner ear. Cochlear implants allow sound and speech to be processed and sent to the brain, thus producing useful hearing sensations. Cochlear implants generally consist of two main parts:

- 15 - an external part comprising a microphone/receiver, a sound processor (or speech processor), and a transmitter system; and
- an internal part comprising a receiver-stimulator, which receive signals from the external part and convert them into electric impulses, and an electrode array (sometimes simply referred to as “electrode”) which is a group of electrodes that
20 collects the impulses from the stimulator and sends them to different regions of the auditory nerve.

[0043] Different designs or types of cochlear implants exist. In particular, cochlear implants can be equipped with various types of electrodes, which may either be straight, curved or perimodiolar, and vary in length, from short to long.

25 [0044] In some embodiments, the cochlear implant is designed specifically to preserve residual hearing. The choice of implant may take into account factors such as the type of electrode, length, and position, which all play a significant role in minimizing damage to existing auditory structures and thus in preserving residual hearing.

[0045] In some embodiments, the cochlear implant has a slim straight electrode. Examples of cochlear implants having a slim straight electrode include cochlear implant Nucleus® CI-622 (Cochlear™).

5 [0046] In some embodiments, the subject in need of treatment suffers from sensorineural hearing loss. Examples of causes of sensorineural hearing loss include genetic causes, ototoxic compounds, excessive noise exposure (such as, for example, exposure to a noise of more than about 70 dB, 80 dB, 90 dB, 100 dB, 110 dB, 120 dB, or 130 dB) or blast exposure, aging, inflammation, inner ear infection (such as, for example, viral and bacterial infections), autoimmunity (such as, for example, autoimmune inner ear
10 diseases), vasculopathy, illnesses (including but not limited to high blood pressure and diabetes), head trauma, and tumors.

[0047] In some embodiments, sensorineural hearing loss is unilateral. That is to say, in some embodiments, only one ear of the subject in need of treatment is affected by sensorineural hearing loss. In some embodiments, sensorineural hearing loss is bilateral.
15 That is to say, in some embodiments, both ears of the subject in need of treatment are affected by sensorineural hearing loss.

[0048] In some embodiments, the subject in need of treatment is yet to undergo cochlear implantation. In some embodiments, the subject in need of treatment has already undergone cochlear implantation.

20 [0049] In some embodiments, the subject in need of treatment may be more severely affected, with an unaided audiometric threshold at baseline greater than 65 dB.

[0050] By “unaided audiometric threshold” it is meant that the audiometric threshold is determined without any hearing device, for example without any hearing aid aiming at amplifying sounds. In cochlear implant recipients, the unaided audiometric threshold is
25 determined after turning off the device or after removing the external part of the device.

[0051] According to the present invention, the hearing threshold at baseline is determined in at least one ear. In subjects suffering from unilateral hearing loss, the hearing threshold at baseline is determined in the impaired ear.

[0052] By “hearing threshold at baseline” it is meant hearing threshold prior to any administration to the subject of azasetron or an analog of azasetron, or a pharmaceutically acceptable salt and/or solvate thereof, as described herein. In some embodiments, the hearing threshold at baseline corresponds to the hearing threshold prior to any administration to the subject of azasetron or an analog of azasetron, or a pharmaceutically acceptable salt and/or solvate thereof, as described herein and prior to the insertion of the cochlear implant.

[0053] In some embodiments, the unaided audiometric threshold is expressed as the average of at least 2 values, preferably of at least 3 values, each determined at a different frequency within the range from 0.125 kHz to 4 kHz, preferably within the range from 0.125 kHz to 2 kHz, more preferably within the range from 0.125 kHz to 1 kHz. In some embodiments, the unaided audiometric threshold is expressed as the average of at least 2 values, preferably of at least 3 values, each determined at a different frequency selected from 0.125 kHz, 0.25 kHz, 0.5 kHz, 0.75 kHz, 1 kHz, 2 kHz, 3 kHz, and 4 kHz. In particular, the unaided audiometric threshold may be expressed as the average of the values determined at 2 or more, preferably 3 or more, consecutive frequencies selected from 0.125 kHz, 0.25 kHz, 0.5 kHz, 0.75 kHz, 1 kHz, 2 kHz, 3 kHz and 4 kHz. Examples of 2 consecutive frequencies selected from 0.125 kHz, 0.25 kHz, 0.5 kHz, 0.75 kHz, 1 kHz, 2 kHz, 3 kHz and 4 kHz include 0.125 kHz and 0.25 kHz; 0.25 kHz and 0.5 kHz; 0.5 kHz and 0.75 kHz; 0.75 kHz and 1 kHz; and so on.

[0054] In some embodiments, the unaided audiometric threshold is expressed as the average of at least 2 values, preferably of at least 3 values, each determined at a different frequency within the range from 0.25 kHz to 0.75 kHz.

[0055] In some embodiments, the unaided audiometric threshold is expressed as the average of at least 2 values, preferably of at least 3 values, each determined at a different frequency selected from 0.25 kHz, 0.5 kHz and 0.75 kHz. In some embodiments, the unaided audiometric threshold is expressed as the average of the values determined at 0.25 kHz, 0.5 kHz and 0.75 kHz.

[0056] In some embodiments, the unaided audiometric threshold is an unaided pure-tone average (PTA).

[0057] In some embodiments, the subject in need of treatment has a hearing threshold at baseline corresponding to a pure-tone average (PTA) at baseline greater than 65 dB, the
5 PTA being expressed as the average of at least 3 values each determined at a different frequency within the range from 0.25 kHz to 0.75 kHz, preferably as the average of the values determined at 0.25 kHz, 0.5 kHz and 0.75 kHz.

[0058] In some embodiments, the unaided audiometric threshold is expressed as the value determined at a single frequency within the range from 0.125 kHz to 4 kHz,
10 preferably within the range from 0.125 kHz to 2 kHz, more preferably within the range from 0.125 kHz to 1 kHz. In some embodiments, the unaided audiometric threshold is expressed as the value determined at a single frequency selected from 0.125 kHz, 0.25 kHz, 0.5 kHz, 0.75 kHz, 1 kHz, 2kHz, 3 kHz, and 4 kHz. In some embodiments, the unaided audiometric threshold is expressed as the value determined at 0.125 kHz,
15 0.25 kHz, 0.5 kHz, 0.75 kHz or 1 kHz. In some embodiments, the unaided audiometric threshold is expressed as the value determined at a single frequency within the range from 0.25 kHz to 0.75 kHz. In some embodiments, the unaided audiometric threshold is expressed as the value determined at a single frequency selected from 0.25 kHz, 0.5 kHz, and 0.75 kHz. In some embodiments, the unaided audiometric threshold is expressed as
20 the value determined at 0.25 kHz, 0.5 kHz, or 0.75 kHz. In some embodiments, the unaided audiometric threshold is expressed as the value determined at 0.5 kHz.

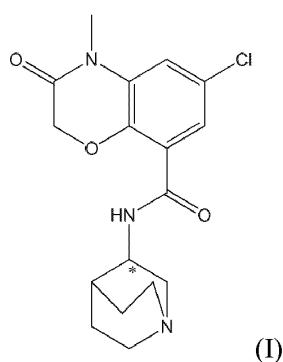
[0059] In some embodiments, the unaided audiometric threshold as described herein is determined with pure tone audiometry, in particular air conduction pure tone audiometry (or pure tone audiometric air conduction testing).

25 [0060] In some embodiments, the subject in need of treatment is a child, *i.e.*, a subject below the age of 21, 20, 19, or 18. In some embodiments, the subject in need of treatment is a child being at least 12-, 18-, 24-, or 36-month old. In some embodiments, the subject in need of treatment is an adult, *i.e.*, a subject aged 18, 19, 20, 21 or more. In some embodiments, the subject in need of treatment is at least 18-, 20-, 25-, 30-, 35-, 40-, 45-,

50-, 55-, 60-, 65- 70-, 75-, or 80-year-old. In some embodiments, the subject in need of treatment is 18-year-old or older, 20-year-old or older, 25-year-old or older, 30-year-old or older, 40-year-old or older, 50-year-old or older, 60-year-old or older, or 70-year-old or older.

- 5 [0061] In some embodiments, the subject in need of treatment is female. In some embodiments, the subject in need of treatment is male.

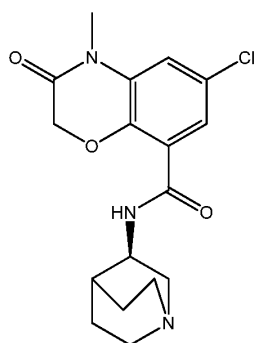
[0062] Azasetron (also known as arazasetron) is a compound of formula (I), wherein * stands for the (*R*)-enantiomer (or (+)-enantiomer), the (*S*)-enantiomer (or (-)-enantiomer), the racemate or a non-racemic mixture of (*R*)- and (*S*)-enantiomers
10 (corresponding to mixtures of (+)-and (-)-enantiomers):



[0063] Azasetron thus corresponds to N-(1-azabicyclo[2.2.2]octan-3-yl)-6-chloro-4-methyl-3-oxo-1,4-benzoxazine-8-carboxamide.

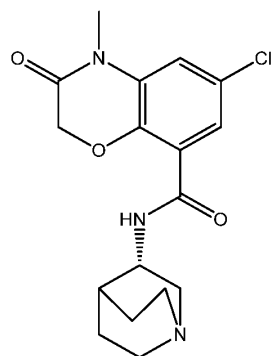
- 15 [0064] As indicated above, azasetron has one chiral center that can give rise to two stereoisomers. In some embodiments, azasetron is racemic azasetron, or a pharmaceutically acceptable salt and/or solvate thereof.

[0065] In some embodiments, azasetron is the (*R*)-enantiomer of azasetron, or a pharmaceutically acceptable salt and/or solvate thereof. The (*R*)-enantiomer of azasetron is called (*R*)-azasetron or (+)-azasetron, corresponding to formula (*R*)-I:



(R)-I

- [0066] Examples of processes that may be used to synthesize (*R*)-azasetron or a pharmaceutically acceptable salt and/or solvate thereof are well-known in the art (see for example Chinese patent applications CN101786963 and CN104557906). In some
- 5 embodiments, synthesis of (*R*)-azasetron or of a pharmaceutically acceptable salt and/or solvate thereof includes *ab initio* synthesis and/or chiral resolution. In some embodiments, when *ab initio* synthesis of (*R*)-azasetron or of a pharmaceutically acceptable salt and/or solvate thereof is implemented, at least one racemic starting compound and/or intermediate compound is substituted by a chiral compound.
- 10 [0067] In some embodiments, azasetron is the (*S*)-enantiomer of azasetron, or a pharmaceutically acceptable salt and/or solvate thereof. The (*S*)-enantiomer of azasetron is called (*S*)-azasetron or (-)-azasetron, corresponding to formula (*S*)-I:



(S)-I

- [0068] In some embodiments, azasetron includes the compound of formula I, preferably
- 15 of formula (*R*)-I, and all polymorphs, crystals and crystal habits thereof, and isotopically-labeled compound of formula I, preferably of formula (*R*)-I.

[0069] Azasetron, or an analog thereof as described herein, may be in the form of a pharmaceutically acceptable salt. Pharmaceutically acceptable salts of azasetron, or of an analog of azasetron, include the acid addition salts thereof. Suitable acid addition salts are formed from acids which form non-toxic salts. Examples of acid addition salts include

5 besylate, hydrochloride/chloride, malate, benzoate, ethane-1,2-disulfonate, fumarate, tartrate, acetate, adipate, ascorbate, aspartate, bicarbonate/carbonate, bisulphate/sulphate, borate, camsylate, citrate, cyclamate, edisylate, esylate, ethanesulfonate, formate, gluceptate, gluconate, glucuronate, glutamate, hexafluorophosphate, hibenzenate, hydrobromide/bromide, hydroiodide/iodide, isethionate, lactate, maleate, malonate,

10 mesylate, methylsulphate, naphthylate, 2-napsylate, nicotinate, nitrate, orotate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, pyroglutamate, saccharate, stearate, succinate, tannate, *p*-toluenesulfonate, tosylate, trifluoroacetate, and xinofoate salts.

[0070] Pharmaceutically acceptable salts of azasetron may be prepared by reacting

15 azasetron with the desired acid, or by converting one salt of azasetron to another by reaction with an appropriate acid or by means of a suitable ion exchange column. All these reactions are typically carried out in solution. The salt may precipitate from solution and be collected by filtration or may be recovered by evaporation of the solvent. The degree of ionization in the salt may vary from completely ionized to not ionized

20 resulting in a co-crystal.

[0071] In some embodiments, azasetron, or an analog thereof as described herein, is in the form of a pharmaceutically acceptable salt selected from a besylate, hydrochloride, malate, benzoate, ethane-1,2-disulfonate, fumarate, and tartrate salt; more preferably from a besylate, hydrochloride, malate, and benzoate salt; even more preferably from a

25 besylate, hydrochloride, and malate salt.

[0072] As used herein, “pharmaceutically acceptable solvate” in connection with azasetron or an analog thereof refers to a molecular complex comprising azasetron or an analog thereof and stoichiometric or sub-stoichiometric amounts of one or more pharmaceutically acceptable solvent molecules such as ethanol or water. The term

“hydrate” (as in “pharmaceutically acceptable hydrate”) may be specifically used when the solvent is water.

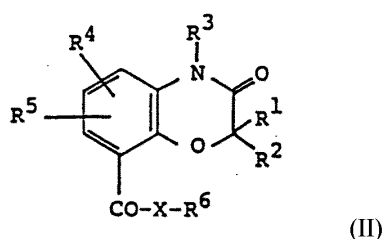
[0073] In some embodiments, azasetron is (*R*)-azasetron besylate, (*R*)-azasetron hydrochloride, (*R*)-azasetron malate, (*R*)-azasetron benzoate, (*R*)-azasetron ethane-1,2-disulfonate, (*R*)-azasetron fumarate, and/or (*R*)-azasetron tartrate. In some
5 embodiments, azasetron is (*R*)-azasetron besylate, (*R*)-azasetron hydrochloride, (*R*)-azasetron malate, and/or (*R*)-azasetron benzoate; more preferably azasetron is (*R*)-azasetron besylate, (*R*)-azasetron hydrochloride, and/or (*R*)-azasetron malate.

[0074] In some embodiments, azasetron is (*R*)-azasetron besylate, also referred to as
10 “SENS-401”.

[0075] In some embodiments, the present invention relates to an analog of azasetron, or a pharmaceutically acceptable salt and/or solvate thereof, for use in the preservation of residual hearing following insertion of a cochlear implant in a subject in need of treatment as described herein.

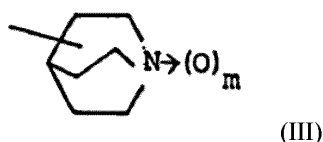
15 [0076] As used herein, “analog” refers to the modification or substitution of one or more chemical moieties on a parent compound, *i.e.*, azasetron, and may include functional derivatives, positional isomers, tautomers, zwitterions, enantiomers, diastereomers, racemates, isosteres or stereochemical mixtures thereof.

[0077] In some embodiments, the analog of azasetron is a benzoxazine compound, or a
20 pharmaceutically acceptable salt and/or solvate thereof. In some embodiments, the analog of azasetron is a benzoxazine compound of the formula (II):

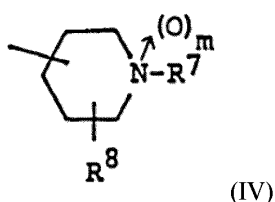


wherein R¹ and R² are the same or different, and each represents hydrogen or C₁₋₈ alkyl; R³ represents hydrogen, C₁₋₈ alkyl, phenylalkyl or substituted phenylalkyl; R⁴ and R⁵ are

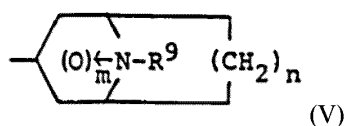
the same or different, and each represents hydrogen, halogen, C₁₋₈ alkyl, alkoxy, amino, acylamino, C₂₋₅ alkylamino, hydroxy or nitro; X represents oxygen or NH; R⁶ represents a group of the formula (III):



- 5 wherein m is 0 or 1,
or a group of the formula (IV):



- wherein R⁷ represents C₁₋₈ alkyl, phenyl C₁₋₄ alkyl, phenoxyalkyl, substituted phenyl C₁₋₄ alkyl or substituted phenoxyalkyl, R⁸ represents hydrogen or C₁₋₈ alkoxy and m is as defined above,
10 or a group of the formula (V):



- wherein R⁹ represents C₁₋₈ alkyl, phenyl C₁₋₄ alkyl or substituted phenyl C₁₋₄ alkyl, n is 0 or 1, and m is as defined above,
15 or a pharmaceutically acceptable salt thereof.

[0078] In some embodiments, the analog of azasetron is a benzoxazine compound selected from the group comprising or consisting of 6-chloro-3,4-dihydro-2-methyl-3-oxo-N-(3-quinuclidinyl)-2H-1,4-benzoxazine-8-carboxamide, 6-chloro-3,4-dihydro-2,4-dimethyl-3-oxo-N-(3-quinuclidinyl)-2H-benzoxazine-8-carboxamide, 6-chloro-2-ethyl-3,4-dihydro-4-methyl-3-oxo-N-(3-quinuclidinyl)-2H-1,4-benzoxazine-8-carboxamide,
20 3,4-dihydro-4-methyl-3-oxo-N-(3-quinuclidinyl)-2H-1,4-benzoxazine-8-carboxamide,

6-bromo-3,4-dihydro-2,4-dimethyl-3-oxo-N-(3-quinuclidinyl)-2H-1,4-benzoxazine-8-carboxamide, 6-chloro-3,4-dihydro-2,2,4-trimethyl-3-oxo-N-(3-quinuclidinyl)-2H-1,4-benzoxazine-8-carboxamide, and pharmaceutically acceptable salts or solvates thereof.

[0079] In some embodiments, azasetron or an analog of azasetron, or a pharmaceutically acceptable salt and/or solvate thereof, is for administration at a therapeutically effective dose.

[0080] In some embodiments, azasetron or an analog of azasetron, or a pharmaceutically acceptable salt and/or solvate thereof, is for administration at a daily dose ranging from about 20 mg to about 200 mg.

10 [0081] As used herein, a free base equivalent dose refers to the dose of active ingredient as such, *i.e.*, azasetron or an analog of azasetron, and not to its pharmaceutically acceptable salt and/or solvate form. Thus, compositional variations of a pharmaceutically acceptable salt and/or solvate of azasetron or an analog of azasetron will not impact the free base equivalent dose to be administered.

15 [0082] In some embodiments, azasetron or an analog of azasetron, or a pharmaceutically acceptable salt and/or solvate thereof, is for administration at a free base equivalent dose ranging from about 0.1 to about 2 mg/kg/day (mg per kilo body weight per day), preferably from about 0.2 to about 1 mg/kg/day. In some embodiments, azasetron or an analog of azasetron, or a pharmaceutically acceptable salt and/or solvate thereof, is for administration at a free base equivalent dose of about 0.5, 0.6, 0.7, 0.8, 0.9 or 1 mg/kg/day.

[0083] In some embodiments, azasetron or an analog of azasetron, or a pharmaceutically acceptable salt and/or solvate thereof, is for administration at a daily free base equivalent dose ranging from about 10 to about 500 mg, preferably from about 20 to about 200 mg, more preferably from about 30 to about 100 mg, even more preferably from about 40 to about 60 mg. In some embodiments, azasetron or an analog of azasetron, or a pharmaceutically acceptable salt and/or solvate thereof, is for administration at a daily free base equivalent dose of about 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, or 120 mg. In some embodiments, azasetron or an analog of azasetron, or a pharmaceutically acceptable

salt and/or solvate thereof, is for administration at a daily free base equivalent dose of about 40 mg or of about 60 mg.

[0084] In some embodiments, azasetron or an analog of azasetron, or a pharmaceutically acceptable salt and/or solvate thereof, is for administration at least once a day, preferably
5 twice a day. In some embodiments, azasetron or an analog of azasetron, or a pharmaceutically acceptable salt and/or solvate thereof, is for administration for at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, or 31 day(s). In some embodiments, azasetron or an analog of azasetron, or a pharmaceutically acceptable salt and/or solvate thereof, is for administration for at
10 least 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 week(s). In some embodiments, azasetron or an analog of azasetron, or a pharmaceutically acceptable salt and/or solvate thereof, is for administration for at least 1, 2, 3, 4, 5, or 6 month(s).

[0085] In some embodiments, azasetron or an analog of azasetron, or a pharmaceutically acceptable salt and/or solvate thereof, is to be administered systemically.

15 [0086] In some embodiments, azasetron or an analog of azasetron, or a pharmaceutically acceptable salt and/or solvate thereof, is to be administered orally. Thus, in some embodiments, azasetron or an analog of azasetron, or a pharmaceutically acceptable salt and/or solvate thereof, is adapted for oral administration. Examples of formulations adapted for oral administration include: solid forms, liquid forms, and gels. Examples of
20 solid forms adapted for oral administration include tablets, pills, capsules, soft gelatine capsules, hard gelatine capsules, caplets, compressed tablets, cachets, wafers, dispersing and/or disintegrating tablets, powders, solid forms suitable for solution, or suspension, in liquid prior to oral administration, and effervescent tablets. Examples of liquid forms adapted for oral administration include solutions, suspensions, drinkable solutions,
25 elixirs, potions, drenches, syrups and liquors.

[0087] In some embodiments, azasetron or an analog of azasetron, or a pharmaceutically acceptable salt and/or solvate thereof, is to be administered as an oral-route form (immediate or sustained-released), preferably as tablets.

[0088] In some embodiments, a tablet for oral-route administration comprises or consists of about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 mg free base equivalent, preferably about 10 mg free base equivalent, of azasetron or an analog of azasetron, or a pharmaceutically acceptable salt and/or solvate thereof, preferably of
5 (R)-azasetron besylate.

[0089] In some embodiments, azasetron or an analog of azasetron, or a pharmaceutically acceptable salt and/or solvate thereof, is to be administered locally.

[0090] In some embodiments, azasetron or an analog of azasetron, or a pharmaceutically acceptable salt and/or solvate thereof, is to be topically administered. Thus, in some
10 embodiments, azasetron or an analog of azasetron, or a pharmaceutically acceptable salt and/or solvate thereof, is adapted for topical administration. Examples of formulations adapted for topical administration include sticks, waxes, creams, lotions, ointments, balms, gels, masks, and leave-on washes.

[0091] In some embodiments, azasetron or an analog of azasetron, or a pharmaceutically
15 acceptable salt and/or solvate thereof, is to be administered directly in the ear, such as in the inner ear, middle ear, and/or external ear, for example by transtympanic or intratympanic administration. Thus, in some embodiments, azasetron or an analog of azasetron, or a pharmaceutically acceptable salt and/or solvate thereof, is adapted for administration directly in the ear, preferably in the inner ear, for example by
20 transtympanic or intratympanic administration. Examples of formulations adapted to such administration include otowicks, round window catheters, various types of gels, foams, fibrins, emulsions, solutions, patches or other drug carriers, which are placed in the ear and loaded with azasetron or an analog of azasetron, or a pharmaceutically acceptable salt and/or solvate thereof.

[0092] In some embodiments, azasetron or an analog of azasetron, or a pharmaceutically
25 acceptable salt and/or solvate thereof, is to be administered (*i.e.*, first administered) from at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or 14 days prior to insertion of the cochlear implant.

[0093] In some embodiments, azasetron or an analog of azasetron, or a pharmaceutically acceptable salt and/or solvate thereof, is for administration with at least one further pharmaceutically active agent.

[0094] In some embodiments, azasetron or an analog of azasetron, or a pharmaceutically acceptable salt and/or solvate thereof, is to be administered simultaneously, separately, or sequentially with said at least one further pharmaceutically active agent.

[0095] In some embodiments, azasetron or an analog of azasetron, or a pharmaceutically acceptable salt and/or solvate thereof, and the at least one further pharmaceutically active agent, are to be administered separately.

[0096] In some embodiments, said further pharmaceutically active agent is a corticosteroid. Thus, in some embodiments, azasetron or an analog of azasetron, or a pharmaceutically acceptable salt and/or solvate thereof, is for administration with at least one corticosteroid. For example, corticosteroids may be selected from oral corticosteroids and/or intra-tympanic corticosteroids. In some embodiments, said corticosteroid is an oral corticosteroid. Examples of oral corticosteroids include dexamethasone, methylprednisolone, prednisone, and prednisolone. In some embodiments, said corticosteroid is an intra-tympanic corticosteroid. Examples of intra-tympanic corticosteroids include dexamethasone, prednisone, hydrocortisone, betamethasone and methylprednisolone.

[0097] Another object of the present invention is a method for preserving residual hearing following insertion of a cochlear implant in a subject in need of treatment as described herein, said method comprising administering to the subject azasetron or an analog of azasetron, or a pharmaceutically acceptable salt and/or solvate thereof, as described herein.

[0098] Another object of the present invention is a method for treating, in particular preventing, residual hearing loss following insertion of a cochlear implant in a subject in need of treatment as described herein, said method comprising administering to the subject azasetron or an analog of azasetron, or a pharmaceutically acceptable salt and/or solvate thereof, as described herein.

[0099] In some embodiments, the method further comprises a step of determining that the subject in need of treatment is susceptible to respond to azasetron or an analog of azasetron, or a pharmaceutically acceptable salt and/or solvate thereof.

5 [0100] In some embodiments, the step of determining that the subject in need of treatment is susceptible to respond to azasetron or an analog of azasetron, or a pharmaceutically acceptable salt and/or solvate thereof, comprises assessing the hearing threshold of the subject at baseline as described herein.

[0101] In some embodiments, assessing the hearing threshold at baseline comprises assessing the pure-tone average (PTA) at baseline as described herein. Examples of
10 methods for assessing the PTA at baseline are mentioned herein.

[0102] In some embodiments, a subject susceptible to respond to azasetron or an analog of azasetron, or a pharmaceutically acceptable salt and/or solvate thereof is a subject having a pure-tone average (PTA) at baseline greater than 65 dB, the PTA being expressed as the average of at least 3 values each determined at a different frequency
15 within the range from 0.25 kHz to 0.75 kHz, preferably as the average of the values determined at 0.25 kHz, 0.5 kHz and 0.75 kHz.

[0103] Another object of the present invention is a pharmaceutical composition for use in the preservation of residual hearing following insertion of a cochlear implant in a subject in need of treatment as described herein, said pharmaceutical composition
20 comprising azasetron or an analog of azasetron, or a pharmaceutically acceptable salt and/or solvate thereof, and optionally at least one pharmaceutically acceptable excipient.

[0104] Another object of the present invention is the use of azasetron or an analog of azasetron, or a pharmaceutically acceptable salt and/or solvate thereof, for the manufacture of a medicament or a kit for the preservation of residual hearing following
25 insertion of a cochlear implant in a subject in need of treatment as described herein.

[0105] In some embodiments, the pharmaceutical composition, medicament or kit is for administration with at least one further pharmaceutically active agent as described herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0106] **Figure 1** is a scheme depicting the phase IIa, open-label, randomized and controlled study in adult participants with a preoperative hearing threshold in the impaired ear demonstrating unaided audiometric threshold of 80 dB or better (*i.e.*, ≤ 80 dB) at 500 Hz, who meet the locally approved indication for, and have consented to receiving, cochlear implant Nucleus® CI-622 (Cochlear™).

EXAMPLES

[0107] The present invention is further illustrated by the following example.

Example:

10 [0108] A phase IIa, multicenter, randomized, controlled, open-label study has been initiated to investigate repeated twice-daily administration of (*R*)-azasetron in adult participants given at least 7 days before cochlear implantation. In addition to the primary objective of evaluating the presence of (*R*)-azasetron in the perilymph of participants, the phase IIa study also aims at (i) assessing the efficacy of (*R*)-azasetron in preserving
15 residual hearing in subjects undergoing cochlear implant surgery at the end of the treatment period and at the end of the study follow-up, and (ii) assessing the safety and tolerability of (*R*)-azasetron for the whole duration of the study.

[0109] Hereinafter, the designation “SENS-401” corresponds to the investigational product (*R*)-azasetron (administered as (*R*)-azasetron besylate to the participants included
20 in the study).

Materials and Methods

Participants included in the study

[0110] Potential participants are adults aged from 18 years and older with preoperative threshold levels in the impaired ear demonstrating unaided audiometric threshold
25 of 80 dB or better (*i.e.*, ≤ 80 dB) at 500 Hz, who meet the locally approved indication for, and have already consented to receiving, the cochlear implant Nucleus® CI-622

(Cochlear™) prior to study entry.

[0111] In total, the study is to include 27 participants to be randomized on day 1 to either arm A (participants receiving SENS-401 for 7 to 13 days before cochlear implant surgery and for 5 to 6 weeks after) or arm B (participants receiving no treatment with SENS-401).

5 [0112] Residual hearing (*i.e.*, remaining hearing in the impaired ear at low frequencies) is assessed unaided (*i.e.*, without any hearing aid) with pure tone audiometry (also referred to as pure tone audiometric testing), in particular with pure tone audiometric air conduction testing. After insertion of the cochlear implant, residual hearing is assessed in cochlear implant recipients with the device turned off.

10 [0113] Pure tone audiometry is a behavioral subjective test used to determine hearing thresholds (expressed in decibels or dB). Air conduction hearing thresholds are usually measured for tonal stimuli at set frequencies within the range from 0.125 kHz to 8 kHz, with the use of headphones. Then, bone conduction hearing thresholds are usually measured for tonal stimuli at set frequencies within the range from 0.25 to 4 kHz, with
15 the use of a headband with oscillator. A hearing threshold, in particular a hearing threshold determined with pure tone audiometry, may be referred to as pure-tone average (PTA), which corresponds to the average of hearing thresholds determined at a set of fixed frequencies.

[0114] In the present study, pure tone air-conduction hearing thresholds are determined
20 for the impaired ear to be implanted at 0.125, 0.25, 0.5, 0.75, 1, 2, 3, and 4 kHz. Low frequencies (*e.g.*, 0.25, 0.5, and 0.75 kHz) are of particular importance for assessing residual hearing because cochlear implants are typically proposed to subjects experiencing hearing loss at the higher frequencies. Therefore, at the time of cochlear implantation, it is at the lower frequencies that some cochlear implant recipients tend to
25 retain some level of hearing. For assessing residual hearing, pure tone air-conduction hearing thresholds at low frequencies (*i.e.*, 0.25, 0.5 and 0.75 kHz) are of particular relevance as the most common type of residual hearing is low-frequency residual hearing.

[0115] In the present study, bone-conduction hearing thresholds are determined for the impaired ear to be implanted at 0.25, 0.5, 0.75, 1, 2, 3, and 4 kHz.

[0116] For all participants, pure tone audiometry is performed as described above at screening, on day 1 after randomization (prior to first dose of SENS-401 for participants included in arm A), at the day 49 visit, and at the end of study visit (day 105).

[0117] Hearing thresholds determined at day 1 (*i.e.*, prior to any SENS-401 administration and prior to cochlear implantation which occurs between day 8 and day 14) are defined as the hearing thresholds at baseline. Thus, a pure-tone average (PTA) determined at day 1 (*i.e.*, prior to any SENS-401 administration and prior to cochlear implantation which occurs between day 8 and day 14) is defined as the PTA at baseline. The PTA at baseline is preferably expressed as the average of the hearing thresholds (in dB) determined at 0.25, 0.5 and 0.75 kHz (air conduction).

[0118] A higher pure-tone average (PTA) corresponds to a higher hearing threshold and thus to a poorer hearing. In a subject, an increase of the PTA over time may generally correspond to a decrease in hearing, *i.e.*, to a hearing loss. Conversely, a lower PTA corresponds to a lower hearing threshold and thus to a better hearing. In a subject, a decrease of the PTA over time may generally correspond to an improvement of hearing.

[0119] For participants of the study, a decrease of the unaided pure-tone average (PTA) over time or an increase of the unaided PTA over time of less than 10 dB is defined as a preservation of residual hearing. Conversely, for participants of the study, an increase of the unaided PTA over time of 10 dB or more may be defined as a decrease in residual hearing, *i.e.*, as a residual hearing loss.

[0120] Of note, exclusion criteria precluding recruitment in the study include in particular:

- Any therapy known as ototoxic (*e.g.*, aminoglycosides, cisplatin, quinine, etc.) at the current time or in the past 6 months prior to study inclusion. Loop diuretics at normal therapeutic doses are permitted.
- Radiological evidence of bony obliteration of the round window membrane on pre-operative high resolution CT (computer tomography) imaging of the temporal bone.
- Loss of cochlear fluid signals on pre-operative MRI (magnetic resonance imaging), suggestive of fibrosis or ossification of the cochlea.

Drug administration

[0121] After written informed consent is obtained and screening procedures completed, the eligible participants are randomized on day 1 to either arm A (SENS-401 arm) or arm B (control arm) in ratio 2:1 (18 participants in arm A and 9 participants in arm B).

- 5 [0122] Arm A (SENS-401 arm) participants are administered SENS-401 twice daily for 7 to 13 days prior to their scheduled cochlear implant surgery (day 8 to day 14). Arm A (SENS-401 arm) participants continue to take SENS-401 twice daily including on the day of surgery and until attending the day 49 visit. SENS-401 is thus administered for 7 weeks (49 days). SENS-401 is administered orally, twice a day at a dose of 43.5 mg-BID (*bis in die*), corresponding to a total daily dose of 87 mg (60 mg free base equivalent).
- 10

[0123] Arm B (control arm) participants do not receive SENS-401. Arm B (control arm) participants similarly undergo their planned cochlear implant surgery (day 8 to 14) and return for the day 49 and end of study (day 105) visits.

- [0124] All participants undergo cochlear implant surgery between day 8 and day 14 to be fitted with the Nucleus® CI-622 cochlear implant (Cochlear™).
- 15

[0125] Participants in either arm (SENS-401 arm or control arm) may receive local corticosteroids during cochlear implant surgery.

Monitoring of subjects and objectives

- [0126] Participants included in the study are monitored with a first visit at day -42 to day -1 (screening), followed by a visit at day 1 (D1 - randomization), day 49 (± 7 days), and day 105 (± 21 days - follow-up visit marking the end of study or EOS). In addition, participants are fitted with the Nucleus® CI-622 cochlear implant (Cochlear™) between day 8 and day 14. For the convenience of the participants, the day 49 visit and day 105 visit (EOS) should ideally, but not necessarily, coincide with standard-of care visits for switching on and programming of the cochlear implant, respectively. Monitoring include hearing test (pure tone audiometry), immittance audiometry, and otoscopic examination. Electrocochleography is conducted during cochlear implant surgery. For participants who receive SENS-401 (arm A), a blood sample is collected on the day of cochlear implant
- 20
- 25

surgery and a perilymph sample is collected during cochlear implant surgery. Additionally, participants are closely monitored for adverse events throughout the study.

[0127] The primary objective is to detect the presence of SENS-401 in the perilymph of participants undergoing cochlear implant surgery after 7 days of oral administration of SENS-401. SENS-401 concentrations are measured and compared in the perilymph and plasma samples of participants undergoing cochlear implant surgery after 7 days of oral administration of SENS-401.

[0128] Additional objectives include (i) assessing the efficacy of repeated oral administration with SENS-401 to protect against low frequency residual hearing loss in participants undergoing cochlear implant surgery at the day 49 visit and at the day 105 visit (EOS), and (ii) assessing the safety and tolerability of SENS-401 for the whole duration of the study. In particular, efficacy is to be assessed by determining the change of hearing threshold from baseline in the implanted ear at 0.25, 0.5 and 0.75 kHz after repeated administration of SENS-401, as evaluated by pure tone audiometry at the day 49 visit and at the day 105 visit (EOS). At day 49 and day 105, pure tone audiometry testing is conducted in the participants with the cochlear implant turned off.

[0129] Monitoring also includes immittance audiometry, otoscopic examination and electrocochleography (ECoChG). Immittance audiometry evaluates middle ear function by three procedures: static immittance, tympanometry, and the measurement of acoustic reflex threshold sensitivity. Tympanometry tests the condition of the middle ear and mobility of the eardrum (tympanic membrane) and the conduction bones by creating variations of air pressure in the ear canal. Otosopic examination allows evaluation of the structure of the ear canal, tympanic membrane and the middle ear. Otoscopy is part of standard of care, to rule out possible outer-ear abnormality such as otitis media or tympanic perforation. Electrocochleography (ECoChG) records electrical potentials generated in the inner ear and auditory nerve in response to acoustic sound stimulation.

Results

[0130] Residual hearing was assessed prior to the treatment period (day 1 - baseline) and immediately after (day 49) for all participants with cochlear implants. Hearing thresholds

were determined across the tested frequencies ranging from 0.125 to 4 kHz. The pure-tone average (PTA) was calculated by averaging the hearing thresholds at three consecutive frequencies from 0.250 to 0.750 kHz. To evaluate the change in PTA at day 49 from baseline, the averaged hearing thresholds at 0.25, 0.5, and 0.75 kHz were compared.

- [0131] For the purposes of the present study, a positive responder (*i.e.*, a participant whose residual hearing is preserved) was defined as someone whose increase in pure-tone average (PTA) from baseline was less than 10 dB. The responder rate refers to the number of positive responders compared to the total number of participants in a given group.
- 10 [0132] The change in pure-tone average (PTA) from baseline was determined both in the overall study population and in specific subpopulations of subjects defined by the pure-tone average (PTA) value at baseline.

[0133] **Table 1** below displays the baseline pure-tone average (PTA) measurements for participants in arm A who were treated with SENS-401. The PTA values indicate the average hearing thresholds at frequencies of 0.25, 0.5, and 0.75 kHz. In the overall study population, the mean baseline PTA was 66 dB. Within a specific subgroup of participants, whose baseline PTA was greater than 65 dB, the mean baseline PTA was 75 dB. In another specific subgroup of participants whose baseline PTA was equal to or below 65 dB, the mean baseline PTA was 52.5 dB.

20 **Table 1: PTA average (dB) across three frequencies (250-750 Hz) at baseline – SENS-401 arm**

SENS-401 arm	mean	SD	n
PTA > 65 dB	75.0	1.7	3
PTA ≤ 65 dB	52.5	10.6	2
Overall study population - SENS-401	66.0	13.5	5

PTA: pure-tone average. SENS-401 arm: SENS-401 administered at a daily dose of 43.5 mg/BID corresponding to a total daily dose of 60 mg free base equivalent. SD: standard deviation. n: number of participants.

- 25 [0134] **Table 2** below displays the pure-tone average (PTA) measurements at day 49 for

participants in arm A who were treated with SENS-401. The PTA values indicate the average hearing thresholds at frequencies of 0.25, 0.5, and 0.75 kHz. In the overall study population, the mean PTA at day 49 was 78.2 dB. Within a specific subgroup of participants, whose baseline PTA was greater than 65 dB, the mean PTA at day 49 was 78.9 dB. In another specific subgroup of participants whose baseline PTA was equal to or below 65 dB, the mean PTA at day 49 was 77.1 dB.

Table 2: PTA average (dB) across three frequencies (250-750 Hz) at day 49 – SENS-401 arm

SENS-401 arm	mean	SD	n
PTA > 65 dB	78.9	8.6	3
PTA ≤ 65 dB	77.1	0.6	2
Overall study population - SENS-401	78.2	6.1	5

PTA: pure-tone average. SENS-401 arm: SENS-401 administered at a daily dose of 43.5 mg/BID corresponding to a total daily dose of 60 mg free base equivalent. SD: standard deviation. n: number of participants.

[0135] **Table 3** below displays the baseline pure-tone average (PTA) measurements for participants in arm B (control arm) who did not receive SENS-401. The PTA values indicate the average hearing thresholds at frequencies of 0.25, 0.5, and 0.75 kHz. In the overall study population, the mean baseline PTA was 69.6 dB. Within a specific subgroup of participants, whose baseline PTA was greater than 65 dB, the mean baseline PTA was 74.2 dB. In another specific subgroup of participants whose baseline PTA was equal to or below 65 dB, the mean baseline PTA was 65 dB.

Table 3: PTA average (dB) across three frequencies (250-750 Hz) at baseline - control arm (untreated)

Control arm	mean	SD	n
PTA > 65 dB	74.2	1.2	2
PTA ≤ 65 dB	65.0	0.0	2
Overall study population - untreated	69.6	5.3	4

PTA: pure-tone average. Control arm: no administration of SENS-401. SD: standard deviation. n: number of participants.

[0136] **Table 4** below displays the pure-tone average (PTA) measurements at day 49 for participants in arm B (control arm) who did not receive SENS-401. The PTA values indicate the average hearing thresholds at frequencies of 0.25, 0.5, and 0.75 kHz. In the overall study population, the mean PTA at day 49 was 95.4 dB. Within a specific subgroup of participants, whose baseline PTA was greater than 65 dB, the mean PTA at day 49 was 95 dB. In another specific subgroup of participants whose baseline PTA was equal to or below 65 dB, the mean PTA at day 49 was 95.8 dB.

Table 4: PTA average (dB) across three frequencies (250-750 Hz) at day 49 - control arm (untreated)

Control arm	mean	SD	n
PTA > 65 dB	95.0	16.5	2
PTA ≤ 65 dB	95.8	17.7	2
Overall study population - untreated	95.4	14.0	4

10 PTA: pure-tone average. Control arm: no administration of SENS-401.SD: standard deviation. n: number of participants.

[0137] **Table 5** below shows the mean change in pure-tone average (PTA) from baseline (calculated as PTA at day 49 minus PTA at baseline, both expressed as the average of the hearing thresholds determined at 0.25, 0.5 and 0.75 kHz). In the overall study population, the mean change in PTA from baseline is + 12.17 dB in the SENS-401 arm, vs. + 25.83 dB in the control arm (difference of 13.67 dB), supporting an effect of SENS-401 in preserving residual hearing following insertion of a cochlear implant. In the specific group of participants having a PTA at baseline greater than 65 dB (expressed as the average of the hearing thresholds determined at 0.25, 0.5 and 0.75 kHz), the mean change in PTA from baseline is + 3.89 dB in the SENS-401 arm, vs. + 20.83 dB in the control arm (difference of 16.94 dB).

Table 5: Mean change in PTA from baseline in a subpopulation of more severely affected patients (PTA > 65 dB) versus overall study population

Group	Treatment arm	n	Mean change in PTA from baseline (dB)
Overall study population	Untreated	4	+25.8333
	SENS-401	5	+12.1667
PTA > 65 dB	Untreated	2	+20.8333
	SENS-401	3	+3.8889

PTA: pure-tone average. n: number of participants.

[0138] **Table 6** below shows the responder rate, corresponding to the proportion of participants whose increase in PTA from baseline was less than 10 dB. In the overall study population, the responder rate is 40% with SENS-401 treatment. In the specific group of participants having a PTA at baseline greater than 65 dB (expressed as the average of the hearing thresholds determined at 0.25, 0.5 and 0.75 kHz), the responder rate is 67% with SENS-401 treatment.

Table 6: Responder rate at day 49 in a subpopulation of more severely affected patients (PTA > 65 dB) at baseline versus overall study population

Group	Treatment arm	n	Responder rate
Overall study population	Untreated	4	0%
	SENS-401	5	40%
PTA > 65 dB	Untreated	2	0%
	SENS-401	3	67%

PTA: pure-tone average. The responder rate corresponds to the proportion of participants whose increase in PTA from baseline was less than 10 dB. n: number of participants.

[0139] The clinical data presented herein provide evidence of an increased benefit of SENS-401 in a specific group of cochlear implant recipients with a baseline PTA greater than 65 dB.

CLAIMS

1. Azasetron or an analog of azasetron, or a pharmaceutically acceptable salt and/or solvate thereof, for use in the preservation of residual hearing following insertion
5 of a cochlear implant in a subject in need thereof, wherein the subject has a hearing threshold at baseline in at least one ear corresponding to an unaided audiometric threshold at baseline greater than 65 dB, the unaided audiometric threshold being expressed as the average of at least 3 values each determined at a different frequency within the range from 0.25 kHz to 0.75 kHz.
- 10 2. Azasetron or the analog of azasetron, or the pharmaceutically acceptable salt and/or solvate thereof, for use according to claim 1, wherein the unaided audiometric threshold is expressed as the average of the values determined at 0.25 kHz, 0.5 kHz and 0.75 kHz.
- 15 3. Azasetron or the analog of azasetron, or the pharmaceutically acceptable salt and/or solvate thereof, for use according to claim 1 or 2, wherein the unaided audiometric threshold is unaided pure-tone average (PTA).
4. Azasetron or the analog of azasetron, or the pharmaceutically acceptable salt and/or solvate thereof, for use according to any one of claims 1 to 3, wherein the pharmaceutically acceptable salt is selected from a besylate salt, a malate salt, and
20 a hydrochloride salt.
5. Azasetron or the analog of azasetron, or the pharmaceutically acceptable salt and/or solvate thereof, for use according to any one of claims 1 to 4, wherein azasetron is (*R*)-azasetron, (*S*)-azasetron, a mixture thereof, or a pharmaceutically acceptable salt and/or solvate thereof.
- 25 6. Azasetron or the analog of azasetron, or the pharmaceutically acceptable salt and/or solvate thereof, for use according to any one of claims 1 to 5, wherein azasetron is (*R*)-azasetron or a pharmaceutically acceptable salt and/or solvate thereof.

7. Azasetron or the analog of azasetron, or the pharmaceutically acceptable salt and/or solvate thereof, for use according to any one of claims 1 to 6, wherein the pharmaceutically acceptable salt of azasetron is (*R*)-azasetron besylate.
8. Azasetron or the analog of azasetron, or the pharmaceutically acceptable salt and/or solvate thereof, for use according to any one of claims 1 to 4, wherein the analog of azasetron is a benzoxazine compound or a pharmaceutically acceptable salt and/or solvate thereof, preferably selected from 6-chloro-3,4-dihydro-2-methyl-3-oxo-N-(3-quinuclidinyl)-2H-1,4-benzoxazine-8-carboxamide, 6-chloro-3,4-dihydro-2,4-dimethyl-3-oxo-N-(3-quinuclidinyl)-2H-benzoxazine-8-carboxamide, 6-chloro-2-ethyl-3,4-dihydro-4-methyl-3-oxo-N-(3-quinuclidinyl)-2H-1,4-benzoxazine-8-carboxamide, 6-bromo-3,4-dihydro-2,4-dimethyl-3-oxo-N-(3-quinuclidinyl)-2H-1,4-benzoxazine-8-carboxamide, 6-chloro-3,4-dihydro-2,2,4-trimethyl-3-oxo-N-(3-quinuclidinyl)-2H-1,4-benzoxazine-8-carboxamide, and pharmaceutically acceptable salts and/or solvates thereof.
9. Azasetron or the analog of azasetron, or the pharmaceutically acceptable salt and/or solvate thereof, for use according to any one of claims 1 to 8, wherein azasetron or the analog of azasetron, or the pharmaceutically acceptable salt and/or solvate thereof, is for administration at a daily dose ranging from about 20 mg to about 200 mg.
10. Azasetron or the analog of azasetron, or the pharmaceutically salt and/or solvate thereof, for use according to any one of claims 1 to 8, wherein azasetron or the analog of azasetron, or the pharmaceutically acceptable salt and/or solvate thereof, is for administration at a daily free base equivalent dose of about 40 mg or of about 60 mg.
11. Azasetron or the analog of azasetron, or the pharmaceutically acceptable salt and/or solvate thereof, for use according to any one of claims 1 to 10, wherein azasetron or the analog of azasetron, or the pharmaceutically acceptable salt and/or solvate thereof, is for oral administration.

- 12.** Azasetron or the analog of azasetron, or the pharmaceutically acceptable salt and/or solvate thereof, for use according to any one of claims **1** to **10**, wherein azasetron or the analog of azasetron, or the pharmaceutically acceptable salt and/or solvate thereof, is for local administration.
- 5 **13.** Azasetron or the analog of azasetron, or the pharmaceutically acceptable salt and/or solvate thereof, for use according to any one of claims **1** to **12**, wherein azasetron or the analog of azasetron, or the pharmaceutically acceptable salt and/or solvate thereof, is for administration from at least 3 days prior to insertion of the cochlear implant.