Innovation Observatory

NHS National Institute for Health Research

HEALTH TECHNOLOGY BRIEFING FEBRUARY 2019

Pioglitazone for sudden sensorineural hearing loss

NIHRIO ID	17151	**NICE ID**	9723
Developer/Company	Strekin AG	**UKPS ID**	N/A

Licensing and market availability plans	Currently in phase III clinical trials.

SUMMARY

Pioglitazone given both as an injection (directly into the inner ear) and oral tablets is being investigated as a treatment option for sudden sensorineural hearing loss (SSNHL) in adults. SSNHL, also known as sudden deafness, is an unexplained loss of hearing, typically in one ear and can happen instantly or over a span of several days. During this time, sound gradually becomes muffled or faint. SSNHL happens when organs in the inner ear or the nerve pathways between the ear and the brain become damaged. Whilst no medicines are authorised to treat the hearing loss itself, steroids are used to treat the symptoms or antibiotics if the cause is infection. Cochlear implants can be used but this does not completely restore hearing but amplifies sounds to a more normal level.

Pioglitazone is typically a blood glucose-lowering drug licensed for the treatment of type 2 diabetes mellitus. While the way it works in SSNHL is not yet fully understood, it is thought to reduce inflammation and improve oxygen supply to cells in the inner ear that are involved in SSNHL. Pioglitazone is known to regulate the expression of proteins (receptors) involved in a variety of physiological processes, including lipid and glucose homeostasis, inflammation, and organ protection. If licensed, pioglitazone, via its multiple favourable mechanisms of inner ear protection, may offer a new option for the treatment of SSNHL.

PROPOSED INDICATION

Sudden sensorineural hearing loss (SSNHL) in adults.[1]

TECHNOLOGY

DESCRIPTION

Pioglitazone (STR001-IT/STR001-ER) when administered as a tablet is used to lower blood glucose and mediates its effect by a reduction of insulin resistance. It activates a receptor called peroxisome proliferator activated receptor gamma (PPARγ) in cells.[2] PPARs are members of the family of ligand-regulated nuclear hormone receptors. In response to various ligands, these transcription factors (PPARα, β/δ and γ) regulate the expression of genes involved in a variety of physiological processes, including lipid and glucose homeostasis, inflammation, and organ protection.[3] Moreover, PPARs participate in the regulation of redox balance by upregulating the transcription of antioxidant related genes and by inhibiting the generation of reactive oxygen species (ROS).[4]

PPARγ and PPARα have been found to be highly expressed in several cochlear cell types, including inner and outer hair cells (OHCs). PPARγ agonists could be effective therapeutic agents in preventing hearing loss that arises from various etiologies.[3]

Pioglitazone is in clinical development for adults with sudden sensorineural hearing loss (SSNHL). In the phase III clinical trial NCT03331627, patients were randomly assigned to pioglitazone 1.2% (W/W) intratympanic administration of a gel injection (STR001-IT) followed by 12 weeks of 5mg prolonged-release oral pioglitazone tablets (STR001-ER).[1,5]

INNOVATION AND/OR ADVANTAGES

Preclinical studies suggest pioglitazone has multiple protective mechanisms in the cochlea, favourably affecting oxidative stress and inflammation. Early intervention is expected to provide the greatest protection against external factors, while later favourable effects on inflammation may contribute to either greater or sustained efficacy and will also extend the window of opportunity for effective therapy. These factors are important in the treatment of hearing loss after acute noise trauma or SSNHL, where rapid intervention is critical. If licensed, pioglitazone, via its multiple favourable mechanisms of cochlear protection, may offer an attractive option for the treatment of SSNHL.[4]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Pioglitazone has a Marketing Authorisation in the EU/UK for the treatment of type 2 diabetes mellitus as second or third line as monotherapy, dual oral therapy and triple oral therapy.[2] Common or very common adverse effects include bone fracture; increased risk of infection, numbness, visual impairment and weight increased.[2]

Pioglitazone is in phase III/II clinical trials for several cancer and non-cancer indications including leukaemia, polycystic kidney disease and hepatitis.[6]

Pioglitazone was awarded orphan drug designation for SSNHL from EMA in January 2017.[7]

PATIENT GROUP

DISEASE BACKGROUND

Sensorineural hearing loss (SSNHL) occurs as a consequence of degeneration and apoptosis of auditory hair cells (HCs) and spiral ganglion neurons (SGNs).[3] The causes of sensorineural hearing loss are varied but can be generally categorised as, congenital; present from birth and is the most common problem seen in new-born babies and acquired; caused after birth by wide ranging factors.[8] Hearing loss can be inherited with more than 40 genes identified to cause deafness. Recessive, dominant, X-linked or mitochondrial genetic mutations can affect the structure or metabolism of the inner ear.[9]

Progressive age-related loss most often occurs in both ears, with changes arising in the inner or middle ear or along the nerve pathways from the ear to the brain as we age.[10] SSNHL has wide age distribution, but occurs most commonly in people aged 50-60 years, usually affects one ear only, and can be associated with tinnitus and vertigo.[11] Rapidly progressive sensorineural hearing loss, which develops over weeks to months, has also been described.[12] These patients often initially present with sudden SSNHL, followed by a rapid progression or additional sudden drops in hearing. SSNHL and rapidly progressive loss may have many common features and possible causes and it has been suggested that these be investigated and managed in a similar way.[13]

SSNHL also commonly known as sudden deafness is an unexplained, rapid loss of hearing either all at once or over a few days. SSNHL happens because there is something wrong with the sensory organs of the inner ear. A variety of disorders affecting the ear can cause SSNHL, but only about 10 percent of people diagnosed with SSNHL have an identifiable cause. Some of these conditions include infections, head trauma, autoimmune diseases, exposure to certain drugs that treat cancer or severe infections, blood circulation problems, neurological disorders, such as multiple sclerosis, disorders of the inner ear, such as Ménière's disease.[14]

Formation of oxygen-free radicals has been recognised as a key mediator in several types of hearing loss. Reactive oxygen species (ROS) that have been identified in cochlear tissue are derived from mitochondrial production and include hydroxyl radicals, superoxide anions, and hydrogen peroxide. Accumulation of ROS overwhelms endogenous detoxification pathways leading to oxidative modification and damage to lipids, proteins, and nucleic acids. Ultimately, pro-apoptotic signalling pathways are activated, which may induce HCs to undergo apoptotic cell death.[3]

Sensorineural hearing loss is a global health problem with profound socioeconomic impact and high unmet medical need.[3]

CLINICAL NEED AND BURDEN OF DISEASE

There are 11 million people with hearing loss across the UK.[15] There are 9,235,000 and 575,500 people with hearing loss in England and Wales respectively. It is estimated by 2035, there will be more than 15.6 million people with hearing loss in the UK.[16]

Population studies of SSNHL show a wide age distribution, with an average of 50–60 years and no sex preference. The hearing loss is unilateral in most cases, with bilateral involvement reported in less than 5%.[17]

SSNHL incidence varies from 5 to 30 cases per 100,000 per year, although one European study estimated 160 per 100,000 per year.[11,13] Applying this figure to the 2017 mid-year population, the estimated incidence of SSNHL in England and Wales would be from 2,937 to 17,623 per year.[18]

Whilst not representative of SSNHL precisely, there were 2,164 hospital admissions, resulting in 985 bed days and 1,336 day cases in England (2017/2018) for those with a primary diagnosis of; sensorineural hearing loss, bilateral (ICD-10 code H90.3); sensorineural hearing loss, unilateral with unrestricted hearing on the contralateral side (ICD-10 code H90.4); Sensorineural hearing loss, unspecified (ICD-10 code H90.5).[18]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Patients who have sudden onset or rapid worsening of hearing loss in one or both ears, which is not explained by external or middle ear causes are to be referred to ear, nose and throat service, emergency department or audiovestibular medicine service depending on duration and progression of symptoms.[19]

Various medicines are authorised in the EU to treat symptoms associated with SSNHL such as tinnitus and vertigo. There are no medicines authorised to treat the hearing loss itself.[7] There are also no satisfactory effective medical treatments for preventing sensorineural hearing loss.

CURRENT TREATMENT OPTIONS

Currently, the only treatment options available are offered by devices such as hearing aids and cochlear implants.[3]

According to NICE recommendation, patients with idiopathic sudden SSNHL may be given a steroid.[19]

PLACE OF TECHNOLOGY

If licensed, pioglitazone will offer a treatment option for patients with sudden SSNHL who currently have no effective therapies available specific to treating the cause of SSNHL.

CLINICAL TRIAL INFORMATION

Trial	NCT03331627, EudraCT 2017-000242-22; Safety and efficacy of STR001-IT and STR001ER in patients with SSHL; phase III
Sponsor	Strekin AG
Status	Ongoing
Source of Information	Trial registry[1,5]
Location	EU (not incl UK)
Design	Randomised, placebo-controlled, parallel assignment
Participants	n=165 (planned); aged 18 years and older; SSNHL
Schedule	Patients are given intratympanic gel injection followed by 12 weeks oral treatment
Follow-up	3 month follow up
Primary Outcomes	Absolute hearing improvement after 12 weeks measured with PTA using the mean value of the 3 most affected contiguous baseline frequencies.

Secondary Outcomes	Complete hearing recovery after 12 weeks measured with PTA using the mean value of the 3 most affected contiguous frequencies at baseline
Key Results	Expected late 2019
Adverse effects (AEs)	Not reported
Expected reporting date	Late 2019

ESTIMATED COST

The cost of pioglitazone as intratympanic injection or prolonged release oral tablet is not yet decided and depends on the clinical efficacy.

ADDITIONAL INFORMATION

Strekin AG did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE Technology appraisal. Cochlear implants for children and adults with severe to profound deafness (TA166). January 2006.
- NICE guideline. Hearing loss in adults: assessment and management (NG98). June 2018.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. Commissioning Services for People with Hearing Loss. A framework for clinical commissioning groups. July 2016.
- NHS England. Clinical Commissioning Policy: Active Middle Ear Implants. NHSCB/ D09/PS/a. April 2013.
- NHS England. Clinical Commissioning Policy: Bone Anchored Hearing Aids NHSCB/D09/PS/a. April 2013.
- NHS England. Standard Contract for Cochlear Implants (All Ages). D09/S/A.

OTHER GUIDANCE

- Clinical Practice Guideline: Sudden Hearing Loss. American Academy of Otolaryngology – Head and Neck Surgery. 2012.[20]

REFERENCES

1 ClinicalTrials.gov. *Safety and Efficacy of STR001-IT and STR001-ER in Patients With SSHL. Trial ID:* Available from: https://clinicaltrials.gov/ct2/show/record/NCT03331627?view=record [Accessed 28/01/2019].

2 electronic Medicines Compendium. *Actos Tablets.* Available from: https://www.medicines.org.uk/emc/product/1287/smpc#INDICATIONS [Accessed

3 Sekulic-Jablanovic M, Petkovic V, Wright MB, Kuchrava K, Huerzeler N, Levano S, et al. Effects of peroxisome proliferator activated receptors (PPAR)-γ and -α agonists on cochlear protection from oxidative stress. *PLoS One*. 2017;12(11):e0188596. Available from: https://dx.doi.org/10.1371%2Fjournal.pone.0188596.

4 Paciello F, Fetoni AR, Rolesi R, Wright MB, Grassi C, Troiani D, et al. Pioglitazone Represents an Effective Therapeutic Target in Preventing Oxidative/Inflammatory Cochlear Damage Induced by Noise Exposure. *Frontiers in pharmacology*. 2018;9(1103):1-15. Available from: https://dx.doi.org/10.3389%2Ffphar.2018.01103.

5 EU Clinical Trials Register. *2017-000242-22*. *Trial ID:* Available from: https://www.clinicaltrialsregister.eu/ctr-search/trial/2017-000242-22/DE [Accessed 31 January 2019].

6 ClinicalTrials.gov. *Search: Pioglitazone.* Available from: https://clinicaltrials.gov/ct2/results?term=Pioglitazone&recrs=b&recrs=a&recrs=f&recrs=d&age_v=&gndr=&type=&rslt=&phase=1&phase=2&Search=Apply [Accessed 29 January 2019].

7 European Medicines Agency. *EMA/5816/2017*. 2017. Available from: https://www.ema.europa.eu/documents/orphan-designation/eu/3/16/1823-public-summary-opinion-orphan-designation-pioglitazone-hydrochloride-treatment-sudden_en.pdf.

8 Cochlear Ltd. *Sensorineural hearing loss.* 2019. Available from: https://www.cochlear.com/uk/home/understand/hearing-and-hl/what-is-hearing-loss-/types-of-hl/sensorineural-hearing-loss [Accessed 31 January 2019].

9 Matsunaga T. Value of Genetic Testing in the Otological Approach for Sensorineural Hearing Loss. *The Keio Journal of Medicine*. 2009;58(4):216-22. Available from: https://www.jstage.jst.go.jp/article/kjm/58/4/58_4_216/_article https://doi.org/10.2302/kjm.58.216.

10 Disorders NIoDaOC. *Age-Related Hearing Loss.* 2019. Available from: https://www.nidcd.nih.gov/health/age-related-hearing-loss [Accessed 05 February 2019].

11 Audiology Online. *Short-Course Corticosteroids Recommended for Sudden Hearing Loss After Life-Threatening Caused Ruled Out.* 2019. Available from: https://www.audiologyonline.com/releases/short-course-corticosteroids-recommended-for-2768 [Accessed 31 January 2019].

12 McCabe B. Autoimmune Sensorineural Hearing Loss. *Annals of Otology, Rhinology & Laryngology*. 1979;88(5):585-9. Available from: https://journals.sagepub.com/doi/pdf/10.1177/000348947908800501 https://doi.org/10.1177%2F000348947908800501.

13 Schreiber BE, Agrup C, O' Haskard D, Luxon LM. Sudden sensorineural hearing loss. *The Lancet*. 2010;375(9721):1203-11. Available from: https://doi.org/10.1016/S0140-6736(09)62071-7.

14 Disorders NIoDaOC. *Sudden Deafness.* Available from: https://www.nidcd.nih.gov/health/sudden-deafness [Accessed 31 January 2019].

15 Action on Hearing Loss. *Facts and figures.* Available from: https://www.actiononhearingloss.org.uk/about-us/our-research-and-evidence/facts-and-figures/ [Accessed 31 January 2019].

16 Action on Hearing Loss. *Hearing Matters*. Available from: https://www.actiononhearingloss.org.uk/-/media/ahl/documents/research-and-policy/reports/hearing-matters-report.pdf.

17 Oh J-H, Park K, Lee SJ, Shin YR, Choung Y-H. Bilateral versus unilateral sudden sensorineural hearing loss. *Otolaryngology–Head and Neck Surgery*. 2007;136:87-91. Available from: http://doi:10.1016/j.otohns.2006.05.015

18 Office for National Statistics. *Population Estimates for UK, England and Wales, Scotland and Northern Ireland: mid-2017*. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/datasets/populationestimatesforukenglandandwalesscotlandandnorthernireland

19 National Institute for Health and Care Excellence. *Hearing loss in adults: assessment and management* (*NG98)*. Last Update Date: June 2018. Available from: https://www.nice.org.uk/guidance/ng98/resources/hearing-loss-in-adults-assessment-and-management-pdf-1837761878725 [Accessed 29/01/2019].

20 Stachler RJ, Chandrasekhar SS, Archer SM, Rosenfeld RM, Schwartz SR, Barrs DM, et al. Clinical Practice Guideline: Sudden Hearing Loss. *Otolaryngology–Head and Neck Surgery*. 2012;146(3):S1-S35. Available from: https://journals.sagepub.com/doi/10.1177/0194599812436449 https://doi.org/10.1177%2F0194599812436449.

NB: This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.