Single Technology Appraisal

Anhydrous sodium thiosulfate for preventing hearing loss caused by cisplatin chemotherapy in people 1 month to 17 years with localised solid tumours [ID1001]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Anhydrous sodium thiosulfate for preventing hearing loss caused by cisplatin chemotherapy in people 1 month to 17 years with localised solid tumours [ID1001]

Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **Company submission from** Norgine Limited**:**
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**

3. **Patient group, professional group, and NHS organisation submissions** from:
   a. The National Deaf Children's Society (NDCS) and The Royal National Institute for Deaf People (RNID)

4. **Expert personal perspectives** from:
   a. Milind Ronghe – clinical expert, nominated by Norgine Limited

5. **External Assessment Report** prepared by ScHARR

6. **External Assessment Report – factual accuracy check**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Anhydrous sodium thiosulfate (Pedmarqsi) for preventing ototoxicity caused by cisplatin chemotherapy in people aged 1 month to 17 years with localised solid tumours [ID1001]

Document B

Company evidence submission

April 2024

File name	Version	Contains confidential information	Date
ID1001_Pedmarqsi (STS) in cisplatin induced ototoxicity_Document B_29Aug2024_REDACTED	**V1.0**	**No**	**29th August 2024**

List of figures 5
List of tables 6
Abbreviations 8
B.1 Decision problem, description of the technology and clinical care pathway 11
B.1.1 Decision problem 12
B.1.2 Description of the technology being appraised 15
B.1.3 Health condition and position of the technology in the treatment pathway 16
B.1.3.1 Disease overview 16
B.1.3.2 Burden of cisplatin-induced ototoxicity 21
B.1.3.3 Current treatment pathway 24
B.1.3.4 Place of Pedmarqsi in the treatment pathway 25
B.1.4 Equality considerations 26
B.2 Clinical effectiveness 28
B.2.1 Identification and selection of relevant studies 29
B.2.2 Summary of methodology of the relevant clinical effectiveness evidence 32
B.2.2.1 The relevance of reporting Pedmarqsi doses in anhydrous form 32
B.2.2.2 SIOPEL 6 trial methodology 33
B.2.2.3 SIOPEL 6 trial population 36
B.2.2.4 COG ACCL0431 trial methodology 39
B.2.2.5 COG ACCL0431 trial population 43
B.2.3 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence 45
SIOPEL 6 trial statistical analysis and definition of study groups 45
B.2.3.1 COG ACCL0431 trial statistical analysis and definition of study groups 47
B.2.4 Critical appraisal of the relevant clinical effectiveness evidence 48
B.2.5 Clinical effectiveness results of the relevant studies 48
B.2.5.1 SIOPEL 6 trial clinical effectiveness results 48
B.2.5.2 COG ACCL0431 trial clinical effectiveness results 52
B.2.6 Subgroup analysis 56
B.2.7 Post-hoc analysis 57
B.2.8 Meta-analysis 59
B.2.9 Indirect and mixed treatment comparisons 59
B.2.10 Adverse reactions 59
B.2.10.1 SIOPEL 6 trial adverse reactions 59
B.2.10.2 COG ACCL0431 trial adverse reactions 60
B.2.11 Ongoing studies 62
B.2.12 Interpretation of clinical effectiveness and safety evidence 62
B.3 Cost effectiveness 65
B.3.1 Published cost-effectiveness studies 66

B.3.2 Economic analysis 75
B.3.3 Patient population 75
B.3.3.1 Model structure 75
B.3.3.2 Intervention technology and comparators 81
B.3.4 Clinical parameters and variables 81
B.3.4.1 Generalisability of COG ACCL0431 to England and Wales 82
B.3.4.2 Baseline patient characteristics 84
B.3.4.3 Efficacy 85
B.3.4.4 Safety 88
B.3.4.5 Mortality 88
B.3.5 Measurement and valuation of health effects 89
B.3.5.1 Health-related quality-of-life data from clinical trials 89
B.3.5.2 Mapping 89
B.3.5.3 Health-related quality-of-life studies 90
B.3.5.4 Targeted literature review 90
B.3.5.5 Adverse reactions 90
B.3.5.6 Health-related quality-of-life data used in the cost-effectiveness analysis 91
B.3.6 Cost and healthcare resource use identification, measurement and valuation 94
B.3.6.1 Intervention and comparators' costs and resource use 94
B.3.6.2 Health state unit costs and resource use 98
B.3.6.3 Adverse reaction unit costs and resource use 106
B.3.6.4 Societal costs and resource use 107
B.3.7 Severity 110
B.3.7.1 Severity modifier 110
B.3.8 Uncertainty 111
B.3.9 Managed access proposal 112
B.3.10 Summary of base case analysis inputs and assumptions 113
B.3.10.1 Summary of base case analysis input 113
B.3.10.2 Assumptions 121
B.3.11 Base case results 124
B.3.11.1 Base case incremental cost-effectiveness analysis results 124
B.3.12 Exploring uncertainty 125
B.3.12.1 Probabilistic sensitivity analysis 125
B.3.12.2 Deterministic sensitivity analysis 128
B.3.12.3 Scenario analysis 130
B.3.13 Subgroup analysis 133
B.3.14 Benefits not captured in the QALY calculation 133

B.3.15 Validation 133
B.3.15.1 Independent technical cost-effectiveness model QC 133
B.3.15.2 Expert validation of cost-effectiveness analysis 134
B.3.15.3 External validation 134
B.3.16 Interpretation and conclusions of economic evidence 134
B.4 References 137

List of figures

Figure 1: Proposed positioning of Pedmarqsi for cisplatin-treated paediatric patients in England and Wales 26
Figure 2: SIOPEL 6 trial design 34
Figure 3: SIOPEL 6 trial patient disposition 37
Figure 4: COG ACCL0431 trial design 40
Figure 5: COG ACCL0431 trial patient disposition 44
Figure 6: SIOPEL 6 overall survival (ITT population) 52
Figure 7: COG ACCL0431 overall survival (ITT population) 56
Figure 8: Model schematic – decision tree (year 1) 76
Figure 9: Model schematic - post-decision-tree health state model (years 2+) 77
Figure 10: Sources and data used to inform the severity of hearing loss (as a proportion of those with hearing loss) 86
Figure 11: Cumulative survival of the internal component of a cochlear implant[48] 101
Figure 12: Incremental cost-effectiveness plane (with PAS) 126
Figure 13: Incremental cost-effectiveness plane - assignment to the Minimal/no HL health state removed from the PSA (with PAS) 127
Figure 14: Cost-effective acceptability curve (with PAS) 127
Figure 15: Cost-effectiveness acceptability frontier (with PAS) 128
Figure 16: Tornado plot showing OWSA results on the ICER 130

List of tables

Table 1: The decision problem 13
Table 2: Technology being appraised 15
Table 3: Ototoxicity classification systems 18
Table 4: Eligible population 20
Table 5: SIOPEL 6 clinical effectiveness evidence 29
Table 6: COG ACCL0431 clinical effectiveness evidence 31
Table 7: Anhydrous dosing conversion for Pedmarqsi 33
Table 8: SIOPEL 6 inclusion and exclusion criteria 34
Table 9: Baseline characteristics of SIOPEL 6 (ITT population) 37
Table 10: COG ACCL0431 inclusion and exclusion criteria 41
Table 11: Baseline characteristics of COG ACCL0431 (ITT population) 44
Table 12: Summary of hearing loss (SIOPEL 6 ITT population) 49
Table 13: Summary of hearing loss (SIOPEL 6 mITT population) 49
Table 14: Brock Grades amongst 101 children evaluated in SIOPEL 6 (mITT population) 50
Table 15: Percentage of children experiencing hearing loss of at least Brock Grade 1 in SIOPEL 6 (mITT population) 51
Table 16: Summary of overall survival in SIOPEL 6 (ITT Population) 51
Table 17: Summary of hearing loss (COG ACCL0431 efficacy population) 52
Table 18: Summary of hearing loss (COG ACCL0431 ITT population) 53
Table 19: Summary of mean change from baseline hearing loss (COG ACCL0431 efficacy population) 53
Table 20: Summary of overall survival in COG ACCL0431 (ITT Population) 55
Table 21: Summary of hearing loss by age subgroup (COG ACCL0431 efficacy population) 56
Table 22: Summary of hearing loss (SIOPEL 6 and COG ACCL0431 pooled ITT population) 57
Table 23: Summary of hearing loss (SIOPEL 6 and COG ACCL0431 pooled mITT population) 58
Table 24: Between treatment difference in OS (SIOPEL 6 and COG ACCL0431 pooled ITT population) 58
Table 25: Summary of Most Common (Frequency of ≥ 10% in Either Arm) AEs with Maximum Severity of CTCAE Grade 3 or Higher during the Treatment Phase (SIOPEL 6 Safety Population) 60
Table 26: Summary of Most Common Grade 3 Severity or Higher AEs (Frequency of ≥ 10% in Either Arm) (COG ACCL0431 Safety Population) 61
Table 27: Summary list of published cost-effectiveness studies 67
Table 28: Features of the economic analysis 79
Table 29: Pedmarqsi doses in the SIOPEL 6 study 81
Table 30: Percentage distribution of cancer types in COG ACCL0431 and the England and Wales population 83
Table 31: Baseline patient characteristics informing the economic model 84
Table 32: Number and percentage of patients experiencing hearing loss 85
Table 33: Hearing loss severity reported by Knight *et al.* (2005) 86
Table 34: Severity of hearing loss (as a proportion of those with hearing loss) – scenario analyses 87
Table 35: Grade 3+ adverse events included in the model (Scenario) 88
Table 36: Percentage of patients alive and mortality probability in years 1-5* 89

Table 37: Disutilities for adverse events 91
Table 38: Summary of utility values for the cost-effectiveness analysis 93
Table 39: Pedmarqsi dose inputs used in the model 96
Table 40: Antiemetic premedication costs 97
Table 41. Hearing assessment unit costs and resource use included in the model 99
Table 42. Hearing loss management unit costs and resource use included in the model .. 102
Table 43. Speech and language therapy unit costs and resource use included in the model 105
Table 44: Depression and anxiety unit costs and resource use included in the model 106
Table 45: Adverse event costs included in the model 107
Table 46: Societal unit costs and resource use included in scenario analysis 109
Table 47: QALY weightings for severity as per the NICE health technology evaluations manual 110
Table 48: Summary features of QALY shortfall analysis 110
Table 49: Results of the QALY shortfall analysis 111
Table 50: Summary of variables applied and tested in the economic model 111
Table 51: Summary of base case variables applied in the economic model 113
Table 52: Summary of key model assumptions 121
Table 53: Base case results (with PAS) 124
Table 54: Mean PSA results (with PAS) 125
Table 55: OWSA results (with PAS) 129
Table 56: Scenario analysis 131

Abbreviations

Abbreviation	Definition
ABR	Auditory brainstem response
ACE	Active communication education
AdEERS	Adverse Event Expedited Reporting System
AE	Adverse Event
AFP	Alpha-fetoprotein
AHL	Average Hearing Level
ALDVMM	Adjusted limited dependent variable mixture model
ALT	Alanine Aminotransferase
AQoL	Assessment of quality of life
ASHA	American Speech-Language-Hearing Association
AUD	Australian Dollar
BAER	Brainstem auditory evoked response
BSC	Best supportive care
CA	Conference Abstract
CEAC	Cost-effectiveness acceptability curve
CEAF	Cost-effectiveness acceptability frontier
CI	Confidence interval
CINECA	Consorzio Interuniversitario
CMH	Cochran-Mantel-Haenszel
COG	Children's Oncology Group
CPI	Consumer Price Index
CNS	Central nervous system
CRD	Centre for Reviews and Dissemination
CSR	Clinical study report
CT	Computed tomography
CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
dB	Decibel
DPOAE	Distortion product otoacoustic emissions
DSU	Decision Support Unit
EED	Economic Evaluation Database
EFS	Event-free survival
EMA	European Medicines Agency
eMIT	electronic Market Information Tool
ENT	Ear, nose and throat
EPAR	European Public Assessment Report
EQ-5D	EuroQol 5-dimensions
FDA	Food and Drug Administration
FM	Frequency modulation
GB	Great Britain
GBP	Great British Pounds
GFR	Glomerular filtration rate

Abbreviation	Definition
GP	General Practitioner
HCHS	Hospital and Community Health Services
HL	Hearing Loss
HR	High-risk; Hazard Ratio
HRQoL	Health-related quality of life
HTA	Health technology assessment
HTE	Health technology evaluation
HUI	Health Utility Index
ICECAP	Icepop capability measure for adults
ICEP	Incremental cost-effectiveness plane
ICER	Incremental cost-effectiveness ratio
ICTRP	International Clinical Trials Registry Platform
ICUR	Incremental cost-utility ratio
IQR	Interquartile range
ITT	Intention-to-treat
IV	Intravenous
LS	Least squares
LYG	Life years gained
Max	Maximum
MESH	Medical Subject Headings
mg	milligram
MHRA	Medicines and Healthcare products Regulatory Agency
Min	Minimum
mITT	Modified Intention-to-treat
MRI	Magnetic resonance imaging
MVH	York Measurement and Valuation of Health
NELS	Non-elective long stay
NESS	Non-elective short stay
NHB	Net health benefit
NHS	National Health Service
NHSCII	NHS cost inflation index
NICE	National Institute of Health and Care Excellence
NOS	Not otherwise specified
NR	Not reported
NS	Not specified
OAE	Otoacoustic emissions
OECD	Office for Economic Co-operation and Development
ONS	Office for National Statistics
OR	Odds Ratio
OS	Overall Survival
OWSA	One-way sensitivity analysis
PAS	Patient access scheme
PICOS	Population, Intervention, Comparator, Outcome, Study

Abbreviation	Definition
PLN	Polish Złoty
PNET	Primitive neuroectodermal tumour
PP	Per protocol
PPP	Purchasing power parities
PRETEXT	Pre-treatment tumour extension
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PTA	Pure-tone audiometry
QALY	Quality-adjusted life year
QoL	Quality of life
QWB	Quality of wellbeing
RCT	Randomised controlled trial
RePEc	Research Papers in Economics
RHR	Relative hazard ratio
SAE	Serious Adverse Event
ScHARRHUD	Sheffield Centre for Health and Related Research Health Utilities Database
SD	Standard deviation
SE	Standard error
SEK	Swedish krona
SIOP	International Society of Paediatric Oncology
SIOPEL	Childhood Liver Tumours Strategy Group
SLR	Systematic literature review
SmPC	Summary of product characteristics
SMR	Standardised mortality ratio
SoC	Standard of Care
STS	Sodium thiosulfate
TA	Technology Assessment
TAU	Hearing aid provision alone
TEOAE	Transient evoked otoacoustic emissions
TL	Turkish lira
TLR	Targeted literature review
TTO	Time trade-off
UHF	Ultra-high frequency
UK	United Kingdom
UKCISG	UK cochlear implant study group
ULN	Upper limit of normal
US	United States
VAS	Visual Analog Scale
VAT	Value Added Tax
WBC	White blood cell
WHO	World Health Organization
WTP	Willingness-to-pay

B.1 Decision problem, description of the technology and clinical care pathway

Summary

Cisplatin is one of the most effective chemotherapy options for treating childhood cancer.[1] However, it is associated with ototoxicity, leading to irreversible bilateral sensorineural hearing loss.[2,3] This is caused by the production of toxic levels of reactive oxygen species resulting in in the inflammation and destruction of sensory outer hair cells in the inner ear. Initially, hearing loss occurs at high frequencies (4,000 to 8,000 Hz) in the first cycle of cisplatin chemotherapy and worsens with subsequent cycles – hearing loss progression eventually impacts lower frequencies of hearing, impacting the ability to comprehend speech.[4–8]

Hearing loss resulting from ototoxicity is a permanent and debilitating side effect of cisplatin chemotherapy in children. Infants and young children are at a critical stage of development in which hearing loss can negatively impact speech and language development and literacy, resulting in a life-long effect on quality of life (QoL).[9–11] Caregivers of children with hearing loss also suffer from an increased burden of care which can be severely detrimental to their quality of life and wellbeing.[12] Childhood hearing loss is also associated with a severe economic burden due to the costs of management strategies, additional educational support and productivity losses.[13,14]

Pedmarqsi is a water-soluble thiol compound which is administered via a 15-minute intravenous infusion, six hours after the completion of every cisplatin infusion.[15,16] The mechanism of action is not completely understood but may work through increasing levels of endogenous antioxidants, inhibition of intracellular oxidative stress, and/or a direct interaction between cisplatin and the thiol group in Pedmarqsi in ear fluid, where cisplatin becomes trapped (the latter produces an inactive platinum species which is not cytotoxic and is readily excretable).[15,17]

Pedmarqsi is licensed for the prevention of ototoxicity induced by cisplatin chemotherapy in patients 1 month to < 18 years of age with localised, non-metastatic, solid tumours. Cisplatin-induced ototoxicity develops in approximately 60% (26% to more than 90%) of children receiving cisplatin-based chemotherapy, resulting in a devastating life-long impact.[11,18] Approximately 222 patients in England and Wales with non-metastatic, localised cancer per year are expected to receive cisplatin chemotherapy and meet the eligibility requirements for preventative treatment with Pedmarqsi.[19]

Additionally, Pedmarqsi, a novel, anhydrous formulation of sodium thiosulfate, is the first and only preventative treatment developed for cisplatin-induced ototoxicity.[20] There are no options for preventative treatment, with the current treatment pathways consisting only of non-preventative management strategies once ototoxicity has occurred – inclusive of interventions such as hearing aids and cochlear implants.[14] Existing options do not address the underlying cause of hearing loss, and do not restore the hearing function or QoL of children with hearing loss to the levels associated with normal hearing.[14,15,21] Therefore, there is a severe unmet need for a preventative treatment option such as Pedmarqsi.

B.1.1 Decision problem

This submission focuses on a novel form of anhydrous sodium thiosulfate (STS), Pedmarqsi®, specifically formulated for children as a treatment for the prevention of cisplatin-induced ototoxicity.

This submission covers the technology's full marketing authorisation for this indication and is consistent with the final scope issued by the National Institute of Health and Care Excellence (NICE) and the NICE reference case.

The marketing authorisation for Pedmarqsi is for the following indication: for the prevention of ototoxicity induced by cisplatin chemotherapy in patients 1 month to <18 years of age with localised, non-metastatic, solid tumours.

The decision problem for this appraisal is presented in Table 1.

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People aged 1 month to less than 18 years of age with localised, non-metastatic, solid tumours having cisplatin chemotherapy.	Pedmarqsi is indicated for the prevention of ototoxicity induced by cisplatin chemotherapy in patients 1 month to < 18 years with localised, non-metastatic, solid tumours.	Whilst there is no difference between the final NICE scope and the decision problem addressed in the company submission, the wording used in the company submission aligns with the marketing authorisation for Pedmarqsi.
Intervention	Anhydrous sodium thiosulfate (Pedmarqsi).	Pedmarqsi.	Following the above rationale, whilst sodium thiosulfate is the active ingredient, Pedmarqsi is a novel formulation of anhydrous sodium thiosulfate, specifically manufactured for the prevention of cisplatin-induced hearing loss in patients 1 month to < 18 years of age.[15] Given the specific and novel formulation of Pedmarqsi, and to ensure clarity throughout this appraisal, the product is referred to as Pedmarqsi.
Comparator(s)	Established clinical management without anhydrous sodium thiosulfate (Pedmarqsi).	Established clinical management without Pedmarqsi.	The comparator arm in the economic model is cisplatin without Pedmarqsi, which aligns with the comparator arms in the Pedmarqsi clinical trials. Patients in the comparator arms of these trials received established clinical management without Pedmarqsi. The comparator in the decision problem addressed in the company submission is therefore aligned with the NICE final scope, however, see the above rationale regarding the wording of the intervention.
Outcomes	The outcome measured to be considered include: • Frequency and severity of hearing loss. • Audiological outcomes (e.g. sound perception, speech recognition and sound localisation).	The outcome measures from SIOPEL 6 and COG ACCL0431 that are presented in this submission include: • Percentage of patients experiencing hearing loss • Hearing loss severity	The company submission includes outcome measures from SIOPEL 6 and COG ACCL0431. Additional outcomes issued in the final scope such as speech recognition, sound localisation, language and communication outcomes, and psychosocial development/adjustment were not measured in

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	• Language and communication outcomes (e.g. intelligibility, sentence comprehension). • Psychosocial development/adjustment. • Adverse effects of treatment including impact on response to cisplatin and survival. • Health-related quality of life (HRQoL).	• Audiological outcomes – mean change in hearing threshold • Overall Survival • Adverse effects of treatment In addition, HRQoL data for hearing loss from published literature are also presented in this evidence submission as HRQoL data were not collected in the SIOPEL 6 or COG ACCL0431 trials.	the SIOPEL 6 or COG ACCL0431 trials. No additional sources were identified which measured these outcomes in patients treated with Pedmarqsi, therefore data for these outcomes could not be included in the company submission. Please also note that the HRQoL data presented is reflective of hearing loss, but not specific to Pedmarqsi, given that HRQoL data for patients treated with Pedmarqsi is not available.
Economic analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year (ICER/QALY). The reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from a National Health Service (NHS) and Personal Social Services perspective (PSS).	A cost-utility analysis was performed, with the cost-effectiveness expressed in terms of an incremental cost per quality-adjusted life year. A lifetime time horizon was used. Costs were considered from an NHS and PSS perspective.	In line with the NICE final scope.

Abbreviations: HRQoL – Health-related quality of life; ICER – Incremental cost-effectiveness ratio; NHS – National Health Service; NICE – National Institute for Health and Care Excellence; PSS – Personal Social Services; QALY – Quality-adjusted life year

B.1.2 Description of the technology being appraised

Table 2: Technology being appraised

UK approved name and brand name	Anhydrous sodium thiosulfate (Pedmarqsi®).
Mechanism of action	Pedmarqsi ($Na_2S_2O_3.5H_2O$) is a water-soluble thiol compound with reducing agent properties and is a normal metabolite in humans and other mammals.[17] Following intravenous (IV) injection, Pedmarqsi is distributed throughout the extracellular fluid; up to 95% is excreted unchanged in the urine and the biological half-life is 0.65 hours.[17] The mechanism of action of Pedmarqsi is not fully understood, but may include increasing levels of endogenous antioxidants, inhibition of intracellular oxidative stress, and direct interaction between cisplatin and the thiol group in Pedmarqsi in ear fluid, where cisplatin becomes trapped.[22] The latter produces an inactive platinum species which is not cytotoxic and is readily excretable.[9,22] Concurrent incubation of Pedmarqsi with cisplatin decreased *in vitro* cytotoxicity to tumour cells; delaying the addition of Pedmarqsi to these cultures prevented the protective effect.[22] Studies have emphasised the importance of separating platinum chemotherapy from thiol chemoprotection by either the route or timing of administration.[10,23]
Marketing authorisation/CE mark status	Marketing authorisation was granted by the European Commission on 26/5/2023, with reference to EU/1/23/1734/001.[24] The GB marketing authorisation number is PLGB 20011/0078. Initial MHRA (Medicines and Healthcare products Regulatory Agency) approval was granted on 11/10/2023.[4]
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The licensed indication for Pedmarqsi is:[22] • For the prevention of ototoxicity induced by cisplatin chemotherapy in patients 1 month to < 18 years of age with localised, non-metastatic, solid tumours. • There are no other licensed indications relevant to this appraisal.
Method of administration and dosage	Pedmarqsi should be administered intravenously as a 15-minute infusion, ideally through a central vein, 6 hours after the completion of every cisplatin infusion.[22,25] It is intended for hospital use only, under the supervision of an appropriately qualified physician. The timing of Pedmarqsi administration relative to cisplatin chemotherapy is critical. If Pedmarqsi is administered: • Less than 6 hours after end of cisplatin infusion: may reduce cisplatin efficacy against the tumour. • More than 6 hours after end of cisplatin infusion: may not be effective in preventing ototoxicity. The recommended dose of Pedmarqsi is weight-based and normalised to body surface area according to the table below:[22]

Body Weight	Anhydrous dose	Volume
> 10 kg	12.8 g/m^2	160 mL/m^2
5 to 10 kg	9.6 g/m^2	120 mL/m^2

	< 5 kg	6.4 g/m^2	80 mL/m^2
Additional tests or investigations	Most specialist paediatric cancer centres offer basic audiometry testing for children receiving platinum-based chemotherapy.[5] No additional tests are required to determine the child's eligibility for Pedmarqsi.		
List price and average cost of a course of treatment	List price: [redacted] per 8g vial (excluding VAT).		
Patient access scheme (if applicable)	A simple PAS discount of [redacted] has been submitted, as of 22nd April 2024.		

Abbreviations: EMA – European Medicines Agency; IV – Intravenous; MHRA – Medicines and Healthcare products Regulatory Agency; PAS – Patient access scheme; PLGB – Great Britain Product Licence; VAT – Value Added Tax

B.1.3 Health condition and position of the technology in the treatment pathway

B.1.3.1 Disease overview

B.1.3.1.1 Cisplatin-induced ototoxicity overview

Cisplatin is a platinum-based chemotherapy widely used to treat a variety of cancers in children and young people.[1] It remains one of the most effective chemotherapy treatments for childhood cancer and is a key component in the treatment of solid tumours, in particular, intracranial and intraspinal tumours, ependymoma, neuroblastoma, retinoblastoma, hepatoblastoma, osteosarcoma, malignant germ cell tumours, and nasopharyngeal carcinoma.[6,26]

A leading concern for the use of cisplatin chemotherapies within a paediatric population is the development of irreversible hearing loss due to cisplatin-induced ototoxicity.[2,3] Cisplatin triggers hearing loss in three major tissue areas within the cochlea: the organ of Corti, spiral ganglion cells and the lateral wall (stria vascularis and spiral ligament). The production of toxic levels of reactive oxygen species at these locations leads to the inflammation and destruction of sensory outer hair cells, resulting in widespread cochlear damage.[7,8,27] The extent of this damage is exacerbated by the prolonged presence of cisplatin in the inner ear, facilitated by the blood-labyrinth barrier.[28]

Ototoxicity initially presents as bilateral, high-frequency (4,000 to 8,000 Hz) sensorineural hearing loss, which may occur in the first cycle of treatment and once acquired, tends to worsen with increasing cumulative doses of cisplatin, extending to lower frequencies which relate to speech.[2,6,8] It should be noted that in current clinical practice, especially in younger patients, early presentation of hearing loss can be missed – see further details in Section B.1.3.1.2. Risk factors for more severe hearing loss include younger age at exposure (under five years) and a high cumulative dose of cisplatin ($\geq$ 400 mg/m^2).[2]

For the comparison to Pedmarqsi, there are currently no treatments that prevent the onset of ototoxicity in children who are being treated with platinum-based chemotherapy. Whilst there are several different options available for managing hearing loss once it has developed, the quality of these management interventions are incomparable to the maintenance of natural hearing. As such, an unmet need remains for a protective treatment that can prevent cisplatin-induced hearing loss and improve QoL for survivors of childhood cancer.[29]

B.1.3.1.2 Diagnosis of cisplatin-induced hearing loss in a paediatric population

As cisplatin is known to cause ototoxicity, patients receiving cisplatin chemotherapy are monitored for ototoxic hearing loss using pure-tone audiometry (PTA) assessments. Typically monitoring is performed using baseline and serial PTA measurements within a conventional frequency range of 0.25 to 8 kHz. Loss of hearing at these frequencies is indicative of cisplatin-induced hearing loss.[30] Ototoxicity monitoring is therefore essential for early identification of changes in hearing.

However, within current clinical practice, there is a frequent issue in delayed diagnosis. The impact of ototoxicity often progresses undetected until a noticeable decline in hearing, particularly in the frequencies necessary for speech comprehension, becomes apparent.[19] Confirming that hearing loss has occurred can present issues as an accurate diagnosis requires a comparative baseline audiometric measurement pre-ototoxic drug. Issues in the collection of such baseline measurements can lead to delay in confirming whether a child has experienced hearing loss and therefore results in a delayed diagnosis.[19]

Once diagnosed that ototoxic hearing loss has occurred, the extent of decline in hearing can be qualified. Variable factors impact the severity of both the measurable hearing loss and the impact it has on QoL experienced. Notable factors include the age at exposure, with a younger age correlating to more severe impact of hearing loss, and the cumulative dosage of cisplatin received, with a greater expose to cisplatin correlating to a more severe impact of hearing loss.[6]

Determining what constitutes a significant change in hearing is essential to qualify the severity of the decline.[31] Within the existing literature, there are a range of systems which can be used to define severity. For example, in COG ACCL0431, a pivotal Pedmarqsi trial, the American Speech Language and Hearing Association (ASHA) criteria is used and this defines a significant change in hearing as either a 10 dB change from baseline at two consecutive frequencies, or a 20 dB change at one frequency, or loss of measurable hearing for three consecutive frequencies where there was previously measurable hearing.[31] Whereas in SIOPEL 6, another of Pedmarqsi's core clinical trials, the Brock scale is used to assess hearing loss. The Brock scale is one of the most widely used paediatric-specific ototoxicity scales and was specifically designed to evaluate paediatric patients treated with cisplatin, focusing on high frequencies. Hearing loss Grades 0-4 are assigned based on standard pure-tone audiograms and reflect absolute hearing loss as opposed to a shift from baseline.[13,31] The use of the Brock system is particularly helpful for very young children where an accurate baseline assessment may not be feasible.

Beyond the gradings used within Pedmarqsi's core clinical trials, a study published by Orgel *et al.* (2023)[32] (identified in the systematic literature review (SLR)) and discussed in Section B.2.7), reports the use of the International Society of Paediatric Oncology (SIOP) Boston classification as an alternative measure of hearing loss. This scale was developed as a measure to report hearing outcomes in international clinical trials for paediatric patients treated with platinum therapy, taking into account the functional outcome of a patient at the end of treatment.[33] Furthermore, additional ototoxicity grading systems have been developed which are noted below:

- The National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) scale requires a baseline evaluation before treatment initiation and subsequent evaluations to measure change in hearing level as treatment progresses.[33]
- The Chang criteria was developed as a modification of the Brock scale, resulting in a more clinically-sensitive assessment correlating with the expected course of treatment-induced ototoxicity in clinical trials.[33]

The grading criteria used in the ototoxicity classification systems described above are compared in Table 3. As shown, there are differences in the thresholds for each grade of ototoxicity between the grading systems. Some of the variability in reported incidences of ototoxicity is therefore due to the inconsistencies in the assessment and grading tools.[13]

Table 3: Ototoxicity classification systems

ASHA	Brock	CTCAE v4.03	Chang	SIOP Boston
Normal: -10-15 dB	**Grade 0:** <40 dB at all frequencies	**Grade 0:** <20dB at all frequencies	**Grade 0:** ≤20 dB at 1,000 Hz, 2,000 Hz and 4,000 Hz	**Grade 0:** ≤20 dB at all frequencies
Slight: 16-25 dB	**Grade 1:** ≥40 dB at 8,000 Hz	**Grade 1:** >20 dB at 8,000 Hz	**Grade 1a:** ≥40 dB at 6,000-12,000 Hz	**Grade 1:** >20 dB at >4,000 Hz
Mild: 26-40 dB			**Grade 1b:** >20 dB and <40 dB at 4,000 Hz	
Moderate: 41-55 dB	**Grade 2:** ≥40 dB at ≥4,000 Hz	**Grade 2:** >20 dB at ≥4,000 Hz	**Grade 2a:** ≥40 dB at ≥4,000 Hz	**Grade 2:** >20 dB at ≥4,000 Hz
Moderately severe: 56-70 dB			**Grade 2b:** >20 and <40 dB at 1,000 Hz, 2,000 Hz or 3,000 Hz	
Severe: 71-90 dB	**Grade 3:** ≥40 dB at ≥2,000 Hz	**Grade 3:** >20 dB at ≥3,000 Hz Indication for hearing aids	**Grade 3:** ≥40 dB at ≥2,000 Hz or 3,000 Hz	**Grade 3:** >20 dB at 2,000 Hz or 3,000 Hz Indication for hearing aids
Profound: 91+ dB	**Grade 4:** ≥40 dB at ≥1,000 Hz	**Grade 4:** ≥50 dB at ≥1,000 Hz Audiological indication for cochlear implants	**Grade 4:** ≥40 dB at ≥1,000 Hz	**Grade 4:** >40 dB at ≥2,000 Hz

*Hearing loss at Grade 2 and above is considered deleterious hearing loss.
Abbreviations: ASHA – American Speech-Language-Hearing Association; CTCAE – Common Terminology Criteria for Adverse Events; SIOP – International Society of Paediatric Oncology.
Source: Clemens *et al.* 2019[33], Clark 1981[34]

B.1.3.1.3 Epidemiology

Pedmarqsi is indicated for the prevention of hearing loss in patients treated with cisplatin chemotherapy. As such, the eligible population is not a single specific disease population (i.e. a single type of cancer), but a subpopulation of children diagnosed with tumours that are treated with cisplatin. Therefore, disease prevalence is not simply defined. Additionally, Pedmarqsi is considered to be administered for a period of less than one year given that cisplatin treatment would also not be expected to be given beyond 12 months (see Section B.3.3.1.1).

Given these two factors, an incidence statistic (i.e. the identification of new cases who would undergo cisplatin treatment), as opposed to a prevalence statistic, is considered the most representative method to identify the population of interest.

To present an epidemiology statistic, calculations (summarised in Table 4) take the number of newly diagnosed paediatric cancer cases from 2012 to 2016, showing there to be an average of 470 solid tumour cancer cases recorded in children and adolescents (those aged under 18 years) in England and Wales every year.[35] From this it can be said that, on average, 69.4% (min: 56%, max: 90%) of these patients will present with non-metastatic, localised, disease at the point of diagnosis. Of this cohort, it is assumed that 70% of annual diagnosed localised patient will be treated with a cisplatin-containing chemotherapy. As such, it is estimated that there will be an eligible population for Pedmarqsi in England and Wales of 222 patients – this should therefore be considered a ‘very rare’ patient population.

Table 4: Eligible population

Newly diagnosed tumours potentially treated with cisplatin therapy	Number diagnosed 2012 to 2016 in the UK. *(Aged 0-19 years)*[a]	Number diagnosed 2012 to 2016 in the UK. *(Aged 0-18years)*[b]	Number diagnosed 2012 to 2016 in England and Wales	Mean number per year	Number diagnosed with localised disease[c]	Number treated with cisplatin chemotherapy[d]
Intracranial and intraspinal tumours	463	417	371	93	70	49
Ependymoma	314	283	252	63	57	40
Neuroblastoma	533	481	427	107	31	22
Retinoblastoma	221	199	177	44	41	29
Hepatoblastoma	110	99	88	22	17	12
Osteosarcomas	364	328	292	73	52	36
Malignant extracranial germ cell tumours	158	142	127	32	18	12
Malignant gonadal germ cell tumours	136	123	109	27	16	12
Nasopharyngeal carcinoma	48	43	38	10	2	1
Total	2,347	2,116	1,881	470	304	213
Total – inflated to a 2024 population					317	222

[a]Based on Appendix B CTYA cancer incidence, birth to 19 years from 2012-2016.[35]
[b]Within the reference for the number of newly diagnosed tumours, the data are grouped into age categories which do not suit the indication for Pedmarqsi. As such, the number diagnosed aged 0-19 years (sourced from the CTYA cancer incidence statistics)[35] is multiplied by the proportion of children aged under 18 within the under 19 age category (sourced from the ONS),[36] to calculate the number diagnosed aged 0-18 years.
[c]Taken from COG ACCL0431 study and literature for those tumours not represented in the study.
[d]It is anticipated that only a proportion of paediatric patients with localised cancers will receive a chemotherapy regimen containing cisplatin and therefore be eligible for Pedmarqsi. A flat-rate estimate across all cancer subgroups of 70% of patients being treated with cisplatin is applied.

B.1.3.2 Burden of cisplatin-induced ototoxicity

B.1.3.2.1 Clinical burden

Approximately 60% (26% to more than 90%) of children receiving cisplatin-based treatments will develop irreversible ototoxicity, resulting in a devastating life-long impact for these patients.[11,18] Hearing loss resulting from this ototoxicity is a permanent and debilitating side effect of cisplatin chemotherapy.[6] If a patient experiences high-frequency hearing loss, this renders certain consonants (f/th/p/k/h/t) inaudible and therefore infants and young children who are at a critical stage of development, will experience a negative impact on both their speech and language development and literacy skills.[1,3] In older children and adolescents, high-frequency hearing loss has been reported to impact on educational achievement, social-emotional development, and QoL.

Alongside development and social-emotional impacts, up to 75% of paediatric patients with cisplatin-induced hearing loss become eligible for hearing aids or auditory support.[37] Even with hearing aids or auditory support, cancer survivors with hearing loss experience abnormal hearing, tinnitus, compromised speech comprehension in noisy settings, social challenges, and significant financial burden. Whilst there are existing management strategies for those experiencing hearing loss, using such medical devices is inferior, in terms of patients' QoL, to the prevention of hearing loss altogether.[37]

B.1.3.2.2 Quality of life burden

As described above, the hearing loss induced by cisplatin ototoxicity is a side effect that can severely hinder the QoL in children. A child is at increased risk of academic difficulty, social and emotional problems, and fatigue in the learning environment from even minimal hearing loss in frequency ranges above 2,000 Hz.[11] In general, the younger the child is when hearing loss develops, the more significant the impact on speech and language development, however hearing loss also impacts the educational achievement and emotional wellbeing of older children.[38]

Hearing loss is particularly detrimental in younger (pre-lingual) children, as language development and general learning are dependent on hearing, the development of verbal and communication skills, comprehension ability and social development are all hindered.[11,39–41] In school-aged children, problems such as poor academic performance, emotional development and self-esteem/behaviour issues commonly arise.[40,41] In adolescents and young adults social isolation, depression and the inability to live independently are often reported.[41]

Regardless of age, those with hearing loss have reported feeling excluded in social settings, having social fatigue and because of these issues, preferring to avoid such social situations.[42] Such anxiety frequently leads to social exclusion and individuals feeling isolated within their social networks. Prolonged social exclusion can lead to depression and other mental health concerns which can be severely detrimental to the patient.[41,43]

Whilst the indicated population for Pedmarqsi is that of people aged under 18 years, the impact of ototoxic hearing loss is irreversible, and therefore lifelong. Among a study of adults, who were survivors of childhood cancer and who suffer from treatment-induced hearing loss, 45% had never married (compared to 37.9% for the general population) and 34% were unemployed (compared to 5.3% for non-disabled adults) or had not graduated high school.[43–45] The

challenges of hearing loss can also lead to anxiety and depressive symptoms amongst survivors.[41,42]

Beyond patients, the caregivers of patients with hearing loss experience a quality of life burden. Parents and teachers are reported to face difficulties dealing with the communicative, behavioural, and social consequences of childhood hearing impairment.[12] Communication between the caregiver and the child may be poorly established, creating frustration for both parties.[12] Children with hearing impairment are also more susceptible to behavioural issues, which may create or increase stress for the parents and caregivers.[12] Additionally, hearing impairment can hinder a child's psychosocial development and social skills, collectively contributing to heightened parental psychological distress.[12]

B.1.3.2.3 Patient perspectives from FDA Patient-Focused Drug Development Program: Voice of the Patient Report - Childhood Cancer Hearing Loss

As summarised from the literature in the above Section B.1.3.2.2, cisplatin-induced ototoxicity presents a significant QoL burden to patients and their caregivers. In addition to the referenced publications, data are available from a published document titled "The Voice of the Patient: Childhood Cancer Hearing Loss" which covers details of a public meeting conducted as part of the Food and Drug Administration's (FDA's) patient focused drug development initiative.[46] The outputs of the meeting echo the key messages presented in Section B.1.3.2.2 (as well as section B.1.3.1.1 which covers limitations with currently available management strategies); however, given the importance of the patient perspective and the severe impact hearing loss has on patients, this report is described in greater detail below.

The Patient-Focused Drug Development meeting was hosted in 2018 by four advocacy organisations in childhood cancer to share insights with researchers and senior officials at the US FDA, as well as other chemotherapy-induced paediatric hearing loss stakeholders presenting the perspectives of people living with chemotherapy-induced hearing loss. The cause of hearing loss was mostly related to the use of platinum-based chemotherapy in childhood and the vast majority of children had at least moderate hearing loss. The meeting aimed to assess the impact on patient's daily lives, and their expectations and priorities for both current and future ototoxic induced hearing loss treatments.

Key impacts identified in the meeting were the unprecedented impacts on their day-to-day lives, and deterioration in their mental health.

Day-to-day impacts were reported across a significant list of categories, inclusive but not limited to; socialisation, learning and academic experiences, employment opportunities, participation in sports, recreational activities, performing arts, and general quality of life, indicating the burden of the disease upon their daily lives. To the point on socialisation, following the loss of their hearing, many described the development of severe social isolation coupled with anxiety when participating in social situations both in school, and in their adult lives.

In broader terms, some older patients in the group expressed that their hearing loss had been so impactful, they wished that their cancer had not been treated. One patient stated that due to the hearing loss they were experiencing, they discontinued their chemotherapy to preserve what hearing they had left.

To support the above impacts, the following quotes from the meeting from cancer survivors with hearing loss are presented to help build the story of impact:

- *"Before my hearing loss, I was a happy, active, extroverted child. Now I'm too anxious or exhausted to enjoy new environments or activity. I am a lonely and typically anxious person. I'm a different person because of my hearing loss. I've told my parents many times that I wish I didn't go through my cancer treatment because of my hearing loss, it makes life difficult and unbearable."*

- *"It's hard to pick one thing that worries me the most. One day, it might be missing something that other people my age are doing…Overall, my biggest worry about my hearing is it makes my world so much smaller."*

Following from statements such as those above, the advocacy organisations also included discussions with patient caregivers, who expressed fears that their children would continue to withdraw from the world:

- *"The hearing loss…is the single reason that he says, 'I wish the cancer had killed me.' He thinks that the life we gave him by saving his life isn't worth it right now."*

- *"He works so hard to try be independent, but he finds workplace options lacking because of his hearing."*

Beyond reporting perspectives on what the patient experiences in terms of living with hearing loss, the meeting also gathered insights into how patients currently perceive their management of deafness following cisplatin treatment. Whilst patients use a variety of management devices, they state their effectiveness to be limited, and note significant disadvantages associated with each modality.

- Hearing aids were most widely deployed as a strategy to improve hearing following loss, however participants reported several disadvantages, including that they do not work well in noisy environments and they can fail due to battery drain or breakage as well as being uncomfortable, both physically and socially.

- Whilst systems are in place within the educational system, e.g. FM systems, they are dependent on the compliance of teachers. Additionally, feeding into prior points on mental health impacts, these systems often make patients feel like they stand out as not only a person with poor hearing, but also a consistent self-reminder that they are a cancer survivor.

- Finally, there were also those who were using cochlear implants. Many reported them to be extremely invasive, requiring a complete destruction of what remains of their natural hearing, leaving full reliability to the management device. Additional concerns were raised on their links to migraines and skin sensitivity.

Overall, a key conclusion and message from participants in these meetings was the significant unmet need for treatments that can prevent hearing loss, and the lack of effective treatment options currently available for patients.

B.1.3.2.4 Economic burden

The hearing loss associated with cisplatin-induced ototoxicity presents a significant economic burden. Approximately 60% of children with moderate hearing loss require additional individualised tutoring from a specialist teacher for the deaf.[38] The vast majority of children with severe or profound hearing loss also require additional educational support, such as

specialist schooling or tutoring.[38] Extra teaching support represents a substantial resource use in England and Wales.

The typical approach for children judged to have moderate or severe hearing loss is to provide them with a hearing aid. It is reported that the typical cost of a high-frequency digital hearing aid is £250-300 per pair; these are replaced every four years and may also require additional amplification technology.[14,38] Children suffering from profound hearing loss typically have a bilateral cochlear implant costing approximately £41,000 with the requirement for external processor replacement being every five years and costing approximately £5,800.[47,48] In addition, frequency modulation (FM) systems are provided in classrooms to assist all children with hearing loss.[38] The cost of a binaural FM system is estimated to be approximately £2,300[14]; these systems are typically replaced every five years.[38]

Aside from the costly expense associated with treating hearing loss, there is a considerable economic strain on the NHS linked to its management, including costs for hearing assessments and speech and language therapy.[38] In addition, patients with marked and severe hearing loss are also less likely to be able to gain employment, with a relative reduction in work of 24% observed compared to the general population of England and Wales.[14,38] Finally, carers of children with hearing loss are impacted by the disease, facing challenges such as missed employment opportunities and reduced productivity due to attendance of medical appointments with physicians and specialists.[38]

B.1.3.3 Current treatment pathway

B.1.3.3.1 Treatment options

There are no existing pharmacological interventions for the prevention of hearing loss caused by cisplatin-induced ototoxicity, despite the significant impact hearing loss has on patients.[20]

Current guidelines for the management of ototoxicity resulting from cisplatin chemotherapy include monitoring the level of hearing loss which, in some cases, is used to inform switching the platinum-based chemotherapy agent from cisplatin to carboplatin.[49] Although carboplatin is less ototoxic than cisplatin, it has been reported that cisplatin is more effective at treating certain tumours, such as germ cell and liver malignancies.[49,50] This trade-off between minimising the severity of acquired hearing loss whilst potentially compromising the efficacy of chemotherapy highlights the unmet need for a treatment to prevent cisplatin-induced ototoxicity, so patients can confidently continue to take cisplatin to treat their underlying cancer.

For those continuing with a cisplatin-based treatment pathway, once hearing loss has occurred, the current management strategies involve the use of non-pharmacological interventions which are not preventative (cannot reverse hearing loss), and are of a quality incomparable to that of natural hearing. The most common management strategy for those with lesser severities of hearing loss is the use of hearing aids throughout a patient's life.[7] Although hearing aids amplify sound, they indiscriminately amplify all sounds – reducing the patient's ability to discriminate speech in noisy environments.[7,21] Further issues with hearing aids include the fact that children are required to frequently recharge the batteries for them to function, they are easily lost or broken, and children may avoid wearing hearing aids altogether due to a perceived social stigma.[51] Coupled to hearing aids, additional strategies can be used to further utilise the benefit of hearing aids, inclusive of auditory trainers, telephone amplifiers and audio streamers to enhance the effect of hearing aids in loud environments, however care

must be taken to ensure compatibility between these devices and the specific model of hearing aid.[7] As an additional concern, hearing aids must be replaced every four years and may also require additional amplification technology. Hearing aids are far less effective than approaches which protect a person's natural hearing.[14,33,41,42]

For those children with severe to profound sensorineural hearing loss who are unable to benefit from hearing aids, bilateral cochlear implants may be used.[14,22] These provide a modified sense of sound but require commitment to an audiology and speech therapy rehabilitation programme.[7] However, as with hearing aids, they present limitations inclusive of the need for external processors requiring replacement every five years, and the internal electrode also being at risk of requiring replacement due to device failure.[14,33,41,42]

Finally, a third mainstream approach to hearing loss management in the UK, is the use of FM systems in classrooms to support all children with hearing loss in the education environment. These devices allow the transmission of sounds (e.g. lessons in a classroom) directly to a child's hearing device, however these systems typically need replacement every five years.[38]

Given the lack of preventative pharmacological treatment options, Pedmarqsi remains the only potential option for patients to prevent cisplatin-induced ototoxicity and avoid the suboptimal management strategies as described above.

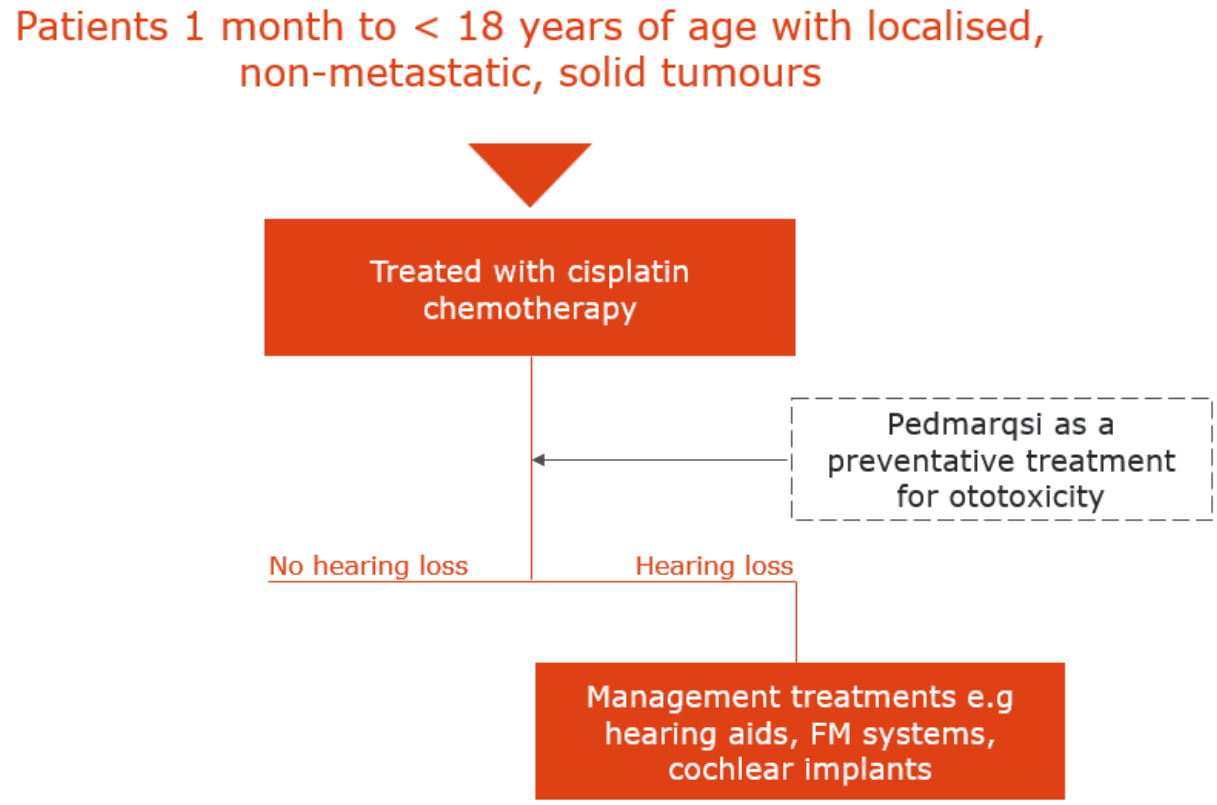
B.1.3.4 Place of Pedmarqsi in the treatment pathway

The introduction of Pedmarqsi will represent a step change in the treatment pathway through access to a preventative intervention to avoid cisplatin-induced ototoxicity in children with cancer.

To be eligible for Pedmarqsi, no additional testing beyond standard ototoxicity monitoring would be required. Therefore, the majority of patients who meet the eligibility criteria defined in the marketing authorisation for Pedmarqsi (i.e. patients 1 month to < 18 years of age with localised, non-metastatic, solid tumours who are receiving cisplatin chemotherapy) would be eligible for treatment.

The anticipated positioning of Pedmarqsi in England and Wales is summarised in Figure 1.

Figure 1: Proposed positioning of Pedmarqsi for cisplatin-treated paediatric patients in England and Wales



Abbreviations: FM – Frequency modulation

Pedmarqsi has demonstrated robust efficacy in terms of preventing cisplatin-induced hearing loss through the SIOPEL 6 and COG ACCL0431 clinical trials. Both studies reported statistically significant results in hearing related outcomes favouring Pedmarqsi over cisplatin treatment without Pedmarqsi (Section B.2.5). Further to this, Pedmarqsi does not impact the OS of cancer patients whilst demonstrating a safety profile which suggests the medicine is safe and generally well tolerated (Section B.2.10). Therefore, the Pedmarqsi represents a safe and effective treatment that will benefit patients in terms of preventing cisplatin-induced hearing loss in children.

In addition, there is significant humanistic and economic burden associated with cisplatin-induced hearing loss and the availability of Pedmarqsi will improve educational, social-emotional, and QoL outcomes for survivors of childhood cancer, as well as removing the costs and perceived social stigma associated with assistive devices needed to manage the condition.[41]

Therefore, the introduction of Pedmarqsi will fill a substantial unmet need for a treatment that can prevent cisplatin-induced hearing loss in children, and the evidence confirms that Pedmarqsi should be made available as soon as possible for patients in England and Wales.

B.1.4 Equality considerations

Pedmarqsi is licensed for use in children 1 month to <18 years of age with localised, non-metastatic, solid tumours to prevent hearing loss caused by cisplatin-based chemotherapy

regimens. Preventing hearing loss from occurring, or the severity at which it does occur, is vital to enable children to reach their full potential. As established in Section B.1.3, once cisplatin-induced hearing loss has occurred, management strategies may be available but will not compensate for the irreversible damage to the inner ear caused by cisplatin, and are therefore not as effective in restoring patients' QoL when compared to the prevention of hearing loss altogether. The introduction of Pedmarqsi for routine use will greatly improve the QoL, opportunities and prospects for children receiving cisplatin chemotherapy and surviving their childhood cancer.

Furthermore, although the NHS offers a basic service which includes hearing aids, patients requiring more advanced hearing aids may be forced to search elsewhere. This can shift the financial burden to parents and carers who will need to purchase these for their children. This inequity is further enhanced by household income, as families living in challenging financial and social conditions are less likely to be able to afford more advanced equipment and, more generally, have an increased burden when caring for a child suffering from hearing loss.

Finally, although speech and language therapy is offered by the NHS, wealthier families may pay for their children to have lessons with a better teacher-to-child ratio. Again, this creates an inequity where the prospects of a child with hearing loss are heavily impacted by household income. Pedmarqsi can have a positive impact on this inequity by offering a safe and effective treatment to prevent ototoxicity and therefore avoid hearing loss in children receiving cisplatin chemotherapy.

B.2 Clinical effectiveness

Summary

The clinical effectiveness of Pedmarqsi is demonstrated across two randomised, open-label clinical trials; the SIOPEL 6 trial and the COG ACCL0431 trial. Both trials compared the efficacy and safety of cisplatin with Pedmarqsi against cisplatin without Pedmarqsi in the prevention of cisplatin-induced ototoxicity in paediatric patients.

The SIOPEL 6 trial demonstrated a statistically significant benefit in its primary efficacy endpoint, the proportional incidence of children with Brock Grade >1 hearing loss after the end of treatment or at >3.5 years of age (whichever was later) in the intention-to-treat (ITT) population. The proportion of children in the cisplatin with Pedmarqsi arm with Brock Grade ≥1 hearing loss at age ≥3.5 years (20 children, 35.1%) was approximately one-half compared with the cisplatin without Pedmarqsi arm (35 children, 67.3%). The risk of experiencing hearing loss was statistically significantly lower in the cisplatin with Pedmarqsi arm compared with the cisplatin without Pedmarqsi arm (relative risk: 0.521, 95% confidence interval (CI): 0.349, 0.778; p<0.001), corresponding to a clinically meaningful 48% lower risk after Pedmarqsi treatment.[16]

Pedmarqsi also reduced the severity of hearing loss in the SIOPEL 6 trial. Of children in the mITT population who experienced hearing loss of at least Brock Grade 1, 55% of children treated with Pedmarqsi experienced Brock Grade 1 hearing loss, 33% Grade 2, 6% Grade 3 and 6% Grade 4. In comparison, 41% of children treated with cisplatin without Pedmarqsi experienced Brock Grade 1 hearing loss, 38% Grade 2, 18% Grade 3 and 3% Grade 4.[52]

The COG ACCL0431 trial also demonstrated a statistically significant benefit in its primary efficacy endpoint, the proportional incidence of hearing loss between the cisplatin with Pedmarqsi arm and the cisplatin without Pedmarqsi arm in the efficacy population. The proportion of children in the cisplatin with Pedmarqsi arm with hearing loss (14 children, 28.6%) was approximately one-half of the proportion of the cisplatin without Pedmarqsi arm (31 children, 56.4%). The odds of having hearing loss as defined by ASHA criteria were statistically significantly lower in the cisplatin with Pedmarqsi arm compared with the cisplatin without Pedmarqsi arm (odds ratio: 0.274; 95% CI: 0.114, 0.660; p=0.0039), when adjusted for the stratification variables of prior cranial irradiation (yes vs no), age subgroup (<5 years of ≥5 years), and duration of cisplatin infusion (<2 vs ≥2 hours).[25]

An additional post-hoc analysis of the COG ACCL0431 trial results published by Orgel *et al*. (2023)[32] using the more recent International SIOP ototoxicity scale also demonstrated that Pedmarqsi reduced the severity of hearing loss in the COG ACCL0431 trial. After the end of cisplatin treatment, a lower incidence of Grade ≥2 cisplatin-induced hearing loss occurred in the cisplatin with Pedmarqsi arm (4.0%) versus the cisplatin without Pedmarqsi arm (27.1%). In addition, it was concluded that the odds of developing SIOP Grade ≥2 cisplatin-induced hearing loss were significantly lower for patients in the cisplatin with Pedmarqsi arm (odds ratio (OR) 0.10, 95% CI 0.02-0.50, p=0.005). The same pattern was seen for SIOP Grade ≥1; a lower incidence of Grade ≥1 cisplatin-induced hearing loss occurred in the cisplatin with Pedmarqsi arm versus the cisplatin without Pedmarqsi arm (18.0% versus 45.8%; OR 0.25, 95% CI 0.10-0.64, p=0.004).[32]

Patients receiving Pedmarqsi experienced adverse events (AEs) at a similar rate as those who did not receive Pedmarqsi in both the SIOPEL 6 and COG ACCL0431 trials, demonstrating that Pedmarqsi is safe and generally well tolerated.

Neither trial demonstrated that Pedmarqsi affected the OS of patients, suggesting that Pedmarqsi does not affect the efficacy of cisplatin as a chemotherapy treatment for the underlying tumour when administered 6 hours after the end of a cisplatin infusion lasting no more than 6 hours.

Overall, the SIOPEL 6 and COG ACCL0431 trials represent a comprehensive evidence base and demonstrate the robust clinical efficacy and safety of Pedmarqsi in preventing cisplatin-induced ototoxicity in patients 1 month to < 18 years with localised, non-metastatic, solid tumours.

B.2.1 Identification and selection of relevant studies

A SLR was conducted to identify relevant literature regarding the efficacy and safety of treatments for the prevention of cisplatin-induced ototoxicity in children. Full details of the methodology of the SLR are presented in Appendix D. List of relevant clinical effectiveness evidence.

The SLR identified two clinical trials that evaluated the efficacy and safety of Pedmarqsi for the prevention of ototoxicity in children: the SIOPEL 6 and COG ACCL0431 trials.

- SIOPEL 6 was a multicentre, open-label, phase 3, randomised trial assessing the efficacy and safety of delayed Pedmarqsi infusion in reducing ototoxicity in 129 children. These children were receiving single agent cisplatin therapy for the treatment of standard-risk hepatoblastoma (defined as pre-treatment tumour extension [PRETEXT] classification I, II or III, serum alpha-fetoprotein (AFP) >100 µg/L, and no additional PRETEXT criteria).
- COG ACCL0431 was a multicentre, open-label, phase 3, randomised trial assessing the efficacy of delayed Pedmarqsi infusion for preventing hearing loss in 131 children. These children were receiving cisplatin-containing chemotherapy regimens for the treatment of newly diagnosed germ cell tumour, hepatoblastoma, medulloblastoma, neuroblastoma, osteosarcoma, or any other solid malignancy treated with cisplatin.

The SIOPEL 6 and COG ACCL0431 trials are summarised below and in Table 5 and Table 6, respectively:

Table 5: SIOPEL 6 clinical effectiveness evidence

Study	**SIOPEL 6** **ClinicalTrials.gov registration: NCT00652132[53]** **Brock *et al*. (2018)[52] – CSR[16]**
Study design	Multicentre, open-label, phase III randomised trial performed at 52 centres across 12 countries: United Kingdom, Ireland, Belgium, Denmark, France, Italy, Switzerland, Spain, Australia, New Zealand, United States and Japan.
Population	Children aged >1 month to ≤18 years receiving cisplatin chemotherapy for a newly diagnosed, histologically confirmed, hepatoblastoma. Children must have had standard-risk hepatoblastoma, defined as PRETEXT I, II or III, serum AFP >100 µg/L, and with no additional PRETEXT criteria.
Intervention(s)	Pedmarqsi

<table>
<tr><td>Study</td><td>SIOPEL 6
ClinicalTrials.gov registration: NCT00652132[53]
Brock et al. (2018)[52] – CSR[16]</td></tr>
<tr><td></td><td>The dose of Pedmarqsi was dependent on the child's body weight and reflected the dosing in the table below:<table><tr><th>Body weight</th><th>Anhydrous dose</th><th>Volume</th></tr><tr><td>>10 kg</td><td>12.8 g/m^2</td><td>160 mL/m^2</td></tr><tr><td>≥5 and ≤10 kg</td><td>9.6 g/m^2</td><td>120 mL/m^2</td></tr><tr><td><5 kg</td><td>6.4 g/m^2</td><td>80 mL/m^2</td></tr></table>Pedmarqsi was infused intravenously over 15 minutes, six hours after cisplatin infusion was completed, in an inpatient setting. Cisplatin was dosed as per the comparator arm and was infused over six hours.
More information on the reporting of Pedmarqsi doses in the anhydrous form is presented in Section B.2.2.1.</td></tr>
<tr><td>Comparator(s)</td><td>Cisplatin without Pedmarqsi.
In both arms of the trial, cisplatin was administered by IV infusion over six hours, and the dose of cisplatin was dependent on the child's body weight as follows:<table><tr><th>Body weight</th><th>Dose</th></tr><tr><td>>10 kg</td><td>80 mg/m^2</td></tr><tr><td>≥5 and ≤10 kg</td><td>2.7 mg/kg</td></tr><tr><td><5 kg</td><td>1.8 mg/kg</td></tr></table></td></tr>
<tr><td>Indicate if study supports application for marketing authorisation</td><td>Yes</td></tr>
<tr><td>Indicate if study used in the economic model</td><td>Yes</td></tr>
<tr><td>Rationale if study not used in model</td><td>N/A</td></tr>
<tr><td>Reported outcomes specified in the decision problem</td><td>• Hearing loss as assessed by Brock Grade.
• Adverse effects of treatment.
• Overall survival.</td></tr>
<tr><td>All other reported outcomes</td><td>Other audiological outcomes:
• Measurement of bilateral pure-tone air conduction thresholds at 8, 6, 4, 2, 1, and 0.5 kHz.
• Immittance evaluation including middle ear pressure and compliance, and acoustic reflex thresholds.
• Measurement of transient evoked otoacoustic emissions (TEOAEs) and distortion product otoacoustic emissions (DPOAEs).
• Bone conduction auditory brainstem response (ABR).
• Tumour status after preoperative chemotherapy:
  ◦ Tumour response after two and four cycles of cisplatin chemotherapy.
  ◦ Resection after preoperative chemotherapy.
  ◦ Tumour status at end of treatment.
  ◦ Tumour status at last follow-up.</td></tr>
</table>

Study	SIOPEL 6 ClinicalTrials.gov registration: NCT00652132[53] Brock *et al*. (2018)[52] – CSR[16]
	• Event-free survival. • Long-term renal clearance. • Feasibility of central audiology review. • AFP levels.

Abbreviations: ABR – Auditory brainstem response; AFP – Alpha-fetoprotein; DPOAE – Distortion product otoacoustic emissions, PRETEXT – Pre-treatment tumour extension; TEOAE – Transient evoked otoacoustic emissions

Table 6: COG ACCL0431 clinical effectiveness evidence

Study	COG ACCL0431 ClinicalTrials.gov registration: NCT00716976[54] Freyer *et al*. (2016)[26] – CSR
Study design	Multicentre, open-label, phase III randomised trial in the United States and Canada.
Population	Children aged ≥1 to ≤18 years newly diagnosed with any histologically confirmed germ cell tumour, hepatoblastoma, medulloblastoma, neuroblastoma, osteosarcoma, or other solid malignancy requiring cisplatin chemotherapy.
Intervention(s)	Pedmarqsi. Pedmarqsi was dosed at 10.2 g/m^2 (anhydrous dosing). Note that for children whose therapeutic protocol administered cisplatin on a "per kg" basis due to young age or small body size, Pedmarqsi was dosed at 341 mg/kg (anhydrous dosing). For all doses, Pedmarqsi was administered by intravenous infusion over 15 minutes, beginning six hours after the completion of each cisplatin infusion. Cisplatin was infused over ≤6 hours. More information on the reporting of Pedmarqsi doses in the anhydrous form is presented in Section B.2.2.1.
Comparator(s)	Cisplatin-containing regimen without Pedmarqsi ("Cisplatin without Pedmarqsi " arm). In both arms of the trial, cisplatin was administered according to the sites' disease-specific cancer treatment protocols in use at the time. Other chemotherapy agents were also permitted as per these protocols.
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Rationale if study not used in model	N/A
Reported outcomes specified in the decision problem	• Hearing loss as defined by ASHA. • Adverse effects of treatment. • Overall survival.
All other reported outcomes	Other audiological outcomes:

Study	COG ACCL0431 ClinicalTrials.gov registration: NCT00716976[54] Freyer *et al*. (2016)[26] – CSR

	• Measurement of bilateral pure-tone air conduction thresholds at 0.5 to 8 kHz.
	• Immittance evaluation.
	• Measurement of evoked otoacoustic emissions (OAEs).
	• Brainstem auditory evoked response (BAER).
	• Ultra-high frequency (UHF) audiometry.
	  • Components of reported haematological toxicity.
	  • Components of reported nephrotoxicity.
	  • Event-free survival.

Abbreviations: ASHA – American Speech-Language-Hearing Association; BAER – Brainstem auditory evoked response; OAE – Otoacoustic emissions; UHF – Ultra-high frequency

B.2.2 Summary of methodology of the relevant clinical effectiveness evidence

B.2.2.1 The relevance of reporting Pedmarqsi doses in anhydrous form

It should be noted that in the following sections, where the dose of Pedmarqsi is referred to, the dose reported is the anhydrous dose. This is because the active ingredient of Pedmarqsi is anhydrous sodium thiosulfate. Additionally, this aligns with the GB Summary of Product Characteristics (SmPC) for Pedmarqsi, which reports the recommended dose in anhydrous form.[22,25] However, it should be noted that the clinical study reports (CSR) and publications for the SIOPEL 6 and COG ACCL0431 trials report the dose of Pedmarqsi in pentahydrate-equivalent form (due to an existing US monograph for a pentahydrate form of sodium thiosulfate) and therefore do not align with the SmPC. As this discrepancy is due to the higher molecular mass of the pentahydrate form compared to the anhydrous form of sodium thiosulfate, it should be noted that the amount of active ingredient for a given dose is the same regardless of whether it is hydrated or anhydrous. For clarification, a conversion table between the doses for the pentahydrate-equivalent and anhydrous forms of Pedmarqsi used in the SIOPEL 6 and COG ACCL0431 clinical trials is presented below in Table 7. To avoid any potential ambiguity, the approved formulation in both GB and EU is anhydrous.

Table 7: Anhydrous dosing conversion for Pedmarqsi

Pedmarqsi pentahydrate-equivalent dose (g/m^2) [Reported in publications and CSRs][16,25]	Pedmarqsi anhydrous dose (g/m^2) [Aligns with EMA and GB SmPC and formulation][22]
20.0	12.8
16.0	10.2
15.0	9.6
10.0	6.4

Abbreviations: CSR – Clinical study report; EMA – European Medicines Agency; GB – Great Britain; SmPC – Summary of product characteristics

B.2.2.2 SIOPEL 6 trial methodology

The SIOPEL 6 trial was an open-label, phase III randomised trial performed at 52 centres across 12 countries: United Kingdom, Ireland, Belgium, Denmark, France, Italy, Switzerland, Spain, Australia, New Zealand, United States and Japan.[16]

The primary objective of the trial was to assess the efficacy of Pedmarqsi for reducing hearing impairment caused by cisplatin chemotherapy.[16]

The secondary objectives were to:

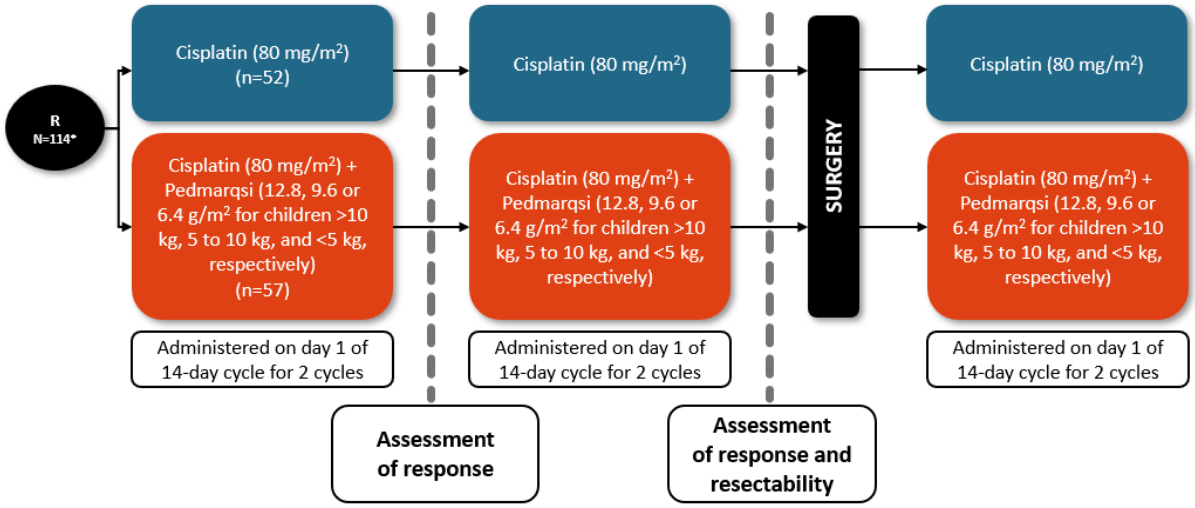
- Monitor any potential impact of Pedmarqsi on the child's response to cisplatin and subsequent survival.[16]
- Assess the short- and long-term tolerability of the combination of Pedmarqsi and cisplatin.[16]
- Prospectively evaluate and validate biological, radiological and pathological features of standard-risk hepatoblastoma for future risk adapted management.[16]

During the screening phase, children were randomised 1:1 to receive Pedmarqsi after each cisplatin dose (cisplatin with Pedmarqsi arm) or to receive cisplatin without Pedmarqsi. This randomisation was stratified by country, median age (above vs below 15 months), and PRETEXT classification (I and II vs III). A total of 129 children were registered, 114 of which were randomised in the study: 61 children in the cisplatin with Pedmarqsi arm and 53 children in the cisplatin without Pedmarqsi arm.[16] Of the 15 children registered but not randomised: 13 children were withdrawn due to unspecified reasons; one child was withdrawn due to parental consent; and one child was withdrawn due to ineligibility (for details of the SIOPEL 6 exclusion criteria, see Table 8). Although the trial was open-label due to the emergence of treatment-related side effects during infusion, blinded assessment of the primary endpoint was feasible and thus offsets any introduction of bias resulting from open-label trial status.

During the treatment phase, children received preoperative chemotherapy including four courses of cisplatin with or without Pedmarqsi (dependent on their randomisation status) on Days 1, 15, 29, and 43, followed by surgery, and received two additional chemotherapy courses postoperatively (on Days 1 and 15 post-surgery). If surgery was delayed for any reason, two further courses may also have been given (on Days 57 and 71).[16]

In the cisplatin with Pedmarqsi arm, six hours following each cisplatin dose, children received Pedmarqsi by intravenous (IV) infusion. The design of the SIOPEL 6 trial is summarised in Figure 2.

Figure 2: SIOPEL 6 trial design



*Of the 114 children randomised, five were not treated (two children were withdrawn due to parental consent, two children were reclassified as high-risk, and one child was ineligible for treatment).
**If surgery was delayed for any reason, two further courses of preoperative chemotherapy could have been given on Days 57 and 71.
Source: SIOPEL 6 CSR.[16]

SIOPEL 6 eligibility criteria

The SIOPEL 6 trial inclusion and exclusion criteria are shown in Table 8.

Table 8: SIOPEL 6 inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria

• Aged >1 month and ≤18 years
• Newly diagnosed, histologically confirmed hepatoblastoma
  • Standard-risk hepatoblastoma:
  • PRETEXT I, II or III
  • Serum AFP >100 µg/L
  • No additional PRETEXT criteria.
• Written informed consent and national/local ethics committee and regulatory approval.
• Centre/country willing and able to organise audiometry and minimum require quality standard.
• Ability to comply with requirements for submission of material for central review (radiology, pathology and audiology).
• For females of child-bearing potential, a negative pregnancy test prior to study treatment was required.
• Any child of reproductive age should have agreed to use adequate contraception for the duration of the study.
	• High-risk hepatoblastoma:
	  • Serum AFP ≤100 µg/L
	  • Tumour involving all four hepatic sections (PRETEXT IV)
	  • Additional PRETEXT criteria (extrahepatic abdominal disease, intraperitoneal haemorrhage or tumour rupture, distant metastases, lymph node metastases, involvement of the main portal vein, involvement of all three hepatic veins and/or the inferior vena cava).
	• Hepatocellular carcinoma
	• Treatment starting more than 15 days from written biopsy report
	• Abnormal renal function defined as calculated glomerular filtration rate (GFR) <75% of the lower limit of normal for age at diagnosis (for over two years of age) is <60 mL/min/1.73m^2
	• Any previous chemotherapy
	• Recurrent disease
	• Previous hypersensitivity to Pedmarqsi

	• Child unable to follow the protocol for any reason

Abbreviations: AFP – Alpha-fetoprotein; GFR – Glomerular filtration rate; PRETEXT – Pre-treatment tumour extension
Source**:** SIOPEL 6 CSR[16].

Interventions

As noted above, Pedmarqsi was administered as a 15 minute IV infusion, six hours after cisplatin (maximum dose cisplatin: 80 mg/m^2).[16] Pedmarqsi doses correspond to the body weight of the child (>10 kg, 5 to 10 kg, and <5 kg received Pedmarqsi 12.8 g/m^2, 9.6 g/m^2, and 6.4 g/m^2, respectively (anhydrous dosing).

Analysis of the safety population concluded that the mean cumulative cisplatin exposure was similar between the cisplatin with Pedmarqsi and cisplatin without Pedmarqsi arms (363.860 mg/m^2 vs 362.851 mg/m^2, respectively).[16]

Outcomes

The primary endpoint was the proportional incidence of hearing loss defined as Brock Grade ≥1 hearing loss determined by PTA after the end of treatment or at age ≥3.5 years (whichever timepoint was later). The Brock Grade of the better ear was used for analysis of hearing impairment in the primary endpoint. Hearing impairment rates were calculated and compared between the two randomised treatment groups. As a method of censoring patients, children without a hearing loss assessment were counted as a failure (i.e. had hearing loss) in this analysis.[16] The handling of missing data is further discussed in Section 0.

The following key secondary endpoints were measured:

- **Hearing loss measurements**: Pure-tone audiograms were performed by an experienced audiological technician. The resulting audiogram was uploaded through the Consorzio Interuniversitario (CINECA) remote data entry website. A central audiology reviewer accessed the CINECA remote data entry and graded the audiogram by providing a Brock Grade (0, 1, 2, 3, or 4).[16]

- **Percentage of children per disease status:** Complete remission, partial remission, stable disease, progressive disease (all relating to the underlying cancer), and children who were not evaluable (presented overall and by randomised group).[16]

- **Event-free survival (EFS):** this was measured from the time of randomisation to the first of the following events: progression, relapse, second primary malignancy, or death (all relating to the underlying cancer).[16]

- **Overall survival:** this was calculated from the time of randomisation to death (relating to the underlying cancer). OS was graphically compared between the randomised groups by Kaplan-Meier plots. A stratified log-rank test was calculated and stratified by the stratification factors used for randomisation. The hazard ratio between the two groups was calculated by stratified Cox regression and was presented together with its asymmetrical 95% CI.[16]

- **Satisfactory renal clearance:** defined as a calculated creatinine clearance of ≥ 60 mL/min/1.73m^2 (a value less than this was considered as being of clinical concern).[16]

- **The log_{10} change in AFP from baseline** to any later assessment as well as the change from nadir to a higher value (indicative of tumour progression) were evaluated on a per child level as a biomarker assessment of hepatoblastoma response and remission status.[16]

SIOPEL 6 concomitant medicines

Cisplatin is a highly emetogenic drug, therefore patients frequently experience significant levels of nausea and/or vomiting. Pedmarqsi is also reported to be a highly emetogenic drug, hence concomitant antiemetic therapy was considered essential. The anti-emetic regimen was scheduled such that a 5-HT_3 receptor antagonist and other antiemetics (i.e. dexamethasone with chlorpheniramine and/or metoclopramide) were given 30 minutes prior to Pedmarqsi treatment. Sites were encouraged to administer children a multi agent anti-emetics lasting six to eight hours for the first 24 to 48 hours of treatment and adequate anti-emetic treatment was to be continued as long as required.[16]

The following medications are known to be ototoxic and were prohibited where possible to avoid additional sources of ototoxicity during cisplatin treatment: amikacin, aminoglycosides, aspirin, bumetanide, desferroxamine, ethacrynic acid, erythromycin (give intravenously), furosemide, gentamycin, hexachlorobenzene, interferon alpha 2 therapy, kanamycin, 4-methylthiobenzoic acid (interacts with platinum-based medication), mercury (if ingested), mitomycin (topical), neomycin, norvancomycin, propylthiouracil, quinine, streptomycin, streptidine, styrene, super oxides (Paraquat), teicoplanin, tirapazamine, paracetamol, vancomycin, and vincristine.[16]

SIOPEL 6 supportive therapies

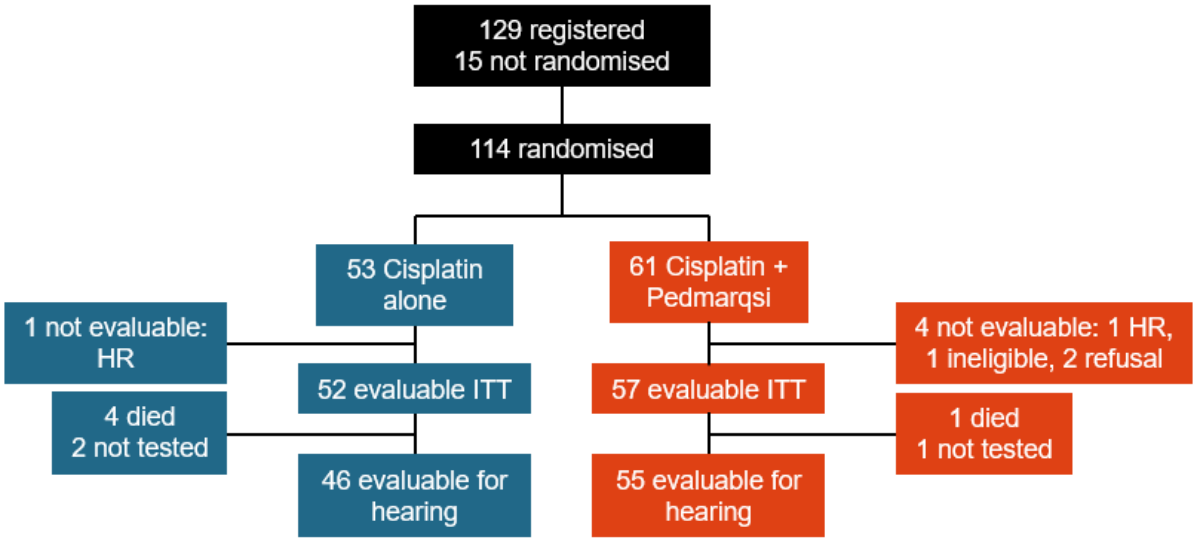
Cisplatin-related supportive therapies remained the same irrespective of whether Pedmarqsi was also administered. A careful record of fluid input and output was kept during administration of each treatment cycle. If the child's diuresis fell below 3 mL/kg/h for 2 hours, the hospital was to give the child a bolus of mannitol 0.5 g/kg over 15 to 30 minutes. The use of loop diuretics such as furosemide were to be avoided, as they are ototoxic. Serum electrolytes, especially serum sodium, were monitored daily prior to Pedmarqsi treatment and at 1, 6, and 18 hours post-Pedmarqsi treatment. If the child's serum sodium exceeded 150 mmol/L at one-hour post-Pedmarqsi treatment, then the patient was to receive a bolus of mannitol 0.5 g/kg over 15 to 30 minutes with a 10 mL/kg fluid bolus of dextrose in addition to standard cisplatin hydration. Oral magnesium supplements were also given to all children (if necessary) between cycles.[16]

B.2.2.3 SIOPEL 6 trial population

Patient disposition

The details of the SIOPEL 6 trial patient disposition are depicted in Figure 3.

Figure 3: SIOPEL 6 trial patient disposition



Abbreviations: HR – High-risk; ITT – Intention-to-treat
Source: SIOPEL 6 CSR[16].

Baseline characteristics

Patient characteristics of the SIOPEL 6 study are summarised in Table 9. The intention-to-treat (ITT) population (defined in SIOPEL 6 trial statistical analysis and definition of study groups) included a total of 109 children (52 in the cisplatin without Pedmarqsi arm and 57 in the cisplatin with Pedmarqsi arm).[16] Of the 114 children randomised, five were not treated (two children were withdrawn due to parental consent, two children were reclassified as high-risk, and one child was ineligible for treatment).

Table 9: Baseline characteristics of SIOPEL 6 (ITT population)

Characteristic	Cisplatin without Pedmarqsi (N=52)	Cisplatin with Pedmarqsi (N=57)	Total (N=109)
Age in months*, mean ± SD [median] (min, max)	18.2 ± 15.0 [13.4] (3.0, 70.2)	18.8 ± 16.7 [12.8] (1.2, 98.6)	18.5 ± 15.8 [13.0] (1.2, 98.6)
Female, n (%)	23 (44.2)	27 (47.4)	50 (45.9)
Male, n (%)	29 (55.8)	30 (52.6)	59 (54.1)
Race, n (%)			
White	32 (61.5)	32 (56.1)	64 (58.7)
Asian	7 (13.5)	6 (10.5)	13 (11.9)
Other	5 (9.6)	8 (14.0)	13 (11.9)
Black or African American	2 (3.8)	0	2 (1.8)
Missing	6 (11.5)	11 (19.3)	17 (15.6)
Height (cm)			
n	48	50	98
Mean (SD)	77.7 (12.3)	79.7 (14.6)	78.7 (13.5)

Characteristic	Cisplatin without Pedmarqsi (N=52)	Cisplatin with Pedmarqsi (N=57)	Total (N=109)
Median (min, max)	75.8 (58, 113)	77.0 (45, 126)	76.0 (45, 126)
Weight (kg)**			
n	52	57	109
Mean (SD)	10.25 (3.26)	10.23 (3.76)	10.24 (3.51)
Median (min, max)	9.53 (4.8, 20.7)	9.10 (2.6, 25.8)	9.30 (2.6, 25.8)
GFR (mL/min/1.73 m^2)			
n	49	57	106
Mean (SD)	127.8 (48.1)	132.5 (50.5)	130.3 (49.2)
Median (min, max)	122.0 (41, 278)	128.0 (44, 309)	124.0 (41, 309)
AFP at diagnosis (ng/mL)			
n	52	57	109
Mean (SD)	374,405.06 (565,678.77)	496,084.69 (888,294.08)	438,035.69 (750,986.67)
Median	79,251.50	181,500.00	109,872.00
(min, max)	187.0, 2,632,584.9	273.0, 5,489,165.0	187.0, 5,489,165.0
AFP Category, n (%)			
<1,000 ng/mL	4 (7.7)	4 (7.0)	8 (7.3)
1,000 ng/mL to <1,000,000 ng/mL	42 (80.8)	45 (78.9)	87 (79.8)
>1,000,000 ng/mL	6 (11.5)	8 (14.0)	14 (12.8)
PRETEXT classification, n (%)			
I†	0	11 (19.3)	11 (10.1)
II††	31 (59.6)	30 (52.6)	61 (56.0)
III‡	21 (40.4)	16 (28.1)	37 (33.9)
Caudate lobe involvement, n (%)			
Yes	5 (9.6)	4 (7.0)	9 (8.3)
No	40 (76.9)	49 (86.0)	89 (81.7)
Uncertain	7 (13.5)	4 (7.0)	11 (10.1)
Tumour focality, n (%)			
F0 (solitary tumour)	45 (86.5)	53 (93.0)	98 (89.9)
F1 (two or more tumours ‡‡)	7 (13.5)	4 (7.0)	11 (10.1)
Tumour rupture or intraperitoneal haemorrhage, n (%)			
H0 (no evidence of rupture or haemorrhage)	51 (98.1)	55 (96.5)	106 (97.2)

Characteristic	Cisplatin without Pedmarqsi (N=52)	Cisplatin with Pedmarqsi (N=57)	Total (N=109)
Uncertain	1 (1.9)	2 (3.5)	3 (2.8)
Distant metastases, n (%)			
M0 (no metastases)	52 (100.0)	55 (96.5)	107 (98.2)
Uncertain	0	2 (3.5)	2 (1.8)
Lymph node metastases, n (%)			
N0 (no nodal metastases)	51 (98.1)	56 (98.2)	107 (98.2)
Uncertain	1 (1.9)	1 (1.8)	2 (1.8)
Portal vein involvement, n (%)			
Yes	8 (15.4)	5 (8.8)	13 (11.9)
No	41 (78.8)	50 (87.7)	91 (83.5)
Uncertain	3 (5.8)	2 (3.5)	5 (4.6)

Note: Some characteristics could not be measured in very young children, accounting for the discrepancies between the total columns.
*Age recorded at time of diagnosis.
**Weight was recorded prior to course 1 administration as part of the physical exam prior to dosing at each course for the calculation of the correct cisplatin and Pedmarqsi doses.
†One section of the liver was involved, and three sections were free from disease.
††One or two sections of the liver were involved, but two adjoining sections were free from disease.
‡Two or three sections of the liver were involved, and no two adjoining sections were free from disease.
‡‡Regardless of nodule size or PRETEXT classification.
Abbreviations: AFP – Alpha-fetoprotein; GFR – Glomerular filtration rate; Max – Maximum; Min – Minimum; PRETEXT – Pre-treatment tumour extension; SD – Standard deviation
Source: SIOPEL 6 CSR[16].

B.2.2.4 COG ACCL0431 trial methodology

The COG ACCL0431 study was a multicentre, open-label, phase III randomised trial in the United States and Canada investigating the efficacy of Pedmarqsi infusion (six hours after the completion of each cisplatin infusion) for preventing hearing loss in children.[25]

The primary objective of the study was to evaluate the efficacy of Pedmarqsi infusion (following cisplatin treatment), compared with the cisplatin without Pedmarqsi arm, for preventing hearing loss in children receiving cisplatin chemotherapy for the treatment of newly diagnosed germ cell tumour, hepatoblastoma, medulloblastoma, neuroblastoma, osteosarcoma, or any other malignancy treated with cisplatin.[25]

The secondary objectives were to:

- Compare the mean change in hearing thresholds from baseline to four weeks after treatment with cisplatin for key frequencies (500, 1000, 2000, 4000 and 8,000 Hz) between the cisplatin with Pedmarqsi arm and the cisplatin without Pedmarqsi arm.[25]
- Compare the incidences of cisplatin-related Grade 3 and 4 nephrotoxicity and Grade 3 and 4 cytopenia between the cisplatin with Pedmarqsi arm and the cisplatin without Pedmarqsi arm.[25]

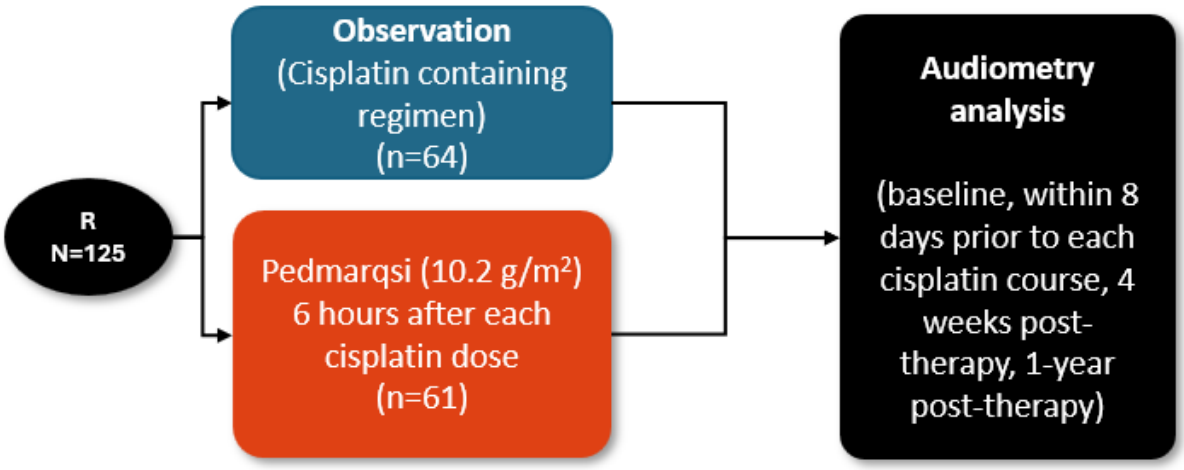
- Monitor EFS and OS relating to the underlying cancer in the cisplatin with Pedmarqsi arm and the cisplatin without Pedmarqsi arm.[25]
- Evaluate the association of two key gene mutations (thiopurine S-methyltransferase and catechol-O-methyltransferase) with the development of cisplatin-induced hearing loss (however, no analysis was conducted due to an insufficient number of samples).[25]

Children were randomised to either the cisplatin with Pedmarqsi arm or to the cisplatin without Pedmarqsi arm. A total of 131 children were enrolled in the study across 38 sites in the US and Canada; data was provided from a total of 125 eligible children. The randomisation was stratified by prior cranial irradiation (yes vs no); and for children without prior cranial irradiation, randomisation was further stratified by age (<5 years vs ≥5 years) and duration of cisplatin infusion (<2 hours vs ≥2 hours). Similar to SIOPEL 6 (see B.2.2.2), randomisation was blinded for central reviewers of audiometry data, but the study was open-label for children and treating physicians.[25]

Cisplatin was administered according to the sites' disease-specific cancer treatment protocols in use at the time, without specification by the COG ACCL0431 study with regard to individual or cumulative cisplatin dose, schedule, number of cycles, other chemotherapy administered, infusion rate or associated hydration/mannitol diuresis. When multiple daily doses of cisplatin were scheduled, there must have been at least a 10-hour delay before beginning of the subsequent cisplatin infusion following Pedmarqsi infusion.[25] Furthermore, all cisplatin infusions must have been completed within 6 hours.

Children completed follow-up audiograms at four weeks and one year after completion of the planned treatment regimen. Children who discontinued Pedmarqsi prematurely before completion of the planned treatment regimen also completed audiograms at four weeks and one year after completion of the planned treatment regimen.[25] The design of the COG ACCL0431 trial is summarised in Figure 4.

Figure 4: COG ACCL0431 trial design



Source: COG ACCL0431 CSR[25].

COG ACCL0431 eligibility criteria

The COG ACCL0431 trial inclusion and exclusion criteria are shown in Table 10.

Table 10: COG ACCL0431 inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria

• Aged ≥1 year and ≤18 years.
• Newly diagnosed with any histologically confirmed germ cell tumour, hepatoblastoma, medulloblastoma, neuroblastoma, osteosarcoma, or other malignancy that was to be treated with cisplatin chemotherapy.
• A chemotherapy treatment regimen plan that included a cumulative cisplatin dose of ≥200 mg/m^2, with individual cisplatin doses to be infused over ≤6 hours.
• Children not enrolled in any other COG study for their disease-specific treatment.
• Children may have been enrolled in non-COG studies or not enrolled in any therapeutic study.
• Performance score of ≥50 using Karnofsky criteria for children >16 years of age and Lansky criteria for children ≤16 years of age.
• Children who have no had previous platinum-based chemotherapy.
• Children who completed a hematopoietic stem cell transplant ≥6 months prior to enrolment.
• No evidence of active graft-versus-host disease.
• Normal audiometry results prior to enrolment.
• Serum sodium levels within a normal range.
• Adequate haematological function defined as:
  ○ Absolute granulocyte count >1.0 x 10^3/mm.
  ○ Platelets >100 x 10^3/mm.
• Adequate renal function defined as:
  ○ Creatinine clearance or radioisotope GFR ≥70 mL/min/1.73 m^2 or
  ○ Serum creatine based on age/gender (see COG ACCL0431 CSR for more details)[25].
• Adequate liver function defined as:
  ○ Total bilirubin ≤1.5 x upper limit of normal (ULN) for age, and
	• Females of child-bearing age must not have been pregnant. Females with germ cell tumours, which occasionally result in false-positive pregnancy tests, may have been enrolled, provided pregnancy was ruled out by other tests.
	• Female children who were lactating must have agreed to stop breastfeeding.
	• Children must not have had any previous hypersensitivity to Pedmarqsi or other thiol agents.
	• Children must not have been enrolled in any COG therapeutic study for treatment of the underlying malignancy.

Inclusion criteria	Exclusion criteria
○ Serum glutamic-oxaloacetic transaminase aspartate aminotransferase) or serum glutamic pyruvic transaminase (alanine aminotransferase) <2.5 x ULN for age.	

Abbreviations: CSR – Clinical Study Report; GFR – Glomerular filtration rate; ULN – Upper limit of normal
Source: COG ACCL0431 CSR[25].

Interventions

Pedmarqsi was administered by IV infusion over 15 minutes, beginning six hours after the completion of each cisplatin infusion. The Pedmarqsi dose was 10.2 g/m^2 on each day it was administered (anhydrous dosing).[25]

Analysis of the safety population concluded that the mean cumulative cisplatin exposure for the cisplatin with Pedmarqsi and cisplatin without Pedmarqsi arms were 337.57 mg/m^2 and 391.47 mg/m^2, respectively. This difference is reflected in the differences observed in the number of cisplatin cycles received in each treatment arm (3.1 in the cisplatin with Pedmarqsi arm and 3.8 in the cisplatin without Pedmarqsi arm).[25]

Outcomes

The primary efficacy endpoint was the proportional incidence of hearing loss between the cisplatin with Pedmarqsi arm and the cisplatin without Pedmarqsi arm, measured in the efficacy population. For the primary analysis, hearing loss was treated as a dichotomous variable measured using the ASHA criteria for hearing loss via comparison of the baseline audiology assessment (prior to first dose of cisplatin) and four-week follow-up evaluation following the final cisplatin course. A logistic regression model was used to evaluate if there was any association between Pedmarqsi treatment and hearing loss when adjusting for the stratification variables. The odds ratio with associated 95% CI and p-value for the between treatment comparison was estimated based on the logistic regression model. Similarly, subgroup analyses were performed for hearing loss by age group (<5 or ≥5 years). These analyses were based on logistic regression, including only the treatment as a fixed effect in the logistic regression model and the odds ratio with associated 95% CI and p-value for the between treatment comparison was estimated.[25]

The following secondary efficacy endpoints were measured:

- The mean change in hearing thresholds for key frequencies (500, 1000, 2000, 4000, and 8,000 Hz) between the cisplatin with Pedmarqsi arm and the cisplatin without Pedmarqsi arm. Linear regression analyses were used to assess whether Pedmarqsi treatment reduced the mean change in hearing thresholds when adjusting for stratification variables.[25]

- EFS and OS: Kaplan-Meier curves (and corresponding 95% CI) of EFS/OS for the two arms were estimated. As exploratory analyses, EFS and OS between the two arms were compared using log-rank tests. These analyses were performed at each scheduled interim monitoring assessment during accrual and in follow-up after accrual was completed. Exploratory analyses of EFS/OS outcomes using Cox models with randomisation stratification as covariates were also performed to test the influence of each covariate on EFS and OS.[25]

- For the secondary analyses related to toxicities, presence of toxicity was treated as a dichotomous variable. Incidence of Grades 3 and 4 nephrotoxicity and the incidence of Grades 3 and 4 cytopenia between the two arms were compared using logistic regression with adjustment for the stratification variables.[25]

COG ACCL0431 concomitant medicines

Anti-emetics were indicated to prevent nausea and vomiting due to chemotherapy and Pedmarqsi. Concurrent administration of loop diuretics (e.g. ethacrynic acid, furosemide, and bumetanide) and/or aminoglycosides with cisplatin were to be avoided, if possible, because concurrent usage could have increased the risk of ototoxicity. If concurrent administration of these agents with cisplatin was indicated, administration information was recorded on standardised report forms.[25]

COG ACCL0431 concomitant therapies

Cranial irradiation was permissible prior to study enrolment, however, children receiving cranial irradiation were only eligible if their baseline pre-study audiometry was normal. The baseline audiometry must have been performed after cranial irradiation and prior to cisplatin chemotherapy. This primarily applied to older children with medulloblastoma. Children may have received cranial irradiation following completion of all systemic cisplatin chemotherapy provided their post end of treatment audiometry was completed prior to beginning irradiation. This primarily applied to infants and toddlers with medulloblastoma treated on non-COG therapeutic studies. Cranial irradiation may not have been administered following study enrolment unless the child had completed all systemic cisplatin chemotherapy.[25]

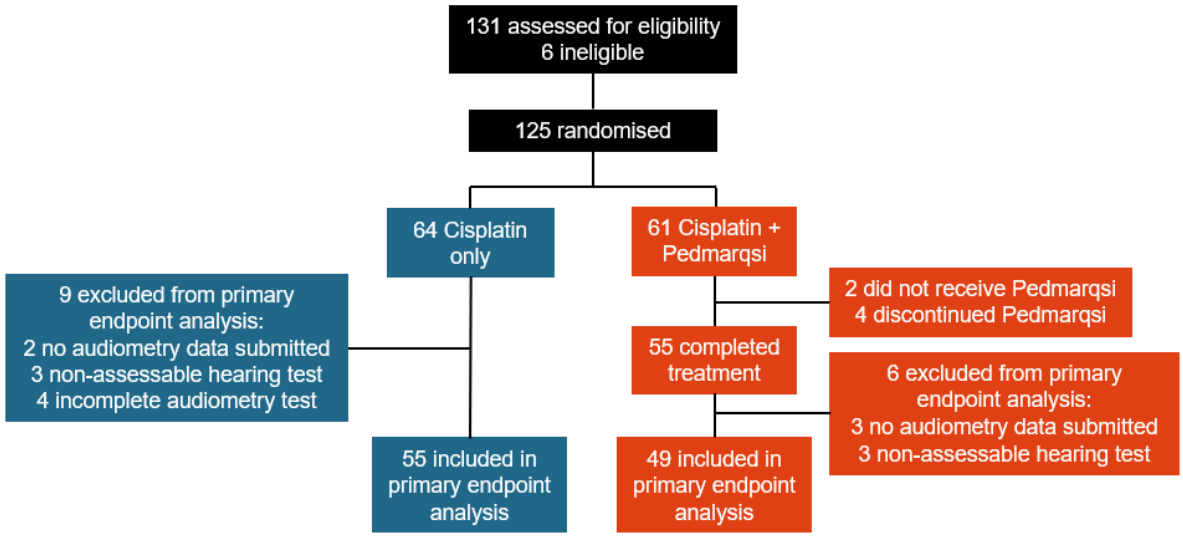
It was also recognised that children requiring hematopoietic stem cell transplants may have been exposed to further ototoxic medication. For these children, following an induction phase that contained cisplatin, it was noted that high-dose carboplatin could have been used in some conditioning regimens. Details of carboplatin administration during the transplant conditioning were recorded on standardised report forms.[25]

B.2.2.5 COG ACCL0431 trial population

Patient disposition

The details of the COG ACCL0431 trial patient disposition are depicted in Figure 5.

Figure 5: COG ACCL0431 trial patient disposition



Source: COG ACCL0431 CSR[25].

Baseline characteristics

The baseline characteristics of the COG ACCL0431 study population are summarised in Table 11. The ITT population included a total of 125 children (61 children in the cisplatin with Pedmarqsi arm and 64 children in the cisplatin without Pedmarqsi arm). Two children in the cisplatin with Pedmarqsi arm did not receive any Pedmarqsi and were excluded from both the safety and efficacy populations (defined in B.2.3.1).[25]

Table 11: Baseline characteristics of COG ACCL0431 (ITT population)

Characteristic	Cisplatin without Pedmarqsi (N=64)	Cisplatin with Pedmarqsi (N=61)	Total (N=125)
Age (years)			
n	64	61	125
Mean (SD)	8.9 (5.9)	9.4 (6.0)	9.2 (5.9)
Median (min, max)	8.3 (1, 18)	10.7 (1, 18)	9.5 (1, 18)
<5, n (%)	22 (34.4)	22 (36.1)	44 (35.2)
≥5, n (%)	42 (65.6)	39 (63.9)	81 (64.8)
Sex, n (%)			
Male	41 (64.1)	35 (57.4)	76 (60.8)
Female	23 (35.9)	26 (42.6)	49 (39.2)
Race, n (%)			
White	39 (60.9)	42 (68.9)	81 (64.8)
Black	10 (15.6)	5 (8.2)	15 (12.0)
Asian	2 (3.1)	1 (1.6)	3 (2.4)
American Indian or Alaska Native	0	1 (1.6)	1 (0.8)

Characteristic	Cisplatin without Pedmarqsi (N=64)	Cisplatin with Pedmarqsi (N=61)	Total (N=125)
Native Hawaiian or other Pacific Islander	1 (1.6)	1 (1.6)	2 (1.6)
Unknown	12 (18.8)	11 (18.0)	23 (18.4)
Ethnicity, n (%)			
Not Hispanic or Latino	46 (71.9)	41 (67.2)	87 (69.6)
Hispanic or Latino	15 (23.4)	18 (29.5)	33 (26.4)
Unknown	3 (4.7)	2 (3.3)	5 (4.0)
Diagnosis, n (%)			
Germ cell tumour	16 (25.0)	16 (26.2)	32 (25.6)
Osteosarcoma	15 (23.4)	14 (23.0)	29 (23.2)
Medulloblastoma	14 (21.9)	12 (19.7)	26 (20.8)
Medulloblastoma	14 (21.9)	10 (16.4)	24 (19.2)
Supratentorial PNET	0	2 (3.3)	2 (1.6)
Neuroblastoma	12 (18.8)	14 (23.0)	26 (20.8)
Hepatoblastoma	5 (7.8)	2 (3.3)	7 (5.6)
Other	2 (3.1)	3 (4.9)	5 (4.0)
Atypical teratoid/rhabdoid tumour	0	2 (3.3)	2 (1.6)
Carcinoma NOS	0	1 (1.6)	1 (0.8)
Choroid plexus carcinoma	1 (1.6)	0	1 (0.8)
Anaplastic astrocytoma	1 (1.6)	0	1 (0.8)
Extent of disease, n (%)			
No metastases detected at diagnosis	38 (59.4)	39 (63.9)	77 (61.6)
Metastases present at diagnosis	26 (40.6)	21 (34.4)	47 (37.6)
Unknown	0 (0)	1 (1.6)	1 (0.8)
Prior cranial irradiation	5 (7.8)	4 (6.6)	9 (7.2)

Abbreviations: ITT – Intention-to-treat; NOS – Not otherwise specified; PNET – Primitive neuroectodermal tumour; SD – Standard deviation
Source: COG ACCL0431 CSR[25].

B.2.3 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

SIOPEL 6 trial statistical analysis and definition of study groups

Study groups

The following populations were defined in the SIOPEL 6 trial, wherein the ITT population was the primary population for the efficacy analyses and the safety population was the primary population for all safety analyses:

- ITT population (N=109; cisplatin without Pedmarqsi=52, cisplatin with Pedmarqsi=57): The ITT population comprised all randomised children except those for which informed consent was withdrawn prior to start of study treatment and those for whom study treatment would have been inappropriate because they had were subsequently diagnosed with high-risk hepatoblastoma, regardless of whether or not study medication was administered.[16]

- Safety population (N=109; cisplatin without Pedmarqsi=56, cisplatin with Pedmarqsi=53): The safety population was defined as all randomised children who received at least one dose of study medication.[16]

- mITT population (N=101; cisplatin without Pedmarqsi=46, cisplatin with Pedmarqsi=55): The mITT population consisted of children in the ITT population for whom the primary endpoint "hearing impairment after the end of treatment or at ≥3.5 years of age (whichever was later)" was measured and the Brock Grade was adjudicated by the central audiology reviewer (i.e. children for whom an assessment of the primary endpoint could not be made were excluded from the mITT population).[16]

- PP (per protocol) population (N=105; cisplatin without Pedmarqsi=52, cisplatin with Pedmarqsi=53): The PP population was defined as all children who were in the ITT population and, if randomised to the cisplatin with Pedmarqsi arm, had received at least one Pedmarqsi dose.[16]

Statistical methods

Continuous variables (e.g. age) were summarised using descriptive statistics (the number of children with available data, the mean, standard deviation [SD], median, minimum and maximum). Categorical variables (e.g. race) were summarised using counts and percentages. Percentages were calculated using the total children per treatment group. All statistical tests performed were 2-sided and at the 5% significance level.[16]

Primary hypothesis

The hypothesis tested was a reduction of the rate of hearing loss from 60% in the cisplatin without Pedmarqsi arm to 35% in the cisplatin with Pedmarqsi arm.

Sample size and power calculation

The primary hypothesis was tested with a Chi-square test with significance level of 5% and power of 80%, which required a sample size of 102 evaluable children. The ITT population therefore had ≥80% power to detect an absolute reduction in hearing loss of 25% in the Pedmarqsi arm. In addition, the relative risk of hearing loss in both randomised treatment arms was calculated alongside an exact 95% confidence interval (CI) (2.5% confidence limit to 97.5% confidence limit).[16]

Missing data

For all populations, if the definitive assessment of the primary efficacy endpoint at ≥3.5 years of age was not available, the reason for the missing data informed the decision on how to handle the missing information. If the hearing assessment was not feasible due to the condition of the patient, then the patient was excluded from the analysis of the endpoint. This included patients who died before the assessment could have been done. If the hearing assessment was not done due to a logistical problem (e.g. the site failed to organise the hearing assessment), then the result was not imputed, and the patient was excluded from the primary analysis of hearing impairment. Sensitivity analyses using the complete mITT and PP populations were performed to analyse the effect of the missing data.

B.2.3.1 COG ACCL0431 trial statistical analysis and definition of study groups

Study groups

The following populations were defined in the COG ACCL0431 trial, wherein the ITT population was the primary population for assessment of survival parameters, the safety population was the primary population for all safety assessments, and the efficacy population was the primary population for the analyses of hearing loss endpoints:

- ITT population (N=125; cisplatin without Pedmarqsi=64, cisplatin with Pedmarqsi=61): The ITT population included all children who were randomised. This population was the primary population for the analysis of EFS and OS.[25]
- Safety population (N=123; cisplatin without Pedmarqsi=64, cisplatin with Pedmarqsi=59): The safety population included all children who received at least one dose of cisplatin without Pedmarqsi or cisplatin with Pedmarqsi. Children were analysed according to the treatment received.[25]
- Efficacy population (N=104; cisplatin without Pedmarqsi=55 cisplatin with Pedmarqsi=49): The efficacy population included all children in the ITT population who had both baseline and 4-week follow-up hearing assessments. This population was the primary population for the analyses of the hearing loss endpoints.[25]

Statistical methods

Analyses were performed using SAS® version 9.3 or higher. For primary efficacy analysis, a logistic regression model was used to evaluate if there was any association between Pedmarqsi treatment and hearing loss when adjusting for the stratification variables. The odds ratio with associated 95% CI intervals and p-values for the between treatment comparison was estimated based on the logistic regression model.[25] For the comparison of mean change in hearing thresholds between the two arms, hearing threshold was treated as a continuous variable and the mean change in hearing thresholds from baseline to the 4-week follow-up evaluation was compared between the two arms for five key frequencies (500, 1000, 2000, 4000 and 8,000 Hz). Linear regression analyses were used to assess whether Pedmarqsi treatment reduced the mean change in hearing thresholds when adjusting for stratification variables. Analyses were performed individually for each key frequency; no multiple comparison adjustment was made for these analyses. Hearing data were collected and reviewed by two different blinded central reviewers.

Primary hypothesis

The primary hypothesis was that there would be a 50% relative reduction in the proportion of children with hearing loss in the cisplatin with Pedmarqsi arm versus the cisplatin without Pedmarqsi arm.

Sample size and power calculation

Sample size estimation was based on the primary efficacy endpoint. The incidence of hearing loss in the cisplatin without Pedmarqsi arm was assumed to be 45% and a treatment effect of Pedmarqsi with a 50% reduction in hearing loss for the cisplatin with Pedmarqsi arm was hypothesised, i.e. a 22.5% hearing loss rate in the cisplatin with Pedmarqsi arm was assumed. Assuming a one-sided significance level of 5% (as it was expected that hearing loss frequency would not increase in the cisplatin with Pedmarqsi arm), 54 children per arm were needed to achieve 80% power for detecting a 50% reduction in hearing loss.

Missing data

Children who dropped out of the study were not replaced, and missing data were not imputed. A sensitivity analysis was performed using the ITT population with the assumption that patients without a valid hearing assessment had lost their hearing. This is discussed later in B.2.5.2.

B.2.4 Critical appraisal of the relevant clinical effectiveness evidence

A complete quality assessment of the evidence informing the clinical effectiveness of Pedmarqsi is provided in Appendix G.

B.2.5 Clinical effectiveness results of the relevant studies

The following results presented for the SIOPEL 6 and COG ACCL0431 trials are those relevant to hearing loss (i.e. those relevant to the scope of the appraisal and included in the economic modelling). The secondary outcomes of the studies which are related to tumour progression, such as EFS, are not related to hearing loss and therefore have not been reported in this submission as they are not relevant to the scope of the appraisal and were not used in the economic modelling. However, these results are available in both the SIOPEL 6 (Brock *et al*. 2018)[52] and COG ACCL0431 (Freyer *et al*. 2017)[26] key publications and in the relevant CSRs. Results of the OS secondary outcomes have been reported for both studies, as OS is used in the economic modelling to inform mortality.

B.2.5.1 SIOPEL 6 trial clinical effectiveness results

The primary efficacy endpoint of the SIOPEL 6 trial strongly supported the effectiveness of Pedmarqsi in preventing hearing loss and reducing the severity of hearing impairment caused by cisplatin chemotherapy. This is shown by the reduction in the proportion of children experiencing Brock Grade $\geq$1 hearing loss from 67.3% in the cisplatin without Pedmarqsi arm, to 35.1% in the cisplatin with Pedmarqsi arm.

OS results also showed that there was no statistically significant difference in mortality in children treated with Pedmarqsi compared to those who were not.

Primary efficacy endpoint: proportional incidence of children with Brock Grade ≥1 hearing loss

As described in SIOPEL 6 trial methodology, the primary efficacy endpoint was the proportional incidence of children with Brock Grade ≥1 hearing loss, measured by PTA, after the end of treatment or at ≥3.5 years of age (whichever was later). Based on analyses in the ITT population, the proportion of children in the cisplatin with Pedmarqsi arm with hearing loss at age ≥3.5 years (20 children, 35.1%) was approximately one-half compared with the cisplatin without Pedmarqsi arm (35 children, 67.3%). The probability of experiencing hearing loss was statistically significantly lower in the cisplatin with Pedmarqsi arm compared with the cisplatin without Pedmarqsi arm (relative risk: 0.521, 95% CI: 0.349, 0.778; p<0.001), corresponding to a clinically meaningful 48% lower risk after Pedmarqsi treatment.[16] Results for the ITT population are presented in Table 12.

Table 12: Summary of hearing loss (SIOPEL 6 ITT population)

Results – hearing loss	Cisplatin without Pedmarqsi (N=52)	Cisplatin with Pedmarqsi (N=57)
Yes, n (%)	35 (67.3)	20 (35.1)
No, n (%)	17 (32.7)	37 (64.9)
Relative Risk (95% CI)*	0.521 (0.349, 0.778)	
P-value*	<0.001	
Relative Risk (95% CI)†	0.519 (0.356, 0.755)	
P-value†	<0.001	

*P-value and relative risk from Chi-square test.
†P-value and relative risk from CMH test stratified by country group, PRETEXT group and age group.
Abbreviations: CI – Confidence interval; CMH – Cochran-Mantel-Haenszel; ITT – Intention-to-treat; PRETEXT – Pre-treatment tumour extension
Source: SIOPEL CSR[16].

Hearing loss results were similar in the mITT population. The risk of experiencing hearing loss was statistically significantly lower in the cisplatin with Pedmarqsi arm compared with the cisplatin without Pedmarqsi arm (relative risk: 0.519, 95% CI: 0.335, 0.805; p=0.002), corresponding to a clinically meaningful 48% lower risk after Pedmarqsi treatment.[16] Results for the mITT population are presented in Table 13.

Table 13: Summary of hearing loss (SIOPEL 6 mITT population)

Results – hearing loss	Cisplatin without Pedmarqsi (N=46)	Cisplatin with Pedmarqsi (N=55)
Yes, n (%)	29 (63.0)	18 (32.7)
No, n (%)	17 (37.0)	37 (67.3)
Relative Risk (95% CI)*	0.519 (0.335, 0.805)	
P-value*	0.002	
Relative Risk (95% CI)†	0.516 (0.339, 0.787)	
P-value†	0.002	

*P-value and relative risk from Chi-square test.
†P-value and relative risk from CMH test stratified by country group, PRETEXT group and age group.
Abbreviations: CI – Confidence interval; CMH – Cochran-Mantel-Haenszel, ITT – Intention-to-treat; PRETEXT – Pre-treatment tumour extension
Source: SIOPEL CSR[16].

Further to this, Table 14 shows the centrally reviewed Brock grading with PTA that was performed at a minimum age of 3.5 years in the mITT population. As defined in SIOPEL 6 trial statistical analysis and definition of study groups, patients in the mITT population must have reached the primary endpoint of any hearing loss (Brock Grade 1, 2, 3, or 4) and had this Brock Grade adjudicated by the audiology reviewer. This primary end point could be assessed in 101 children in the mITT (eight children had a missing hearing assessment and were recorded as "hearing impaired or failure").[52]

Table 14: Brock Grades amongst 101 children evaluated in SIOPEL 6 (mITT population)

Brock Grade	Percentage of children in each Grade	
	Cisplatin without Pedmarqsi (N=46)	Cisplatin with Pedmarqsi (N=55)
0	37%	67%
1	26%	18%
2	24%	11%
3	11%	2%
4	2%	2%

Note: A Brock Grade of 0 indicates hearing at less than 40 dB at all frequencies and does not necessarily equate to completely normal hearing. Grades 1, 2, 3, and 4 indicate hearing levels at 40 dB or higher at 8 kHz, 4 kHz, 2 kHz, and 1 kHz and above, respectively. The Grade was determined according to the hearing level in the child's better ear.
Source: Brock *et al*. 2018[52].

For further analysis of the results in Table 14, a post-hoc analysis was performed by the Company, the results of which are presented in Table 15; for more information on the Brock grading scale, see Section B.1.3.1.2B.1.3.1.

By removing the children who did not experience hearing loss (i.e. Brock Grade 0) from the analysis, it could be determined that not only were there fewer children with any hearing loss in the cisplatin with Pedmarqsi group, but the hearing loss these children experienced (i.e. Brock Grade $\geq$1) was less severe than that of children in the cisplatin without Pedmarqsi arm.

Table 15: Percentage of children experiencing hearing loss of at least Brock Grade 1 in SIOPEL 6 (mITT population)

Brock Grade	Percentage of children experiencing hearing loss of at least Brock Grade 1	
	Cisplatin without Pedmarqsi (N=29)	Cisplatin with Pedmarqsi (N=18)
1	41%	55%
2	38%	33%
3	18%	6%
4	3%	6%

Source: analysis based on Brock *et al*. 2018[52].

Secondary efficacy endpoint: overall survival

There was no statistically significant difference between the proportion of children who died during the SIOPEL 6 trial in the cisplatin with Pedmarqsi arm ([redacted] patients [redacted%]) and the cisplatin without Pedmarqsi arm ([redacted] patients [redacted%]) (hazard ratio: [redacted]; 95% CI: [redacted]; p=[redacted]). A summary of OS results in the ITT population is presented in Table 16 and Figure 6.

Table 16: Summary of overall survival in SIOPEL 6 (ITT Population)

Parameter Category/Statistic	Cisplatin without Pedmarqsi (N=52)	Cisplatin with Pedmarqsi (N=57)
Number of patients who died, n (%)	[redacted]	[redacted]
Number of patients censored, n (%)	[redacted]	[redacted]
Treatment comparison (cisplatin with Pedmarqsi vs cisplatin without Pedmarqsi)		
Hazard ratio (95% CI)	[redacted]	
P-value (log-rank)	[redacted]	

Time to event was calculated from the time of randomisation to death. Subjects alive were censored at the time of last known follow-up visit.
Abbreviations: CI – Confidence interval; ITT – Intention-to-treat
Source: SIOPEL CSR[16]

Figure 6: SIOPEL 6 overall survival (ITT population)

Abbreviations: CI – Confidence interval; ITT – Intention-to-treat; RHR – Relative hazard ratio
Source: SIOPEL CSR[16]

B.2.5.2 COG ACCL0431 trial clinical effectiveness results

The results of COG ACCL0431 show that Pedmarqsi treatment was effective in the prevention of cisplatin-induced ototoxicity when given six hours following the completion of cisplatin treatment. This is shown by the reduction in the incidence of hearing loss from 56.4% in the cisplatin without Pedmarqsi arm to 28.6% in the cisplatin with Pedmarqsi arm.

Primary efficacy endpoint: proportional incidence of hearing loss between the cisplatin with Pedmarqsi arm and the cisplatin without Pedmarqsi arm

As described in COG ACCL0431 trial methodology, the primary efficacy endpoint was the proportional incidence of hearing loss between the cisplatin with Pedmarqsi arm and the cisplatin without Pedmarqsi arm, measured in the efficacy population. Based on analyses in the efficacy population, following the last dose of cisplatin, the proportion of children in the cisplatin with Pedmarqsi arm with hearing loss (14 children, 28.6%) was approximately one-half of the proportion in the cisplatin without Pedmarqsi arm (31 children, 56.4%). The odds of having hearing loss as defined by ASHA criteria were statistically significantly lower in the cisplatin with Pedmarqsi arm compared with the cisplatin without Pedmarqsi arm (odds ratio: 0.274; 95% CI: 0.114, 0.660; p=0.0039), when adjusted for the stratification variables of prior cranial irradiation (yes vs no), age subgroup (<5 years or ≥5 years), and duration of cisplatin infusion (<2 vs ≥2 hours).[25] These results are presented in Table 17.

Table 17: Summary of hearing loss (COG ACCL0431 efficacy population)

Results	Cisplatin without Pedmarqsi (N=55)	Cisplatin with Pedmarqsi (N=49)	Odds ratio (95% CI)*	P-value*
n	55	49	0.274 (0.114, 0.660)	0.0039
Yes, n (%)	31 (56.4)	14 (28.6)		
No, n (%)	24 (43.6)	35 (71.4)		

*Based on logistic regression including treatment and stratification variables as covariates in the model.
Abbreviations: CI – Confidence interval
Source: COG ACCL0431 CSR[25]

The results of a sensitivity analysis for hearing loss conducted in the ITT population are presented in Table 18 and support the conclusion that Pedmarqsi is effective in preventing hearing loss. As described in COG ACCL0431 trial statistical analysis and definition of study groups, the ITT population contained all patients who received cisplatin without Pedmarqsi or cisplatin with Pedmarqsi treatment, regardless of whether they had a follow-up assessment at 4-weeks post-treatment or not. These results therefore demonstrate that even when patients without 4-week follow-up data are included as patients with hearing loss, the odds of having hearing loss (as defined by the ASHA criteria) were statistically significantly lower in the cisplatin with Pedmarqsi arm (26 children, 42.6%) compared with the cisplatin without Pedmarqsi arm (35 children, 57.4%).[25]

Table 18: Summary of hearing loss (COG ACCL0431 ITT population)

Results	Cisplatin without Pedmarqsi (N=64)	Cisplatin with Pedmarqsi (N=61)	Odds ratio (95% CI)*	P-value*
n	64	61	0.411 (0.191, 0.886)	0.0234
Yes, n (%)	40 (62.5)	26 (42.6)		
No, n (%)	24 (37.5)	35 (57.4)		

*Based on logistic regression including treatment and stratification variables as covariates in the model.
Abbreviations: CI – Confidence interval
Source: COG ACCL0431 CSR[25]

Secondary efficacy endpoint: mean change in hearing thresholds

As described in COG ACCL0431 trial statistical analysis and definition of study groups hearing data corresponding to the secondary efficacy endpoint were collected and reviewed by two different blinded central reviewers. For both the left and right ears, there were no significant differences in the change in hearing threshold from baseline to 4 weeks after cisplatin treatment for frequencies ≤ 2000 Hz between the cisplatin with Pedmarqsi arm and the cisplatin without Pedmarqsi arm. Greater differences were observed in the cisplatin with Pedmarqsi arm compared to the cisplatin without Pedmarqsi arm at frequencies ≥ 4,000 Hz for both the left and right ears for both reviewers, with less hearing loss observed for the cisplatin with Pedmarqsi arm than the cisplatin without Pedmarqsi arm at the higher frequencies. Results for this secondary endpoint are presented in Table 19.

Table 19: Summary of mean change from baseline hearing loss (COG ACCL0431 efficacy population)

	Reviewer 1		Reviewer 2	
	Cisplatin without Pedmarqsi (N=55)	Cisplatin with Pedmarqsi (N=49)	Cisplatin without Pedmarqsi (N=55)	Cisplatin with Pedmarqsi (N=49)
500 Hz – Left Ear, n	41	36	41	36
LS mean (SE)	0.3 (1.21)	0.9 (1.27)	0.3 (1.14)	0.5 (1.20)
LS mean treatment difference	--	0.7	--	0.1

	Reviewer 1		Reviewer 2	
	Cisplatin without Pedmarqsi (N=55)	**Cisplatin with Pedmarqsi (N=49)**	**Cisplatin without Pedmarqsi (N=55)**	**Cisplatin with Pedmarqsi (N=49)**
p-value	--	0.6006	--	0.9327
500 Hz – Right Ear, n	41	36	41	36
LS mean (SE)	-0.0 (1.33)	-0.9 (1.40)	-0.3 (1.33)	-1.3 (1.39)
LS mean treatment difference	--	-0.8	--	-1.0
p-value	--	0.5657	--	0.4915
1,000 Hz – Left Ear, n	42	36	42	36
LS mean (SE)	-0.7 (1.86)	-0.8 (2.02)	-0.6 (1.85)	-1.3 (2.02)
LS mean treatment difference	--	-0.0	--	-0.7
p-value	--	0.9812	--	0.6768
1,000 Hz – Right Ear, n	43	36	43	36
LS mean (SE)	-0.2 (1.72)	-1.8 (1.87)	-0.1 (1.72)	-1.6 (1.87)
LS mean treatment difference	--	-1.6	--	-1.4
p-value	--	0.2799	--	0.3460
2000 Hz – Left Ear, n	43	36	43	36
LS mean (SE)	3.5 (3.03)	1.0 (3.35)	3.5 (3.02)	1.1 (3.35)
LS mean treatment difference	--	-2.5	--	-2.4
p-value	--	0.3588	--	0.3630
2000 Hz – Right Ear, n	43	36	43	36
LS mean (SE)	2.2 (2.64)	0.8 (2.91)	1.9 (2.61)	0.4 (2.88)
LS mean treatment difference	--	-1.4	--	-1.5
p-value	--	0.5440	--	0.5128
4,000 Hz – Left Ear, n	43	36	43	36
LS mean (SE)	10.7 (3.98)	3.5 (4.38)	11.2 (3.95)	3.2 (4.37)
LS mean treatment difference	--	-7.2	--	-8.0
p-value	--	0.0395	--	0.0221
4,000 Hz – Right Ear, n	43	36	43	36
LS mean (SE)	11.2 (4.24)	4.1 (4.70)	11.2 (4.24)	4.0 (4.71)
LS mean treatment difference	--	-7.0	--	-7.3
p-value	--	0.0625	--	0.0553

	Reviewer 1		Reviewer 2	
	Cisplatin without Pedmarqsi (N=55)	Cisplatin with Pedmarqsi (N=49)	Cisplatin without Pedmarqsi (N=55)	Cisplatin with Pedmarqsi (N=49)
8,000 Hz – Left Ear, n	42	36	42	36
LS mean (SE)	31.4 (3.87)	22.1 (4.18)	31.2 (3.85)	22.5 (4.17)
LS mean treatment difference	--	-9.2	--	-8.7
p-value	--	0.0363	--	0.0488
8,000 Hz – Right Ear, n	42	36	42	36
LS mean (SE)	31.4 (4.05)	23.0 (4.34)	31.6 (4.06)	23.2 (4.35)
LS mean treatment difference	--	-8.5	--	-8.4
p-value	--	0.0662	--	0.0707

Note: Linear regression was used. Covariates included baseline values, stratum, and treatment. Missing values were excluded from the model.
Abbreviations: CI – Confidence interval; LS – Least squares; SE – Standard error
Source: COG ACCL0431 CSR[25]

Secondary efficacy endpoint: overall survival

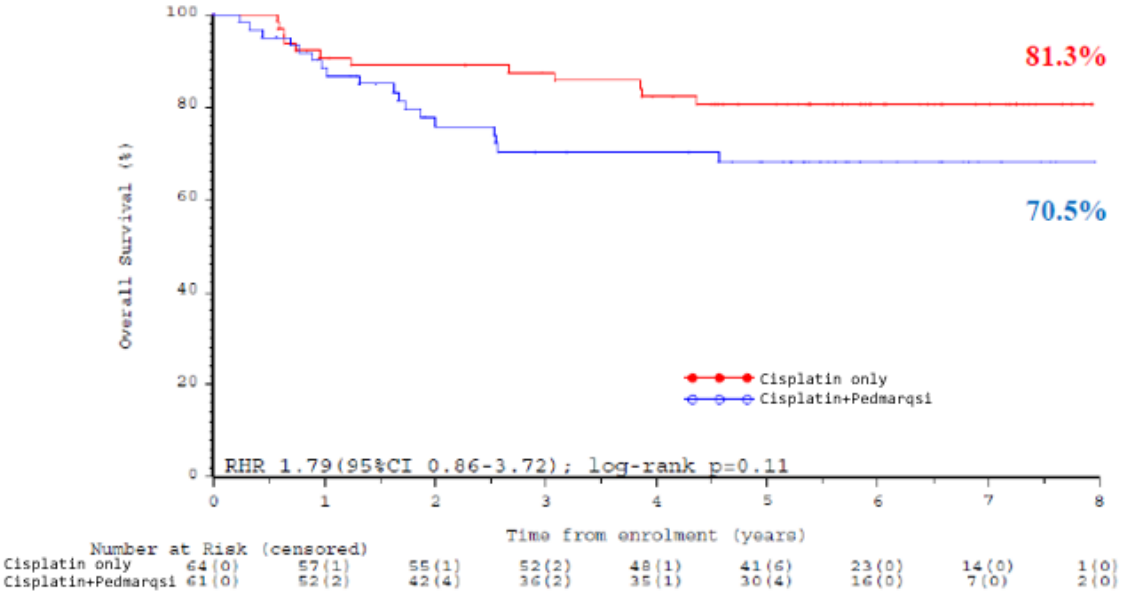
All 125 patients in the COG ACCL0431 ITT population were considered in the analysis of OS, at a median follow-up of 5.33 years (interquartile range: 2.54 to 6.45 years) after study entry. At the median 5.33-year follow-up, 18 children (29.5%) in the cisplatin with Pedmarqsi arm and 12 children (18.8%) in the cisplatin without Pedmarqsi arm died during the trial. There was no statistically significant difference in OS between the arms of the trial (hazard ratio: 1.79; 95% CI: 0.86, 3.72; p=0.1132). The median OS could not be calculated because fewer than 50% of patients in either arm died. A summary of OS results in the ITT population is presented in Table 20 and Figure 7.

Table 20: Summary of overall survival in COG ACCL0431 (ITT Population)

Parameter Category/Statistic	Cisplatin without Pedmarqsi (N=64)	Cisplatin with Pedmarqsi (N=61)
Number of patients who died, n (%)	12 (18.8)	18 (29.5)
Number of patients censored, n (%)	52 (81.3)	43 (70.5)
Treatment comparison (cisplatin with Pedmarqsi vs cisplatin without Pedmarqsi)		
Hazard ratio (95% CI)	1.79 (0.86, 3.72)	
P-value (log-rank)	0.1132	

Abbreviations: CI – Confidence interval; ITT – Intention-to-treat
Source: COG ACCL0431 CSR[25]

Figure 7: COG ACCL0431 overall survival (ITT population)



Abbreviations: CI – Confidence interval; ITT – Intention-to-treat; RHR – Relative hazard ratio
Source: COG ACCL0431 CSR[25]

B.2.6 Subgroup analysis

SIOPEL 6 subgroups

No results of subgroup analyses were reported from the SIOPEL 6 trial.

COG ACCL0431 subgroups

The COG ACCL0431 trial carried out a pre-planned subgroup analysis on the proportion of children with cisplatin-induced hearing loss who were <5 years of age compared to those ≥5 years of age as children under 5 years are more susceptible to hearing loss, especially at high frequencies, since they have hearing that has not yet been subjected to normal age-related decline.[25] The odds of having hearing loss as defined by ASHA criteria were statistically significantly lower in the cisplatin with Pedmarqsi arm compared with the cisplatin without Pedmarqsi arm for children <5 years of age (odds ratio: 0.099; 95% CI: 0.018, 0.551; p=0.0082) and were numerically lower for children ≥5 years of age (odds ratio: 0.458; 95% CI: 0.178, 1.180; p=0.1058).[25] The results of this subgroup analysis are presented in Table 21.

Table 21: Summary of hearing loss by age subgroup (COG ACCL0431 efficacy population)

	Cisplatin without Pedmarqsi	Cisplatin with Pedmarqsi	Odds ratio (95% CI)*	P-value*
All			0.310 (0.137, 0.701)	0.0049
n	55	49		
Yes, n (%)	31 (56.4)	14 (28.6)		
No, n (%)	24 (43.6)	35 (71.4)		
<5 years				
n	15	14		

Yes, n (%)	11 (73.3)	3 (21.4)	0.099 (0.018, 0.551)	0.0082
No, n (%)	4 (26.7)	11 (78.6)		
>5 years			0.458 (0.178, 1.180)	0.1058
n	40	35		
Yes, n (%)	20 (50.0)	11 (31.4)		
No, n (%)	20 (50.0)	24 (68.6)		

*Based on logistic regression including only treatment in the model.
Abbreviations: CI – Confidence interval
Source: COG ACCL0431 CSR[25]

B.2.7 Post-hoc analysis

Pooled data analysis

Due to the small sample sizes of both trials, previously the EMA had requested a pooled analysis for hearing loss and EFS/OS using data from both SIOPEL 6 and COG ACCL0431 trials. All analyses were performed using the ITT population where subjects were analysed based on the treatment they were randomised to receive, and overall hearing loss was assessed using the mITT population.[55]

The primary efficacy endpoints from SIOPEL 6 and COG ACCL0431 were combined to determine the overall proportional incidence of children with hearing loss. Based on the analysis in the ITT pooled population, the proportion of children in the cisplatin with Pedmarqsi arm with hearing loss (n=[redacted]; [redacted]) was less than that of the cisplatin without Pedmarqsi arm (n=[redacted]; [redacted]).[56] The odds ratio for the between treatment difference was estimated using logistic regression including treatment and study as a covariate in the model. The odds of having hearing loss were statistically significantly lower in the cisplatin with Pedmarqsi arm compared with the cisplatin without Pedmarqsi arm (odds ratio: [redacted]; 95% CI: [redacted], [redacted]; p[redacted]).[56] The relative risk was estimated using the Cochran-Mantel-Haenszel (CMH) test, adjusting for study. The risk of experiencing hearing loss was statistically significantly lower in the cisplatin with Pedmarqsi arm compared with the cisplatin without Pedmarqsi arm (relative risk: [redacted]; 95% CI: [redacted], [redacted]; p[redacted]).[56] These results are presented in Table 22.

Table 22: Summary of hearing loss (SIOPEL 6 and COG ACCL0431 pooled ITT population)

Results – hearing loss	Cisplatin without Pedmarqsi (N=[redacted])	Cisplatin with Pedmarqsi (N=[redacted])
Yes, n (%)	[redacted]	[redacted]
No, n (%)	[redacted]	[redacted]
Odds Ratio (95% CI)*	[redacted]	
P-value*	[redacted]	
Relative Risk (95% CI)†	[redacted]	
P-value†	[redacted]	

*P-value and odds ratio based on logistic regression including treatment and study as a covariate in the model.
†P-value and relative risk from Cochran-Mantel-Haenszel (CMH) test adjusting for study.
Abbreviations: CI – Confidence interval; ITT – Intention-to-treat
Source: Norgine, ACCL0431 and SIOPEL 6 pooled analysis results [Data on file][56]

Hearing loss results from the ITT analysis remained similar in the mITT population (Table 23). The risk of experiencing hearing loss was statistically significantly lower in the cisplatin with Pedmarqsi arm compared with the cisplatin without Pedmarqsi arm (relative risk: [redacted]; 95% CI: [redacted], [redacted]; p[redacted]).

Table 23: Summary of hearing loss (SIOPEL 6 and COG ACCL0431 pooled mITT population)

Results – hearing loss	Cisplatin without Pedmarqsi (N=[redacted])	Cisplatin with Pedmarqsi (N=[redacted])
Yes, n (%)	[redacted]	[redacted]
No, n (%)	[redacted]	[redacted]
Odds Ratio (95% CI)*	[redacted]	
P-value*	[redacted]	
Relative Risk (95% CI)†	[redacted]	
P-value†	[redacted]	

*P-value and odds ratio based on logistic regression including treatment and study as a covariate in the model.
†P-value and relative risk from Cochran-Mantel-Haenszel (CMH) test adjusting for study.
Abbreviations: CI – Confidence interval; mITT – Modified intention-to-treat

For OS, Kaplan-Meier estimates were presented by treatment group and the between treatment comparisons were performed using the un-stratified log-rank test. In addition, hazard ratios with corresponding two-sided 95% CIs between treatment groups were estimated using Cox's Proportional Hazard model. In the ITT population, there was no statistically significant difference in the proportion of children who died during the study in the cisplatin with Pedmarqsi arm ([redacted] patients [[redacted]]) and in the cisplatin without Pedmarqsi arm ([redacted] patients [[redacted]]) (hazard ratio: [redacted]; 95% CI [redacted], [redacted]; p[redacted]) (Table 24).

Table 24: Between treatment difference in OS (SIOPEL 6 and COG ACCL0431 pooled ITT population)

Analysis parameter	Cisplatin without Pedmarqsi (N=116)	Cisplatin with Pedmarqsi (N=118)
Subjects with event n (%)	16 (13.8)	20 (16.9)
Subjects censored n (%)	100 (86.2)	98 (83.1)
Hazard Ratio	1.29	
95% CI	(0.67, 2.53)	
Log-rank p-value	0.4464	

Abbreviations: CI – Confidence interval; ITT – Intention-to-treat; OS – Overall survival

Further COG ACCL0431 analysis on hearing loss severity

Orgel *et al*. (2023)[32] performed a secondary analysis of audiology data collected in the COG ACCL0431 clinical trial to provide benchmark data for Pedmarqsi efficacy using the more recent International Society of Paediatric Oncology (SIOP) Ototoxicity Scale. The post-hoc analysis was performed by an audiologist investigator blinded to randomised allocation.

To replicate the COG ACCL0431 trial primary endpoint, hearing endpoints from COG ACCL0431 were re-evaluated using hearing loss at the end of cisplatin therapy and prior to autologous bone marrow transplantation. Hearing thresholds of SIOP Grade ≥2 and Grade ≥1 were evaluated.

Following repeat audiological central review, 121 of 125 (97%) of patients were evaluable for hearing loss using the SIOP scale. After the end of cisplatin treatment, a lower incidence of Grade ≥2 cisplatin-induced hearing loss occurred in the cisplatin with Pedmarqsi arm (4.0%) versus the cisplatin without Pedmarqsi arm (27.1%). In addition, it was concluded that the odds of developing SIOP Grade ≥2 were significantly lower for patients in the cisplatin with Pedmarqsi arm (OR 0.10, 95% CI 0.02-0.50, p=0.005).[32] The same pattern was seen for SIOP Grade ≥1; a lower incidence of Grade ≥1 cisplatin-induced hearing loss occurred in the cisplatin with Pedmarqsi arm versus the cisplatin without Pedmarqsi arm (18.0% versus 45.8%; OR 0.25, 95% CI: 0.10, 0.64; p=0.004).[32]

Results from this re-analysis of hearing outcomes from the COG ACCL0431 trial confirm the otoprotective effects of Pedmarqsi using the SIOP Ototoxicity Scale. It was concluded that, compared to the cisplatin without Pedmarqsi arm, children receiving cisplatin with Pedmarqsi were approximately 90% less likely to develop Grade ≥2 cisplatin-induced hearing loss at the end of cisplatin therapy.[32]

B.2.8 Meta-analysis

A meta-analysis was not conducted, as the only relevant clinical trials identified were the SIOPEL 6 trial and the COG ACCL0431 trial.

B.2.9 Indirect and mixed treatment comparisons

As head-to-head comparison data from the SIOPEL 6 and COG ACCL0431 randomised clinical trials were available to inform the clinical efficacy of cisplatin with Pedmarqsi versus cisplatin without Pedmarqsi, no indirect or mixed treatment comparisons were undertaken.

B.2.10 Adverse reactions

Safety data were available from both the SIOPEL 6 and COG ACCL0431 trials. In both trials, Pedmarqsi was generally well tolerated and had a safety profile similar to that of the cisplatin without Pedmarqsi arm.

B.2.10.1 SIOPEL 6 trial adverse reactions

Adverse reactions in the SIOPEL 6 trial were analysed in the safety population, which included 53 children in the cisplatin with Pedmarqsi arm and 56 children in the cisplatin without Pedmarqsi arm (four children that were randomised to the cisplatin with Pedmarqsi arm did not receive Pedmarqsi and were included in the cisplatin without Pedmarqsi arm).[16] AEs were summarised by AE Grade, serious AE (SAE), and AE Grade 3 or higher.

The overall incidence of Grade ≥3 AEs was similar in both treatment arms of the SIOPEL 6 trial. During the treatment phase, a total of 35 patients (66.0%) in the cisplatin with Pedmarqsi arm and 34 patients (60.7%) in the cisplatin without Pedmarqsi arm reported Grade ≥3 AEs. The most frequently reported Grade ≥3 AEs were the same in both arms and occurred at similar incidences in the cisplatin with Pedmarqsi arm and the cisplatin without Pedmarqsi

arm: infection (14 patients [26.4%] and 15 patients [26.8%], respectively), neutrophil count decreased (12 patients [22.6%] and nine [16.1%], respectively), haemoglobin decreased (10 patients [18.9%] and nine patients [16.1%], respectively), and febrile neutropenia (8 patients [15.1%] and nine patients [16.1%], respectively).[16] A summary of AEs that occurred at CTCAE Grade ≥3 at a frequency of ≥10% in either arm is presented below in Table 25.

Table 25: Summary of Most Common (Frequency of ≥ 10% in Either Arm) AEs with Maximum Severity of CTCAE Grade 3 or Higher during the Treatment Phase (SIOPEL 6 Safety Population)

Preferred term	Cisplatin without Pedmarqsi (N=56) n (%)	Cisplatin with Pedmarqsi (N=53) n (%)	Total (N=109) n (%)
Any Grade 3 Severity or Higher AE	34 (60.7)	35 (66.0)	69 (63.3)
Investigations	19 (33.9)	20 (37.7)	39 (35.8)
Neutrophil count decreased*	9 (16.1)	12 (22.6)	21 (19.3)
Haemoglobin decreased	9 (16.1)	10 (18.9)	19 (17.4)
Infections and infestations	15 (26.8)	14 (26.4)	29 (26.6)
Infection*	15 (26.8)	14 (26.4)	29 (26.6)
Blood and lymphatic system disorders	10 (17.9)	8 (15.1)	18 (16.5)
Febrile neutropenia	9 (16.1)	8 (15.1)	17 (15.6)

One instance of neutrophil count decreased was attributed as possibly related to Pedmarqsi in the cisplatin with Pedmarqsi arm. One instance of neutrophil count decreased was attributed as probably related to Pedmarqsi in the cisplatin with Pedmarqsi arm. One instance of infection was attributed as probably related to Pedmarqsi in the cisplatin with Pedmarqsi arm. No additional fatal AEs were observed during the trial.
Abbreviations: AE – adverse event; CTCAE – Common Terminology Criteria for Adverse Events
Source: SIOPEL 6 CSR[16]

SAEs were defined as any untoward medical occurrence or effect that at any dose resulted in death, was life-threatening, required hospitalisation or prolongation of existing inpatients' hospitalisation, resulted in persistent or significant disability or incapacity, was a congenital anomaly/birth defect or was otherwise considered medically significant by the investigator. SAEs were also assessed as to whether they were related to Pedmarqsi. During the treatment and follow-up phases, a total of four children (7.5%) in the cisplatin with Pedmarqsi arm experienced an SAE that was determined to be related to Pedmarqsi. Of these four children, two (3.8%) experienced an SAE of neutrophil count decreased, one (1.9%) experienced an SAE of infection, and one (1.9%) experienced an SAE of hypersensitivity, which led to discontinuation of Pedmarqsi and was also considered as a suspected unexpected serious adverse reaction. No additional AEs led to discontinuation of Pedmarqsi. There was one fatal SAE in the cisplatin without Pedmarqsi arm (1.8%) after a tumour relapse in which the patient died due to cardiac arrest, which was determined to be related to paclitaxel chemotherapy.[16] No additional fatal AEs were observed during the trial, demonstrating that Pedmarqsi was generally well tolerated by patients in this study and had a safety profile similar to that of cisplatin without Pedmarqsi.

B.2.10.2 COG ACCL0431 trial adverse reactions

Adverse reactions in the COG ACCL0431 trial were analysed in the safety population, which included 59 children in the cisplatin with Pedmarqsi arm and 64 children in the cisplatin without

Pedmarqsi arm.[25] AEs were summarised by AEs Grade >3, SAEs, and drug-related AEs (only applicable to the cisplatin with Pedmarqsi arm).

The overall incidence of Grades ≥3 AEs was similar in both treatment arms of the COG ACCL0431 trial. In the cisplatin with Pedmarqsi arm and cisplatin without Pedmarqsi arm, 55 children (93.2%) and 57 children (89.1%), respectively, experienced an AE graded CTCAE category 3 or higher. The three most frequently reported Grade ≥3 AEs during the reporting period were the same in both arms and occurred at similar incidences: neutrophil count decreased (49 children [83.1%] in the cisplatin with Pedmarqsi arm vs. 53 children [82.8%] in the cisplatin without Pedmarqsi arm), white blood cell count decreased (38 children [64.4%] vs. 42 children [65.6%], respectively), and platelet count decreased (38 children [64.4%] vs. 39 children [60.9%], respectively).[25] A summary of Grade ≥3 AEs occurring in ≥10% of children in either treatment arm is presented in below in Table 26.

Table 26: Summary of Most Common Grade 3 Severity or Higher AEs (Frequency of ≥ 10% in Either Arm) (COG ACCL0431 Safety Population)

Preferred term	Cisplatin without Pedmarqsi (N=64) n (%)	Cisplatin with Pedmarqsi (N=59) n (%)	Total (N=123) n (%)
Any Grade 3 Severity or Higher AE	57 (89.1)	55 (93.2)	112 (91.1)
Investigations	57 (89.1)	54 (91.5)	111 (90.2)
Neutrophil count decreased	53 (82.8)	49 (83.1)	102 (82.9)
White blood cell count decreased	42 (65.6)	38 (64.4)	80 (65.0)
Platelet count decreased	39 (60.9)	38 (64.4)	77 (62.6)
Alanine aminotransferase increased	9 (14.1)	10 (16.9)	19 (15.4)
Lymphocyte count decreased	9 (14.1)	6 (10.2)	15 (12.2)
Blood and lymphatic system disorders	38 (59.4)	32 (54.2)	70 (56.9)
Anaemia	36 (56.3)	30 (50.8)	66 (53.7)
Febrile neutropenia	19 (29.7)	14 (23.7)	33 (26.8)
Metabolism and nutrition disorders	22 (34.4)	29 (49.2)	51 (41.5)
Hypokalaemia	13 (20.3)	16 (27.1)	29 (23.6)
Hypophosphatemia	7 (10.9)	12 (20.3)	19 (15.4)
Hyponatremia	4 (6.3)	7 (11.9)	11 (8.9)
Gastrointestinal disorders	8 (12.5)	12 (20.3)	20 (16.3)
Stomatitis	4 (6.3)	8 (13.6)	12 (9.8)

Abbreviations: AE – Adverse event
Source: COG ACCL0431 CSR[25]

SAEs were only reported for patients in the cisplatin with Pedmarqsi arm and were defined as AEs that fulfilled the Adverse Event Expedited Reporting System (AdEERS) requirement. A total of 21 children (35.6%) in the cisplatin with Pedmarqsi arm experienced at least one SAE. The most common SAEs were febrile neutropenia (12 children [20.3%]), neutrophil count decreased (10 children [16.9%]), platelet count decreased and white blood cell count decreased (both eight children [13.6%]), and anaemia (seven children [11.9%]). A total of six

children (10.2%) experienced SAEs that were determined to be related to Pedmarqsi. These were related to blood and lymphatic system disorders (anaemia and febrile neutropenia), investigations (alanine aminotransferase increased and lymphocyte, neutrophil, platelet and white blood cell count decreased), and gastrointestinal disorders (abdominal pain, colitis, nausea, stomatitis and vomiting).[25]

Although the COG ACCL0431 trial did not specifically report discontinuations due to AEs, it has been noted that one patient in the cisplatin with Pedmarqsi arm discontinued due to reasons related to a Grade 2 hypersensitivity reaction, and an additional four children discontinued Pedmarqsi in close proximity to an AE but not specifically due to an AE. No additional fatal AEs were observed during the trial, demonstrating that Pedmarqsi was well tolerated by patients in this study and had a safety profile similar to that of cisplatin without Pedmarqsi.

B.2.11 Ongoing studies

There are no ongoing studies that will provide additional evidence, in the next 12 months, for Pedmarqsi in the indication being appraised within this submission.

B.2.12 Interpretation of clinical effectiveness and safety evidence

Clinical effectiveness

As presented in Section B.2.5, the clinical study programme demonstrated the robust efficacy of Pedmarqsi in preventing cisplatin-induced hearing loss in children. In the ITT populations of both the SIOPEL 6 trial (relative risk = 0.521; p <0.001 [Table 12]) and the COG ACCL0431 trial (odds ratio = 0.411; p = 0.0234 [Table 18]), statistically significant reductions in the proportion of patients who experienced hearing loss when treated with cisplatin with Pedmarqsi compared to treatment with cisplatin without Pedmarqsi were reported.

In addition, the results of the SIOPEL 6 trial demonstrated that the hearing loss experienced by children receiving Pedmarqsi alongside cisplatin chemotherapy is less severe than hearing loss experienced by those receiving cisplatin without Pedmarqsi (Table 15). The Orgel *et al.* (2023) re-analysis of the COG ACCL0431 study supported this finding.

Thus, the results of both trials demonstrate the clinical effectiveness of Pedmarqsi in reducing the proportional incidence of hearing loss (i.e. the prevention of hearing loss) and reducing the severity of hearing loss in those patients who still develop the condition, for cisplatin-treated children.

Safety

The safety evidence demonstrates that in both SIOPEL 6 and COG ACCL0431 trials, Pedmarqsi was safe and generally well tolerated. As presented in Section B.2.10Adverse reactions, the nature and frequency of AEs reported in children receiving Pedmarqsi in conjunction with cisplatin chemotherapy was similar to those observed in children having cisplatin chemotherapy without Pedmarqsi. The similarities between the safety profiles of cisplatin with Pedmarqsi and cisplatin without Pedmarqsi provide evidence in support of a favourable benefit-risk assessment for Pedmarqsi in the treatment of cisplatin-induced ototoxicity.

Of note, the cisplatin renal and haematological toxicity observed was similar between the treatment arms in both studies. This lends support to the notion that Pedmarqsi preferentially targets the auditory system. If Pedmarqsi had a broader spectrum of action and interacted with cisplatin it would have been reasonable to expect a decrease in the toxicity of other system organs that are known to be adversely affected by cisplatin.[57]

Strength of the clinical evidence

SIOPEL 6 and COG ACCL0431 represent two well-conducted, randomised, controlled clinical trials. Pedmarqsi demonstrated robust clinical effectiveness in both trials, with statistically significant reductions in a clinically meaningful and highly relevant endpoint – the proportional incidence of hearing loss. Furthermore, the populations studied in both trials were highly relevant to the indication for Pedmarqsi and the scope for this HTA, as both trials were carried out in populations of children receiving cisplatin aged ≥1 month to ≤18 years. In addition, comprehensive adverse event data were also collected in both trials, allowing robust safety assessments of Pedmarqsi to be made. Lastly, both studies confirmed that Pedmarqsi administration six hours post cisplatin infusion, when cisplatin infusions last no longer than 6 hours, did not affect the efficacy of cisplatin chemotherapy in treatment of the underlying cancer.

Limitations of the clinical evidence

One limitation of the COG ACCL0431 trial was that the ASHA criteria (described in Section B.1.3.1.2), used to assess hearing loss, does not assess the severity of the acquired hearing loss, only whether the patient's hearing levels meet a certain threshold. However, it is noted that the scale was selected because at the time of the study, it was regarded as the most sensitive scale available to assess hearing loss.[26] This issue was addressed in the SIOPEL 6 trial, which used the Brock scale, specifically developed for measuring cisplatin-induced ototoxicity and by Orgel *et al*. (2023)[32] who re-evaluated COG ACCL0431 endpoints according to the SIOP Ototoxicity Scale. This study is further discussed previously in Section B.2.7.

The sample size for both trials was relatively small (SIOPEL 6, n=114; COG ACCL0431, n=125). However, due to the nature of cisplatin ototoxicity as a very rare disease, this is a limitation of the available number of children to recruit for clinical trials and thus is to be expected. In addition, this concern is also offset by the availability of two randomised controlled trials (RCTs) with similar outcomes, implying that a comprehensive evidence base is available for the assessment of Pedmarqsi in a relevant patient population.

Conclusion

As outlined in Section B.1.3.3, there are no existing treatments for the prevention of cisplatin-induced hearing loss in the current treatment pathway. The current management of hearing loss involves the use of non-pharmacological interventions which are not preventative and cannot reverse hearing loss. In addition, current management options are suboptimal and not as effective at restoring QoL when compared to prevention.

A comprehensive evidence base is available through the SIOPEL 6 and COG ACCL0431 studies to support the use of Pedmarqsi as an effective and safe treatment for the prevention of hearing loss in the relevant indication.[26,52] Pedmarqsi is therefore able to address the unmet need for the prevention of cisplatin-induced ototoxicity and support children in reaching their full potential and leading fulfilling lives. Pedmarqsi will also be the first and only licensed treatment for the prevention of cisplatin-induced hearing loss in children with localised, solid

tumours in England and Wales, and therefore will represent a step change in the clinical pathway for the prevention of ototoxicity in patients treated with cisplatin.

B.3 Cost effectiveness

Summary

A *de novo* economic model was developed to assess the cost-effectiveness of Pedmarqsi in cisplatin-treated paediatric patients aged 1 month to <18 years of age with localised, non-metastatic, solid tumours. The model is cohort-based and has five hearing loss health states based on the Brock grading scale used in SIOPEL 6; Minimal/no hearing loss (HL), Mild HL, Moderate HL, Marked HL and Severe HL, with an absorbing state for Dead. Patients enter the model and are said to experience or not experience measurable hearing loss, as presented through assignment to either the Minimal/no HL health state or one of the hearing loss severity health states (Mild HL, Moderate HL, Marked HL, Severe HL). From year two onwards, patients either stay in their respective health states for the remainder of the model time horizon or move to the Dead state.

In the base case, clinical inputs of the model were based on COG ACCL0431 trial data as the distribution of tumour types within this study can be considered generalisable to the relevant patient population in England and Wales. Utilities were sourced from a study which assessed the HRQoL of children by hearing loss severity. A cancer disutility was applied to all health state utilities to ensure they were reflective of patients undergoing cisplatin treatment. Unit costs were sourced from the NHS Cost Collection, Personal Social Services Research Unit (PSSRU), and the electronic Market Information Tool (eMIT), or where not available, from published literature sources. Resource use was sourced from published literature. The model structure and inputs were validated with external clinical and health economics and outcomes research experts.

Base case results show that at PAS price, cisplatin with Pedmarqsi is associated with a QALY gain of 1.525 compared to cisplatin without Pedmarqsi, and this benefit is associated with an incremental cost of £[redacted]. This results in an ICER of £[redacted], which is below NICE's willingness-to-pay (WTP) threshold of £30,000 per QALY gained. Uncertainty was explored through deterministic and probabilistic sensitivity analysis. One-way sensitivity analysis (OWSA) results showed that the model results were most sensitive to changes in the percentage of patients with Minimal/no hearing loss in both treatment arms of the model. The mean probabilistic sensitivity analysis (PSA) ICER was within [redacted] of the base case ICER, highlighting the robustness of model results. Probabilistic scenario analyses explored the structural uncertainty of the model, and in 11 out of 15 scenarios explored, cisplatin with Pedmarqsi remained cost-effective against the WTP threshold of £30,000.

B.3.1 Published cost-effectiveness studies

A SLR was conducted to identify relevant economic evaluations for the prevention/management of patients with acquired hearing loss. This population was expanded from the population criteria in the clinical search (which aligned with the licensed indication of Pedmarqsi) as it was determined that economic evidence in patients with hearing loss acquired through other causes (besides cisplatin-induced ototoxicity) and in patients of all age groups may be relevant to inform the economic modelling due to the lifetime horizon applied and the lack of economic data in the specific licensed population. Because of this, the non-clinical SLR included, but was not confined to, patients with cisplatin-induced hearing loss, whereas the clinical SLR was limited to the licensed indication only of cisplatin-induced hearing loss. A detailed description of the review methods and results are reported in Appendix G.

Following this expanded search, a total of 13 cost-effectiveness references were identified as part of this SLR which provided economic evidence for the prevention/management of acquired hearing loss. These studies are summarised in Table 27.

Table 27: Summary list of published cost-effectiveness studies

Study	Cost year (currency)	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)
Palmer *et al.* 1999	1999 ($)	NR	Severely to profoundly hearing-impaired adults 18 years or older who exhibited limited speech understanding with conventional (hearing aid) amplification.	NR	NR	**ICER:** Cochlear implant vs. non-implant recipients: $14,670.
Montes *et al.* 2017	2017 ($)	Productivity and cost-effectiveness estimates were estimated using influence diagrams and Monte Carlo simulations. Decision analysis methodology was used to incorporate uncertainty into the parameters, which permitted simulation of different scenarios to select the best approach. length: NR. Time horizon: NR.	Patients with profound deafness. Data were obtained from audiometric tests of the 100 randomly selected cochlear implant pre-treatment patients who were using hearing aids before being implanted with the cochlear implant, from 1998 to 2013 at Cochlear Implant Group of the Hospital Universitario de la Fundación Santa Fe de Bogota.	**Incremental QALYs:** Cochlear implant vs no treatment: 5.7. Hearing aids vs no treatment: 4.6.	NR	**ICER:** Cochlear implant vs. no treatment: $15,169. Hearing aids vs. no treatment: $11,172.
Mohiuddin *et al*. 2014	2014 (£)	A decision-analytic model was used to determine the incremental cost-effectiveness. The model followed a hypothetical cohort of	Patients with persistent bilateral otitis media with effusion and cleft palate under the age of 12 years.	**Total QALYs:** Grommets strategy: 0.2175. Hearing aids strategy: 0.1017.	NR	**ICER:** Grommets strategy vs. do-nothing strategy: £9,053. Hearing aids strategy was extendedly

Study	Cost year (currency)	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)
		10,000 children under the age of 12 years with cleft palate and persistent otitis media with effusion. Cycle length: NR. Time horizon: 24 months.		Do-nothing strategy: 0.0528.		dominated by the grommets strategy.
Landry *et al.* 2022 (Journal article)	2022 (£)	A state-transition model, following the ISPOR-SMDM Best Practice Guidelines, was created using Microsoft Excel (Redmond, Wash). Markov model of health states used to assess regenerative hearing loss therapeutics. The model starts with a cohort of 50-year old patients with various degrees of hearing loss with or without hearing aids. In every cycle subjects could progress to 1 of 11 mutually exclusive disease states including death. Cycle length: 1 year. Time horizon: Lifetime.	Adult patients (both men and women) comprising of five different age groups: 50-59, 60-69, 70-79 and 80-89 and 90 with age-related sensorineural hearing loss.	**Total QALYs:** Standard care pathway: 15.59. Novel hearing therapeutic strategy: 16.37. **Incremental QALYs:** Standard care pathway vs. novel hearing therapeutic strategy: 0.78.	NR	**Incremental net monetary benefit:** £20,017.
Cutler *et al.* 2022 (Journal article)	2022 (£)	The model explores various economic evaluation scenarios to compare unilateral cochlear implants against	UK adults assumed to have been diagnosed with severe to profound sensorineural	**Incremental QALYs:** Unilateral cochlear implants vs. hearing aid: 3.18.	**Incremental costs:** Unilateral cochlear implants vs hearing aid: £37,988.	**ICER:** Unilateral cochlear implants vs. hearing aid: £11,946.

Study	Cost year (currency)	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)
		hearing aids or no hearing aids. Multiple health states are incorporated into the model to represent the treatment pathway, accounting for potential AEs, device failures, and death from other causes. Internal and external device failures or upgrades can occur immediately after surgery or over time, with probabilities calculated from cumulative survival values. Cycle length: 6 months. Time horizon: Lifetime.	hearing loss in both ears.	Unilateral cochlear implants vs. no hearing aid: 3.66.	Unilateral cochlear implants vs no hearing aid: £38,449.	Unilateral cochlear implants vs. no hearing aid: £10,499.
Kiesewetter *et al.* 2022a (Conference abstract)	2022 (£)	A decision-analytic model was developed to calculate the incremental cost and QALYs. Cycle length: NR. Time horizon: 10 years.	Patients suffering from conductive or mixed hearing loss or single-sided deafness.	NR	NR	**ICUR:** Active transcutaneous bone conduction implant vs. percutaneous bone conduction implants: £333.25.
Gumbie *et al.* 2021 (Journal article)	2021 (SEK)	The analysis was performed using a Markov model which incorporated several states to capture the treatment pathway, potential AEs, internal	Adults aged 19 years and older with severe to profound hearing loss with an average age of 61 years.	**Total QALYs:** Unilateral cochlear implant: 8.84. Hearing aid: 5.74.	NR	**ICER:** Unilateral cochlear implant vs. hearing aid: SEK 140,474.

Study	Cost year (currency)	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)
		and sound processer device failures, and death from other causes. Patients could remain in their initial state or experience a short-term adverse event or long-term adverse event. If there was an internal device failure, the patient could receive a revised cochlear implant, or use a hearing aid, or not use a hearing aid. Cycle length: 6 months. Time horizon: Lifetime.				
Skarzynski *et al.* 2022 (Journal article)	2021 (PLN)	A Markov model, executed as a microsimulation, was developed to compare different treatment options. A distinction is made between bilateral sequential cochlear implantation where the second implant is implanted 3 months after the first implant (Scenario 1), a bilateral sequential cochlear implantation where the second implant is implanted 1 year after the first implant (Scenario	Adult Polish patients with severe to profound sensorineural hearing loss in both ears.	**Total QALYs:** Scenario 1 Bilateral sequential (short delay) cochlear implant: 5.85. No treatment: 4.64. Scenario 2 Bilateral sequential (long delay) cochlear implant: 5.85. No treatment: 4.64. Scenario 3 Bilateral simultaneous cochlear implant: 5.86.	NR	**ICUR:** Scenario 1: bilateral sequential short delay cochlear implant vs. no treatment: PLN 236,804.09. Scenario 2: bilateral sequential long delay cochlear implant vs. no treatment: PLN 232,564.94. Scenario 3: bilateral simultaneous cochlear implant vs. no treatment: PLN 227,414.8.

Study	Cost year (currency)	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)
		2) and a theoretical bilateral simultaneous cochlear implantation (Scenario 3). Cycle length: 3 or 12 months. Time horizon: 10 years.		No treatment: 4.64.		
Hoch *et al.* 2022 (Conference abstract)	2022 (€)	A decision-analytic model was developed to determine incremental costs and quality-adjusted life years of active middle ear implants implantation compared with no treatment. Cycle length: NR. Time horizon: 10 years.	Patients with mild to severe sensorineural hearing loss.	NR	NR	**ICER:** Active middle ear transplant vs. no treatment: €11,770.
Seebacher *et al.* 2021 (Journal article)	2021 (€)	A Markov model analysed as microsimulation was developed using TreeAge Pro 2019 software. Two treatment pathways for single-sided deafness patients: first, deciding to get a cochlear implant (cochlear implant strategy) and second, deciding against a cochlear implant and leaving the ear with	Patients were aged 18 years or older and implanted with a cochlear implant for the first time. On the ‘‘normal’’ hearing ear a pure-tone average of less than 30 decibels hearing level was required, whilst on the cochlear implant side, all patients suffered from severe	**Total QALYs:** Cochlear implant: 10.23. No intervention: 8.58.	NR	**ICUR:** Cochlear implant vs. no intervention: €34,845.

Study	Cost year (currency)	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)
		single-sided deafness untreated (no intervention strategy). For the cochlear implant strategy, three different health states were considered. For the ‘‘no intervention strategy,’’ only two different health states are possible: patients can either stay without any treatment or they die. Cycle length: NR. Time horizon: 20 years.	to profound hearing loss. The patients were fitted with Synchrony or Concerto implants (MED-EL), with FLEX28 or FLEXSOFT electrodes and all of them used a SONNET speech processor.			
Kosaner Kliess *et al.* 2017 (Journal article)	2017 (AUD)	A Markov model was developed and analysed as microsimulation to estimate the ICUR in individuals with sensorineural hearing loss and an outer ear medical condition. The baseline strategy of “no intervention” is followed for patients who do not fulfill active middle ear implants candidacy criteria or decide against receiving an implant. Patients who remain unaided are assumed to be at constant risk of experiencing recurring	Male and female adults aged 18 to 75 years who had postlingual mild to severe sensorineural hearing loss and could not use or benefit from hearing aids because of medical reasons.	**Total QALYs:** Vibrant Soundbridge implant: 9.86. No intervention: 8.52	NR	**ICUR:** Vibrant Soundbridge implant vs. no intervention: AUD 9,913.72.

Study	Cost year (currency)	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)
		pathologies in the same ear. Cycle length: 6 months. Time horizon: 10 years.				
Joore *et al.* 2003 (Journal article)	2003 (€)	A Markov model was used to determine the cost-effectiveness of fitting hearing aids in adult hearing-impaired persons. The starting year of the model was 1995. The model was distinguished among the three different groups of patients; those with hearing complaints without a hearing aid (non-hearing aid users with hearing complaints), those with hearing complaints who are satisfied with their hearing aid (satisfied hearing aid users), and those with hearing complaints who are dissatisfied with their hearing aid (dissatisfied hearing aid users). Cycle length: 1 year. Time horizon: Lifetime.	Hearing-impaired persons aged 18 years and older were asked to enter the study when they received a prescription for a hearing aid from their ENT specialist or audiologist. Patients were recruited from February 1, 1998, to March 31, 1999.	**Total QALYs:** Hearing aids: 0.44 **Incremental QALYS:** Fitting hearing aids vs. not fitting them: 0.05.	NR	**ICER:** Youngest group: €11,984. Oldest group: €34,902. Base case outcome based on EQ-5D: €15,807. 15 to 19 years: €17,996. 95 to 99 years: €52,502. Average 15 to 99 years: €23,745.

Study	Cost year (currency)	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (intervention, comparator)	ICER (per QALY gained)
Kiesewetter *et al.* 2022b (Conference abstract)	(TL)	A Markov model was used to determine the ICUR and to compare the cost-effectiveness of an active transcutaneous bone conduction implant to a passive transcutaneous bone conduction implant as well as percutaneous bone conduction implant. Cycle length: NR. Time horizon: 10 years.	Adults and children with conductive/mixed hearing loss or single-sided deafness in Turkey.	**Total QALYs:** Percutaneous bone conduction implant: 3.62. Passive transcutaneous bone conduction implant: 5.79. Active transcutaneous bone conduction implant: 7.14.	NR	**ICUR:** Passive transcutaneous bone conduction implant vs. percutaneous bone conduction implant: TL 4,224. Active transcutaneous bone conduction implant vs. percutaneous bone conduction implant: TL 8,745.

Abbreviations: AUD – Australian Dollar; AE – Adverse event; EQ-5D – EuroQol 5-dimensions; ICER – Incremental cost-effectiveness ratio; ICUR – Incremental cost-utility ratio; NHS – National Health Service; NR – Not reported; PLN – Polish Złoty; QALY – Quality-adjusted life year; SEK – Swedish Krona; TL – Turkish lira
Source: Norgine 2024 (Economic SLR report, Data on File)

B.3.2 Economic analysis

No published economic evaluations of Pedmarqsi were identified in the cost-effectiveness SLR (see Section B.3.1 and Appendix G). Therefore, a *de novo* cost-effectiveness model structure was developed to assess the cost-effectiveness of cisplatin with Pedmarqsi versus cisplatin without Pedmarqsi. Whilst there are no previous NICE evaluations of preventative treatments for cisplatin-induced ototoxicity, the NICE appraisal of cochlear implants for children and adults with severe to profound hearing loss (TA566, formerly TA166) should be considered relevant through its status as a NICE TA which partially captures the Pedmarqsi label through its assessment of hearing loss in children.[58] HTE6 was also identified which is a NICE health technology evaluation which evaluated a genetic test for the prevention of paediatric hearing loss.[59] Whilst this is also not entirely aligned to the patient population under consideration in this submission, elements of the analysis are relevant due to it being a NICE evaluation for hearing loss in paediatric patients. Therefore, these economic evaluations were used alongside publications identified within the economic SLR to inform the *de novo* model structure, assumptions, and data sources.

B.3.3 Patient population

The cost-effectiveness analysis presented considers cisplatin-treated patients aged 1 month to <18 years of age with localised, non-metastatic, solid tumours. This is in line with the population in the pivotal trials SIOPEL 6 and COG ACCL0431,[16,25] the final scope issued by NICE,[60] and the European Medicines Agency (EMA) marketing authorisation for Pedmarqsi,[15] and Food and Drug Administration prescribing information.[61]

B.3.3.1 Model structure

The *de novo* cost-effectiveness model was developed in Microsoft Excel® (version 2311; build 17029.20068) using both deterministic and probabilistic (Monte Carlo simulation) frameworks. In the first year, the model structure is that of a cohort-based decision tree (Figure 8). The model structure has five hearing loss health states based on the Brock grading scale used in SIOPEL 6 (Described in Section B.1.3.1.2, Table 3); Minimal/no HL, Mild HL, Moderate HL, Marked HL and Severe HL, with an absorbing state for Dead.

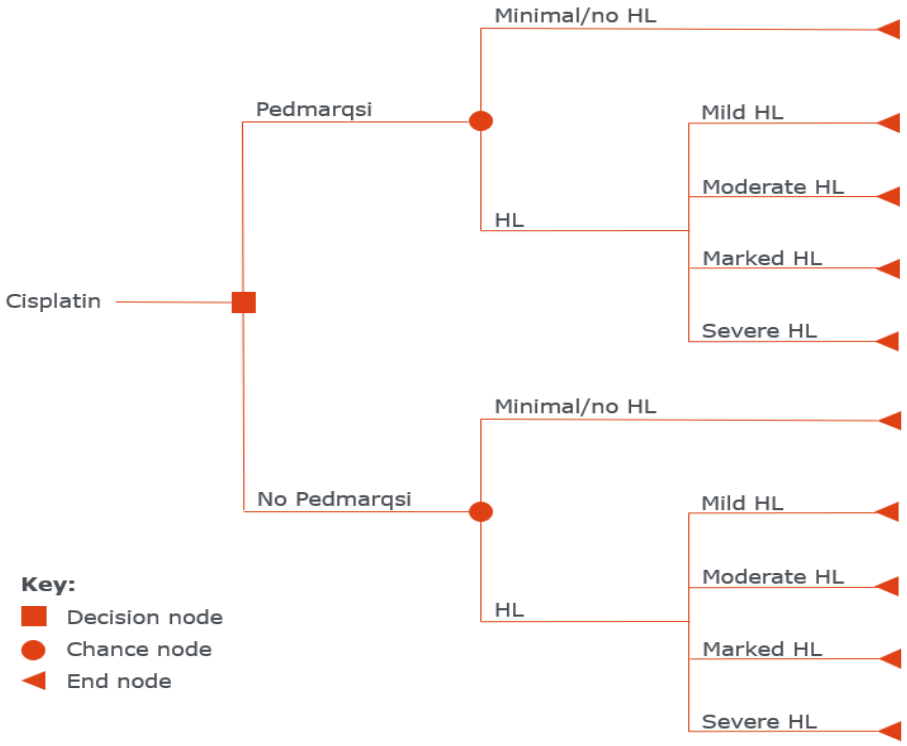
Patients enter the decision tree in the Minimal/no HL health state and by the end of year one they are said to experience measurable hearing loss or not, as presented through transitioning to one of the hearing loss severity health states (Mild HL, Moderate HL, Marked HL, Severe HL), or remaining in the Minimal/no HL health state. From year two onwards, patients cannot transition between hearing loss health states and are only at risk of moving to the absorbing state for Dead (Figure 9).

This model structure was selected based on the following reasons:

- It best captures the efficacy data that is available for Pedmarqsi; the primary outcome of COG ACCL0431 and SIOPEL 6 was the proportion of patients with hearing loss after the end of study treatment, as defined by the ASHA criteria (COG ACCL0431) or the Brock grading scale (SIOPEL 6).

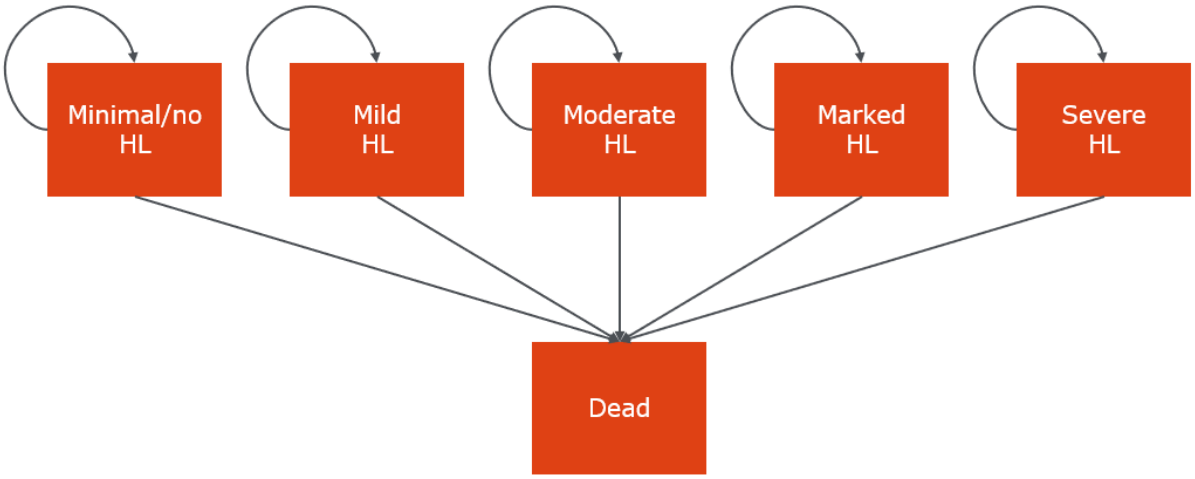
- The inability to revert to less severe hearing loss health states is representative of the fact that cisplatin-induced ototoxicity is permanent and irreversible.[2,3]
- Similarly, patients are unable to move to more severe hearing loss health states over the time horizon. Whilst a degree of age-related hearing loss may be expected in the general population, including such an approach in the economic analysis would present challenges and increase uncertainty, given data are not available to capture the natural decline in hearing for the general population. It is also noted that general population hearing loss was not modelled in a previous NICE health technology evaluation, HTE6,[59] which evaluated a genetic test for the prevention of paediatric hearing loss over a lifetime horizon.

Figure 8: Model schematic – decision tree (year 1)



Abbreviations: HL – Hearing loss

Figure 9: Model schematic - post-decision-tree health state model (years 2+)



Abbreviations: HL – Hearing loss

B.3.3.1.1 Time horizon and cycle length

The base case analysis adopts a 'lifetime' horizon of [redacted] years (calculated as 100 minus the baseline age), which is considered long enough to adequately capture the lifetime costs and QoL of patients in this setting. Section B.3.4.2 provides more information about the baseline age in the model.

A cycle length of one year is selected because, on average, cisplatin treatment (and therefore Pedmarqsi treatment) is completed within one year. This was validated by clinician feedback and is also demonstrated by the total duration of treatment in COG ACCL0431 (median of 15 weeks for patients across both treatment arms[62]). This was validated by clinician feedback and is also demonstrated by the total duration of treatment in COG ACCL0431 (median of 15 weeks for patients across both treatment arms[61]). One year is also considered short enough to adequately capture and reflect changes in costs and QoL over the lifetime horizon. The model applies a half-cycle correction to account for uncertainty in the exact timing of transitions to the Dead state and thus the point at which patients no longer accrue costs and QALYs. However, Pedmarqsi acquisition, administration and antiemetic premedication costs, as well as AE costs in both treatment arms were applied in the first cycle only to all patients entering the model and therefore a half-cycle correction was not applied for these. This is a conservative approach, which assumes that patients will incur these costs even if they move to the Dead state throughout the first cycle.

B.3.3.1.2 Discount rate and perspective

As per the NICE reference case, all health outcomes are measured in QALYs and a 3.5% discount rate per annum is used for QALYs and costs.[62] The analysis is conducted from the perspective of the NHS and PSS for costs and health outcomes.

As scenario analyses, the model explores separate analyses using a discount rate of 1.5% for QALYs and costs, including education costs within the perspective, and including a wider societal perspective (education and productivity costs).

B.3.3.1.3 Features of the economic analysis

There are no previous NICE evaluations for the prevention of cisplatin-induced ototoxicity, however the NICE appraisal of cochlear implants for children and adults with severe to profound hearing loss (TA566) may be considered relevant due to its status as a NICE TA assessing the management of hearing loss in children.[58] Therefore this was used alongside publications identified within the economic SLR to inform the *de novo* model structure, assumptions, and data sources. The features of the economic analysis are summarised in Table 28.

Table 28: Features of the economic analysis

	Previous evaluations	Current appraisal (ID1001)	
Factor	**TA566[58] (previously TA166)**	**Chosen values**	**Justification**
Model structure	Markov model	Cohort-based decision tree (year 1), post-decision tree health state model (year 2+)	As outlined in Section B.3.3.1.
Perspective	NHS and PSS	NHS and PSS	As per the NICE reference case.[62]
Time horizon	NR	Lifetime	As per the NICE reference case.[62]
Cycle length	NR	1 year	Considered appropriate as on average, cisplatin treatment is completed within one year. This was validated by clinician feedback and is also demonstrated by the duration of treatment in COG ACCL0431 (median of 15 weeks for patients across both treatment arms[61]).
Discount rate	3.5% for costs and QALYs	3.5% for costs and QALYs	As per the NICE reference case.[62]
Outcome measure	Costs, QALYs, ICER	Costs, QALYs, ICER	As per the NICE reference case.[62]
Treatment waning effect	NR	None	Hearing loss is irreversible therefore a treatment waning effect is not relevant in this instance throughout the time horizon; patients complete their cisplatin and Pedmarqsi treatment within one year (one model cycle) and thereafter are said to either have developed, or not developed, irreversible hearing loss due to their cisplatin therapy. Those that avoid hearing loss throughout their cisplatin therapy

	Previous evaluations	Current appraisal (ID1001)	
Factor	**TA566[58] (previously TA166)**	**Chosen values**	**Justification**
			through the use of Pedmarqsi, will continue to have this benefit throughout their lifetime as hearing loss will have been prevented.
Source of utilities	NR	• Barton *et al*. 2006[63] • Chen *et al*. 2022[64]	HUI3 utilities specific to paediatric hearing loss patients are derived from Barton *et al*. 2006. HUI3 cancer-related disutilities on- and off treatment sourced from Chen *et al*. 2022 are applied in year 1 and years 2+. The HUI3 utility measure is considered to be the most sensitive to capture the effects of hearing treatment on overall health status.[65]
Source of costs	NR	• NHS Cost collection[66] • PSSRU[67] • TA566[58] • Cutler *et al*. 2022[68] • Bond *et al*. 2009[48] • Dionne *et al*. 2012[14] • Smulders *et al*. 2016[69]	As per the NICE reference case,[62] where possible, unit costs are sourced from national cost databases. Where current unit costs are not available, costs are sourced from published literature; UK costs pre-2015 are inflated using the hospital and community health services (HCHS) inflation index and costs post-2015 are inflated using the NHS cost inflation index (NHSCII), whilst non-UK costs are inflated using the Office for Economic Co-operation and Development (OECD) consumer price index (CPI),[70] then converted to Great British Pounds (GBP) using the OECD purchasing power parities (PPP).

Abbreviations: CPI – Consumer Price Index; HCHS – Hospital and community health services; HUI – Health Utility Index; ICER – Incremental cost-effectiveness ratio; NHS – National Health Service; NHSCII – NHS Cost Inflation Index; NICE – National Institute for Health and Care Excellence; NR – Not reported; OECD – Office for Economic Co-operation and Development; PPP – Purchasing power parities; PSS – Personal Social Services; PSSRU – Personal Social Services Research Unit; QALY – Quality-adjusted life year; TA – Technology appraisal.

B.3.3.2 Intervention technology and comparators

The intervention modelled in the analysis is Pedmarqsi. In line with the final scope, the identified comparator is "established clinical management without anhydrous sodium thiosulfate (Pedmarqsi)" as there are currently no other licensed treatments for the prevention of cisplatin-induced ototoxicity.[60] Therefore, the comparator in the model is cisplatin-based chemotherapy without Pedmarqsi treatment, as per the COG ACCL0431 and SIOPEL 6 clinical trials.

Pedmarqsi treatment is administered as a 15-minute intravenous infusion, beginning six hours after the completion of each cisplatin infusion. Pedmarqsi was dosed at 10.2 g/m^2 in COG ACCL0431. For children whose therapeutic protocol administered cisplatin on a "per kg" basis due to young age or small body size, Pedmarqsi was dosed at 341 mg/kg (anhydrous dosing).

The dose of Pedmarqsi given in SIOPEL 6 was dependent on weight and reflected the dosing shown in Table 29 (expressed in anhydrous form):

Table 29: Pedmarqsi doses in the SIOPEL 6 study

Body weight	Dose
>10 kg	12.8 g/m^2
5 to 10 kg	9.6 g/m^2
<5 kg	6.4 g/m^2

Abbreviations: g – Gram; kg – Kilogram; m^2 – Meters squared

B.3.4 Clinical parameters and variables

As outlined in Section B.2.1, there are two clinical trials that have evaluated the safety and efficacy of Pedmarqsi for the prevention of cisplatin-induced ototoxicity. The principal source of clinical data used to inform the economic analysis is the COG ACCL0431 clinical trial as it included patients with a range of tumour types which were considered generalisable to the patient population in England and Wales (further discussed in Section B.3.4.1). On the other hand, SIOPEL 6 was limited to patients with standard-risk hepatoblastoma with an average age of 1.54 years. As scenario analyses, clinical data from SIOPEL 6 is used.

Clinical data for the following inputs/endpoints/events are used to inform the estimation of costs and outcomes within the model:

- Baseline characteristics (Section B.3.4.2)
- Efficacy (Section B.3.4.3)
    - Proportion of patients experiencing hearing loss
    - Distribution of hearing loss severity
- Safety (Section B.3.4.4)
- Mortality (Section B.3.4.5)

As defined in Section B.1.1, the approved licence for Pedmarqsi is within a cisplatin-treated paediatric population with localised solid tumours. However, it should be noted that whilst the

COG ACCL0431 trial is the most generalisable to the UK setting (see Section B.3.4.1), it included patients with both localised and metastatic disease. The trial was designed as a hearing study and sought to include all children receiving cisplatin for any newly diagnosed solid tumour.

To ensure close alignment with the label population of Pedmarqsi, for the majority of clinical inputs in the economic model, data is sourced from the subgroup of patients with localised disease within COG ACCL0431. This includes baseline characteristics, mortality, and dose inputs. Use of mortality inputs for localised disease only is of particular relevance, as survival is known to be impacted by the extent of the cancer. However, there are some inputs where it was considered more robust and appropriate to use data from the full trial population (localised and metastatic)– specifically for AEs and treatment efficacy.

In terms of AEs, a patient's underlying cancer prognosis will not be impactful to the safety profile associated with Pedmarqsi. Therefore, it is considered more robust to use data utilising the larger sample size of COG ACCL0431 to accurately reflect the impact.

Furthermore, for the primary endpoint – assessment of hearing loss, COG ACCL0431 was not powered for an analysis in the subpopulation of localised patients (n=33/55 children treated with Pedmarqsi). This categorisation was not considered in the stratification variables at randomisation and therefore it is considered inappropriate to further restrict an analysis of treatment effect from an already limited population size. Further to this, Pedmarqsi is a treatment for the prevention of hearing loss, and not a treatment for the underlying cancer, and therefore the efficacy of Pedmarqsi in terms of hearing outcomes is independent of whether the patient has localised or metastatic disease. The limitations of this approach are further mitigated by the results of SIOPEL-6 trial, which corroborate the otoprotectant effect of Pedmarqsi in patients with localised disease, as well as Pedmarqsi's mechanism of action being confined to the ear, as summarised in section B.1.2, and hence in terms of Pedmarqsi's efficacy, there is no rational to consider any differentiation in effect based on tumour characteristics.

Accounting for the reasons above, to ensure presentation of a robust and clinically relevant economic model, the Company concluded it would be appropriate to use efficacy data which is powered by the overall COG ACCL0431 population.

B.3.4.1 Generalisability of COG ACCL0431 to England and Wales

COG ACCL0431 was a hearing study conducted in North America and included children with any solid tumour that is treated with cisplatin. The trial included paediatric patients with a range of cancer types which are generally aligned to the distribution of key cisplatin-treated paediatric localised cancers in England and Wales, as published in the CTYA UK cancer incidence 1997-2016 statistics,[71] as shown in Table 30.

Whilst Table 30 presents slight differences between the proportions of tumours in the trial and those seen in the CTYA UK cancer incidence statistics, they can be explained through some of the more common localised cancers in the UK not always being treated with cisplatin. For example, retinoblastomas can sometimes be managed with surgery alone. Further, whilst none of the tumours appearing in the CTYA UK statistics were excluded from the COG ACCL0431 trial, the tumour types included in the trial are those which are treated with cisplatin

most commonly. Most importantly, it should be remembered that Pedmarqsi is a preventative treatment of cisplatin-induced ototoxicity. Its mechanism of action, when given 6 hours after cisplatin infusions that last no longer than six hours, is confined to the ear, and hence the underlying cancer type is not important. Finally it should be noted that to assess generalisability based on the distribution of cancer types, some assumptions were required to present comparable data; teratoid/rhabdoid, choroid plexus, astrocytoma and medulloblastoma cancers, which were listed in COG ACCL0431, were grouped into the intracranial and intraspinal tumours category, as they are all central nervous system (CNS) tumours.

COG ACCL0431 also includes patients of a wide range of ages, and hence a wide range of dose quantities required (as dose is weight based), which makes the study most generalisable to the eligible population of patients in England and Wales. Cancer treatment protocols in paediatrics are determined by collaborative groups who share information globally because of the challenges of conducting research in this area. Therefore, despite COG ACCL0431 being conducted in North America, the number of cisplatin doses (and therefore Pedmarqsi doses) used in the trial is anticipated to reflect what would be used in UK clinical practice.

As shown by the baseline characteristics of patients within COG ACCL0431 (reported in Section B.3.4.2, Table 31), the percentage of males within the trial is higher than that of the general population, however this aligns with published literature which shows that the incidence of many cancers is higher in men than women, including in the paediatric population.[72–74] Therefore, given the above, the COG ACCL0431 trial is considered a robust data source and generalisable to UK clinical practice.

Table 30: Percentage distribution of cancer types in COG ACCL0431 and the England and Wales population

Cancer type	Percentage distribution of cancer types in COG ACCL0431 (localised only)	Percentage distribution of key paediatric localised cancers which are commonly treated with cisplatin in England and Wales[71]
Intracranial and intraspinal tumours[a]	[redacted]	23.1%
Ependymomas	[redacted]	18.7%
Neuroblastomas	[redacted]	10.1%
Retinoblastomas	[redacted]	13.6%
Hepatoblastomas	[redacted]	5.5%
Osteosarcomas	[redacted]	17.1%
Malignant extracranial germ cell tumours[b]	[redacted]	5.8%
Malignant gonadal germ cell tumours[b]		5.4%
Nasopharyngeal carcinoma	[redacted]	0.5%

[a]Teratoid/rhabdoid, choroid plexus, astrocytoma and medulloblastoma cancers, which were listed in COG ACCL0431, were compared to the intracranial and intraspinous tumours category from the CTYA dataset. [b]In

COG ACCL0431, the percentage of malignant extracranial and malignant gonadal germ cell tumours was grouped under the cancer type "germ cell tumours"
Source: COG ACCL0431 CSR[25], Appendix B CTYA UK cancer incidence 1997-2016[35]

B.3.4.2 Baseline patient characteristics

In the base case, the economic analysis utilises baseline patient characteristics from the COG ACCL0431 trial and as discussed in Section 0, only data from localised patients is considered. As a scenario, efficacy inputs (and consequently baseline characteristics) from SIOPEL 6 are evaluated. Baseline patient characteristics used in the model are presented in Table 31, with a more detailed summary of baseline patient demographics provided within Section B.2.2.3 and B.2.2.5.

Table 31: Baseline patient characteristics informing the economic model

Characteristic	Trial	Value (SE)	Use in model		
Proportion male, %	**COG ACCL0431*** (base case)	[redacted]% (N/A)	Used to inform the estimation of background mortality and for adjusting utilities according to age.		
	SIOPEL 6 (scenario)	54.13% (N/A)			
Mean age, years	**COG ACCL0431*** (base case)	[redacted]	Age at baseline impacts the time horizon and the mean age of the cohort in each cycle of the model, subsequently impacting the period in which costs for those aged <18 years are applied.		
	SIOPEL 6 (scenario)	1.5 (0.13)			
Age distribution, %	**COG ACCL0431*** (base case) & **SIOPEL 6** (scenario)		**COG ACCL0431**	**SIOPEL 6**	Age distribution is used to inform the weighted average unit costs for patients <18 years old. These costs are applied for every model cycle where the mean age of the cohort <18 years old.
		≥1mo - <1yr	[redacted]	45.87%	
		≥1yr - <2yrs	[redacted]	30.28%	
		≥2yr - <3yrs	[redacted]	12.84%	
		≥3yr - <4yrs	[redacted]	6.42%	
		≥4yr - <5yrs	[redacted]	0.92%	
		≥5yr - <6yrs	[redacted]	2.75%	
		≥6yr - <7yrs	[redacted]	0.00%	
		≥7yr - <8yrs	[redacted]	0.00%	
		≥8yr - <9yrs	[redacted]	0.92%	
		≥9yr - <10yrs	[redacted]	0.00%	
		≥10yr - <11yrs	[redacted]	0.00%	
		≥11yr - <12yrs	[redacted]	0.00%	
		≥12yr - <13yrs	[redacted]	0.00%	
		≥13yr - <14yrs	[redacted]	0.00%	
		≥14yr - <15yrs	[redacted]	0.00%	
		≥15yr - <16yrs	[redacted]	0.00%	
		≥16yr - <17yrs	[redacted]	0.00%	

		≥17yr - <18yrs	[redacted]	0.00%	

*Only data from localised patients is considered to align with the Pedmarqsi license.
Abbreviations: SD – standard deviation.

B.3.4.3 Efficacy

The efficacy of Pedmarqsi is captured within the one year decision tree by two elements: firstly, the percentage of patients who experience cisplatin-induced hearing loss through the percentage of patients assigned to the Minimal/no HL health state, and secondly the severity of hearing loss for those that experience it, as depicted by the distribution of patients between the Mild HL, Moderate HL, Marked HL and Severe HL health states.

In the base case, the percentage of patients who experience cisplatin-induced hearing loss is based on the primary outcome of COG ACCL0431 measured in the efficacy population (Section B.2.5.2) and as discussed in Section 0 data from both localised and metastatic patients is used. The efficacy population is considered appropriate to use as it included all children in the ITT population who had both baseline and four-week follow-up hearing assessments and therefore an assessment of the change in hearing loss can be conducted. This population was also the primary population for the analyses of the hearing loss endpoints in COG ACCL0431. As the efficacy population was pre-specified in the trial protocol,[75] the Company consider any bias associated with this exclusion method to be minimal (as discussed by Rehman *et al.* 2020).[76] Results from the SIOPEL 6 mITT population and the Orgel *et al*. (2023)[32] re-analysis of COG ACCL0431 (previously described in Section B.2.7) are considered in scenario analyses. The efficacy inputs for the base case and scenarios are presented in Table 32.

Table 32: Number and percentage of patients experiencing hearing loss

Percentage of patients	COG ACCL0431 efficacy population (base case)[25]		SIOPEL 6 mITT (scenario)[16]		Orgel *et al*. (2023) re-analysis of COG ACCL0431 (scenario)[32]	
	Cisplatin without Pedmarqsi	Cisplatin with Pedmarqsi	Cisplatin without Pedmarqsi	Cisplatin with Pedmarqsi	Cisplatin without Pedmarqsi	Cisplatin with Pedmarqsi
With hearing loss	31 (56.36%)	14 (28.57%)	29 (63.04%)	18 (32.73%)	27 (45.76%)	9 (18.00%)
Without hearing loss	24 (43.64%)	35 (71.43%)	17 (36.96%)	37 (67.27%)	32 (54.24%)	41 (82.00%)

Abbreviations: mITT – Modified intention-to-treat

Hearing loss severity (i.e. the grade at which those assigned to “with hearing loss” in Table 32) was not measured in COG ACCL0431, therefore the severity of hearing loss is based on Orgel *et al.* (2023),[32] in combination with Knight *et al.* (2005).[11]

Orgel *et al.* (2023) conducted a re-analysis of COG ACCL0431 data using the SIOP scale and reported the number of patients with Grade 1+ and Grade 2+ hearing loss at the end of cisplatin therapy (results are reported in Section B.2.7).[32] This data is used to inform the percentage of patients with Grade 1 and 2+.[32] Of those that have Grade 2+ hearing loss, these are further differentiated into Grades 2, 3 and 4 using the percentage distribution of these grades reported in Knight *et al.* (2005) (Table 33).[11] For the purpose of assigning patients into

model health states based on these data sources, Grades 1, 2, 3 and 4 hearing loss are assumed equal to the Mild HL, Moderate HL, Marked HL and Severe HL health states in the model.

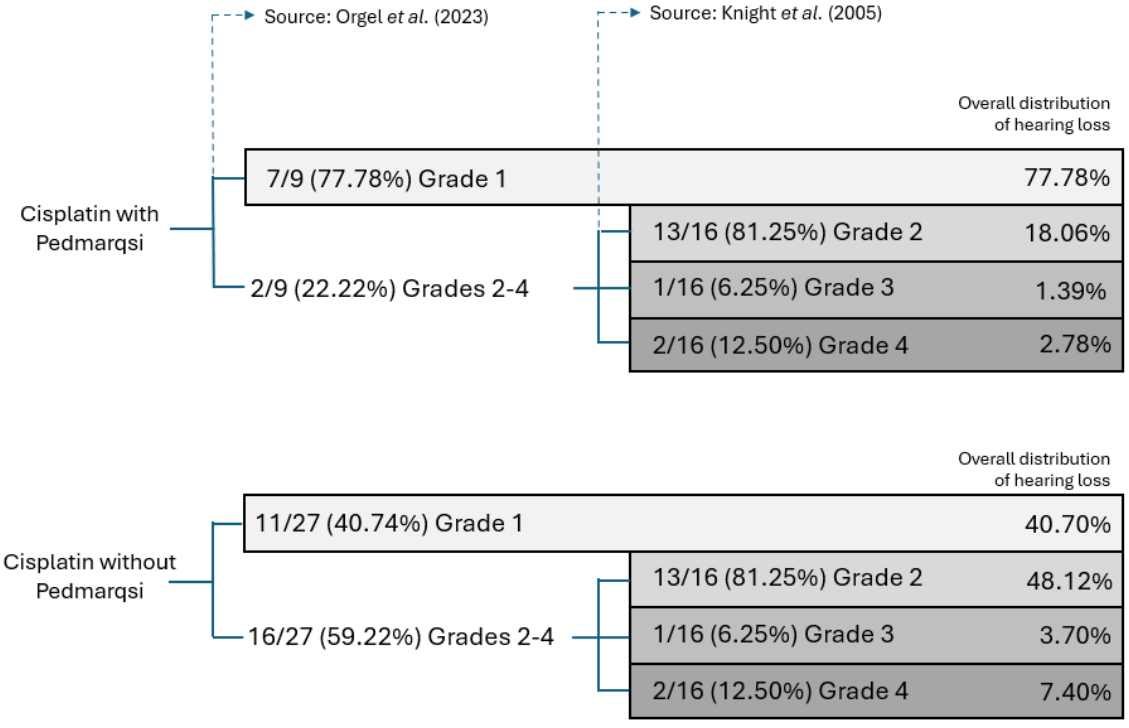
Knight *et al.* (2005)[11] was considered appropriate as the population characteristics of patients within this study (such as mean age and the distribution of tumour types) closely align with that of the principle source of data in the model (COG ACCL0431). The sources and data used to inform distribution of hearing loss severity in the base case is summarised in Figure 10.

Table 33: Hearing loss severity reported by Knight *et al.* (2005)

Hearing loss severity	Distribution of patients	Re-weighted distribution for Brock Grades 2-4
Brock grade 1	12 (42.9%)	N/A
Brock grade 2	13 (46.4%)	81.25%
Brock grade 3	1 (3.6%)	6.25%
Brock grade 4	2 (7.1%)	12.50%

Abbreviations: N/A – Not applicable

Figure 10: Sources and data used to inform the severity of hearing loss (as a proportion of those with hearing loss)



Although SIOPEL 6 reported the percentage of patients experiencing hearing loss, this trial focused on paediatric patients with one tumour type, hepatoblastoma, and is therefore less representative of the distribution of patients observed in England and Wales. As a result,

SIOPEL 6 is not used in the base case. However, two scenarios are considered to inform the hearing loss severity in the model (i.e. the distribution of patients within the Mild HL, Moderate HL, Marked HL and Severe HL health states):

1) Scenario using SIOPEL 6 data[16] alone to distribute patients into the Mild HL, Moderate HL, Marked HL and Severe HL health states.

2) Scenario using Orgel *et al.* (2023)[32] in combination with SIOPEL 6.[16] Similar to the base case, Orgel *et al.* (2023) data is used to inform the percentage of patients within the Mild HL health state, and Moderate HL to Severe HL health states. However, instead of Knight *et al.* (2005),[11] SIOPEL 6 data is used to further differentiate the patients into the Moderate HL, Marked HL and Severe HL health states.

The distribution of hearing loss severity in the two scenarios is presented in**Error! Reference source not found.**.

Table 34: Severity of hearing loss (as a proportion of those with hearing loss) – scenario analyses

Percentage of patients	SIOPEL 6 (scenario)[16]		Orgel *et al.* (2023) and SIOPEL 6 (scenario)[16,32]	
	Cisplatin without Pedmarqsi	Cisplatin with Pedmarqsi	Cisplatin without Pedmarqsi	Cisplatin with Pedmarqsi
Mild HL	41.38%	55.56%	40.78%	77.78%
Moderate HL	37.93%	33.33%	38.32%	16.67%
Marked HL	17.24%	5.56%	17.42%	2.78%
Severe HL	3.45%	5.56%	3.48%	2.78%

Abbreviations: HL – Hearing loss

B.3.4.4 Safety

The base case model considers Pedmarqsi treatment-related SAEs occurring in ≥2% of patients. The focus is on Pedmarqsi treatment-related AEs as it is assumed that cisplatin-related AEs will be equal in both arms. The source for AE inputs aligns with the source of trial data used to inform the efficacy in the model; in the base case COG ACCL0431 AE rates are used (taken from the full safety population as discussed in Section 0) and as a scenario, efficacy inputs (and consequently AE inputs) are taken from the safety population in SIOPEL 6. Note that in the base case, none of the treatment-related SAEs met the threshold of being observed in ≥2% of patients (and therefore no AEs are included in the base case analysis), and under the scenario where SIOPEL data is used, only one treatment-related SAE met the threshold (Neutrophil count decreased occurring in 3.77% of patients). As a further scenario, CTCAE Grade ≥3 AEs occurring in ≥10% of patients in either treatment arm were evaluated (presented in Table 35).

Table 35: Grade 3+ adverse events included in the model (Scenario)

Adverse event	Grade 3+ AEs occurring in ≥10% of patients in either arm (COG ACCL0431)	
	Cisplatin without Pedmarqsi	Cisplatin with Pedmarqsi
Neutrophil count decreased	82.18%	83.05%
Febrile neutropenia	29.69%	23.73%
WBC count decreased	65.63%	64.41%
Platelet count decreased	60.94%	64.41%
ALT increased	14.06%	16.95%
Lymphocyte count decreased	14.06%	10.17%
Anaemia	56.25%	50.85%
Hypokalaemia	20.31%	27.12%
Hypophosphatemia	10.94%	20.34%
Hyponatremia	6.25%	11.86%
Stomatitis	6.25%	13.56%

Note: AEs reported as 0% occur in <10% of patients in both treatment arms
Abbreviations: AE – adverse event; ALT – alanine aminotransferase increased; WBC – white blood cell.

B.3.4.5 Mortality

The pivotal trials SIOPEL 6 and COG ACCL0431, showed that there was no statistically significant difference between the proportion of children who died in the cisplatin with Pedmarqsi and cisplatin without Pedmarqsi treatment arms (see Section B.2.5). As such, the mortality inputs of the cost-effectiveness model are not treatment dependent.

Despite mortality being equal between treatment arms, it is important to accurately capture the mortality for the population of interest as this impacts the average length of time that costs and QALYs are accrued for, and therefore the ICER. For the first five years of the model, mortality probabilities are based on the percentage of patients alive at years one, two, three, four and five of COG ACCL0431 and as discussed in Section 0, only data from localised patients is considered.

As a scenario, the OS results of SIOPEL 6 are considered (reported in Section B.2.5.1). The five-year trial mortality probabilities are presented in Table 36. Mortality differs between COG ACCL0431 and SIOPEL 6 due to each trial's patient characteristics (notably, the tumour types and age of patients). Where mortality percentages are less than that of the general population mortality, the general population values are used.

Table 36: Percentage of patients alive and mortality probability in years 1-5*

Year	COG ACCL0431 (base case)[25]		SIOPEL 6 (scenario)[16]	
	Percentage of patients alive*	Mortality probability	Percentage of patients alive	Mortality probability
1	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]

*Only data from localised patients is considered to align with the Pedmarqsi license. **Where mortality percentages are less than that of the general population mortality, the general population values are used.

As the OS data from both trials is immature, it is not appropriate to extrapolate these outcomes over the time horizon of the model. However, the Company acknowledge that beyond five years, patients are likely to still have an increased rate of mortality compared to that of the general population. A cure point of 10 years was preferred by the Committee in TA538[77] and TA817[78], both of which were oncology appraisals with comparable tumour types to those relevant to this appraisal (neuroblastoma and invasive urothelial cancer, respectively - for which the current standard of care [SoC] is platinum-based chemotherapy). Therefore, from years six to 10 of the model, a post-cancer standardised mortality ratio (SMR) of 9.1 is applied to general population mortality. The SMR was sourced from a large population based cohort study of five-year paediatric cancer survivors in England and Wales,[79] whilst general population mortality was sourced from the Office for National Statistics (ONS).[80] Beyond model year 10, general population mortality data is applied.

B.3.5 Measurement and valuation of health effects

B.3.5.1 Health-related quality-of-life data from clinical trials

No HRQoL data was collected as part of COG ACCL0431 or SIOPEL 6.

B.3.5.2 Mapping

No mapping was conducted for the cost-effectiveness analysis.

B.3.5.3 Health-related quality-of-life studies

An SLR to identify relevant HRQoL studies for patients with acquired hearing loss was conducted on 25th October 2023. This population was expanded from the population criteria in the clinical search (which aligned with the licensed indication of Pedmarqsi), and the reasons for this are described in Section B.3.1. Appendix H provides full details of the methods, overview of studies and results of the identified studies, together with the quality assessments. The SLR identified 38 utility studies, 10 of which reported HRQoL data by hearing loss severity level. Of these 10, seven were publications in adult patients or reported utility values derived from adult populations and therefore were less relevant to inform the utility values of the model. Of the remaining three studies, one study published by Oostenbrink *et al.* (2002) reported utility values for deafness and mild hearing loss only and therefore did not provide the level of granularity required for the model.[81] Another study published by Verkleij *et al.* (2021) reported utility values for bilateral mild, moderate, severe and profound childhood hearing loss derived from a study published by Barton *et al.* (2006).[63,82] The final study published by Gumbie *et al.* (2022) reported utility values for mild, moderate and severe/profound hearing loss in children with and without hearing aids and cochlear implants, also primarily derived from Barton *et al.* (2006).[83]

B.3.5.4 Targeted literature review

To overcome the small number of publications found in the SLR that consider paediatric patients and report utilities according to hearing loss severity, a targeted literature search (TLR) for HRQoL in paediatric patients with hearing loss was conducted. Barton *et al.* (2006)[63] was identified through a TLR and was the main source of utility inputs for two of the SLR papers identified above. Although this study was not identified directly in the SLR, it was considered the most appropriate reference to inform health state utilities in the base case due to its close alignment with the population for which Pedmarqsi is indicated. Barton *et al.* (2006) was a cost-effectiveness analysis of cochlear implants in children with bilateral hearing impairment in the UK and included utility values for hearing loss categories by severity level.[63] The utility values used in this study were elicited using the Health Utilities Index mark 3 (HUI3) utility measurement, which is an appropriate tool for assessing QoL in patients with hearing loss.[84]

B.3.5.5 Adverse reactions

AE disutilities were sourced from published literature and were adjusted according to the duration that they typically last for (also sourced from published literature). As detailed in B.3.3.1.1, all key paediatric cancer types are treated with cisplatin (and therefore Pedmarqsi) for no more than one year. Therefore, disutilities were applied to the percentage of patients experiencing each AE in the first year of the cost-effectiveness model only.

Incidence of AEs were obtained from the COG ACCL0431 clinical trial in the base case (Section B.3.4.4). Table 37 includes the list of AE disutilities and durations included in the model. Note that the AE inputs listed only have an impact on model results under the scenarios mentioned in Section B.3.4.4, as none of the treatment-related SAEs met the threshold for inclusion in the base case.

Table 37: Disutilities for adverse events

Adverse event	Utility decrement	Duration (days)	Source (disutility)	Source (duration)
Neutrophil count decreased	-0.01	40.10	Hudgens (2014)[85]	TA704[86] and TA862[87]
Haemoglobin decreased	-0.07	42.90	Assumed to be equal to anaemia	
Infection	-0.04	182.50	Cutler (2022)[68]	
Febrile neutropenia	-0.09	7.00	Nafees (2008)[88]	AJMC (2017)[89]
White blood cell count decreased	-0.03	42.90	Hudgens (2014)	TA704[86] and TA862[87]
Platelet count decreased	-0.11	58.30	Shao (2022)[90]	TA862[87]
Alanine aminotransferase increased	-0.05	28.00	Telford (2019)[91]	Assumed due to lack of data
Lymphocyte count decreased	-0.20	4.10	Shao (2022)[90]	McNamara (2008)[92]
Anaemia	-0.07	42.90	Shao (2022)[90]	TA704[86] and TA862[87]
Hypokalaemia	-0.03	13.00	Shao (2022)[90]	Schlögl (2021)[93]
Hypophosphatemia	-0.08	3.30	HST8[94]	Corona (2016)[95]
Hyponatremia	-0.52	2.00	Szymanski (2020)[96]	Assumption from Lee (2014)[97] (<48 hours is acute hyponatremia)
Stomatitis	-0.15	14.00	Lloyd (2006)[98]	Plewa (2023)[99] (Assumed RAS)

Abbreviations: RAS – Recurrent aphthous stomatitis.

B.3.5.6 Health-related quality-of-life data used in the cost-effectiveness analysis

For the model base case, utility values were taken from Barton *et al.* 2006, a cross-sectional study in which 8,876 hearing-impaired children had their HRQoL assessed by proxy from parents using the HUI3.[63] This is in line with the utility values used in Bond *et al*. 2009,[48] which was the basis of the economic evaluation within the HTA submission for cochlear implants for severe to profound deafness in both children and adults (TA566).[58] The Company understand that EQ-5D is NICE's preferred generalised utility measure and that there are no HUI3 social preference weights available for the UK general population (only available for Canada and the US). However it has been widely reported that EQ-5D lacks construct validity in patients with

hearing impairment.[100,101] The HUI3 is therefore the HRQoL measurement of choice in a population with hearing impairment,[100,101] and is used by the UK cochlear implant study group (UKCISG) in research.[65,102] For these reasons, the Company believe that HUI3 derived utility values are appropriate for this submission.

Barton *et al*. 2006 reported utility values of 0.677, 0.616, 0.497 and 0.353 for patients with Moderate (average hearing level [AHL] 40-70dB), Severe (AHL 71-95dB), Profound (AHL 96-105dB) and Profound (AHL >105dB) hearing loss, respectively.[63] These utility values were considered to be equal to the Moderate HL, Marked HL and Severe HL health states respectively (a weighted average of the profound utility values was used for the Severe HL health state, based on patient numbers in the publication). For the Mild HL health state, utilities were calculated as an average of the Minimal/no HL health state (discussed later in this section) and the Moderate HL health state value mentioned above. Barton *et al.* 2006 also reported the utility gain associated with cochlear implant use for subsets of paediatric patients according to their age at implantation (<5 years and ≥5 years old) and duration of use.[63] To align with the baseline age of the model (see Section B.3.4.2) and the assumption that once used, cochlear implant would be used by patients for their entire lifetime, the model utilises the cochlear implant utility gain reported for paediatric patients implanted over five years old and with a duration of cochlear implant use more than four years (utility gain of 0.183). This was applied to each health state according to the percentage of patients using cochlear implants (as shown in Table 31). Barton *et al.* 2006 included patients with moderate to profound hearing loss, therefore it was assumed that all patients not using cochlear implants would have received hearing aids, and therefore a hearing aid utility gain was not applied to the utility values reported for Moderate, Severe and Profound hearing loss.

A scenario analysis considering utility values from Gumbie *et al.* 2022 was conducted.[83] Disutility values for the bilateral mild hearing loss (-0.161), bilateral moderate hearing loss (-0.323) and unilateral severe/profound hearing loss (-0.437) were used for the Mild HL, Moderate HL, and Severe HL health states. The Marked HL health state was calculated as an average of the Moderate HL and Severe HL health states. As in the base case, a utility gain for cochlear implants was applied, sourced from Barton *et al.* 2006.[63] Gumbie *et al.* 2022 also reported a utility gain for hearing aids of 0.120 therefore this was also applied to health state utilities according to the percentage of patients using hearing aids (as shown in Table 42).

The utility values for the Minimal/no HL health state of the model were taken from Pogany *et al.* 2006,[103] which is the source of the HUI3 population norms for the Canadian general population, reported on the HUI3 website. The utility reported for children aged 5-12 years old was used (0.920), as this is in line with the baseline starting age in the model. It is noted that there is likely to be small differences between the health preferences of the Canadian and UK general populations, however using a HUI3 value for the Minimal/no HL health state is appropriate given that HUI3 values are used for other health states, and as previously mentioned, there is no UK value set available for HUI3. This approach was also taken in a previous NICE health technology evaluation, HTE6.[59] It is also of note that the HUI3 utility value used is not dissimilar from the UK general population EQ-5D utility value for people aged 16 (the youngest age at which EQ-5D values are available);[104] when the EQ-5D utility value is adjusted according to the gender distribution from COG ACCL0431, this results in a utility of 0.931 (only 1.2% higher than the HUI3 value of 0.920 used in the model).

Since the utility values from Barton *et al.* 2006 (and Gumbie *et al.* 2022 when used in the scenario) are not specific to cancer patients,[63] it is likely that they represent an overestimation for the patient cohort considered within the cost-effectiveness analysis in the initial years

following completion of their cisplatin treatment. Therefore, a cancer-related disutility was applied to all health states in the model for the first 10 years of the model, sourced from Chen *et al*. 2022,[64] which is a recent systematic review and meta-analysis of health utilities in paediatric cancer patients. The HUI3 proxy-reported disutility value for patients on treatment was applied in the first year of the model, whilst between years two and 10 of the model, the HUI3 proxy-reported disutility for patients off treatment for 2-5 years was applied (no value was available for patients off treatment for 0-2 years). The off treatment cancer-related disutility was applied up to year 10 of the model to align with the cure points reported in TA538 and TA817,[77,78] as described in Section B.3.4.5. This disutility value is only applied for this length of time to reflect that fact that utilities are likely to return to population norms after multiple years of being cancer free.

Table 38: Summary of utility values for the cost-effectiveness analysis

State	Utility value: mean (SE)	95% confidence interval	Reference in submission (section and page number)	Justification
Base case				
Minimal/no HL	0.92 (0.00)	NR	B.3.5.6	Derived from Pogany *et al.* 2006,[103] as there is no UK value set to HUI3
Mild HL	0.80 (NR)	NR	B.3.5.4	Average of the Minimal/no HL and Moderate HL health states due to lack of data
Moderate HL	0.68 (NR)	NR	B.3.5.4	Derived from Barton *et al.* 2006[63] and previously used within Bond *et al.* 2009[48]
Marked HL	0.63 (NR)	NR	B.3.5.4	
Severe HL	0.52 (NR)	NR	B.3.5.4	
Cancer-related disutility, on treatment (applied to all health states in year 1)	-0.15	(-0.24,-0.05)	B.3.5.6	Derived from Chen *et al.* 2022.[64] Applied to account for the additional disutility that cancer patients experience
Cancer-related disutility, off treatment (applied to all health states in years 2+)	-0.07	(-0.20,0.06)	B.3.5.6	
Scenario – Gumbie *et al.* 2022				
Minimal/no HL	As above.			
Mild HL	0.82 (NR)	NR	B.3.5.3	Explore using alternative utility
Moderate HL	0.72 (NR)	NR	B.3.5.3	

State	Utility value: mean (SE)	95% confidence interval	Reference in submission (section and page number)	Justification
Marked HL	0.66 (NR)	NR	B.3.5.3	values derived from Gumbie *et al.* 2022[83]
Severe HL	0.64 (NR)	NR	B.3.5.3	
Cancer-related disutility, on treatment (applied to all health states in year 1)	As above.			
Cancer-related disutility, off treatment (applied to all health states in years 2+)	As above.			

Abbreviations: HL – Hearing loss; HUI3 – Health Utilities Index mark 3; NR – Not reported; SE – Standard error

NICE guidance states that "If baseline utility values are extrapolated over long time horizons, they should be adjusted to reflect decreases in health-related quality of life seen in the general population".[62] Therefore utility values were age-adjusted over the model time horizon using the EQ-5D UK general population norms reported by the Decision Support Unit (DSU).[104] Male and female population utility norms were weighted according to the gender distribution in COG ACCL0431, to obtain overall population utility norms for each age. A multiplicative approach was used, meaning in each cycle, the EQ-5D derived utility norm for the average age of the cohort was compared to the EQ-5D derived utility norm of the baseline starting age of the cohort entering the model, and the percentage difference was applied to the baseline HUI3 derived health state utilities mentioned above in Table 38.

B.3.6 Cost and healthcare resource use identification, measurement and valuation

An SLR was undertaken to identify cost and resource use studies for the prevention/management of paediatric patients with cisplatin-induced ototoxicity. This population was expanded from the population criteria in the clinical search (which aligned with the licensed indication of Pedmarqsi), and the reasons for this are described in Section B.3.1. Appendix I provides full details of the methods, overview of studies and results of the identified studies, together with the quality assessments.

B.3.6.1 Intervention and comparators' costs and resource use

B.3.6.1.1 Drug acquisition costs

The cost of cisplatin was not considered in the economic analysis on the basis that it is equal between each treatment arm.

The Company presents a list price for Pedmarqsi based on the only available vial size of 8g. Concurrent to the submission dossier, the Company has submitted a confidential simple

discount Patient access scheme (PAS) for Pedmarqsi resulting in a fixed net price of [redacted] per 8g vial (equivalent to a discount of [redacted] to the list price).

Pedmarqsi is administered as a 15-minute infusion, six hours after the completion of each cisplatin infusion (i.e. Pedmarqsi is administered on a 1:1 frequency basis with cisplatin). Therefore, the dose frequency of Pedmarqsi is dependent on the frequency of the patients' cisplatin regimen.

The average per patient acquisition cost of Pedmarqsi in the model is based on the average number of doses per patient, and the average number of 8g Pedmarqsi vials required per dose, calculated from patient-level Pedmarqsi trial data. The source of data is aligned to the trial which is used to inform the efficacy in the model (previously presented in Table 32; COG ACCL0431 in the base case and SIOPEL 6 as a scenario). Only data from localised patients is considered for dose inputs to align with Pedmarqsi's licence. No dose modifications are recommended for Pedmarqsi.[22]

As previously mentioned in Section B.3.4.1, despite COG ACCL0431 being conducted in North America, the number of cisplatin doses (and therefore Pedmarqsi doses) used in the trial is anticipated to reflect what would be used in UK clinical practice.

In the base case, it was conservatively assumed that no vial sharing is allowed and therefore full drug wastage is accounted for. Note that the number of vials required per dose, including wastage, is calculated on a per patient basis (as shown on the 'ACCL0431 doses' and 'SIOPEL doses' sheet in the model) before being combined into an average for all patients within the trial, and therefore the number of vials is not a whole number even when wastage is included. Taking this approach to calculate wastage at the patient-level is considered more accurate than calculating wastage at the cohort level where the distribution of doses is not fully reflected.

In clinical practice, if only a small amount of a new vial is required, it is plausible that clinicians may not open the new vial after considering the cost and wastage associated with doing so. This dose banding approach is supported by NHS England in chemotherapy dosing in order to reduce waste.[105] The impact of assuming a dose banding approach was tested via scenario analyses which explored the impact of not costing for a new vial if less than 10% or 5% was required. A further scenario of assuming no wastage was conducted.

The mean number of doses and mean number of vials per dose (with and without wastage scenarios) are reported in Table 39.

Table 39: Pedmarqsi dose inputs used in the model

Trial	Average number of doses	Average number of 8g Pedmarqsi vials per dose			
		Wastage (base case)	Wastage (new vial not opened if less than 10% required) (scenario)	Wastage (new vial not opened if less than 5% required) (scenario)	No wastage (scenario)
COG ACCL0431 (base case)[25]	6.79	1.87	1.63	1.68	1.19
SIOPEL 6 (scenario)[16]	5.28	1.98	1.77	1.94	1.29

Abbreviations: g - Grams

B.3.6.1.2 Antiemetic premedication costs

As specified in the Birmingham children's hospital guideline for the management of chemotherapy-induced nausea and vomiting,[106] antiemetic medication should be given to all children receiving cisplatin to prevent chemotherapy-induced nausea and vomiting. Similarly, the Pedmarqsi SmPC recommends that antiemetics are given around 30 minutes prior to Pedmarqsi administration to reduce the chance of nausea and vomiting.[22] However, in practice is it unlikely that additional antiemetic medication would be required given that patients will be receiving multiple doses of antiemetic medication for their cisplatin infusion. For this reason, the costs of antiemetics are not considered in the economic model base case on the basis that they are equal in both arms and additional antiemetic medication is not required. However, a scenario analysis is provided which explores the impact of assuming one additional dose (on top of the antiemetics administered for cisplatin) of ondansetron, dexamethasone and metoclopramide prior to each Pedmarqsi administration. The choice of antiemetics is based on the Birmingham children's hospital guideline for the management of chemotherapy-induced nausea and vomiting.[106] The average weight used for the purpose of dose calculations aligns with the trial data used to inform the efficacy of the model (COG ACCL0431 (although localised only) in the base case and SIOPEL 6 as a scenario).[16,25] Unit costs and pack sizes were taken from the eMIT;[107] where multiple pack sizes were available the most expensive option was used as a conservative estimate.

The antiemetic premedication costs included in the model for the scenario analysis are shown in Table 40.

Table 40: Antiemetic premedication costs

Antiemetic	Dose (mg/kg)	Pack size (mg)	Unit cost	Total dose per administration (mg)		Total cost per administration		Dose source	Cost source
				COG ACCL0431 (base case)*	SIOPEL 6 (mg) (scenario)*	COG ACCL0431 (base case)	SIOPEL 6 (mg) (scenario)		
Ondansetron	0.15	40	£5.01	5.27	1.54	£0.66	£0.19	COG ACCL0431 protocol[75]	eMIT[107] (Ondansetron 4mg/2ml solution for injection ampoules/ pack size 10)
Dexamethasone	0.10	38	£17.01	3.51	1.02	£1.57	£0.46	COG ACCL0431 protocol[75]	eMIT[107] (Dexamethasone 3.8mg/1ml solution for injection ampoules/ pack size 10)
Metoclopramide	0.20	100	£1.60	7.03	2.05	£0.11	£0.03	Birmingham children's hospital guideline[106]	eMIT[107] Metoclopramide 10mg/2ml solution for injection ampoules/ pack size 10

*The average weight used for the purpose of dose calculations aligns with the trial data used to inform the efficacy of the model (COG ACCL0431[25] in the base case and SIOPEL 6[16] as a scenario). Abbreviations: eMIT – Electronic Market Information Tool; Kg – Kilograms; mg – Milligrams; ml - Millilitres

B.3.6.1.3 Administration costs

As stated in the SmPC, Pedmarqsi is intended for hospital use only, under the supervision of an appropriately qualified physician, and should be administered intravenously as a 15-minute infusion.[22] Due to the hypertonic formulation, administration through a central vein is recommended.

The Pedmarqsi administration cost includes 30 minutes of nurse time (15 minutes for infusion and 15 minutes for preparation), at a cost per hour of £106.00, which corresponds to hospital-based nurse band 8c taken from the PSSRU.[67] No cost of administration materials is included given that Pedmarqsi will not be commissioned by specialised services and that no additional equipment is required for administration or patient care.

Accounting for the average number of Pedmarqsi doses from the COG ACCL0431 and SIOPEL 6 trials (previously reported in Table 39), this equates to a total average administration cost per patient of £359.84 and £280.00 respectively.

B.3.6.2 Health state unit costs and resource use

Health state costs in the model include the cost of hearing assessments, hearing loss management (hearing aids, cochlear implants, and FM systems), speech and language therapy costs, and the costs associated with depression and anxiety.

B.3.6.2.1 Hearing assessment

The frequency of audiology assessment per health state for children aged 6-17 were sourced from Dionne *et al*. 2012[14], a study which assessed the economic impact of a test to determine if a cisplatin-treated paediatric patient would develop ototoxicity, which aligns with the licensed population being considered in this cost-effectiveness analysis. Interviews with audiologists in 2018 verified these inputs, and also provided the frequency of assessments for patients aged under five years old and over 18 years old.[38] The unit costs were sourced from the NHS Cost Collection 2021/2022.[66] These model inputs are presented in Table 41.

Table 41. Hearing assessment unit costs and resource use included in the model

Resource	Health state	Frequency (per cycle)			Unit cost		Frequency source	Cost source
		0-5 years	6-17 years	≥18 years	1 month to <18 years	≥18 years		
Audiology assessment	Mild HL	2.00	1.00	0.25	£144.14	£132.09	6-17 years old: Dionne *et al*. 2012[14] and verified by interviews with audiologists in 2018[38] 0-5 and >18 years old: Assumption verified by interviews with audiologists in 2018[38]	NHS Cost Collection 21/22[66] – CA37B (Audiometry and Hearing Assessment, between 5 and 18 years) and CA73C (Audiometry and Hearing Assessment, 4 years and under) for 0-18 years old; CA37A (Audiometry and Hearing Assessment, 19 years and over) for 18+ years old
	Moderate HL							
	Marked HL	3.00						
	Severe HL							

Abbreviations: HL – hearing loss; NHS – National Health Service

B.3.6.2.2 Hearing loss management

The costs and resource use corresponding to hearing aids, FM systems and cochlear implants are summarised in Table 42. Costs were sourced from the NHS Cost Collection 2021/2022[66] and published literature (Cutler *et al*. 2021,[68] TA566,[58] Bond *et al*. 2009[48] and Dionne *et al*. 2012[14]). Whilst the Company understand that the preference is to extract cost data from the NHS Cost Collection, it was not always possible, so for costs associated with cochlear implants these were taken from Bond *et al*. 2009[48] (the cost-effectiveness analysis used to inform TA166 and subsequently TA566),[58] and inflated from 2009 using the NHSCII.[108] Similarly, costs associated with FM systems were sourced from Dionne *et al.* 2012,[14] inflated using the OECD CPI[70] and converted to GBP using OECD PPP.[109] Data for the percentage of patients requiring these management strategies were also sourced from published literature (Dionne *et al*. 2012,[14] Chorozoglou *et al*. 2018[110]) and interviews with audiologists in 2018.[38]

Published literature shows that on average, hearing aids are replaced every four years, whilst FM systems are replaced every five years.[14] Therefore from year two onwards in the model, an average annual costs is calculated for hearing aids and FM systems based on the replacement frequency, and applied to the percentage of patients requiring these management strategies in each health state.

A report from NHS England cochlear implantation services states that the external processor of a cochlear implant is replaced on average every five years to ensure the technology is kept up to date.[111] Therefore from year two onwards in the model, an average annual cost is calculated for the external processor replacement, and applied to the percentage of patients requiring cochlear implants in each health state. However, Bond *et al*. 2009 reported that the external component of a cochlear implant is under warranty for free repairs/replacements for three years,[48] therefore during the first three years from initial implantation, the model does not account for external processor replacement costs and only the annual maintenance and programming cost is applied.

Although not common, the internal component of a cochlear implant can sometimes fail which requires replacement and re-implantation.[48] Analysis of internal device failure is commonly presented in the form of cumulative survival graphs which show the proportions of cochlear implants which survive to a particular point in time, as shown in Bond *et al*. 2009 (Figure 11).[48] This graph was digitized and then used in the model to determine the probability of internal cochlear implants requiring replacement in each cycle of the model. Due to a lack of data being available after 40 years post initial implantation, a last observation carried forward approach was used whereby the probability of replacement in years 40+ of the model was assumed equal to the probability of replacement in year 40. Similar to the external components, the internal components are reported to be under warranty for 10 years,[48] therefore during the first 10 years from initial implantation, the model does not account for the cost of the internal electrode and only applies the costs associated with re-implantation.

Figure 11: Cumulative survival of the internal component of a cochlear implant[48]

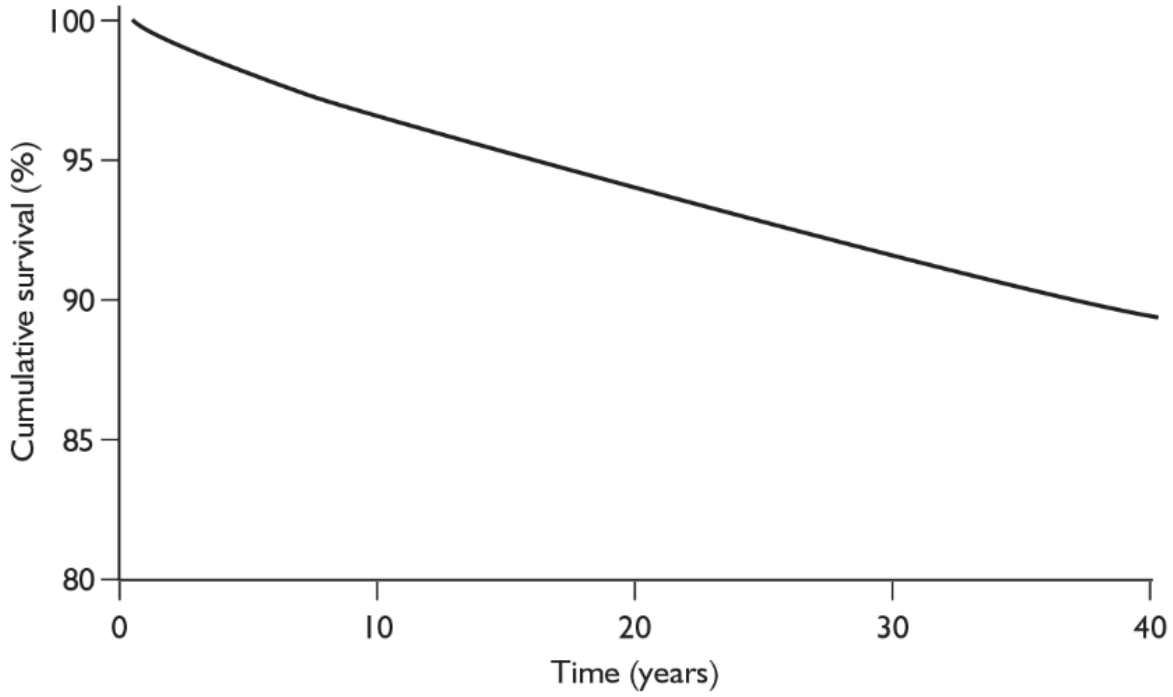


Table 42. Hearing loss management unit costs and resource use included in the model

Resource	% patients requiring treatment	Unit cost		Frequency source	Cost source
		1 month to <18 years	≥18 years		
Hearing aid	Mild HL: 50% Moderate HL: 100% Marked HL: 94% Severe HL: 48% Replacement frequency: 4 years	Hearing aid: £298.88 Fitting: £121.70 Follow-up: £159.77	Hearing aid: £243.62 Fitting: £128.08 Follow-up: £76.08	Mild HL: Audiologist report 2018[38] Moderate HL, Marked HL & Severe HL: Calculation based on one minus the percentage receiving cochlear implants in these health states Replacement frequency: Dionne *et al*. 2012[14] and validated in interviews with audiologists in 2018[38]	Hearing aid: NHS Cost Collection 21/22[66] – AS07 (<18 years old), weighted average of AS05 and AS06 (≥18 years old) Fitting: NHS Cost Collection 21/22[66] – AS02 (<18 years old), AS01 (≥18 years old) Follow-up: NHS Cost Collection 21/22[66] – AS09 (<18 years old), AS08 (≥18 years old).*
Cochlear implant	Mild HL: 0% Moderate HL: 0% Marked HL: 6% Severe HL: 52% Replacement frequency for the external processor**: 5 years Replacement frequency for the internal electrode: based on survival curve (see Figure 11)	Initial pre-implantation: £2,145.45 Initial bilateral cochlear implant (including external processor): £40,897.68 Initial fitting: £7,305.66 Annual maintenance and programming: £377.98 Replacement external processor: £5,757.75	Maintenance and programming: £377.98 Replacement external processor: £5,757.75 Replacement internal electrode: £20,290.69 Re-implantation of internal electrode: £3,938.34	Mild HL & Moderate HL: Assumption Marked HL & Severe HL: Chorozoglou *et al*. 2018[110] Replacement frequency: NHS England cochlear implantation services[100] and Bond *et al*. 2009[48]	Initial pre-implantation: Cutler *et al*. 2021[68] Initial bilateral cochlear implant: TA566[58] Initial fitting: Bond *et al*. 2009[48] inflated from 2009 Annual maintenance and programming: NHS Cost Collection 21/22[66] – AS13 and AS11 Replacement external processor, replacement internal electrode and re-implantation of

Resource	% patients requiring treatment	Unit cost		Frequency source	Cost source
		1 month to <18 years	≥18 years		
		Replacement internal electrode: £20,290.69 Re-implantation of internal electrode: £4,870.44			internal electrode: Bond *et al*. 2009[48] inflated from 2009
FM system	Mild HL: 100% Moderate HL: 100% Marked HL: 100% Severe HL: 100% Replacement frequency: 5 years	Binaural system: £2,333.37 Microphone replacement: £218.75 Annual cost of maintenance/repairs: £116.67		Audiologist report 2018[38]	Dionne *et al*. 2012[14] inflated from 2012 and converted to GBP

*Hearing aid costs extracted from NHS Cost Collection 21/22 are assumed to be per hearing aid. Hearing aid costs are therefore doubled for bilateral hearing loss.
**It is assumed that only the external processor of the cochlear implant is replaced
Abbreviations: FM – Frequency modulation; GBP – Great British Pounds; HL – Hearing loss; NHS – National Health Service

B.3.6.2.3 Speech and language therapy

The costs and resource use associated with speed and language therapy are presented in Table 43. The number of sessions per person, per cycle were sourced from Dionne *et al*. 2012[14] and Smulders *et al*. 2016[69], whilst the unit cost per session was obtained from the NHS Cost Collection 2021/2022.[66] Dionne *et al*. 2012[14] estimated the economic impact of a test to determine if a cisplatin-treated paediatric patient would develop ototoxicity, and therefore the study population aligns with the licensed population being considered in this cost-effectiveness analysis. Meanwhile, Smulders *et al*. 2016 focused on adult patients receiving cochlear implants,[69] therefore whilst not aligned to the licensed population for Pedmarqsi, this study provides a better estimate of speech and language therapy resource use for patients when they reach adulthood.

Table 43. Speech and language therapy unit costs and resource use included in the model

Resource	Frequency (per person, per cycle)		Unit cost		Frequency source	Cost source
	1 month to <18 years	≥18 years	1 month to <18 years	≥18 years		
Speech and language therapy	Mild HL: 0.00 Moderate HL: 0.00 Marked HL: 52.14 Severe HL: 52.14	Mild HL: 0.00 Moderate HL: 0.00 Marked HL: 0.00 Severe HL: 0.90	£143.21	£128.16	Dionne *et al*. 2012[14] Smulders *et al*. 2016[69]	NHS Cost Collection 21/22[66] – A13C1 (Speech and Language Therapist, Child, One to One) and A13A1 (Speech and Language Therapist, Adult, One to One).

Abbreviations: HL – Hearing loss; NHS – National Health Service.

B.3.6.2.4 Depression and anxiety

The percentage of patients who experience depression and anxiety within each health state, and associated unit costs are presented in Table 44. The SLR did not contain any sources which could be used to inform the percentage of hearing loss patients experiencing depression and anxiety, therefore TLR searches were conducted.

The TLR process identified Gurney *et al.* (2007)[112], a report from the COG assessing the hearing loss, QoL, and academic problems in childhood neuroblastoma survivors. Deemed an appropriate source to inform this aspect of the model as it considered children (mean age of 12.1 years) with neuroblastoma, which is one of the top five most prevalent paediatric tumours to be treated with cisplatin in England and Wales (Table 30), and presents a meaningful overlap with the population of interest. The study reports that 11/43 (25.58%) patients with hearing loss of all severities experienced depression, meanwhile 14/94 (14.89%) patients without hearing loss had depression. Although the study also reports the incidence of anxiety, this was not considered in the model to prevent the possibility of double counting those that suffer from both depression and anxiety.

The unit cost for depression and anxiety was calculated from a NICE resource impact statement on depression and anxiety disorder.[113] The resource impact statement reported the total eligible population of people with depression and anxiety in England in 2015 (847,858), along with the estimated total cost of treatment (£133,706,308). This was used to calculate the cost per patient in 2015, which was then inflated using the NHSCII.[70]

Table 44: Depression and anxiety unit costs and resource use included in the model

Resource	% of patients experiencing depression	Unit cost	Frequency source	Cost source
Depression and anxiety	Minimal/no HL: 14.89% Mild HL: 25.58% Moderate HL: 25.58% Marked HL: 25.58% Severe HL: 25.58%	£196.65	Gurney *et al.* (2007)[112]	NICE resource impact statement: depression and anxiety disorder,[113] inflated from 2015

Abbreviations: HL – Hearing loss; NICE – National Institute for Health and Care Excellence

B.3.6.3 Adverse reaction unit costs and resource use

The unit costs associated with the management of AEs were sourced from the NHS Cost Collection 2021/2022 in combination with published literature.[58,81,82,86,102,103] Table 45 summarises the costs associated with each adverse event. As described in Section B.3.4.4, the base case includes Pedmarqsi treatment-related SAEs occurring in ≥2% of patients sourced from COG ACCL0431, and as there were no AEs that met this criteria the AE costs have no impact on model results in the base case. However, Table 45 below lists the costs of all AEs that are included in the model for use in the scenarios mentioned in Section B.3.4.4. That is, Pedmarqsi treatment-related SAEs occurring in ≥2% sourced from SIOPEL 6, and AEs graded CTCAE category 3+ and occurring in ≥10% in either arm sourced from COG ACCL0431. The unit cost of each AE is applied to the incidence rate within each treatment arm (as described in Section B.3.4.4 and Table 35). The total weighted cost per treatment arm was calculated and applied as a one-off cost within the first cycle of the economic model

following the assumption that all key paediatric cancer types are treated with cisplatin (and therefore Pedmarqsi) for no more than one year.

Table 45: Adverse event costs included in the model

Adverse event	Cost per adverse event	Source
Neutrophil count decreased	£2,335.50	NHS Cost Collection 21/22[66] – NESS and NELS – SA35A-E – Agranulocytosis*
Haemoglobin decreased	£855.35	Assumed equal to anaemia
Infection	£4,877.51	NHS Cost Collection 21/22[66] – NESS and NELS – WHO7C-D – Infections or Other Complications of Procedures, with Single Intervention*
Febrile neutropenia	£10,491.61	NHS Cost Collection 21/22[66] – Elective, NESS and NELS – PM45A-D – Paediatric Febrile Neutropenia with Malignancy*
White blood cell count decreased	£2,335.50	NHS Cost Collection 21/22[66] – NESS and NELS – SA35A-E – Agranulocytosis*
Platelet count decreased	£948.21	NHS Cost Collection 21/22[66] – NESS, NELS, day case and regular day or night admissions – SA12G-K – Thrombocytopenia*
Alanine aminotransferase increased	£2,035.25	Telford *et al*. 2019[91] inflated from 2019
Lymphocyte count decreased	£1,079.47	Campone *et al*. 2014[114] inflated from 2014 and converted to GBP
Anaemia	£855.35	NHS Cost Collection 21/22[66] – NESS, NELS, day case and regular day or night admissions – SA04G-L – Iron Deficiency Anaemia*
Hypokalaemia	£2,044.64	Shao *et al*. 2022[90]
Hypophosphatemia	£2,044.64	Assumed equal to hypokalaemia
Hyponatremia	£1,873.79	Corona *et al*. 2016[95] inflated from 2016 and converted to GBP
Stomatitis	£2,046.53	Wong *et al*. 2018[115] inflated from 2018 and converted to GBP
Hypersensitivity	£541.61	NHS Cost Collection 21/22[66] – Elective, NESS, NELS, day case and regular day or night admissions – WH05Z – Allergy or Adverse Allergic Reaction*

*Weighted average of costs based on the number of finished consultant episodes and the national average unit cost associated with each code. Abbreviations: GBP – Great British Pounds; NELS – Non-elective long stay; NESS – Non-elective short stay; NHS – National Health Service.

B.3.6.4 Societal costs and resource use

Cisplatin-indued ototoxicity has a significant negative impact on diagnosed patients and caregivers. As such, in addition to direct costs, a scenario has been explored to consider the societal impact of cisplatin-induced ototoxicity. This included the cost of education and productivity losses for hearing loss patients and their parents (Table 46).

Education costs were sourced from Chorozoglou *et al*. 2018 which reported the percentage of patients with moderate, severe and profound hearing loss attending various types of schools (mainstream schools, mainstream school with unit for deaf, special school for deaf, other special school, residential school), as well as the unit cost of each type of school.[110] These values were used to inform the incremental education costs for the Moderate HL, Marked HL and Severe HL health states compared to the Minimal/no HL health state. As there was no resource use available for the Mild HL health state it was assumed that there was no incremental education cost for Mild HL patients compared to Minimal/no HL patients. Education costs were applied to all patients aged five to 18, based on information on the Gov.uk school admissions website.[116]

Chorozoglou *et al*. 2018 also reported the productivity loss for parents of patients with different hearing loss severities,[110] which was used for the societal perspective scenario. The productivity loss of hearing loss patients once they reach working age was also included in the scenario, and was based on the expected relative reduction in work for patients (sourced Dionne *et al*. 2012[14]), and the average full-time and part-time salary in the UK (sourced from and the ONS[117]). The results of this scenario analysis are provided in Table 56. Inclusion of education costs and not productivity costs was also included as a separate scenario, given that this represents a significant cost to Governmental bodies.

Table 46: Societal unit costs and resource use included in scenario analysis

Resource	Resource use		Annual unit cost	Frequency source	Cost source
Education (included under societal perspective scenario and education cost scenario)	Starting age: 5 years Ending age: 18 years		Incremental education cost: Mild HL: £0.00 Moderate HL: £10,601.98 Marked HL: £25,725.06 Severe HL: £58,394.86	Starting and ending age: Gov.uk school admissions[116]	Chorozoglou *et al*. 2018[110] inflated from 2018
Productivity loss for parents (included under a societal perspective scenario only)	N/A		Mild HL: £0.00 Moderate HL: £16.88 Marked HL: £49.75 Severe HL: £82.61	N/A	Chorozoglou *et al*. 2018[110] (Marked is calculated as the average of ‘’moderate’ and ‘profound’ in the publication), inflated from 2018
Productivity loss for patients when they reach working age (included under a societal perspective scenario only)	Relative reduction in work compared to England and Wales population:		Average full-time salary: £35,586.76 Average part-time salary: £12,575.38	Dionne *et al*. 2012[14] (24% is calculated as the weighted average of age groups 18-44 and 45-65)	ONS[117]
	Full-time work: Minimal/no HL: 0% Mild HL: 0% Moderate HL: 0% Marked HL: 24% Severe HL: 24%	Part-time work: Minimal/no HL: 0% Mild HL: 0% Moderate HL: 0% Marked HL: 24% Severe HL: 24%			

Abbreviations: HL – Hearing loss; ONS – Office for National Statistics

B.3.7 Severity

Given the irreversible effects of cisplatin-induced hearing loss, coupled with the fact that cisplatin ototoxicity is a side effect that can severely hinder the QoL in children, there is a clear unmet need for a treatment that can prevent cisplatin-induced hearing loss. As the first licensed therapeutic treatment for this disease, Pedmarqsi addresses this unmet need.

B.3.7.1 Severity modifier

In line with the NICE 2022 manual,[62] the absolute and proportional QALY shortfall associated with established clinical management without Pedmarqsi (i.e. cisplatin without Pedmarqsi) was calculated. Within the updated framework, differential QALY weights may be applied if the absolute or proportional shortfalls estimated lie within specified cut-off ranges (Table 47).

Table 47: QALY weightings for severity as per the NICE health technology evaluations manual

QALY weight	Proportional QALY shortfall	Absolute QALY shortfall
1	Less than 0.85	Less than 12
x1.2	0.85 to 0.95	12 to 18
x1.7	At least 0.95	At least 18

Abbreviations: NICE – National Institute of Health and Care Excellence; QALY – Quality-adjusted life year

To estimate the shortfall, the Schneider *et al*. 2021 estimator was used, which was cited by NICE as a potential option for calculating applicability of a severity modifier.[118] This tool uses ONS data from England to generate the general population survival with various sources of data to inform utility estimates. The NICE DSU guidance indicates that directly collected EQ-5D-3L using the Health Survey for England (HSE) 2014 dataset is a preferred method of capturing utility values, therefore the reference case data source in the Schneider *et al*. tool which uses directly collected EQ-5D-3L from the HSE 2014 dataset was used to represent the most recent and robust source for the base case QALY shortfall calculations.

The QALY shortfall was calculated assuming a mean age of 9 years and 39% female (as per the COG ACCL0431 baseline patient characteristics of [redacted] years old and [redacted]% female, Table 48). The expected total QALYs for the general population were calculated using the Schneider *et al*. tool reference case for general population utilities (MVH value set + HSE 2014 ALDVMM model [Hernandez Alava *et al*.]). The total expected QALYs for patients with localised solid tumours treated with cisplatin without Pedmarqsi (i.e. the current SoC) was based on the modelled cisplatin without Pedmarqsi arm of the Company base case. This value was then compared to the general population QALYs to calculate the absolute and proportional shortfall.

Table 48: Summary features of QALY shortfall analysis

Factor	Value	Reference to section in submission
Sex distribution	39% female	Section B.3.4.2
Starting age	9 years	Section B.3.4.2

Abbreviations: QALY – Quality-adjusted life year

Based on the above, the absolute QALY shortfall is estimated to be [redacted] and the proportional shortfall to be [redacted] (Table 49). The results show that this appraisal does not meet the threshold of a QALY weight of 1.2 for both absolute and proportional QALY shortfall under the current NICE cut-off threshold criteria.

Table 49: Results of the QALY shortfall analysis

General population QALY source	Expected total QALYs for the general population	Total discounted QALYs that people living with a condition would be expected to have with current treatment*	QALY shortfall	QALY weight*
Reference case: MVH value set + HSE 2014 ALDVMM [Hernandez Alava M, *et al*.]	24.18	[redacted]	Absolute: [redacted] Proportional: [redacted]	1.0x

*All calculations based on the tool developed by Schneider *et al*. 2021[118]
Abbreviations: ALDVMM – Adjusted limited dependent variable mixture model; HSE – Health Survey for England; MVH – York Measurement and Valuation of Health; QALY – Quality-adjusted life year

As demonstrated, despite the rarity and severe burden of cisplatin-induced ototoxicity outlined above, Pedmarqsi does not currently qualify for the severity modifier. This is primarily due to the fact that ototoxicity does not have an impact on the survival of cisplatin-treated patients, and the calculations do not generate enough of a difference in the long-term survival rates of paediatric cisplatin-treated patients and the general population. The results of the QALY shortfall analysis may also be due to the conservative approach not to model the disutility of the emotional burden on parents and caregivers, thereby not capturing some of the disutilities associated with current practice.

As mentioned previously, cisplatin-induced ototoxicity has a severe burden on patients. Hearing loss resulting from cisplatin chemotherapy can severely hinder the QoL for survivors of childhood cancer throughout their lifetime. Children are at increased risk of academic difficulty, social and emotional problems, and fatigue in the learning environment from even minimal hearing loss.[11] Furthermore, cisplatin-induced ototoxicity is very rare, with an estimated 222 patients in England and Wales expected to be treated in the first year (see Section B.1.3.1.3). Given that this is a very rare and severe disease that can affect a child throughout their lifetime, the Company urge NICE to consider the severe impact cisplatin-induced ototoxicity has on patients in England and Wales and the step change Pedmarqsi would present in the prevention of this disease.

B.3.8 Uncertainty

The model base case has been based on Pedmarqsi trial data, NHS and PSSRU costs databases and published literature, and has been externally validated (Section B.3.15). Extensive sensitivity analyses have been performed to test the structural and parameter uncertainty with a summary of components and approaches tested provided in Table 50 (see also Section B.3.11 for results). Scenario analyses have also been explored to determine the impact of uncertainty (Section B.3.12.3).

Table 50: Summary of variables applied and tested in the economic model

Component	Parameter grouping	Tested in OWSA?	Tested in PSA?	Tested in Scenario analysis?
Model settings	Time horizon			
	Cycle length			

Component	Parameter grouping	Tested in OWSA?	Tested in PSA?	Tested in Scenario analysis?
	Discount rates			✓
	Perspective			✓
Patient characteristics	Age at baseline	✓	✓	
	% male	✓	✓	
Efficacy	Percentage of patients experiencing hearing loss	✓	✓	✓
	Severity of hearing loss	✓	✓	✓
Safety	AE rates	✓	✓	✓
Mortality	Five-year cancer mortality	✓	✓	
	Post-cancer SMR	✓	✓	
Utilities	Health state utilities	✓	✓	✓
	AE disutilities			✓
Costs	Pedmarqsi acquisition costs			
	Pedmarqsi administration costs			
	Hearing assessment costs	✓	✓	
	Hearing aid costs	✓	✓	
	Bilateral cochlear implant costs	✓	✓	
	Speech and language therapy costs	✓	✓	
	Depression and anxiety costs	✓	✓	
	AE costs			✓

Abbreviations: AE – adverse event; OWSA – one-way sensitivity analysis; PSA – probabilistic sensitivity analysis; SMR – Standardised mortality ratio

B.3.9 Managed access proposal

The Company consider the Phase III RCTs COG ACCL0431 (assessing the efficacy of Pedmarqsi for the prevention of cisplatin-induced ototoxicity in children) and SIOPEL 6 (assessing the efficacy of Pedmarqsi in reducing ototoxicity in patients receiving cisplatin chemotherapy for standard-risk hepatoblastoma) to be suitable foundations for a decision regarding the routine commissioning of Pedmarqsi. In accordance with the trial protocols,[17,75] no further efficacy analyses are currently planned as cisplatin with Pedmarqsi demonstrated a statistically significant reduction in the proportional incidence of hearing loss compared to patients receiving cisplatin without Pedmarqsi (see section B.2.5 for more details).

B.3.10 Summary of base case analysis inputs and assumptions

B.3.10.1 Summary of base case analysis input

In the NICE reference case, the analysis was conducted from the NHS and PSS perspective using a lifetime horizon and with costs and QALYs discounted at 3.5% (B.3.2). Table 51 summarises base case variables and ranges used for probabilistic and one-way sensitivity analysis.

Table 51: Summary of base case variables applied in the economic model

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Patient characteristics			
Age (years)	[redacted]	SE: 0.69 (Gamma)	Section B.3.4.2
% male	[redacted]	Variation: 0.20 (Beta)	
Efficacy			
Percentage of patients experiencing hearing loss – Cisplatin with Pedmarqsi	28.57%	Variation: 0.20 (Beta)	Section B.3.4.3
Percentage of patients experiencing hearing loss – Cisplatin without Pedmarqsi	56.36%	Variation: 0.20 (Beta)	
Percentage of hearing loss patients with Mild HL - Cisplatin with Pedmarqsi	77.78%	Dirichlet distribution	
Percentage of hearing loss patients with Moderate HL - Cisplatin with Pedmarqsi	18.06%		
Percentage of hearing loss patients with Marked HL - Cisplatin with Pedmarqsi	1.39%		
Percentage of hearing loss patients with Severe HL - Cisplatin with Pedmarqsi	2.78%		
Percentage of hearing loss patients with Mild HL - Cisplatin without Pedmarqsi	40.78%	Dirichlet distribution	
Percentage of hearing loss patients with Moderate HL - Cisplatin without Pedmarqsi	48.12%		
Percentage of hearing loss patients with Marked HL - Cisplatin without Pedmarqsi	3.70%		

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Percentage of hearing loss patients with Severe HL - Cisplatin without Pedmarqsi	7.40%		
Mortality			
Mortality probability Year 1	[redacted]	Variation: 0.20 (Beta)	Section B.3.4.5
Mortality probability Year 2	[redacted]		
Mortality probability Year 3	[redacted]		
Mortality probability Year 4	[redacted]		
Mortality probability Year 5	[redacted]		
Post-cancer survival SMR	9.10	SE: 0.13 (Gamma)	
Length of time to apply the post-cancer survival SMR for (years)	5.00	Variation: 0.20 (Gamma)	
Utilities			
Minimal/no HL	0.92	SE: 0.00 (Beta)	Section B.3.5.6
Mild HL	0.80	Variation: 0.20 (Beta)	
Moderate HL	0.68		
Marked HL	0.63		
Severe HL	0.52		
Cancer-related disutility, on treatment (year 1)	0.15		
Cancer-related disutility, off treatment (years 2+)	0.07		
AE rates			
Neutrophil count decreased – Cisplatin with Pedmarqsi	0.00%	N/A	Section B.3.4.4
Haemoglobin decreased – Cisplatin with Pedmarqsi	0.00%		
Infection – Cisplatin with Pedmarqsi	0.00%		
Febrile neutropenia – Cisplatin with Pedmarqsi	0.00%		
White blood cell count decreased – Cisplatin with Pedmarqsi	0.00%		
Platelet count decreased – Cisplatin with Pedmarqsi	0.00%		
Alanine aminotransferase increased – Cisplatin with Pedmarqsi	0.00%		

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Lymphocyte count decreased – Cisplatin with Pedmarqsi	0.00%		
Anaemia – Cisplatin with Pedmarqsi	0.00%		
Hypokalaemia – Cisplatin with Pedmarqsi	0.00%		
Hypophosphatemia – Cisplatin with Pedmarqsi	0.00%		
Hyponatremia – Cisplatin with Pedmarqsi	0.00%		
Stomatitis – Cisplatin with Pedmarqsi	0.00%		
Hypersensitivity – Cisplatin with Pedmarqsi	0.00%		
Neutrophil count decreased – Cisplatin without Pedmarqsi	0.00%		
Haemoglobin decreased – Cisplatin without Pedmarqsi	0.00%		
Infection – Cisplatin without Pedmarqsi	0.00%		
Febrile neutropenia – Cisplatin without Pedmarqsi	0.00%		
White blood cell count decreased – Cisplatin without Pedmarqsi	0.00%		
Platelet count decreased – Cisplatin without Pedmarqsi	0.00%		
Alanine aminotransferase increased – Cisplatin without Pedmarqsi	0.00%		
Lymphocyte count decreased – Cisplatin without Pedmarqsi	0.00%		
Anaemia – Cisplatin without Pedmarqsi	0.00%		
Hypokalaemia – Cisplatin without Pedmarqsi	0.00%		
Hypophosphatemia – Cisplatin without Pedmarqsi	0.00%		
Hyponatremia – Cisplatin without Pedmarqsi	0.00%		
Stomatitis – Cisplatin without Pedmarqsi	0.00%		

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Hypersensitivity – Cisplatin without Pedmarqsi	0.00%		
AE disutilities			
Neutrophil count decreased	0.01	Variation: 0.20 (Beta)	Section B.3.5.5
Haemoglobin decreased	0.07		
Infection	0.04		
Febrile Neutropenia	0.09		
White blood cell count decreased	0.03		
Platelet count decreased	0.11		
Alanine aminotransferase increased	0.05		
Lymphocyte count decreased	0.20		
Anaemia	0.07		
Hypokalaemia	0.03		
Hypophosphatemia	0.08		
Hyponatremia	0.52		
Stomatitis	0.15		
Hypersensitivity	0.09		
AE durations (days)			
Neutrophil count decreased	40.10	Variation: 0.20 (Gamma)	Section B.3.5.5
Haemoglobin decreased	42.90		
Infection	182.50		
Febrile neutropenia	7.00		
White blood cell count decreased	42.90		
Platelet count decreased	58.30		
Alanine aminotransferase increased	28.00		
Lymphocyte count decreased	4.10		
Anaemia	42.90		
Hypokalaemia	13.00		
Hypophosphatemia	3.30		
Hyponatremia	2.00		
Stomatitis	14.00		
Hypersensitivity	7.00		
AE costs			
Neutrophil count decreased	£2,335.50	Variation: 0.20 (Gamma)	Section B.3.6.3
Haemoglobin decreased	£855.35		

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Infection	£4,877.51		
Febrile neutropenia	£10,491.61		
White blood cell count decreased	£2,335.50		
Platelet count decreased	£948.21		
Alanine aminotransferase increased	£1,850.20		
Lymphocyte count decreased	£1,079.47		
Anaemia	£855.35		
Hypokalaemia	£2,044.64		
Hypophosphatemia	£2,044.64		
Hyponatremia	£1,873.79		
Stomatitis	£2,046.53		
Hypersensitivity	£541.61		
Pedmarqsi drug costs			
Cost per 8 g vial (with PAS)*	[redacted]	Not varied	Section B.3.6.1
Mean number of Pedmarqsi doses	6.79	Not varied	
Mean 8 g vials per Pedmarqsi dose (assumes wastage)	1.87	Not varied	
Pedmarqsi administration costs			
Nurse time to administer Pedmarqsi (hours)	0.50	Not varied	Section B.3.6.1
Cost per hour of nurse time	£106.00	Not varied	
Depression and anxiety			
Percentage of patients with depression and anxiety – no hearing loss	14.89%	Variation: 0.20 (Beta)	Section B.3.6.2
Percentage of patients with depression and anxiety – hearing loss	25.58%		
Cost of depression per patient	£178.11	Variation: 0.20 (Gamma)	
Resource use			
% patients with Mild HL requiring FM system	100%	Variation: 0.20 (Beta)	Section B.3.6.2
% patients with Moderate HL requiring FM system	100%		

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
% patients with Marked HL requiring FM system	100%		
% patients with Severe HL requiring FM system	100%		
Replacement frequency for FM systems (every X years)	5.00	Variation: 0.20 (Gamma)	
% patients with Mild HL requiring hearing aids	50%	Variation: 0.20 (Beta)	
% patients with Moderate HL requiring hearing aids	100%		
% patients with Marked HL requiring hearing aids	94%		
% patients with Severe HL requiring hearing aids	48%		
Replacement frequency for hearing aids (every X years)	4.00	Variation: 0.20 (Gamma)	
% patients with Mild HL requiring cochlear implants	0%	Variation: 0.20 (Beta)	
% patients with Moderate HL requiring cochlear implants	0%		
% patients with Marked HL requiring cochlear implants	6%		
% patients with Severe HL requiring cochlear implants	52%		
Replacement frequency for the external processor of the cochlear implants (every X years)	5.00	Variation: 0.20 (Gamma)	
Length of warranty for external processor (years)	3.00		
Length of warranty for internal electrode (years)	10.00		
Frequency of audiology assessments for Mild HL and Moderate HL who are 0-5 years old (per year)	2.00	Variation: 0.20 (Gamma)	
Frequency of audiology assessments for Marked HL and Severe HL who are 0-5 years old (per year)	3.00		

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Frequency of audiology assessments for patients who are 6-18 years old (per year)	1.00		
Frequency of audiology assessments for patients who are over 18 years old (per year)	0.25		
Number of speech and language therapy sessions for Mild HL patients – under 18 (per year)	0.00	Variation: 0.20 (Gamma)	
Number of speech and language therapy sessions for Moderate HL patients – under 18 (per year)	0.00		
Number of speech and language therapy sessions for Marked HL patients – under 18 (per year)	52.14		
Number of speech and language therapy sessions for Severe HL patients – under 18 (per year)	52.14		
Number of speech and language therapy sessions for Mild HL patients – 18+ (per year)	0.00		
Number of speech and language therapy sessions for Moderate HL patients – 18+ (per year)	0.00		
Number of speech and language therapy sessions for Marked HL patients – 18+ (per year)	0.00		
Number of speech and language therapy sessions for Severe HL patients – 18+ (per year)	0.90		
Costs			
Cost of hearing assessments age 0-18 years old	£144.14	Variation: 0.20 (Gamma)	Section B.3.6.2
Cost of hearing assessments age 18+ years old	£132.09		
FM system – binaural system cost	£2,333.37	Variation: 0.20 (Gamma)	Section B.3.6.2
FM system – microphone replacement cost	£218.75		
FM system – maintenance/repairs cost	£116.67		

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Bilateral cochlear implants – initial pre-implantation cost, under 18 years old	£1,959.59	Variation: 0.20 (Gamma)	Section B.3.6.2
Bilateral cochlear implants: Initial cost of bilateral cochlear implant (including external processor), under 18 years old	£36,147.15		
Bilateral cochlear implants: Initial cost of fitting cochlear implants, under 18 years old	£6,457.06		
Bilateral cochlear implants: Annual cost of maintenance and programming, under 18 years old	£377.98		
Bilateral cochlear implants: Replacement external processor cost, under 18 years old	£5,088.95		
Bilateral cochlear implants: Replacement internal electrode cost, under 18 years old	£17,933.80		
Bilateral cochlear implants: Replacement re-implantation cost, under 18 years old	£4,304.70		
Bilateral cochlear implants: Annual cost of maintenance and programming, over 18 years old	£377.98		
Bilateral cochlear implants: Replacement external processor cost, over 18 years old	£5,088.95		
Bilateral cochlear implants: Replacement internal electrode cost, over 18 years old	£17,933.80		
Bilateral cochlear implants: Replacement re-implantation cost, over 18 years old	£3,480.87		
Hearing aids in patients 0-18 years: cost of hearing aid	£289.88	Variation: 0.20 (Gamma)	Section B.3.6.2
Hearing aids in patients 0-18 years: cost of fitting hearing aid	£121.70		
Hearing aids in patients 0-18 years: cost of hearing aid follow-up	£159.77		

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution: confidence interval (distribution)	Reference to section in submission
Hearing aids in patients over 18 years: cost of hearing aid	£243.62		
Hearing aids in patients over 18 years: cost of fitting hearing aid	£128.08		
Hearing aids in patients over 18 years: cost of hearing aid follow-up	£76.08		
Cost per speech and language therapy session – under 18	£143.21	Variation: 0.20 (Gamma)	Section B.3.6.2
Cost per speech and language therapy session – 18+	£128.16		

Abbreviations: FM – Frequency modulation; HL – Hearing loss; PAS – Patient access scheme; SE – Standard error; SMR – Standardised mortality ratio

B.3.10.2 Assumptions

Assumptions underlying the base case analysis are summarised in Table 52. The table also outlines a summary of how each assumption was tested in sensitivity or scenario analyses.

Table 52: Summary of key model assumptions

Topic	Assumption	Justification/reason	Sensitivity
Model structure	Hearing loss is irreversible.	Cisplatin chemotherapy produces toxic levels of reactive oxygen species which result in the inflammation and destruction of sensory outer hair cells, beginning at the base of the cochlear and continuing towards the cochlear apex with continued exposure.[7,8] This damage causes irreversible hearing loss which progresses in severity with continued exposure to the ototoxic agent.[2,6]	Not tested.
Cycle length	The model has a cycle length of one year.	A cycle length of one year is selected as on average, cisplatin treatment is completed within one year. This was validated by clinician feedback and is also demonstrated by the average duration of treatment in COG ACCL0431 (median of 15 weeks for patients across both treatment arms[61]). One year is also considered short enough to adequately capture and reflect changes in costs and QoL over the lifetime horizon. The model base	Not tested.

Topic	Assumption	Justification/reason	Sensitivity
		case applies a half-cycle correction* to account for uncertainty in the exact timing of transitions.	
Time horizon	A lifetime horizon is used in the model.	The base case analysis adopts a 'lifetime' horizon of [redacted] years (calculated as 100 minus the baseline age), which is considered long enough to adequately capture the lifetime of patients in this setting. The mean baseline age in the cost-effectiveness analysis is 9.2 years, which is aligned with the baseline characteristics of localised patients in COG ACCL0431.	Not tested.
Overall survival (OS)	Pedmarqsi has no impact on OS therefore no treatment-specific mortality is modelled.	Both the COG ACCL0431 and SIOPEL 6 trials measured OS as a secondary efficacy endpoint. In both trials, there was no statistically significant difference between the proportion of children who died in the cisplatin with Pedmarqsi arm and the cisplatin without Pedmarqsi arm. For more details, see Section B.2.5.	Not tested.
Cancer-specific mortality	Patients who have completed cisplatin treatment initially have an increased risk of mortality compared to the general population.	Published literature shows that children who survive from cancer are at higher risk of long-term mortality. However, there is no published literature which follows patients over their whole lifetime, and it may be unrealistic to apply this higher risk for the whole model lifetime horizon; it is likely that patients have a higher risk of mortality in the initial years following their cancer treatment. Therefore, a cancer-specific SMR is applied for five years, the duration of which is based on the cure rates reported in TA538[77] and TA817[78]. Beyond this, patients are assumed to have the same mortality as the general population.	Variations in the SMR and the length of time it is applied are tested through OWSA and PSA.
Cochlear implants	All patients receiving cochlear implants will receive bilateral	NICE guidelines TA566[58] state that bilateral cochlear implants are provided for children. It is assumed that patients who are given bilateral cochlear implants as	Not tested.

Topic	Assumption	Justification/reason	Sensitivity
	cochlear implants.	children will continue to receive them into adulthood.	
Antiemetics	Additional antiemetics are not required for Pedmarqsi administration.	The SmPC for Pedmarqsi specifies that patients should receive antiemetic medication 30 minutes prior to Pedmarqsi administration. However, in practice is it unlikely that additional antiemetic medication would be required given that patients will be receiving multiple doses of antiemetic medication for their cisplatin infusion. For this reason, the costs of antiemetics are not considered in the economic model base case on the basis that they are equal in both arms and additional antiemetic medication is not required. For more information, see Section B.3.6.1.2.	Not tested.
Health state utility values	Health state utility values are derived using the HUI3 index.	The hearing loss health state utility values are based on Barton *et al.* 2006[63] which derived utilities using the HUI3 index. It has been extensively reported in the literature that the HUI3 index is a more appropriate tool than EQ-5D for measuring HRQoL in hearing loss patients.	Variations in health state utility values are tested through OWSA and PSA.
Minimal/no HL utility value	A non-UK utility value is used for the "Minimal/no HL" health state.	To ensure alignment across health states, a HUI3 utility value was sourced for the Minimal/no HL health state. There is no UK value set for the HUI3 index, therefore the Canadian value set used in HTE6,[59] reported by Pogany *et al*. 2006[103], was used.	Alongside all other health state utility values, variations in the Minimal/no HL utility are tested through OWSA and PSA.

*Pedmarqsi acquisition, administration and antiemetic premedication costs, as well as AE costs in both treatment arms were applied in the first cycle only to all patients entering the model and therefore a half-cycle correction was not applied for these. This is a conservative approach, which assumes that patients will incur these costs even if they move to the Dead state throughout the first cycle.Abbreviations: AE – Adverse event; EQ-5D – EuroQol 5-dimensions; FM – Frequency modulation; HRQoL – Health-related quality of life; HUI – Health Utilities Index; NHS – National Health Service; NICE – National Institute for Health and Care Excellence; OWSA – One-way sensitivity analysis; PSA – Probabilistic sensitivity analysis; SMR – Standardised mortality ratio

B.3.11 Base case results

B.3.11.1 Base case incremental cost-effectiveness analysis results

The base case deterministic cost-effectiveness results for cisplatin with Pedmarqsi versus cisplatin without Pedmarqsi are presented in Table 53 (at the PAS price). The results demonstrate that, compared with cisplatin without Pedmarqsi, cisplatin with Pedmarqsi is associated with a QALY gain of 1.525. This suggests a substantial improvement in the proportional incidence of hearing loss and QoL in children receiving cisplatin chemotherapy. This benefit is associated with incremental costs of £[redacted] per patient over a lifetime, translating into an ICER of £[redacted]. The base case results for disaggregated costs by treatment arm are given in Appendix J.

Table 53: Base case results (with PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) vs. baseline
Cisplatin without Pedmarqsi	10,148.88	22.042	16.735	N/A	N/A	N/A	N/A
Cisplatin with Pedmarqsi	[redacted]	22.042	18.260	[redacted]	0.000	1.525	[redacted]

Abbreviations: ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; N/A – Not applicable; PAS – Patient access scheme; QALY – Quality-adjusted life year

B.3.12 Exploring uncertainty

B.3.12.1 Probabilistic sensitivity analysis

Joint parameter uncertainty was explored through PSA where all parameters are assigned probability distributions and varied jointly (Table 51). If variance in any inputs was not available, a simplified assumption was made assuming that the standard error was 20% of the mean value. PSA was run for 10,000 iterations, by which point, results had stabilised and therefore considered reliable to explore the uncertainty.

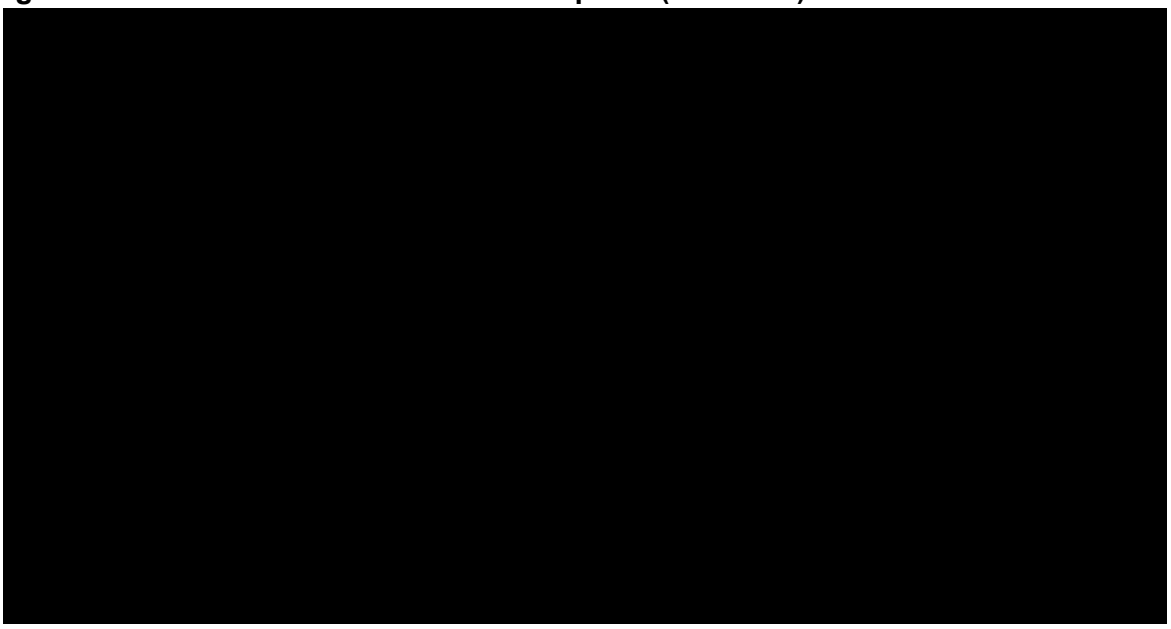
The mean results from the probabilistic analysis are presented in Table 54 and the incremental cost-effectiveness plane (ICEP) in Figure 12. The probabilistic results show consistency with the deterministic analysis providing a mean incremental QALY of 1.526 at an incremental cost of £[redacted], resulting in an ICER of £[redacted] As shown in Figure 12, the majority of iterations lie in the North-East quadrant demonstrating a positive QALY gain and confirming the clinical benefit of cisplatin with Pedmarqsi versus cisplatin without Pedmarqsi. Probabilistic results demonstrate that Pedmarqsi represents a cost-effective use of NHS resources and results are consistent with the deterministic evaluation.

Table 54: Mean PSA results (with PAS)

Technologies	Total		Incremental		ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
Cisplatin without Pedmarqsi	10,210.04	16.715	N/A	N/A	N/A
Cisplatin with Pedmarqsi	[redacted]	18.241	[redacted]	1.526	[redacted]

Abbreviations: ICER – Incremental cost-effectiveness ratio; PAS – Patient access scheme; QALY – Quality-adjusted life year

Figure 12: Incremental cost-effectiveness plane (with PAS)



Abbreviations: GBP – Great British Pounds; PAS – Patient access scheme; QALYs – Quality-adjusted life years

The Company acknowledge that, as shown in Figure 12, the results from some iterations of the PSA lie in the North-West quadrant of the ICEP, suggesting negative incremental QALYs in accompaniment to the increased incremental costs. This is caused through varying two parameters in the PSA: the percentage of patients assigned to the Minimal/no HL health state in the cisplatin with Pedmarqsi arm, and the percentage of patients assigned to the Minimal/no HL health state in the cisplatin without Pedmarqsi arm of the model. By varying these parameters simultaneously, it causes an artifact whereby in some iterations, the cisplatin without Pedmarqsi arm becomes more efficacious than the cisplatin with Pedmarqsi arm. It should be noted that the statistical confidence intervals drive this impact – no SE or 95% confidence intervals are available for these parameters, therefore a standard error of 20% of the mean value is assumed, in line with other parameters in the model. By removing these two parameters from the PSA, the cloud of results all lie in the North-East quadrant of the ICEP, as shown in Figure 13.

Figure 13: Incremental cost-effectiveness plane - assignment to the Minimal/no HL health state removed from the PSA (with PAS)

Abbreviations: GBP – Great British Pounds; HL – Hearing loss; PAS – Patient access scheme; PSA – Probabilistic sensitivity analysis; QALYs – Quality-adjusted life years

Figure 14 and Figure 15 present the cost-effectiveness acceptability curve (CEAC) and cost-effectiveness acceptability frontier (CEAF), respectively, for cisplatin with Pedmarqsi versus cisplatin without Pedmarqsi with the inclusion of the hearing loss parameters previously mentioned. At a WTP threshold of £30,000 per QALY, the probability that cisplatin with Pedmarqsi is a cost-effective treatment option is [redacted]%.

Figure 14: Cost-effective acceptability curve (with PAS)

Abbreviations: GBP – Great British Pounds; PAS – Patient access scheme

Figure 15: Cost-effectiveness acceptability frontier (with PAS)

Abbreviations: GBP – Great British Pounds; PAS – Patient access scheme

B.3.12.2 Deterministic sensitivity analysis

OWSA was conducted to test the impact of individual parameters when their values are set to the lower and upper limits of the confidence intervals (Table 51) whilst all other parameters are maintained at the base case setting. If the variance in any inputs was not available, a simplified assumption was made assuming that the standard error was 20% of the mean value. Table 55 presents the 10 parameters which had the largest impact on the ICER, and these results are also represented in a tornado plot in Figure 16.

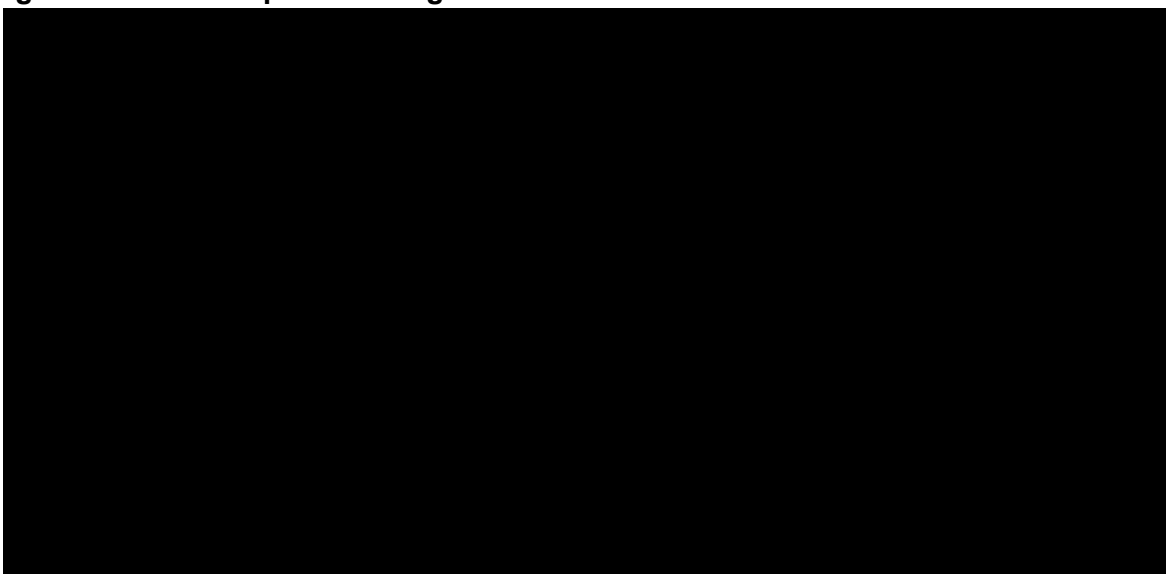
The percentage of patients with Minimal/no hearing loss in the cisplatin with Pedmarqsi treatment arm had the largest impact on the ICER followed by the percentage of patients with Minimal/no hearing loss in the cisplatin without Pedmarqsi arm. Other parameters had a marginal impact on the ICER when varied between their upper and lower bounds.

Table 55: OWSA results (with PAS)

Parameter	Base case value	Lower bound value	Upper bound value	ICER at lower bound	ICER at upper bound
Cisplatin with Pedmarqsi percentage with Minimal/no HL	0.71	0.40	0.94	£94,419.95	£19,163.16
Cisplatin without Pedmarqsi percentage with Minimal/no HL	0.44	0.27	0.61	£19,085.88	£62,168.36
Mortality probability – year 1	[redacted]	0.01	0.20	£27,460.31	£34,969.35
Barton *et al*. Utility: Moderate HL – no CI utility gain applied	0.68	0.65	0.70	£27,643.01	£32,141.83
Utility: Minimal/no HL	0.92	0.91	0.93	£30,867.78	£28,753.43
Cisplatin without Pedmarqsi severity distribution	Dirichlet	-	-	£30,764.06	£28,809.03
Cost per speech and language therapy session – under 18	143.21	£92.68	£204.56	£30,347.34	£29,014.82
Cisplatin with Pedmarqsi severity distribution	Dirichlet	-	-	£29,101.21	£30,423.21
Age	[redacted]	7.30	10.00	£29,300.87	£30,329.84
Mortality probability – year 3	[redacted]	0.02	0.05	£29,348.81	£30,252.38

Abbreviations: CI – cochlear implant; HL – hearing loss; ICER – incremental cost-effectiveness ratio; OWSA – one-way sensitivity analysis.

Figure 16: Tornado plot showing OWSA results on the ICER



Abbreviations: CI – cochlear implant; HL – hearing loss; ICER – incremental cost-effectiveness ratio.

B.3.12.3 Scenario analysis

Scenario analyses were performed to test key structural and input assumptions. A PSA was run for all scenarios where all parameters are assigned probability distributions and varied jointly under a given scenario. The results of probabilistic scenario analyses are also presented in Table 56. PSAs for all scenarios were run for 1,000 iterations. The largest deviations from the base case ICER came from changing the perspective from payer to societal. This resulted in a reduction in the base case probabilistic ICER of £ to £. The results show that in 11 out of the 15 scenarios explored, cisplatin with Pedmarqsi remained cost-effective compared to cisplatin without Pedmarqsi at a WTP threshold of £30,000.

Of note, when ran deterministically, using Gumbie *et al*. 2022[83] as the source for health state utilities resulted in an ICER of £ per QALY which is £7,216.00 less than the probabilistic ICER of £ per QALY when ran probabilistically. This is due to the significant variance in utilities when this source is selected, and in particular due to the large standard error that is reported by Gumbie *et al*. 2022[83] for severe/profound hearing loss (used for the Severe HL health state in the model). This highlights the uncertainty that results from using this source, further demonstrating Barton *et al*. (2006)[63] as the most appropriate source for utility inputs in the model.

Table 56: Scenario analysis

Parameter	Scenario number	Base case	Scenario	Incremental costs (£)	Incremental QALYs	ICER (£)	Difference from base case (£)
Base case probabilistic results				[redacted]	1.526	[redacted]	N/A
Perspective	1	Payer	Societal	[redacted]	1.521	[redacted]	[redacted]
	2		Payer with education costs included	[redacted]	1.491	[redacted]	[redacted]
Discount rate	3	3.5%	1.5%	[redacted]	2.410	[redacted]	[redacted]
Clinical efficacy source	4	COG ACCL0431 mITT	SIOPEL 6 mITT	[redacted]	2.018	[redacted]	[redacted]
	5		Orgel *et al*. 2023 re-analysis of COG ACCL0431[32]	[redacted]	1.418	[redacted]	[redacted]
Source for HL severity	6	Orgel *et al*. 2023[32] combined with Knight *et al*. 2005[11]	Orgel *et al*. 2023[32] combined with SIOPEL 6[16]	[redacted]	1.520	[redacted]	[redacted]
	7		SIOPEL 6	[redacted]	1.357	[redacted]	[redacted]
Post-cancer SMR	8	9.1 from Fidler *et al*. 2016[79]	5.6 from Laverdiere *et al*. 2009[119]	[redacted]	1.507	[redacted]	[redacted]
	9		6.2 from Suh *et al*. 2020[120]	[redacted]	1.544	[redacted]	[redacted]
Wastage	10	Wastage included	No wastage included	[redacted]	1.538	[redacted]	[redacted]
	11		New vial not costed for if less than 10% required	[redacted]	1.530	[redacted]	[redacted]
	12		New vial not costed for if less than 5% required	[redacted]	1.508	[redacted]	[redacted]
Adverse events	13	COG ACCL0431 – Pedmarqsi treatment-	COG ACCL0431 – Grade 3+ AEs occurring in >10% of patients.	[redacted]	1.549	[redacted]	[redacted]

Parameter	Scenario number	Base case	Scenario	Incremental costs (£)	Incremental QALYs	ICER (£)	Difference from base case (£)
Base case probabilistic results				[redacted]	1.526	[redacted]	N/A
		related AEs occurring in >2% of patients					
Source for utilities	14	Barton *et al*. 2006[63]	Gumbie *et al*. 2022[83]	[redacted]	1.036	[redacted]	[redacted]
Antiemetics	15	Cost of additional antiemetics not included	Cost of additional antiemetics included	[redacted]	1.539	[redacted]	[redacted]

Abbreviations: AE – Adverse event; FM – Frequency modulation; HL – Hearing loss; ICER – Incremental cost-effectiveness ratio; mITT – Modified intent-to-treat; N/A – Not applicable; QALY – Quality-adjusted life year; SMR – Standardised mortality ratio.

B.3.13 Subgroup analysis

Due to the rarity of paediatric cisplatin-induced hearing loss and the limited patient numbers from clinical trials, no subgroup analyses were performed or considered relevant for the economic evaluation. The Company consider this appraisal should be based on the full anticipated licensed population.

B.3.14 Benefits not captured in the QALY calculation

Due to the severe impact of hearing loss on patients' QoL, especially in children undergoing chemotherapy for cancer, it is likely that the introduction of Pedmarqsi as the first preventative treatment for cisplatin-induced hearing loss, would result in substantial benefits outside of both the NICE reference case and the QALY calculation.

Given the impact that Pedmarqsi would have on education costs and employment opportunities for patients, it is important to consider scenarios outside the typical NICE reference case. Based on this, the Company has provided separate scenario analyses (Table 56), which include costs from the Department for Education perspective, and from a societal perspective. Further to this, the Company has also provided a scenario which applied a 1.5% discount rate with results also available in Table 56. All these analyses improve the cost-effectiveness of Pedmarqsi which indicates that the base case analysis is conservative, and if wider perspectives on the impact of hearing loss are adopted (which are particularly relevant in the cases of education and societal costs) this only further supports that Pedmarqsi is a cost-effective treatment option.

In addition, the introduction of Pedmarqsi will result in substantial benefits outside the QALY calculation. Pedmarqsi will reduce the need for parents and caregivers of children with cancer to choose between an appropriate chemotherapy regimen which includes cisplatin and risks irreversible hearing loss, or another chemotherapy regimen which may be less efficacious in treating the cancer but reduces the risk of ototoxic hearing loss. Further, the COG ACCL0431 and SIOPEL 6 trials did not record data on the non-hearing effects of cisplatin-induced ototoxicity such as dizziness and vertigo. As such, these factors, which are also likely to affect patients' QoL, may be considered qualitatively outside the QALY calculation. Finally, the base case analysis does not include the disutility associated with the emotional burden on parents and caregivers, which is a further benefit outside the QALY calculation that has not been considered.

Given the above, the economic analysis presented in this submission is conservative as when wider perspectives are adopted, such as the inclusion of education costs, or societal costs, the cost-effectiveness improved, and the economic modelling also does not take in to account various other benefits of Pedmarqsi which are not captured in the QALY calculation.

B.3.15 Validation

B.3.15.1 Independent technical cost-effectiveness model QC

The cost-effectiveness model was quality assured by a senior health economist not involved in the model building who reviewed the model for coding errors, inconsistencies, and plausibility of inputs and outputs. The model was also subject to stress testing of extreme scenarios to test for technical modelling errors and plausibility of results.

B.3.15.2 Expert validation of cost-effectiveness analysis

Expert validation was sought for the cost-effectiveness analysis consisting of model input, protocol and structure ratification by external clinicians and a HEOR expert. Firstly, a series of interviews were conducted in 2018 with 10 audiologists from the USA (n=5) and UK (n=5) to validate inputs for early economic modelling.[38] Many of the inputs in the current cost-effectiveness analysis were validated during these interviews, and this has been indicated throughout the submission. During the development of the current cost-effectiveness model for this submission, a protocol validation meeting was held in October 2023 with a leading UK clinician in cisplatin-induced hearing loss. Additional validation on the model was undertaken after its development during a meeting in January 2024 with a HEOR expert who is an Associate Professor of Health Economics and Health Policy at PenTAG (who are a NICE EAG) and a member of NICE's Interventional Procedures Advisory. This expert provided input and validation on the methdology applied in the economic model given the available data. The following key aspects were discussed and validated:

- The model structure and appropriateness to the decision problem
- The generalisability of COG ACCL0431 and SIOPEL 6 trial data to the UK population
- Validity of model inputs including hearing loss management costs, cost and resource use
- The application of a cancer-specific SMR

Feedback from these clinical and HEOR validation meetings has been incorporated into the cost-effectiveness model.

B.3.15.3 External validation

The economic analysis conducted as part of this appraisal is, to the Company's knowledge, the first cost-effectiveness analysis in cisplatin-induced ototoxicity. This means that it is not possible to compare the outputs of this model with other economic analyses relevant to this appraisal. Additionally, because on average patients are on treatment for less than a year, the efficacy of Pedmarqsi is captured within the follow-up period of the clinical trials COG ACCL0431 and SIOPEL 6, which allows trial data to be directly modelled without any requirement to extrapolate outcomes and subsequently introduce uncertainty.

B.3.16 Interpretation and conclusions of economic evidence

The cost-effectiveness analysis developed as part of this appraised is relevant to the prevention of hearing loss in paediatric patients aged 1 month to <18 years of age with localised, non-metastatic solid tumours having cisplatin chemotherapy in England and Wales. Although there are a range of management options available for hearing loss once it has occurred, there are currently no licensed treatments for the prevention of cisplatin-induced ototoxicity in paediatric patients in the UK. Even with the hearing loss management options available, cisplatin-induced hearing loss has a severe impact on patient and carer QoL that lasts a lifetime. Therefore, Pedmarqsi would provide a step change in the care of cisplatin-treated paediatric patients in England and Wales, by being the first and only licensed

preventative treatment for ototoxicity in this population, thereby fulfilling a large unmet need and improving outcomes and life chances for patients.

A *de novo* model was developed as part of this submission. The clinical data informing the model are primarily taken from the randomised, double-blind, placebo-controlled, multicentre COG ACCL0431 trial in which 131 newly diagnosed paediatric patients across the US and Canada were randomised to either the cisplatin with Pedmarqsi arm or to the cisplatin without Pedmarqsi arm. Baseline characteristics and dose inputs were also in line with COG ACCL0431. As shown in Section B.3.4.1, the patient population of COG ACCL0431 used in the economic model is generalisable to the paediatric patients in the UK which are commonly treated with cisplatin. The inputs and structure of the model has been validated by clinical and HEOR experts, as described in Section B.3.15.2.

The cost-effectiveness analysis confirms that Pedmarqsi is expected to generate transformative and substantial clinical and economic benefits to cisplatin-treated paediatric patients. In the base case, Pedmarqsi is expected to generate 1.525 additional QALYs at an incremental cost of £[redacted], resulting in an ICER of £[redacted], within NICE's WTP threshold of £30,000.

In line with the guidance from the NICE manual (2022)[62], uncertainty has been extensively explored. The robustness of base case results was assessed through probabilistic, deterministic, and scenario analyses with results demonstrating the stability of the base case with a high level of certainty:

- PSA was performed to explore the joint parameter uncertainty. The probabilistic results are consistent with the deterministic results with a probabilistic QALY gain of 1.602 at an incremental cost of £[redacted], resulting in a probabilistic ICER of £[redacted]. At the PAS price, Pedmarqsi has a [redacted]% chance of being cost-effective at a WTP threshold of £30,000 per QALY gained.

- Parameter uncertainty was evaluated through OWSA. The analysis showed that the cost-effectiveness results are most sensitive to the percentage of patients with Minimal/no hearing loss in both treatment arms of the model. Other parameters had a marginal impact on the ICER when varied between their upper and lower bounds, with results showing that Pedmarqsi (at PAS price) is a cost-effective use of NHS resources.

- A range of probabilistic scenario analyses were performed to evaluate key model assumptions and alternative choices of inputs to test the robustness of the base case results. The model was most sensitive to the perspective applied in the model.

The *de novo* cost-effectiveness analysis has a number of strengths:

- The clinical inputs of the model are directly based on data from a well-conducted multicentre, open-label, Phase III randomised trial (COG ACCL0431) which showed statistically significant reductions in the incidence of hearing loss for patients receiving Pedmarqsi.

- The model has a relatively simple and transparent structure.

- A conservative approach has been taken for many aspects of the model for example Pedmarqsi treatment costs are applied to all patients entering the model as opposed

to patient numbers after a mid-cycle correction is applied, disease progression beyond year 1 is not modelled, and carer disutilities are not included.

- The structure and inputs of the model are aligned with prior NICE evaluations where possible. Notably, Bond *et al.* 2009 which was the economic evaluation that TA566 was based on, and HTE6 which is a NICE evaluation which also considered paediatric hearing loss patients (although not those cisplatin-induced ototoxicity).
- Extensive sensitivity analyses have been conducted including multiple scenario analyses to assess the structural uncertainty of the model. Results show that Pedmarqsi (at PAS price) is regularly cost-effective at a WTP threshold of £30,000.

Despite the steps taken to develop a robust model, the cost-effectiveness analysis has some limitations:

- There is a lack of long-term data for cisplatin-treated paediatric patients that experience hearing loss to inform long-term disease progression and mortality. As noted in Section B.3.3.1, a conservative approach has been taken whereby hearing loss deterioration has not been modelled in years 2+ of the model despite it being likely that a proportion of patients might experience a decline in hearing in line with that of the general population. Furthermore, COG ACCL0431 and SIOPEL 6 demonstrated that Pedmarqsi has no impact on OS (Section B.2.5.2) meaning that mortality is equal amongst the two treatment arms of the model, and the long-term mortality of cisplatin-treated patient has been captured through inputs sourced from published literature and previous NICE submissions (Section B.3.4.5).
- HRQoL was not measured in COG ACCL0431 and SIOPEL 6, and there are no utility values available in the literature for paediatric cisplatin-treated patients by hearing loss severity. Despite this, the source of utility values used in this cost-effectiveness analysis are aligned to those used in the NICE evaluation HTE6, and Bond *et al.* 2009 which is the economic evaluation that informed TA566. Additionally, a cancer disutility has been applied to ensure that utility values are representative of those undergoing cisplatin treatment.

The clinical studies and cost-effectiveness analysis outlined in this submission have established Pedmarqsi as the first preventative treatment for cisplatin-induced ototoxicity to demonstrate a substantial clinical and economic benefit for preventing hearing loss in paediatric patients receiving cisplatin-based chemotherapy. By preventing permanent hearing loss due to cisplatin treatment, Pedmarqsi offers an improvement in QoL for patients in a setting where there is a substantial unmet need and therefore its introduction would represent a step change in the care of cisplatin-treated paediatric patients in England and Wales.

B.4 References

1. Langer T, am Zehnhoff-Dinnesen A, Radtke S, *et al.* Understanding platinum-induced ototoxicity. *Trends Pharmacol Sci* 2013. 34: 458–469.
2. Rajput K, Edwards L, Brock P, *et al.* Ototoxicity-induced hearing loss and quality of life in survivors of paediatric cancer. *Int J Pediatr Otorhinolaryngol* 2020. 138: 110401.
3. Neuwelt EA & Brock P. Critical need for international consensus on ototoxicity assessment criteria. *J Clin Oncol* 2010. 28: 1630–1632.
4. MHRA. *Grant / Renewal of Marketing Authorisation*. (2023).
5. Brown ECM, Caimino C, Benton CL, *et al.* An audit of UK audiological practice in specialist paediatric oncology centres regarding hearing assessment of children at risk of ototoxicity due to chemotherapy. *The Journal of Laryngology & Otology* 2021. 135: 14–20.
6. Brock P, Rajput K, Edwards L, *et al.* in *Hearing Loss - From Multidisciplinary Teamwork to Public Health* (IntechOpen, 2021). doi:10.5772/intechopen.96744
7. Landier W. Ototoxicity and cancer therapy. *Cancer* 2016. 122: 1647–1658.
8. Gurney JG & Bass JK. New International Society of Pediatric Oncology Boston Ototoxicity Grading Scale for pediatric oncology: still room for improvement. *J Clin Oncol* 2012. 30: 2303–2306.
9. Ivankovich AD, Braverman B, Stephens TS, *et al.* Sodium Thiosulfate Disposition in Humans: Relation to Sodium Nitroprusside Toxicity. *Anesthesiology* 1983. 58: 11–17.
10. Neuwelt EA, Brummett RE, Remsen LG, *et al.* In vitro and animal studies of sodium thiosulfate as a potential chemoprotectant against carboplatin-induced ototoxicity. *Cancer Res* 1996. 56: 706–709.
11. Knight KRG, Kraemer DF & Neuwelt EA. Ototoxicity in Children Receiving Platinum Chemotherapy: Underestimating a Commonly Occurring Toxicity That May Influence Academic and Social Development. *JCO* 2005. 23: 8588–8596.

12. Mundayoor SA, Bhatarai P & Prabhu P. A comparison of the quality of life of parents of children using hearing aids and those using cochlear implants. *Journal of Otology* 2022. 17: 211–217.
13. Yancey A, Harris MS, Egbelakin A, *et al.* Risk Factors for Cisplatin-Associated Ototoxicity in Pediatric Oncology Patients. *Pediatr Blood Cancer* 2012. 59: 144–148.
14. Dionne F, Mitton C, Rassekh R, *et al.* Economic impact of a genetic test for cisplatin-induced ototoxicity. *Pharmacogenomics J* 2012. 12: 205–213.
15. EMA. Pedmarqsi. *European Medicines Agency* 2023. at <https://www.ema.europa.eu/en/medicines/human/EPAR/pedmarqsi>
16. SIOPEL CSR [data on file] A MULTICENTER, OPEN-LABEL, RANDOMIZED PHASE III TRIAL OF THE EFFICACY OF SODIUM THIOSULFATE IN REDUCING OTOTOXICITY IN PATIENTS RECEIVING CISPLATIN CHEMOTHERAPY FOR STANDARD-RISK HEPATOBLASTOMA. 2019.
17. *Clinical Study Protocol: SIOPEL 6*. (2013).
18. Brock PR, Knight KR, Freyer DR, *et al.* Platinum-Induced Ototoxicity in Children: A Consensus Review on Mechanisms, Predisposition, and Protection, Including a New International Society of Pediatric Oncology Boston Ototoxicity Scale. *J Clin Oncol* 2012. 30: 2408–2417.
19. Ganesan P, Schmiedge J, Manchaiah V, *et al.* Ototoxicity: A Challenge in Diagnosis and Treatment. *J Audiol Otol* 2018. 22: 59–68.
20. Foster AC, Jacques BE & Piu F. Hearing loss: The final frontier of pharmacology. *Pharmacol Res Perspect* 2022. 10: e00970.
21. Paken J, Govender CD, Pillay M, *et al.* Cisplatin-Associated Ototoxicity: A Review for the Health Professional. *Journal of Toxicology* 2016. 2016: e1809394.
22. *Pedmarqsi 80 mg/mL solution for infusion - Summary of Product Characteristics (SmPC)*. (2024). at

<https://mhraproducts4853.blob.core.windows.net/docs/9d7e056132aeb4546401b82de128113f89dcf418>

23. Doolittle ND, Muldoon LL, Brummett RE, *et al.* Delayed sodium thiosulfate as an otoprotectant against carboplatin-induced hearing loss in patients with malignant brain tumors. *Clin Cancer Res* 2001. 7: 493–500.
24. European Medicines Agency. *Committee for medicinal products for human use (CHMP)*. (2023).
25. ACCL0431 CSR [Data on file] RANDOMIZED PHASE 3 STUDY OF SODIUM THIOSULFATE (IND #72877, NSC #45624) FOR THE PREVENTION OF CISPLATIN-INDUCED OTOTOXICITY IN CHILDREN. 2019.
26. Freyer DR, Chen L, Krailo MD, *et al.* Effects of sodium thiosulfate versus observation on development of cisplatin-induced hearing loss in children with cancer (ACCL0431): a multicentre, randomised, controlled, open-label, phase 3 trial. *The Lancet Oncology* 2017. 18: 63–74.
27. Rybak L, Mukherjea D & Ramkumar V. Mechanisms of Cisplatin-Induced Ototoxicity and Prevention. *Semin Hear* 2019. 40: 197–204.
28. Wang X, Zhou Y, Wang D, *et al.* Cisplatin-induced ototoxicity: From signaling network to therapeutic targets. *Biomedicine & Pharmacotherapy* 2023. 157: 114045.
29. van As JW, van den Berg H & van Dalen EC. Medical interventions for the prevention of platinum-induced hearing loss in children with cancer. *Cochrane Database Syst Rev* 2019. 5: CD009219.
30. Knight KR, Kraemer DF, Winter C, *et al.* Early Changes in Auditory Function As a Result of Platinum Chemotherapy: Use of Extended High-Frequency Audiometry and Evoked Distortion Product Otoacoustic Emissions. *JCO* 2007. 25: 1190–1195.
31. King KA & Brewer CC. Clinical Trials, Ototoxicity Grading Scales,and the Audiologist's Role in Therapeutic Decision Making. *Int J Audiol* 2018. 57: S89–S98.

32. Orgel E, Knight KR, Villaluna D, *et al.* Reevaluation of sodium thiosulfate otoprotection using the consensus International Society of Paediatric Oncology Ototoxicity Scale: A report from the Children's Oncology Group study ACCL0431. *Pediatric Blood & Cancer* 2023. 70: e30550.
33. Clemens E, Brooks B, de Vries ACH, *et al.* A comparison of the Muenster, SIOP Boston, Brock, Chang and CTCAEv4.03 ototoxicity grading scales applied to 3,799 audiograms of childhood cancer patients treated with platinum-based chemotherapy. *PLoS One* 2019. 14: e0210646.
34. Clark JG. Uses and abuses of hearing loss classification. *ASHA* 1981. 23: 493–500.
35. NHS England. Cancer incidence. *NDRS* at <https://digital.nhs.uk/ndrs/data/data-outputs/ctya-uk-cancer-statistics-report-2021/cancer-incidence>
36. ONS. *Ethnic group by age and sex, England and Wales: Census 2021*. (2023). at <https://www.ons.gov.uk/peoplepopulationandcommunity/culturalidentity/ethnicity/articles/ethnicgroupbyageandsexenglandandwales/census2021#ethnic-group-by-age>
37. Minasian LM, Frazier AL, Sung L, *et al.* Prevention of cisplatin-induced hearing loss in children: Informing the design of future clinical trials. *Cancer Med* 2018. 7: 2951–2959.
38. Apex Healthcare Consulting. *Managing ototoxicity in paediatric cancer patients and assessment of PEDMARK from an audiology perspective: audiologist market research report for Fennec Pharmaceuticals*. (2018).
39. Fligor BJ. Pediatric Ototoxicity: Current Trends and Management. *Semin Hear* 2019. 40: 154–161.
40. Bess FH, Dodd-Murphy J & Parker RA. Children with Minimal Sensorineural Hearing Loss: Prevalence, Educational Performance, and Functional Status: *Ear and Hearing* 1998. 19: 339–354.
41. Bass JK, Knight KR, Yock TI, *et al.* Evaluation and Management of Hearing Loss in Survivors of Childhood and Adolescent Cancers: a Report from the Children's Oncology Group. *Pediatr Blood Cancer* 2016. 63: 1152–1162.

42. Khan A, Mubdi N, Budnick A, *et al.* The Experience of Hearing Loss in Adult Survivors of Childhood and Young Adult Cancer: A Qualitative Study. *Cancer* 2020. 126: 1776–1783.
43. Brinkman TM, Bass JK, Li Z, *et al.* Treatment-induced hearing loss and adult social outcomes in survivors of childhood CNS and non-CNS solid tumors: Results from the St. Jude Lifetime Cohort Study. *Cancer* 2015. 121: 4053–4061.
44. Understanding unemployment: what role does ethnicity and disability play? *Office for National Statistics* at <https://www.ons.gov.uk/visualisations/dvc2281/>
45. Marriage and civil partnership status in England and Wales - Office for National Statistics. at <https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/marriagecohabitationandcivilpartnerships/articles/marriageandcivilpartnershipstatusenglandandwalescensus2021/2023-02-22>
46. FDA. The Voice of the Patient A series of reports from the U.S. Food and Drug Administration's (FDA's) Patient-Focused Drug Development Initiative Childhood Cancer Hearing Loss. 2019. at <https://www.childhoodcancerpfdd.org/final-report>
47. NHS England. NHS England SCHEDULE 2 – THE SERVICES A. Service Specifications. D09/S/A – 230503S. 2023. at <https://www.england.nhs.uk/wp-content/uploads/2013/05/D09sa-cochlear-implantation-services.pdf>
48. Bond M, Mealing S, Anderson R, *et al.* The effectiveness and cost-effectiveness of cochlear implants for severe to profound deafness in children and adults: a systematic review and economic model. *Health Technology Assessment* 2009. 13: 1–330.
49. American Academy of Audiology. *American Academy of Audiology Position Statement and Clinical Practice Guidelines: Ototoxicity Monitoring*. (2009). at <https://audiology-web.s3.amazonaws.com/migrated/OtoMonGuidelines.pdf_539974c40999c1.58842217.pdf>
50. Lindeborg MM, Jung DH, Chan DK, *et al.* Prevention and management of hearing loss in patients receiving ototoxic medications. *Bull World Health Organ* 2022. 100: 789-796A.

51. Wheeler LR & Tharpe AM. Young Children's Attitudes Toward Peers Who Wear Hearing Aids. *Am J Audiol* 2020. 29: 110–119.
52. Brock PR, Maibach R, Childs M, *et al.* Sodium Thiosulfate for Protection from Cisplatin-Induced Hearing Loss. *New England Journal of Medicine* 2018. 378: 2376–2385.
53. ClinicalTrials.gov. *Cisplatin With or Without Sodium Thiosulfate in Treating Young Patients With Stage I, II, or III Childhood Liver Cancer (SIOPEL6)*. at <https://clinicaltrials.gov/study/NCT00652132>
54. ClinicalTrials.gov. *Sodium Thiosulfate in Preventing Hearing Loss in Young Patients Receiving Cisplatin for Newly Diagnosed Germ Cell Tumor, Hepatoblastoma, Medulloblastoma, Neuroblastoma, Osteosarcoma, or Other Malignancy*. at <https://clinicaltrials.gov/study/NCT00716976>
55. *ACCL0431 and SIOPEL 6 Pooled analysis methods [Data on file]*. (2021).
56. *ACCL0431 and SIOPEL 6 Pooled analysis results [Data on file]*. (2021).
57. EMA. *Assessment report - Pedmarqsi*. (2023). at <https://www.ema.europa.eu/en/documents/assessment-report/pedmarqsi-epar-public-assessment-report_en.pdf>
58. NICE. TA566 Overview | Cochlear implants for children and adults with severe to profound deafness | Guidance | NICE. at <https://www.nice.org.uk/guidance/ta566>
59. NICE. *Genedrive MT-RNR1 ID Kit for detecting a genetic variant to guide antibiotic use and prevent hearing loss in babies: early value assessment*. (2023). at <chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://www.nice.org.uk/guidance/hte6/resources/genedrive-mtrnr1-id-kit-for-detecting-a-genetic-variant-to-guide-antibiotic-use-and-prevent-hearing-loss-in-babies-early-value-assessment-pdf-1396174036165>
60. Project information | Sodium thiosulfate for preventing ototoxicity in people aged 1 month to 17 years with localised cancer having cisplatin chemotherapy ID1001 | Guidance | NICE. at <https://www.nice.org.uk/guidance/indevelopment/gid-ta10611>

61. FDA prescribing information - PEDMARK® (sodium thiosulfate injection), for intravenous use. 2022. at <https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/212937s000lbl.pdf>
62. 4 Economic evaluation | NICE health technology evaluations: the manual | Guidance | NICE. 2022. at <https://www.nice.org.uk/process/pmg36/chapter/economic-evaluation#discounting>
63. Barton GR, Stacey PC, Fortnum HM, *et al.* Hearing-Impaired Children in the United Kingdom, IV: Cost-Effectiveness of Pediatric Cochlear Implantation. *Ear & Hearing* 2006. 27: 575–588.
64. Chen P, Hudson MM, Li M, *et al.* Health utilities in pediatric cancer patients and survivors: a systematic review and meta-analysis for clinical implementation. *Qual Life Res* 2022. 31: 343–374.
65. UK Cochlear Implant Study Group. Criteria of Candidacy for Unilateral Cochlear Implantation in Postlingually Deafened Adults I: Theory and Measures of Effectiveness. *Ear and Hearing* 2004. 25: 310.
66. NHS England » National Cost Collection for the NHS. at <https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/>
67. Home | PSSRU. at <https://www.pssru.ac.uk/>
68. Cutler H, Gumbie M, Olin E, *et al.* The cost-effectiveness of unilateral cochlear implants in UK adults. *Eur J Health Econ* 2022. 23: 763–779.
69. Smulders YE, van Zon A, Stegeman I, *et al.* Cost–Utility of Bilateral Versus Unilateral Cochlear Implantation in Adults: A Randomized Controlled Trial. *Otology & Neurotology* 2016. 37: 38.
70. OECD. Consumer price indices (CPIs) - Complete database : Consumer prices - Annual inflation, All items non-food non-energy. at <https://stats.oecd.org/index.aspx?queryid=82183#>

71. CTYA UK Cancer statistics report 2021, Appendix and downloads. *NDRS* at <https://digital.nhs.uk/ndrs/data/data-outputs/ctya-uk-cancer-statistics-report-2021/appendix-and-downloads>
72. Edgren G, Liang L, Adami H-O, *et al.* Enigmatic sex disparities in cancer incidence. *Eur J Epidemiol* 2012. 27: 187–196.
73. Cook MB, Dawsey SM, Freedman ND, *et al.* Sex disparities in cancer incidence by time period and age. *Cancer Epidemiol Biomarkers Prev* 2009. 18: 1174–1182.
74. Cancer Research UK. *Children's cancers incidence statistics*. at <https://www.cancerresearchuk.org/health-professional/cancer-statistics/childrens-cancers/incidence#heading-Zero>
75. *Clinical Study Protocol: COG ACCL0431*. (2008).
76. Rehman AM, Ferrand R, Allen E, *et al.* Exclusion of enrolled participants in randomised controlled trials: what to do with ineligible participants? *BMJ Open* 2020. 10: e039546.
77. Overview | Dinutuximab beta for treating neuroblastoma | Guidance | NICE. 2018. at <https://www.nice.org.uk/guidance/ta538>
78. Overview | Nivolumab for adjuvant treatment of invasive urothelial cancer at high risk of recurrence | Guidance | NICE. 2022. at <https://www.nice.org.uk/guidance/ta817>
79. Fidler MM, Reulen RC, Winter DL, *et al.* Long term cause specific mortality among 34 489 five year survivors of childhood cancer in Great Britain: population based cohort study. *BMJ* 2016. 354: i4351.
80. Mortality rates (qx), by single year of age - Office for National Statistics. at <https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/mortalityratesqxbysingleyearofage>
81. Oostenbrink R, A Moll H & Essink-Bot M-L. The EQ-5D and the Health Utilities Index for permanent sequelae after meningitis. *Journal of Clinical Epidemiology* 2002. 55: 791–799.

82. Verkleij ML, Heijnsdijk EAM, Bussé AML, *et al.* Cost-Effectiveness of Neonatal Hearing Screening Programs: A Micro-Simulation Modeling Analysis. *Ear & Hearing* 2021. 42: 909–916.
83. Gumbie M, Parkinson B, Dillon H, *et al.* Cost-Effectiveness of Screening Preschool Children for Hearing Loss in Australia. *Ear & Hearing* 2022. 43: 1067–1078.
84. Borre ED, Kaalund K, Frisco N, *et al.* The Impact of Hearing Loss and Its Treatment on Health-Related Quality of Life Utility: a Systematic Review with Meta-analysis. *J GEN INTERN MED* 2023. 38: 456–479.
85. Hudgens S, Briggs A, Velikova G, *et al.* Impact of Treatment with Eribulin (Eri) or Capecitabine (Cap) for Metastatic Breast Cancer (Mbc) on Eq–5D Utility Derived from Eortc Qlq–C30. *Annals of Oncology* 2014. 25: iv360.
86. NICE. Trastuzumab deruxtecan for treating HER2-positive unresectable or metastatic breast cancer after 2 or more anti-HER2 therapies | NICE [TA704]. at <https://www.nice.org.uk/guidance/ta704>
87. NICE. *Trastuzumab deruxtecan for treating HER2-positive unresectable or metastatic breast cancer after 1 or more anti-HER2 treatments*. (2023). at <https://www.nice.org.uk/guidance/ta862>
88. Nafees B, Stafford M, Gavriel S, *et al.* Health state utilities for non small cell lung cancer. *Health and Quality of Life Outcomes* 2008. 6: 84.
89. Guidelines in the Management of Febrile Neutropenia for Clinical Practice. 2017. at <https://www.ajmc.com/view/guidelines-in-the-management-of-febrile-neutropenia-for-clinical-practice>
90. Shao T, Zhao M & Tang W. Cost-effectiveness analysis of sintilimab vs. placebo in combination with chemotherapy as first-line therapy for local advanced or metastatic oesophageal squamous cell carcinoma. *Frontiers in Oncology* 2022. 12:

91. Telford C, Bertranou E, Large S, *et al.* Cost-Effectiveness Analysis of Fulvestrant 500 mg in Endocrine Therapy-Naïve Postmenopausal Women with Hormone Receptor-Positive Advanced Breast Cancer in the UK. *Pharmacoecon Open* 2019. 3: 559–570.
92. McNamara MG, Fitzpatrick F, Smyth E, *et al.* Lymphopenia and duration of hospital stay in patients with cancer and febrile neutropenia secondary to chemotherapy. *JCO* 2008. 26: 20590–20590.
93. Schlögl M, Käch I, Beeler PE, *et al.* Trauma patients with hypokalemia have an increased risk of morbidity and mortality. *Surgery in Practice and Science* 2021. 7: 100041.
94. NICE. *Burosumab for treating X-linked hypophosphataemia in children and young people*. (2018). at <https://www.nice.org.uk/guidance/hst8>
95. Corona G, Giuliani C, Parenti G, *et al.* The Economic Burden of Hyponatremia: Systematic Review and Meta-Analysis. *The American Journal of Medicine* 2016. 129: 823-835.e4.
96. Szymanski T. Is comprehensive medication review cost-effective for patients admitted to hospital? 2020. doi:10.25560/101598
97. Lee JJY, Kilonzo K, Nistico A, *et al.* Management of hyponatremia. *CMAJ* 2014. 186: E281–E286.
98. Lloyd A, Nafees B, Narewska J, *et al.* Health state utilities for metastatic breast cancer. *Br J Cancer* 2006. 95: 683–690.
99. Plewa MC & Chatterjee K. in *StatPearls* (StatPearls Publishing, 2024). at <http://www.ncbi.nlm.nih.gov/books/NBK431059/>
100. Grutters JPC, Joore MA, van der Horst F, *et al.* Choosing between measures: comparison of EQ-5D, HUI2 and HUI3 in persons with hearing complaints. *Qual Life Res* 2007. 16: 1439–1449.

101. Yang Y, Longworth L & Brazier J. An assessment of validity and responsiveness of generic measures of health-related quality of life in hearing impairment. *Qual Life Res* 2013. 22: 2813–2828.

102. UK Cochlear Implant Study Group. Criteria of candidacy for unilateral cochlear implantation in postlingually deafened adults II: cost-effectiveness analysis. *Ear Hear* 2004. 25: 336–360.

103. Pogany L, Barr RD, Shaw A, *et al.* Health Status in Survivors of Cancer in Childhood and Adolescence. *Qual Life Res* 2006. 15: 143–157.

104. Alava MH, Pudney S & Wailoo A. ESTIMATING EQ-5D BY AGE AND SEX FOR THE UK. REPORT BY THE DECISION SUPPORT UNIT. 2022. at <https://www.sheffield.ac.uk/sites/default/files/2022-02/DSU%20Age%20based%20utility%20-%20Final%20for%20website.pdf>

105. NHS commissioning » Chemotherapy dose banding. at <https://www.england.nhs.uk/commissioning/spec-services/npc-crg/group-b/b02/chemotherapy-dose-banding/>

106. Birmingham Childrens Hospital. GUIDELINE FOR THE MANAGEMENT OF CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING. 2016. at <https://www.england.nhs.uk/mids-east/wp-content/uploads/sites/7/2018/04/antiemetic-policy-2016.pdf>

107. Drugs and pharmaceutical electronic market information tool (eMIT). *GOV.UK* 2023. at <https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit>

108. PSSRU. *Unit Costs of Health and Social Care 2021: V. Sources of Information*. (2021).

109. OECD. *Purchasing power parities (PPP) (indicator)*. at <doi: 10.1787/1290ee5a-en>

110. Chorozoglou M, Mahon M, Pimperton H, *et al.* Societal costs of permanent childhood hearing loss at teen age: a cross-sectional cohort follow-up study of universal newborn hearing screening. *bmjpo* 2018. 2: e000228.

111. NHS England. *Schedule 2 - The services. Cochlear implant implantation services (adults and children)*. (2023). at <https://www.england.nhs.uk/wp-content/uploads/2013/05/D09sa-cochlear-implantation-services.pdf>

112. Gurney JG, Tersak JM, Ness KK, *et al.* Hearing Loss, Quality of Life, and Academic Problems in Long-term Neuroblastoma Survivors: A Report From the Children's Oncology Group. *Pediatrics* 2007. 120: e1229–e1236.

113. NICE. INDICATOR DEVELOPMENT PROGRAMME (QOF) Resource impact statement: Depression and anxiety disorder. 2015. at <https://www.nice.org.uk/Media/Default/Standards-and-indicators/QOF%20Indicator%20Key%20documents/NM123-cost-impact-report.pdf>

114. Campone M, Yang H, Faust E, *et al.* Cost of adverse events during treatment with everolimus plus exemestane or single-agent chemotherapy in patients with advanced breast cancer in Western Europe. *Journal of Medical Economics* 2014. 17: 837–845.

115. Wong W, Yim YM, Kim A, *et al.* Assessment of costs associated with adverse events in patients with cancer. *PLOS ONE* 2018. 13: e0196007.

116. School admissions. *GOV.UK* at <https://www.gov.uk/schools-admissions/school-starting-age>

117. Employee earnings in the UK - Office for National Statistics. at <https://www.ons.gov.uk/employmentandlabourmarket/peopleinwork/earningsandworkinghours/bulletins/annualsurveyofhoursandearnings/2023>

118. Schneider P, McNamara S, Love-Koh J, *et al.* QALY Shortfall Calculator. 2021. at <https://shiny.york.ac.uk/shortfall>

119. Laverdière C, Liu Q, Yasui Y, *et al.* Long-term Outcomes in Survivors of Neuroblastoma: A Report From the Childhood Cancer Survivor Study. *JNCI: Journal of the National Cancer Institute* 2009. 101: 1131–1140.

120. Suh E, Stratton KL, Leisenring WM, *et al.* Late mortality and chronic health conditions in long-term survivors of early-adolescent and young adult cancers: a retrospective cohort analysis from the Childhood Cancer Survivor Study. *The Lancet Oncology* 2020. 21: 421–435.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Anhydrous sodium thiosulfate (Pedmarqsi) for preventing ototoxicity caused by cisplatin chemotherapy in people aged 1 month to 17 years with localised solid tumours [ID1001]

Summary of Information for Patients (SIP)

April 2024

File name	Version	Contains confidential information	Date
ID1001_Pedmarqsi (STS) in cisplatin induced ototoxicity _SIP 23Apr2024	1.0	No	23rd April 2024

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

- Sodium thiosulfate anhydrous (Pedmarqsi®).

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

- The UK and EU marketing authorisations for Pedmarqsi state that *Pedmarqsi is indicated for the prevention of ototoxicity induced by cisplatin chemotherapy in patients 1 month to < 18 years of age with localised, non-metastatic, solid tumours*.
- The population that is being appraised by NICE is aligned to the full indication.

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

- Marketing authorisation was granted by the European Commission on 26/5/2023, with reference to EU/1/23/1734/001. https://www.ema.europa.eu/en/documents/all-authorised-presentations/pedmarqsi-epar-all-authorised-presentations_en.pdf
- The GB marketing authorisation number is PLGB 20011/0078. MHRA (Medicines and Healthcare products Regulatory Agency) initial approval was granted on 11/10/2023. https://assets.publishing.service.gov.uk/media/653123c60b5392000da929e4/Marketing_authorisations_granted_1_October_to_14_October_2023.pdf

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

The Company has no existing collaborations with any relevant patient group.

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

What is cisplatin-induced ototoxicity?

Cisplatin is a type of platinum-based chemotherapy used to treat a variety of cancers in children and young people.[1] Following administration of cisplatin, the body produces too many harmful reactive oxygen molecules that attack and damage the outer hair cells in the ear. These cells are critical for allowing sound to travel into the brain for it to be heard. The damage starts at the bottom part of the inner ear where high-frequency (i.e., high-pitched; 4,000 to 8,000 Hz) sounds are detected, and then spreads towards the top part where lower-frequency (i.e., lower-pitched) sounds are detected.[2,3] As a patient receives more doses of cisplatin, hearing loss tends to worsen, extending to lower frequencies with continued exposure.[4,5]

Ototoxicity refers to the damaging effects that certain substances, such as medications or chemicals, can have on the inner ear, initially presenting as bilateral (i.e., in both ears), high-frequency, sensorineural (i.e., relating to the inner ear or the auditory nerve pathways in the brain) hearing loss.

How common is cisplatin-induced ototoxicity?

Pedmarqsi is indicated for the prevention of hearing loss in patients treated with a chemotherapy treatment plan containing cisplatin. Depending on how much cisplatin a child receives, around 60% of them will experience some degree of hearing loss.[6] Cisplatin is only used to treat cancer and paediatric cancer is rare, so the group of patients eligible for Pedmarqsi is very small.

Based on the number of newly diagnosed paediatric cancer cases from 2012 to 2016, there are an average of 470 solid tumour cases recorded in children and adolescents (those aged under 18 years) in England and Wales every year.[7] On average, 69.4% of these patients will have non-metastatic localised disease at the point of diagnosis (i.e., they have cancer that has not spread from its original site to other parts of the body), of which around 70% are treated with a cisplatin-containing chemotherapy. Based on these figures, it is estimated that in 2024, 222 children in England and Wales will be eligible for treatment with Pedmarqsi (the total estimated number of patients at risk from cisplatin-induced ototoxicity).

Clinical impact

Cisplatin-induced ototoxicity presents a significant clinical burden. Approximately 60% (26% to more than 90%) of children receiving cisplatin-based treatments will suffer permanent hearing damage that cannot be reversed, resulting in a potentially devastating life-long impact.[6,8] Of those patients impacted, there exists no marker (i.e., test) to determine the likelihood of experiencing hearing loss due to treatment with cisplatin-based chemotherapy. In other words, it is not possible to predict whether or how badly any particular child might be affected.

Even mild hearing loss may severely affect learning, development, and quality of life (QoL) in young children.[4] When a patient loses the ability to hear high-frequency sounds, some consonants in words become impossible to hear, such as "f," "th," "p," "k," "h," and "t". For infants and young children, this is a critical time for learning to talk and understand language, so hearing problems can have a significant impact on speech and language development and literacy.[1,9] For older children and adolescents, high-frequency hearing loss impacts educational achievement, social-emotional development, and QoL.[9]

As a result of these impacts, up to 75% of children with cisplatin-induced hearing loss become eligible for hearing aids or auditory support.[10] Even with hearing aids or auditory support, cancer survivors with cisplatin-induced hearing loss experience a range of debilitating problems, including abnormal hearing, ringing in the ears, trouble understanding speech in noisy places, but may also have difficulties in social situations resulting in an impact on mental health. Management of hearing loss using such medical devices is therefore inferior, in terms of patients' QoL, to the prevention of hearing loss altogether.[10]

Patient and caregiver impact

As described above, cisplatin-induced hearing loss has a substantial negative impact on patient QoL, particularly in younger children, hindering language development, academic success, and social integration.[11–13] Similarly, adolescents and young adults may face social isolation and

difficulty living independently due to treatment-induced hearing loss, which can exacerbate anxiety and depression amongst cancer survivors.[13,14] Caregivers of patients with hearing loss are also impacted by the condition and may experience heightened stress due to the behavioural and psychosocial challenges faced by their children, as well as the additional burden of accessing appointments and technology for their child.[15] Hearing aids and other management strategies may also cause significant financial burdens for caregivers. Further details on the impact of hearing loss on the QoL of cancer survivors and their caregivers is provided in Section 2d.

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

As cisplatin is known to cause ototoxicity, patients receiving cisplatin chemotherapy are monitored for ototoxic hearing loss via pure-tone audiometry (PTA) assessments, a diagnostic test used to measure hearing sensitivity and detect hearing loss. Ototoxicity monitoring is essential for early identification of changes in hearing; however, in current clinical practice, delayed diagnosis of hearing loss is a common issue, especially in younger patients whereby early presentation can be easily missed. This means the effects of ototoxicity often progress without detection until a noticeable decline in hearing becomes evident, especially in the frequencies crucial for understanding speech.[16]This is a poignant concern, as it must be reiterated that hearing loss caused by cisplatin-induced ototoxicity is irreversible.

Following the diagnosis that ototoxic hearing loss has occurred, the extent of decline in hearing can be quantified. This severity generally varies dependent on age at exposure and the number of doses of cisplatin received. Determining what constitutes a significant change in hearing is essential to qualify the severity of the decline. Within the existing literature, there are a range of systems that can be used to define severity. For example, in COG ACCL0431, a pivotal Pedmarqsi clinical trial, the American Speech Language and Hearing Association (ASHA) criteria was used. ASHA defines a significant change in hearing as either a ten decibel (dB) change from baseline at two consecutive frequencies, or a 20 dB change at one frequency, or loss of response at maximum audiometer outputs for three consecutive frequencies where there was previously measurable hearing.[17] In SIOPEL 6, another pivotal Pedmarqsi trial, an alternative measurement grade was used, the Brock scale. The Brock scale is one of the most widely used paediatric-specific ototoxicity scales and was specifically designed to evaluate paediatric patients treated with cisplatin, focusing on high frequencies. Hearing loss grades 0-4 reflect absolute hearing loss as opposed to a change from a baseline measurement.[17,18]

Of course, children and their parents are also pivotal to the diagnosis of hearing loss as they are often the first people to notice it and bring it to the attention of their doctors and nurses. They are also best placed to determine the impact of the hearing loss since any degree of hearing loss can be detrimental to an individual, even if formal tests classify the extent as mild.

2c) Current treatment options:

There are no existing treatments for the prevention of hearing loss caused by cisplatin-induced ototoxicity, despite the significant impact hearing loss has on patients.[19] As such, current practice for cisplatin-induced hearing loss is the management once it has already occurred, using strategies which do not reverse hearing loss, nor return hearing to a quality pre-ototoxicity. Instead, the existing management offered to patients involves the use of non-pharmacological interventions (i.e. not medicines) such as hearing aids.[2] While hearing aids can be used for a lifetime, they only amplify sounds and cannot restore normal hearing. The nature of hearing aids increasing the volume of all sounds, can mean they reduce a patient's ability to understand speech in noisy places.[14,22]

Additional technologies can be used alongside hearing aids to support patients, these include assistive devices such as auditory trainers, telephone amplifiers and audio streamers to enhance the effect of hearing aids in loud environments. However, care must be taken to ensure compatibility between these devices and the specific model of hearing aid.[2] In the UK, frequency modulation (FM) systems are provided in classrooms to support children with hearing loss in the

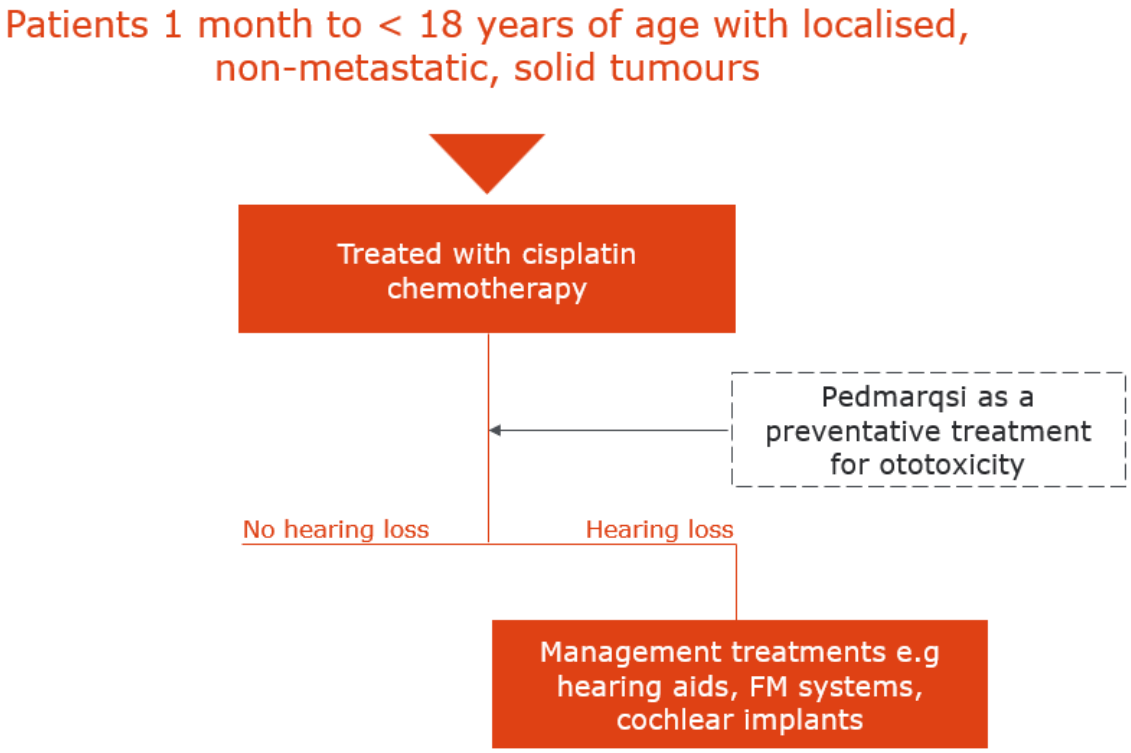
education environment. Most children also have access to personal FM devices that allow children to transmit sounds (e.g., lessons in a classroom) directly to their hearing devices.[20]

When the hearing loss is more extreme (for children with severe to profound sensorineural hearing loss who are unable to benefit from hearing aids), cochlear implants may be used.[14,22] These provide a modified sense of sound but require commitment to an audiology and speech therapy rehabilitation programme.[2] The requirement to replace these interventions presents an additional limitation; hearing aids must be replaced every four years and may also require additional amplification technology,[21] the external cochlear implant processor needs to be replaced every five years and the internal electrode is also occasionally replaced due to failure.[22,23] Meanwhile FM systems must be replaced every five years.[21]

Unlike these current strategies for managing hearing loss, Pedmarqsi is a preventative treatment that is administered before hearing loss has occurred.

The anticipated positioning of Pedmarqsi within the treatment pathway is summarised in Figure 1.

Figure 1. Anticipated positioning of Pedmarqsi in patients receiving cisplatin chemotherapy



Abbreviations: FM – Frequency modulated

2d) Patient-based evidence (PBE) about living with the condition

Impact on patient QoL

To understand the long-term impact of hearing loss on children with cancer who are receiving cisplatin chemotherapy, in-depth telephone interviews were conducted with a total of ten audiologists or audio vestibular physicians in both the US and the UK. Due to the irreversible nature of hearing loss, a substantial negative impact on patient QoL was reported. Hearing loss is particularly detrimental in younger (pre-lingual) children, as language development and general learning are dependent on hearing.[8] As such, the development of verbal and communication skills, comprehension ability and social development are all hindered in this population.[11–13] In school-aged children, problems such as poor academic performance, emotional development and self-esteem/behaviour issues commonly arise.[12,13] Similarly, social isolation and the inability to live independently are often seen in adolescents and young adults suffering from treatment-induced hearing loss.[13] The audiologist report referred to above found that among a study of adults, who were survivors of childhood cancer and who suffer from treatment-induced hearing loss, 45% had never married (compared to 37.9% for the general population) and 34% were unemployed (compared to 5.3% for non-disabled adults) or had not graduated high school.[24–26]

The challenges of hearing loss can also lead to anxiety and depressive symptoms amongst cancer survivors.[13,14] Those with hearing loss have reported feeling excluded in social settings, having social fatigue and because of these issues, preferring to avoid such social situations.[14] Such anxiety frequently leads to social exclusion and individuals feeling isolated within the social networks. Prolonged social exclusion can lead to depression and other mental health concerns which can be severely detrimental to the patient.[13,24]

Patient-based evidence is available from a published document titled “The Voice of the Patient: Childhood Cancer Hearing Loss” which covers details of a public meeting conducted as part of the Food and Drug Administration’s (FDA’s) Patient Focused Drug Development Initiative.[27] This was a meeting hosted in 2018 by four advocacy organisations in childhood cancer to share with researchers and senior officials at the FDA. The meeting aimed to assess the impact on patient’s daily lives, and their expectations and priorities for both current and future ototoxic induced hearing loss treatments.

The following quotes from cancer survivors support the concerns impacting the indicated population:

- *“Before my hearing loss, I was a happy, active, extroverted child. Now I’m too anxious or exhausted to enjoy new environments or activity. I am a lonely and typically anxious person. I’m a different person because of my hearing loss. I’ve told my parents many times that I wish I didn’t go through my cancer treatment because of my hearing loss, it makes life difficult and unbearable.”*
- *“It’s hard to pick one thing that worries me the most. One day, it might be missing something that other people my age are doing…Overall, my biggest worry about my hearing is it makes my world so much smaller.”*

Additionally, the following quote from a patient caregiver further presents concerns for patients:

- *“He works so hard to try be independent, but he finds workplace options lacking because of his hearing.”*

Beyond reporting perspectives on what the patient experiences in terms of living with hearing loss, the meeting also gathered insights into how patients currently perceive their management of deafness following cisplatin treatment. While patients use a variety of management devices, they state their effectiveness to be limited, and note significant disadvantages associated with each modality.

- Hearing aids were most widely deployed as a strategy to improve hearing following loss, however participants reported several disadvantages, including that they do not work well in noisy environments and they can fail due to battery drain or breakage as well as being uncomfortable, both physically and socially.
- While systems are in place within the educational system, e.g. FM systems, they are dependent on the compliance of teachers. Additionally, feeding into prior points on mental health impacts, these systems often make patients feel like they stand out as not only a

person with poor hearing, but also a consistent self-reminder that they are a cancer survivor.

- Finally, there were also those who were using cochlear implants. Many reported them to be extremely invasive, requiring a complete destruction of what remains of their natural hearing, leaving full reliability to the management device. Additional concerns were raised on their links to migraines and skin sensitivity.

Overall, a key conclusion from this meeting was that participants felt a significant unmet need exists for treatments that can prevent hearing loss, and the lack of effective treatment options currently available for patients.

Impact on caregiver QoL

Caregivers of patients with hearing loss, traditionally parents, relatives and teachers, are also impacted by the disease as they may face difficulty dealing with the communicative, behavioural, and social consequences of childhood hearing impairment.[15] Communication between the caregiver and the child may be poorly established, creating frustration for both parties.[15] Children with hearing impairment are also more susceptible to behavioural issues, which may create or increase stress for the parents.[15] Additionally, hearing impairment can hinder a child's psychological development and social skills, both of which contribute to increased psychological distress of their parents.[15] In addition, parents will need to navigate multiple appointments in order to obtain monitoring and services to assist their child.

SECTION 3: The treatment

3a) How does the new treatment work?

As outlined in Section 2a, cisplatin-induced ototoxicity is caused by damage to sensory cells within the inner ear. Cisplatin causes inflammation and subsequently damages these cells, which impairs the ability of them to detect sounds and send nerve signals to the brain.

Pedmarqsi is administered as a 15-minute intravenous infusion six hours after each infusion of cisplatin chemotherapy. The exact mechanism by which Pedmarqsi prevents ototoxicity is not fully understood but may involve several chemical processes which reduce the level of inflammation and damage to sensory cells within the inner ear, and subsequently Pedmarqsi protects against hearing loss when it is administered after cisplatin.

Pedmarqsi is used to prevent hearing loss caused by cisplatin ototoxicity in children aged 1 month to <18 years of age with localised, non-metastatic, solid tumours, and it does not affect the efficacy of the cancer treatment – to receive Pedmarqsi has no impact on the cancer treatment prognosis. Therefore, there has been no reported statistically significant impact of Pedmarqsi on overall survival in patients with localised, non-metastatic, solid tumours, and instead the primary clinical benefits of treatment are, as described, the prevention and reduction of hearing loss in children receiving cisplatin.[28]

Pedmarqsi is the only treatment presently available which addresses the underlying cause of cisplatin-induced hearing loss. As described above in Section 2c, the current treatment options for cisplatin-induced hearing loss only include management strategies for hearing loss once it has already occurred, such as hearing aids. However, these strategies do not restore patients' hearing fully and do not restore QoL to the level of patients with normal hearing. Therefore, there is a benefit to preventing cisplatin-induced hearing loss before it occurs using protective treatments such as Pedmarqsi. Through preventing hearing loss, Pedmarqsi would have life-long benefits for survivors of childhood cancer as childhood hearing loss is severely detrimental to QoL. The introduction of Pedmarqsi will also reduce the number of people requiring hearing loss management strategies, thereby allowing these services to be focused on people who have congenital hearing loss or hearing loss acquired through means other than ototoxicity.

3b) Combinations with other medicines

Pedmarqsi is a preventative treatment against cisplatin-induced ototoxicity and is administered exactly six hours after the end of each cisplatin infusion during chemotherapy.

There are no other medicines which are intended to be administered in combination with Pedmarqsi for the prevention of cisplatin-induced hearing loss.

3c) Administration and dosing

Pedmarqsi is intended for hospital use only and is administered under the supervision of a qualified physician. Pedmarqsi must be administered as an intravenous infusion (drip) lasting 15 minutes, ideally through a central vein which is already used for delivery of chemotherapy. It is administered six hours after the completion of every cisplatin infusion. Children will be having their cisplatin chemotherapy via an intravenous infusion and Pedmarqsi will be delivered in the same way. The dose of Pedmarqsi administered is dependent on the patient's weight and body surface area (Table 2).[29]

Table 2: Dose of Pedmarqsi

Body weight	Dose	Volume
> 10 kg	12.8 g/m^2	160 mL/m^2
5 to 10 kg	9.6 g/m^2	120 mL/m^2
< 5 kg	6.4 g/m^2	80 mL/m^2

3d) Current clinical trials

Pedmarqsi has been extensively studied in two Phase III clinical trials in children receiving cisplatin chemotherapy through the SIOPEL 6 and COG ACCL0431 clinical trials.

SIOPEL 6 was a multicentre, open-label, phase III, randomised trial assessing the efficacy and safety of Pedmarqsi in reducing ototoxicity in children. These children were receiving single agent cisplatin therapy for the treatment of standard-risk hepatoblastoma.

COG ACCL0431 was a multicentre, open-label, phase III, randomised trial assessing the efficacy of Pedmarqsi infusion for preventing hearing loss in children. These children were receiving cisplatin-containing chemotherapy regimens for the treatment of newly diagnosed germ cell tumour, hepatoblastoma, medulloblastoma, neuroblastoma, osteosarcoma, or any other solid malignancy treated with cisplatin.

A summary of both trials is provided in Table 3.

Table 3: Summary of Pedmarqsi randomised controlled trials in cisplatin-induced hearing loss

Title	Location	Population	Patient group size	Key inclusion and exclusion criteria	Completion dates	References
SIOPEL 6 (NCT00652132)	United Kingdom, Ireland, Belgium, Denmark, France, Italy, Switzerland, Spain, Australia, New Zealand, United States, Japan	Children aged >1 month to ≤18 years receiving cisplatin chemotherapy for a newly diagnosed, histologically confirmed, hepatoblastoma. Children must have had standard-risk hepatoblastoma	Cisplatin: 52 Cisplatin with Pedmarqsi: 57	Inclusion criteria: • Aged >1 month and ≤18 years • Has newly diagnosed, histologically confirmed hepatoblastoma • Has standard-risk hepatoblastoma • Has given written informed consent and received approval from the ethics committee and regulators at a local/national level • The centre/country can set up hearing tests and meet the minimum quality standards needed • Can provide necessary materials like X-rays, tissue samples, and hearing tests for central review • Females capable of bearing children must have a negative pregnancy test before starting study treatment • For any child of reproductive age, has agreed to use adequate contraception for the duration of the study Exclusion criteria: • Has high-risk hepatoblastoma • Has hepatocellular carcinoma	Primary completion: 4th September 2017 Study completion: 28th February 2018	ClinicalTrials.gov[30] Brock *et al.* 2018[31]

Title	Location	Population	Patient group size	Key inclusion and exclusion criteria	Completion dates	References
				• Had treatment starting more than 15 days from written biopsy report • Had any previous chemotherapy • Has abnormal renal function • Has recurrent disease • Has had previous hypersensitivity to Pedmarqsi • The child was unable to follow the protocol for any other reason		
COG ACCL0431 (NCT00716976)[32]	United States, Canada	Children aged ≥1 to ≤18 years newly diagnosed with any histologically confirmed germ cell tumour, hepatoblastoma, medulloblastoma, neuroblastoma, osteosarcoma, or other solid malignancy requiring cisplatin chemotherapy	Cisplatin: 64 Cisplatin with Pedmarqsi: 61	Inclusion criteria: • Aged ≥1 year and ≤18 years • Has been newly diagnosed with any histologically confirmed germ cell tumour, hepatoblastoma, medulloblastoma, neuroblastoma, osteosarcoma, or other malignancy that was to be treated with cisplatin chemotherapy • Has a chemotherapy regimen plan that included a cumulative cisplatin dose of ≥200 mg/m^2. With individual cisplatin doses to be infused over ≤6 hours • Children cannot have been enrolled in any other COG study for their disease specific treatment • Children may have been enrolled in non-COG studies or not enrolled in any therapeutic study • Has a performance score of ≥50 using Karnofsky criteria for children >16 years or age and Lansky criteria for children ≤16 years of age • Has had no previous platinum-based chemotherapy • Has completed a bone marrow transplant ≥6 months prior to enrolment • Has no evidence of active graft-versus-host disease • Has normal audiometry results prior to enrolment	Primary completion: 9th April 2015 Study completion: 30th June 2021	ClinicalTrials.gov[32] Freyer *et al.* 2017[28]

Summary of information for patients for anhydrous sodium thiosulfate (Pedmarqsi) for preventing ototoxicity caused by cisplatin chemotherapy in people aged 1 month to 17 years with localised solid tumours. [ID1001]

Title	Location	Population	Patient group size	Key inclusion and exclusion criteria	Completion dates	References
				• Has serum sodium levels within a normal range • Has adequate haematological function • Has adequate renal function • Has adequate liver function Exclusion criteria: • Females of child-bearing age must not have been pregnant. Females with germ cell tumours, which occasionally result in false-positive pregnancy tests, may have been enrolled, provided pregnancy was ruled out by other tests • Female children who were lactating must have agreed to stop breastfeeding • Children must not have had any previous hypersensitivity to Pedmarqsi or any other thiol agents • Children must not have been enrolled in any COG therapeutic for treatment of the underlying tumour		

Abbreviations: COG – Children's Oncology Group.

3e) Efficacy

SIOPEL 6

The effectiveness and safety of Pedmarqsi in children receiving cisplatin chemotherapy was established in SIOPEL 6, a trial in children with standard-risk hepatoblastoma which is a liver cancer affecting small children and babies. Standard-risk means that there are no metastases to any parts of the body outside of the liver. In this study, approximately half the children were randomly selected to receive the usual chemotherapy with cisplatin and the other half received the same cisplatin treatment in addition to a dose of Pedmarqsi six hours after the completion of each cisplatin infusion.

Pedmarqsi doses corresponded to the body weight of the child (>10 kg, 5 to 10 kg, and <5 kg received Pedmarqsi 12.8 g/m^2, 9.6 g/m^2, and 6.4 g/m^2, respectively). SIOPEL 6 demonstrated that receiving cisplatin with Pedmarqsi is associated with significant benefits to the hearing when compared to children receiving cisplatin without Pedmarqsi:

- The main result was an assessment of the proportion of children who had hearing loss when they were given Pedmarqsi (18 children, 32.7%) compared to those who did not receive Pedmarqsi (29 children, 63.0%).
    - So, the proportion of hearing loss among patients given Pedmarqsi was approximately half that of those who did not receive it. The risk of experiencing hearing loss was also statistically significantly lower in patients given Pedmarqsi compared to those who did not receive it, corresponding to a clinically meaningful 48% lower risk of having any hearing loss after Pedmarqsi treatment (relative risk: 0.519, 95% confidence interval [CI]: 0.335, 0.805; p=0.002).[31]
- As well as reducing the risk of hearing loss occurring, if hearing loss did occur, Pedmarqsi reduced the severity of any hearing loss.
    - Severity was assessed using the Brock grading system. Brock Grade 0 indicates that there is no appreciable problem with hearing, Brock Grade 1 is the least impact on hearing up to Brock Grade 4 which is severe hearing loss.
    - Of children who experienced hearing loss, 55%, 33%, 6% and 6% of children treated with Pedmarqsi experienced hearing loss at Brock Grades 1-4, respectively, whereas 41%, 38%, 18% and 3% of children treated with cisplatin without Pedmarqsi experienced hearing loss at Brock Grades 1-4, respectively.[31]
- For the secondary endpoint of overall survival from cancer, there was no clinical or statistically significant difference between the proportion of children who died during the SIOPEL 6 trial in the cisplatin with Pedmarqsi arm (2 patients, 3.5%) and the cisplatin without Pedmarqsi arm (4 patients, 7.7%).[31]

COG ACCL0431

The effectiveness and safety of Pedmarqsi in children receiving cisplatin chemotherapy was also established in COG ACCL0431, a trial in children with newly diagnosed germ cell tumour, hepatoblastoma, medulloblastoma, neuroblastoma, osteosarcoma, or any other solid tumour treated with cisplatin. As above, around half the children in this study were randomly chosen to receive the usual chemotherapy with cisplatin and the other half received the same cisplatin treatment in addition to a dose of Pedmarqsi six hours after the completion of each cisplatin infusion.

COG ACCL0431, like SIOPEL 6, demonstrated that Pedmarqsi is associated with significant benefits when compared to children receiving cisplatin without Pedmarqsi.

- The main result was an assessment of the proportion of children who had hearing loss when they were given Pedmarqsi (14 children, 28.6%) compared to those who did not receive Pedmarqsi (31 children, 56.4%).
    - So, the proportion of hearing loss among patients given Pedmarqsi was approximately half that of those who did not receive it.
    - The odds of experiencing hearing loss was also statistically significantly lower in patients given Pedmarqsi compared to those who did not receive it, corresponding to a clinically meaningful lower odds of having any hearing loss after Pedmarqsi treatment when adjusted for stratification variables.[28]

- For the secondary endpoint of overall survival from cancer, there was no clinical or statistically significant difference between the proportion of children who died between the arms of the COG ACCL0431 trial.[28]

3f) Quality of life impact of the medicine and patient preference information

QoL data were not collected in the clinical trials of Pedmarqsi (COG ACCL0431 and SIOPEL 6), and no studies collecting QoL data reported by patients have been carried out in patients treated with Pedmarqsi. In the absence of these data, QoL data for children with hearing loss were sourced from published literature sources.

The QoL of children with hearing loss decreases as the severity of hearing loss increases, as presented in a 2006 study published by Barton *et al*.[33] Utility values can range from 0 to 1, where 0 indicates death, and 1 indicates full health. The utility values used in this study were elicited using the HUI3 utility measurement, which is an appropriate tool for assessing QoL in patients with hearing loss.[34]

For the economic model (which is required for a submission to NICE; see Section 3i below) utility values for the hearing loss severity states were taken from Barton *et al.* 2006.[33] The utility value for the minimal/no hearing loss health state was taken from Pogany *et al.* 2006, which is the source of the HUI3 population norms for the Canadian general population.[35]

Health state utility values applied in the model are presented in Table 4 below and show that more severe hearing loss is associated with worse QoL. In the economic model, these values were adjusted to reflect QoL changes with age.

Table 4: Health state utility values

Health state	Utility value
Minimal/no hearing loss	0.92
Mild hearing loss	0.80
Moderate hearing loss	0.68
Marked hearing loss	0.62
Severe hearing loss	0.50

Since the utility values from the published literature used in the model are not specific to cancer patients, it is likely that they represent an overestimation of QoL for patients in the initial years following completion of their cisplatin treatment. Therefore, a cancer related utility decrement (i.e. the utility values are adjusted downwards denoting a reduction in quality of life) is applied to all health states for the first five years of the model.[36]

Pedmarqsi is expected to allow patients to maintain a higher QoL throughout their lifetimes by preventing or reducing the severity of cisplatin-induced hearing loss. Patients treated with Pedmarqsi in the economic model on average gained additional quality-adjusted life years (QALYs) over their lifetimes compared to patients treated without Pedmarqsi.

As described in Section 2d, childhood hearing loss also impacts the QoL of caregivers. Caregiver QoL was not considered in the base case of the economic evaluation. Although Pedmarqsi may have additional benefits for caregivers by alleviating the burden of caring for children with hearing loss, sufficient data are not available to support this claim without uncertainty.

Due to the severe and paediatric nature of cisplatin-induced ototoxicity, there is no information available on patients' preference or willingness to accept side effects to receive the benefit of Pedmarqsi.

3g) Safety of the medicine and side effects

It should be noted that Pedmarqsi can cause side effects, although not everybody experiences them. The safety profile of Pedmarqsi has been studied in the SIOPEL 6 trial and the COG ACCL0431 trial. In both trials, the side effects experienced by patients treated with Pedmarqsi were similar and occurred at a similar rate to side effects experienced by patients who did not

receive Pedmarqsi treatment with cisplatin chemotherapy, indicating many events are not specific to Pedmarqsi. In many cases the side effects caused by chemotherapy are similar to those caused by Pedmarqsi so it could be difficult to know which treatment was the cause.

- In the SIOPEL 6 trial, one instance of neutrophil count decreased i.e., a reduction in the number of white blood cells called neutrophils in the blood, possibly related to Pedmarqsi, and one instance probably related to Pedmarqsi, were observed. One instance of infection was attributed as probably related to Pedmarqsi and one patient discontinued treatment due to hypersensitivity i.e., experience of an allergic reaction, related to Pedmarqsi.
- In the COG ACCL0431 trial, a total of six children (10.2%) experienced side effects that were determined to be related to Pedmarqsi. These were related to:
    - Blood and lymphatic system disorders (anaemia and febrile neutropenia i.e., a medical condition characterised by fever and a low white blood cell count),
    - Blood tests showing increased levels of the liver enzymes such as transaminases, and decreased levels of white blood cells and platelets,
    - Gastrointestinal disorders (abdominal pain, colitis i.e., inflammation of the colon, nausea, stomatitis i.e., inflammation of the mucous membrane of the mouth, and vomiting).
- One patient discontinued treatment due to hypersensitivity.

Table 5 and Table 6 below present the most common side effects experienced at a severity level of Grade 3 or higher in ≥10% of patients in the SIOPEL 6 trial[37] and COG ACCL0431 trial,[38] respectively. Based on the safety results from these trials, it can be concluded that Pedmarqsi is safe and generally well-tolerated. If side effects are experienced in clinical use, clinicians may manage them by pausing or stopping treatment with Pedmarqsi completely, if the side effects are severe.

Table 5: Side effects reported in SIOPEL 6

Side effect	Patients receiving cisplatin without Pedmarqsi (N=56) n (%)	Patients receiving cisplatin with Pedmarqsi (N=53) n (%)	Total (N=109) n (%)
Any Grade 3* Severity or Higher AE	34 (60.7)	35 (66.0)	69 (63.3)
Investigations	19 (33.9)	20 (37.7)	39 (35.8)
Neutrophil count decreased	9 (16.1)	12 (22.6)	21 (19.3)
Haemoglobin decreased	9 (16.1)	10 (18.9)	19 (17.4)
Infections and infestations	15 (26.8)	14 (26.4)	29 (26.6)
Infection	15 (26.8)	14 (26.4)	29 (26.6)
Blood and lymphatic system disorders	10 (17.9)	8 (15.1)	18 (16.5)
Febrile neutropenia	9 (16.1)	8 (15.1)	17 (15.6)

Abbreviations: AE – Adverse event.
**__Grade 3 side effect__: Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care activity of daily living. __Grade 4__: Life-threatening consequences; urgent intervention indicated. __Grade 5__: Death related to side effect.*

Table 6: Side effects reported in COG ACCL0431

Side effect	Patients receiving cisplatin without Pedmarqsi (N=64) n (%)	Patients receiving cisplatin with Pedmarqsi (N=59) n (%)	Total (N=123) n (%)
Any Grade 3* Severity or Higher AE	57 (89.1)	55 (93.2)	112 (91.1)
Investigations	57 (89.1)	54 (91.5)	111 (90.2)
Neutrophil count decreased	53 (82.8)	49 (83.1)	102 (82.9)
White blood cell count decreased	42 (65.6)	38 (64.4)	80 (65.0)
Platelet count decreased	39 (60.9)	38 (64.4)	77 (62.6)
Alanine aminotransferase increased	9 (14.1)	10 (16.9)	19 (15.4)
Lymphocyte count decreased	9 (14.1)	6 (10.2)	15 (12.2)
Blood and lymphatic system disorders	38 (59.4)	32 (54.2)	70 (56.9)
Anaemia	36 (56.3)	30 (50.8)	66 (53.7)
Febrile neutropenia	19 (29.7)	14 (23.7)	33 (26.8)
Metabolism and nutrition disorders	22 (34.4)	29 (49.2)	51 (41.5)
Hypokalaemia	13 (20.3)	16 (27.1)	29 (23.6)
Hypophosphatemia	7 (10.9)	12 (20.3)	19 (15.4)
Hyponatremia	4 (6.3)	7 (11.9)	11 (8.9)
Gastrointestinal disorders	8 (12.5)	12 (20.3)	20 (16.3)
Stomatitis	4 (6.3)	8 (13.6)	12 (9.8)

Abbreviations: AE – Adverse event.
**__Grade 3 side effect__: Severe or medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; limiting self-care activity of daily living. __Grade 4__: Life-threatening consequences; urgent intervention indicated. __Grade 5__: Death related to side effect.*

3h) Summary of key benefits of treatment for patients

The introduction of Pedmarqsi will be highly beneficial for paediatric patients undergoing cisplatin chemotherapy. Currently there are no preventative treatments for cisplatin-induced ototoxicity, and therefore children are at risk of suffering from irreversible hearing loss, which has a life-long impact on their QoL. Patients suffer significantly from hearing loss in childhood as it has substantial negative impacts on their ability to learn to talk, their education, and their ability to partake in social and recreational activities.

Unlike current management strategies which can only manage the symptoms of ototoxicity once hearing loss has occurred and do not restore hearing to a normal level, Pedmarqsi addresses the underlying cause of the hearing loss and therefore represents a step change for the treatment of childhood cancer, by allowing patients to receive cisplatin chemotherapy at a lower risk of hearing loss. Pedmarqsi is the first and only licensed preventative treatment for cisplatin-induced ototoxicity for children aged 1 month to <18 years of age with localised, non-metastatic, solid tumours.

Both clinical trials for Pedmarqsi demonstrated that it is an effective preventative treatment which showed a significant reduction in the number of patients who experienced hearing loss. Both trials also showed that Pedmarqsi is safe and generally well-tolerated, as side effects that were experienced by patients receiving Pedmarqsi were similar and occurred at a similar rate to those experienced by patients who did not receive Pedmarqsi.

As outlined in Section 2d, childhood hearing loss also has a severe impact on the QoL of both patients and caregivers. Therefore, by preventing or reducing the severity of cisplatin-induced

hearing loss, Pedmarqsi is also likely to have life-long benefits for patients and for caregivers by alleviating the burden of supporting children with hearing loss.

Additionally, the clinical trials for Pedmarqsi showed that despite reducing the incidence of hearing loss, it did not have any effect on the effectiveness of cisplatin chemotherapy, meaning patients were still able to receive the full anti-tumour benefit of their chemotherapy regimens while receiving Pedmarqsi to reduce the risk of hearing loss.

3i) Summary of key disadvantages of treatment for patients

As Pedmarqsi represents a significant progression over the current established management of cisplatin-induced ototoxicity, there are very few disadvantages for patients, caregivers, and their communities.

It should be noted however that as a pharmacological intervention, Pedmarqsi may cause additional side effects which would not occur with current established management. Despite this, both Pedmarqsi clinical trials demonstrated that side effects experienced by patients receiving Pedmarqsi treatment were similar and occurred at a similar rate as those experienced by patients who did not receive Pedmarqsi, showing that it is generally a safe and well-tolerated medicine.

3j) Value and economic considerations

For a treatment to be reimbursed by the NHS, the manufacturer must provide an economic model (also called a cost-effectiveness model) to demonstrate that the treatment will provide value for money and is therefore a good use of NHS resources. An overview of the economic model for Pedmarqsi in patients with cisplatin-induced ototoxicity is provided below.

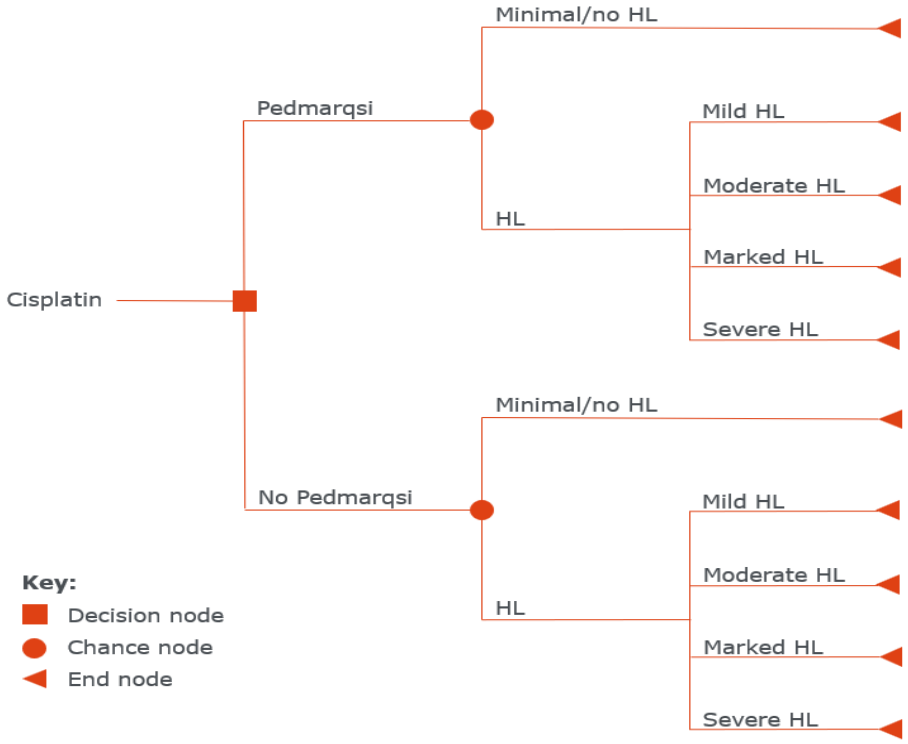
How the model reflects the condition

The economic model for this submission uses data from COG ACCL0431 and SIOPEL 6 and published literature and compares survival, QoL and costs for patients with cisplatin-induced ototoxicity receiving cisplatin with Pedmarqsi compared with cisplatin without Pedmarqsi across a lifetime period.

In the first year, to reflect the fact that cisplatin-induced ototoxicity is permanent and irreversible i.e., once the damage has occurred, patients cannot return to normal hearing, the model structure is that of a cohort-level decision tree.[5,9] A decision tree is a form of analytical model, in which distinct branches are used to represent a potential set of outcomes for a patient or patient cohort. The model consists of five hearing loss health states, reflecting varying degrees of hearing loss severity experienced by patients with cisplatin-induced ototoxicity:

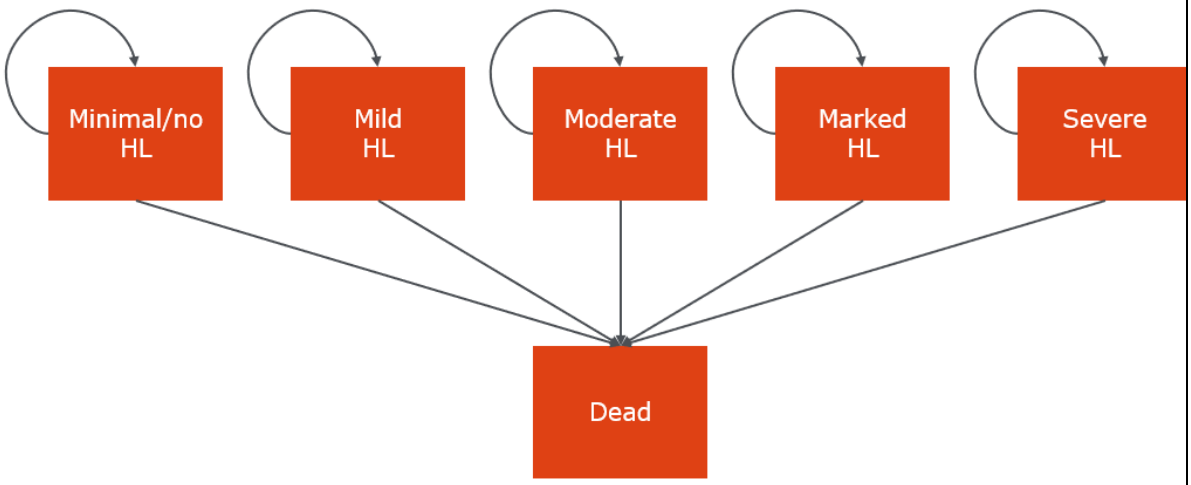
- Minimal/no hearing loss
- Mild hearing loss
- Moderate hearing loss
- Marked hearing loss
- Severe hearing loss
- Death

Figure 2: Cost-effectiveness model structure – decision tree (year 1)



Abbreviations: HL – Hearing loss

Figure 3: Cost-effectiveness model structure – post-decision tree health state model



Abbreviations: HL – Hearing loss

Patients enter the model and are said to experience or not experience measurable hearing loss due to treatment with cisplatin chemotherapy, as presented through assignment to either the minimal/no hearing loss health state or one of the hearing loss severity states (mild hearing loss, moderate hearing loss, marked hearing loss, severe hearing loss). From year two onwards, patients either stay in their respective health state for the remainder of the model time horizon i.e., keep their current level of hearing or die, transitioning out of the model and entering the 'death' state.

Summary of information for patients for anhydrous sodium thiosulfate (Pedmarqsi) for preventing ototoxicity caused by cisplatin chemotherapy in people aged 1 month to 17 years with localised solid tumours. [ID1001]

Each health state is associated with specific healthcare resource use and costs, survival and QoL (referred to as "utility"). Patients in the minimal/no hearing loss health state feel better, i.e., have higher utility than those in the severe hearing loss health state.

As mentioned in Section 3e, Pedmarqsi is used to prevent hearing loss caused by cisplatin ototoxicity and there was no reported impact of Pedmarqsi on overall survival in COG ACCL0431 and SIOPEL 6. As such, the mortality estimates in the cost-effectiveness model are not dependent on treatment and the primary clinical benefits of treatment are the prevention and reduction of hearing loss in children receiving cisplatin.[28]

Modelling how much a treatment improves quality of life

Pedmarqsi is expected to greatly improve the opportunities and prospects for children receiving chemotherapy for the treatment of cancer, therefore improving patient QoL. The QoL benefit expected with Pedmarqsi is captured in the economic model, where patient QoL varies based on health state and treatment received.

QoL data were not collected in the clinical trials of Pedmarqsi (COG ACCL0431 and SIOPEL 6); therefore, for the model base case, utility values for the hearing loss severity states were taken from Barton *et al.* 2006,[33] and adjusted to reflect QoL changes with age. Health state utility values derived from this study show that more severe hearing loss is associated with worse QoL. The utility value for the minimal/no hearing loss health state of the model was taken from Pogany *et al.* 2006, which is the source of the HUI3 population norms for the Canadian general population.[35]

Since the utility values from the published literature used in the model are not specific to cancer patients, it is likely that they represent an overestimation of QoL for patients in the initial years following completion of their cisplatin treatment. Therefore, a cancer related adjustment is applied to all health states for the first five years of the model.[36]

The economic model shows that cisplatin with Pedmarqsi is associated with modelled QoL benefit compared to cisplatin without Pedmarqsi.

Modelling how much costs of treatment differ with the new treatment

Costs considered in the model for both treatment arms include treatment costs, health state costs i.e., monitoring and resource use costs, and adverse event (AE) costs. In addition to direct costs, cisplatin-induced ototoxicity has a significant negative impact on diagnosed patients and caregivers and therefore a scenario is explored to consider the societal impact of cisplatin-induced ototoxicity, inclusive of the cost of education and productivity losses.

Health state costs considered in the model include the cost of hearing assessments, hearing loss management (hearing aids, cochlear implants and FM systems), speech and language therapy costs, and the costs associated with anxiety and depression.

The total costs associated with cisplatin with Pedmarqsi are higher than the total costs associated with cisplatin without Pedmarqsi. Management costs and depression and anxiety costs are lower with cisplatin with Pedmarqsi than with cisplatin without Pedmarqsi, as Pedmarqsi alleviates the need for hearing loss management strategies and reduces anxiety and depressive symptoms amongst cancer survivors.

Uncertainty

Pedmarqsi is the first and only preventative treatment developed for cisplatin-induced ototoxicity. Therefore, there is a lack of long-term data for this patient population or established treatment pathway, with current treatment pathways consisting only of non-preventative management strategies such as hearing aids and cochlear implants.

Every effort has been made to reduce the impact of uncertainties in the economic model, including discussion and validation of the methods used with external clinicians and a Health Economics and Outcomes Research expert. Furthermore, the uncertainty in model assumptions and data sources has been explored through extensive scenario and sensitivity analyses.

Key uncertainties in the model include:

- The lack of long-term data for this patient population to inform mortality and resource use over a patient's lifetime.

- COG ACCL0431 and SIOPEL 6 did not capture QoL and therefore utilities were derived from the published literature.

Cost-effectiveness results

Cost-effectiveness results for cisplatin with Pedmarqsi compared with cisplatin without Pedmarqsi are presented in **Section B.3.11 in the Company Submission** as a metric known as the incremental cost-effectiveness ratio (ICER), which measures the cost per additional QALY with an intervention vs. a comparator. The QALY is a generic measure of disease burden, with only QALY equivalent to one year of life in perfect health.

The results of the cost-effectiveness analysis indicate that cisplatin with Pedmarqsi improves patient QoL, resulting in greater QALYs compared with cisplatin without Pedmarqsi. Treatment with cisplatin with Pedmarqsi also leads to additional costs, reflective of its status as a novel medicine compared with cisplatin without Pedmarqsi.

For more information of the cost-effectiveness results, please refer to Section B.3.11 in the Company Submission.

Additional factors

In line with the NICE 2022 manual,[39] the severity modifier recognises the value that society places on the most severe and/or life-limiting diseases by determining the number and/or proportion of QALYs remaining in patients treated with current standard of care, compared to age- and sex-matched members of the general UK population.

Appraisals may meet the criteria for one of two severity modifiers: the 1.2x severity modifier or the 1.7x severity modifier. The 1.7x severity modifier suggests a more severe condition than the 1.2x severity modifier. Application of the 1.2x or 1.7x severity modifier means that the incremental QALY gain with Pedmarqsi is multiplied by a factor of 1.2 or 1.7, respectively.

Despite the rarity and severe burden of cisplatin-induced ototoxicity, this appraisal does not qualify for the a severity modifier. This is primarily due to the fact that ototoxicity does not have an impact on the survival of cisplatin-treated patients and calculations do not generate enough of a difference in the long-term survival rates of paediatric cisplatin-treated patients and the general population. Given that this is a very rare (with an estimated 222 patients expected to be treated in the first year) and severe disease that can affect a child throughout their lifetime, the company urge NICE to consider the severe impact cisplatin-induced ototoxicity has on patients in England and Wales and the step change Pedmarqsi would present in the prevention of this disease.

Additionally, the economic model does not capture the disutility associated with the emotional burden on parents and caregivers, thereby not capturing some of the benefits that would be demonstrated in the cisplatin with Pedmarqsi treatment arm.

3k) Innovation

Pedmarqsi is a novel treatment specifically formulated for use in children and is the first and only preventative treatment for cisplatin-induced ototoxicity. The current treatment pathway for cisplatin-induced ototoxicity involves simply managing the effects of hearing loss after they have occurred. These management strategies (described in Section 2c) do not restore hearing adequately and do not restore patients' QoL to a normal level, whereas Pedmarqsi addresses the underlying cause of hearing loss and prevents hearing loss. Pedmarqsi therefore represents a step change in the treatment of cisplatin-induced ototoxicity, allowing patients receiving cisplatin chemotherapy to protect their hearing, which has life-long benefits in terms of their QoL as childhood cancer survivors.

It is also likely that the introduction of Pedmarqsi would result in substantial benefits outside of the QALY calculation in the economic model that should be considered. Notably, as a preventative treatment, Pedmarqsi will reduce the emotional burden on parents and caregivers of children with cancer of choosing between an appropriate chemotherapy regimen which includes cisplatin and risks irreversible hearing loss, or a less preferable chemotherapy regimen which may be less efficacious in treating the cancer but reduces the risk of ototoxic hearing loss. By preventing cisplatin-induced hearing loss, Pedmarqsi removes one of the major challenges associated with cisplatin chemotherapy as a treatment option for children with cancer. The benefits of this cannot

be quantified in an economic model. Additionally, the SIOPEL 6 and COG ACCL0431 trials did not record data on the non-hearing effects of ototoxicity such as dizziness and vertigo. As such, Pedmarqsi may have additional benefits in terms of preventing these effects, which are also likely to affect patients' QoL. These benefits are not captured in the economic model.

Finally, the Company has also provided in its economic analysis separate scenario analyses which included costs for the Department of Education, and conducted an analysis from a societal perspective. These scenarios would be considered outside the typical NICE reference case; however, it is important to consider these benefits given the impact that Pedmarqsi would have on the life chances, education costs, and employment opportunities for patients.

3l) Equalities

As described above, the current management strategies available for children with hearing loss have limitations in compensating for the irreversible damage to the inner ear caused by cisplatin and are not effective in restoring patients' QoL when compared to the prevention of hearing loss altogether. Children with hearing loss suffer life-long disadvantages because their hearing loss may prevent them from being able to receive a full education without significant support. This leaves patients at a significant disadvantage in terms of their ability to work and function in later life. Therefore, Pedmarqsi would greatly improve the opportunities and prospects for children receiving chemotherapy and surviving their childhood cancer.

Furthermore, although the NHS offer a basic service which includes hearing aids, patients desiring more advanced hearing aids may be forced to search elsewhere. This can shift the financial burden to parents and carers who will need to purchase these for their children. This inequity is further enhanced by household income, as families living in challenging financial and social conditions are less likely to be able to afford more advanced equipment and, more generally, have an increased burden when caring for a child suffering from hearing loss.

Finally, although speech and language therapy are offered by the NHS, wealthier families may choose for their children to have private sessions with a better teacher-to-child ratio. Again, this creates an inequity where the prospect of a child with hearing loss are heavily impacted by household income.

Pedmarqsi can have a positive impact on these inequities by offering the first safe and effective treatment to prevent ototoxicity and therefore avoid hearing loss in children receiving cisplatin chemotherapy.

SECTION 4: Further information, glossary and references

4a) Further information

- What is ototoxicity? Information for parents. Available here: https://kidshealth.org/en/parents/ototoxicity.html#:~:text=Ototoxicity%20is%20when%20a%20person,%2C%20infections%2C%20or%20other%20illnesses
- COG ACCL0431 clinical trial. Available here: https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(16)30625-8/abstract
- SIOPEL 6 clinical trial. Available here: https://www.nejm.org/doi/full/10.1056/nejmoa1801109

Further information on NICE and the role of patients**:**

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/

- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

- **EuroQol-5 Dimensions 5-Levels (EQ-5D-5L):** EQ-5D-5L is a tool to measure the QoL of a person, based on their response to questions covering mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. EQ-5D is NICE's preferred QoL measure and is scored from a scale of 0–1, with 1 denoting perfect health.
- **The Health Utilities Index Mark 3 (HUI3):** HUI3 is a tool to measure the QoL of a person, based on their response to question's covering vision, hearing, mobility, emotion, pain, and cognition. Based on the responses, the HUI3 assigns a score to each person's health status in each domain. The scores range from perfect health (1) to severe disability (0).
- **Incremental cost-effectiveness ratio (ICER):** The incremental cost-effectiveness ratio is calculated by dividing the difference in total costs by the difference in health outcomes for an intervention (e.g., cisplatin with Pedmarqsi) vs. a comparator (e.g., cisplatin without Pedmarqsi). It provides a value of the extra cost per unit of the health effect.
- **Quality-adjusted life year (QALY):** The QALY is a standardised unit of measure of the state of health of a person or group in which remaining years of life are adjusted to reflect the QoL during those remaining years of life. One QALY is equal to 1 year of life in perfect health.
- **Randomised controlled trial (RCT)**: An RCT is a study in which a number of similar people are randomly assigned to two (or more) groups to test a specific drug, treatment or other intervention.
- **Utility:** The measure of the preference or value that an individual or society gives a particular health state. Utility is usually scored from 0–1, with 1 reflecting perfect health.

4c) References

1. Langer T, am Zehnhoff-Dinnesen A, Radtke S, Meitert J, Zolk O. Understanding platinum-induced ototoxicity. Trends Pharmacol Sci. 2013 Aug;34(8):458–69.

2. Landier W. Ototoxicity and cancer therapy. Cancer. 2016;122(11):1647–58.

3. Gurney JG, Bass JK. New International Society of Pediatric Oncology Boston Ototoxicity Grading Scale for pediatric oncology: still room for improvement. J Clin Oncol. 2012 Jul 1;30(19):2303–6.

4. Brock P, Rajput K, Edwards L, Meijer A, Simpkin P, Hoetink A, et al. Cisplatin Ototoxicity in Children. In: Hearing Loss - From Multidisciplinary Teamwork to Public Health [Internet]. IntechOpen; 2021 [cited 2023 Sep 19]. Available from: https://www.intechopen.com/chapters/75723

5. Rajput K, Edwards L, Brock P, Abiodun A, Simpkin P, Al-Malky G. Ototoxicity-induced hearing loss and quality of life in survivors of paediatric cancer. Int J Pediatr Otorhinolaryngol. 2020 Nov;138:110401.

6. Brock PR, Knight KR, Freyer DR, Campbell KCM, Steyger PS, Blakley BW, et al. Platinum-Induced Ototoxicity in Children: A Consensus Review on Mechanisms, Predisposition, and Protection, Including a New International Society of Pediatric Oncology Boston Ototoxicity Scale. J Clin Oncol. 2012 Jul 1;30(19):2408–17.

7. NHS England. Cancer incidence [Internet]. NDRS. [cited 2023 Oct 26]. Available from: https://digital.nhs.uk/ndrs/data/data-outputs/ctya-uk-cancer-statistics-report-2021/cancer-incidence

8. Knight KRG, Kraemer DF, Neuwelt EA. Ototoxicity in Children Receiving Platinum Chemotherapy: Underestimating a Commonly Occurring Toxicity That May Influence Academic and Social Development. JCO. 2005 Dec;23(34):8588–96.

9. Neuwelt EA, Brock P. Critical need for international consensus on ototoxicity assessment criteria. J Clin Oncol. 2010 Apr 1;28(10):1630–2.

10. Minasian LM, Frazier AL, Sung L, O'Mara A, Kelaghan J, Chang KW, et al. Prevention of cisplatin-induced hearing loss in children: Informing the design of future clinical trials. Cancer Med. 2018 May 30;7(7):2951–9.

11. Fligor BJ. Pediatric Ototoxicity: Current Trends and Management. Semin Hear. 2019 May 1;40(2):154–61.

12. Bess FH, Dodd-Murphy J, Parker RA. Children with Minimal Sensorineural Hearing Loss: Prevalence, Educational Performance, and Functional Status: Ear and Hearing. 1998 Oct;19(5):339–54.

13. Bass JK, Knight KR, Yock TI, Chang KW, Cipkala D, Grewal SS. Evaluation and Management of Hearing Loss in Survivors of Childhood and Adolescent Cancers: a Report from the Children's Oncology Group. Pediatr Blood Cancer. 2016 Jul;63(7):1152–62.

14. Khan A, Mubdi N, Budnick A, Feldman DR, Williams SW, Patel S, et al. The Experience of Hearing Loss in Adult Survivors of Childhood and Young Adult Cancer: A Qualitative Study. Cancer. 2020 Apr 15;126(8):1776–83.

15. Mundayoor SA, Bhatarai P, Prabhu P. A comparison of the quality of life of parents of children using hearing aids and those using cochlear implants. Journal of Otology. 2022 Oct 1;17(4):211–7.

16. Ganesan P, Schmiedge J, Manchaiah V, Swapna S, Dhandayutham S, Kothandaraman PP. Ototoxicity: A Challenge in Diagnosis and Treatment. J Audiol Otol. 2018 Apr;22(2):59–68.

17. King KA, Brewer CC. Clinical Trials, Ototoxicity Grading Scales,and the Audiologist's Role in Therapeutic Decision Making. Int J Audiol. 2018 Sep;57(SUP4):S89–98.

18. Yancey A, Harris MS, Egbelakin A, Gilbert J, Pisoni DB, Renbarger J. Risk Factors for Cisplatin-Associated Ototoxicity in Pediatric Oncology Patients. Pediatr Blood Cancer. 2012 Jul 15;59(1):144–8.

19. Foster AC, Jacques BE, Piu F. Hearing loss: The final frontier of pharmacology. Pharmacol Res Perspect. 2022 May 22;10(3):e00970.

20. Apex Healthcare Consulting. Managing ototoxicity in paediatric cancer patients and assessment of PEDMARK from an audiology perspective: audiologist market research report for Fennec Pharmaceuticals. 2018 Feb.

21. Dionne F, Mitton C, Rassekh R, Brooks B, Ross C, Hayden M, et al. Economic impact of a genetic test for cisplatin-induced ototoxicity. Pharmacogenomics J. 2012 Jun;12(3):205–13.

22. NHS England. NHS England SCHEDULE 2 – THE SERVICES A. Service Specifications. D09/S/A – 230503S [Internet]. 2023. Available from: https://www.england.nhs.uk/wp-content/uploads/2013/05/D09sa-cochlear-implantation-services.pdf

23. Bond M, Mealing S, Anderson R, Elston J, Weiner G, Taylor RS, et al. The effectiveness and cost-effectiveness of cochlear implants for severe to profound deafness in children and adults: a systematic review and economic model. Health Technology Assessment. 2009 Oct 13;13(44):1–330.

24. Brinkman TM, Bass JK, Li Z, Ness KK, Gajjar A, Pappo AS, et al. Treatment-induced hearing loss and adult social outcomes in survivors of childhood CNS and non-CNS solid tumors: Results from the St. Jude Lifetime Cohort Study. Cancer. 2015 Nov 15;121(22):4053–61.

25. Understanding unemployment: what role does ethnicity and disability play? [Internet]. Office for National Statistics. [cited 2024 Feb 28]. Available from: https://www.ons.gov.uk/visualisations/dvc2281/

26. Marriage and civil partnership status in England and Wales - Office for National Statistics [Internet]. [cited 2024 Feb 28]. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/marriagecohabitationandcivilpartnerships/articles/marriageandcivilpartnershipstatusenglandandwalescensus2021/2023-02-22

27. FDA. The Voice of the Patient A series of reports from the U.S. Food and Drug Administration's (FDA's) Patient-Focused Drug Development Initiative Childhood Cancer Hearing Loss [Internet]. 2019 [cited 2024 Apr 18]. Available from: https://www.childhoodcancerpfdd.org/final-report

28. Freyer DR, Chen L, Krailo MD, Knight K, Villaluna D, Bliss B, et al. Effects of sodium thiosulfate versus observation on development of cisplatin-induced hearing loss in children with cancer (ACCL0431): a multicentre, randomised, controlled, open-label, phase 3 trial. The Lancet Oncology. 2017 Jan 1;18(1):63–74.

29. Pedmarqsi 80 mg/mL solution for infusion - Summary of Product Characteristics (SmPC). 2023 Oct.

30. ClinicalTrials.gov. Cisplatin With or Without Sodium Thiosulfate in Treating Young Patients With Stage I, II, or III Childhood Liver Cancer (SIOPEL6) [Internet]. Available from: https://clinicaltrials.gov/study/NCT00652132

31. Brock PR, Maibach R, Childs M, Rajput K, Roebuck D, Sullivan MJ, et al. Sodium Thiosulfate for Protection from Cisplatin-Induced Hearing Loss. New England Journal of Medicine. 2018 Jun 21;378(25):2376–85.

32. ClinicalTrials.gov. Sodium Thiosulfate in Preventing Hearing Loss in Young Patients Receiving Cisplatin for Newly Diagnosed Germ Cell Tumor, Hepatoblastoma, Medulloblastoma, Neuroblastoma, Osteosarcoma, or Other Malignancy [Internet]. Available from: https://clinicaltrials.gov/study/NCT00716976

33. Barton GR, Stacey PC, Fortnum HM, Summerfield AQ. Hearing-Impaired Children in the United Kingdom, IV: Cost-Effectiveness of Pediatric Cochlear Implantation. Ear & Hearing. 2006 Oct;27(5):575–88.

34. Borre ED, Kaalund K, Frisco N, Zhang G, Ayer A, Kelly-Hedrick M, et al. The Impact of Hearing Loss and Its Treatment on Health-Related Quality of Life Utility: a Systematic Review with Meta-analysis. J GEN INTERN MED. 2023 Feb 1;38(2):456–79.

35. Pogany L, Barr RD, Shaw A, Speechley KN, Barrera M, Maunsell E. Health Status in Survivors of Cancer in Childhood and Adolescence. Qual Life Res. 2006 Feb 1;15(1):143–57.

36. Chen P, Hudson MM, Li M, Huang IC. Health utilities in pediatric cancer patients and survivors: a systematic review and meta-analysis for clinical implementation. Qual Life Res. 2022 Feb 1;31(2):343–74.

37. SIOPEL CSR [data on file] A MULTICENTER, OPEN-LABEL, RANDOMIZED PHASE III TRIAL OF THE EFFICACY OF SODIUM THIOSULFATE IN REDUCING OTOTOXICITY IN PATIENTS RECEIVING CISPLATIN CHEMOTHERAPY FOR STANDARD-RISK HEPATOBLASTOMA. 2019.

38. ACCL0431 CSR [Data on file] RANDOMIZED PHASE 3 STUDY OF SODIUM THIOSULFATE (IND #72877, NSC #45624) FOR THE PREVENTION OF CISPLATIN-INDUCED OTOTOXICITY IN CHILDREN. 2019.

39. 4 Economic evaluation | NICE health technology evaluations: the manual | Guidance | NICE [Internet]. NICE; 2022 [cited 2024 Jan 26]. Available from: https://www.nice.org.uk/process/pmg36/chapter/economic-evaluation#discounting

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Anhydrous sodium thiosulfate (Pedmarqsi) for preventing ototoxicity caused by cisplatin chemotherapy in people aged 1 month to 17 years with localised solid tumours [ID1001]

Clarification questions

May 2024

File name	Version	Contains confidential information	Date
ID1001 Ototoxicity - sodium thiosulfate EAG clarification letter_v3 FINAL 16052024 [noCON]	3	No	31.05.2024

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

Decision problem:

A1. Company's submission (CS), Sections B.1.1, B.1.3.3 and B.1.3.4. Please clarify the company's intended positioning of sodium thiosulfate (STS) e.g., is it for patients receiving cisplatin monotherapy only or for patients being treated by any cisplatin-containing chemotherapy, or both?

The licensed indication for Pedmarqsi is for the prevention of ototoxicity induced by cisplatin chemotherapy in patients 1 month to <18 years of age with localised, non-metastatic, solid tumours. The licence does not reference a particular type of cisplatin regimen such as cisplatin monotherapy, or a multi-drug cisplatin-containing chemotherapy regimen, and therefore a patient would be eligible for Pedmarqsi as long as they had received a cisplatin-containing chemotherapy regimen for their underlying cancer.

This positioning is also supported by the evidence base included in this submission. In the COG ACCL0431 study, a specific inclusion or exclusion criterion relating to the type of cisplatin regimen (i.e. specifying whether patients receive cisplatin monotherapy or a multi-drug cisplatin-containing chemotherapy regimen) was not

applied. Instead, cisplatin was administered according to the sites' disease-specific cancer treatment protocols in use at the time of the study (discussed in more detail in question 14b). Similarly, in SIOPEL 6, a specific criterion for cisplatin monotherapy or a multi-drug cisplatin-containing chemotherapy regimen was not applied.

A2. CS, Section B.1.1, Table 1. For completeness, please provide further details on how Pedmarqsi is different to other formulations of sodium thiosulfate that are available in some European countries for the treatment of cyanide poisoning.

Pedmarqsi is a *novel* formulation of anhydrous sodium thiosulfate, specifically manufactured for the prevention of ototoxicity induced by cisplatin chemotherapy in patients 1 month to <18 years of age with localised, non-metastatic, solid tumours.

Pedmarqsi is different to other formulations of sodium thiosulfate in a number of ways:

- Firstly, Pedmarqsi is licensed specifically for the population as described above and is the only approved medicine for this indication. Other formulations of sodium thiosulfate are available, however their use in the population included in this appraisal would be considered "off-label".[1]
- Secondly, there is an absence of clinical effectiveness and safety data for alternative formulations of sodium thiosulfate, both generally and in the population under review.[1] This is in contrast to Pedmarqsi which has been studied in two high quality, relevant, randomised controlled trials (COG ACC0431 and SIOPEL 6).
- Thirdly, the EMA has officially recommended Pedmarqsi for the prevention of ototoxicity and recognises the value of Pedmarqsi in addressing the high unmet need in this patient population (product number EMEA/H/C/005130). Such EMA recommendations are not available for alternative formulations of sodium thiosulfate.
- Fourthly, the excipients included in the formulation of Pedmarqsi are different to those included in other formulations of sodium thiosulfate. For example, the product sodium thiosulfate 250 mg/mL Solution for Injection manufactured by Hope Pharmaceuticals Ltd (indicated for the treatment of acute cyanide

poisoning) contains potassium chloride, which is not present in Pedmarqsi. Pedmarqsi also contains a lower concentration of boric acid (0.25 mg/mL) than this formulation of sodium thiosulfate (2.8 mg/mL).[1,2] These differences are particularly relevant and may represent a risk to patients' health. In January 2024, the FDA released a statement which specifically highlights the serious risks related to substitution of Pedmarqsi with other formulations of sodium thiosulfate, such as potassium chloride exposure (which the FDA notes can lead to increased risk of acute cardiac events and other serious adverse reactions at high doses) and overexposure to boric acid (which the FDA notes can cause health risks such as headache, hypothermia, restlessness, weariness, renal injury, dermatitis, alopecia, anorexia and indigestion).[3]

- Further to the above, the FDA highlights that Pedmarqsi is different to other formulations of sodium thiosulfate available in the US market "*FDA reminds health care providers that as stated in Pedmark's prescribing information, Pedmark is not substitutable with other sodium thiosulfate products.*"[3]. The Company shares FDA position regarding the different formulations of sodium thiosulfate available in the UK market, as there is no evidence that demonstrates their interchangeability.

- Finally, Pedmarqsi's formulation allows a 15-minute infusion time and does not require reconstitution or dilution so is straight-forward to administer.

A3. Please comment on whether there are any specific groups that may be more susceptible to cisplatin-induced ototoxicity. If so, how could they be screened/ identified?

The primary risk factors for cisplatin-induced ototoxicity are young age and cumulative cisplatin dose (≥400 mg/m² (Li et al, 2004)[4]). Contributing factors include dose schedule, pre-existing hearing loss, co-existing renal dysfunction, and prior cranial radiotherapy when the cochlea is within the radiation field (Knight et al., 2005; Li et al., 2004; Whelan et al., 2011)[4–6].

In addition, the Company has recently consulted with an audiovestibular physician who has highlighted additional risk factors for more severe cisplatin-induced ototoxicity; these are increased genetic susceptibility (such as a family history of sensorineural hearing loss), prolonged jaundice as an infant, or prematurity.[7] However, these risk factors are not clearly defined, and there is a significant lack of evidence supporting the increased susceptibility of certain subgroups.

All patients treated with ototoxic agents are at risk of developing ototoxic hearing loss and given the highly detrimental impact of ototoxicity in children's lives, the Company's position is that Pedmarqsi should be given to all patients within the licence, and it is not appropriate to focus on subgroups within the patient population.

The prevention of hearing loss by Pedmarqsi was similar in SIOPEL 6 (hepatoblastoma only) and COG ACCL0431 (including hepatoblastoma, neuroblastoma, CNS tumours, germ cell tumours and osteosarcoma) supporting the notion that the mechanism of action is directed at cisplatin ototoxicity and independent of tumour type.

In addition, the two pivotal studies combined included patients with ages ranging from 1.2 months to 18 years, and weights ranging from [redacted] kg to [redacted] kg, further supporting that Pedmarqsi is effective across a heterogenous paediatric patient population.[8,9]

A4. Although not part of the licence indication, for completeness, please comment on whether sodium thiosulfate could be considered for patients with advanced or disseminated disease.

The Company confirms that Pedmarqsi must only be considered for use within its licensed indication, which includes only paediatric patients with localised, non-metastatic, solid tumours.

Pedmarqsi is indicated for the prevention of ototoxicity induced by cisplatin chemotherapy in patients 1 months to < 18 years of age with localised, non-metastatic, solid tumours.

A5. As the PRETEXT classification system is used to stratify risk and guide treatment of hepatoblastoma, please clarify if sodium thiosulfate would be used for all PRETEXT

stages (I to IV). Our clinical advisors have suggested that clinicians may be reluctant to start treatment in high-risk patients with hepatoblastoma (PRETEXT III and above) due to their worse state and the potential effect on cisplatin's efficacy.

The Company can confirm that Pedmarqsi will be used in localised patients only, as per its licensed indication. Localised disease is aligned with a standard-risk hepatoblastoma PRETEXT classification of I-III, with PRETEXT IV being high-risk hepatoblastoma including patients with metastatic disease.[10,11] Therefore, it is unlikely that Pedmarqsi would be used in high-risk patients (PRETEXT IV) given that this would be considered outside the licence.

It is also worth noting that the SIOPEL 6 study applied PRETEXT I-III as an inclusion criterion with PRETEXT IV as a specified exclusion criterion. Over a third (n = 37 [33.9%]) of the patients in the SIOPEL 6 trial had a PRETEXT III classification, which makes the evidence generated in this trial representative of this subgroup of patients. As the trial demonstrated that there was no significant difference in OS between the two treatment arms, indicating that Pedmarqsi did not affect the efficacy of cisplatin.

Finally, the discussion regarding PRETEXT criteria has limited relevance to the COG ACC0431 study given that only seven patients in the trial had hepatoblastoma.

Evidence Searches:

A6. CS Appendix D, Section D.1.1 (also applies to Section G.1.1). The CS states that '*Filters were used to ensure the search results were relevant for the review question*.' As published filters are validated for different databases, it is unclear whether the optimal filter for the study designs of interest (randomised controlled trials and non-randomised controlled trials for the clinical systematic literature review [SLR]; economic, cost and utility evidence for the other SLRs) have been used. Please indicate the source of these filters and any adaptations to them that may have been made.

Study design filters for RCTs, observational studies, and economic evaluations were based on filters published by the Scottish Intercollegiate Guidelines Network (SIGN).[12] Similarly, the study design filter for quality of life evidence was based on a filter published by Arber et al. (2015).[13] Additionally, each of the study design filters

used in the SLRs have been applied and accepted in previous SLRs submitted to NICE.

A7. CS Appendix D, Sections D.1.1 and D.1.1.1. Regarding the SLR searches for clinical effectiveness evidence:

a) The CS states that MEDLINE was searched on PubMed, but Table 1 reports a search of Embase and MEDLINE on embase.com, while the PubMed search has not been reported. Please provide a transcript/report of the PubMed search.

The Company would like to clarify that the MEDLINE database was not searched using PubMed, but was searched through Embase.com using the clinical SLR search strategy listed in Appendix Table 1 of the CS.

b) When comparing the search strategies for the Embase/MEDLINE search in Table 1 and the CENTRAL search in Table 2, it is notable that terms for cancer have been included in the CENTRAL search but not the Embase/MEDLINE search. Please clarify the rationale behind this difference in strategies.

The Embase/MEDLINE search strategy originally included additional search terms for cancer, similar to the CENTRAL search strategy. However, in the process of refining the search strategy for the submission, it was decided to remove these terms from the strategy due to the low number of hits found. Removing the terms relating to cancer was deemed appropriate because it expanded the number of hits, ensuring that the search was comprehensive, whilst terms such as ‘cisplatin’ and ‘ototoxicity’ were maintained to ensure the searches remained relevant to the target population. However, this expansion of the search strategy was not performed for the CENTRAL search strategy, therefore search terms relating to cancer were included because the inclusion of these terms did not have a significant effect on the number of search results identified. Only two additional hits were identified when the terms associated with cancer were removed, both of which were already identified in the Embase/MEDLINE search.

c) The CS refers to supplementary searches of the World Health Organisation (WHO) International Clinical Trials Registry Platform, clinicaltrials.gov and

several relevant conference series. Please provide details of the searches performed for these sources, including search terms used and results.

Full details of the grey literature searches, including search terms used and results are provided in Table 1 (databases) and Table 2 (conferences).

Table 1: Grey literature database search strategy and results

Database	Search terms	Filters applied	Number of results	Studies meeting eligibility criteria
Clinicaltrials.gov (Searched 25th October 2023)	Ototoxicity OR Ototoxic Hearing Loss OR Hearing Loss OR Cisplatin Ototoxicity OR Cisplatin Induced Tinnitus	Age: - Child (birth-17) - Adult (18-64) Study results: - With results	164	1 (NCT0071976; COG ACCL0431)
WHO ICTRP (Searched 25th October 2023)	Ototoxicity OR Ototoxic Hearing Loss OR Hearing Loss OR Cisplatin Ototoxicity OR Cisplatin Induced Tinnitus	Recruitment status: - All Study results: - With results only	115	1 (Same study included as identified through searching clinicaltrials.gov)
NICE Website (Searched 20th November 2023)	Ototoxicity	None	5	0
	Ototoxic Hearing Loss		3	0
	Hearing Loss		102	0
	Cisplatin Ototoxicity		1	0
	Cisplatin Induced Tinnitus		0	0

Abbreviations: ICTRP – International clinical trials registry platform; WHO – World Health Organisation

Table 2: Grey literature conferences search strategy and results

Conference	Search terms	Number of results	Studies included
European Society for Medical Oncology (ESMO) 2021 (Searched 27th October 2023)	Ototoxicity	0	0
European Society for Medical Oncology (ESMO) 2021 (Searched 27th October 2023)	Deaf	0	0
European Society for Medical Oncology (ESMO) 2021 (Searched 27th October 2023)	Hearing	3	0

Conference	Search terms	Number of results	Studies included
European Society for Medical Oncology (ESMO) 2021 (Searched 27th October 2023)	Auditory	0	0
European Society for Medical Oncology (ESMO) 2022 (Searched 27th October 2023)	Ototoxicity	1	0
European Society for Medical Oncology (ESMO) 2022 (Searched 27th October 2023)	Deaf	0	0
European Society for Medical Oncology (ESMO) 2022 (Searched 27th October 2023)	Hearing	0	0
European Society for Medical Oncology (ESMO) 2022 (Searched 27th October 2023)	Auditory	1	0
European Society for Medical Oncology (ESMO) 2023 (Searched 27th October 2023)	Ototoxicity	1	0
European Society for Medical Oncology (ESMO) 2023 (Searched 27th October 2023)	Deaf	0	0
European Society for Medical Oncology (ESMO) 2023 (Searched 27th October 2023)	Hearing	2	0
European Society for Medical Oncology (ESMO) 2023 (Searched 27th October 2023)	Auditory	1	0
ISPOR 2021 (Searched 30th October 2023)	ototoxicity OR deaf OR hearing OR auditory	1	0
ISPOR Europe 2021 (Searched 30th October 2023)	ototoxicity OR deaf OR hearing OR auditory	3	0
ISPOR 2022 (Searched 30th October 2023)	ototoxicity OR deaf OR hearing OR auditory	8	0
ISPOR Europe 2022 (Searched 30th October 2023)	ototoxicity OR deaf OR hearing OR auditory	11	0

Conference	Search terms	Number of results	Studies included
ISPOR 2023 (Searched 30th October 2023)	ototoxicity OR deaf OR hearing OR auditory	8	0
ISPOR Europe 2023 (Searched 30th October 2023)	ototoxicity OR deaf OR hearing OR auditory	20	0
ASCO 2021 (Searched 30th October 2023)	Ototoxicity	2	0
ASCO 2021 (Searched 30th October 2023)	Deaf	0	0
ASCO 2021 (Searched 30th October 2023)	Hearing	48	0
ASCO 2021 (Searched 30th October 2023)	Auditory	1	0
ASCO 2022 (Searched 30th October 2023)	Ototoxicity	3	0
ASCO 2022 (Searched 30th October 2023)	Deaf	0	0
ASCO 2022 (Searched 30th October 2023)	Hearing	15	0
ASCO 2022 (Searched 30th October 2023)	Auditory	2	0
ASCO 2023 (Searched 30th October 2023)	Ototoxicity	2	0
ASCO 2023 (Searched 30th October 2023)	Deaf	0	0
ASCO 2023 (Searched 30th October 2023)	Hearing	15	0
ASCO 2023 (Searched 30th October 2023)	Auditory	0	0
International Society for Paediatric Oncology (SIOP) 2021 (Searched 9th November 2023)	Ototoxicity	17	0
International Society for Paediatric Oncology (SIOP) 2021 (Searched 9th November 2023)	Deaf	2	0
International Society for Paediatric Oncology (SIOP) 2021 (Searched 9th November 2023)	Hearing	49	0
International Society for Paediatric Oncology (SIOP) 2021 (Searched 9th November 2023)	Auditory	6	0
International Society for Paediatric Oncology (SIOP) 2022 (Searched 9th November 2023)	Ototoxicity	24	0

Conference	Search terms	Number of results	Studies included
International Society for Paediatric Oncology (SIOP) 2022 (Searched 9th November 2023)	Deaf	1	0
International Society for Paediatric Oncology (SIOP) 2022 (Searched 9th November 2023)	Hearing	75	1 (Freyer et al. 2022, INTRATYMPANIC INJECTION OF SUSTAINED-EXPOSURE DEXAMETHASONE THERMOSENSITIVE GEL (OTO-104) FOR PREVENTION OF CISPLATIN-INDUCED HEARING LOSS IN CHILDREN IS FEASIBLE AND SAFE)
International Society for Paediatric Oncology (SIOP) 2022 (Searched 9th November 2023)	Auditory	1	0
International Society for Paediatric Oncology (SIOP) 2023 (Searched 20th November 2023)	Ototoxicity	25	1 (Cabi et al. 2023, PEDMARK® REDUCED THE RISK OF CISPLATIN-INDUCED OTOTOXICITY IN PEDIATRIC PATIENTS WITH HEPATOBLASTOMA, SEEN IN A TURKISH COMPASSIONATE USE TREATMENT PROTOCOL)
International Society for Paediatric Oncology (SIOP) 2023 (Searched 20th November 2023)	Deaf	0	0
International Society for Paediatric Oncology (SIOP) 2023 (Searched 20th November 2023)	Hearing	50	1 (Same study as identified in 'ototoxicity' search)
International Society for Paediatric Oncology (SIOP) 2023 (Searched 20th November 2023)	Auditory	5	0
International Symposium on Late Complications after Childhood Cancer (ISLCCC) 2022 (Searched 10th November 2023)	Ototoxicity	2	0
International Symposium on Late Complications after Childhood Cancer (ISLCCC) 2022 (Searched 10th November 2023)	Deaf	0	0
International Symposium on Late Complications after Childhood Cancer (ISLCCC) 2022 (Searched 10th November 2023)	Hearing	18	0
International Symposium on Late Complications after Childhood	Auditory	2	0

Conference	Search terms	Number of results	Studies included
Cancer (ISLCCC) 2022 (Searched 10th November 2023)			
International Symposium on Late Complications after Childhood Cancer (ISLCCC) 2023 (Searched 10th November 2023)	Ototoxicity	5	0
International Symposium on Late Complications after Childhood Cancer (ISLCCC) 2023 (Searched 10th November 2023)	Deaf	0	0
International Symposium on Late Complications after Childhood Cancer (ISLCCC) 2023 (Searched 10th November 2023)	Hearing	14	0
International Symposium on Late Complications after Childhood Cancer (ISLCCC) 2023 (Searched 10th November 2023)	Auditory	0	0

A8. CS, Appendix D, Section D.1.1, page 6. The CS states that '*Comprehensive literature searches were undertaken in electronic databases on 31st October 2023'*. Please clarify if any search updates have been carried out since October 2023. Please also confirm that no further studies of anhydrous sodium thiosulfate or other relevant interventions in the target population have been published since this date.

The Company confirms that no updates to the database searches have been carried out since October 2023, as the searches were performed within six months of the submission date. Additionally, the grey literature searches were also completed within six months of the submission date (completed in December 2023). The Company is not aware of any additional relevant studies of Pedmarqsi or other relevant interventions in the target population that have been published since this date.

A9. CS, Appendix G, Section G.1.1, page 19. The CS reports that the Centre for Reviews and Dissemination (CRD) HTA Database was searched as part of the SLR for economic evidence. However, this database has not been updated since 2018. Please confirm whether the International Network of Agencies for Health Technology

Assessment (INAHTA) database (https://database.inahta.org/) was also searched for more up-to-date coverage.

The Company confirms that the INAHTA database was not searched as part of the SLR for economic evidence. As described in Appendix G.1.1 of the CS, the economic evidence SLR searches were performed in the Embase and MEDLINE database, the Centre for Reviews and Dissemination HTA and NHS Economic Evaluation Databases, the Sheffield Centre for Health and Related Research Health Utilities Database and the EuroQol database.

Additionally, as detailed in Appendix G.1.1, several additional sources of "grey" literature were searched. Therefore, the Company strongly believe that economic evidence for hearing loss was comprehensively identified in the SLRs.

However, to ensure that no relevant references were missed, the Company conducted a search of the INAHTA database on 23rd May 2024 using the search terms listed in Appendix G.1.1.1 Table 7. 11 results were identified, none of which met the eligibility criteria for inclusion in the non-clinical SLRs. A summary of the studies identified and reason for exclusion is provided in Appendix Table 1.

Systematic literature review (SLR)

A10. CS, Appendix D, Sections D.1.2., D.2.1 and D.2.2. CS Section D.1.2 provides inclusion criteria for a broader systematic review which identified 546 unique citations. Appendix D.2.1 (Figure 1) and Appendix D.2.2. (Table 4) then list seven references associated with five unique randomised controlled trials (RCTs) (Gallegos-Castorena 2007 and Katzenstein et al. 2009 [amifostine administration]; Freyer 2022 [sustained-exposure dexamethasone thermosensitive gel]; SIOPEL 6 (Brock 2018) and COG ACCL0431 (Freyer 2017 and Orgel 2023) [sodium thiosulfate]), and one observational study (Cabi 2023 [sodium thiosulfate]).

a) The CS Section B.2.1 lists only two sodium thiosulfate studies that were identified from the SLR (SIOPEL 6 and COG ACCL0431). Please explain the

inconsistency between the ‘included’ studies listed in the CS and the ‘included’ studies listed in Appendix D.2.

The three RCTs identified for interventions other than Pedmarqsi were not reported in the CS because, although they met the eligibility requirements to be included in the SLR, they were not relevant to the decision problem considered in the appraisal.

Amifostine and sustained-exposure dexamethasone thermosensitive gel are not recommended in the UK for the prevention or management of cisplatin-induced hearing loss and were not listed as comparators in the NICE decision problem for the appraisal. The studies published by Gallegos-Castorena (2007)[14] and Katzenstein et al. (2009)[15], and Freyer (2022)[16] are therefore not relevant to the decision problem. However, these studies were reported in the SLR because no exclusion criteria were applied for interventions/comparators (i.e. all prevention/management strategies for cisplatin-induced hearing in paediatric patients were considered) to ensure efficacy data for management strategies were comprehensively identified.

The single-armed observational study published by Cabi et al. (2023)[17] was also not reported in the CS. All patients in this study received Pedmarqsi treatment, and no patients developed hearing loss, therefore the study could not be used to inform the relative clinical effectiveness of Pedmarqsi against treatment without Pedmarqsi.

The SIOPEL 6 and COG ACCL0431 trials met the eligibility criteria for the SLR and included interventions and comparators relevant to the decision problem. Both were also randomised, controlled trials. Therefore, these trials were considered to be the most suitable sources of clinical evidence to inform the appraisal.

b) Please provide the narrower inclusion/exclusion criteria relevant to this appraisal.

As stated above, whilst additional non-Pedmarqsi studies (Gallegos-Castorena 2007[14]; Katzenstein et al. 2009[15]; and Freyer 2022[16]) met the inclusion criteria for the clinical SLR, they did not include comparators relevant to the current appraisal therefore they were not included in the CS. The study reported by Cabi et al. (2023)[17] did not include a comparator arm and no patients treated with Pedmarqsi experienced hearing loss. This study was therefore not relevant to inform the clinical

efficacy of Pedmarqsi, however, the details of these studies were provided in Appendix D for completeness.

c) Please confirm which studies meet the inclusion criteria for this appraisal. If further studies meet the inclusion criteria for this appraisal, in addition to the studies listed in (a), please provide them.

The SIOPEL 6 (Brock 2018)[8] and COG ACCL0431 (Freyer 2017 and Orgel 2023)[9,18] trials met the inclusion criteria for the clinical SLR. These studies were included in the CS as they represented the only evidence available meeting the criteria defined in the decision problem. No other studies providing relevant clinical effectiveness data for Pedmarqsi and considered relevant to the decision problem were identified in the clinical SLR.

d) Please provide a copy of the conference abstract published by Cabi 2023.

The conference abstract published by Cabi et al. (2023)[17] is available from Pediatric Blood & Cancer 2023; 70:8 e30748, pageS572. A copy of the abstract has been provided with the responses to the clarification questions.

e) The EAG identified an additional conference abstract not identified by the company's searches: Tanaka et al. (2023). Please provide further details, outcomes/results and updates of the 'Named Patient Program Use of Pedmark' as reported by this study. Reference: Tanaka et al. Named patient program use of PEDMARK® to reduce the risk of cisplatin-induced ototoxicity in pediatric patients with varied solid tumours. Pediatric Blood & Cancer 2023; 70:8 e30748, pageS432. Available at: https://onlinelibrary.wiley.com/doi/10.1002/pbc.30748

Whilst the results of the Named Patient Program Use of Pedmark study may be of interest when considering the efficacy and safety profile of Pedmarqsi, it should be noted that the study did not meet the eligibility criteria for the clinical SLR (defined in Appendix Table 3, Appendix D.1.2 of the CS) because the study included patients with an age range of 3-19 years and did not report results in the subgroup of patients aged 18 or younger. The SLR eligibility criteria state that studies with a mixed population that do not present outcomes separately for patients of interest and those not of interest should be excluded. The age criteria in the clinical SLR were defined

as patients up to the age of 18 years to identify the data most relevant to the licensed population.

The named patient program reported by Tanaka et al. (2023) observed that of the 13 patients treated with Pedmarqsi with available data, 58% maintained a Brock Grade of 0 and that Grade 1-2 nausea or vomiting was observed in 10 patients. No Grade ≥ 3 adverse events were observed in the study. The authors concluded that real-world post-treatment hearing and tumour outcomes were consistent with Phase-3 trial results. However, as noted above, it should be noted when considering the results in relation to the current appraisal that the population included in this study did not fully align with the UK license for Pedmarqsi.

A11. CS, Appendix D.2.2.3, Table 5. The CS appears to have excluded an analysis by Orgel et al. (2023) which provides updated survival data from the COG ACCL0431 study, with a median follow up of 7.8 years. For completeness, please explain why this information has not been reported in the CS (Section A.7.6 and Section B.2.5.2) and why this is not considered relevant to this appraisal.

Although the analysis of updated survival published by Orgel et al. (2023) provides updated data from the COG ACCL0431 trial, it did not meet the inclusion criteria for the clinical SLR (see Appendix Table 3, Appendix D.1.2 of the CS) because overall survival was not listed as an outcome of interest. Therefore the study was excluded during the full text review stage of the SLR. As Pedmarqsi is intended as a treatment for hearing loss, and is not a treatment for the underlying cancer, outcomes relating to tumour progression, such as overall survival and progression-free survival were not considered in the SLR. Instead, the outcomes of interest included in the clinical SLR were related to hearing loss and safety outcomes, as these were identified as the most relevant outcomes for the indication.

Despite not being considered as an outcome of interest for the clinical SLR, overall survival has been assessed in the Pedmarqsi's clinical trials, the SIOPEL 6 and COG ACCL0431 trials, which were identified in the SLR. The overall survival results from these trials are reported in the CS. No other studies reporting overall survival of paediatric patients treated with Pedmarqsi were identified in the SLR, except the study published by Orgel et al. (2022)[19].

For completeness, the Company has presented the results of the study published by Orgel et al. (2022)[19], which shows that with a median follow-up of 7.8 years, 6-year overall survival rate in patients with localised disease remained stable and similar between cisplatin without Pedmarqsi group (84% [95% CI 68-92]) and cisplatin with Pedmarqsi group (80% [62-90]; p = 0.67). In patients with disseminated disease, patients in the cisplatin without Pedmarqsi group had a significantly higher 6-year overall survival rate (73% [48-87] versus 45% [23-65]; relative hazard ratio = 2.74 [1.01-7.44]; p=0.040) compared to the cisplatin with Pedmarqsi group. The authors concluded that the survival difference observed in patients with disseminated disease in the COG ACCL0431 trial was not an artefact of short follow-up, but may have been a result of unbalanced randomisation of participants for disease-specific prognostic factors not measured in the trial, as previously hypothesised.

A12. CS Appendix D and Appendix G. Please confirm if study selection, data extraction and quality assessment was undertaken independently by a minimum of two reviewers for each systematic review in the clinical and cost sections. If not, please justify the approach undertaken.

The Company confirms that for each systematic literature review, study selection, data extraction and quality assessment were undertaken independently by two reviewers. Where there were disagreements between reviewers, conflicts were arbitrated by a third reviewer.

Clinical effectiveness evidence

A13. PRIORITY. Please provide the results for overall survival, treatment efficacy (hearing loss experience and hearing loss severity) and adverse event (AE) outcomes (Grade 3+ and SAEs) from a pooled analysis using data from both SIOPEL 6 and COG ACCL0431 trials similar to that requested by the EMA, but excluding metastatic patients. Please also provide the baseline characteristics for this pooled population per arm and mean number of doses and vials of sodium thiosulphate received.

The Company notes that providing the pooled analysis requested above would also require a subgroup analysis of localised only patients from COG ACCL0431, in order to pool these data with SIOPEL 6. The Company do not believe that it is appropriate

to assess Pedmarqsi's efficacy in the subpopulation of localised only patients in COG ACCL0431, either alone or when included in the pooled analysis. This issue is further discussed in the response to Question B6; however, the primary reason is that the COG ACCL0431 trial (which included localised and metastatic patients) was not powered for an assessment of efficacy in the localised only patients.

Despite this, the Company has provided the information as requested. The information is available as follows:

- OS is available in the PDF Document titled "Pooled analysis_16SEP21"
- Efficacy, adverse events and baseline characteristics for the pooled analysis is available in the PDF document titled "NICE Request_23MAY240"
- Mean number of doses is available in the Excel file titled "Pooled analysis dose data"
- Please note that a pooled analysis which includes hearing loss severity is not available as the COG ACCL0431 trial did not assess hearing loss severity.

The results of these analyses support and validate the findings presented in the CS. Pedmarqsi is an effective and safe treatment for the prevention of ototoxicity as demonstrated by the significant reduction in the proportional incidence of hearing loss between the cisplatin with Pedmarqsi arm and the cisplatin without Pedmarqsi arm. Based on analyses in the mITT population, the proportion of children with hearing loss in the cisplatin with Pedmarqsi arm was [redacted]% compared to [redacted]% in the cisplatin without Pedmarqsi arm. The probability of experiencing hearing loss was statistically significantly lower in the cisplatin with Pedmarqsi arm compared to the cisplatin without Pedmarqsi arm (relative risk: [redacted]; 95% CI: [redacted], [redacted]; p=[redacted]), corresponding to a clinically meaningful 47% lower risk after Pedmarqsi treatment. Results of the mITT population are presented in Table 3.

Table 3: Summary of hearing loss (pooled COG ACCL0431 and SIOPEL 6 mITT population – localised disease)

Results – hearing loss	Cisplatin without Pedmarqsi (N=79)	Cisplatin with Pedmarqsi (N=86)
Yes, n (%)	[redacted]	[redacted]
No, n (%)	[redacted]	[redacted]
Relative Risk (95% CI)*	[redacted]	
P-value*	[redacted]	

*P-value and relative risk from CMH test adjusting for study.

Hearing loss results were similar in the ITT population (Table 4). The risk of experiencing hearing loss was statistically significantly lower in the cisplatin with Pedmarqsi arm compared to the cisplatin without Pedmarqsi arm (relative risk: [redacted], 95% CI: [redacted], [redacted]; p[redacted]), corresponding to a clinically meaningful 39% lower risk after Pedmarqsi treatment.

Table 4: Summary of hearing loss (pooled COG ACCL0431 and SIOPEL 6 ITT population – localised disease)

Results – hearing loss	Cisplatin without Pedmarqsi (N=90)	Cisplatin with Pedmarqsi (N=96)
Yes, n (%)	[redacted]	[redacted]
No, n (%)	[redacted]	[redacted]
Relative Risk (95% CI)*	[redacted]	
P-value*	[redacted]	

*P-value and relative risk from CMH test adjusting for study.

Additionally, there was no statistically significant difference in overall survival between treatment arms. A summary of OS results in the ITT population is presented in Table 5 and Figure 1.

Table 5: Summary of overall survival (pooled COG ACCL0431 and SIOPEL 6 ITT population – localised disease)

Parameter Category/Statistic	Cisplatin without Pedmarqsi (N=90)	Cisplatin with Pedmarqsi (N=96)
Number of patients who died, n (%)	[redacted]	[redacted]
Number of patients censored, n (%)	[redacted]	[redacted]
Treatment comparison (cisplatin with Pedmarqsi vs cisplatin without Pedmarqsi)		
Hazard ratio (95% CI)	[redacted]	
P-value (log-rank)	[redacted]	

Abbreviations: CI – Confidence interval; ITT – Intention-to-treat.

Figure 1: Overall survival (ITT population – localised disease)

[redacted]

Abbreviations: CI – Confidence interval; ITT – Intention-to-treat; RHR – Relative hazard ratio.

A14. CS, Section B2:

a) Please clarify how the cisplatin regimens from the trials included in the CS (in particular COG ACCL0431 trial conducted in North America) are anticipated to reflect the current pathway and regimens currently used in UK clinical practice for the target population eligible to receive sodium thiosulphate.

The Company consider that the cisplatin regimens patients received as part of the COG ACCL0431 study are generalisable to the UK. As noted in response to question A1, the chemotherapy regimen a patient received was administered according to the sites' disease-specific cancer treatment protocols in use at the time of the study. In addition, cancer treatment protocols in paediatrics are determined by collaborative groups who share information globally due to the challenges of conducting research in this area. Therefore, although the COG ACCL0431 was

conducted in North America, given the global nature of cancer treatment protocols, the cisplatin regimens and the number of cisplatin doses (and therefore Pedmarqsi doses) are expected to reflect what would be applied in UK clinical practice.

Further to the above, and as noted in Section B.3.4.1 of the CS, the COG ACCL0431 trial included paediatric cancer patients with a range of cancer types which are generally aligned to the distribution of key cisplatin-treated paediatric localised cancers in England and Wales, as published in the CTYA UK cancer incidence 1997-2016 statistics.[20] This finding further supports that the cisplatin regimens used in COG ACCL0431 are generalisable to the UK, given that the tumour types for which they are treated, also reflects the distribution of tumours in the UK.

The SIOPEL study was conducted in 47 European centres including 14 from the UK. The inclusion of UK centres combined with the global nature of paediatric information sharing supports the generalisability of the cisplatin regimes used in SIOPEL 6 to UK practice.

b) In addition, please provide a full breakdown (number and percent of patients by treatment group) of the treatments received in the COG ACCL0431 study: cisplatin monotherapy; cisplatin combination therapy and type of chemotherapy regimens, including for the localised subgroup of patients.

The Company would like to clarify that the type of chemotherapy regimen received was not recorded in the COG ACCL0431 trial, therefore this data is not directly available. To indirectly obtain this information, the Company assessed the frequency of cisplatin dosing (i.e. doses per cycle, number of cycles, length of time between doses) received by each patient (which is available in trial records) and compared it to the chemotherapy treatment protocols which were in use for each tumour type in the US at the time the trial.

Being an indirect assessment, there are limitations to it. Please note however that Ppatients may have received modifications to these chemotherapy protocols which were not reported in the study data, therefore protocols may have varied between patients who have been listed as receiving the same protocol. This data should therefore be viewed as an *estimate* of the distribution of patients who received

similar various chemotherapy regimens (with potential modifications) in the COG ACCL0431, rather than exactly the same regimens study..

A summary of the chemotherapy treatment protocols in use for each tumour type at the time of the trial is presented in Appendix Table 2. Table 6 below presents the number of patients with each tumour type in each treatment arm of the COG ACCL0431 study who were on each chemotherapy regimen (as estimated via the protocols), and the distribution of chemotherapy within each treatment arm for each tumour type. The breakdown also includes metastatic and localised patients. The table demonstrates that generally the cisplatin treatments that patients received in both arms were similar.

Table 6: Chemotherapy regimen distributions by tumour type in the COG ACCL0431 trial

Tumour type	Cisplatin treatment protocol	n (cisplatin without Pedmarqsi)	% of patients in cisplatin without Pedmarqsi arm with tumour type	n (cisplatin with Pedmarqsi)	% of patients in cisplatin with Pedmarqsi arm with tumour type
Localised germ cell tumours	Cisplatin, etoposide, bleomycin (CCG8891 or CCG8891-like)	[redacted]	[redacted]	[redacted]	[redacted]
	Cisplatin, etoposide, bleomycin (AGCT0132 or AGCT0132-like)	[redacted]	[redacted]	[redacted]	[redacted]
Localised medulloblastoma	Cisplatin, cyclophosphamide, etoposide, vincristine, methotrexate, carboplatin, thiotepa (Head Start II or Head Start II-like)	[redacted]	[redacted]	[redacted]	[redacted]
	Cisplatin, cyclophosphamide, etoposide, vincristine, methotrexate, carboplatin, thiotepa, temozolomide (Head Start III or Head Start III-like)	[redacted]	[redacted]	[redacted]	[redacted]
	Cisplatin, vincristine, cyclophosphamide, etoposide (Lafay-Cousin Protocol or Lafay-Cousin-like Protocol)	[redacted]	[redacted]	[redacted]	[redacted]
	Cisplatin, lomustine vincristine (Packer Protocol or Packer-like Protocol)	[redacted]	[redacted]	[redacted]	[redacted]
	Temozolomide, irinotecan, bevacizumab (ACNS0821 or ACNS0821-like)	[redacted]	[redacted]	[redacted]	[redacted]
	Protocol unclear	[redacted]	[redacted]	[redacted]	[redacted]
Localised neuroblastoma	Cisplatin, carboplatin, etoposide, melphalan, thiotepa, cyclophosphamide (ANBL0532 or ANBL0532-like)	[redacted]	[redacted]	[redacted]	[redacted]
Localised osteosarcoma	Cisplatin, doxorubicin, methotrexate, ifosfamide, etoposide (AOST0331 or AOST0331-like)	[redacted]	[redacted]	[redacted]	[redacted]
	Protocol unclear	[redacted]	[redacted]	[redacted]	[redacted]
	Cisplatin, doxorubicin (SIOPEL 3 or SIOPEL 3-like)	[redacted]	[redacted]	[redacted]	[redacted]

Tumour type	Cisplatin treatment protocol	n (cisplatin without Pedmarqsi)	% of patients in cisplatin without Pedmarqsi arm with tumour type	n (cisplatin with Pedmarqsi)	% of patients in cisplatin with Pedmarqsi arm with tumour type
Localised hepatoblastoma Other tumour types	Cisplatin, etoposide, cyclophosphamide, methotrexate, vincristine, carboplatin, thiotepa (ACNS0333 or ACNS0333-like)	[redacted]	[redacted]	[redacted]	[redacted]
	Protocol unclear	[redacted]	[redacted]	[redacted]	[redacted]
Disseminated germ cell tumours	Standard dose cisplatin with bleomycin and etoposide	[redacted]	[redacted]	[redacted]	[redacted]
	High dose cisplatin with bleomycin and etoposide (later decreased to standard dose)	[redacted]	[redacted]	[redacted]	[redacted]
	Protocol unclear	[redacted]	[redacted]	[redacted]	[redacted]
Disseminated medulloblastoma	Cisplatin, lomustine, vincristine (Packer Protocol or Packer-like Protocol)	[redacted]	[redacted]	[redacted]	[redacted]
	Cisplatin, cyclophosphamide, etoposide, vincristine, methotrexate, carboplatin, thiotepa (Head Start II or Head Start II-like)	[redacted]	[redacted]	[redacted]	[redacted]
	Topotecan, cisplatin, cyclophosphamide, vincristine (Strother protocol or Strother-like protocol)	[redacted]	[redacted]	[redacted]	[redacted]
Disseminated neuroblastoma	Cisplatin, carboplatin, etoposide, melphalan, thiotepa, cyclophosphamide (ANBL0532 or ANBL0532-like)	[redacted]	[redacted]	[redacted]	[redacted]
	Protocol unclear	[redacted]	[redacted]	[redacted]	[redacted]
Disseminated osteosarcoma	Cisplatin, doxorubicin, methotrexate, ifosphamide (AOST0331 or AOST0331-like)	[redacted]	[redacted]	[redacted]	[redacted]
	Zolendronic acid, cisplatin, doxorubicin, methotrexate, ifosfamide, etoposide (AOST06P1 or AOST06P1-like)	[redacted]	[redacted]	[redacted]	[redacted]
	Protocol unclear	[redacted]	[redacted]	[redacted]	[redacted]

Tumour type	Cisplatin treatment protocol	n (cisplatin without Pedmarqsi)	% of patients in cisplatin without Pedmarqsi arm with tumour type	n (cisplatin with Pedmarqsi)	% of patients in cisplatin with Pedmarqsi arm with tumour type
Disseminated hepatoblastoma and other tumour types	Cisplatin 100 mg/m^2, bleomycin, cyclophosphamide, doxorubicin, etoposide and vinblastine	[redacted]	[redacted]	[redacted]	[redacted]
	Protocol unclear	[redacted]	[redacted]	[redacted]	[redacted]

A15. CS, Section B.2.3.1, page 47. Please clarify how missing data were dealt with in the COG ACCL0431 trial for reasons other than infeasible hearing assessments or logistical issues.

Missing data were treated in the same way, regardless of the reason for missingness. The primary efficacy assessment for COG ACCL0431 was conducted in the efficacy population, which included all children in the ITT population who had both baseline and 4-week follow-up hearing assessments. Any patients with missing data due to any reason (for example death, infeasible hearing assessment, logistical issues) were excluded from the efficacy population. This was pre-specified in the statistical analysis plan for the trial (as discussed in response to B6). In the ITT population however, patients with missing data for any reason were included and were assumed to have hearing loss.

A16. CS, Section B.2.10.1, page 60. Please clarify the statement and reasons why *'...four children that were randomised to the cisplatin with Pedmarqsi arm did not receive Pedmarqsi and were included in the cisplatin without Pedmarqsi arm'*.

In SIOPEL 6, patient numbers [redacted], [redacted], [redacted] and [redacted] were randomised to the cisplatin with Pedmarqsi arm. However, as Pedmarqsi was not available at the respective sites, these children were subsequently included in the cisplatin without Pedmarqsi arm.

A17. CS, Section B2.2.4 page 40, and Sections B.2.10.1 and B.2.10.2. The CS mentions that in the COG ACCL0431 study *"children who discontinued Pedmarqsi prematurely before completion of the planned treatment regimen also completed audiograms at four weeks and one year after completing the planned treatment regimen*"; however, it does not mention how discontinuation was dealt with in SIOPEL 6. Please clarify if and when the planned hearing assessments were carried out in children who discontinued treatment with sodium thiosulfate in COG ACCL0431 and SIOPEL 6. In addition, only discontinuations related to adverse events were reported in the CS. Please provide further details on treatment adherence for sodium thiosulphate and the reasons for discontinuing treatment in the SIOPEL 6 and COG

ACCL0431 studies (e.g., adverse events, refusal of protocol therapy, other reasons), including for the localised disease subgroup of patients.

In COG ACCL0431, children were considered “off protocol” and discontinued Pedmarqsi treatment if any of the following circumstances occurred:

- Completion of planned chemotherapy treatment regimen for the newly diagnosed disease that made the child eligible for entry into COG ACCL0431.
- Premature discontinuation of cisplatin therapy for any reason.
- Administration of cranial irradiation prior to performing the post-end of treatment audiometry tests.
- Grade 2 or greater allergic reaction to Pedmarqsi or Grade 1 allergic reaction to Pedmarqsi that had been pretreated and worsened with subsequent treatments.
- Repeated hypernatraemia that resulted in the child receiving ≤ 50% of the scheduled Pedmarqsi doses in each of two consecutive courses (cycles) of cisplatin (applicable to multiple-day dosing regimens).
- Refusal of further protocol therapy by the child/parent/guardian.
- Pregnancy.
- Physician determined it was in the child’s best interest to discontinue protocol therapy or the study.
- Development of a second malignancy.

Children who were off protocol therapy were to be followed-up for hearing assessments and survival outcomes as per the COG ACCL0431 protocol,[21] until they met the criteria for “Off Study”. Children were considered “Off Study” if any of the following criteria were met:

- Death.
- Lost to follow-up.
- Entry into another COG therapeutic study for treatment of the underlying cancer that made the patient eligible for enrolment into COG ACCL0431.
- Withdrawal of consent for any further data submission.
- Tenth anniversary of study entry.

Table 7 and 8 presents COG ACCL0431 patient disposition – all patients and localised patients only, respectively .

Table 7: COG ACCL0431 patient disposition (all patients)

Parameter	Cisplatin without Pedmarqsi (N=64)	Cisplatin with Pedmarqsi (N=59)	Total (N=123)
Patients who completed planned chemotherapy treatment	[redacted]	[redacted]	[redacted]
Patients who discontinued protocol therapy due to (primary reason), n (%)			
Premature discontinuation of cisplatin therapy for any reason	[redacted]	[redacted]	[redacted]
Refusal of further protocol therapy by patient/parent/guardian	[redacted]	[redacted]	[redacted]
Physician determined it was in the patient's best interest	[redacted]	[redacted]	[redacted]
Administration of cranial irradiation prior to performing post-end of treatment audiometry tests	[redacted]	[redacted]	[redacted]
Adverse event[a]	[redacted]	[redacted]	[redacted]
Death[b]	[redacted]	[redacted]	[redacted]

[a] Grade 2 or greater allergic reaction to Pedmarqsi or Grade 1 allergic reaction to Pedmarqsi that was pretreated and worsened with subsequent treatments.

[b] Patient [redacted] died due to cardiac arrest during chemotherapy, unrelated to Pedmarqsi.

Table 8: COG ACCL0431 patient disposition (localised only)

Parameter	Cisplatin without Pedmarqsi (N=38)	Cisplatin with Pedmarqsi (N=38)	Total (N=76)
Patients who completed planned chemotherapy treatment	[redacted]	[redacted]	[redacted]
Patients who discontinued protocol therapy due to (primary reason), n (%)			
Premature discontinuation of cisplatin therapy for any reason	[redacted]	[redacted]	[redacted]
Refusal of further protocol therapy by patient/parent/guardian	[redacted]	[redacted]	[redacted]
Physician determined it was in the patient's best interest	[redacted]	[redacted]	[redacted]
Administration of cranial irradiation prior to performing post-end of treatment audiometry tests	[redacted]	[redacted]	[redacted]

Parameter	Cisplatin without Pedmarqsi (N=38)	Cisplatin with Pedmarqsi (N=38)	Total (N=76)
Adverse event[a]	[redacted]	[redacted]	[redacted]
Death[b]	[redacted]	[redacted]	[redacted]

[a] Grade 2 or greater allergic reaction to Pedmarqsi or Grade 1 allergic reaction to Pedmarqsi that was pretreated and worsened with subsequent treatments

[b] Patient [redacted] died due to cardiac arrest during chemotherapy, unrelated to Pedmarqsi.

For SIOPEL 6, the protocol stipulated that patients with progressive disease after two or more courses of cisplatin with or without Pedmarqsi should stop study treatment and were considered treatment failures. The usual criteria for withdrawal of consent and adverse events leading to withdrawal were also mentioned. The protocol further states that children who did not receive the full planned chemotherapy treatment assigned would still be included in the hearing assessment evaluation when they reached 3.5 years of age, or if they had already reached that age by the completion of their last cisplatin treatment, their hearing would be assessed 6-12 weeks later.

Patient disposition in SIOPEL 6 is shown in Table 9. No patients were lost to follow-up and one child was withdrawn from the cisplatin with Pedmarqsi arm due to a serious adverse event. No dose alterations were required due to AEs. All patients in SIOPEL 6 had localised disease.

Table 9: SIOPEL 6 patient disposition (all patients)

Status	Cisplatin without Pedmarqsi	Cisplatin with Pedmarqsi	Total
All Patients			
Registered, n	--	--	129
Not randomised, n	--	--	15
Parental consent withdrawn	--	--	1
Eligibility criteria	--	--	1
Other reasons	--	--	13
Randomised, n	53	61	114
Not treated [a]	1	4	5
Parental consent withdrawn	0	2	2
Reclassified as high-risk	1	1	2
Eligibility criteria	0	1	1
Treated			
As randomised (ITT Population), n	52	57	109
Completed study, n (%) [b, c]	46 (88.5)	55 (96.5)	101 (92.7)
Did not complete study, n (%) [b, c]	6 (11.5)	2 (3.5)	8 (7.3)
As treated (Safety Population) [d], n	56	53	109
Total deaths, n (%) [e]	4 (7.1)	2 (3.8)	6 (5.5)
Disease progression	2 (3.6)	2 (3.8)	4 (3.6)
Other causes	2 (3.6)	0	2 (1.8)

[a] The following five patients were excluded: [redacted] (ineligible), [redacted] and [redacted] (due to parental refusal), [redacted] and [redacted] (reclassified as high-risk not standard-risk disease).
[b] Study completion was defined as completion of the Post-Treatment Hearing Assessment.
[c] Percentage was computed based on the ITT Population.
[d] Four patients ([redacted], [redacted], [redacted], [redacted]) that were randomised to the cisplatin with Pedmarqsi arm did not receive Pedmarqsi were included in the cisplatin without Pedmarqsi arm.
[e] Includes the two deaths that occurred before the end of treatment as well as four additional deaths that occurred during follow-up. Percentage was computed based on the Safety population.
Abbreviations: ITT – Intention-to-treat

A18. CS, Document A, Section A.1, page 4. The CS notes that *'...Ototoxicity…tends to worsen with increasing cumulative doses of cisplatin…Risk factors for more severe hearing loss include … a high cumulative dose of cisplatin (> 400 mg/m2)'*. Please provide further details on dose reductions/adjustments in the SIOPEL 6 and COG ACCL0431 studies, including for the localised disease subgroup of patients.

As specified in the COG ACCL0431 protocol, if toxicities arose as a result of cisplatin treatment, dose reductions were followed according to the patient's disease-specific cancer treatment protocol or program. Similarly, the SIOPEL 6 study also allowed dose reduction of cisplatin and suggested that patients should contact their chemotherapy co-ordinators to discuss particular cases. The SIOPEL 6 protocol also states that severe cisplatin toxicity may have led to an alternative treatment being sought, with the child remaining on the trial but having any treatment changes clearly documented and any change being carefully assessed.

Despite the possibility of dose modifications, comparison of cumulative cisplatin doses across the arms in both studies, show that the amount of cisplatin that patients received was similar. The response to Question B13 displays a breakdown of the cumulative cisplatin dose that patients received in the cisplatin with Pedmarqsi and the cisplatin without Pedmarqsi arms, and in both studies the mean cumulative dose is not significantly different across treatment arms.

Dose modifications for Pedmarqsi were defined as follows in the study protocols:

COG ACCL0431: doses could be withheld in cases of hypernatraemia (serum sodium concentration >145 mEq/L in a multiple-day cisplatin dosing regimen) or allergic reaction (leading to Pedmarqsi discontinuation)

SIOPEL 6: Pedmarqsi should be stopped and not given at further treatment cycles if metabolic, vascular, neurological or other, presumed to be related, toxicity of CTCAE Grade 3+ is experienced. Pedmarqsi should not be given to a patient with previous hypersensitivity to Pedmarqsi.

Some Pedmarqsi doses were reduced in SIOPEL 6 based on a manual evaluation of the data in the clinical databases. In this study a dose reduction occurred in five patients and in all cases, this was noted as a clinician decision. In two patients, the dose was adjusted for ease of administration, and in one patient, no reason for the dose reduction was given. In one patient, the dose given was always 12.5 g, and it was noted that the dose was rounded to one vial. Finally in one patient, the reason given was poor renal function for a 6-week old infant at diagnosis. No patients in SIOPEL 6 required a dose alteration due to a serious AE.

In COG ACCL0431, dose alterations were not permitted and no information on this is captured in the clinical database.

A19. CS, Sections B.2.2.2. and B.2.2.4. Please provide further details on the strengths and limitations on the different hearing loss (HL) grading scales used in the SIOPEL 6, COG ACCL0431 studies and Orgel et al. (2023). In addition, how and which ototoxicity scales are commonly used in UK clinical practice, and how do they correspond to each other when evaluating hearing loss severity.

It is noted that different hearing loss grading scales were used for each of the available efficacy sources presented in the CS, and included in the economic modelling; the ASHA scale was used in COG ACCL0431, the Brock scale was used in SIOPEL 6, and Orgel et al. (2023)[18] reanalysed COG ACCL0431 data using the SIOP ototoxicity scale.

Clinical expert opinion from an audiovestibular physician[7] noted that there is a degree of variability in terms of scales used in UK clinical practice. All scales referenced above (Brock, SIOP and ASHA) may be used by clinicians, although the ASHA is more commonly used in the USA..[7] Further to this, the physician confirmed that Great Ormond Street Hospital (GOSH) has been the leading centre in paediatric ototoxicity in the UK and use both the Brock and SIOP ototoxicity grading scales.[7] During interviews conducted in 2018 with audiologists who confirmed that the Brock scale was most commonly used in clinical practice in the UK for grading cisplatin-induced hearing loss. It was highlighted that this scale is considered easy to use and is better understood by oncologists than other scales.

Clemens et al. (2019)[22] studied the concordance between ototoxicity grading scales, including the Brock, SIOP, Muenster and Chang scales. The authors concluded that there was generally good concordance between the scales, whilst caveating there is diversity in the definition of functionality across the instruments. Concordance between the Brock scale and the SIOP ototoxicity scale was also the third highest ($\kappa = 0.840$) amongst comparisons of the included instruments. A study by Knight et al. (2016)[23] compared the ASHA, Brock, and SIOP ototoxicity scales in a large cohort of children and young adults treated for the first time with a cisplatin-containing regimen. The study concluded that the SIOP ototoxicity scale may be superior to ASHA, Brock and CTCAE instruments; although the study also suggested that the

sensitivity in detecting any ototoxicity was comparable between the SIOP ototoxicity (55%) and ASHA (56%) scales, whilst it was slightly lower for the Brock scale (40%).

In terms of strengths and weaknesses of the scales, the ASHA criteria were applied in the COG ACCL0431 trial as this instrument was regarded as the most sensitive scale available to assess hearing loss at the time of the study. However, this scale defines ototoxic change as binary (yes/no) based on threshold changes from baseline, and these criteria cannot describe the degree of ototoxicity experienced. This issue is addressed via the Brock scale which is applied in the SIOPEL 6 study. This scale was specifically developed for measuring cisplatin-induced ototoxicity, it is based on absolute hearing thresholds, and has four grades using 40 dB HL as a boundary level differentiating significant from non-significant changes. Therefore, the Brock scale also has the capability of measuring hearing loss severity.

This issue related to the ASHA criteria is also addressed via the SIOP scale, which is similarly based on absolute thresholds and uses cut-offs of 20- and 40-dB HL with more weight, and higher ototoxicity grades given to hearing loss in the mid-frequencies than the high-frequencies. It is worth noting that the Orgel et al. (2023)[18] study re-evaluated the COG ACCL0431 endpoints according to the SIOP ototoxicity scale.[7]

Importantly, the otoprotective effect of Pedmarqsi has been consistently demonstrated across a range of ototoxicity scales. For example, as defined by the ASHA criteria, in COG ACCL4031, children receiving cisplatin with Pedmarqsi were approximately 73% less likely to develop hearing loss than children receiving cisplatin without Pedmarqsi.[24] According to the Orgel et al. (2023)[18] re-analysis using the SIOP scale, children receiving cisplatin with Pedmarqsi were approximately 75% less likely to develop Grade $\geq$1 cisplatin-induced hearing loss than children receiving cisplatin without Pedmarqsi. Therefore, results from this re-analysis confirm the otoprotective effects of Pedmarqsi using a different ototoxicity scale.

The Company does however acknowledge there is variability in the ototoxicity scales and has therefore performed cost-effectiveness using a range of scales. The results

of these analyses, some of which were presented in the initial CS, are available below in Table 10.

Table 10: Cost-effectiveness results

Analysis	Hearing loss yes/no	Severity	ICER
Base case	Data source: COG ACCL0431 Scale: ASHA criteria	Data source: Orgel et al (2023) (COG ACCL0431 reanalysed) and Knight et al. (2005) Scale: SIOP and Brock	£[redacted]
Scenario	Data source: COG ACCL0431 Scale: ASHA criteria	Data source: Orgel et al (2023) (COG ACCL0431 reanalysed) and SIOPEL 6 Scale: SIOP and Brock	£[redacted]
Scenario	Data source: Orgel et al (2023) (COG ACCL0431 reanalysed) Scale: SIOP	Data source: Orgel et al (2023) (COG ACCL0431 reanalysed) and Knight et al. (2005) Scale: SIOP and Brock	£[redacted]
Scenario	Data source: Orgel et al (2023) (COG ACCL0431 reanalysed) Scale: SIOP	Data source: Orgel et al (2023) (COG ACCL0431 reanalysed) and SIOPEL 6 Scale: SIOP and Brock	£[redacted]
Scenario	Data source: SIOPEL 6 Scale: Brock	Data source: SIOPEL 6 Scale: Brock	£[redacted]
Scenario	Data source: COG ACCL0431 Scale: ASHA criteria	Data source: SIOPEL 6 Scale: Brock	£[redacted]

Abbreviations: ICER – Incremental cost-effectiveness ratio; SIOP – International Society of Paediatric Oncology.

A20 CS, Section B.2.2.2 page 35. Please provide further details on how the primary endpoint in SIOPEL 6 of absolute hearing threshold, as measured by pure tone audiometry (PTA), at a minimum age of 3.5 years, was obtained in children of the age group of the study (mean age of 1.5 years). Please also clarify how the potential delay in measuring the outcome could affect the interpretation of the results of the study.

As stated in Section B.2.2.2, the primary endpoint of SIOPEL 6 (proportional incidence of hearing loss) was measured by pure tone audiometry after the end of treatment, or at age ≥3.5 years (whichever timepoint was later). This is because it is

not possible to achieve a reliable pure tone audiometry test in children under the age of 3.5 years old. For patients older than 3.5 years, audiometry results were obtained 6-12 weeks after the administration of the last cisplatin dose.

Given that hearing loss is irreversible, there are no concerns with the interpretation of results for those where the hearing assessment was after a prolonged period of time. That is patients that experience cisplatin-induced ototoxicity under the age of 3.5 years old, will still present with ototoxicity when they reach 3.5 years old. It is more important to obtain a reliable pure tone audiometry result, hence delaying the assessment until the age of 3.5 years is necessary.

A21. CS, Sections B.2.3 and B.2.7. Please clarify whether the type-1 error was controlled for in the SIOPEL 6 and COG ACCL0431 trials at a level of 0.05 (one-sided). Please also clarify whether subsequent statistical tests of clinical outcomes, such as those outlined in CS Section B.2.3 and the pooled analysis in CS Section 2.7, were one- or two-sided.

A single formal hypothesis was designed for both the COG ACCL0431 and SIOPEL 6 studies. The comparisons for the primary endpoint of hearing loss were assessed using a two-sided P-value of 0.05. No other formal comparisons were conducted apart from the primary hearing loss endpoint. In addition, the studies were not designed for comparing event free survival and overall survival, and nominal two-sided P-values were reported without Type-1 error control for these survival endpoints.

A22. CS, Section B.1.2, Table 2. Given the complex regimen of administration and the need to observe accurate timing of sodium thiosulphate administration relative to cisplatin chemotherapy, please comment on how potential medication errors and the potential loss of effectiveness for both products can be mitigated in UK clinical practice. Please also comment on the concerns noted in the CHMP Assessment Report (Procedure No. EMEA/H/C/005130/0000; page 104-105) that the main potential risk associated with sodium thiosulphate use is its interaction with cisplatin that could possibly lead to reduced effectiveness of cisplatin, and that evidence of

such a detrimental effect was observed in the COG ACCL0431 study in terms of EFS.

Medication errors have not been identified as a potential risk for Pedmarqsi and no medication errors were identified throughout either the COG ACCL0431 or SIOPEL 6 programmes. It should be noted that Pedmarqsi does not need to be reconstituted or diluted before use. Furthermore, the product will be prepared and administered by highly trained specialist nurses in paediatric oncology units. Such experts are familiar with and experienced in complicated chemotherapy regimens. On the point of complexity therefore, the Company does not anticipate this is a safety risk for sodium thiosulphate.

The potential interaction between cisplatin and Pedmarqsi has been considered very carefully. Administration times of cisplatin and Pedmarqsi were separated by six hours in both SIOPEL 6 and COG ACCL0431 to ensure that sodium thiosulphate and cytotoxically active unbound cisplatin were never in the plasma at the same time, thus limiting any potential interaction. The 6-hour administration time separation was retrospectively checked for relapsed patients with disseminated disease (n=[redacted]) in the COG ACCL0431 study, and data returned for [redacted] patients confirmed the mean separation interval being [redacted] hours (range [redacted]-[redacted]).[24] In SIOPEL 6, [redacted] out of [redacted] records ([redacted]%) of Pedmarqsi administration indicated that Pedmarqsi was not given within 15 minutes of the required 6-hour time interval. For one record, there was no further information, but for the remaining [redacted] records, the Pedmarqsi administration was delayed by up to two hours for a variety of mostly administrative reasons. The most common reasons were delay in receiving drug from pharmacy, ward staff changeovers and blocked or unusable infusion lines. In terms of the duration of Pedmarqsi infusion, [redacted] doses ([redacted]%) were not administered during an infusion time of 15 minutes +/- 5 minutes. These data indicate that the minimum time interval between cisplatin and Pedmarqsi administration was respected in both clinical trials.

It is acknowledged, that the timing of Pedmarqsi administration is critical and this has the potential for errors which may impact efficacy. However clear labelling is provided in the SmPC[1] and in the instructions for use included in the healthcare HCP section of

the Patient Information Leaflet[25], to ensure that a gap of six hours is implemented between the end of Pedmarqsi infusion and the next cisplatin infusion.

Regarding the risk of interaction between cisplatin and Pedmarqsi, in SIOPEL 6 there was no difference in EFS or OS between the treatment groups. In the COG ACCL0431 study analysis, there was no effect of Pedmarqsi on EFS or OS in the total population studied nor in the patients categorised post-hoc as having localised disease.

Pooled analysis of survival in all localised disease patients in COG ACCL0431 and SIOPEL6 in the ITT population noted [redacted] deaths in the cisplatin without Pedmarqsi arm (n=[redacted]) compared with [redacted] deaths in the cisplatin with Pedmarqsi arm (n=[redacted]) yielding a hazard ratio of [redacted] (95% CI [redacted], [redacted]; p[redacted]) indicating clearly that there is no difference in survival in localised disease.

It was only among patients categorised post-hoc as having disseminated disease where there was an observed disparity in OS between the cisplatin with Pedmarqsi arm versus the cisplatin without Pedmarqsi arm.

A post-hoc analyses extensively investigated the potential reasons for the reduced OS observed in cisplatin with Pedmarqsi treated children categorised post-hoc as having disseminated disease in COG ACCL0431. As COG ACCL0431 was a hearing study, prognostic risk was not considered during randomisation and only factors relating to hearing loss were considered in stratification. The outcome of the evaluation clearly indicated that the most likely explanation for the difference was an imbalance in prognostic indicators relating to the underlying tumour types in the two arms, with [redacted] of [redacted] ([redacted]%) children with disseminated disease in the cisplatin with Pedmarqsi arm having been identified with poor prognostic indicators for survival at the outset of the study compared to [redacted] of [redacted] ([redacted]%) children with disseminated disease in the cisplatin without Pedmarqsi arm. These prognostic indicators were not controlled for during randomisation and were not stratification variables. Additionally, the study was not sufficiently large such that the variability in prognostic indicators would be taken care of during randomisation without stratification since the study was powered for the hearing loss endpoint only. A similar evaluation for children categorised with localised disease showed to the contrary that children randomised to cisplatin with Pedmarqsi did not have better prognostic chances from the outset.

Another important aspect to consider on interaction potential is the assessment of nephrotoxicity and haematological toxicity. Researchers have studied the use of sodium thiosulphate to prevent cisplatin nephrotoxicity and haematological toxicity as a 'systemic rescue' in situations where tumours require high doses of cisplatin for efficacy, but toxicities limit the ability to deliver high doses e.g., head and neck cancer, ovarian cancer.[26] In these situations, the cisplatin and STS must be given concurrently and, to avoid an effect on tumour efficacy, the two agents are given into different body compartments e.g., intraperitoneal cisplatin and IV STS, or intraarterial cisplatin and IV STS. If there could be an interaction between sodium thiosulphate and cisplatin that might reduce anti-tumour efficacy, then reductions in cisplatin-induced haematological toxicity or renal toxicity might also be observed when comparing STS-treated patients with those not receiving STS. Findings related to haematological toxicity may be particularly relevant as these also concern an effect of cisplatin on proliferating cells.

Results of both renal and haematological toxicities from COG ACCL0431 and SIOPEL 6 are summarised in Table 11. There was no observed protection offered by Pedmarqsi against cisplatin-induced renal or haematological toxicity when it was given 6 hours after a cisplatin infusion. Of note, there was no difference to rates of haematological toxicity between the cisplatin with Pedmarqsi and cisplatin without Pedmarqsi arms, suggesting no interference by Pedmarqsi in the toxicity of cisplatin in rapidly multiplying cells.

Table 11: Comparison of cisplatin toxicity on organs other than the ear reported within SIOPEL 6 and COG ACCL0431

Preferred term	SIOPEL 6		COG ACCL0431	
	Cisplatin without Pedmarqsi (N=56) n (%)	Cisplatin with Pedmarqsi (N=53) n (%)	Cisplatin without Pedmarqsi (N=64) n (%)	Cisplatin with Pedmarqsi (N=59) n (%)
Renal toxicity (Grade 3 or above)				
GFR decreased	0	0	0	0
Acidosis	0	0	1 (1.6)	2 (3.4)
Creatinine increased	0	0	0	0
Hypophosphataemia	0	5 (9.4)	7 (10.9)	12 (20.3)
Hypomagnesaemia	1 (1.8)	1 (1.9)	2 (3.1)	3 (5.1)
Hypokalaemia	0	5 (9.4)	13 (20.3)	16 (27.1)
Haematological toxicity (Grade 3 or above)				
Febrile neutropenia	9 (16.1)	8 (15.1)	19 (29.7)	14 (23.7)
Neutrophil count decreased	9 (16.1)	12 (22.7)	53 (82.8)	49 (83.1)
White cell count decreased	2 (3.6)	2 (3.8)	42 (65.6)	38 (64.4)
Platelet count decreased	2 (3.6)	2 (3.8)	39 (60.9)	38 (64.4)
Haemoglobin decreased/Anaemia	9 (16.1)	10 (18.9)	36 (56.3)	30 (50.8)

Source: COG ACCL0431 CSR[24] and SIOPEL 6 CSR[28]

Measurements of free cisplatin show levels in blood are <5% of peak within four hours of the end of an infusion suggesting a wide margin of error if Pedmarqsi is given six hours after infusion.[27]

Finally, a recently published narrative review of the literature (n=31 articles) pertaining to the use of sodium thiosulphate as an otoprotectant in patients with cancer treated with platinum compounds found that delayed systemic administration of sodium thiosulphate at six hours after the cisplatin infusion does not affect cisplatin-induced inhibition of tumour growth or cellular toxicity in the pre-clinical setting, nor affect cisplatin efficacy and survival in children with localised disease in the clinical setting. (Meijer, Diepstraten, Ansari et al, 2024).[28]

A23. CS, Sections B.2.10 and B.2.12. Please comment on the concerns noted in the CHMP Assessment Report (Procedure No. EMEA/H/C/005130/0000; page 104-105) on the interpretability of sodium thiosulphate efficacy in subgroups (e.g., based on age, chemotherapy regimen or underlying disease) and clinically relevant consequences of adverse events related to electrolyte imbalance.

Interpretability of Pedmarqsi efficacy in subgroups

SIOPEL 6 evaluated a homogeneous population of 109 patients with standard-risk hepatoblastoma, which by definition are localised tumours. The median age of children in this study was 13.0 months, with ages ranging from 1.2 months to 98.6 months (approximately 8 years old) (SIOPEL 6 CSR, Table 14.1.4.2). This age range is representative of a patient population with standard-risk hepatoblastoma.

COG ACCL0431 evaluated a heterogeneous population of 123 children newly diagnosed with solid tumours that were to be treated with cisplatin chemotherapy, including patients with histologically-confirmed germ cell tumour, hepatoblastoma, medulloblastoma, neuroblastoma, osteosarcoma, or other solid tumour. The median age of children in this study was 9.5 years old, with ages ranging from 1 year old to 18 years old (COG ACCL0431 CSR, Table 14.1.3.1). In COG ACCL0431, a subset of patients (n=[redacted]) was categorised (post-hoc) as having localised disease. Of these [redacted] patients, the median age of children in this study was [redacted] years old, with ages ranging from [redacted] year old to [redacted] years old.

In addition to the two studies demonstrating the efficacy of Pedmarqsi in reducing the risk of cisplatin-induced hearing loss in children from 1 month to 18 years old, it is worth noting that STS efficacy has also been demonstrated where STS is used to reduce cisplatin-induced ototoxicity in adult patients treated for head and neck cancers.[29] In this indication, high intensity cisplatin (150 mg/m^2) was given directly into the artery supplying the tumour, whilst STS was given concurrently. A comparison of this regimen versus standard intravenous cisplatin without STS protection showed that adults treated with STS had a 10% lower incidence of low and high frequency hearing loss ($p<0.001$). This provides further evidence that the effectiveness of STS in reducing hearing loss is not age dependent.

Taken together, the children in SIOPEL 6 and COG ACCL0431 represent the entire age range in the proposed indication (patients aged from 1 month to <18 years). Both studies showed a statistically significant reduction in ototoxicity in patients aged 1 month to ≤18 years with various types of solid tumours treated with cisplatin with Pedmarqsi, as shown in Table 12. Further support is provided by the effectiveness of

Pedmarqsi in reducing hearing loss in adults receiving cisplatin for head and neck cancers.

Table 12: Summary of hearing loss in Phase 3 studies of Pedmarqsi

Results	SIOPEL 6 ITT population		COG ACCL0431 efficacy population			
			Overall		Localised disease	
	Cisplatin without Pedmarqsi (N=52), n (%)	Cisplatin with Pedmarqsi (N=57), n (%)	Cisplatin without Pedmarqsi (N=55), n (%)	Cisplatin with Pedmarqsi (N=49), n (%)	Cisplatin without Pedmarqsi (N=33), n (%)	Cisplatin with Pedmarqsi (N=31), n (%)
Yes, n (%)	35 (67.3)	20 (35.1)	31 (56.4)	14 (28.6)	[redacted]	[redacted]
No, n (%)	17 (32.7)	37 (64.9)	24 (43.6)	35 (71.4)	[redacted]	[redacted]
Relative risk (95% CI)	0.521 (0.349, 0.778)		0.516 (0.318, 0.839)		[redacted]	
P-value[a]	<0.001		0.0040		[redacted]	
Odds ratio (95% CI)	0.254 (0.111, 0.579)		0.274 (0.114, 0.660)		[redacted]	
P-value[b]	0.001		0.0039		[redacted]	

Note: In SIOPEL 6, patients without hearing loss assessment were included as a 'Yes' for hearing loss. Hearing impairment was defined as Brock Grade ≥1 hearing loss determined by PTA at age ≥3.5 years.
[a] In SIOPEL 6, relative risk was calculated non-stratified. In COG ACCL0431, relative risk was calculated using a CMH test including stratification variable.
[b] In SIOPEL 6 and COG ACCL0431, the odds ratio was based on logistic regression including treatment and stratification variable as a covariate in the model.
Abbreviations: ASHA – American-Speech-Language-Hearing Association; CI – Confidence interval; CMH – Cochran-Mantel-Haenszel; ITT – Intention-to-treat; PTA – Pure tone audiometry.

The mechanism of action of Pedmarqsi in the prevention of cisplatin-induced ototoxicity is not tumour specific, as efficacy has been demonstrated in a range of paediatric solid tumours where various cisplatin-based chemotherapy regimens are used in the two pivotal trials. Paediatric solid tumours are, relatively speaking, rare occurrences, so to extensively study efficacy in every individual tumour type would be extremely challenging. Conducting SIOPEL 6 and COG ACCL0431 has taken approximately 12 years (2006 to 2018).

Overall, 234 children with a wide variety of tumours were studied in SIOPEL 6 and COG ACCL0431, where the efficacy and safety of Pedmarqsi were demonstrated. In total, these studies included 118 children (50%) who were treated with Pedmarqsi (57 in SIOPEL 6 and 61 in COG ACCL0431).

In terms of the range of tumours included in both studies where the efficacy and safety of Pedmarqsi were demonstrated, there were 116 cases of hepatoblastoma (59 treated with Pedmarqsi), 32 germ cell tumours (16 treated with Pedmarqsi), 29 osteosarcomas (14 treated with Pedmarqsi), 26 CNS tumours (12 treated with Pedmarqsi), 26 neuroblastomas (14 treated with Pedmarqsi) and five other types of tumours (three treated with Pedmarqsi).

In summary, the prevention of hearing loss by Pedmarqsi was similar in SIOPEL 6 (hepatoblastoma only) and COG ACCL0431 (including hepatoblastoma, neuroblastoma, CNS tumours, germ cell tumours and osteosarcoma) which supports the notion that the mechanism of action is directed at cisplatin-induced ototoxicity and is therefore independent of underlying disease (i.e. tumour type) and chemotherapy regimen.

Clinically relevant consequences of adverse events related to electrolyte imbalance

The CHMP report commented that some AEs were reported with significantly higher incidence in the cisplatin with Pedmarqsi arm compared to the cisplatin without Pedmarqsi arm, and specifically highlighted AEs related to electrolyte imbalance (namely especially hypernatraemia, hypermagnesaemia, hypokalaemia and hypophosphataemia).

AEs related to electrolyte imbalance observed in the SIOPEL 6 and COG ACCL0431 trials are presented in Table 13 and Table 14, respectively. It should be noted that the safety results from both the SIOPEL and COG ACCL0431 studies also showed that the most frequently reported AEs attributable to Pedmarqsi were vomiting, nausea and transient changes in electrolytes. However, none of these AEs were considered dose limiting.[24, 28,32] In addition, no dose reductions occurred during the COG ACCL0431 trial due to hypernatraemia, or other AEs related to electrolyte imbalances, and of children who discontinued Pedmarqsi, none had hypernatraemia or other AEs related to electrolyte imbalances, in the cycle in which they were withdrawn from the study.[31] In the SIOPEL 6 trial, one patient had a dose of Pedmarqsi withheld due to low potassium levels and no patients discontinued Pedmarqsi due to electrolyte imbalances.[30]

Table 13: Electrolyte Imbalance Adverse Drug Reactions (≥ 10%) in Patients Who Received cisplatin with Pedmarqsi with a Difference Between Arms of > 5% Compared to cisplatin without Pedmarqsi in SIOPEL 6

Adverse Reaction	Cisplatin with Pedmarqsi (N=53)		Cisplatin without Pedmarqsi (N=56)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Metabolism and nutrition disorders				
Hypernatraemia	[redacted]	[redacted]	[redacted]	[redacted]
Hypokalaemia	[redacted]	[redacted]	[redacted]	[redacted]
Hypophosphataemia	[redacted]	[redacted]	[redacted]	[redacted]
Hypermagnesaemia	[redacted]	[redacted]	[redacted]	[redacted]

Source: Data on file: MED_US_SRL_PEDMARK_Electrolyte Imbalances v3[32]

Table 14: Electrolyte Imbalance Adverse Drug Reactions (≥ 10%) in Patients Who Received cisplatin with Pedmarqsi with a Difference Between Arms of > 5% Compared to cisplatin without Pedmarqsi in COG ACCL0431

Adverse Reaction	Cisplastin with Pedmarqsi (N=59)		Cisplatin without Pedmarqsi (N=64)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Metabolism and nutrition disorders				
Hypokalaemia	[redacted]	[redacted]	[redacted]	[redacted]
Hyponatraemia	[redacted]	[redacted]	[redacted]	[redacted]
Hypernatraemia	[redacted]	[redacted]	[redacted]	[redacted]
Hypophosphataemia	[redacted]	[redacted]	[redacted]	[redacted]

Source: Data on file: MED_US_SRL_PEDMARK_Electrolyte Imbalances v3[32]

In the SIOPEL 6 study, there were no serious cases of hypernatraemia, hypomagnesaemia, hyperphosphataemia or hypokalaemia associated with Pedmarqsi. The majority of hypernatraemia AEs were Grade 1, and a single episode of hypernatraemia was associated with Grade 2 hypertension. There were no effects on renal function as measured by long term assessment of glomerular filtration rate, and no concurrent seizures, ocular or neurological effects were seen in association with hypernatraemia.

In the COG ACCL0431 study, focus was placed on AEs CTCAE Grade 3 or more and seriousness was only assessed for children in the cisplatin with Pedmarqsi arm. There were no serious cases of hypernatraemia; mean levels of serum sodium were similar in the cisplatin with Pedmarqsi and cisplatin without Pedmarqsi arms of the study. Levels of 145 mmol/L or more were reported in [redacted] cisplatin without Pedmarqsi arm patients ([redacted] events of hypernatraemia ranging 145-146 mmol/L) and in [redacted] cisplatin with Pedmarqsi arm patients ([redacted] events of hypernatraemia 145-151 mmol/L). Overall, whilst hypernatraemia occurred slightly more often in the cisplatin with Pedmarqsi arm, levels were only modestly raised, and events were sporadic. A review of AdEERs forms did, however, identify [redacted] children with Grade 3 or 4 hypokalaemia and [redacted] with nausea +/- vomiting. In all cases, the event was considered unrelated to Pedmarqsi; chemotherapy was considered the most likely cause. Hypokalaemia was an incidental finding and not associated with the reason for hospital admission and the hypokalaemia resolved quickly.

A 12.8 g/m^2 dose of Pedmarqsi delivers a sodium load of 162 mmol/m^2, a 9.6 g/m^2 dose delivers a sodium load of 121 mmol/m^2 and a 6.4 g/m^2 dose delivers a sodium load of 81 mmol/m^2.[1] In the SIOPEL 6 trial, doses of Pedmarqsi equivalent to these resulted in a small, transient increase in serum sodium levels, independent of age, body surface area, body weight, total daily Pedmarqsi dose or cisplatin cycle. Most sodium levels had returned to baseline by 6 hours post administration, and all levels were returned to baseline by 18 hours. The analysis of serum sodium levels in patients receiving Pedmarqsi showed that across all courses of Pedmarqsi, patients had a mean pre-course serum sodium level of 137.0 mmol/L, which increased at one hour after Pedmarqsi dosing (143.1 mmol/L) and returned to a similar level to pre-Pedmarqsi administration at 6 hours after dosing (138.4 mmol/L) and 18 hours after dosing (136.4 mmol/L). No deterioration in renal function was observed during the study and sodium levels were similar from course 1 through course 6. A summary of the analysis of sodium levels in the SIOPEL 6 trial is presented in Table 15.

Table 15: Summary of Mean Sodium Data Across All Cycles (SIOPEL 6 Safety Population)

Parameter Category/Statistic	Cisplatin with Pedmarqsi N=53
Pre-Course serum sodium (mmol/L)	
N	51
Mean (SD)	137.0 (1.5)
Median (min, max)	137.0 (134, 141)
1 Hour Post-Pedmarqsi serum sodium (mmol/L)	
N	49
Mean (SD)	143.1 (2.1)
Median (min, max)	143.2 (139, 147)
6 Hours Post- Pedmarqsi serum sodium (mmol/L)	
n	50
Mean (SD)	138.4 (1.7)
Median (min, max)	138.4 (135, 143)
18 Hours Post- Pedmarqsi serum sodium (mmol/L)	
n	39
Mean (SD)	136.4 (2.5)
Median (min, max)	136.4 (131, 141)

Abbreviations: SD – Standard deviation

Source: SIOPEL 6 CSR[30]

In the COG ACCL0431 study, when cisplatin with Pedmarqsi were administered on multiple days of a cycle, it was a pre-requisite that the patient must have had a normal serum sodium (<145 mEq/L, which was to be evaluated daily) to receive Pedmarqsi. Only maximum serum sodium levels were measured in this trial. Across all reporting periods, no maximum serum sodium values were greater than 151 mmol/L in the cisplatin with Pedmarqsi arm or 146 mmol/L in the cisplatin without Pedmarqsi arm.[31]

Information is also available with respect to how electrolyte imbalances should be controlled in clinical practice; the Pedmarqsi SmPC states the following:

"*Electrolyte balance and blood pressure should be monitored carefully, and sodium thiosulfate should not be given if serum sodium is > 145 mmol/litre at baseline before sodium thiosulfate is administered within a treatment cycle.*

Patients < 1 month of age have less well-developed sodium homeostasis; therefore, sodium thiosulfate is contraindicated in neonates.

Serum magnesium, potassium and phosphate levels should also be monitored, and supplementation given if needed as the combination of fluid loading in association with cisplatin-based chemotherapy and the administration of sodium thiosulfate may cause transient electrolyte disturbance."[33]

Therefore, given the above, the Company suggest that the electrolyte imbalances that result from Pedmarqsi and related AEs highlighted by the CHMP are transient. Additionally, to control these AEs, there are strategies in place (such as monitoring of electrolytes, and supportive care and supplementation as appropriate) to manage electrolyte imbalances as outlined in the SmPC, and Pedmarqsi is contraindicated in neonates for the reasons outlined above.

Section B: Clarification on cost-effectiveness data

New company base case

The following questions resulted in updates being made to the cost-effectiveness model: B10, B21, B26, B27, B28, and B29. The ICER and associated change from the CS ICER for the updates are presented in Table 16. In response to B17, the Company have also amended the base case to include antiemetic pre-medication costs, the ICER and associated change from the CS ICER is also presented in Table 16. Together the updates result in a new base case ICER of £[redacted]. This is subsequently referred to as the "new base case ICER". The original CS ICER of £[redacted] is referred to as the "CS base case ICER".

Table 16: A summary of corrections and updates made to the base case CEA

Question that the change relates to	Change	ICER	Change from CS base case ICER
CS base case		£[redacted]	–
B10	Update to the most recent life tables for England and Wales (2020-2022)	£[redacted]	-£274.64
B21	Adjustment of the frequency of weekly speech and language therapy sessions for patients with 'Marked HL' and 'Severe HL'		
B26	Removal of the cost of elective stays for febrile neutropenia and hypersensitivity		
B27	Adjustment of the =VLOOKUP() formula to return the appropriate all-cause mortality		
B28	Application of the SMR to cease from year 11 onwards		
B29	Removal of the cycle length by time horizon division when calculating QALYs, LYs and generating general population mortality estimates		
B17	Addition of antiemetic pre-medication costs	£[redacted]	+£10.44
New base case ICER		£[redacted]	-£264.30

Abbreviations: CEA – Cost-effectiveness analysis; CS – Company submission; HL – Hearing loss; ICER – Incremental cost-effectiveness ratio; LY – Life year; QALY – Quality-adjusted life year; SMR – Standardised mortality ratio

The new Company deterministic base case results (Pedmarqsi PAS price) are presented in Table 17. For reference, the CS deterministic base case results (Pedmarqsi PAS price) are presented in Table 18.

Table 17: New base case deterministic results (Pedmarqsi PAS price)

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER
Cisplatin without Pedmarqsi	[redacted]	22.251	16.887	N/A	N/A	N/A	N/A
Cisplatin with Pedmarqsi	[redacted]	22.251	18.426	[redacted]	0.000	1.539	[redacted]

Abbreviations: ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; PAS – Patient access scheme; QALY – Quality-adjusted life year

Table 18: Company submission base case deterministic results (Pedmarqsi PAS price)

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
Cisplatin without Pedmarqsi	[redacted]	22.042	16.735	N/A	N/A	N/A	N/A
Cisplatin with Pedmarqsi	[redacted]	22.042	18.260	[redacted]	0.000	1.525	[redacted]

Abbreviations: ICER – Incremental cost-effectiveness ratio; LYG – Life years gained; PAS – Patient access scheme; QALY – Quality-adjusted life year

Population baseline characteristics

B1. CS, Section B.3.4.2, Table 31. Please clarify which population groups in SIOPEL 6 and COG ACCL0431 studies the age distributions included in the model to inform the costs for hearing assessments in patients <18 years old correspond to (e.g., intention to treat (ITT), efficacy, or safety populations, if it includes patients from both treatment arms from the trials, and if the data from COG ACCL0431 study includes only localised disease patients).

For both SIOPEL 6 and COG ACCL0431, the age distributions used to inform the costs for hearing assessments in patients <18 years old are derived from the ITT population and includes patients in both treatment arms from the trials. The ITT population was chosen to reflect the largest sample of randomised patients available from the trials. Data from the COG ACCL0431 study includes only localised disease patients in order to align with Pedmarqsi's license.

B2. Model, 'Data Store' worksheet, cells G11:G12. Please clarify if the data on the proportion of males included in the model from the COG ACCL0431 study corresponds to data from ITT, efficacy, safety populations, or only localised disease patients (the label in cell F12 suggests it is from the ITT population).

Data on the proportion of males in COG ACCL0431 corresponds to localised only patients within the ITT population and includes patients in both treatment arms. The ITT population was chosen to reflect the largest sample of randomised patients available from the trial. Localised only patients are considered in order to align with Pedmarqsi's license.

Model structure

B3. PRIORITY. CS, Section B.3.3.1, pages 75-77. Please clarify how the health states in the model (Minimal/no HL, Mild HL, Moderate HL, Marked HL and Severe HL) were defined in terms of their correspondence to the different hearing loss grading systems used in the SIOPEL 6 and COG ACCL0431 trials and in the post-analysis study from Orgel et al. 2023 (ASHA, SIOP and Brock), with corresponding thresholds and severity levels.

As stated in Section B.3.4.3 of the CS, the model structure captures efficacy of preventative treatment via the different hearing loss grading scales at two stages. Firstly, the percentage of patients who experience cisplatin-induced hearing loss through the percentage of patients assigned to the 'Minimal/no HL' health state. In the base case, this yes/no decision is based on the COG ACCL0431 trial which uses the ASHA criteria to determine whether patients experience hearing loss or not. Secondly, once hearing loss has been defined, for those who experience hearing loss, the severity of hearing loss is then captured through the classification of patients between the 'Mild HL', 'Moderate HL', 'Marked HL', and 'Severe HL' health states, with these health states based on the Brock grading scale (as described in Section B.1.3.1.2, Table 3 of the CS). In the base case, the distribution of patients between these states is based on Orgel et al. (2023)[18] (which uses the SIOP ototoxicity scale) in combination with Knight et al. (2005)[5] (which uses the Brock scale, the same scale that is used in SIOPEL 6). The methods for distributing patients between hearing loss severity health states is discussed further in response to B7.

Therefore, given the above, the Company would like to clarify that the ASHA criteria are not relevant for defining the severity-based health states in the model, and data from this scale are used once at the beginning of the model to answer the hearing loss yes/no aspect of the decision tree, based on the results of the COG ACCL0431 study. As a result, this scale in terms of the severity health states, or concordance with other scales, is not discussed any further in this response.

The Company acknowledges that the thresholds for each scale differ, as shown in Section B.1.3.1.2 Table 3 of the CS. However, as highlighted by the Company as part of the response to A19, Clemens et al. (2019)[22] studied the concordance

between a range of ototoxicity grading scales (including Brock and SIOP) and concluded that, generally, there was good concordance between the scales (whilst caveating there is diversity in the definition of functionality across the instruments). Concordance between the Brock scale and the SIOP ototoxicity scale was also the third highest amongst comparisons of the included instruments (κ = 0.840 indicating strong agreement[34]).[22]

Further to this, the Company notes that both scales consist of five severity levels. Therefore, although the thresholds differ slightly between the scales, they do not differ significantly enough to result in a different number of possible grades.

Finally, and as noted in the Company's response to clarification question A19, a range of scenario analyses have been presented applying different scales within the model structure, and thus exploring the uncertainty in the use of different scales in the model.

B4. CS, Section B.3.3.1.1, page 77. Please justify the use of an annual cycle length in the model or comment on whether a shorter cycle length would be appropriate, providing evidence to support the statement on the length of the cisplatin-containing and sodium thiosulfate treatment regimens received in the SIOPEL 6 and COG ACCL0431 studies.

A one-year cycle length is appropriate for the economic model for a number of reasons as noted below:

- The model applies a relatively long- time horizon of [redacted] years (which is to be expected given the starting age of cohort) and there are limited health state transitions in the model from year two onwards. That is, once patients are allocated to their respective health states at the end of the decision tree in year one, the only transition patients can make is to the death health state (with transitions being based on published annual life tables). Therefore, a one-year cycle length is appropriate, and no additional accuracy can be achieved through applying a shorter cycle length. Please note that the assumption used in the model that hearing loss cannot worsen after year one is further discussed in the Company's response to B5.

- The majority of costs and outcomes occur in the first year of the model and are therefore not discounted. Consequently, shortening the cycle length (i.e. the frequency at which costs and outcomes are evaluated) will have no impact on the overall cost and outcomes for this period.

Further to this, and as requested, additional evidence is available from the COG ACCL0431 study which supports the position that in the COG ACCL0431 and SIOPEL 6 studies, the duration of cisplatin treatment did not exceed one year. That is, in the COG ACCL0431 safety population, the mean duration of cisplatin treatment in patients with localised disease was [redacted] weeks (SD: [redacted]; Range: [redacted]) and [redacted] weeks (SD: [redacted]; Range: [redacted]) for the cisplatin without Pedmarqsi and cisplatin with Pedmarqsi arms respectively. In addition, in the overall safety population of COG ACCL0431, including both localised and metastatic patients, the mean duration of cisplatin treatment was [redacted] weeks (SD: [redacted]; Range: [redacted]) and [redacted] weeks (SD: [redacted]; Range: [redacted]) for cisplatin without Pedmarqsi and cisplatin with Pedmarqsi respectively.

The Company has also previously sought clinical expert feedback on this issue who noted that cisplatin treatment would typically be completed within one year. This information further strengthens the rationale for a one-year cycle length as all Pedmarqsi costs (which are dependent on the duration of cisplatin treatment) have accrued within this time frame.

B5. CS, Section B.3.3.1, page 76. Please justify the assumption used in the model that severity of hearing loss cannot be reverted or worsened after people finish treatment with cisplatin and sodium thiosulfate, and therefore people cannot transition between the alive health states (Minimal/no HL, Mild HL, Moderate HL, Marked HL and Severe HL) after the first year. Our clinical advisors have suggested that potential late detection or late effects of HL (worsening HL) may be observed after that period.

Permanent and irreversible hearing loss as an adverse consequence of cisplatin chemotherapy is noted in the literature by Brock et al. (2021)[35]. Irreversible damage to the hair cells of the cochlea apparatus occurs after cisplatin becomes permanently trapped within the perilymph.[35] Despite the exact mechanism of action of cisplatin-induced ototoxicity being currently unknown, it is thought to involve the production and activation of reactive oxygen species (ROS) within the cell cytoplasm, which the

cell attempts to neutralise.[35] Once the cell's ability to neutralise ROS becomes exhausted with time or exceeded by the cisplatin dose, hair cell death occurs. Since these hair cells in the cochlea cannot regrow, the patient's hearing ability is irreversibly damaged.[35]

In terms of worsening of hearing loss over time, as cisplatin is retained in the cochlea, it is possible that a proportion of patients with hearing loss will experience a further decline in their hearing.[36,37] The Company considered modelling this further decline in hearing; however, this was not included in the economic model due to the lack of data to model this robustly (i.e. a lack of data on the timing and rate of deterioration), and the fact that this effect would apply to both arms having a limited impact on the results. In addition, as reported by Weissenstein et al. (2012),[37] only patients with some degree of hearing loss at the end of treatment are at risk of further deterioration. Therefore excluding this deterioration from the model is considered conservative given that more patients in the cisplatin without Pedmarqsi arm of the model would be assigned to one of the four hearing loss health states, and thus, more susceptible to the deterioration.

Nevertheless, the Company have conducted an exploratory analysis whereby a proportion of hearing loss patients experience a further decline in their hearing over the course of the model time horizon. Due to the lack of data available, a number of assumptions were required for this exploratory analysis. Firstly, it was assumed that this deterioration only applies to those that have measurable hearing loss at the end of cisplatin therapy (i.e. the end of year one in the model), which is in line with the findings from Weissenstein et al. (2012).[37] Secondly, it was assumed that 26.3% of hearing loss patients experience a further decline in their hearing loss, as reported by Fetoni et al. (2022).[38] It was also assumed that patients cannot deteriorate more than one health state in each model cycle. Finally, a probability per cycle of progressing to the next worst health state was calculated based on the assumption that the deterioration occurs over the course of the model time horizon. This exploratory analysis is included in the updated model that has been sent along with these responses. Including this deterioration aspect results in an ICER of £[redacted] which is £537.68 lower than the base case.

Similarly, the Company also considered modelling the decline in hearing loss seen with aging, as when patients become older, hearing ability may decline as observed in the general population. Again, however, including such an approach in the economic analysis would present challenges and increase uncertainty, given data are not available to capture the pattern of age-related decline for this patient population. In addition, and as noted above, this affect would apply to both arms equally having a limited impact on the cost-effectiveness results.

Further to the above, a review of relevant previous NICE evaluations also confirmed that age-related hearing loss was not modelled. Firstly, in a HTE6, a NICE evaluation of kit to guide antibiotic use to prevent hearing loss in babies,[39] the EAG model did not include hearing loss due to age. Secondly, TA566 which assessed cochlea implants for children and adults with severe to profound deafness (based on Bond et al. (2009)[40] which used a model created by PenTAG), similarly did not include additional age-related hearing loss, and this was not considered a key parameter for further data collection.

Finally, it is also worth noting that the model structure was discussed with the EAG at the Decision Problem meeting. Specifically, the lack of transitions due to age-related hearing loss was discussed, and the EAG did not raise any concerns with the Company's proposed approach.

Efficacy (HL experience and HL severity)

B6. CS, Section B.3.4.3, page 85. Please provide the rationale (and evidence, if available) for using data from the efficacy population of the COG ACCL0431 trial (instead of the ITT population or from the localised disease subgroup of patients) to inform efficacy (HL experience and HL severity) in the model.

The Company consider it appropriate and robust to use data from the efficacy population of COG ACCL0431 to model hearing loss outcomes, as opposed to using the ITT population, or subgrouping efficacy to localised patients only. Each issue is discussed in turn below.

Efficacy population versus ITT population

As stated in Section B.3.4.3 of the CS, the efficacy population is considered appropriate to use as it included all children in the ITT population who had both baseline and four-week follow-up hearing assessments and in whom an assessment of the change in hearing loss can be conducted. This population reflected the primary population for the analyses of the hearing loss endpoints in COG ACCL0431, as specified in the CSR. In addition, as the efficacy population was pre-specified in the statistical analysis plan, the pre-specified criteria for exclusion were defined at the outset of the study and therefore were not influenced by the final outcomes. As such, the Company consider any bias created by this exclusion method to be minimal (as discussed by Rehman et al. 2020[41]). Finally, by excluding patients without their hearing loss assessed, the analysis focuses on participants who contribute relevant data to the assessment of hearing loss; thereby enhancing the reliability of the results.

The alternative to using the efficacy population would be to use the ITT population, however in this population, any patients who did not have hearing loss data available were assumed to have hearing loss. This is an overly conservative assumption which is likely to impact the estimate of treatment effect.

In Sections B.2.5.1 and B.2.5.2 of the CS, the Company have presented the results from the ITT population of SIOPEL 6 (relative risk: 0.521; 95% CI: 0.349, 0.778; p<0.001) and COG ACCL0431 (OR = 0.411; 95% CI: 0.191, 0.886; p=0.023). These findings validate the results from the efficacy population of COG ACCL0431, and support the conclusion that Pedmarqsi is effective in preventing hearing loss.

Subgrouping efficacy for localised disease in COG ACCL0431

Firstly, it is important to note that Pedmarqsi is a treatment for the prevention of hearing loss, and not a treatment for the underlying cancer, and based on the evidence available, the efficacy of Pedmarqsi in preventing hearing loss is independent on the extent of disease (i.e. whether the patient has localised or metastatic disease).

The Company recognise that the COG ACCL0431 study included patients with metastatic disease who would fall outside the licensed population; however, the Company also consider it appropriate to retain these patients in the analysis of

hearing outcomes and be included in the economic model. Firstly, it should be noted that the COG ACCL0431 study was not powered for an analysis in the subpopulation of localised patients (n=[redacted] children treated with Pedmarqsi). Such categorisation was also not considered in the stratification variables at randomisation; and therefore, a subgroup analysis in localised patients breaks randomisation.[42] Further to this, restricting the trial population to localised patients only, would restrict an analysis of treatment effect from an already limited population size. Both ITT population (47/125 patients) and efficacy population (40/104 patients) included [redacted]% of patients who were classified as having metastatic disease. Therefore, restricting the trial population further reduces the sample size and increases the uncertainty in the analysis. For these reasons, the Company does not consider it appropriate to perform subgroup analysis on localised patients only in COG ACCL0431.

B7. CS, Section B.3.4.3, pages 85-87. Please justify the approach used to combine different sources of data for efficacy in terms of HL experience and HL severity which use different grade systems to inform the base case analysis (COG ACCL0431 study [ASHA system] for HL experience, and Orgel 2003 [re-analyses of COG ACCL0431 data using the SIOP system] with Knight 2005 study [Brock system] for HL severity). Please clarify if any adjustments were (or should be) necessary to account for any differences in the thresholds of each system, and how to interpret the combined results.

The Company acknowledges that the efficacy data used in the submission is taken from different sources; however, sources were selected in order to derive a robust and conservative base case.

Starting with the first clinical effectiveness parameter in the decision tree (i.e. the hearing loss yes/no decision), the data was taken from the COG ACCL0431 trial, as this study is considered most generalisable to UK practice, given the range of tumour types that are included in the study population (see Section B.3.4.1 and Table 30 of the CS).

In the following stage of the decision tree, hearing loss is broken down into four severity health states that reflect the Brock criteria. As severity data is not available from the COG ACCL0431 trial, alternative sources were used for informing this stage of the decision tree. Following a review of the available data, a decision was taken to

use data from Orgel et al. (2023) to inform the percentage of patients in the 'Mild HL' health state. Orgel et al. (2023)[18] conducted a re-analysis of COG ACCL0431 using the SIOP ototoxicity scale and reported the percentage of patients with Grade 0, Grade 1 and Grade 2+ hearing loss. This is an appropriate source to apply in the model, since the study population is taken from the same trial as the yes/no criteria, whilst there is good concordance between the SIOP ototoxicity scale, and the Brock scale used to measure health states; as noted in question B3. As a final step, Knight et al. (2005)[5] was used to categorise patients into Grades 2, 3 and 4 hearing loss. This study used the Brock scale, and the patients were similar to those enrolled in COG ACCL0431 (see response to B8). In addition, the use of Knight et al. (2005)[5] is aligned with clinician feedback that this paper is an appropriate source to use in the submission.

Table 19 below presents a comparison of the original COG ACCL0431 results (using the ASHA scale) and the Orgel et al. (2023)[18] re-analysis (using the SIOP ototoxicity scale). Results demonstrate that there is not a large difference in the percentage of patients assigned to Grade 0 and Grade 1+ hearing loss health states (the yes/no stage of the decision tree), and most importantly the direction of the change is the same in each treatment arm, i.e. less patients in both treatment arms are determined to have hearing loss when assessed using the SIOP ototoxicity scale compared to the ASHA criteria.

Table 19: Comparison of results from COG ACCL0431 and Orgel et al. (2023)

Source	Total number (%) of patients in Grade 0			Total number (%) of patients in Grade 1+		
	Cisplatin with Pedmarqsi	Cisplatin without Pedmarqsi	Total	Cisplatin with Pedmarqsi	Cisplatin without Pedmarqsi	Total
COG ACCL0431 Scale: ASHA	35/59 (71.4%)	24/55 (43.6%)	59/104 (56.7%)	14/59 (28.6%)	31/55 (56.4%)	45/104 (43.3%)
Orgel et al. (2023)[18] re-analysis of COG ACCL0431 Scale: SIOP	41/50 (82.0%)	32/59 (52.2%)	73/109 (67.0%)	9/50 (18.0%)	27/59 (45.8%)	36/109 (33.0%)

It is acknowledged that the sources used in the model to capture efficacy apply different scales to measure hearing loss, which may create some uncertainty and this is noted as a limitation of the analysis. However, alternative approaches were presented via scenario analyses, none of which resulted in significant increases to the ICER (presented in response to A19). The largest increase to the ICER occurs when using COG ACCL0431 for the hearing loss experience (yes/no) parameter whilst using SIOPEL 6 to differentiate patients into the mild to severe hearing loss health states. However, as noted previously, SIOPEL 6 only included hepatoblastoma patients, with a young average age (1.5 years old) and therefore this study is considered less generalisable to the whole licensed population in the UK compared to Orgel et al. (2023)[18] and Knight et al. (2005).[5] Together, the results show that using alternative scales/sources to inform the efficacy of the model has little impact on the conclusion of the analysis.

To clarify, no adjustments were made, or can be made with the data available, to account for differences between the different scales. Analyses have been provided in the submission using the Orgel et al. (2023)[18] paper which reanalysed data from the COG ACCL0431 trial and supports the conclusion that regardless of the scale used, Pedmarqsi significantly reduces the incidence of hearing loss.

B8. CS, Section B.3.4.3, page 86. Please clarify how the patients included in Knight et al (2005) are comparable to the patients included in COG ACCL043 study in terms

of baseline characteristics such as age, therapy regimens received, and type of cancers included.

Table 20 compares the baseline characteristics, tumour types and chemotherapy treatments in COG ACCL0431 and Knight et al. (2005)[5]. In terms of the similarity between patients in Knight et al. (2005)[5] and COG ACCL0431, both studies reported a similar baseline age and gender distribution. It is also noted that the vast majority of patients in Knight et al. (2005)[5] were treated with regimens containing cisplatin (59 of 67, 88%), which aligns well with patients in COG ACCL0431, who were treated with any cisplatin-containing regimen. Further to this, despite the small sample size in Knight et al. (2005)[5], similarities in the four most common tumour types can be observed across both studies.

Finally, it is worth noting that the Knight et al. (2005)[5] paper was recommended as a valid source of hearing loss outcomes data following consultation with a clinician as part of the model development process.

Table 20: Baseline characteristics, tumour types and chemotherapy treatment in COG ACCL0431 and Knight et al. (2005)

	Knight et al. (2005)[5]	COG ACCL0431
Baseline characteristics		
Mean age (years)	9.65	[redacted]
Percentage male	67.2%	[redacted]%
Most common tumour types		
Medulloblastoma	17/67 (25.4%)	26/125 (20.8%)
Neuroblastoma	12/67 (17.9%)	26/125 (20.8%)
Osteosarcoma	12/67 (17.9%)	29/125 (23.2%)
Germ cell tumour	9/67 (13.4%)	32/125 (25.6%)
Chemotherapy treatment type		
Any cisplatin-containing regimen	(59 of 67, 88%)	100%
Cisplatin only	40/67 (60%)	0%
Carboplatin only	8/67(12%)	0%
Cisplatin and carboplatin combined	19/67 (28%)	NR*

**As reported in response to question A14b, patients within COG ACCL0431 were on cisplatin combination protocols, none of which were cisplatin with carboplatin alone*

Mortality

B9. CS, Section B.3.4.5, page 89. The model assumes that patients still alive after 10 years have the same mortality risk as the general population (10- year cure time point). Our clinical advisor has suggested that the risk of death in this population is still higher compared to the general population even after 40 years (as reported by Dixon et al [2023], available at https://doi.org/10.1016/S0140-6736(22)02471-0). Please justify or amend this assumption as appropriate.

The Company would like to clarify that a 10-year cure time point was chosen to align with previous NICE TAs and is supported by the published literature.

Starting with previous NICE TAs, the Company note that a 10-year cure point was considered appropriate in both TA538[43] and TA817[44]. These appraisals are considered relevant given that TA538[43] and TA817[44] were oncology appraisals with comparable tumour types to those relevant to this Pedmarqsi appraisal (neuroblastoma and invasive urothelial cancer, respectively, for which the current standard of care [SoC] is platinum-based chemotherapy).

The Company also performed a targeted literature search to further identify suitable data to support the 10-year cure time point. Brosa et al. (2014)[45] reported that for a hypothetical cohort of young patients under the age of 30 with high-grade, non-metastatic, resectable osteosarcoma, patients were assumed to have a mortality rate equivalent to the general population at 12.25 years. Further to this, it is noted that typically cancer relapse occurs between one month and 12 years amongst paediatric cancer patients with Aerts et al. (2004)[46] and Oldenburg et al. (2009)[47] reporting 11.2- and 12-year relapse time periods, respectively. These data further support that a 10-year cure point is appropriate given that the time points reported in the literature are similar to those applied in TA538[43] and TA817[44].

The EAG have referenced a study by Dixon et al. (2023) to support a cure point of 40 years; however, the Company disagree that this paper is appropriate to include in the economic modelling. Firstly, the study includes patients older than 18 years (diagnosis at <21 years) and although the NICE TAs specified above also include older patients, the 10-year cure points in the NICE TAs are consistent with the clinical studies noted above. Secondly, the Company notes that Dixon et al. (2023)

reports an SMR of 6.2 (5.8–6.6) at 10-14 years from diagnosis, which plateaus to 3.8 (3.5–4.1) at 20 years from diagnosis and increases slightly to 4.0 (3.5–4.5) at ≥40 years from diagnosis. The approach used in the Company base case is to apply an SMR of 9.1 (based on Fidler et al. (2016)[48] – see QB11) for 10 years, and therefore the Company base case is potentially conservative as the SMR is materially higher than that which is reported by Dixon et al. (2023), and it would not be appropriate to apply an SMR of 9.1 for 40 years in the economic model.

B10. Model, worksheet 'Data Store', cells D567:E667. Please clarify the source of the general population mortality risks used in the model, including the country/countries and year. The EAG was unable to verify the values for the mortality rates included in the model from the source included in the references. Please provide an updated version of the model that contains the most recent life tables for England.

Thank you for bringing this to the Company's attention. The model has been updated to contain data from the most recent life tables for England and Wales (2020-2022) from the ONS (worksheet 'Data Store', cells D563:E663).

B11. CS, Section B.3.4.5, page 89. A standardised mortality ratio (SMR) of 9.1 is applied to general population mortality from years 6 to 10 in the model, with the SMR estimate taken from Fidler et al (2016). Please clarify how the population from this study relates to the targeted population in the current appraisal and COG ACCL0431 and SIOPEL 6 trials in terms of baseline characteristics and range of cancers included, and if the estimate of 9.1 relates to all patients in the study (which comprised patients diagnosed under the age of 15 years from 1940 to 2006 in Britain). Please also comment on the appropriateness of the period of time the estimate is applied for in the model, and on how this estimate may not reflect the improvements in cancer diagnosis, treatment and five-year survival rates experienced in the UK since the 1940s.

The Company believe that the application of the SMR of 9.1. from Fidler et al. (2016)[48] to model the increased risk of death for cancer survivors is appropriate, and also potentially conservative, as demonstrated below.

Relevance of Fidler et al. (2016)[48] to the current appraisal

The Fidler et al. (2016)[48] study aimed to investigate the risk of late cause specific mortality after treatment across almost seven decades (1940-2006) within the recently extended British Childhood Cancer Survivor Study (BCCSS). The BCCSS is a population-based cohort that comprises 34,489 five-year survivors of childhood cancer with a diagnosis under the age of 15 years from 1940 to 2006 in Britain. Cohort characteristics of the BCCSS indicate that more than ten solid tumour cancer types were investigated, inclusive of neuroblastoma, retinoblastoma, and bone sarcoma. Data from this study is appropriate to apply in the economic model as the study captures a large UK cohort focusing on paediatric oncology, includes patients who were treated for cancer at an age cut-off (15 years old) which is within the licence for Pedmarqsi, and includes a broad range of solid cancer tumour types.

Similarly, the Fidler et al. (2016)[48] paper also has a degree of concordance with the COG ACCL04321 study as both studies include children diagnosed with a range of solid tumour types, including neuroblastoma, retinoblastoma and bone sarcoma. It is also worth noting that although the COG ACCL0431 was a hearing study conducted in North America, the Company believe that this population is generalisable to a UK setting, which again supports concordance with the BCCSS study which is a UK data set. The Company does acknowledge that there may be less concordance between Fidler et al. (2016)[48] and SIOPEL 6, as it included a young patient population and a single tumour type (hepatoblastoma). However, as noted elsewhere the COG ACCL0431 is the Company's preferred source to model treatment efficacy and SIOPEL6 study is included in the economic model as a scenario.

Conservative approach

As noted in the question, the BCSS may not reflect recent improvements in cancer survival and therefore the SMR reported of 9.1 may be towards the upper range. However, inclusion of this SMR is conservative as reductions in this parameter reduce the ICER. In addition to this, two other sources of the post-cancer SMR were identified through targeted literature searches. Laverdiere et al. (2009)[49] studied 954 five-year neuroblastoma survivors who were diagnosed in 1970–1986 across 26 participating clinical research centres in the United States and one research centre in Canada. Suh et al. (2020)[50] studied 24,363 five-year cancer survivors diagnosed in 1970–1999 at 27 academic institutions in North America. Both these sources

presented lower SMR values of 5.6 and 6.2, respectively, when compared to Fidler et al (2016)[48]. However, a conservative approach was taken to use the higher value of 9.1 from the BCCSS and was preferred given that these data were taken from UK patients.

Treatment regimens

B12. PRIORITY. Model, 'ACCL0431 doses' and 'SIOPEL 6 doses' worksheets, column B. Please clarify if the 'total number of Pedmarqsi doses' corresponds to the total number of infusion visits/administrations of sodium thiosulfate received by each patient. Please also clarify if any patients were still receiving treatment with sodium thiosulfate at the end of the study, and if any patients were censored for treatment discontinuation in the COG ACCL0431 and SIOPEL 6 studies.

We can confirm that within the dosing worksheets of the model, 'total number of Pedmarqsi doses' corresponds to the total number of Pedmarqsi administrations. This should not be confused with the cumulative Pedmarqsi dose (g) and Total number of 8g Pedmarqsi vials that is reported in columns C and D of the dose sheets, respectively. Furthermore, no patients were receiving treatment with Pedmarqsi at the end of the studies; all patients stopped receiving Pedmarqsi treatment once their cisplatin therapy stopped. Hence if the patient was withdrawn from cisplatin-based chemotherapy, the Pedmarqsi was also withdrawn. Those that discontinued Pedmarqsi treatment were not censored unless follow-up hearing assessment data was not available. This is further discussed in response to A17.

B13. CS, Section B.3.6.1.1, page 94. Please provide evidence to support the assumption used in the model that the doses of cisplatin in the COG ACCL0431 and SIOPEL 6 trials were equivalent between the treatment groups. The COG ACCL0431 clinical study report (CSR) reports that '*Notably, the mean cumulative dose of CIS administered was also higher in the Observation arm compared with the CIS+STS arm (see Section 7.1),*' which suggests that the doses received were not equivalent between treatment groups. In particular, clarify how these regimens were given in each arm of the trial for the different types of cancers, and for different stages of disease (localised and metastatic patients). Please also provide evidence on the doses

received for the pooled trial data with localised disease patients required by the EAG (see question A13).

When considering doses in the model from a cost perspective, it is appropriate to focus on the localised population only (as per the CS when assessing Pedmarqsi costs), given that these patients are reflective of the licence. Table 21 provides data on the mean cumulative dose of cisplatin by treatment arm in COG ACCL0431 (localised only), SIOPEL 6, and the pooled analysis (localised only) as requested by the EAG. As shown, despite there being numerical differences between the treatment arms there is no statistically significant difference ($p<0.05$). The Company therefore believe that it is appropriate to assume that the dose of cisplatin is equivalent between treatment arms.

Finally, as noted elsewhere, patients in the COG ACCL0431 study received chemotherapy based on the sites' disease-specific cancer treatment protocols in use at the time, and the protocols in use are listed in response to A14b.

Table 21: Cumulative dose of cisplatin by treatment arm

Cumulative dose of cisplatin (mg/m^2)	Cisplatin without Pedmarqsi	Cisplatin with Pedmarqsi
Pooled analysis, localised only patients		
Mean	[redacted]	[redacted]
Min	[redacted]	[redacted]
Max	[redacted]	[redacted]
SD	[redacted]	[redacted]
P-value	[redacted]	
COG ACCL0431, localised only patients		
Mean	[redacted]	[redacted]
Min	[redacted]	[redacted]
Max	[redacted]	[redacted]
SD	[redacted]	[redacted]
P-value	[redacted]	
SIOPEL 6		
Mean	[redacted]	[redacted]
Min	[redacted]	[redacted]
Max	[redacted]	[redacted]
SD	[redacted]	[redacted]
P-value	[redacted]	

Utilities

B14. PRIORITY. CS, Section B.3.5.6, pages 91-94. The HRQoL in the base-case analysis is informed by Barton et al. (2006). Regarding the utility estimates, address the following questions:

a) **Please justify the assumption that the utility for the mild HL state consists of the midpoint between the 'minimal/no HL' and 'moderate HL';**

Due to a lack of reported data in the literature on the quality of life of patients with mild hearing loss, the Company made the simplifying assumption that utility for the 'Mild HL' health state consists of the midpoint between the 'Minimal/no HL' and 'Moderate HL' health states. This approach was validated by a UK audiovestibular physician.[7]

This approach can be considered conservative as patients who experience mild hearing loss still experience a material impact on their quality of life and therefore a utility value for mild hearing loss may be considered closer to moderate hearing loss than no hearing loss. This position is supported by Clemens et al. (2019)[22] who state that children will experience significant difficulty understanding language in the presence of background noise, once their hearing threshold is greater than 20 dB at 6,000 Hz and above.[22] The Brock scale defines mild hearing loss as ≥40 dB at 8,000 Hz, whilst the SIOP ototoxicity scale defines Mild HL as ≥20 dB at >4,000 Hz, both of which are worse than the range stated by Clemens et al. [2019][22]), thereby implying that mild hearing loss is correlated with a quality of life burden.

Further to this, it is also worth noting that a similar approach has been used previously in the literature, such as in Gumbie et al (2022)[51], whereby the utility of mild hearing loss was assumed to be an average of the normal and moderate hearing loss utilities.

b) **Please justify the assumed correspondence between the estimates for 'Severe (AHL 71–95 dB)', 'Profound (AHL 96–105 dB)', and 'Profound (AHL 105 dB)' in the study with the estimates for 'Marked HL' and 'Severe HL' health states in the model.**

The Company have used the estimate for the 'Severe (AHL 71–95 dB)' category from Barton et al. (2006)[52] to inform the 'Marked HL' health state, and a weighted average of the 'Profound (AHL 96–105 dB)' and 'Profound (AHL 105 dB)' categories to inform the 'Severe HL' health state.

The Company are aware that the use of the different scales is a limitation of the analysis. However, Barton et al. (2006)[52] was selected for use in the economic model given that it reflected the best available evidence to inform the quality of life associated with hearing loss in the relevant patient population. The Company believe that the health states from Barton et al. (2006)[52] are appropriate proxies for the two most severe health states in the model (Severe HL and Marked HL), given that patients within Barton et al. (2006)[52] were eligible for cochlea implants, (which implies a certain level of hearing loss), and this aligns with the two most severe health states in the model in which cochlea implants are used. Further to this, a conservative approach was taken when it came to deriving utilities for the marked

and severe health states by applying a weighted average for the two lowest utility values from Barton (2006)[52] (which were as low as 0.497 and 0.353 respectively) to the worst health state in the economic model.

Further to this, the Company sought expert validation from an audiovestibular physician regarding the appropriateness of the health state utility values used in the Company's base case analysis, and whether these would transfer to the Brock and SIOP scales. The expert considered that generally the values used for the four hearing loss health states, sourced from Barton et al. (2006)[52], would generalise across the Brock scales 1-4 and similarly, across the SIOP scales 1-4.[7]

Finally, the Company also explored the uncertainty in utility values through the provision of scenario analyses which used utility values from Gumbie et al (2022).[51] The results of these analyses are presented in the CS; however as noted under B14e) the Company does not consider the utility values from Gumbie et al (2022)[51] robust.

c) **Please clarify the selection of the utility estimate for 'Minimal/No HL' from Pogany et al (2006) from the group of controls (with no cancer) in the study with age at survey completion of 5-12 years old, and the appropriateness of the value that uses Canadian norms to a UK population.**

As just described, the utility values used in the model are taken from Barton et al. (2006)[52], which was considered the most appropriate source to inform the model health states. This study uses the HUI3 to capture health related quality of life data, a measurement of choice in a population with hearing impairment,[53,54] and used by the UK cochlea implant study group (UKCISG) in research.

In addition to the hearing loss health states, the economic model also requires a utility value for the no hearing loss health state, which is considered to reflect general population utility. However, no additional data were found and an HUI3 value for this population is not available for the UK, and therefore, being the only appropriate source available, a Canadian HUI value is used in the model instead. The Company do not consider this approach to be linked to a significant uncertainty given the very

close proximity of the value used in the model (0.92) to the UK-specific EQ-5D utility value for a 16-year-old (the youngest age for which this data is available) (0.93).

d) Please justify the approach used to estimate the utility values for the marked and severe HL states, which included a utility gain associated with cochlear implants for all cycles in the model.

The utility values for the 'Marked HL' and 'Severe HL' health states of the model are taken from Barton et al. (2006)[52] and these values refer to children who are not implanted with cochlea implants. It is widely reported in the literature that the use of cochlea implants results in a significant utility gain.[52,55] Therefore a utility gain associated with the use of cochlea implants (also sourced from Barton et al. [2006][52]) is applied to the percentage of patients receiving cochlea implants in these health states in the model.

To derive the utility gain associated with cochlea implants, Barton et al. (2006)[52] conducted a linear regression analysis including age at implantation and duration of use as covariates for the model. Results showed that, for patients diagnosed ≥ 5 years old, the utility gain was higher for those that had used a cochlea implant for ≥ 4 years (utility gain of 0.183) compared to those having used cochlea implants for < 2 years (0.130) or ≥ 2 and < 4 years (0.172). The Company model includes the highest utility gain for this age group (0.183) and applies this to all cycles of the model. Using the highest utility gain can be considered a conservative approach as it is only applied to the health states in which cochlea implants are used (i.e. the 'Marked HL' and 'Severe HL' health states), therefore applying a higher utility gain results in a smaller incremental difference in utilities across the health states and therefore reduces the incremental QALYs associated with Pedmarqsi. It should also be noted that in the base case analysis for adults, Bond et al. (2009)[40], which formed the basis of TA566[56], also applied a single utility gain which was assumed to hold for the duration of an individual's lifetime.

It is well established that the quality of life of the general population declines over time.[57] Therefore a potential weakness of using a single, age-independent value for utility gain is that a patient receiving a cochlea implant could end up having a better estimated quality of life than their normal-hearing peers. To mitigate this, the baseline health state utilities in the model are age-adjusted over the model time

horizon *after* the cochlea implant utility gain is applied, as opposed to before the utility gain is applied. This ensures that total health state utilities do not exceed that of the general population. The age-adjustment of utilities using this multiplicative approach is further discussed in response to B15.

e) **Please justify the assumption that patients in the model not using cochlear implants would have received hearing aids, and how it relates to the utility values used in the model. Please also justify not including the utility gain associated with hearing aids of 0.12 in the base-case analysis.**

The Barton et al. (2006)[52] study reports the utility of children with cochlea implants, and non-implanted children with moderate, severe or profound deafness. Although the study does not explicitly state that all non-implanted children had hearing aids, due to the severity of their hearing loss, it is appropriate to assume that they did. This also aligns with feedback from interviews with audiologists whereby all 10 audiologists agreed that all patients with moderate hearing loss would be fitted with hearing aids.

Further to this, within Barton et al. (2006)[52] it is stated that, "the incremental cost is the additional cost of providing implants over and above the cost of management with acoustic hearing aids". This suggests that the incremental analysis was performed between children with cochlea implants and un-implanted children who did receive hearing aids, as opposed to children without hearing aids. It can therefore be assumed that the incremental utility gain associated with cochlea implants also reflects that which is over and above the utility of management with hearing aids, otherwise the comparison of incremental costs and quality-adjusted life years would not be appropriate.

However, to avoid any doubt as to whether patients in Barton et al. (2006)[52] received hearing aids, the Company contacted the authors of the paper, who confirmed it would be reasonable to interpret the utility data for children without implants as including the utility gain offered by hearing aids.

For these reasons it is therefore not appropriate to apply a utility gain associated with hearing aids as any utility gain is expected to already be reflected in the utility values

reported in the paper for non-implanted children with moderate, severe and profound hearing loss, and applying a utility gain would risk double counting.

Gumbie et al. (2022)[51] conducted a cost-effectiveness analysis using utility values from Barton et al. (2006)[52] and took a different approach, whereby they applied a utility gain for hearing aid use. For the reasons noted above, the Company feel that this is inappropriate and results in an overestimation of utilities for the moderate to severe health states. It is also noted that there is no data on the utility gain associated with hearing aids in children, therefore Gumbie et al. (2022)[51] used a utility gain reported in adults, further adding to the uncertainty of these estimates. Further weaknesses with the Gumbie study (2022)[51] study are referenced in question 16, however, despite these limitations, we have reported the results of using this study as a scenario analysis.

B15. CS, Section B.3.5.6, page 94. Please comment on the appropriateness of adjusting HUI3 utility values by using UK general population EQ-5D utility values.

NICE guidelines suggest that when baseline utility values are extrapolated over long time horizons, they should be adjusted to reflect the decline in quality of life that is seen in the general population.[57] Given the lifetime horizon of the model, it was therefore important for the model to incorporate this adjustment. The HUI3 utility values in the model have been age-adjusted according to the UK general population EQ-5D utility values as the equivalent age-specific utility values are not available for the HUI3 (for the UK nor for Canada).

It is acknowledged that there may be small differences in the EQ-5D and HUI3 scales. Therefore, to overcome this, a multiplicative approach has been used whereby in each cycle, the EQ-5D derived utility norm for the average age of the cohort was compared to the EQ-5D derived utility norm of the baseline starting age of the cohort entering the model, and the percentage difference was applied to the baseline HUI3 derived health state utilities. This approach mitigates the issue of using different scales in the analysis, given that a proportional decrease is applied, based on the EQ-5D, as opposed to using an absolute decrement from this scale.

It is also important to note that the adjustment over the time horizon is to reflect utility changes due to the impact of aging (which is not specific to hearing loss) and

therefore this is best captured by NICE's preferred measure, EQ-5D. On the other hand, the HUI3 is more appropriate to capture the impact of hearing loss for which the EQ-5D has been found to have limitations in its ability to differentiate.[58,59] Therefore, the approach of using HUI3 utility values to quantify the impact of hearing loss and age-adjusting these using UK general population EQ-5D utility values is considered appropriate.

B16. CS, Section B.3.5.6, page 92. In the scenario analysis, the company uses a different approach to estimate the health-state utilities, where utility decrements for mild to severe HL states are generated from utility values from Gumbie et al (2022) and applied to the minimal/no HL utility value,. Please justify or reconsider the use of this approach instead of using the utilities informed in the paper directly in the model (with adjustments to inform marked HL state).

The Company acknowledge that there are two approaches that can be used to utilise data from Gumbie et al. (2022)[51]. The first approach, and the one which was used in the CS, is to take the utility decrement reported for each health state and apply this to the utility of the 'Minimal/no HL' health state in the model. The Company believe this to be the best approach given the limitations of the Gumbie et al. (2022)[51] publication which are discussed further below (with additional limitations also referenced in response to B14e). The second approach, as the EAG have noted, is to use the utility values reported in the paper and apply these directly in the model.

It should be noted that after an analysis of the study by Gumbie et al. (2022)[51], the Company decided to include utility decrements from this paper as a scenario only due to several limitations with the analysis. Firstly, this study assumes that the 'Minimal/no HL' health state has a utility value of 1 (i.e. perfect health), and as referenced by ScHARR this assumption is not appropriate, even for a population without a health condition.[60] In addition, Gumbie et al. (2022)[51] combines data from multiple sources (Barton et al. (2006)[52], Grutters et al. (2007)[53], de Wolf et al. (2011), and Bond et al. (2009)[40]) and in some cases the methods used are not transparent, for example it states that the moderate unilateral hearing loss utility value is "calculated based on applying the ratio of [unilateral] and [bilateral] in de Wolf et al. (2011) and applying to Barton et al. (2006)", yet Barton et al. (2006)[52] does not report a separate utility for unilateral and bilateral hearing loss. The Company believe that

using the primary source of data (in this case, Barton et al. (2006)[52]) reduces uncertainty and thus is a fairer representation of the health state utility values.

Nevertheless, the Company have conducted an exploratory analysis utilising the alternative method mentioned by the EAG, the results of which are reported in Table 22. As shown, this results in no change to the ICER compared to the Gumbie et al. (2023)[51] scenario that was presented in the CS because the incremental difference between health state utilities remains the same. The Company believe that the approach used in the CS is considered more appropriate as it doesn't assume perfect health to the Minimal/no HL health state.

Table 22: Exploratory analysis of the approach used for the Gumbie scenario

Health state	Utility value	
	Gumbie et al. (2023) CS scenario	Gumbie et al. (2023) Alternative exploratory scenario
Minimal/no HL	0.92	1.00
Mild HL	0.82	0.90
Moderate HL	0.72	0.80
Marked HL	0.66	0.74
Severe HL	0.64	0.72
ICER	£[redacted]	£[redacted]

Abbreviations: HL – Hearing loss; ICER – Incremental cost-effectiveness ratio

Resource Use

B17. PRIORITY. CS, Section B.3.6.1, page 96. Our clinical advisor suggested that patients receiving sodium thiosulfate would receive additional antiemetics over and above those received for cisplatin. Please include the costs of these antiemetics as part of the base-case analysis, according to what was observed in the pivotal studies and analyses required by the EAG (see questions A13 and B13).

As noted in the CS, the Pedmarqsi SmPC references that antiemetic medication is recommended to be administered 30 minutes prior to each Pedmarqsi dose. The use of antiemetics for patients treated with Pedmarqsi is also supported by the SIOPEL 6 and COG ACCL0431 protocols which suggest that antiemetics should be given to reduce nausea and vomiting. However, the Company also notes that in practice it is unlikely that additional antiemetic medication would be required, given that patients would already be receiving multiple doses of antiemetic medication for their cisplatin

infusion. Therefore, the original Company base case did not include antiemetic costs and instead presented an alternative scenario with these costs included.

The Company acknowledge the request by the EAG to include antiemetic costs in the base case, however, note that the specific antiemetic use was not recorded in either trial. As discussed at the NICE clarification teleconference, the Company will instead apply the initial scenario analysis (which estimated the cost of antiemetic pre-medication from the Birmingham children's hospital guideline for the management of chemotherapy-induced nausea and vomiting) in the base case.

For clarity, this scenario assumed that three antiemetics (ondansetron, dexamethasone and metoclopramide) were administered 30 minutes prior to each Pedmarqsi dose, and the cost of this pre-medication was added to the Pedmarqsi acquisition and administration costs. The Company also note that this resulted in a minimal change to the ICER.

B18. PRIORITY. CS, Section B.3.6.2.2, pages 100-103. Regarding the costs of frequency modulation (FM) systems, please clarify the following:

a) **The following source was not provided as part of the reference pack. Please share this the EAG: "Apex Healthcare Consulting. Managing ototoxicity in paediatric cancer patients and assessment of PEDMARK from an audiology perspective: audiologist market research report for Fennec Pharmaceuticals (2018)."**

Thank you for bringing this to the Company's attention. A copy of the "Apex Healthcare Consulting. Managing ototoxicity in paediatric cancer patients and assessment of PEDMARK from an audiology perspective: audiologist market research report for Fennec Pharmaceuticals (2018)" has been provided with the responses to the clarification questions.

b) **Please justify the inclusion of the costs of FM systems for all children with any hearing loss severity, since Dione et al (2012) included the costs of FM systems only for patients with grades 2+.**

The Company included FM system costs for all children with any hearing loss based on the audiologist market research report (mentioned in A18a). Page 11 of this

report stated that “most children have personal FM devices or other accessories”, with a UK audiovestibular physician commenting that “The new recommendations from the National Deaf Children’s Society (NDCS) is that all children irrespective of their age, even babies, little ones, should have access to some FM systems”. Additionally, research has highlighted the benefits that radio aids and FM systems offer deaf infants and young children to overcome barriers to language and communication. For example the briefing paper by the NDCS states that “Every deaf child should be considered as a potential candidate for provision of a personal radio aid as part of their amplification package, at first hearing aid fitting”.[61]

Further to this, the Company also note that Dionne et al. (2012) is conducted from a Canadian perspective, and therefore the Company understandably preferred to apply assumptions from the UK experts interviewed in the audiologist report.

c) **In the model, a higher proportion of patients receive FM systems (100% of all patients with hearing loss) when compared to hearing aids (50% mild HL, 100% moderate HL, 94% marked HL and 48% severe HL). Please justify this difference by providing evidence if available.**

As noted in response to clarification question A18b, responses from the audiologist market research report stated that all children, irrespective of age, should have access to FM systems. Therefore, in the model, 100% of patients with hearing loss are said to receive FM systems.

The proportion of patients with ‘Mild HL’ and ‘Moderate HL’ receiving hearing aids is also derived from the audiologist market research report (Page 10), which states that “all [moderate hearing loss] patients would be fitted with a hearing aid”, and that “a proportion of children (50%) of those with mild hearing loss would also have hearing aids”.

For the more severe hearing loss health states (‘Marked HL’ and ‘Severe HL’), the proportion of patients receiving hearing aids was calculated as one minus the proportion of patients receiving cochlea implants. This was based on TA566 which states that “unilateral cochlea implantation is recommended as an option for people with severe to profound deafness who do not receive adequate benefit from acoustic hearing aids”. Therefore, this calculation was implemented to avoid double counting

the number of patients with hearing support (see Table 42 of the CS) and as it was assumed that patients would not receive both devices.

B19. CS, Section B.3.6.2.1, pages 98-99. Please justify the approach of applying a weighted cost for hearing assessments for all patients <18 year-olds, based on the distribution of patients aged ≥1 month to <18 years and the unit costs for <5 years and 5-18 years age groups, instead of applying the specific costs for each age group (<5 years and 5-18 years) to each cycle in the model.

The model uses a weighted average cost for hearing assessments for all patients <18 years old, which was calculated using the unit costs for <5 years and 5-18 years age groups, sourced from the NHS cost collection, along with the distribution of ages reported in the COG ACCL0431 trial. This approach was taken as a simplifying assumption, given that the difference in cost between the age groups is minimal (<5 years: £151.16; 5-18 years: 139.41).

Nevertheless, the Company acknowledges the EAG's request to apply the specific costs for each age group (<5 years and 5-18 years) to each cycle in the model, and have conducted an exploratory analysis using this approach. This analysis results in a minimal decrease to the ICER, as shown in Table 23.

Table 23: Exploratory analysis for the application of hearing assessment costs in the model

Modelling approach	ICER	Change from base case ICER
Base case: Weighted average unit cost applied to all patients <18 years old	£[redacted]	N/A
Exploratory analysis: Specific costs for each age group applied to each cycle of the model	£[redacted]	-£[redacted] (-0.27%)

B20. CS, Section B.3.6.2.2, pages 100-103. Regarding the costs related to hearing aids, please clarify:

a) If the values reported in the CS and model for hearing aid fitting of £121.70 and £128.08 (for children and adults, respectively) are per ear or per patient, since

the referred source reports the values on a per ear basis. Provide a justification if the same value is assumed for both.

The cost of hearing aid fitting of £121.70 for children (NHS cost code AS02) and £128.08 for adults (NHS cost code AS01) reported in the CS and model are per patient. The NHS cost collection does not specify if the cost is per ear or per patient, therefore it was conservatively assumed that fitting a second hearing aid would add no additional cost compared to fitting a singular hearing aid.

b) How to obtain the value used in the model for the cost of hearing aid for adults of £243.62. The EAG tried to obtain the same value by following the instructions of the company (weighted average of AS05 and AS06 (18+ years old) using the values in 'other currencies' worksheet and doubling the value), but a different cost estimate was obtained (£248.51).

The Company would like to clarify that the value used in the model for the cost of hearing aids for adults is correct (£243.62). The cost was derived by taking a weighted average of NHS cost collection codes AS05 and AS06 (≥18 years old) located on the 'other currencies' sheet. The weighted average cost for one hearing aid was doubled to obtain a value of £243.62. The full calculation can be found in cell E236 of the 'Datastore' sheet in the model, and a summary of this cost calculation is shown in Table 24.

Table 24: Hearing aid cost (≥18 years old)

Currency code	Currency description	Activity	Unit cost
AS05	Hearing Aid, Adult, Any Qualified Provider Contract	116,727	£134.71
AS06	Hearing Aid, Adult, Other Contract	188,210	£113.81
Weighted average cost for one hearing aid:			£121.81

c) Please justify the inclusion of the costs of hearing aids for all HL severity levels, including patients with mild HL. Our clinical advisor suggested that hearing aids would be fitted only in patients with marked and severe HL.

As noted in response to clarification question B18c, page 10 of the audiologist market research report states "a proportion (50%) of those with mild hearing loss

would also have hearing aids". As also previously mentioned, for the more severe hearing loss health states ('Moderate HL', 'Marked HL', and 'Severe HL'), the proportion of patients receiving hearing aids was calculated as one minus the proportion of patients receiving cochlea implants, supported by TA566[56], to avoid double counting the number of patients with hearing support and as it was assumed that patients would not receive both devices. Please refer to question B18c.

B21. Model worksheet 'Data Store', cells D246:E247. Please clarify the source or the choice of the values for the frequency of speech and language therapy sessions per adult with severe HL (of 0.9 sessions per year). Please also adjust the number of annual sessions for patients 0-18 years with marked and severe HL to correctly represent the intended frequency of weekly sessions (from 52.14 sessions per year to =365.25/7).

The source for the frequency of speech and language therapy sessions per adult in the 'Severe HL' health state (of 0.9 sessions per year) is Smulders et al (2015)[62]. The Smulders et al. (2015)[62] reference in the model and CS was incorrectly labelled as 2016. The relevant text has now been updated in the economic model with the appropriate reference provided in the PDF reference pack submitted alongside these responses. For further clarification, Table 1 in Smulders et al. (2015)[62] presents the number of speech therapist visits before cochlea implantation (preoperative) and in the first and second year after surgery. The Company took the conservative approach of using the lowest number of visits (preoperative) in the model.

Regarding the number of speech and language therapy sessions for patients aged 1 month to <18 years old, the model has been updated to reflect the intended frequency of weekly sessions for patients in the 'Marked HL' and 'Severe HL' health states (365.25/7).

B22. CS, Section B.3.6.2.2, page 100 and model, Trace worksheets, columns BF to BI. Please explain the calculations included in the model regarding the costs of cochlear implants, in particular the costs of replacement of the internal component of the implant and what each cost component represents. In these calculations, within the period of the warranty (first 10 years from initial implantation) a cost of '*Re-implantation cost for internal electrode*' is applied to the proportion of patients who require an internal cochlear implant replacement, whilst after the period of the warranty

ends this cost is applied in addition to the cost of '*Replacement internal electrode'*. Please also clarify if after the replacement of an external or internal electrodes, these would be under new warranties.

A targeted review of the literature showed that, separate to the replacement of the external processor, the internal component of a cochlea implant can sometimes fail which requires replacement and re-implantation.[40] As the cost of such replacements is considerable, it was deemed appropriate to include this in the model. Analysis of internal device failure is commonly presented in the form of cumulative survival graphs which show the proportions of cochlea implants which survive to a particular point in time, as shown in Bond et al. (2009).[40] The survival graph reported by Bond et al. (2009)[40] was digitized to determine the probability of the internal component requiring replacement in each cycle of the model. Due to a lack of data being available after 40 years post initial implantation, a last observation carried forward approach was used whereby the probability of replacement in years 40+ of the model was assumed to be equal to the probability of replacement in year 40. However, in terms of costs, as stated in Bond et al. (2009)[40], "The internal component of a cochlea implant is under warranty for free repairs and/or replacements (information supplied to NICE by manufacturers) and therefore separate costs need to be used for the periods of time inside and outside the warranty". Therefore, for the first 10 years after initial implantation, the cost of a new implant is not considered, yet the cost associated with re-implantation (e.g. the labour cost) is still considered.

Finally, since the model is a cohort model and therefore does not track patients individually, a simplifying assumption was required whereby after the first replacement of an external or internal electrode, any further replacements were not considered to be under new warranties. Therefore, to clarify, the external and internal warranty periods are only considered since the initial implantation in year 1 of the model.

The Company notes that the calculations in columns BF to BI in the traces (which capture the cost of bilateral cochlea implants) include a number of cost components. Therefore, for clarity, Table 25 below shows a description of each named range

included in the calculations (taken from the economic model), and when these component costs are applied in the model.

Table 25: Summary of bilateral cochlea implant cost components included in the model

Named range in the model	Description of named range	Source of input	Years in the model that the cost is applied
CI_cost1_under18	The pre-implantation cost. This includes the cost of referral, initial assessment, testing, electrophysiology, medical assessments and pre-procedural assessment outcome discussions.	Cutler et al. (2022)[55]	Year 1 only
CI_cost2_under18	The cost of a bilateral cochlea implant. This includes the cost of internal and external components at first implantation.	TA566[56]	Year 1 only
CI_cost3_under18	The initial cost of fitting a bilateral cochlea implant.	Bond et al. (2009)[40]	Year 1 only
CI_cost4_under18 CI_cost4_over18	Annual cost of maintenance and programming. A separate cost is considered for patients <18 and ≥18 years old.	NHS cost collection[63]	All years of the model
CI_cost5_under18 CI_cost5_over18	Cost of a replacement external processor. A separate cost is considered for patients <18 and ≥18 years old.	Bond et al. (2009)[40]	Converted to an annual cost based on the replacement frequency (named range Replace_freq_CI) and applied in all years of the model beyond the external warranty period (named range Warranty_external)
CI_cost6_under18 CI_cost6_over18	Cost of a replacement internal electrode. A separate cost is considered for patients <18 and ≥18 years old.	Bond et al. (2009)[40]	Applied for all years beyond the warranty period (named range Warranty_internal). The cost is adjusted according to the annual replacement frequency for internal electrodes

Named range in the model	Description of named range	Source of input	Years in the model that the cost is applied
			(table on the cost input sheet).
CI_cost7_under18 CI_cost7_over18	Re-implantation cost for an internal electrode. This is the cost labour to re-implant the patient. A separate cost is considered for patients <18 and ≥18 years old.	Bond et al. (2009)[40]	Applied in all years of the model. The cost is adjusted according to the annual replacement frequency for internal electrodes (table on the cost input sheet).
Replace_freq_CI	The frequency at which the external processor is replaced.	NHS England Cochlea implant services (2023)[64]	N/A
Warranty_external	The warranty for the external processor (years). During this time, the cost of a new external processor is not considered in the model.	Bond et al. (2009)[40]	N/A
Warranty_internal	The warranty for the internal processor (years). During this time, the cost of a new internal electrode is not considered in the model, whilst the cost of re-implantation is still considered (named ranges CI_cost7_under18 and CI_cost7_over18)	Bond et al. (2009)[40]	N/A
CI_internal_replace_yr40	The annual probability of an internal cochlea implant requiring replacement 40 years after initial implantation. This is the last year for which there is data on the probability of an internal implant being replaced. A last observation carried forward approach is used whereby this annual probability is used in all subsequent years of the model.	Bond et al. (2009)[40]	N/A

B23. CS, Section B.3.6.2.4, page 106. The model includes the costs of 'depression and anxiety' based on the incidence of depression by the status of hearing loss reported in Guerney et al (2007). However, this study reports that '*Substantive differences by hearing loss were not observed for problems with writing skills, behavioral concerns, anxiety, or depression (Table 3).'* Please justify the inclusion of the costs related to depression in the model, and how it is linked to the hearing loss instead of the effects of cancer treatment.

Thank you for bringing this to the Company's attention. The Company firmly believe that costs related to depression should be included in the economic model. Whilst Gurney et al. (2007)[65] concludes that substantive differences by hearing loss were not observed for depression, more patients with hearing loss were reported to experience depression than those without hearing loss.

Further to this, as stated in Section B.1.3.2.3 of the CS, paediatric childhood cancer survivors participating in the FDA's Patient Voice meeting highlighted the significant impacts of hearing loss on their day-to-day lives, and the deterioration of their mental health. Depression was commonly mentioned by participants at the meeting, and many spoke of feelings of isolation and loneliness. One patient stated that, "*I feel left out and isolated which makes me feel like I'm not part of this world. I'm sad about that*." The advocacy organisations also included discussions with patient caregivers, who expressed fears that their children would continue to withdraw from the world, with one caregiver sharing that *"the hearing loss…is the single reason that he says, 'I wish the cancer had killed me.' He thinks that the life we gave him by saving his life isn't worth it right now."*

Additionally, as noted in Section B.1.3.2.2 of the CS, the literature indicates that hearing loss can contribute to anxiety and depressive symptoms amongst cancer survivors.[66,67] Therefore, the Company do not believe it would be appropriate to exclude the costs of anxiety and depression for patients with hearing loss given that both conditions are highly relevant to the patient population under review.

Adverse events

B24. CS, Section B.3.4.4, page 88. Please provide the rationale (and evidence, if available) for using data to inform the AE frequencies in the model from the COG

ACCL0431 full safety population, instead of the localised disease subgroup of patients. Please provide the data for the Grade 3+ AEs and serious adverse events (SAEs) for the localised disease subgroup of patients and for the additional analysis requested by the EAG (see question A13). Please provide a version of the model that includes in the base case the incidence of Grade 3+ AEs for ≥5% for the localised disease subgroup, instead of SAEs for ≥2%, (for the pooled data if available – see A13).

As noted in Section B.3.4.4 of the CS, the data informing AE frequencies in the model were sourced from the COG ACCL0431 full safety population, to align with the approach for the base case efficacy data, where inputs are sourced from the full efficacy population instead of the localised disease subgroup of patients. Furthermore, it is appropriate to include AEs from the whole safety population, given that this data set reflects the largest sample size and to ensure all AEs are captured.

However, as requested, the Company has provided the data for Grade 3+ AEs occurring in ≥5% of patients, and Pedmarqsi treatment-related serious adverse events (SAEs) occurring in ≥2% of patients for the localised disease subgroup of patients, and the localised subgroup of the pooled analysis. This data can be found in the PDF document titled “NICE Request_23MAY2024”.

Further to this, the Company notes the request from the EAG to use Grade 3+ AEs rather than Pedmarqsi treatment-related SAEs in the economic model. However, the Company believe it is more appropriate to use the latter, as the list of Grade 3+ AEs includes AEs which are related to cisplatin, and there is no reason to believe cisplatin-related AEs would differ between treatment arms. This position is supported by the fact that the overall incidence of AEs was similar between the two arms, as shown in Section B.2.10.2 of the CS.

Furthermore, the Company has already provided a scenario analysis in the CS whereby AEs of Grade 3+ are considered with a cut-off of ≥10% applied. The Company believe that a cut-off of ≥5% (as requested by the EAG) would not be appropriate because it requires very few patients to experience an AE for it to be included in the model. Furthermore, as shown by the data provided for Grade 3+ AEs in relation to this response, there is very little difference in the incidence of AEs between the treatment arms when focusing on the AEs experienced by 5-10% of patients (i.e. those that were not captured in the scenario analysis of the CS).

Despite this, the economic model has been updated to include an exploratory analysis which includes Grade 3+ AEs occurring in ≥5% of patients in either arm, for the localised only subgroup of the pooled analysis. The Company would like to note that this analysis should be considered as exploratory only, given that assumptions were required for the AE cost and disutility inputs due to a lack of data. This exploratory scenario results in an ICER of £[redacted] which is £328.09 above the Company's new base case ICER.

B25. CS, Section B.3.4.4 page 88 and Model, 'Data Store' worksheet cells R360:R373. Please clarify the source for the incidence of SAEs included in the model base case. The model refers to 'CSR Table 14.3.6.3', which was not found by the EAG in the COG ACCL0431 CSR document. Please clarify the differences between the incidence of SAEs reported in the CS and the incidence reported in Table 25 of the CSR.

The incidence of SAEs included in the model base case are sourced from CSR Table 14.3.6.3, which can be found in the 'COG ACCL0431 additional tables' PDF. provided in the reference pack associated with these responses. Table 14.3.6.3 reports the incidence of SAEs that were considered related to Pedmarqsi. In terms of the economic model, a criterion was applied whereby only Pedmarqsi treatment-related SAEs occurring in ≥2% of patients were included in the base case. Therefore, as none of the SAEs met the threshold of being observed in ≥2% of patients, no AEs are included in the base case analysis.

Table 25 of the CSR reports the incidence of SAEs experienced by patients over the reporting period that were not specifically considered related to Pedmarqsi.

B26. Model, 'Data Store' worksheet, cells G283:G286 and G337. Please justify the inclusion of the costs of elective stays in the estimates of costs for treating some adverse events (i.e., febrile neutropenia and hypersensitivity). Please consider reviewing your approach regarding this issue.

After reviewing the model assumptions, the Company agree that it is appropriate to remove the cost of elective stays from the estimates of costs for treating adverse events. Therefore, the adverse event costs for febrile neutropenia and hypersensitivity have been updated in the model.

Model implementation

B27. Model, worksheet 'Clinical inputs', cells D69:D168. The =VLOOKUP() formula that returns the all-cause mortality seems to be applied in the trace worksheet to the wrong age (offset by 1 year). Please check this error and fix it as appropriate.

Thank you for bringing this to the Company's attention. The formula for general population mortality on the clinical inputs sheet of the model has been amended to ensure that the all-cause mortality for the appropriate age group is used. For example, in the first cycle of the model, where the base case average age of the cohort is [redacted], the all-cause mortality rate of [redacted] years old is used.

B28. Please clarify if the intended use of the SMR is, in the base case, to cease from year 10 onwards or from year 11 onwards.

Thank you for bringing this to the Company's attention. In the base case, the intended use of the SMR is to cease from year 11 onwards. This has been updated in the model.

B29. Model, Trace worksheets, columns DY to EC. Please justify the approach to adjust the quality-adjusted life years (QALYs) by total number of cycles and time horizon since the cycle length is already 1 year. The same applies for when calculating the life years (LYs) gained (columns DQ to DU) and generating the general population mortality estimates ('Data Store' worksheet, cells F568:F667 and 'Clinical inputs' worksheet, cells D69:D168). Please consider removing this adjustment or justify its inclusion.

Thank you for your comment. The Company have removed this adjustment from the model.

Probabilistic sensitivity analysis (PSA)

B30. Model, 'Model Parameters' worksheet. Please clarify which parameters were included in the PSA. Some parameters that would be expected to be included are not included in the PSA (columns I and J), such as mean number of sodium thiosulfate doses and mean number of vials (with or without wastage), whilst other parameters that would be expected to be fixed given its nature are included (such as the length of time to apply the SMR for, the frequencies of replacement of hearing aids, cochlear

implants and FM systems, and the length of warranty for the cochlear implants external and internal electrodes). Please confirm if this was an error or justify why the current approach is appropriate.

Please refer to Table 26 regarding parameters included/excluded in the PSA and reasons for their inclusion/exclusion.

Table 26: Parameters tested in PSA

Parameter grouping	Tested in PSA?	Reason for inclusion/exclusion
Baseline age	Y	Varied to account for heterogeneity in the trial population.
% male	Y	
% of patients experiencing hearing loss	Y	Varied to account for uncertainty in clinical effectiveness data.
Severity of hearing loss	Y	
AE rates	Y	Varied to account for uncertainty in adverse event data.
Five-year cancer mortality	Y	Varied to account for uncertainty in survival estimates.
Post-cancer SMR	Y	
Length of time to apply SMR	Y	Thank you for bringing this to the Company's attention. This parameter has been removed from the PSA.
Health state utilities	Y	Varied to account for uncertainty in utility estimates.
Hearing assessment costs	Y	Varied to account for uncertainty in cost estimates.
Hearing aid costs	Y	
Bilateral cochlear implant costs	Y	
Speech and language therapy costs	Y	
Depression and anxiety costs	Y	
Replacement frequency of hearing loss treatments	Y	These parameters are averages and so are varied in the PSA. The actual replacement frequency will vary between patients, creating uncertainty in these values.
Length of warranty for cochlear implants internal and external electrodes	Y	The Company agree that the warranty for internal and external electrodes of cochlear implants will be fixed in nature and have removed this parameter from the PSA.
Mean number of Pedmarqsi doses	N	Thank you for bringing this to the Company's attention. These parameters are now included in the PSA.
Mean number of Pedmarqsi vials (with wastage)	N	
Mean number of Pedmarqsi vials (without wastage)	N	

Abbreviations: AE – Adverse event; PSA – Probabilistic sensitivity analysis; SMR – Standardised mortality ratio

The removal/addition of the parameters specified in Table 26 results in an ICER of £[redacted] which is £130.05 below the CS base case probabilistic ICER. The

probabilistic results show consistency with the new base case deterministic ICER of £[redacted].

Section C: Textual clarification and additional points

C1. CS, page 53 and Table 18. The text regarding the results of a sensitivity analysis for the primary outcome in COG ACCL0431 ITT population says that '*These results therefore demonstrate that even when patients without 4-week follow-up data are included as patients with hearing loss, the odds of having hearing loss (as defined by the ASHA criteria) were statistically significantly lower in the cisplatin with Pedmarqsi arm (26 children, 42.6%) compared with the cisplatin without Pedmarqsi arm (35 children, 57.4%).*' However, the results in Table 18 suggest that in the cisplatin without Pedmarqsi arm 40 children (62.5%) suffered hearing loss. Please clarify which value is correct, and confirm if the value for the odds ratio informed in Table 18 is correct.

Thank you for your comment. The Company confirm that in the cisplatin without Pedmarqsi arm of the COG ACCL0431 trial, [redacted] children ([redacted]%) suffered hearing loss. The Company also confirm that the odds ratio of [redacted] informed in Table 18 is correct.

C2. CS, Section B.3.6.2.2., Table 42 and model worksheet 'Data Store', cell D236. The CS reports the cost of hearing aids as £298.88, but the model uses £289.88 for a pair of hearing aids. Please clarify which value is correct.

The Company can confirm that the cost for a pair of hearing aids used in the model of £289.88 is correct. This is derived from the NHS cost collection 2021/22, cost code AS07 (Hearing Aid, Child = £144.94) and multiplied by two.

References

1. *Pedmarqsi 80 mg/mL solution for infusion - Summary of Product Characteristics (SmPC)*. (2024). at <https://mhraproducts4853.blob.core.windows.net/docs/9d7e056132aeb4546401b82de128113f89dcf418>
2. *Sodium Thiosulfate 250 mg/mL Solution for Injection - Summary of Product Characteristics (SmPC)*. (2019). at <https://mhraproducts4853.blob.core.windows.net/docs/4e968c4d76366876649d06935e91109827773ba2>
3. FDA. FDA approves sodium thiosulfate to reduce the risk of ototoxicity associated with cisplatin in pediatric patients with localized, non-metastatic solid tumors. *Center for Drug Evaluation and Research* 2024. at <https://www.fda.gov/drugs/resources-information-

approved-drugs/fda-approves-sodium-thiosulfate-reduce-risk-ototoxicity-associated-cisplatin-pediatric-patients>
4. Li C-M, Zhang X, Hoffman HJ, *et al.* Hearing Impairment Associated With Depression in US Adults, National Health and Nutrition Examination Survey 2005–2010. *JAMA Otolaryngol Head Neck Surg* 2014. 140: 293–302.
5. Knight KRG, Kraemer DF & Neuwelt EA. Ototoxicity in Children Receiving Platinum Chemotherapy: Underestimating a Commonly Occurring Toxicity That May Influence Academic and Social Development. *JCO* 2005. 23: 8588–8596.
6. Whelan K, Stratton K, Kawashima T, *et al.* Auditory complications in childhood cancer survivors: A report from the childhood cancer survivor study. *Pediatric Blood & Cancer* 2011. 57: 126–134.
7. *Clinician feedback notes [Data on file]*. (2024).
8. Brock PR, Maibach R, Childs M, *et al.* Sodium Thiosulfate for Protection from Cisplatin-Induced Hearing Loss. *New England Journal of Medicine* 2018. 378: 2376–2385.
9. Freyer DR, Chen L, Krailo MD, *et al.* Effects of sodium thiosulfate versus observation on development of cisplatin-induced hearing loss in children with cancer (ACCL0431): a multicentre, randomised, controlled, open-label, phase 3 trial. *The Lancet Oncology* 2017. 18: 63–74.
10. Liver tumours. *NHS Inform* 2023. at <https://www.nhsinform.scot/illnesses-and-conditions/cancer/cancer-types-in-children/liver-tumours/>
11. Towbin AJ, Meyers RL, Woodley H, *et al.* 2017 PRETEXT: radiologic staging system for primary hepatic malignancies of childhood revised for the Paediatric Hepatic International Tumour Trial (PHITT). *Pediatr Radiol* 2018. 48: 536–554.
12. SIGN. Search filters. *Healthare Improvement Scotland* at <https://www.sign.ac.uk/what-we-do/methodology/search-filters/>
13. Arber M, Garcia S, Veale T, *et al.* Sensitivity of a search filter designed to identify studies reporting health state utility values | Cochrane Colloquium Abstracts. *Cochrane Colloquium Abstracts* 2015 Vienna:
14. Gallegos-Castorena S, Martínez-Avalos A, Mohar-Betancourt A, *et al.* Toxicity Prevention with Amifostine in Pediatric Osteosarcoma Patients Treated with Cisplatin and Doxorubicin. *Pediatric Hematology and Oncology* 2007. 24: 403–408.
15. Katzenstein HM, Chang KW, Krailo M, *et al.* Amifostine does not prevent platinum-induced hearing loss associated with the treatment of children with hepatoblastoma: a report of the Intergroup Hepatoblastoma Study P9645 as a part of the Children's Oncology Group. *Cancer* 2009. 115: 5828–5835.
16. Freyer D, Don D, Orgel E, *et al.* INTRATYMPANIC INJECTION OF SUSTAINED-EXPOSURE DEXAMETHASONE THERMOSENSITIVE GEL (OTO-104) FOR PREVENTION OF CISPLATIN-INDUCED HEARING LOSS IN CHILDREN IS FEASIBLE AND SAFE. *Pediatr Blood Cancer* 2022. 69: S347–S348.
17. Cabi E, Tacyildiz N, Ataseven E, *et al.* PEDMARK® REDUCED THE RISK OF CISPLATIN-INDUCEDOTOTOXICITY IN PEDIATRIC PATIENTS WITHHEPATOBLASTOMA, SEEN IN A TURKISH COMPASSIONATE USETREATMENT PROTOCOL. *Pediatric Blood & Cancer* 2023. 70: e30748.
18. Orgel E, Knight KR, Villaluna D, *et al.* Reevaluation of sodium thiosulfate otoprotection using the consensus International Society of Paediatric Oncology Ototoxicity Scale: A report from the Children's Oncology Group study ACCL0431. *Pediatric Blood & Cancer* 2023. 70: e30550.
19. Orgel E, Villaluna D, Krailo MD, *et al.* Sodium thiosulfate for prevention of cisplatin-induced hearing loss: updated survival from ACCL0431. *The Lancet Oncology* 2022. 23: 570–572.
20. CTYA UK Cancer statistics report 2021, Appendix and downloads. *NDRS* at <https://digital.nhs.uk/ndrs/data/data-outputs/ctya-uk-cancer-statistics-report-2021/appendix-and-downloads>
21. *Clinical Study Protocol: COG ACCL0431 [Data on file]*. (2008).

22. Clemens E, Brooks B, de Vries ACH, *et al.* A comparison of the Muenster, SIOP Boston, Brock, Chang and CTCAEv4.03 ototoxicity grading scales applied to 3,799 audiograms of childhood cancer patients treated with platinum-based chemotherapy. *PLoS One* 2019. 14: e0210646.
23. Knight KR, Chen L, Freyer D, *et al.* Group-Wide, Prospective Study of Ototoxicity Assessment in Children Receiving Cisplatin Chemotherapy (ACCL05C1): A Report From the Children's Oncology Group. *JCO* 2017. 35: 440–445.
24. ACCL0431 CSR [Data on file] RANDOMIZED PHASE 3 STUDY OF SODIUM THIOSULFATE (IND #72877, NSC #45624) FOR THE PREVENTION OF CISPLATIN-INDUCED OTOTOXICITY IN CHILDREN. 2019.
25. Freyer. *SIOP Otoprotection Symposium, unpublished data*. (2018).
26. *Package leaflet: Information for the patient. Pedmarqsi 80 mg/mL solution for infusion*. (2024). at <https://mhraproducts4853.blob.core.windows.net/docs/31a70dbe202b6cfa9e766102945408e0a4cf9f5e>
27. Gandara DR, Wiebe VJ, Perez EA, *et al.* Cisplatin rescue therapy: Experience with sodium thiosulfate, WR2721, and diethyldithiocarbamate. *Critical Reviews in Oncology/Hematology* 1990. 10: 353–365.
28. SIOPEL CSR [data on file] A MULTICENTER, OPEN-LABEL, RANDOMIZED PHASE III TRIAL OF THE EFFICACY OF SODIUM THIOSULFATE IN REDUCING OTOTOXICITY IN PATIENTS RECEIVING CISPLATIN CHEMOTHERAPY FOR STANDARD-RISK HEPATOBLASTOMA. 2019.
29. Norgine: Data on file. *CIO and Pedmark Clinical Data_MED-16390v1*. (2020).
30. Meijer AJM, Diepstraten FA, Ansari M, *et al.* Use of Sodium Thiosulfate as an Otoprotectant in Patients With Cancer Treated With Platinum Compounds: A Review of the Literature. *JCO* 2024. JCO.23.02353. doi:10.1200/JCO.23.02353
31. Zuur CL, Simis YJ, Lansdaal PE, *et al.* Ototoxicity in a Randomized Phase III Trial of Intra-Arterial Compared With Intravenous Cisplatin Chemoradiation in Patients With Locally Advanced Head and Neck Cancer. *JCO* 2007. 25: 3759–3765.
32. Norgine: Data on file. MED_US_SRL_PEDMARK_Electrolyte Imbalances v3.
33. EMA. Pedmarqsi. *European Medicines Agency* 2023. at <https://www.ema.europa.eu/en/medicines/human/EPAR/pedmarqsi>
34. McHugh ML. Interrater reliability: the kappa statistic. *Biochem Med (Zagreb)* 2012. 22: 276–282.
35. Brock P, Rajput K, Edwards L, *et al.* in *Hearing Loss - From Multidisciplinary Teamwork to Public Health* (IntechOpen, 2021). doi:10.5772/intechopen.96744
36. Apex Healthcare Consulting. *Managing ototoxicity in paediatric cancer patients and assessment of PEDMARK from an audiology perspective: audiologist market research report for Fennec Pharmaceuticals*. (2018).
37. Weissenstein A, Deuster D, Knief A, *et al.* Progressive hearing loss after completion of cisplatin chemotherapy is common and more pronounced in children without spontaneous otoacoustic emissions before chemotherapy. *Int J Pediatr Otorhinolaryngol* 2012. 76: 131–136.
38. Fetoni AR, Brigato F, De Corso E, *et al.* Long-term auditory follow-up in the management of pediatric platinum-induced ototoxicity. *Eur Arch Otorhinolaryngol* 2022. 279: 4677–4686.
39. NICE. *Genedrive MT-RNR1 ID Kit for detecting a genetic variant to guide antibiotic use and prevent hearing loss in babies: early value assessment*. (2023). at <chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://www.nice.org.uk/guidance/hte6/resources/genedrive-mtrnr1-id-kit-for-detecting-a-genetic-variant-to-guide-antibiotic-use-and-prevent-hearing-loss-in-babies-early-value-assessment-pdf-1396174036165>
40. Bond M, Mealing S, Anderson R, *et al.* The effectiveness and cost-effectiveness of cochlear implants for severe to profound deafness in children and adults: a systematic review and economic model. *Health Technology Assessment* 2009. 13: 1–330.

41. Rehman AM, Ferrand R, Allen E, *et al.* Exclusion of enrolled participants in randomised controlled trials: what to do with ineligible participants? *BMJ Open* 2020. 10: e039546.
42. Kahan BC & Morris TP. Improper analysis of trials randomised using stratified blocks or minimisation. *Stat Med* 2012. 31: 328–340.
43. Overview | Dinutuximab beta for treating neuroblastoma | Guidance | NICE. 2018. at <https://www.nice.org.uk/guidance/ta538>
44. Overview | Nivolumab for adjuvant treatment of invasive urothelial cancer at high risk of recurrence | Guidance | NICE. 2022. at <https://www.nice.org.uk/guidance/ta817>
45. Brosa M, García del Muro X, Mora J, *et al.* Orphan drugs revisited: cost–effectiveness analysis of the addition of mifamurtide to the conventional treatment of osteosarcoma. *Expert Review of Pharmacoeconomics & Outcomes Research* 2015. 15: 331–340.
46. Aerts I, Pacquement H, Doz F, *et al.* Outcome of second malignancies after retinoblastoma: a retrospective analysis of 25 patients treated at the Institut Curie. *European Journal of Cancer* 2004. 40: 1522–1529.
47. Oldenburg J, Wahlqvist R & Fosså SD. Late relapse of germ cell tumors. *World J Urol* 2009. 27: 493–500.
48. Fidler MM, Reulen RC, Winter DL, *et al.* Long term cause specific mortality among 34 489 five year survivors of childhood cancer in Great Britain: population based cohort study. *BMJ* 2016. 354: i4351.
49. Laverdière C, Liu Q, Yasui Y, *et al.* Long-term Outcomes in Survivors of Neuroblastoma: A Report From the Childhood Cancer Survivor Study. *JNCI: Journal of the National Cancer Institute* 2009. 101: 1131–1140.
50. Suh E, Stratton KL, Leisenring WM, *et al.* Late mortality and chronic health conditions in long-term survivors of early-adolescent and young adult cancers: a retrospective cohort analysis from the Childhood Cancer Survivor Study. *The Lancet Oncology* 2020. 21: 421–435.
51. Gumbie M, Parkinson B, Dillon H, *et al.* Cost-Effectiveness of Screening Preschool Children for Hearing Loss in Australia. *Ear & Hearing* 2022. 43: 1067–1078.
52. Barton GR, Stacey PC, Fortnum HM, *et al.* Hearing-Impaired Children in the United Kingdom, IV: Cost-Effectiveness of Pediatric Cochlear Implantation. *Ear & Hearing* 2006. 27: 575–588.
53. Grutters JPC, Joore MA, van der Horst F, *et al.* Choosing between measures: comparison of EQ-5D, HUI2 and HUI3 in persons with hearing complaints. *Qual Life Res* 2007. 16: 1439–1449.
54. Yang Y, Longworth L & Brazier J. An assessment of validity and responsiveness of generic measures of health-related quality of life in hearing impairment. *Qual Life Res* 2013. 22: 2813–2828.
55. Cutler H, Gumbie M, Olin E, *et al.* The cost-effectiveness of unilateral cochlear implants in UK adults. *Eur J Health Econ* 2022. 23: 763–779.
56. NICE. TA566 Overview | Cochlear implants for children and adults with severe to profound deafness | Guidance | NICE. at <https://www.nice.org.uk/guidance/ta566>
57. 4 Economic evaluation | NICE health technology evaluations: the manual | Guidance | NICE. 2022. at <https://www.nice.org.uk/process/pmg36/chapter/economic-evaluation#discounting>
58. Longworth L, Yang Y, Young T, *et al.* Use of generic and condition-specific measures of health related quality of life in NICE decision-making: systematic review, statistical modeling and survey. *Health Technology Assessment* 2014. 18: 1–224.
59. Shah KK, Mulhern B, Longworth L, *et al.* Views of the UK General Public on Important Aspects of Health Not Captured by EQ-5D. *Patient* 2017. 10: 701–709.
60. ScHARR. *NICE DSU TECHNICAL SUPPORT DOCUMENT 12: THE USE OF HEALTH STATE UTILITY VALUES IN DECISION MODELS*. (2011).
61. NDCS and UK Children's FM Working System. *Quality Stamdards for the use of personal radio aids. Promoting easier listening for deaf children*. (2017).

62. Smulders YE, van Zon A, Stegeman I, *et al.* Cost–Utility of Bilateral Versus Unilateral Cochlear Implantation in Adults: A Randomized Controlled Trial. *Otology & Neurotology* 2015. 37: 38.
63. NHS England » National Cost Collection for the NHS. at <https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/>
64. NHS England. *Schedule 2 - The services. Cochlear implant implantation services (adults and children)*. (2023). at <https://www.england.nhs.uk/wp-content/uploads/2013/05/D09sa-cochlear-implantation-services.pdf>
65. Gurney JG, Tersak JM, Ness KK, *et al.* Hearing Loss, Quality of Life, and Academic Problems in Long-term Neuroblastoma Survivors: A Report From the Children's Oncology Group. *Pediatrics* 2007. 120: e1229–e1236.
66. Bass JK, Knight KR, Yock TI, *et al.* Evaluation and Management of Hearing Loss in Survivors of Childhood and Adolescent Cancers: a Report from the Children's Oncology Group. *Pediatr Blood Cancer* 2016. 63: 1152–1162.
67. Khan A, Mubdi N, Budnick A, *et al.* The Experience of Hearing Loss in Adult Survivors of Childhood and Young Adult Cancer: A Qualitative Study. *Cancer* 2020. 126: 1776–1783.

Appendix

Appendix Table 1: INAHTA Database screening (search 23rd May 2024)

Title	Authors	Year	Reason for exclusion
Genetic testing for childhood hearing impairment	Milverto J, Demir M, Carter D, Hill H, Parsons J, Tamblyn D, Vogan A	2021	Study type - systematic literature review
Effectiveness, safety and economic evaluation of existing alternatives for the early detection of childhood hearing impairment	Ridao López M, Gavín Benavent P, Martín Sánchez JI, Bernal Delgado E	2016	Study type - systematic literature review
Sodium thiosulfate for prevention of hearing loss in children receiving cisplatin chemotherapy	NIHR HSRIC	2015	Study type - clinical trial protocol
Kabuki syndrome	NR	2013	Hearing loss not reported
The role of magnetic resonance imaging in the identification of suspected acoustic neuroma: systematic review of clinical and cost effectiveness, and natural history	Fortnum H, O'Neill C, Taylor R, Lenthall R, Nikolopoulos T, Lightfoot G, O'Donoghue G, Mason S, Baguley D, Jones H, Mulvaney C	2009	Study type - systematic literature review

Electrophysiological testing for diagnosing central auditory processing disorder (CAPD)		2009	Hearing loss not reported
Proton beam therapy for the treatment of neoplasms involving (or adjacent to) cranial structures	Australian Safety and Efficacy Register of New Interventional Procedures - Surgical (ASERNIP-S)	2007	Publication type - review article
Otoacoustic emissions. Clinical applications	Pichon Riviere A, Augustovski F, Bardach A, Regueiro A, Garcia Marti S, Glujovsky D, Lopez A	2005	No intervention of interest
[Proposal for a programme for the early detection of infant deafness in the Basque Autonomous Community]	Algaba J, Asua J, Avellanal S, Esnaola S, Gutiérrez-Ibarluzea I. Gutiérrez F, López L, Miró JL, Municio JA, Paisán LM, Rico R, Tamayo A	2005	Population - not acquired hearing loss
Tinnitus retraining therapy	WCB Evidence Based Practice Group	2004	Hearing loss not reported
Rational antibiotic utilisation in selected paediatric conditions	Malaysian Health Technology Assessment Unit	2003	Hearing loss not reported

Abbreviations: NR – Not reported

Appendix Table 2: Chemotherapy treatment protocols in use in the US at the time of the trial

Tumour type	Summary of protocol
Localised germ cell tumours	CCG8891: Cisplatin 20 mg/m^2/day, D1-5, etoposide 100 mg/m^2 D1-5 and bleomycin 15 U/m^2 Day 1. 4 cycles at 21-day intervals. 2 further cycles to be given if only partial response to chemotherapy.
	AGCT0132: Cisplatin 33mg/m^2/day D1-3, etoposide 167 mg/m^2/day D1-3 and bleomycin 15 U/m^2 D1. 3 further cycles were to be given if only PR to chemotherapy
Localised medulloblastoma	Head Start II: Surgery then 5 cycles of induction chemotherapy containing cisplatin 75 mg/m^2, cyclophosphamide, etoposide, vincristine and high dose methotrexate, followed by myeloablation with carboplatin, thiotepa and etoposide and then stem cell transplantation, finally radiotherapy on relapse.
	Head Start III: Surgery, alternating cycles of Head Start II chemotherapy for cycles 1, 3 and 5 and vincristine, cyclophosphamide, oral etoposide and oral temozolomide for cycles 2 and 4, then same as Head Start II but with reduced amounts of radiotherapy for some subsets.

	Lafay-Cousin protocol: Maximal safe surgical resection, 3 cycles cisplatin 3.5 mg/Kg Day 0, vincristine 0.05 mg/Kg Day 0, 7 and 14, cyclophosphamide 60 mg/Kg Day 1 and 2, etoposide 2.5 mg/Kg Day 0, 1 and 2, given every three weeks. After induction, consolidation chemotherapy given following by stem cell transplantation. Radiotherapy given at physician's discretion.
	Packer Protocol: Six to eight cycles of cisplatin 75 mg/m^2, lomustine and vincristine used for standard-risk medulloblastoma (> 3 years, < 1.5 cm^2 residual disease, CSF negative, no metastases). For high-risk medulloblastoma (> 1.5 cm^2 residual disease) sometimes followed with stem cell transplantation.
	ACNS0821 protocol: Study of treatment with temozolomide and irinotecan with or without bevacizumab for recurrent medulloblastoma.
Localised neuroblastoma	ANBL0532 protocol: This is used for high-risk neuroblastomas regardless of localised or disseminated disease status at diagnosis. All patients received 6 cycles chemotherapy (21-day cycles) – cycles 3 and 5 contain cisplatin 1 hr IV 25 mg/m^2 on D1-4 (total 100 mg/m^2/cycle). Other cycles do not contain cisplatin. Stem cells collected after cycles 1 and 2, surgery after cycle 5. Patients with stable disease or better and sufficient stem cells then receive myeloablative chemotherapy with carboplatin, etoposide and melphalan without (Arm A) or with (Arm B) thiotepa/cyclophosphamide. Radiotherapy after recovery. Patients aged 12-18 months with stage IV mycN non-amplified but unfavourable histology and children >18 months, stage III mycN non-amplified all receive arm A. Some children went on to receive immunotherapy in other COG protocols.
	ANBL0032 protocol: This is used for high-risk neuroblastoma to reduce recurrence. Randomisation to ch14.18 (anti GD-2 antibody), IL-2, GM-CSF and isotretinoin vs isotretinoin alone.
Localised osteosarcoma	AOST0331 (US Arm in EURAMOS-1 study): Randomisation eligible for patients with resectable disease (including metastases). Two cycles of pre-op chemotherapy (every 5 weeks) with cisplatin 120 mg/m^2 as two 4h infusions on two days per cycle, doxorubicin and high dose methotrexate, post operatively randomised to a further two cycles as follows: if >10% viable tumour (poor response, high-risk) in resected specimen either repeat methotrexate or methotrexate plus ifosphamide and etoposide and if <10% viable (good response, lower risk), repeat methotrexate or methotrexate plus PEGylated interferon for 24 months.
Localised hepatoblastoma and other tumour types	SIOPEL 3 or similar: Standard-risk (PRETEXT I-III) randomised to cisplatin 80 mg/m^2 or cisplatin plus doxorubicin given in three preoperative cycles followed by two post-operative cycles.
	ACNS0333: Study of multimodal therapy in children with atypical teratoid rhabdoid tumours. 2 cycles, 3-week intervals, induction chemotherapy including cisplatin, etoposide, cyclophosphamide, high dose methotrexate and vincristine with collection of stem cells post

	chemotherapy. If progressive disease, leave study, if complete response/partial response/stable disease then randomised to consolidation chemotherapy with carboplatin and thiotepa with stem cell rescue followed by 3-D radiotherapy or the opposite way around.
	Head Start III: Surgery, alternating cycles of Head Start II chemotherapy for cycles 1, 3 and 5 and vincristine, cyclophosphamide, oral etoposide and oral temozolomide for cycles 2 and 4, then same as Head Start II but with reduced amounts of radiotherapy for some subsets
Disseminated germ cell tumours	Bleomycin, etoposide and cisplatin (high dose: 40 mg/m^2 D1 to 5 per cycle, standard dose: 20 mg/m^2 D1 to 5 per cycle); 4 cycles given, if residual disease then surgery and two more cycles if malignancy detected in specimens
Disseminated medulloblastoma	Head Start II: Surgery then 5 cycles of induction chemotherapy containing cisplatin 75 mg/m^2, cyclophosphamide, etoposide, vincristine, and high dose methotrexate, followed by myeloablation with carboplatin, thiotepa and etoposide and then stem cell transplantation, and finally radiotherapy on relapse
	Head Start III: Surgery; alternating cycles of Head Start II chemotherapy for cycles 1, 3, and 5 and vincristine, cyclophosphamide, oral etoposide, and oral temozolomide for cycles 2 and 4; and then same as Head Start II but with reduced amounts of radiotherapy for some subsets
	Packer Protocol: Six to eight cycles of cisplatin 75 mg/m^2, lomustine, and vincristine usually used for standard-risk medulloblastoma (> 3 years, < 1.5 cm^2 residual disease, cerebrospinal fluid negative, no metastases). For high-risk medulloblastoma (> 1.5 cm^2 residual disease and disease dissemination) sometimes followed with stem cell transplantation
	Strother et al, 2001: High-risk medulloblastoma receive topotecan and radiotherapy immediately post operatively, followed by four cycles high dose cisplatin 75 mg/m^2, cyclophosphamide, and vincristine
	ACNS0821: Study of treatment with temozolomide and irinotecan with or without bevacizumab for recurrent medulloblastoma.
Disseminated neuroblastoma	ANBL0532 Protocol: This is used for high-risk neuroblastoma. All patient received 6 cycles chemotherapy (21-day cycles) – cycles 3 and 5 contain cisplatin 1 hr IV 25 mg/m^2 on D1 to 4 (total 100 mg/m^2/cycle). Other cycles do not contain cisplatin. Stem cells collected after cycles 1 and 2, surgery after cycle 5. Patients with stable disease or better and sufficient stem cells then receive myeloablative chemotherapy with carboplatin, etoposide and melphalan without (Arm A) or with (Arm B) thiotepa/cyclophosphamide. Radiotherapy after recovery. Patients aged 12 to 18 months with stage IV mycN non-amplified but unfavourable histology and children > 18 months, Stage III mycN non amplified all receive arm A.

	ANBL0032 Protocol: This is used for high-risk neuroblastoma to reduce recurrence. Randomisation to ch14.18 (anti GD-2 antibody), IL 2, GM-CSF and isotretinoin vs isotretinoin alone.
	NANT study of Vorinostat with I-Metaiodobenzylguanidine therapy: Eligibility: refractory disease with no other treatment available and less than or equal to partial response to chemotherapy. Phase I study of ascending doses of Vorinostat plus I-Metaiodobenzylguanidine with stem cell therapy run from March 2010 to December 2014.
Disseminated osteosarcoma	AOST0331 (US Arm in EURAMOS-1 study): Randomisation eligible for patients with resectable disease (including metastases). Two cycles of pre operative chemotherapy (every 5 weeks) with cisplatin 120 mg/m^2 as two 4-hour infusions on 2 days per cycle, doxorubicin, and high dose methotrexate, post operatively randomised to a further two cycles as follows: if > 10% viable tumour (poor response, high-risk) in resected specimen either repeat methotrexate or methotrexate plus ifosphamide and etoposide and if <10% viable (good response, lower risk), repeat methotrexate or methotrexate plus PEGylated interferon for 24 months.
	AOST06P1: Open to patients with newly diagnosed metastatic high-grade osteosarcoma to add zolendronic acid to chemotherapy to maintain bone density. Chemotherapy: 4 cycles including cisplatin 120 mg/m^2 over 2 days, doxorubicin, and methotrexate interspersed with four doses of ifosphamide and etoposide.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Anhydrous sodium thiosulfate (Pedmarqsi) for preventing ototoxicity caused by cisplatin chemotherapy in people aged 1 month to 17 years with localised solid tumours. [ID1001]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1.Your name	NDCS [redacted] RNID [redacted]
2. Name of organisation	The National Deaf Children's Society (NDCS) The Royal National Institute for Deaf People (RNID)
3. Job title or position	NDCS [redacted] RNID [redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	The National Deaf Children's Society (NDCS) is the leading charity in the UK dedicated to supporting deaf children and young people, regardless of their level or type of hearing loss. The NDCS reaches around 42% of the population of permanently deaf children and young people aged 0-25 in the UK. We provide support, information and advice for deaf children and young people, their families, and professionals working with them. The NDCS currently has 105,507 members. Around half are parents/carers/extended family members of a child or young person with hearing loss and around a third are professionals working with children who have hearing loss. The vast majority of NDCS funding comes from individual supporters giving monthly or one-off donations (91%) or through gifts in their wills (5%). The Royal National Institute for Deaf People (RNID) is the national charity supporting the 12 million people in the UK who are deaf, have hearing loss or tinnitus. Together, we will end the discrimination faced by our

	communities, help people hear better now and fund world-class research to restore hearing and silence tinnitus. We work with our communities and partners across industry, government, charity, education and more to change life for the better. RNID has a proud history and big ambitions. We're focused on making the greatest impact possible across the whole of the UK. We champion the latest technology and the opportunities it brings. We also know the value of a friendly face in local communities to support people where they need it most. The RNID has 5,000 members and a panel of 3,500 people with lived experience who help inform RNID's work. RNID also has over 100,000 social media followers. In 2022/23 72% of RNID's income was from voluntary donations and gifts in wills with the remainder from commissioned services and trading activities.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	NDCS > No RNID > No
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	NDCS > No RNID > No

5. How did you gather information about the experiences of patients and carers to include in your submission?	NDCS > Existing NDCS internal research, information and resources and through literature review. RNID > Through existing RNID resources and literature review.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Platinum based chemotherapeutics, such as cisplatin, are highly effective against treating a range of cancers but are unfortunately, also highly ototoxic. As the number of patients diagnosed with cancer continues to grow year on year and with survivors living longer, the impact of ototoxic hearing loss on patient quality of life measures [1] is becoming more apparent with studies showing that people who have hearing loss or tinnitus following treatment with cisplatin were more likely to report a lower quality of life. Hearing loss is a common condition which can occur at any age [2]. It is an often-unrecognised long-term condition and findings from the Global Burden of Disease Study 2019 indicate hearing loss to be the third leading cause of lived years with disability for all ages globally [3]. Without adequate support, people who have hearing loss are more likely to experience health inequalities, have multiple health conditions and to have an overall worse health status compared to those without hearing loss [4]. Strikingly, people who are deaf or have hearing loss are twice as likely to experience mental health problems compared to people without hearing loss [5]. Hearing loss can cause low self-esteem, is often associated with stigma, and can significantly impact the families and communication partners of those living with the condition [6]. Without the right support, living with hearing loss as a deaf child can significantly impact various aspects of life, including speech and language development, academic performance, mental health and social integration [7]. The degree of hearing loss following ototoxicity can range from mild to more severe, but evidence suggests even children with mild or unilateral hearing loss are at a higher risk for academic, speech and language, and social-emotional difficulties compared to their hearing peers [8-11]. Deaf babies and young children are at risk of reduced opportunities for incidental learning in the early years, which is important for their cognitive development [12]. A deaf child without good language and communication development in the early years, be it spoken, sign, or a mixture of both, can experience ongoing challenges. Deaf children may struggle to listen and follow instructions in the classroom, or miss conversations with their peers, leading to feelings of isolation [13]. The majority of carers of deaf children (90%) have no prior knowledge or experience of hearing loss [14]. With appropriate support and early intervention, deaf children have improved language and psychosocial outcomes [15]. However, appropriate support and early intervention can be difficult for all families to access, and some carers feel unsupported, alone and fear for their deaf child's future. Carers report supporting child with hearing loss requires a significant amount of time, responsibility, and effort and that this can have a knock-on effect on

	their social lives and interpersonal relationships [16]. Carers describe experiencing emotions including guilt, confusion, uncertainty, anxiety, fear, being overwhelmed, sadness, anger and loneliness, particularly during the early stages of diagnosis [13]. These emotions can be particularly heightened when hearing loss develops suddenly or unexpectedly, as it can following ototoxicity. Carers also report dealing with challenges relating to their child's mental health and wellbeing, including themes such as anxiety, lack of confidence, impact on friendships, independence, bullying, behaviour and listening or concentration fatigue. Carers of deaf children and young people often report experiencing a lack of deaf awareness from others. Deaf children experience challenges relating to their independence, including developing life skills such as swimming and driving as they often experience barriers to accessing extra-curricular activities [13]. Regarding work and employment despite 1 in 8 adults of working age having a form of hearing loss, people with hearing loss are less likely to be in employment than the general population and commonly report feeling stressed or worried about being treated unfairly in the workplace if they disclose their hearing loss [17]. This has real economic consequences for people living with hearing loss resulting in lower average household incomes and overrepresentation of people with hearing loss in lower status, lower paid occupations [18]. While deaf adults, children and young people can face barriers within our current society, these can be overcome with the right support. Grace's blog about deafness following cancer highlights some first-hand experiences of hearing loss caused by ototoxicity. Her experiences are unique but show that deafness in itself is not a barrier to a happy and fulfilled life. [1] Pearson, Stephanie E., John Taylor, Poulam Patel, and David M. Baguley. "Cancer Survivors Treated with Platinum-Based Chemotherapy Affected by Ototoxicity and the Impact on Quality of Life: A Narrative Synthesis Systematic Review." International Journal of Audiology 58, no. 11 (2019): 685–95. doi:10.1080/14992027.2019.1660918. [2] "Our Facts and Statements." RNID, September 22, 2023. https://rnid.org.uk/get-involved/research-and-policy/facts-and-figures/. [3] Stevens, Gretchen A., et al. "Hearing loss prevalence and years lived with disability, 1990–2019: findings from the Global Burden of Disease Study 2019." The Lancet 397, no. 10278 (2021): 996-1009

[4] McKee, M. M., Stransky, M. L., & Reichard, A. (2018). Hearing loss and associated medical conditions among individuals 65 years and older. Disability and Health Journal, 11(1), 122–125. DOI: 10.1016/j.dhjo.2017.05.007

[5] NHS Digital. (2009). Adult Psychiatric Morbidity in England - 2007, Results of a household survey.

[6] World Health Organization. 2021. World Report on Hearing. Genève, Switzerland: World Health Organization.

[7] Childhood Hearing Loss, Strategies for prevention and care, World Health Organization. URL: https://www.who.int/docs/default-source/imported2/childhood-hearing-loss--strategies-for-prevention-and-care.pdf?sfvrsn=cbbbb3cc_0#:~:text=While%20the%20most%20obvious%20effect,life%20(5%2C%206). [Accessed 09/05/2024]

[8] le Clercq CMP, Labuschagne LJE, Franken MJP, Baatenburg de Jong RJ, Luijk MPCM, Jansen PW, van der Schroeff MP. Association of Slight to Mild Hearing Loss With Behavioral Problems and School Performance in Children. JAMA Otolaryngol Head Neck Surg. 2020 Feb 1;146(2):113-120. doi: 10.1001/jamaoto.2019.3585. PMID: 31774492; PMCID: PMC6902199.

[9] Tharpe, A. M. (2007). Assessment and Management of Minimal, Mild, and Unilateral Hearing Loss in Children. Audiology Online. [Accessed 09/05/2024]

[10] McKay, S., Easterbrooks, S. R., & Tharpe, A. M. (2008). Amplification Considerations for Children With Minimal or Mild Bilateral Hearing Loss and Unilateral Hearing Loss. Trends in Amplification, 12(1), 43–54.

[11] American Speech-Language-Hearing Association. (2007). Mild and Unilateral Hearing Loss in Children. [Accessed 09/05/2024]

[12] National Deaf Children's Society (n.d.) 'Supporting the achievement of hearing impaired children in early years settings' [Accessed 13/05/2024]

[13] National Deaf Children's Society. Deaf Children Today 2023: Challenges in the past year; a summary of findings about the challenges parents/carers have experienced in the past year. Internal research (874 responses from parents/carers, representing children aged 0-5+ with varying levels of deafness)

[14] Rawlings B.W. and Jensema C. Two Studies of the Families of Hearing Impaired Children. Office of Demographics, Washington DC Gallaudet University. 1977.

	[15] Vivienne Marnane, Vivienne Marnane, Harvey Dillon, Mark Seeto, The impact of childhood hearing loss on language and psychosocial outcomes: The LOCHI study, International Journal of Epidemiology, Volume 50, Issue Supplement_1, September 2021 [16] Dikeç G, Türk E, Yüksel E, Çelebi K, Özdemir M. Experiences of Hearing Parents of Children with Hearing Loss: A Qualitative Study. Children (Basel). 2023 Jun 29;10(7):1129. doi: 10.3390/children10071129. PMID: 37508626; PMCID: PMC10378033. [17] Action on Hearing Loss. (2018). Working for Change 2018 Workplace Experiences: Survey results [18] Hear-it. “Hearing Loss – Numbers and Costs.” 2018 https://www.ehima.com/wp-content/uploads/2019/03/HearitReportHearingLossNumbersandCosts.pdf

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Currently in the UK treatments for hearing loss are restricted to hearing aids and cochlear implants, although effective these devices do not restore normal hearing and have several limitations as reported by the people who use them. In the UK it is estimated that around 7 million adults in the UK could benefit from hearing aids but only about 2 million people use them [19] and studies have indicated that adults wait on average 9 years after being confirmed eligible for hearing aids before using them [20]. The reasons underlying the lack of uptake of these devices are multifaceted [21] but commonly include lack of perceived need/benefit for the device, concerns around the stigma related to and cosmetic appearance of the device, difficulties using the device in noisy situations and lack of comfort in wearing the device [22]. Deaf children have varying experiences of hearing technology. Some deaf children have a strong, positive deaf identity, others report feelings of embarrassment or self-consciousness in relation to their hearing loss or use of hearing technology. Some deaf children and/or their carers choose not to use hearing technology [13]. Some deaf children and/or their carers choose alternative communication methods, such as British Sign Language, in addition to or instead of hearing technology. Hearing aids and cochlear implants have limitations in acoustically challenging environments such as noisy environments or group situations, in addition to this there is also extra cognitive effort required by hearing aid wearers to process and understand speech and the sounds around them which can lead to listening fatigue [23]. Children often require the use of additional assistive listening devices. Carers can experience challenges in keeping hearing aids or cochlear implants on very young children. Babies and very young children require increased supervision when using their hearing technology, both to mitigate safety risks such as choking or battery ingestion, but also to ensure the proper maintenance and care of the devices. Carers report that hearing aids can sometimes lead to a build-up of earwax or put a child more at risk of ear infections that further impact on their hearing. Carers report issues with technology becoming faulty, leaving their child without a device until a replacement is issued [13]. Hearing technology alone is not all that is required to support a deaf child. In order to thrive, deaf children require a framework of support and additional services, both within and outside of the NHS. This includes access to specialists such as Audiologists, Speech and Language Therapists and Teachers of the Deaf. Over four in 10

	parents are uncertain about finding their way around healthcare, education and support services to ensure their child gets the support they need [24]. Many carers report their deaf child is not getting the support they need at school. Some carers report paying for services as their child is either not eligible or accessing support is difficult, which causes additional financial burden on the family. Many carers report long waiting times and delays accessing audiology services and not all children currently receive high quality care from audiology or education services [13]. Missed opportunities to spot deafness and provide the support deaf children need can lead to lifelong impacts. The number of qualified Teachers of the Deaf across England has fallen to its lowest level on record [25]. With the right support, deaf children are just as capable as their hearing peers. However, it is not currently guaranteed that every deaf child receives appropriate support for their hearing loss [13]. Deaf children (65%) are almost twice as likely as all children (34%) to complete their first year of school without having achieved a 'good level of development' [24]. On average, deaf children fall an entire grade behind their hearing classmates at GCSE [26]. [19] Hearing Link Services. "Facts About Deafness and Hearing Loss." Hearing Link Services. Accessed April 29, 2024 [20] Simpson AN, Matthews LJ, Cassarly C, Dubno JR. Time From Hearing Aid Candidacy to Hearing Aid Adoption: A Longitudinal Cohort Study. Ear Hear. 2019 May/Jun;40(3):468-476. doi: 10.1097/AUD.0000000000000641. [21] Marcos-Alonso S, Almeida-Ayerve CN, Monopoli-Roca C, et al. Factors Impacting the Use or Rejection of Hearing Aids-A Systematic Review and Meta-Analysis. J Clin Med. 2023 Jun 13;12(12):4030. doi: 10.3390/jcm12124030. [22] Franks, Inga, & Timmer, Barbra H. B. (2023). Reasons for the non-use of hearing aids: perspectives of non-users, past users, and family members. [23] Sarah Allen, Imran Mulla, Zheng Yen Ng, Sue Archbold & Melanie Gregory, Using radio aids with pre-school deaf children, June 2017, The Ear Foundation [24] Deaf children falling behind peers in early years | National Deaf Children's Society (ndcs.org.uk) [25] Consortium for Research in Deaf Education (CRIDE) (2023) '2023 report for England' url: https://www.batod.org.uk/wp-content/uploads/2023/12/CRIDE-2023-England-report.pdf [accessed 10/05/2024].

	[26] Deaf pupils achieve an entire GCSE grade less for sixth year running | National Deaf Children's Society (www.ndcs.org.uk), 09 Aug 2021
8. Is there an unmet need for patients with this condition?	Currently in the UK there are no therapies to prevent hearing loss, slow its progression or to reverse damage caused to the inner ear and therefore restore normal hearing. Results from a public priorities survey conducted by RNID in 2019 revealed that supporting medical research into finding treatments and cures for hearing loss is a priority for those with personal experience [27]. [27] Action on Hearing Loss Survey, internal unpublished report, July 2019

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	We are collectively unable to speak to families' views on this specific technology, however, for families the 'cause' of their child's hearing loss is usually of significant interest. Most carers are keen to explore all options of available support for their deaf child [13].

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	We are collectively unable to speak to families' views on this specific technology, however, there are some families within the Deaf community who view deafness not as a disability but as a cultural identity. They may not view deafness as a condition that needs to be 'fixed' through treatments. Other families may believe that deaf children face too many barriers in life and the best way to overcome these barriers is to find medical treatments for their deafness. The views of carers and deaf children and young people can vary widely, and each individual's perspective is unique.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Unable to comment.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	There is evidence to support that deaf children from ethnic minorities have poorer educational outcomes compared with their hearing counterparts [27]: • Black deaf children have the lowest attainment scores compared to other ethnic groups. • Asian deaf children have lower attainment scores than White deaf children. This is striking given that, among all children (i.e including all children with or without any special educational needs), Asian children have higher attainment scores than other ethnic groups. • Deaf children who are eligible for free school meals or who speak English as an additional language also underachieve. [27] National Deaf Children's Society. Deaf children from ethnic minority groups: A literature review. URL: https://www.ndcs.org.uk/media/6795/ndcs-literature-review-deaf-children-from-ethnic-minority-groups-final.pdf

Other issues

13. Are there any other issues that you would like the committee to consider?	Patients should be able to make decisions based on complete and accurate information. They need high-quality, evidence-based information that helps them understand the risks, benefits, and potential outcomes of their choices. It is also important that patients and their families receive help in evaluating these options. They should be informed about any limitations of the treatment, while also understanding that deafness in itself is not a barrier to a happy and fulfilling life. Patients and their families should be empowered with comprehensive and clear information about deafness, enabling them to make fully informed choices.
14. To be added by technical team at scope sign off. Note that topic-specific questions will be added only if the treatment pathway or likely use of the technology remains uncertain after scoping consultation, for example if there were differences in opinion; this is not expected to be required for every appraisal.] **if there are none delete highlighted rows and renumber below**	

Key messages

24. In up to 5 bullet points, please summarise the key messages of your submission.	• Currently, in the UK there are no therapies to prevent cisplatin-induced hearing loss or to reverse damage caused to the inner ear and therefore restore normal hearing for those that want them. • Many deaf adults, children and young people in the UK currently do not receive the support they need to overcome societal barriers in order to achieve their full potential. Many families of deaf children and young people report a lack of deaf awareness from others. • Hearing loss can have a significant impact on the language and communication skills that lie at the heart of deaf children and young people's social and emotional development, and education. ng • Carers of children with hearing loss can also be significantly impacted affecting their emotional, mental and social wellbeing. • Hearing loss can impact on future employment prospects. People with hearing loss are less likely to be in employment compared to the general population.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

Please select YES if you would like to receive information about other NICE topics - YES

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Anhydrous sodium thiosulfate (Pedmarqsi) for preventing ototoxicity caused by cisplatin chemotherapy in people aged 1 month to 17 years with localised solid tumours [ID1001]

Clinical expert statement

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

NICE National Institute for Health and Care Excellence

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for your response is **5pm** on **09 August 2024.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

Part 1: Preventing ototoxicity caused by cisplatin chemotherapy and current treatment options for hearing loss

Table 1 About you, aim of prevention or treatment, place and use of technology, sources of evidence and equality

1. Your name	Dr Milind Ronghe
2. Name of organisation	Royal Hospital for Children, Glasgow
3. Job title or position	Consultant Paediatric Oncologist
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☐ A specialist in the treatment of people with ototoxicity caused by cisplatin chemotherapy? ☒ A specialist in the clinical evidence base for prevention of ototoxicity caused by cisplatin chemotherapy or the technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☒ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

8. What is the main aim of treatment in preventing ototoxicity caused by cisplatin chemotherapy? (For example, to fully or partially prevent hearing loss, to prevent worsening of hearing loss)	To fully or partially prevent hearing loss caused by Cisplatin chemotherapy To prevent worsening of hearing loss
9. What do you consider a clinically significant treatment response? (For example, a retention of hearing by a certain amount)	Retention of hearing by any amount in patients exposed to Cisplatin chemotherapy, or reduce the percentage of children with ototoxicity who are exposed to Cisplatin chemotherapy.
10. In your view, is there an unmet need for patients and healthcare professionals in preventing ototoxicity caused by cisplatin chemotherapy?	Currently there are no preventative treatment options to avoid Cisplatin induced ototoxicity. Current treatment pathways do not address the underlying cause of hearing loss. Once the ototoxicity/hearing loss has occurred, that is addressed with hearing aids and/or cochlear implants. They do not necessarily restore the hearing function and they do not improve the quality of life of children with hearing loss associated with normal hearing. So, there is an unmet need for patients and professionals in preventing ototoxicity caused by Cisplatin chemotherapy.
11. How is ototoxicity caused by cisplatin chemotherapy currently managed or prevented in the NHS? • Are any clinical guidelines used in preventing or managing ototoxicity caused by cisplatin chemotherapy, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	In paediatric population sometimes it is quite difficult to pick up/diagnose hearing loss and the frequent problem is delayed diagnosis. The next problem is assessing the degree of hearing loss, as different classification systems exist (Brock criteria, ASHA, CTCAE grading, Chang system, SIOP Boston system). Approximately 50 – 60% of children receiving Cisplatin based chemotherapy will develop irreversible ototoxicity. This will have a significant impact in the paediatric population. This leads to delayed speech and language development in young children, which then subsequently impacts on their literacy skills. This reduces their educational achievement and emotional wellbeing. Children will have behavioural issues, low self-esteem, and this may progress during adolescence to depression and inability to live

• What impact would the technology have on the current pathway of care in people aged 1 month to 17 years having cisplatin chemotherapy for localised, non-metastatic, solid tumours who are at risk of ototoxicity? • What treatment/devices are currently available in the NHS for people with hearing loss? What criteria are used when considering offering hearing aids or cochlear implants?	independently. In addition to having an impact on their quality of life and reducing their academic potential, which will lead to reduced potential of that individual, there is an economic burden to the society as these patients would need hearing aids, extra teaching support. Some of these children with profound hearing loss will need bilateral cochlear implant, which is quite expensive. In addition, these patients will need to be followed up regularly by Audiologists and patients with hearing loss are less likely to be able to gain employment. Currently the clinic guidelines exist if Cisplatin induced hearing loss occurs. Some of the protocols recommend switching Cisplatin to Carboplatin which is less ototoxic. However, we know that Cisplatin is a better drug in certain malignancies such hepatoblastoma and germ cell tumours. Once the hearing loss has occurred, there are no pharmacological interventions that can reverse the hearing loss. Patients are referred to Audiologists for hearing aids and those with profound hearing loss, who are unable to benefit from hearing aids, bilateral cochlear implants may indicated. One of the other approaches to hearing loss in the UK is the use of FM systems in classrooms to support all children with hearing loss in education. The pathway of care is not very well defined in the UK. Currently, depending on which institution the child is getting treatment and based on the opinion of clinical professionals across the NHS, the practice varies. Pedmarqsi has shown efficacy in terms of preventing Cisplatin induced hearing loss in some clinical trials (SIOPEL 6 and (COG) ACCL 0431). Both studies reported statistically significant results in reducing hearing loss, favouring the use of Pedmarqsi with Cisplatin chemotherapy. Pedmarqsi has now been licensed for use for prevention of auto-toxicity induced by Cisplatin chemotherapy in patients 1 month to <18 years of age with localised non-metastatic solid tumours. The trials reported about did not show any unfavourable cancer related outcome in this patient population. Therefore,

	Pedmarqsi represents a safe and effective treatment that will benefit a certain proportion of patients exposed to Cisplatin induced hearing loss. In our institution we have to apply for Pedmarqsi to be used in this patient population on a named patient basis. The drug is obtained from the pharma company on compassionate grounds, after filling a ULM (unlicensed medicinal product). After getting the management approval, then the company would send the drug for that individual patient. This obviously sometimes delays the start of treatment. However, as Pedmarqsi by the FDA for prevention of ototoxicity induced by Cisplatin chemotherapy in patients with localised non-metastatic disease, hopefully if the drug gets approval by NICE, the process will be streamlined, and administration of the drug would be easier. If is important to say that if Pedmarqsi is used after the patient gets hearing impairment, the extent of prevention of hearing loss is not as good as if it is used as a preventative strategy rather than a therapeutic strategy after the hearing loss occurs. Currently there are no pharmaceutical strategies to prevent hearing loss caused by Cisplatin. As Pedmarqsi will fill a substantial unmet need for treatment that can prevent Cisplatin induced hearing loss in children. Overall SIOPEL 6 and (COG) ACCL 0431 trials show comprehensively that Pedmarqsi is efficacious and safe in preventing Cisplatin induced hearing loss in children 1 month to <18 years of age with localised non-metastatic solid tumours. Hearing aids, cochlear implants, and FM systems.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Pedmarqsi will be administered six hours after completion of every Cisplatin infusion. The treatment will be inpatient based as for receiving chemotherapy, so would not

• How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	need any extra admission or extra resources. The treatment will be hospital based – specialist clinics and children's hospital administering chemotherapies (principle treatment centres). It is not necessary to have any extra investment.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Overall survival and event-free survival would essentially remain the same in patients with childhood cancer who are treated with Cisplatin chemotherapy. Prevention of hearing loss would lead to significant improvement in quality of life and educational potential and it will significantly reduce socio-economic burden on the society.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Children 1 month to <18 years of age with localised non-metastatic solid tumours.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed) • The Summary of Product Characteristics (SmPC) outlines critical timing requirements for administering	• No significant difficulties for patients as well as for healthcare professionals administering Pedmarqsi • No difficulties or barriers with respect to critical timings in administering Pedmarqsi. One has to make sure that Pedmarqsi is not administered less than six hours after the end of Cisplatin infusion as it may reduce the Cisplatin efficacy against the cancer. This has been shown in vitro studies that if you administer it before six hours, then it may lead to reduced efficacy of Cisplatin

anhydrous sodium thiosulfate (Pedmarqsi) in relation to cisplatin. This includes giving the technology only after a cisplatin infusion lasting 6 hours or less, then waiting 6 hours before giving the technology and giving it over a 15 minute infusion, then leaving at least 6 hours before the next cisplatin infusion. • Do you foresee any difficulties or barriers to following these critical timings in administering the technology in NHS clinical practice? What impact might any difficulties have on the efficacy of the technology or cisplatin chemotherapy? The SmPC states that if the technology is administered (i) less than 6 hours after the end of cisplatin infusion it may reduce cisplatin efficacy against the tumour and (ii) more than 6 hours after end of cisplatin infusion the technology may not be effective in preventing ototoxicity. • Do you expect that the specific requirements for administering the technology will add any costs beyond that of the administration step itself. For example, in relation to cisplatin administration compared with when the technology is not used.	against the tumour. One also has to remember that if you use significantly later (after eight hours), then the Pedmarqsi is not effective in preventing Cisplatin induced auto-toxicity. • I do not expect any specific requirements that are necessary
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	All children who are receiving Cisplatin based chemotherapy should have a baseline hearing assessment before the start of treatment and they should be monitored regularly after the treatment is finished or completed. I believe this treatment would definitely improve the quality of life for those individuals as it will preserve their hearing or prevent the hearing loss, which leads to adverse consequences ad mentioned above.

17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Pedmarqsi is a novel and hydrous formulation of Sodium Thiosulfate which can be used as a preventative treatment developed for Cisplatin induced auto-toxicity. There are no options for preventative treatment. Once the hearing loss occurs/auto-toxicity has occurred, the interventions such as hearing aids and cochlear implants are used which are expensive options and do not actually restore normal hearing. This reduces the quality of life of children with hearing loss. Therefore, there is a severe unmet need for preventative treatment options such Pedmarqsi.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Side effects related to Cisplatin chemotherapy – febrile neutropenia, specific effects related to Sodium Thiosulfate (or Pedmarqsi) – hypocalcaemia, hyponatremia, vomiting. These can be managed without any significant problems.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting?	Results of the SIOPEL 6 trial and also from the (COG) trials suggest that this is a very effective drug in preventing Cisplatin induced hearing loss, so should be used in patients with localised non-metastatic solid tumours. The primary efficacy endpoints from

• What, in your view, are the most important outcomes, and were they measured in the trials? • Which tools are used to identify and measure hearing loss and related audiological outcomes in NHS clinical practice. • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	SIOPEL 6 and (COG) trials was to determine the overall proportional incidence of hearing loss. Based on the analysis those children with Cisplatin with Pedmarqsi had significantly less hearing loss compared to those versus those where Cisplatin without Pedmarqsi arm. To reassure the patients event-free survival and overall survival did not show any significant difference between the two arms of the trial. Following repeat audiological central review, 121 of 125 patients were evaluated for hearing loss using SIOP scale. After the end of Cisplatin treatment a lower incidence of grade 2 or more hearing loss occurred in the Cisplatin with Pedmarqsi arm (4%) versus Cisplatin without Pedmarqsi arm (27.1%). A similar pattern was also observed for SIOP grade 1 or more hearing loss too. These results are reassuring and confirm the otoprotective effects of Pedmarqsi using SIOP auto-toxicity scale. So it is concluded that compared to the Cisplatin without Pedmarqsi arm, children receiving Cisplatin with Pedmarqsi were approximately 90% less likely to develop grade 2 or more Cisplatin induced hearing loss at the end of Cisplatin therapy.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No – we have noticed significant reduction in the ototoxicity in patients using Pedmarqsi.
22. How do data on real-world experience compare with the trial data?	
23. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of	This should not affect all applicable for Pedmarqsi.

people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

NICE National Institute for Health and Care Excellence

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☐ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

Anhydrous sodium thiosulfate (Pedmarqsi) for preventing ototoxicity caused by cisplatin chemotherapy in people aged 1 month to 17 years with localised solid tumours [ID1001]. A Single Technology Appraisal

Produced by	Sheffield Centre for Health and Related Research (SCHARR), Division of Population Health, University of Sheffield
Authors	Aline Navega Biz, Research Fellow, SCHARR, Division of Population Health, University of Sheffield, UK Abdullah Pandor, Senior Research Fellow, SCHARR, Division of Population Health, University of Sheffield, UK Jessica Forsyth, Research Associate, SCHARR, Division of Population Health, University of Sheffield, UK Shijie Ren, Senior Research Fellow, SCHARR, Division of Population Health, University of Sheffield, UK Andrew Rawdin, Research Assistant, SCHARR, Division of Population Health, University of Sheffield, UK Emily Pulsford, Information Specialist, SCHARR, Division of Population Health, University of Sheffield, UK Mark Clowes, Research Fellow, SCHARR, Division of Population Health, University of Sheffield, UK
Correspondence Author	Aline Navega Biz, Research Fellow, SCHARR, Division of Population Health, University of Sheffield, UK
Date completed	Date completed (27/06/2024)

Source of funding: This report was commissioned by the NIHR Evidence Synthesis Programme as project number NIHR166961.

Declared competing interests of the authors

None of the authors have any conflicts of interest to declare.

Acknowledgements

We would like to thank Dr Kaukab Rajput, Great Ormond Street Hospital for Children, London, and Dr Amy Mitchell, Oxford Children's Hospital, Oxford, for clinical advice relating to this project. We would also like to thank Professor Paul Tappenden, SCHARR, for providing comments on the draft report and Andrea Shippam, Programme Manager, SCHARR, for providing administrative support and in preparing and formatting the report.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows:

Navega Biz, A; Pandor, A; Forsyth, J; Ren, S; Rawdin, A; Pulsford, E; Clowes, M. Anhydrous sodium thiosulfate (Pedmarqsi) for preventing ototoxicity caused by cisplatin chemotherapy in people aged 1 month to 17 years with localised solid tumours ID1001: A Single Technology Appraisal. Sheffield Centre for Health and Related Research (SCHARR), Division of Population Health, University of Sheffield 2024.

Contributions of authors

Aline Navega Biz acted as project lead. Emily Pulsford and Mark Clowes critiqued the company's search strategy. Abdullah Pandor summarised and critiqued the clinical effectiveness data reported within the company's submission. Jessica Forsyth and Shijie Ren critiqued the statistical aspects of the submission. Aline Navega Biz and Andrew Rawdin critiqued the health economic analysis submitted by the company. All authors were involved in drafting and commenting on the final report.

About SCHARR

The Sheffield Centre for Health and Related Research (SCHARR), School of Medicine and Population Health at the University of Sheffield. SCHARR brings together a wide range of medical- and health-related disciplines including public health, general practice, mental health, epidemiology, health economics, management sciences, medical statistics, operational research and information science. It includes the Sheffield unit of the Trent Institute for Health Services Research, which is funded by NHS R&D to facilitate high-quality health services research and capacity development.

The SCHARR Technology Assessment Group (SCHARR-TAG) synthesises research on the clinical effectiveness and cost-effectiveness of health care interventions for the NIHR Health Technology Assessment Programme on behalf of a range of policy makers, including the National Institute for Health and Care Excellence (NICE). SCHARR-TAG is part of a wider collaboration of a number of units from other regions including Southampton Health Technology Assessment Centre (SHTAC), University of Southampton; Aberdeen Health Technology Assessment Group (Aberdeen HTA Group), University of Aberdeen; Liverpool Reviews & Implementation Group (LRiG), University of Liverpool; Peninsular Technology Assessment Group (PenTAG), University of Exeter; the NHS Centre for Reviews and Dissemination, University of York; Warwick Evidence, The University of Warwick; the BMJ Group, Kleijnen Systematic Reviews, Bristol Technology Assessment Group (Bristol TAG), University of Bristol and the Newcastle NIHR TAR Team, Newcastle University.

CONTENTS

Abbreviations 8
1 EXECUTIVE SUMMARY 10
1.1 Overview of the EAG's key issues 10
1.2 Overview of key model outcomes 11
1.3 The decision problem: summary of the EAG's key issues 12
1.4 The clinical effectiveness evidence: summary of the EAG's key issues 12
1.5 The cost-effectiveness evidence: summary of the EAG's key issues 14
1.6 Summary of EAG's preferred assumptions and resulting ICER 16
2 BACKGROUND 18
2.1 Critique of company's description of underlying health problem 18
2.2 Critique of company's overview of current service provision 19
2.3 Critique of company's definition of the decision problem 21
3 CLINICAL EFFECTIVENESS 31
3.1 Critique of the methods of review(s) 31
3.2 Critique of trials of the technology of interest, the company's analysis, and interpretation 36
3.3 Clinical effectiveness results 42
3.4 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison 55
3.5 Critique of the indirect comparison and/or multiple treatment comparison 55
3.6 Additional work on clinical effectiveness undertaken by the EAG 55
3.7 Conclusions of the clinical effectiveness section 55
4 COST EFFECTIVENESS 59
4.1 EAG's comment on company's review of cost-effectiveness evidence 59
4.2 Summary of the company's submitted economic evaluation 62
4.3 Critique of company's submitted economic evaluation by the EAG 102
4.4 Exploratory analyses undertaken by the EAG 119
4.5 Discussion 126
5 OVERALL CONCLUSIONS 127
6 REFERENCES 129

List of tables

Table 1: Overview of the EAG's key issues 10
Table 2: Summary of EAG's preferred model results 17
Table 3: The decision problem (adapted from CS, Table 1, and final NICE scope, with comments from the EAG) 22
Table 4: Tumour types and extent of disease in the COG ACCL0431 ITT population (adapted from CS, Table 11) 26
Table 5: Recommended dosing of STS by body weight (reproduced from anhydrous sodium thiosulfate's SmPC) 27
Table 6: Correspondence between ototoxicity classification systems used in the model* (adapted from CS, Table 3 and model) 29
Table 7: Inclusion/exclusion criteria used to select studies of anhydrous STS in the CS (reproduced with minor changes from CS, Appendix D.1.2, Table 3 and clarification response, question A10) 33
Table 8: Summary of the key studies (adapted from CS, Section B.2.1., Tables 5 and 6 and Evidence Submission Summary, Section A.6.2, Table 4) 36
Table 9: Quality assessment results for the SIOPEL 6 and COG ACCL0431 trials, as assessed by the company (adapted from CS, Appendix D4) 41
Table 10: Primary efficacy endpoint in SIOPEL 6 - hearing loss, ITT and mITT populations (adapted from CS, Tables 12, 13 and Table 12 of the clarification response) 43
Table 11: Brock grades for children experiencing hearing loss in SIOPEL 6, mITT population (adapted from CS, Tables 14 and 15) 43
Table 12: Summary of overall survival in SIOPEL 6,* ITT population (adapted from CS, Table 16) 44
Table 13: Primary efficacy endpoint in COG ACCL0431 - hearing loss, efficacy and ITT populations (adapted from CS, Tables 17, 18 and Table 12 of the clarification response) 45
Table 14: Summary of the incidence of hearing loss in the COG ACCL0431, efficacy population-localised patients only (adapted from Table 12 of the clarification response) 45
Table 15: Summary of overall survival in COG ACCL0431, ITT population (adapted from CS, Table 20 and the US FDA assessment review) 46
Table 16: Summary of overall survival in COG ACCL0431, ITT population, localised patients only (adapted from data provided in the clarification response) 47
Table 17: Summary of hearing loss according to the pooled analysis of SIOPEL 6 and COG ACCL0431 - localised and metastatic patients (adapted from CS, Tables 22 and 23) 48
Table 18: Summary of hearing loss according to the pooled analysis of SIOPEL 6 and COG ACCL0431 - localised disease only (adapted from clarification response, question A13) 49

Table 19: Summary of overall survival according to the pooled analysis of SIOPEL 6 and COG ACCL0431 - localised disease only (adapted from company's clarification response, question A13, and the EMA assessment report) 50
Table 20: Summary of most common (frequency of ⩾ 10% in either arm) AEs with maximum severity of CTCAE Grade 3 or higher during the treatment phase - SIOPEL 6 safety population (reproduced with minor changes from CS, Table 25) 53
Table 21: Summary of most common Grade 3 severity or higher AEs (frequency of ⩾ 10% in either arm) - COG ACCL0431 safety population (reproduced with minor changes from CS, Table 26) 54
Table 22: Scope of the company's economic analyses 63
Table 23: Summary of evidence used to inform the company's updated base case model 68
Table 24: Company's survival estimates used in the model for years 1 to 5 (adapted from CS, Table 36 and clarification response, question A13 and additional data for pooled analysis with localised disease subgroup) 70
Table 25: Proportions of patients experiencing HL and HL severity levels (adapted from CS, Tables 33 and 34, CS, Figure 10, and company's model) 73
Table 26: Adverse events incidence included in the economic model (adapted from CS, Table 44 and company's updated model)* 76
Table 27: Utility values for health states (adapted from CS, Table 38) 78
Table 28: Disutility values related to AEs and assumed durations used in the company's model (adapted from CS, Table 37 and company's updated model) 80
Table 29: Summary of costs applied in the company's base case analysis by treatment group 81
Table 30: Cumulative dose of cisplatin by treatment arm, selected analysis with localised disease patients only (reproduced from clarification response, Table 21) 83
Table 31: Costs of premedication antiemetics used in the updated base case (adapted from CS, Table 40) 84
Table 32: Summary of health state resource use and costs per cycle used in the base-case analysis for disease management costs 86
Table 33: Probabilities of internal component of cochlear implants requiring replacement (reproduced from the company's updated version of the model) 90
Table 34: Adverse event costs assumed in the company's base-case and selected scenario analyses, STS and ECM* 94
Table 35: Distributions used in company's PSA 96
Table 36: Company's central estimates of cost-effectiveness, STS versus ECM, generated by the EAG using the company's revised model 99
Table 37: Scenario analysis results for STS versus EMC using the updated version of the model submitted at clarification response (generated by EAG using company's model, deterministic) 102

Table 38: Adherence of the company's economic analysis to the NICE Reference Case 104
Table 39: Results for base case and scenario analyses using different sources for efficacy, updated version of the model submitted at clarification (adapted from clarification response, Table 10)..... 109
Table 40: SMR estimates reported in Fidler *et al.*,[54] all causes of death, by follow-up period..... 112
Table 41: Frequencies of annual hearing assessments reported by Dionne *et al*. 120
Table 42: Comparison of frequencies of annual hearing assessments - company's base case versus EAG's alternative approach 120
Table 43: Frequencies of speech and language therapies from the audiologists report[59] 121
Table 44: EAG preferred analysis results..... 124
Table 45: EAG additional sensitivity analysis results 125

List of figures

Figure 1: Proposed positioning for STS in England and Wales (reproduced from CS, Figure 1).. 20
Figure 2: Overall survival, SIOPEL 6, ITT population (reproduced from CS, Figure 6)..... 44
Figure 3: Overall survival, COG ACCL0431, ITT population (reproduced from CS, Figure 7) ... 46
Figure 4: Overall survival, pooled analysis of SIOPEL 6 and COG ACCL0431 - localised disease only (reproduced from clarification response, question A13) 50
Figure 5: Company's model structure (drawn by the EAG, adapted from CS Figures 8 and 9 and model) 65
Figure 6: CEACs, STS versus ECM (generated by the EAG using the company's model)..... 100
Figure 7: Tornado diagram, STS versus ECM (generated by the EAG using the company's model) 101
Figure 8: Model estimates of survival using different SMR estimates (generated by the EAG using the company's updated version of the model)* 113

List of boxes

Box 1: Summary of the main issues identified within the company's health economic model 106

Abbreviations

AEs	Adverse events
AJMC	American Journal of Managed Care
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ASHA	American Speech-Language-Hearing Association
BSA	Body surface area
CEAC	Cost-effectiveness acceptability curve
CI	confidence interval
CMH	Cochran-Mantel-Haenszel
CPI	Consumer Price Index
CS	Company's submission
CTCAE	Common Terminology Criteria for Adverse Events
CUP	Compassionate Use treatment Protocol
DSA	Deterministic sensitivity analysis
EAG	External Assessment Group
ECM	Established clinical management
EMA	European Medicines Agency
eMIT	electronic Market Information Tool
EQ-5D	EuroQol 5 Dimensions
EQ-5D-3L	EuroQol 5 Dimensions 3-Level
FDA	US Food and Drug Administration
FM	Frequency modulation
GGT	Gamma-glutamyl transferase
HL	Hearing loss
HR	Hazard ratio
HRQoL	Health-related quality of life
HTE	Health technology evaluation
HST	Highly specialised technology
HUI3	Health utility index 3
ICER	Incremental cost-effectiveness ratio
ICTRP	International Clinical Trials Registry Platform
INAHTA	International Network of Agencies for Health Technology Assessment
IQR	Interquartile range
ITT	Intention-to-treat
IV	Intravenous
KM	Kaplan-Meier
mITT	Modified intention-to-treat
MHRA	Medicines and Healthcare products Regulatory Agency

N/A	Not applicable
NCI	National Cancer Institute
NDCS	The National Deaf Children's Society
NHSCII	NHS Cost Inflation Index
NHS EED	National Health Service Economic Evaluation Database
NICE	National Institute for Health and Care Excellence
Non-RCTs	Non-randomised controlled trials
OAE	Otoacoustic emissions
OECD	Organisation for Economic Co-operation and Development
OR	Odds ratio
OS	Overall survival
PAS	Patient Access Scheme
PPP	Purchasing power parities
PRESS	Peer Review of Electronic Search Strategies
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic sensitivity analysis
PSSRU	Personal Social Services Research Unit
PTA	Pure tone audiometry
QALY	Quality-adjusted life year
RCT	Randomised controlled trial
RDI	Relative dose intensity
RNID	Royal National Institute for Deaf People
RR	Relative risk
RTI	Respiratory tract infection
SAE	Serious adverse event
SF-6D	Short-Form Six-Dimension
SIGN	Scottish Intercollegiate Guidelines Network
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
SMR	Standardised mortality ratio
SLR	Systematic literature review
STA	Single Technology Appraisal
STS	Sodium thiosulfate
TA	Technology Appraisal
WBC	White blood cell count
WHO	World Health Organization
Y	Year
YLDs	Years lived with disability

1 EXECUTIVE SUMMARY

This External Assessment Group (EAG) report assesses anhydrous sodium thiosulfate (Pedmarqsi™, hereafter referred to as STS) for preventing ototoxicity caused by cisplatin chemotherapy in people aged 1 month to 17 years with localised solid tumours. This summary provides a brief overview of the key issues identified by the External Assessment Group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.5 explain the key issues in more detail. Background information on the condition, technology and evidence and information on non-key issues are in the main EAG report.

All issues identified represent the EAG's view, and do not necessarily reflect the opinion of the National Institute for Health and Care Excellence (NICE).

1.1 Overview of the EAG's key issues

Key issues identified by the EAG that impact on the incremental costs and quality-adjusted life years (QALYs) for STS compared with established clinical management (ECM) are summarised in

Table 1.

Table 1: Overview of the EAG's key issues

ID1001	Summary of issue	Report sections
Issue 1	Sample sizes in the SIOPEL 6 and COG ACCL0431 trials were small and may lead to uncertainty in estimated treatment effects	3.2.3, 3.3
Issue 2	Different hearing loss grading scales used in the trials and in clinical practice	3.2.3, 3.3
Issue 3	Uncertainty around the accurate timing and administration of STS and its potential effect on anti-tumour efficacy	3.2.3, 3.3.5.1, 3.7.3
Issue 4	Uncertainty regarding efficacy data used in the model	4.2.4.3 and 4.3.3 (critical appraisal point 2)
Issue 5	Uncertainty regarding company's approach to modelling mortality risks after the first five years in the model	4.2.4.2 and 4.3.3 (critical appraisal point 3(b) and 3(c))

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are as follows:

(i) *Source of efficacy data.* The company's model uses data from the overall efficacy population from the COG ACCL0431 trial to estimate the hearing loss (HL) incidence (HL or Minimal/No HL) for both treatment groups. The EAG's preferred analysis includes the data for this outcome from the subgroup of patients with localised disease from COG ACCL0431. This aligns the data on HL incidence used in the model with the licenced indication for STS.

(ii) *Approach to modelling mortality risks after the observed trial period.* The company's base case model uses observed overall survival (OS) data from the localised disease subgroup in the COG ACCL0431 trial for the first five years of the model, followed by the application of a single standardised mortality ratio (SMR) to general population life tables for another five years, and after 10 years the model assumes that surviving patients experience the same mortality risk as the general population (thereby assuming full cure). The EAG's preferred analysis removes the 10-year cure assumption, and applies multiple SMR estimates by time of follow-up period from the same source used by the company (Fidler *et al.*).

(iii) *Cost assumptions.* The company's model assumes that all patients receive FM systems regardless of disease severity and includes the costs associated with treatment of depression related to the hearing loss condition. The EAG's preferred model removes the costs of depression and includes the costs of FM systems only for patients who receive hearing aids or cochlear implants. The EAG's preferred model also assumes different frequencies for hearing assessment and speech and language therapies visits.

(iv) *Alternative approach for AEs incidence.* The company's model includes the impact of treatment-related serious adverse events (SAEs) with an incidence of ≥2% of patients in each of the arms of the COG ACCL0431 trial, whilst the EAG's preferred model includes the incidence from Grade 3+ AEs occurring in ≥10% of patients from the COG ACCL0431 trial.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the model suggests that the technology increases QALYs by:

- Increasing the proportion of patients who do not develop HL (Minimal/No HL);
- Increasing the proportion of patients in lower severity HL health states compared to ECM.

Overall, the model suggests that the technology affects costs by:

- Increasing overall costs due to the acquisition cost of STS;
- When compared to ECM, some of these increased costs are offset mainly by reduced disease management costs and costs of depression (due to the increased proportion of patients in the No/Minimal HL and Mild HL health states and reduced proportion of patients in the marked and severe HL health states). This leads to reduced annual hearing assessments and language and speech therapy sessions, and reduced number of patients receiving cochlear implants and hearing aids.

The modelling assumptions that have the greatest effect on the ICER are:

- Whether the evidence from the COG ACCL0431 trial or the pooled analysis of the COG ACCL0431 trial and SIOPEL 6 is used to model efficacy (HL incidence), and the population in which these efficacy estimates are derived (overall population or subgroup of patients with localised disease);
- The inclusion of an assumption of full cure at 10 years.

1.3 The decision problem: summary of the EAG's key issues

The decision problem addressed in the company's submission (CS) is generally in line with the final NICE scope. The target population in the CS is people aged 1 month to less than 18 years of age with localised, non-metastatic, solid tumours receiving cisplatin-containing chemotherapy. The company's proposed positioning for STS is in line with its licensed indication, that is, for the prevention of ototoxicity induced by cisplatin chemotherapy in patients 1 month to less than 18 years with localised, non-metastatic, solid tumours.

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

The CS presents evidence from two pivotal clinical trials of STS for the prevention of cisplatin-induced ototoxicity in paediatric patients (≥1 month and <18 years old). The SIOPEL 6 and COG ACCL0431 trials were international, multicentre, open label, Phase 3 randomised controlled trials (RCTs). The patient population in the SIOPEL 6 trial comprised a homogeneous patient population of children with a localised tumour type (standard risk hepatoblastoma; mean age was 18.5 months). The COG ACCL0431 trial included a heterogeneous patient population with localised and disseminated disease with various tumour types (mean age was 9.2 years). The marketing authorisation for STS is restricted to patients aged 1 month to <18 years with localised, non-metastatic, solid tumours receiving cisplatin chemotherapy; hence, only the outcomes for the localised, non-metastatic populations are primarily relevant to this appraisal. The key issues with the clinical evidence relate to the small sample sizes in the clinical trials, the use of different hearing loss grading scales in the trials/clinical practice and the

accurate timing and administration of STS and its effect on anti-tumour efficacy. As such, the exact magnitude of observed benefit on outcomes or potential risk is unclear.

Issue 1: Sample sizes in the SIOPEL 6 and COG ACCL0431 trials were small and may lead to uncertainty in estimated treatment effects

Report section	3.2.3, 3.3
Description of issue and why the EAG has identified it as important	The sample sizes in the SIOPEL 6 and COG ACCL0431 trial, including the number of each tumour type/stage were relatively small (n=114 and n=125, respectively). In addition, the company raised concerns that a pooled analysis of localised only patients (or either alone) would be inappropriate as the COG ACCL0431 trial was underpowered for a subgroup analysis of patients with localised disease. However, the marketing authorisation is specifically restricted to patients with localised solid tumours. In general, small sample sizes may lead to uncertainty in estimated treatment effects.
What alternative approach has the EAG suggested?	None
What is the expected effect on the cost-effectiveness estimates?	The potential impact of the uncertainty related to the use of different sources and population groups used to inform treatment effect on hearing loss incidence on the cost-effectiveness estimates is discussed further in Issue 4.
What additional evidence or analyses might help to resolve this key issue?	The EAG cannot recommend any additional analyses that might address this issue as it is a limitation of the SIOPEL 6 and COG ACCL0431 trials. Further studies, if ethical, are needed.

Issue 2: Different hearing loss grading scales used in the trials and in clinical practice

Report section	3.2.3, 3.3
Description of issue and why the EAG has identified it as important	Among the clinical studies, there were variations in audiologic testing and endpoint definitions e.g., frequency range, ototoxicity definitions and consistency in hearing endpoints. For example, the ASHA scale was used in the COG ACCL0431 trial. However, this scale does not assess the severity of the acquired hearing loss, only whether the patient's hearing levels meet a certain threshold, and thus it is a binary indicator of HL. In contrast, the Brock scale was used in the SIOPEL 6 trial. Although the Brock scale describes the severity of the HL and indicates the degree of expected disability, it uses a cut-off of 40 dB HL. Hence, it is less sensitive to early ototoxicity and does not detect mild hearing loss that is communicatively and educationally important for developing children and adolescents. Moreover, in clinical practice, there is wide variability in the use of ototoxicity scales with the ASHA scale being commonly used in the USA and the Brock and SIOP ototoxicity grading scales are commonly used in the UK. Recent evidence suggests that SIOP may be superior to ASHA, Brock, and other scales for classifying ototoxicity in paediatric patients who are treated with cisplatin. As such, careful consideration is needed when interpreting the incidence of hearing loss in studies.

What alternative approach has the EAG suggested?	None
What is the expected effect on the cost-effectiveness estimates?	The potential impact of this on the cost-effectiveness estimates is discussed further in Issue 4.
What additional evidence or analyses might help to resolve this key issue?	Further studies are needed using the SIOP ototoxicity scale to facilitate uniform outcomes regarding cisplatin-induced hearing loss.

Issue 3: Uncertainty around the accurate timing and administration of STS and its potential effect on anti-tumour efficacy

Report section	3.2.3, 3.3.5.1, 3.7.3
Description of issue and why the EAG has identified it as important	Given the complex regimen of administration and the need to observe accurate timing of STS administration relative to cisplatin chemotherapy (i.e., a 15-minute intravenous STS infusion 6 hours after the completion of each cisplatin infusion), there are concerns that delayed administration may reduce the impact of cisplatin chemotherapy against tumour growth and cell survival in clinical practice. The company acknowledges that the timing of STS administration is critical and potential errors may impact efficacy. In addition, the company notes that clear labelling is provided in the Summary of Product Characteristics (SmPC) and in the instructions for use to ensure a 6-hour gap is implemented in clinical practice.
What alternative approach has the EAG suggested?	None
What is the expected effect on the cost-effectiveness estimates?	The estimates of cost-effectiveness for STS relative to ECM in the case of potential delayed administration of STS is not known.
What additional evidence or analyses might help to resolve this key issue?	Further studies are needed to evaluate the effect of delaying STS administration after cisplatin chemotherapy and to what degree it may compromise anti-tumour efficacy and prevention of HL.

1.5 The cost-effectiveness evidence: summary of the EAG's key issues

The company's economic model assesses the cost-effectiveness of STS versus ECM for patients aged 1 month to less than 18 years receiving cisplatin-containing chemotherapy for localised, non-metastatic, solid tumours. The model adopts a hybrid structure of a decision tree followed by a state-transition (Markov) model which includes six health states: (i) minimal/no HL and alive, (ii) mild HL and alive, (iii) moderate HL and alive, (iv) marked HL and alive, (v) severe HL and alive; and (vi) dead. Health outcomes and costs are evaluated from the perspective of the NHS and Personal Social Services (PSS), over a lifetime horizon ([redacted] years). Population baseline characteristics, OS for the first five years of the model and drug costs are based on data from COG ACCL0431 (localised disease subgroup), whilst efficacy (HL incidence) is based on the overall efficacy population of the trial. Health utilities were taken from Barton *et al.*, Pogany *et al.*, and Chen *et al*., based on Health utility index 3 (HUI3) values; caregiver effects are not included. Resource use estimates were derived from COG ACCL0431, previous NICE TAs, additional studies, standard costing sources and assumptions.

A Patient Access Scheme (PAS) is available for STS which takes the form of a simple price discount of [redacted] (PAS price = [redacted] per 100ml vial containing 8.0g/100ml of STS). All results presented in this EAG report include this PAS. As part of their response to clarification questions from the EAG, the company submitted a revised model which includes error corrections. The revised deterministic version of the company's base case model suggests that STS is expected to generate an additional [redacted] QALYs when compared to ECM, at an additional cost of [redacted] per patient; the corresponding ICER is estimated to be [redacted] per QALY gained. The company's QALY shortfall calculations suggest a decision modifier of 1.0.

The EAG's key issues regarding the cost-effectiveness evidence and the company's economic analyses are discussed below.

Issue 4 Uncertainty regarding efficacy data used in the model

Report section	4.2.4.3 and 4.3.3 (critical appraisal point 2)
Description of issue and why the EAG has identified it as important	The company's base case analysis uses three different sources to inform treatment efficacy in terms of HL incidence and HL severity: the COG ACCL0431 trial (overall efficacy population), Orgel *et al.* and Knight *et al.* The EAG believes this is problematic for two reasons: the data from the COG ACCL0431 trial is not specific to the localised disease subgroup of patients, which is the target population for this appraisal, and the analysis combines three different HL grading systems (ASHA, SIOP and Brock), without any further consideration of the differences between the grading scales and their correspondence to the model's health states.
What alternative approach has the EAG suggested?	The EAG prefers to include estimates of HL incidence from the localised disease subgroup of the COG ACCL0431 trial (efficacy population) as part of the EAG's preferred analysis, which aligns the efficacy data (HL incidence) to other parameters already used in the model, such as population baseline characteristics, survival and drug costs. The EAG also explored the use of data from the pooled analysis of COG ACCL0431 and SIOPEL 6 trials (localised disease patients only) and from COG ACCL0431 (overall population, corresponding to the company's original base-case), and of alternative source combinations for HL severity in additional sensitivity analyses.
What is the expected effect on the cost-effectiveness estimates?	Using the EAG's preferred approach increases the ICER for STS versus ECM from [redacted] to [redacted].
What additional evidence or analyses might help to resolve this key issue?	Further studies are needed using the SIOP and Brock ototoxicity scales to facilitate uniform outcomes regarding cisplatin-induced hearing loss.

Issue 5 Uncertainty regarding company's approach to modelling mortality risks after the first five years in the model

Report section	4.2.4.4 and 4.3.3 (critical appraisal point 3(b) and 3(c))
Description of issue and why the EAG has identified it as important	The model assumes that treatment with STS does not impact on survival. OS estimates from the COG ACCL0431 trial (localised disease subgroup) are used directly for both treatment groups during the first five years of the model; for years 6 to 10, an increased risk of death related to the underlying cancer is modelled by applying a SMR of 9.1 to general population life tables. After 10 years, the model assumes that surviving patients experience the same mortality risk as the general population (thereby assuming full cure). A single SMR is applied for the whole period, and one of the clinical advisors for the EAG stated that the risk of death in this population of paediatric patients with solid tumours remains higher than that of the general population, even after 40 years. The EAG believes that there is uncertainty around whether the assumption of full cure is appropriate, and if so, the timepoint at which this should be applied, and around the appropriateness of the SMR estimate applied in the model.
What alternative approach has the EAG suggested?	The EAG prefers to remove the assumption of cure and to apply multiple SMR estimates by the time of follow-up, based on values reported by Fidler *et al.* (same study used by the company) as part of the EAG's preferred analysis. The EAG also explored the re-introduction of the cure assumption at different timepoints (10, 15 and 20 years) in additional sensitivity analyses. The EAG highlights that these analyses include data for the localised disease subgroup of the COG ACCL0431 trial.
What is the expected effect on the cost-effectiveness estimates?	The EAG's preferred approach of removing the cure assumption (retaining the original SMR estimate) increases the ICER for STS versus ECM from [redacted] to [redacted] per QALY gained. Adopting multiple SMR estimates but retaining the cure assumption at 10 years increases the ICER for STS versus ECM only slightly, from [redacted] to [redacted]. Applying both approaches simultaneously increases the ICER to [redacted]
What additional evidence or analyses might help to resolve this key issue?	The EAG is not aware of any additional analyses that might address this issue. However, further studies with longer follow-up of patients relevant to the target population and larger sample sizes may be useful in reducing the uncertainty around the OS data at later time points.

1.6 Summary of EAG's preferred assumptions and resulting ICER

The results of the EAG's preferred model and additional sensitivity analyses are summarised in Table 2. Exploratory analysis 1 (EA1) reflects the EAG-corrected version of the company's model (deterministic). EA2-8 also include these corrections. The EAG's preferred analysis (EA9) suggests that the deterministic ICER for STS versus ECM is estimated to be [redacted] per QALY gained. Additional sensitivity analyses (ASAs) use the EAG's preferred model (EA9) as a starting point. The EAG's full critique of the company's economic analyses, including modelling errors identified and

corrected by the EAG are described in Section 4.3.3. Further details of the EAG's exploratory and sensitivity analyses can be found in Section 4.4.

Table 2: Summary of EAG's preferred model results

Scenario	Inc. QALYs	Inc. costs	ICER
Company's original base case (deterministic)	1.54	[redacted]	[redacted]
EA1: Correction of errors	1.54	[redacted]	[redacted]
EA2: Use of alternative values for SMR (multiple SMRs) from Fidler *et al.*	1.53	[redacted]	[redacted]
EA3: Exclusion of cure assumption	1.36	[redacted]	[redacted]
EA4: Alternative sources for frequencies of hearing assessments and speech and language therapies	1.54	[redacted]	[redacted]
EA5: Costs of FM systems only applied to patients with hearing aids or cochlear implants	1.54	[redacted]	[redacted]
EA6: Exclusion of costs of depression	1.54	[redacted]	[redacted]
EA7: Inclusion of Grade 3+ AEs occurring in ≥10% of patients	1.54	[redacted]	[redacted]
EA8: Alternative source of efficacy for HL (COG ACCL0431 data for localised patients + Orgel *et al.* + Knight *et al.*)	1.31	[redacted]	[redacted]
EA9a: EAG preferred analysis (deterministic)	1.20	[redacted]	[redacted]
EA9b: EAG preferred analysis (probabilistic)	1.19	[redacted]	[redacted]
ASA1a: Inclusion of cure timepoint at 10 years	1.30	[redacted]	[redacted]
ASA1b: Inclusion of cure timepoint at 15 years	1.28	[redacted]	[redacted]
ASA1c: Inclusion of cure timepoint at 20 years	1.26	[redacted]	[redacted]
ASA2: Exclusion of FM systems costs	1.20	[redacted]	[redacted]
ASA3: Re-inclusion of costs of depression	1.20	[redacted]	[redacted]
ASA4: Inclusion of Grade 3+ AEs occurring in ≥5% of patients	1.20	[redacted]	[redacted]
ASA5a: Alternative source of efficacy for HL (Pooled analysis for localised patients + Orgel *et al.* + Knight *et al.*)	1.39	[redacted]	[redacted]
ASA5b: Alternative source of efficacy for HL (Pooled analysis for localised patients + Knight *et al.*)	0.98	[redacted]	[redacted]
ASA5c: Alternative source of efficacy for HL (Orgel *et al.* + Knight *et al.*)	1.30	[redacted]	[redacted]
ASA5d: Alternative source of efficacy for HL (COG ACCL0431 overall population + Orgel et al. + Knight et al.)	1.41	[redacted]	[redacted]

ASA - additional sensitivity analysis; AE - adverse event; EA - exploratory analysis; FM - Frequency modulation; HL - Hearing loss; HRQoL - Health-related quality of life; ICER - incremental cost-effectiveness ratio; Inc. - incremental.; QALY - quality-adjusted life year; SMR - Standardised mortality ratio.

2 BACKGROUND

2.1 Critique of company's description of underlying health problem

The company's submission (CS) describes hearing loss (HL) caused by cisplatin-induced ototoxicity in children as a result of inflammation and damage of sensory outer hair cells within the cochlea by the presence of cisplatin in the inner ear.[1] Platinum-based compounds such as cisplatin, and carboplatin to a lesser degree, are the antineoplastic agents most commonly associated with ototoxicity.[2] The mechanism of platinum ototoxicity is mediated by free-radical production and can manifest during or after treatment as tinnitus or hearing loss (initially at higher frequencies and also in the lower-frequency normal conversation range at more severe stages).[2, 3] Hearing loss can be unilateral or bilateral, but with cisplatin toxicity is usually bilateral, sensorineural (most common type of hearing loss, which is due to pathologies of the cochlea, auditory nerve, or central nervous system), irreversible, and progressive.[2, 4]

Cumulative cisplatin dosing, duration of treatment, concurrent treatment with other types of therapies, young age and other factors have been associated with the degree of hearing loss.[5-7] In response to a request for clarification from the EAG (question A3), the company listed additional contributing risk factors for cisplatin-induced ototoxicity: *"dose schedule, pre-existing hearing loss, co-existing renal dysfunction, and prior cranial radiotherapy when the cochlea is within the radiation field"*.[6-9] Age at exposure and the cumulative dosage of cisplatin received seem to be correlated to the severity of hearing loss experienced and impacts on health-related quality of life (HRQoL), with younger patients and higher levels of exposure being correlated with a more severe decline in hearing.[1, 10]

The CS states that approximately 60% of children will develop ototoxicity after receiving cisplatin-based treatments,[8, 11] and that up to 75% of these patients become eligible for hearing aids or auditory support.[12] A global burden of disease study indicates that, overall, hearing loss was the third leading cause of disability in 2019 for all ages, and was responsible for over 40 million years lived with disability (YLDs) globally.[13]

The CS also highlights that the permanent and debilitating side effects of cisplatin chemotherapy can result in life-long negative impacts for patients, including effects on speech and language and social-emotional developments, educational achievement, and HRQoL.[1] Some of the problems listed relate to compromised verbal, literacy and communication skills, poor academic performance, emotional development and self-esteem/behaviour issues in school-aged children, and social isolation, depression and the inability to live independently in adolescents and young adults.[1] The National Deaf Children's Society (NDCS) and The Royal National Institute for Deaf People (RNID) also report that people who have hearing loss are more likely to have an overall worse health status and have multiple health

conditions compared with those without hearing loss, and that hearing loss can significantly affect families and communication partners of those living with the condition.[14]

Although hearing loss is often associated with stigma and can cause low self-esteem, those affected can have improved language and psychosocial outcomes with appropriate support and early intervention.[14] This support may include additional educational support, the use of frequency modulation (FM) systems in classrooms by school-age children, the use of hearing aids by patients with moderate or severe hearing loss, or the use of bilateral cochlear implants in patients suffering from severe to profound hearing loss.[1] The CS also highlights the economic burden for the NHS linked to hearing assessments and speech and language therapy for these patients, and from a societal perspective, the challenges on employment for patients when they reach adulthood. People with hearing loss are less likely to be in employment compared with the general population,[14] and hearing loss is associated with negative impacts on the productivity of carers of children with hearing loss due to attendance of medical appointments with physicians and specialists.[1]

2.2 Critique of company's overview of current service provision

Section B.1.3.3 of the CS[1] details the company's view of the current treatment pathway for the management of cisplatin-induced ototoxicity in children. The company states that there are no therapies currently available in the UK that prevent, slow the progression of or revert cisplatin-induced hearing loss. Current service provision for the management of cisplatin-induced ototoxicity includes monitoring the onset of hearing loss during each cycle of chemotherapy, and considering switching the platinum-based chemotherapy agent from cisplatin to carboplatin due to its lower risk. After the hearing loss is detected, management strategies for hearing loss are restricted to the use of hearing aids, which can be paired with additional assistive devices such as auditory trainers, telephone amplifiers and audio streamers to enhance the effect of hearing aids in loud environments. Children with severe to profound sensorineural hearing loss can be offered bilateral cochlear implants. The use of FM systems in classrooms can also be added in order to support school-age children with hearing loss in the education environment.[1]

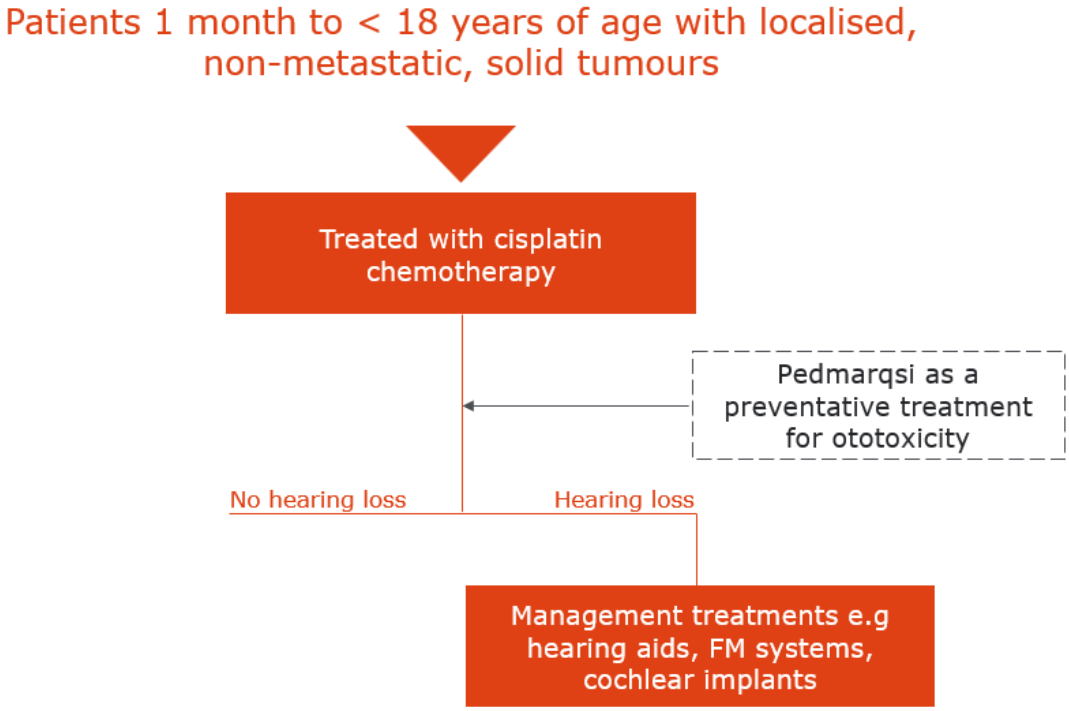
However, these different hearing devices do not restore normal hearing and have several limitations, such as the patient's reduced ability to discriminate speech in noisy environments, the additional effort required to process and assimilate speech and sounds which can lead to listening fatigue, the compatibility between these devices, the frequency at which batteries must be required, and the need to replace some of their components or the whole device. These devices are also required throughout a patient's life.[1, 14] In addition, there may be additional challenges associated with keeping on hearing aids or cochlear implants in very young children, to ensure the proper maintenance and care, and to reduce any safety risks. Waiting times for component or device replacements can potentially leave

children temporally without a device. The use of hearing aids can also lead to an increased risk of ear infections due to a build-up of earwax, which can have further negative impacts on their hearing.[14]

The NDCS and the RNID also report that children with hearing loss require support and additional services, such as access to audiologists for monitoring, speech and language therapists and specialist teachers, in additional to hearing technology. However, long waiting times and delays in accessing these services can lead to lifelong impacts. [14]

The company's proposed positioning of anhydrous sodium thiosulfate (Pedmarqsi™, hereafter referred to as STS) in England and Wales is shown in Figure 1. The proposed positioning is in line with the marketing authorisation for STS, that is, for the prevention of ototoxicity in patients 1 month to < 18 years of age with localised, non-metastatic, solid tumours receiving cisplatin chemotherapy. The company states that no additional testing beyond standard ototoxicity monitoring would be required to determine eligibility for STS, and that approximately 222 patients with non-metastatic, localised cancer in England and Wales would be eligible to receive Pedmarqsi per year.[1] The EAG's clinical advisors broadly agreed with the company's description of the disease and the proposed positioning of STS.

Figure 1: Proposed positioning for STS in England and Wales (reproduced from CS, Figure 1)



FM – Frequency modulation; STS - sodium thiosulfate

2.3 Critique of company's definition of the decision problem

This section presents a summary and critique of the decision problem addressed by the CS. A summary of the decision problem as outlined in the final NICE scope and addressed in the CS is presented in Table 3. The EAG's critique of the decision problem addressed within the CS is presented in the subsequent sections.

Table 3: The decision problem (adapted from CS, Table 1, and final NICE scope, with comments from the EAG)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comments
Population	People aged 1 month to less than 18 years of age with localised, non-metastatic, solid tumours having cisplatin chemotherapy	Pedmarqsi is indicated for the prevention of ototoxicity induced by cisplatin chemotherapy in patients 1 month to < 18 years with localised, non-metastatic, solid tumours.	Whilst there is no difference between the final NICE scope and the decision problem addressed in the company submission, the wording used in the company submission aligns with the marketing authorisation for Pedmarqsi.	The population consists of patients receiving any cisplatin-containing regimens (monotherapy or multi-drug cisplatin-containing chemotherapy regimens), which has been clarified by the company in clarification response to question A1.[7]
Intervention	Anhydrous sodium thiosulfate (Pedmarqsi)	Pedmarqsi	Following the above rationale, whilst STS is the active ingredient, Pedmarqsi is a novel formulation of anhydrous STS, specifically manufactured for the prevention of cisplatin-induced hearing loss in patients 1 month to < 18 years of age.[15] Given the specific and novel formulation of Pedmarqsi, and to ensure clarity throughout this appraisal, the product is referred to as Pedmarqsi.	In line with the final NICE scope.
Comparator(s)	Established clinical management without anhydrous sodium thiosulfate (Pedmarqsi)	Established clinical management without Pedmarqsi.	The comparator arm in the economic model is cisplatin without Pedmarqsi, which aligns with the comparator arms in the Pedmarqsi clinical trials. Patients in the comparator arms of these trials received established clinical management without Pedmarqsi. The comparator in the decision problem addressed in the company submission is therefore aligned with the NICE final scope, however, see the above rationale regarding the wording of the intervention.	The comparator included in the company's economic model is 'established clinical management' (ECM) without STS, which is in line with the final NICE scope. The EAG notes that the clinical data from the pivotal trials include cisplatin; however, the costs of cisplatin-containing regimens were excluded from the analysis based on the assumption that these would be equal between the treatment groups.
Outcomes	The outcome measured to be considered include: • Frequency and severity of hearing loss	The outcome measures from SIOPEL 6 and COG ACCL0431 that are presented in this submission include:	The company submission includes outcome measures from SIOPEL 6 and COG ACCL0431. Additional outcomes issued in the final scope such as speech	The company's economic model includes data on the frequency and severity of hearing loss, and other audiological evaluations, but does not

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comments
	• Audiological outcomes (e.g. sound perception, speech recognition and sound localisation) • Language and communication outcomes (e.g. intelligibility, sentence comprehension) • Psychosocial development/adjustment • Adverse effects of treatment including impact on response to cisplatin and survival • Health-related quality of life (HRQoL)	• Percentage of patients experiencing hearing loss • Hearing loss severity • Audiological outcomes – mean change in hearing threshold • Overall Survival • Adverse effects of treatment In addition, HRQoL data for hearing loss from published literature are also presented in this evidence submission as HRQoL data were not collected in the SIOPEL 6 or COG ACCL0431 trials.	recognition, sound localisation, language and communication outcomes, and psychosocial development/adjustment were not measured in the SIOPEL 6 or COG ACCL0431 trials. No additional sources were identified which measured these outcomes in patients treated with Pedmarqsi, therefore data for these outcomes could not be included in the company submission. Please also note that the HRQoL data presented is reflective of hearing loss, but not specific to Pedmarqsi, given that HRQoL data for patients treated with Pedmarqsi is not available.	explicitly include outcomes related to language, communication and psychosocial development/adjustment. The CS also presents data from COG ACCL0431 or SIOPEL 6 studies for overall and event-free survival, impact on treatment response to cisplatin, safety and other secondary outcomes. No HRQoL data were collected in the COG ACCL0431 or SIOPEL 6 studies, and therefore HRQoL in the company's economic model is based on external sources. Overall, the EAG is satisfied that the CS covers the outcomes specified in the final NICE scope, where data are available.
Economic analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and PSS perspective.	A cost-utility analysis was performed, with the cost-effectiveness expressed in terms of an incremental cost per quality-adjusted life year. A lifetime time horizon was used. Costs were considered from an NHS and PSS perspective.	In line with the NICE final scope.	Overall, the EAG is satisfied that the economic analysis presented at CS is in line with the final NICE scope. The company presented scenario analyses which are outside the NICE Reference Case, such as using an alternative discount rate of 1.5%, analyses using a societal perspective and using payer's perspective which also included educational costs. These analyses are discussed in Section 4.2.5.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	EAG comments
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	N/A	N/A	N/A

CS - company submission; EAG - External Assessment Group; ECM - established clinical management; HRQoL - health-related quality of life; ICER - incremental cost-effectiveness ratio; NHS - National Health Service; N/A - not available; NICE - National Institute for Health and Care Excellence; PSS - Personal Social Services; QALY - quality-adjusted life year

2.3.1 Population

The CS states that the target population for STS is patients aged 1 month to less than 18 years receiving cisplatin-containing chemotherapy for localised, non-metastatic, solid tumours. In response to clarification question A1, the company clarified that patients would be eligible for STS *"as long as they had received a cisplatin-containing chemotherapy regimen for their underlying cancer"*, without restricting the cisplatin regimen to a specific type of regimen, such as cisplatin monotherapy or a particular type of combined cisplatin-containing chemotherapy regimen.[7] The Summary of Product Characteristics (SmPC) for STS (Pedmarqsi) states that the drug is indicated for the *"prevention of ototoxicity induced by cisplatin chemotherapy in patients 1 month to < 18 years of age with localised, non-metastatic, solid tumours."*[15] The SmPC does not specify particular cisplatin-containing regimens or protocols that the licence is restricted to.

The EAG notes that in the trials that support the CS the cisplatin-containing regimens were administered according to disease-specific cancer treatment protocols. In SIOPEL 6, which recruited patients with standard-risk hepatoblastoma, the primary objective of the study was to *"assess the efficacy of STS for reducing the hearing impairment caused by cisplatin [CIS] chemotherapy",*[16] and therefore all patients received cisplatin as monotherapy. Conversely, the COG ACCL0431 study included patients with localised or metastatic disease and with various tumour types (Table 4). The company clarified that in this study, cisplatin was administered according to the sites' disease-specific cancer treatment protocols in use at the time of the study (see clarification response, question A1), and therefore patients received various chemotherapy regimens (with potential modifications). However, the exact types of chemotherapy regimen received by patients were not recorded in the COG ACCL0431 trial. A summary of the chemotherapy treatment protocols in use in the US for each tumour type at the time of the trial, based on the frequency of cisplatin dosing recorded, was presented in Table 6 of the company's clarification response (question A14[b]).[7] For brevity, the table is not displayed here, but the EAG notes that numerous protocols containing cisplatin and other chemotherapy regimens were used.

Table 4: Tumour types and extent of disease in the COG ACCL0431 ITT population (adapted from CS, Table 11)

	CIS + STS (N=61)	CIS (N=64)	Total (N=125)
Tumour type at diagnosis, n (%)			
Germ cell tumour	16 (26.2)	16 (25.0)	32 (25.6)
Osteosarcoma	14 (23.0)	15 (23.4)	29 (23.2)
Medulloblastoma	12 (19.7)	14 (21.9)	26 (20.8)
Medulloblastoma	10 (16.4)	14 (21.9)	24 (19.2)
Supratentorial PNET	2 (3.3)	0	2 (1.6)
Neuroblastoma	14 (23.0)	12 (18.8)	26 (20.8)
Hepatoblastoma	2 (3.3)	5 (7.8)	7 (5.6)
Other	3 (4.9)	2 (3.1)	5 (4.0)
Atypical teratoid/rhabdoid tumour	2 (3.3)	0	2 (1.6)
Carcinoma NOS	1 (1.6)	0	1 (0.8)
Choroid plexus carcinoma	0	1 (1.6)	1 (0.8)
Anaplastic astrocytoma	0	1 (1.6)	1 (0.8)
Extent of disease, n (%)			
No metastases detected at diagnosis	39 (63.9)	38 (59.4)	77 (61.6)
Metastases present at diagnosis	21 (34.4)	26 (40.6)	47 (37.6)
Unknown	1 (1.6)	0 (0)	1 (0.8)

CS - company submission; ITT - intention-to-treat; NOS - not otherwise specified; PNET - primitive neuroectodermal tumour.

The EAG notes that the COG ACCL0431 trial, the main study which informs the company's economic model, was conducted in North America (US and Canada); the EAG sought further information from the company regarding the generalisability of the study to England (see clarification response,[7] question A14). The company's response stated that the chemotherapy protocols in the study were "*administered according to the sites' disease-specific cancer treatment protocols in use at the time of the study*", and that these "*are determined by collaborative groups who share information globally due to the challenges of conducting research in this area.*" For this reason, the cisplatin regimens and dosage, and therefore the STS schedule and dosage are expected to be generalisable to UK clinical practice. The company also noted the range of cancer types included in the COG ACCL0431 trial, which "*are generally aligned to the distribution of key cisplatin-treated paediatric localised cancers in England and Wales*",[17] and that SIOPEL 6 study, which informs one of the company's scenario analysis, included 14 centres from the UK. In addition, the baseline characteristics of patients included in the two studies (age range from 1.2 months to 18 years, weights ranging from 2.6 kg to [redacted] kg [the EAG could not verify the upper limit as data were not reported in the CSR and published studies] and tumour types with similar effects on the prevention of hearing loss) suggests that STS is effective across a heterogenous paediatric patient population (clarification response, question A3).[7]

2.3.2 Intervention

The intervention considered in this appraisal is anhydrous sodium thiosulfate (Pedmarqsi™). STS is a novel formulation of anhydrous STS, specifically manufactured for the prevention of ototoxicity

induced by cisplatin chemotherapy in patients 1 month to <18 years of age with localised, non-metastatic, solid tumours (clarification response,[7] question A2). The CS describes STS as a *"water-soluble thiol compound with reducing agent properties and is a normal metabolite in humans and other mammals"*.[1]

The CS states that this specific formulation of STS is different to other formulations already available since it is the only one licensed specifically for the prevention of ototoxicity, it has clinical evidence for clinical effectiveness and safety data in this indication from two randomized clinical trials ([RCTs], COG ACC0431 and SIOPEL 6), and the excipients included in this formulation are different to those included in other formulations of STS, as it does not contain potassium chloride and it has a lower concentration of boric acid in comparison with other formulations (clarification response,[7] question A2). The company also highlights that due to these differences, the US Food and Drug Administration (FDA) has warned against interchanging the company's product with other STS products.[7]

The company obtained a marketing approval to the Medicines and Healthcare products Regulatory Agency (MHRA) in October 2023.[15] Each vial of STS with 100ml contains 8 g of STS as an anhydrous salt. STS is administered intravenously as a 15-minute infusion at the hospital setting, ideally through a central vein, 6 hours after the completion of every cisplatin infusion. STS' formulation does not require reconstitution or dilution. The recommended dose, as stated in its SmPC, is "*weight-based and normalised to body surface area [BSA]*" (Table 5).[15] The SMPC also recommends the administration of antiemetics prior to STS to reduce the incidence of nausea and vomiting.

Table 5: Recommended dosing of STS by body weight (reproduced from anhydrous sodium thiosulfate's SmPC)

Body Weight	Anhydrous dose	Volume
> 10 kg	12.8 g/m^2	160 mL/m^2
5 to 10 kg	9.6 g/m^2	120 mL/m^2
< 5 kg	6.4 g/m^2	80 mL/m^2

SmPC - Summary of Product Characteristics

During the clarification round, the EAG sought further information from the company regarding whether patients with advanced or disseminated disease would also be considered eligible to receive STS and whether there are any specific groups that may be more susceptible to cisplatin-induced ototoxicity (see clarification response,[7] questions A3 and A4). In their response, the company stated that the drug should only be considered for use by patients within its licence – i.e., for paediatric patients with localised, non-metastatic, solid tumours. The company's response also states that STS is effective across a heterogenous paediatric patient population and that it is not appropriate to focus on subgroups within the patient population. The company also clarified that patients with hepatoblastoma with pre-treatment tumour extension (PRETEXT) classification stage IV are considered high-risk which includes

patients with metastatic disease, and therefore these patients would be unlikely to receive STS, given that this would be considered outside of the licence. These patients were excluded from the population in SIOPEL 6 (clarification response,[7] question A5).

2.3.3 Comparators

The final NICE scope lists a single comparator: ECM without STS. The company's economic analysis includes this single comparator, in line with the final NICE scope.[18] The EAG notes that the economic analysis assumes that patients receive cisplatin as part of ECM, according to the regimens received as part of the COG ACCL0431 and SIOPEL 6 trials, and that the mean cumulative dosages for cisplatin are equivalent between the treatment groups (see Section 4.2.1.6). On this basis, the company's model excludes the costs of cisplatin.

2.3.4 Outcomes

The final NICE scope lists the following outcomes: frequency and severity of hearing loss; audiological outcomes (e.g., sound perception, speech recognition and sound localisation); language and communication outcomes (e.g., intelligibility, sentence comprehension); psychosocial development/adjustment; adverse effects of treatment and HRQoL. The scope also lists impact on response to cisplatin and survival as part of the adverse effects of treatment.[18] The CS includes data on most of these outcomes in the clinical effectiveness section of the CS; however, outcomes relating to language and communication (e.g., intelligibility, sentence comprehension) and psychosocial development/adjustment are not presented.

The EAG notes that the main outcomes related to the frequency and severity of hearing loss presented varied between the studies included in the CS. The primary endpoint in COG ACCL0431 was the proportional incidence of hearing loss between the CIS+STS arm, with the criteria for ototoxic hearing loss defined by the American Speech-Language-Hearing Association (ASHA) and using standard clinical audiometers, middle ear analysers, evoked potentials systems, and evoked otoacoustic emissions (OAE) systems (if available). The assessments were undertaken prior to first dose of CIS and each CIS course, and at both 4 weeks and 1 year after final CIS course.[19] The primary outcome in SIOPEL 6 was the proportion of patients with Brock Grade ≥ 1 hearing loss, measured by pure tone audiometry (PTA) assessments, after end of study treatment or at an age of at least 3.5 years, whichever was later.[16]

The CS[1] notes that a range of systems to define hearing loss severity are in place in clinical practice, and different systems are used in the trials used as the source of clinical evidence by the company. The different grading criteria used in economic analysis presented by the company, and the corresponding thresholds and model heath states are presented in Table 6.

Table 6: Correspondence between ototoxicity classification systems used in the model* (adapted from CS, Table 3 and model)

Model health states	Classification systems		
	ASHA (COG ACCL0431)[19]	SIOP (Orgel *et al.)*[20]	Brock (Knight *et al.* [8]and SIOPEL 6)[16]
Minimal/ No HL	Normal: -10-15 dB	Grade 0: ≤20 dB at all frequencies	Grade 0: <40 dB at all frequencies
Mild HL	Slight: 16-25 dB	Grade 1: >20 dB at >4,000 Hz	Grade 1: ≥40 dB at 8,000 Hz
	Mild: 26-40 dB		
Moderate HL	Moderate: 41-55 dB	Grade 2: >20 dB at ≥4,000 Hz	Grade 2: ≥40 dB at ≥4,000 Hz
	Moderately severe: 56-70 dB		
Marked HL	Severe: 71-90 dB	Grade 3: >20 dB at 2,000 Hz or 3,000 Hz / Indication for hearing aids	Grade 3: ≥40 dB at ≥2,000 Hz
Severe HL	Profound: 91+ dB	Grade 4: >40 dB at ≥2,000 Hz	Grade 4: ≥40 dB at ≥1,000 Hz

ASHA - American Speech-Language-Hearing Association; CS - company submission; dB - decibel; HL - hearing loss; Hz - Hertz; SIOP - International Society of Paediatric Oncology
**The CS also includes the definition of other grading systems, such as Common Terminology Criteria for Adverse Events (CTCAE) v4.03 and Chang; for brevity these are omitted here since they are not used in the model. These are presented in CS,[1] Section B.1.3.1.2, Table 3.*

More importantly, an EAG clinical advisor noted that the use of the term 'marked' to define one of the model's severity level and health state is inadequate, because it does not follow standard British Society of Audiology (BSA) terminology, and it is not a term commonly used in audiology and audio vestibular medicine. Instead, the HL levels should have been defined as recommended by the BSA considering the average hearing threshold levels (dB HL):[21] mild (21-40 dB HL), moderate (41-70 dB HL), severe (71-95 dB HL) and profound (in excess of 95 dB HL). The EAG agrees with the clinical advisor's view, since some of the evidence that informs the model uses 'severe' and 'profound' and it is unclear why the company has chosen this terminology that includes 'marked' HL. Nonetheless, throughout this report the EAG refers to the health states included in the model as defined by the company in the evidence submission.

The EAG notes that COG ACCL0431 reports the mean change in hearing thresholds for key frequencies (500, 1000, 2000, 4000, and 8000 Hz), event-free survival (EFS), overall survival (OS) and safety data as secondary outcomes,[19] whilst SIOPEL 6 reports on a broader range of secondary outcomes (response to preoperative chemotherapy, complete resection, complete remission, EFS, OS, safety data as graded by Common Terminology Criteria for Adverse Events (CTCAE) version 3.0, long-term renal clearance and feasibility of central audiology review).[16] The EAG notes that the key clinical outcomes addressed in the CS are frequency and severity of hearing loss, mortality and adverse events (AEs). HRQoL is not reported as a clinical outcome as it was not measured in COG ACCL0431 and SIOPEL 6 studies. Overall, the EAG is satisfied that the CS covers the majority of outcomes specified in the final NICE

scope where these were available, and all key outcomes that are employed in the economic analysis are presented by the company.

2.3.5 Other relevant factors

The CS includes a discussion of quality-adjusted life year (QALY) weighting for disease severity, as recommended by the NICE Methods Manual,[22] which can be applied for health conditions where there is large absolute or proportionate QALY shortfall for patients with the condition receiving current standard care compared to patients living without the condition.[22] However, the company suggests that a severity modifier of 1.0 will apply in this case, based on an absolute shortfall of [redacted] QALYs and a proportional QALY shortfall of [redacted]%, as estimated by the York Shortfall calculator (CS, Section B.3.7.1).[1, 23]

The final NICE scope does not identify any special considerations related to equity or equality; however, the CS identifies an issue related to inequality in terms of the affordability of more advanced hearing aid equipment and educational resources by households with lower incomes, which impacts on the care burden of children impacted by the hearing loss. The CS argues that STS can impact positively on this inequity.[1] The NDCS and RNID submission report that there is evidence to suggest that deaf children from ethnic minorities have poorer educational outcomes compared with children with no hearing loss, and that black and Asian deaf children have lower attainment scores compared to other ethnic groups or to white deaf children, respectively.[14]

3 CLINICAL EFFECTIVENESS

The clinical evidence submitted by the company as part of the CS,[1] its appendices and the company's clarification response[7] comprises a:

- Systematic literature review (SLR)
- Summary and results of two clinical trials of anhydrous STS.

This chapter summarises and critiques the company's review methods and clinical effectiveness evidence for anhydrous STS for preventing ototoxicity caused by cisplatin chemotherapy in people aged 1 month to 17 years with localised solid tumours. Full details are presented in the CS[1] Section B.2 and the CS[1] Appendix D.

3.1 Critique of the methods of review(s)

3.1.1 Searches

The strategy for the identification and selection of relevant studies as part of the SLR for clinical evidence is presented in Appendix D of the CS.[1] The literature search aimed to identify evidence from RCTs and non-randomised controlled trials (Non-RCTs) related to the efficacy and safety of STS for the prevention of cisplatin-induced ototoxicity in paediatric patients aged 1 month to 17 years (CS[1], Appendix D.1.).

Systematic searches of the following relevant bibliographic databases were performed on 31st October 2023: Embase, including Embase Classic; MEDLINE; CENTRAL and Clinical Answers on the Cochrane Library. The CS[1] stated that Embase was searched using Embase.com, while MEDLINE was searched using PubMed (Section D.1.1), but only one search transcript was provided, which was labelled as 'Embase and MEDLINE search strategy' (CS[1], Appendix D.1.1.1, Table 1). However, the company's clarification response to question A7[7] confirmed that PubMed was not searched, and that MEDLINE was searched in combination with Embase on Embase.com using the search strategy in the CS[1] Appendix D.1.1.1, Table 1. This means that MEDLINE In-Process & Other Non-Indexed Citations and ePub Ahead of Print were not searched and therefore potentially relevant evidence that is only available on those databases could have been missed.

The EAG considers it sub-optimal to search more than one database using a single strategy in this way for a number of reasons. Firstly, Embase and MEDLINE use different controlled vocabularies. Executing a search strategy with subject headings selected from the thesaurus of one database (Embase) on another (MEDLINE) may cause problems as the search interface attempts to map to the closest available heading, which may be an imperfect match that is broader or narrower than the intended category. Similarly, search filters are designed and validated to work on specific databases, and using

one on a combined database search risks missing relevant studies. The company stated that the study design filters for RCTs and observational studies were '*based on filters published by the Scottish Intercollegiate Guidelines Network (SIGN)*' (clarification response,[7] question A6). Further investigation shows that the validated version tailored for Embase was used in full in the search strategy. Whilst it is good practice to use the search filters in their full, validated form, the fact that MEDLINE was searched using the same, Embase-optimised filter presents the issue of potentially missing relevant studies, for the reasons described above.

The search strategies are recorded in CS Appendix D, (D.1.1.1, Appendix Table 1 for the Embase.com search of Embase and MEDLINE; and Appendix D.1.1.1, Appendix Table 2 for the Cochrane search), although, regrettably without the result number for each line of each search. In accordance with the Peer Review of Electronic Search Strategies (PRESS) checklist for peer-reviewing electronic database search strategies (https://doi.org/10.1016/j.jclinepi.2016.01.021), the EAG considers it best practice to include the search results per line for full transparency.

The search strategies themselves have generally been logically devised and make use of both subject headings and free-text search terms. For both the Embase.com search and the Cochrane search, a justifiable date limit of post-1978 was applied for searches because cisplatin was not used as part of chemotherapy until 1978. In the Embase.com search, an additional limit to studies in humans only was applied in the final search line. The EAG notes that this could increase the risk of relevant studies being missed if studies have not been indexed as pertaining to humans only, or if they have been incorrectly indexed.

In addition to the bibliographic database searches, systematic searches for 'grey' literature were performed in October-November 2023. The company's clarification response to question A7[7] provided details of the keywords used and hit numbers from these searches (Table 1 and Table 2), which covered trial registries of World Health Organization (WHO), International Clinical Trials Registry Platform (ICTRP) and clinicaltrials.gov. Additionally, the websites of relevant conference proceedings for papers from the last three years were searched, which identified further studies, one of which was included in the evidence as it met all the criteria and was relevant to the decision problem. An inconsistency remains, however, in the reporting of the 'grey' literature searches in that the CS[1] mentions Google Scholar being searched (Appendix D.1.1) but no details are provided in the company's clarification response. Furthermore, the EAG identified an additional conference abstract not identified by the company's searches: Tanaka *et al*.[24] It is unclear from the company's clarification response to question A10[7] how this relevant material was missed in the literature search, although the date of the conference is close to the dates when the searches were conducted, so it is possible that it had not been indexed at the time of the search and therefore could not have been retrieved.

Overall, the sub-optimal one-search strategy for multiple databases on Embase.com, as well as the study which the EAG identified but had been missed by the company searches, leads to some uncertainty about the comprehensiveness of the literature searches for clinical effectiveness of the intervention in this population.

3.1.2 Inclusion criteria

The CS[1] describes an adequate method of identifying and screening references for inclusion in the SLR of clinical effectiveness. Two independent reviewers applied pre-specified inclusion and exclusion criteria to citations identified by the searches. Any disagreements were resolved through discussion or arbitration by a third reviewer (see clarification response,[7] question A12). A summary of the inclusion and exclusion criteria, as reported in the CS[1] (Appendix D1.2, Table 3 and clarification response,[7] question A10), is reproduced (with minor changes) in Table 7.

Table 7: Inclusion/exclusion criteria used to select studies of anhydrous STS in the CS (reproduced with minor changes from CS, Appendix D.1.2, Table 3 and clarification response, question A10)

Selection criteria	Inclusion criteria	Exclusion criteria
Population (P)	Paediatric patients (≥1 month and <18 years old) with cisplatin-induced ototoxicity	• Studies that do not include patients of interest to the SLR. • Studies with a mixed patient population that do not present outcomes separately for patients of interest and patients not of interest.
Interventions (I)	Anhydrous STS*	None
Comparators (C)	Any	None
Outcomes (O)	• Efficacy outcomes: Degree of ototoxicity assessed using a relevant instrument, including: o The Brock scale o The Boston scale o CTCAE scale o ASHA scale o SIOP ototoxicity grading scale o Chang scale • Safety outcomes: o Adverse events o Discontinuation o Mortality	• No reported outcomes of interest • Outcomes reported only in studies with a mixed population
Study type (S)	• RCTs • Non-RCTs • Observational studies (including patient registries)	• Animal studies • In vitro/ex vivo studies • Individual case study reports

Selection criteria	Inclusion criteria	Exclusion criteria
	• Cross-sectional studies	
Publication type	• Article • Conference abstract • Conference paper • Conference posters • Article in press	• Short surveys • Letters • Editorials • Reviews
Language	Studies reported in English	Studies not reported in English

ASHA - American Speech and Hearing Association; CS - company submission; CTCAE - Common Terminology Criteria for Adverse Events; RCT - randomised controlled trial; SIOP - International Society of Paediatric Oncology; SLR - systematic literature review.
** Criteria updated for greater clarity following a clarification request to question A10.*[7]

The specified inclusion and exclusion criteria were mostly appropriate and generally reflected the decision problem. It is noteworthy that the CS[1] (Section B.2.1, Appendix D.1.1 and Appendix D.1.2, Table 3) initially considered a wider remit to capture the entire evidence base as part of the inclusion criteria for the SLR (i.e., all potential relevant studies [RCTs, non-RCTs, and observational studies including patient registries] of cisplatin-induced ototoxicity in paediatric patients age ≥1 month and <18 years old) but then restricted the SLR only to those studies which were directly relevant to the decision problem (i.e., anhydrous STS only - see CS,[1] Section B.2.1, page 29 and clarification response,[7] question A10).

However, the company's response to clarification questions A10a and A10b[7] suggests that non-comparative evidence for STS was excluded from the SLR. For example, data from a Compassionate Use treatment Protocol (CUP) reported by Cabi *et al*.,[25] and a named patient supply programme (real world evidence reported by Tanaka *et al*.)[24] did not meet the SLR eligibility criteria. Moreover, the study reported by Tanaka *et al*.,[24] was not identified by the company searches. This study reported potential real world data from 50 hospitals across 14 countries for 133 patients; however, this published abstract by Tanaka *et al*.,[24] only reported data for 18 patients (median age: 10 years, range 3 to 19 years; median weight: 28 kg; with varied solid tumours other than hepatoblastoma).

The CS[1] (including the company's clarification response to question A10)[7] does not provide sufficient detail on how the inclusion/exclusion criteria were applied during the study selection process. Ideally, SLRs should have clearly focused research questions and inclusion/exclusion criteria at the outset. In addition, it is unclear whether supplementary supportive evidence was sought by the company for this appraisal, such as from Tanaka *et al*.,[24] a multi-national Named Patient Program for STS, which has been open for approximately 5 years.

3.1.3 Critique of data extraction

The data extracted and presented in the CS[1] for the SLR of clinical evidence appear to be appropriate and comprehensive. As noted in the company's clarification response[7] (question A12), all relevant data were extracted by a single reviewer and checked for accuracy by a second independent reviewer. Any discrepancies were resolved through discussion, or arbitration by a third reviewer. Notwithstanding the issues raised Section 3.1.1 and 3.1.2, neither the EAG nor its clinical advisors are aware of any additional relevant completed studies within the scope of this appraisal.

3.1.4 Quality assessment

The validity assessment tool used to appraise the included studies in the CS[1] (Appendix D.4) is based on the minimum criteria for assessment of risk of bias and generalisability in parallel group RCTs, as recommended in the current NICE user guide template for company evidence submissions.[26] As noted in the company's response to clarification question A12,[7] methodological quality assessment of included studies was performed by two independent reviewers, with disagreements resolved through discussion, or arbitration by a third reviewer. However, neither the CS[1] nor its appendices provide a narrative assessment of the quality of the studies to inform the interpretation of the results of the trials.

3.1.5 Evidence synthesis

The company undertook a narrative synthesis of the evidence for STS; however, no explicit details were provided in the CS[1] on how this approach was undertaken. Ideally, a narrative synthesis approach should be justified, rigorous (i.e., describe results without being selective or emphasising some findings over others) and transparent to reduce potential bias.[27, 28]

Despite the lack of transparency regarding the methods adopted, the company provided the following justification for not undertaking a meta-analysis (CS,[1] Section B.2.8, p59: *"A meta-analysis was not conducted, as the only relevant clinical trials identified were the SIOPEL 6 trial and the COG ACCL0431 trial."* However, within their clarification response (question A13),[7] the company provided a pooled analysis using data from both SIOPEL 6 (included patients with standard-risk hepatoblastoma, non-metastatic solid tumours) and COG ACCL0431 (included patients with mixed solid tumours, non-metastatic and metastatic disease) trials similar to that requested by the European Medicines Agency (EMA)[29] for the localised, non-metastatic subgroup only (the population in the licensed indication). However, the company stated that they *"…do not believe that it is appropriate to assess Pedmarqsi's efficacy in the subpopulation of localised only patients in COG ACCL0431, either alone or when included in the pooled analysis."*

3.2 Critique of trials of the technology of interest, the company's analysis, and interpretation

3.2.1 Studies included in/excluded from the submission

The company's Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram relating to the literature searches does not conform exactly to the PRISMA statement flow diagram (http://www.prisma-statement.org/). Despite this, the flow diagram (and accompanying summary) presented by the company (CS Appendix D.2.1) appears to be a reasonable record of the literature searching and screening process for the SLR of STS for the prevention of cisplatin-induced ototoxicity in paediatric patients. In addition, the CS[1] and the company's clarification response[7] (question A10) provide a full and explicit breakdown of the reasons why each citation was rejected, especially after full text papers were retrieved for detailed evaluation. However, for clarity and to aid the transparency of the identification and selection processes, the PRISMA flow diagram should have ideally included details of the final set of studies that were included in the CS[1] which were directly relevant to the decision problem.

3.2.2 Ongoing studies

The CS[1] (Section B.2.11) does not cite any other ongoing studies that will provide additional evidence for STS in the indication being appraised in the next 12 months.

3.2.3 Main studies included in the CS: SIOPEL 6 and COG ACCL0431 trials

The company's SLR of STS for the prevention of cisplatin-induced ototoxicity in paediatric patients (≥1 month and <18 years old) identified and included two relevant clinical trials: SIOPEL 6[30] and COG ACCL0431[31] trials. A summary of these trials is provided in Table 8.

Table 8: Summary of the key studies (adapted from CS, Section B.2.1., Tables 5 and 6 and Evidence Submission Summary, Section A.6.2, Table 4)

Study	SIOPEL 6[16, 30, 32]	COG ACCL0431[19, 31, 33]
Study design	Multicentre, open-label, Phase III randomised trial	Multicentre, open-label, Phase III randomised trial
Location	52 sites across 12 countries: United Kingdom, Ireland, Belgium, Denmark, France, Italy, Switzerland, Spain, Australia, New Zealand, USA and Japan	38 Children's Oncology Group hospitals in the USA and Canada
Population	• Children aged >1 month to <18 years receiving cisplatin chemotherapy for a newly diagnosed, histologically confirmed, hepatoblastoma (n=109). • Children must have had standard-risk hepatoblastoma, defined as PRETEXT I, II or III, serum AFP >100 µg/L, and with no additional PRETEXT criteria. • Extent of disease: non-metastatic disease	• Children aged ≥1 to <18 years newly diagnosed with any histologically confirmed germ cell tumour (n=32), hepatoblastoma (n=7), medulloblastoma (n=26), neuroblastoma (n=26), osteosarcoma (n=29), or other solid malignancy requiring cisplatin chemotherapy (n=5). • Extent of disease: Localised non-metastatic disease, n=77;

		disseminated metastatic disease, n= 47; unknown, n=1
Number of patients randomised	114 *	125 †
Intervention(s)	Cisplatin plus STS (n=61) • Cisplatin by IV infusion over a duration of 6 hours, with dose dependent on body weight: 80 mg/m^2 (body weight >10 kg), 2.7 mg/kg (body weight ≥5 to ≤10 kg), 1.8 mg/kg (body weight <5 kg) • STS by a 15-minute infusion 6 hours after completion of CIS: 20 g/m^2 (body weight >10 kg), 15 g/m^2 (body weight ≥5 to ≤10 kg), 10 g/m^2 (body weight <5 kg) ‡	Cisplatin plus STS (n=61) • Cisplatin: Eligibility required CIS treatment to be ≥200 mg/m^2 (variable) infused over a duration of ≤6 hours (administered according to the sites' disease-specific cancer treatment protocols in use at the time. Other chemotherapy agents were also permitted as per these protocols). • STS: 16 g/m^2 by a 15-minute IV infusion 6 hours after completion of each CIS infusion (or 533 mg/kg for children whose therapeutic protocol administered CIS on a per-kg basis due to young age or small body size) ‡
Comparator(s)	Cisplatin without STS (n=53) • Cisplatin by IV infusion over a duration of 6 hours, with dose dependent on body weight: 80 mg/m2 (body weight >10 kg), 2.7 mg/kg (body weight ≥5 to ≤10 kg), 1.8 mg/kg (body weight <5 kg)	Cisplatin without STS (n=64) • Cisplatin: Eligibility required CIS treatment to be ≥200 mg/m^2 (variable) infused over a duration of ≤6 hours (administered according to the sites' disease-specific cancer treatment protocols in use at the time. Other chemotherapy agents were also permitted as per these protocols).
Duration of follow-up §	• Per protocol, up to 5 years (or longer as clinically indicated and according to national guidelines); actual median 4.27 years	• Per protocol, 10 years from the date that the patient started the study; actual median 5.33 years
Reported outcomes specified in the decision problem	• Hearing loss as assessed by Brock Grade • Adverse effects of treatment • Overall survival	• Hearing loss as defined by ASHA • Adverse effects of treatment • Overall survival
All other reported outcomes	Other audiological outcomes: • Measurement of bilateral pure-tone air conduction thresholds at 8, 6, 4, 2, 1, and 0.5 kHz • Immittance evaluation including middle ear pressure and compliance, and acoustic reflex thresholds • Measurement of transient evoked otoacoustic emissions (TEOAEs) and distortion product otoacoustic emissions (DPOAEs) • Bone conduction auditory brainstem response (ABR) • Tumour status after preoperative chemotherapy: o Tumour response after two and	Other audiological outcomes: • Measurement of bilateral pure-tone air conduction thresholds at 0.5 to 8 kHz • Immittance evaluation • Measurement of evoked otoacoustic emissions (OAEs) • Brainstem auditory evoked response (BAER) • Ultra-high frequency (UHF) audiometry o Components of reported haematological toxicity o Components of reported nephrotoxicity o Event-free survival

	four cycles of cisplatin chemotherapy o Resection after preoperative chemotherapy o Tumour status at end of treatment o Tumour status at last follow-up • Event-free survival • Long-term renal clearance • Feasibility of central audiology review. • AFP levels	

ABR - auditory brainstem response; AFP - alpha fetoprotein; ASHA - American Speech and Hearing Association; BAER - Brainstem auditory evoked response; CIS - cisplatin; CS - company submission; DPOAEs - distortion product otoacoustic emissions; IV - intravenous; kHz - kilohertz; OAEs - otoacoustic emissions; PRETEXT - pre-treatment tumour extension; STS - sodium thiosulfate; TEOAEs - transient evoked otoacoustic emissions; UHF - ultra-high frequency.
** Five randomised patients in the SIOPEL 6 trial withdrew prior to treatment. Of the 109 patients remaining, 4 children randomised to the CIS+STS arm never received STS. These patients were assigned to the CIS alone arm for the safety population (CIS, n=56; CIS+STS, n=53) but remained in the CIS+STS arm for the ITT Population (CIS, n=52; CIS+STS, n=57)*
† Two COG ACCL0431 patients randomised to the CIS+STS arm did not receive STS and were excluded from both the Safety and Efficacy Populations (CIS, n=64; CIS+STS, n=59)
‡ At the time of the SIOPEL 6 and COG ACCL0431 trials, the yet to be approved STS formulation were manufactured in pentahydrate powder form as reported in Freyer et al.[29] and Brock et al.[28] The current manufacturing process uses the same formula but provides an already prepared aqueous solution of anhydrous STS. This aligns with the GB SmPC which uses the molecular weight of the anhydrous salt for the dose calculation (80 mg/ml). The dose for a child with a body weight over 10 kg is 12.8 g/m2, between 5 and 10 kg, 9.6 g/m2 and less than 5 kg, 6.4 g/m2. Further details of STS doses in the anhydrous form are presented in CS,[1] section B.2.2.1.
§ Information from SmPC[14]

The SIOPEL 6[30] study was an international, multicentre, open-label, randomised, Phase 3 trial designed to evaluate the efficacy and safety of STS plus cisplatin in reducing ototoxicity in patients receiving cisplatin for standard risk hepatoblastoma (defined as PRETEXT classification I, II or III, serum alpha-fetoprotein (AFP) >100 µg/L, and no additional PRETEXT criteria including metastatic disease). The study excluded participants with high-risk hepatoblastoma, hepatocellular carcinoma, abnormal renal function or recurrent disease.[29] The study randomised 109 children (57 participants received STS plus cisplatin and 52 participants received cisplatin alone) at 52 centres across 12 countries, including the UK (50 females: 59 males). Randomisation was stratified by country, median age (≤15 month versus >15 months), and PRETEXT score (I or II versus III). Participants were aged between 0.1 and 8.2 years (mean age was 18.5 months with mean weight of 10.24 kg).[29] Single agent cisplatin therapy (at a dose of 80 mg/m^2) was given by continuous intravenous six-hour infusion every two weeks. STS was given six hours after the end of cisplatin infusion by 15-minute intravenous infusion. Four treatment courses were given pre-surgery, and two courses were given post-surgery. Doses of STS were dependent on the child's weight (>10 kg, 5 to 10 kg, and <5 kg corresponding to 12.8 g/m^2, 9.6 g/m^2, and 6.4 g/m^2, anhydrous dosing respectively). The primary endpoint was any hearing loss defined as Brock Grade ≥1 through 4 (centrally reviewed by blinded reviewers) measured by PTA at the end of study treatment or at an age of ≥3.5 years when a reliable result could be obtained whichever was later (see clarification response,[7] question A20). In general, the primary endpoint analysis was by intention-to-treat (ITT - defined as all randomised participants except those for which informed consent was withdrawn prior to

start of study treatment and those for whom study treatment would have been inappropriate because they had were subsequently diagnosed with high-risk hepatoblastoma, regardless of whether or not study medication was administered) and restricted to evaluable participants (safety population: defined as all randomised children who received at least one dose of study medication). Sensitivity analyses using the complete modified ITT (mITT) and per protocol populations were performed to analyse the effect of the missing data. Further details are provided in the CS[1] (Section B.2.3). The median follow-up was 4.27 years;[29] final audiometry was performed at a median of 3 years (range 3 months to 6.9 years). The study was funded by Cancer Research UK and others.

The COG ACCL0431 study[31] was an international, multicentre, open-label, randomised Phase 3 trial. This study assessed the efficacy and safety of STS plus cisplatin in reducing ototoxicity in patients receiving cisplatin containing chemotherapy for the treatment of newly diagnosed germ cell tumour (25.6%), hepatoblastoma (5.6%), medulloblastoma (20.8%), neuroblastoma (20.8%), osteosarcoma (23.2%), or any other solid malignancy tumours requiring cisplatin chemotherapy (4.0%). As noted in the company's response to clarification question A14b,[7] the COG ACCL0431 trial did not directly record the type of chemotherapy regimen received by each tumour type e.g., cisplatin monotherapy, or a multi-drug cisplatin-containing chemotherapy regimen. The study excluded children who were enrolled in any COG therapeutic study for the treatment of an underlying malignancy, or women who were pregnant or breastfeeding.[29] The study randomised 125 participants (61 participants received STS plus cisplatin and 64 participants received their planned cisplatin chemotherapy regimen) at 38 COG hospitals in the USA and Canada (49 females: 76 males). Randomisation was stratified by prior cranial radiation (yes vs. no), age (< 5 versus ≥5 years), and duration of cisplatin infusion (< 2 versus ≥2 hours). Participants were aged between 1 and 18 years (mean age was 9.2 years with mean approximate weight of 38.2 kg;[15] 77 patients had localised disease and 47 had disseminated disease and 1 unknown). The COG ACCL0431[31] study was designed to administer 16 g/m^2 STS, corresponding to 10.2 g/m^2 anhydrous STS (CS,[1] section B.2.2.1 and B.2.2.4) by a 15-minute intravenous infusion 6 hours after the completion of a cisplatin infusion in patients with various tumour types. The CIS dosing regimen (planned cumulative dose ≥200 mg/m^2) was determined by each site's disease-specific cancer treatment protocols in use at the time, but the durations of CIS infusions were generally between 1 and 6 hours with up to 5 daily administrations per cycle.[34] When multiple daily doses of cisplatin were scheduled, the protocol stipulated at least a 10-hour delay between any STS infusion and the beginning of the next day's cisplatin infusion.[15] The primary endpoint was development of hearing loss (all audiometry data centrally reviewed by blinded reviewers), as defined by ASHA criteria, assessed at baseline, at 4 weeks following the final dose of cisplatin and 1 year later. ASHA define ototoxicity as either a 10 dB change from baseline at two consecutive frequencies, or a 20 dB change at one frequency, or loss of measurable hearing for three consecutive frequencies where previously measurable hearing was obtained (CS,[1] section B.1.3.1.2). Analysis of the primary endpoint was by mITT, which included all randomly

assigned patients irrespective of treatment received but restricted to those assessable for hearing loss.[31] The safety population (defined as all randomised children who received at least one dose of study medication) was the primary population for all safety assessments and the ITT population was the primary population for assessment of survival parameters i.e., EFS and OS (see CS,[1] Section B.2.3.1). The median follow-up was 5.33 years.[15, 29] The study was funded by US National Cancer Institute (NCI).

The company's assessment of the design, conduct and internal validity of the SIOPEL 6[30] and the COG ACCL0431[31] trials is summarised in

Table 9. Although, neither the CS nor its appendices provides a narrative assessment of the quality of the studies to inform the interpretation of the results of the trials, the EAG broadly agrees with the company's risk of bias assessments based on the full trial population of SIOPEL 6[30] and COG ACCL0431.[31] However, the EAG considers it important to highlight that the licensed population from the COG ACCL0431 trial[31] is aligned with a subgroup of participants with localised disease that was not statistically powered to detect differences in efficacy for any of the measured outcomes.

In general, based on this quality assessment, the EAG considered these RCTs to be a well-reported and conducted. However, as noted in the EMA assessment report[29] there were slight baseline imbalances in prognostic factors in SIOPEL 6 (e.g., median AFP level at diagnosis and PRETEXT classification) which could suggest differential prognosis for the two treatment groups. In addition, it was unclear if participants had any prior hearing dysfunction in SIOPEL 6 as the presence of baseline hearing loss in some patients could have confounded the study results.[34] Limited prognostic details were collected in the COG ACCL0431 trial.[31] As noted in the company's response to clarification question A22,[7] prognostic risk was not considered during randomisation and only factors relating to hearing loss were considered in stratification.

Table 9: Quality assessment results for the SIOPEL 6 and COG ACCL0431 trials, as assessed by the company (adapted from CS, Appendix D4)

Quality assessment criteria	SIOPEL 6[30]		COG ACCL0431[31]	
	Company's assessment	EAG's assessment	Company's assessment	EAG's assessment
Was the method used to generate random allocations adequate?	Y	Y	Y	Y
Were the groups similar at the outset of the study in terms of prognostic factors, e.g., severity of disease?	PN	PN	NI	NI
Was the treatment allocation sequence adequately concealed?	PY	Y	Y	Y
Were the care providers, participants and outcome assessors blind to treatment allocation?	N	N	N	N
Were there any unexpected imbalances in drop-outs between groups?	N	N	N	PN
Is there any evidence to suggest that the authors measured more outcomes than they reported?	N	N	Y	Y
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Y	Y	Y	Y

CS - company submission; EAG - External Assessment Group; N - no; NI - no information; PN - probably no; PY - probably yes; Y - yes

The generalisability of the results from both trials to clinical practice in England is unclear. The patient population in the SIOPEL 6[30] trial comprised a homogeneous patient population of children with a localised tumour type (standard risk hepatoblastoma; mean age was 18.5 months). In contrast, the COG ACCL0431 included heterogeneous patient population with localised and disseminated disease with various tumour types (mean age was 9.2 years) that relates to a broader population than that in the licensed indication (localised, non-metastatic disease).[15] For the assessment of the primary endpoint, different hearing loss grading scales were used in both studies: the ASHA scale was used in COG ACCL0431[31] and the Brock scale was used in SIOPEL 6.[30] In their response to clarification question A19,[7] the company acknowledged, based on audiologists feedback in 2018 (*n=10 from the USA [n=5] and UK [n=5];* no further details provided) that there is wide variability in the use of ototoxicity scales, with the ASHA scale being commonly used in the USA and the Brock ototoxicity grading scale commonly used in UK clinical practice for grading cisplatin-induced hearing loss. The company's clarification response[7] also states that the *"Great Ormond Street Hospital (GOSH) has been the leading centre in paediatric ototoxicity in the UK and use both the Brock and SIOP ototoxicity grading scales… [A study by] 'Knight et al. [which] compared the ASHA, Brock, and SIOP ototoxicity scales in a large cohort of children and young adults treated for the first time with a cisplatin-containing regimen… concluded that the SIOP ototoxicity scale may be superior to ASHA, Brock and CTCAE instruments; although the study also suggested that the sensitivity in detecting any ototoxicity was comparable*

between the SIOP ototoxicity (55%) and ASHA (56%) scales, whilst it was slightly lower for the Brock scale (40%).”

3.3 Clinical effectiveness results

This section presents the main results from the SIOPEL 6[30] and COG ACCL0431[31] trials based on information reported in the CS[1] and its appendices. Results where available are reported for the ITT and mITT populations of the SIOPEL 6 trial. The ITT population includes all randomised children except those for which informed consent was withdrawn prior to the start of treatment or for whom the treatment was deemed inappropriate due to the risk status of their disease changing. The mITT population includes children in the ITT population except those for which a measurement of the primary endpoint could not be made. Results where available are reported for the ITT and efficacy populations of the COG ACCL0431 trial. The ITT population in COG ACCL0431 includes all children who were randomised, and the efficacy population includes all children who had both baseline and 4-week follow up hearing assessments. Additional information, not reported in the CS, was provided by the company in the company’s clarification response.[7]

It is noteworthy that the CS (Section B.3.5.1, page 89)[1] reports that no HRQoL data were collected in SIOPEL 6 and COG ACCL0431 trials.

3.3.1 SIOPEL 6 trial

As noted in the CS (section B.2.3 and B.2.5.1), any participants with missing data in the SIOPEL 6 trial due to any reason such death, infeasible hearing assessment or logistical issues were excluded from the primary analysis of hearing loss. Sensitivity analyses using the complete mITT population were conducted to assess the effect of the missingness. Any participants with missing hearing assessments were recorded as “*hearing impaired or failure*” and thus assumed to experience hearing loss.

3.3.1.1 Incidence of hearing loss

The key results from the SIOPEL 6[30] trial are summarised in

Table 10. The proportional incidence of children with Brock Grade ≥1 hearing loss, measured by PTA, after the end of treatment or at ≥3.5 years (whichever was later), was statistically significantly lower in the cisplatin with STS arm compared with the cisplatin without STS arm for both the ITT (p<0.001) and mITT populations (p=0.002).

Table 10: Primary efficacy endpoint in SIOPEL 6 - hearing loss, ITT and mITT populations (adapted from CS, Tables 12, 13 and Table 12 of the clarification response)

Results - hearing loss	ITT		mITT	
	Cisplatin without STS (N=52)	Cisplatin with STS (N=57)	Cisplatin without STS (N=46)	Cisplatin with STS (N=55)
Yes, n (%)	35 (67.3)	20 (35.1)	29 (63.0)	18 (32.7)
No, n (%)	17 (32.7)	37 (64.9)	17 (37.0)	37 (67.3)
Odds ratio (95% CI)	0.254 (0.111, 0.579)		-	
p-value[b]	0.001		-	
Relative risk (95% CI)*	0.521 (0.349, 0.778)		0.519 (0.335, 0.805)	
p-value*	<0.001		0.002	
Relative risk (95% CI)†	0.519 (0.356, 0.755)		0.516 (0.339, 0.787)	
p-value†	<0.001		0.002	

CI - confidence interval; CMH - Cochran-Mantel-Haenszel; CS - company submission; ITT - intention-to-treat; mITT - modified intention-to-treat; PRETEXT - pre-treatment tumour extension.
**p-value and relative risk from Chi-square test.*
†p-value and relative risk from CMH test stratified by country group, PRETEXT group and age group.
b Odds ratio was based on logistic regression including treatment and stratification variable as a covariate in the model.

The CS[1] (Section B.2.5.1, Tables 14 and 15) also provides further analyses of hearing loss (centrally reviewed) according to Brock Grades (all grades, n=101; and ≥1, n=47 [*post hoc* analysis]), using PTA that was performed at a minimum age of 3.5 years in the mITT population (Table 11). The CS notes that by removing the children who did not experience hearing loss (i.e., Brock Grade 0) from the analysis, it was found that fewer children experienced some level of hearing loss in the cisplatin with STS group compared to the cisplatin without STS group, but also that the hearing loss experienced was generally less severe in the cisplatin with STS group.

Table 11: Brock grades for children experiencing hearing loss in SIOPEL 6, mITT population (adapted from CS, Tables 14 and 15)

Brock Grade*	Percentage of children in each grade		Percentage of children experiencing hearing loss of at least Brock Grade 1	
	Cisplatin without STS (N=46)	Cisplatin with STS (N=55)	Cisplatin without STS (N=29)	Cisplatin with STS (N=18)
0	37%	67%	-	-
1	26%	18%	41%	55%
2	24%	11%	38%	33%
3	11%	2%	18%	6%
4	2%	2%	3%	6%

CS - company submission; STS - sodium thiosulfate.
** A Brock Grade of 0 indicates hearing at less than 40 dB at all frequencies and does not necessarily equate to completely normal hearing. Grades 1, 2, 3, and 4 indicate hearing levels at 40 dB or higher at 8 kHz, 4 kHz, 2 kHz, and 1 kHz and above, respectively. The Grade was determined according to the hearing level in the child's better ear.*

3.3.1.2 Overall survival

OS was the secondary efficacy outcome in the SIOPEL 6 trial. No statistically significant difference between the cisplatin with STS and cisplatin without STS groups was reported (*p*=[redacted]). OS for the ITT population is summarised in Table 12, and the Kaplan-Meier (KM) estimates are shown in Figure

2. OS from SIOPEL 6 for the mITT population was not clearly reported in the CS and is therefore not summarised.

Table 12: Summary of overall survival in SIOPEL 6,* ITT population (adapted from CS, Table 16)

Parameter category / statistic	ITT population	
	Cisplatin without STS (N=52)	Cisplatin with STS (N=57)
Number of patients who died, n (%)	[redacted]	[redacted]
Number of patients censored, n (%)	[redacted]	[redacted]
Treatment comparison (cisplatin with STS vs cisplatin without STS)		
Hazard ratio (95% CI)	[redacted]	
p-value (log-rank)	[redacted]	

CI - confidence interval; CS - company submission; ITT - intention-to-treat; STS - sodium thiosulfate.
**Time to event was calculated from the time of randomisation to death. Subjects alive were censored at the time of last known follow-up visit.*

Figure 2: Overall survival, SIOPEL 6, ITT population (reproduced from CS, Figure 6)

[redacted]

CI - confidence interval; CS - company submission; ITT - intention-to-treat; p - p-value; RHR – relative hazard ratio.

3.3.2. COG ACCL0431

As noted in the company's response to clarification question A15,[7] any participants with missing data in the COG ACCL0431 trial, due to any reason such as death, infeasible hearing assessment or logistical issues, were excluded from the efficacy population. The company stated that *"This was pre-specified in the statistical analysis plan for the trial… [and that] in the ITT population…any patients with missing data for any reason were included and were assumed to have hearing loss."*

3.3.2.1 Incidence of hearing loss

The main results from the COG ACCL0431[31] are summarised in

Table 13. The proportional incidence of hearing loss in the efficacy population, defined by the ASHA criteria, were statistically significantly lower in the cisplatin with STS arm compared with the cisplatin without STS arm (p=0.0039). A sensitivity analysis, conducted in the ITT population which includes all patients irrespective of whether they had a follow-up assessment at 4-weeks post-treatment, also demonstrated statistically significant reductions in hearing loss in the cisplatin with STS group compared with the cisplatin without STS group (p=0.0234).

Table 13: Primary efficacy endpoint in COG ACCL0431 - hearing loss, efficacy and ITT populations (adapted from CS, Tables 17, 18 and Table 12 of the clarification response)

Results- hearing loss	ITT		Efficacy	
	Cisplatin without STS (N=64)	Cisplatin with STS (N=61)	Cisplatin without STS (N=55)	Cisplatin with STS (N=49)
Yes, n (%)	40 (62.5)	26 (42.6)	31 (56.4)	14 (28.6)
No, n (%)	24 (37.5)	35 (57.4)	24 (43.6)	35 (71.4)
Odds ratio (95% CI)*	0.411 (0.191, 0.886)		0.274 (0.114, 0.660)	
p-value*	0.0234		0.0039	
Relative Risk (95% CI)	-		0.516 (0.318, 0.839)	
p-value[b]	-		0.0040	

CI - confidence interval; CS - company submission; ITT - intention-to-treat; STS - sodium thiosulfate.
**Based on logistic regression including treatment and stratification variables as covariates in the model.*
b Relative risk was calculated using a CMH test including stratification variable.

The incidence of hearing loss was also reported for the localised population of COG ACCL0431 only, i.e. excluding metastatic patients from the analysis. The incidence of hearing loss of localised patients in the efficacy population ([redacted]) is presented in

Table 14 and shown not to be statistically significant for this subgroup of the COG ACCL0431 efficacy population.

Table 14: Summary of the incidence of hearing loss in the COG ACCL0431, efficacy population- localised patients only (adapted from Table 12 of the clarification response)

Results- hearing loss	Efficacy population - localised only	
	Cisplatin without STS (N=[redacted])	Cisplatin with STS (N=[redacted])
Yes, n (%)	[redacted]	[redacted]
No, n (%)	[redacted]	[redacted]
Odds ratio (95% CI)	[redacted]	
p-value[a]	[redacted]	
Relative Risk (95% CI)	[redacted]	
p-value[b]	[redacted]	

CI - confidence interval; CS - company submission; ITT - intention-to-treat; STS - sodium thiosulfate.
a Based on logistic regression including treatment and stratification variables as covariates in the model.
b Relative risk was calculated using a CMH test including stratification variable.

3.3.2.2 Overall survival

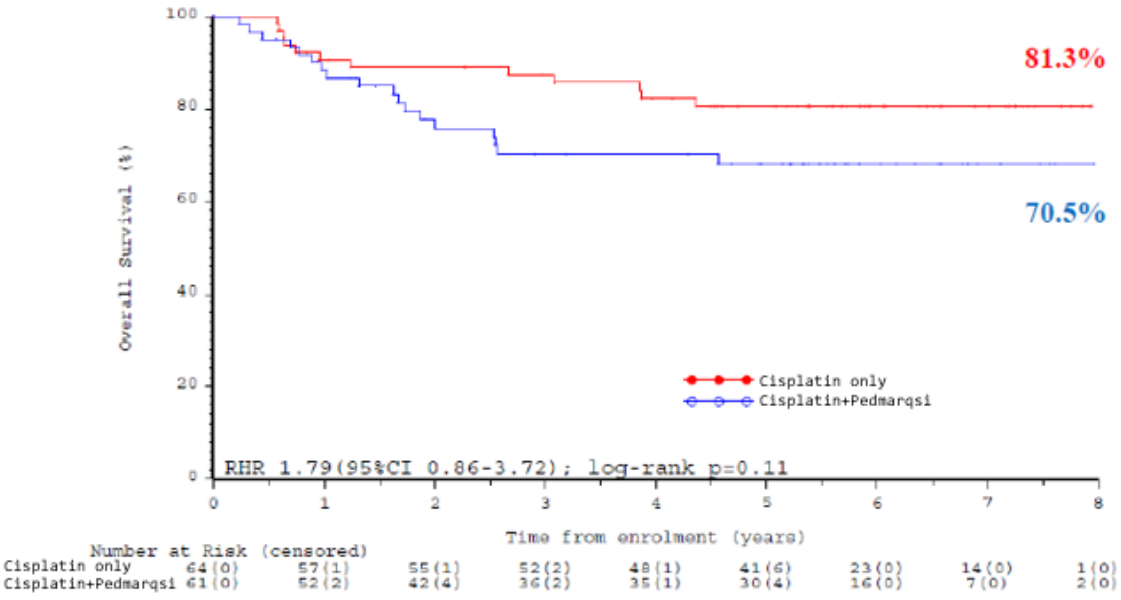
OS was the secondary efficacy outcome in the COG ACCL0431 trial and was reported for the ITT population with a median follow-up of 5.33 years (interquartile range [IQR]: 2.54 to 6.45 years). No statistically significant difference in OS between the cisplatin with STS and cisplatin without STS arms was reported (p=0.1132). A summary of OS results is presented in Table 15 and the corresponding KM estimates are shown in Figure 3.

Table 15: Summary of overall survival in COG ACCL0431, ITT population (adapted from CS, Table 20 and the US FDA assessment review)

Parameter category/statistic	ITT population	
	Cisplatin without STS (N=64)	Cisplatin with STS (N=61)
Number of patients who died, n (%)	12 (18.8)	18 (29.5)
Number of patients censored, n (%)	52 (81.3)	43 (70.5)
Treatment comparison (cisplatin with STS vs cisplatin without STS)		
Hazard ratio (95% CI)	1.79 (0.86, 3.72)	
p-value (log-rank)	0.1132	

CI - confidence interval; CS - company submission; FDA - Food and Drug Administration; ITT - intention-to-treat; STS - sodium thiosulfate.

Figure 3: Overall survival, COG ACCL0431, ITT population (reproduced from CS, Figure 7)



CI - confidence interval; CS - company submission; ITT - intention-to-treat; p - p-value; RHR – relative hazard ratio.

Overall survival was also presented for the COG ACCL0431 ITT population subgroup of localised patients only. No statistically significant difference in OS between the cisplatin with STS and cisplatin without STS arms was reported ([redacted]). A summary of OS results is presented in

Table 16.

Table 16: Summary of overall survival in COG ACCL0431, ITT population, localised patients only (adapted from data provided in the clarification response)

Parameter category/statistic	ITT population – localised only	
	Cisplatin without STS (N=38)	Cisplatin with STS (N=39)
Number of patients who died, n (%)	[redacted]	[redacted]
Number of patients censored, n (%)	[redacted]	[redacted]
Treatment comparison (cisplatin with STS vs cisplatin without STS)		
Hazard ratio (95% CI)	[redacted]	
p-value (log-rank)	[redacted]	

CI - confidence interval; CS - company submission; FDA - Food and Drug Administration; ITT - intention-to-treat; STS - sodium thiosulfate.

3.3.2.3 Mean change in hearing thresholds

The mean change in hearing threshold was assessed by two different blinded central reviewers as a secondary efficacy endpoint. No statistically significant differences were identified in the change in hearing from baseline to 4 weeks after the final cisplatin treatment at frequencies ≤2000Hz between the cisplatin with STS and cisplatin without STS arms. Larger differences were observed at frequencies of ≥4000Hz in both ears, with reduced hearing loss observed for cisplatin with STS compared to cisplatin without STS. Detailed results for this secondary efficacy endpoint are presented in the CS[1] (Section B.2.5.2, Table 19, p54-55).

3.3.3. Post hoc analysis: SIOPEL 6 and COG ACCL0431 trials – pooled data analysis

Due to the small sample sizes of both trials, the EMA requested the company to integrate and pool analyses for hearing loss and OS using the SIOPEL 6 and COG ACCL0431 trial data in the ITT population. Although the CS provided no details on how the data were pooled, the pooled analyses were subsequently presented for the ITT population for OS and the ITT and mITT populations for overall hearing loss in the CS[1]. The generalisability of the pooled analyses due to the different population characteristics of the SIOPEL 6 and COG ACCL0431 trials is uncertain. With relevance to the COG ACCL0431 trial, the EMA highlighted that "…*children less than 5 years of age [are] likely to derive the most benefit of STS on hearing loss induced by platinum"*, and that for "*the population over 5 years of age the benefit of the STS on hearing loss is not as clearly established, as the reported results did not reach statistical significance*". However, the EMA also stated that there is "*no plausible clinical reason why STS would not reduce hearing loss in this older group of patients with localised disease*". However, the pooling of the two trials may not be ideal due to differences such as patient population and study design.

These pooled analyses were presented in the original CS[1] using data from SIOPEL 6 trial which included patients with localised disease and the COG ACCL0431 trial which included metastatic and localised patients. As per the request at the clarification stage, pooled analyses for the localised patients

only (the population in the licensed indication) were subsequently provided by the company.[7] Summaries of the pooled analyses for both populations are presented in the following sections to enable comparison of results across the various pooled analyses.

3.3.3.1 Localised and metastatic disease – pooled analysis

Incidence of hearing loss

The pooled analysis of the SIOPEL 6 and COG ACCL0431 trial data on localised and metastatic patients in the ITT and mITT populations suggests that the proportion of patients who experience hearing loss was reduced in the cisplatin with STS group compared to the cisplatin without STS group. The odds ratio (OR) was statistically significant and indicated that the odds of experiencing hearing loss in the cisplatin with STS group was lower than the odds in the cisplatin without STS group in both the ITT population (*p*=[redacted]) and the mITT population (*p*=[redacted]). The relative risk (RR) was also statistically significant and indicated a lower risk of hearing loss in the cisplatin with STS group compared to the cisplatin without STS group. These results are summarised in Table 17.

Table 17: Summary of hearing loss according to the pooled analysis of SIOPEL 6 and COG ACCL0431 - localised and metastatic patients (adapted from CS, Tables 22 and 23)

Pooled results - hearing loss	ITT		mITT	
	Cisplatin without STS (N=116)	Cisplatin with STS (N=118)	Cisplatin without STS (N=[redacted])	Cisplatin with STS (N=[redacted])
Yes, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
No, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Odds ratio (95% CI)*	[redacted]		[redacted]	
p-value*	[redacted]		[redacted]	
Relative risk (95% CI)†	[redacted]		[redacted]	
p-value†	[redacted]		[redacted]	

CI - confidence interval; CS - company submission; ITT - intention-to-treat; mITT - modified intention-to-treat; STS - sodium thiosulfate.
** p-value and odds ratio based on logistic regression including treatment and study as a covariate in the model.*
† p-value and relative risk from Cochran-Mantel-Haenszel (CMH) test adjusting for study.

Overall survival

A pooled analysis of OS was also conducted by pooling OS data and comparison of the treatments conducted using the unstratified log-rank test. Additionally, hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) were estimated using a Cox proportional hazards model. These analyses were conducted for the ITT population and no statistically significant difference in the proportion of children who died during the two studies in the cisplatin with STS (20 patients [16.9%]) and cisplatin without STS (16 patients [13.8%]) groups was identified (HR: 1.29; 95% CI 0.67, 2.53; *p*=0.4464). For further details see CS, Table 24, Section B.2.7.

3.3.3.2 Localised disease only (the population in the licensed indication) – pooled analysis

Following a request from the EAG (see clarification response,[7] questions A13 and B6), the company provided a pooled analysis for the localised, non-metastatic subgroup only (the population reflected in the licensed indication). This analysis is summarised in the following sections. However, the company raised concerns that it is inappropriate to assess the efficacy of STS via pooled analyses of localised patients only due to the COG ACCL0431 trial not being powered for the assessment of localised patients only. The specific population included within the licence is however for localised patients only, and the EAG therefore believes this subgroup analysis should be presented for completeness and considered alongside the analyses of the populations including metastatic patients. However, as noted in Section 3.3.3, the pooling of the two trials may not be ideal due to study differences such as patient population and study design.

Incidence of hearing loss

A summary of the results of the pooled analysis is presented in Table 18. The pooled analyses excluding metastatic patients demonstrated statistically significant reductions in hearing loss in the cisplatin with STS arm compared with the cisplatin without STS arm in both the ITT population (OR: *p*=[redacted]; RR: *p*=[redacted]) and the mITT population (OR: *p*=[redacted]; RR: *p*=[redacted]).

Table 18: Summary of hearing loss according to the pooled analysis of SIOPEL 6 and COG ACCL0431 - localised disease only (adapted from clarification response, question A13)

Pooled results - hearing loss	ITT		mITT	
	Cisplatin without STS (N=90)	Cisplatin with STS (N=96)	Cisplatin without STS (N=79)	Cisplatin with STS (N=86)
Yes, n (%)	[redacted]			
No, n (%)	[redacted]			
Odds Ratio (95% CI)*	[redacted]			
p-value*	[redacted]			
Relative Risk (95% CI)†	[redacted]			
p-value†	[redacted]			

CI - confidence interval; ITT - intention-to-treat; mITT - modified intention-to-treat; STS - sodium thiosulfate.
**p-value and odds ratio based on logistic regression including treatment and study as a covariate in the model.*
†p-value and relative risk from Cochran-Mantel-Haenszel (CMH) test adjusting for study.

Overall survival

A pooled analyses conducted excluding metastatic patients reported no statistically significant differences in overall survival between the cisplatin with STS and cisplatin without STS groups in the ITT population (*p*=0.7364). The overall survival for the ITT population is summarised in

Table 19, and the KM estimates are shown in

Parameter	ITT

Category/Statistic	Cisplatin without STS (N=90)	Cisplatin with STS (N=96)
Number of patients who died, n (%)	10 (11.1)	9 (9.4)
Number of patients censored, n (%)	80 (88.9)	87 (90.6)
Treatment comparison (cisplatin with STS vs cisplatin without STS)		
Hazard ratio (95% CI)	0.86 (0.34, 2.13)	
p-value (log-rank)	0.7364	

CI - confidence interval; EMA - European Medicines Agency; ITT - intention-to-treat; STS - sodium thiosulfate.

Figure 4.

Table 19: Summary of overall survival according to the pooled analysis of SIOPEL 6 and COG ACCL0431 - localised disease only (adapted from company's clarification response, question A13, and the EMA assessment report)

Parameter	ITT	
Category/Statistic	**Cisplatin without STS (N=90)**	**Cisplatin with STS (N=96)**
Number of patients who died, n (%)	10 (11.1)	9 (9.4)
Number of patients censored, n (%)	80 (88.9)	87 (90.6)
Treatment comparison (cisplatin with STS vs cisplatin without STS)		
Hazard ratio (95% CI)	0.86 (0.34, 2.13)	
p-value (log-rank)	0.7364	

CI - confidence interval; EMA - European Medicines Agency; ITT - intention-to-treat; STS - sodium thiosulfate.

Figure 4: Overall survival, pooled analysis of SIOPEL 6 and COG ACCL0431 - localised disease only (reproduced from clarification response, question A13)

STS - sodium thiosulfate.

3.3.4. Additional analyses

3.3.4.1 SIOPEL 6 subgroup analyses

No subgroup analyses were reported in the SIOPEL 6 trial[30] and therefore this was not discussed in the CS.[1]

3.3.4.2 COG ACCL0431 subgroup analyses

A pre-planned subgroup analysis was included within the COG ACCL0431 trial.[31] The subgroups of children <5 and ≥5 years of age with cisplatin-induced hearing loss were assessed. The subgroup analysis was proposed on the basis that children less than 5 years of age are more susceptible to hearing loss, especially at higher frequencies. The odds of having hearing loss, graded according to the ASHA criteria, was statistically significantly lower for the subgroup of children less than 5 years of age in the cisplatin with STS group compared to the cisplatin without STS group. The odds of having hearing loss, graded according to the ASHA criteria, was only numerically reduced for children ≥5 years of age in the cisplatin with STS group compared to the cisplatin without STS group. Detailed results of the subgroup analysis can be found in Table 21 of the CS.

3.3.4.3 Further analysis of COG ACCL0431

Due to the variations in audiologic testing used within STS core clinical trials (SIOPEL 6 used the Brock scale and COG ACCL0431 used the ASHA criteria), Orgel *et al*.,[20] conducted a *post hoc* re-analysis of COG ACCL0431 data using the more recent International Society of Paediatric Oncology (SIOP) Boston ototoxicity scale as an alternative measure of hearing loss. This scale was developed as a measure to report hearing outcomes in international clinical trials for paediatric patients treated with platinum therapy, taking into account the functional outcome of a patient at the end of treatment. To replicate the COG ACCL0431 trial primary endpoint, hearing endpoints from COG ACCL0431 were re-evaluated using hearing loss at the end of cisplatin therapy and prior to autologous bone marrow transplantation. Hearing thresholds of SIOP Grade ≥2 and Grade ≥1 were evaluated. Re-analysis of hearing outcomes from the COG ACCL0431 trial found that a lower incidence of Grade ≥2 cisplatin-induced hearing loss occurred in the cisplatin with STS arm compared with cisplatin without STS arm (4.0% versus 27.1% respectively; OR 0.10, 95% CI: 0.02, 0.50, p=0.005). A similar pattern was seen for SIOP Grade >1 (18.0% versus 45.8%, respectively; OR 0.25, 95% CI: 0.10, 0.64; p=0.004).[20] Further details are provided in Section B.2.7 of the CS.[1]

3.3.5. Safety and tolerability

This section provides the main safety evidence, as reported by the company, for all patients who received at least one dose of study medication within the SIOPEL 6 and COG ACCL0431 trials (Safety Populations).

3.3.5.1 SIOPEL 6 trial

In the SIOPEL 6 trial,[30] 109 children were included in the safety population, including 53 children in the cisplatin with STS arm and 56 children in cisplatin without STS arm (four children that were randomised to the cisplatin with STS group did not receive STS and were included in the cisplatin without STS group i.e., as treated).

Although not reported in the CS, cisplatin exposure was similar between the cisplatin with STS arm and cisplatin without STS arm as measured by mean number of cycles (5.9 and 5.8 cycles, respectively) and mean cumulative actual dose (363.86 mg/m^2 versus 362.85 mg/m^2, respectively - CS, Section B.2.2.2,). In the cisplatin with STS arm, participants received a mean cumulative STS dose of 85.15 g/m^2. As stated in the EMA assessment report,[29] the mean cumulative cisplatin dose was similar between arms in patients under 10 kg (cisplatin with STS arm: 297.99 mg/m^2 vs cisplatin without STS arm: 296.61 mg/m^2) but higher in patients over 10 kg in the cisplatin with STS arm compared to cisplatin without STS arm (464.72 mg/m^2 vs 437.62 mg/m^2, respectively).

Given the complex regimen of administration and the need to observe accurate timing of STS administration relative to cisplatin chemotherapy (i.e., a 15-minute intravenous STS infusion 6 hours after the completion of each cisplatin infusion), the EMA assessment report[29] raises concerns that the main potential risk associated with STS use is its interaction with cisplatin that could possibly lead to reduced effectiveness of cisplatin. The company's response to clarification question A22[7] states that: *"In SIOPEL 6, [redacted] out of [redacted] records ([redacted]%) of Pedmarqsi administration indicated that Pedmarqsi was not given within 15 minutes of the required 6-hour time interval. For one record, there was no further information, but for the remaining [redacted] records, the Pedmarqsi administration was delayed by up to two hours for a variety of mostly administrative reasons. The most common reasons were delay in receiving drug from pharmacy, ward staff changeovers and blocked or unusable infusion lines. In terms of the duration of Pedmarqsi infusion, [redacted] doses ([redacted]%) were not administered during an infusion time of 15 minutes +/- 5 minutes. These data indicate that the minimum time interval between cisplatin and Pedmarqsi administration was respected in both clinical trials. It is acknowledged, that the timing of Pedmarqsi administration is critical and this has the potential for errors which may impact efficacy. However clear labelling is provided in the SmPC and in the instructions for use included in the healthcare HCP section of the Patient Information Leaflet, to ensure that a gap of six hours is implemented between the end of Pedmarqsi infusion and the next cisplatin infusion."*

A summary of AEs that occurred at CTCAE Grade ≥3 at a frequency of ≥10% in either arm is presented in

Table 20. In general, the majority of Grade ≥3 AEs experienced by patients during the treatment phase were similar in both arms. In addition, as noted in the EMA assessment report,[29] the most frequently reported AEs attributable to STS were vomiting (cisplatin with STS arm, 84.9% vs cisplatin without STS group, 53.6%) and nausea (39.6% vs 30.4%, respectively). The reported events were transient and they were reported to stop soon after the STS infusion had finished. Other frequent AEs that did not meet the 10% threshold were related to electrolyte imbalance and included hypermagnesemia, hypokalaemia and hypophosphatemia, all of which occurred during the treatment phase. For further details on the clinically relevant consequences of AEs related to electrolyte imbalance, see the company's clarification response to question A23.[7]

Table 20: Summary of most common (frequency of ≥ 10% in either arm) AEs with maximum severity of CTCAE Grade 3 or higher during the treatment phase - SIOPEL 6 safety population (reproduced with minor changes from CS, Table 25)

Preferred term	Cisplatin without STS (N=56) n (%)	Cisplatin with STS (N=53) n (%)	Total (N=109) n (%)
Any Grade 3 severity or higher AE	34 (60.7)	35 (66.0)	69 (63.3)
Investigations	19 (33.9)	20 (37.7)	39 (35.8)
Neutrophil count decreased*	9 (16.1)	12 (22.6)	21 (19.3)
Haemoglobin decreased	9 (16.1)	10 (18.9)	19 (17.4)
Infections and infestations	15 (26.8)	14 (26.4)	29 (26.6)
Infection**	15 (26.8)	14 (26.4)	29 (26.6)
Blood and lymphatic system disorders	10 (17.9)	8 (15.1)	18 (16.5)
Febrile neutropenia	9 (16.1)	8 (15.1)	17 (15.6)

AE - adverse event; CS - company submission; CTCAE - Common Terminology Criteria for Adverse Event; STS – anhydrous sodium thiosulfate

**One instance of neutrophil count decreased was attributed as possibly related to Pedmarqsi in the cisplatin with Pedmarqsi arm. One instance of neutrophil count decreased was attributed as probably related to Pedmarqsi in the cisplatin with Pedmarqsi arm.*

***One instance of infection was attributed as probably related to Pedmarqsi in the cisplatin with Pedmarqsi arm. No additional fatal AEs were observed during the trial.*

During the treatment and follow-up phases in SIOPEL 6, a total of four children (7.5%) in the cisplatin with STS arm experienced a serious adverse event (SAE) that was determined to be related to STS. Of these four children, two (3.8%) experienced an SAE of neutrophil count decreased, one (1.9%) experienced an SAE of infection, and one (1.9%) experienced an SAE of hypersensitivity, which led to discontinuation of STS and was also considered as a suspected unexpected serious adverse reaction.

In total, 6 deaths occurred in SIOPEL 6 (2 deaths in the cisplatin with STS arm and 4 deaths in the cisplatin without STS arm); however, no deaths were considered related to STS.[29]

3.3.5.2 COG ACCL0431 trial

In the COG ACCL0431 trial,[31] 123 children were included in the safety population, including 59 children in the cisplatin with STS arm and 64 children in cisplatin without STS arm (two patients that were randomised to the cisplatin with STS group did not receive STS and were excluded from both the safety and efficacy populations).

As noted in the CS (Section B.2.2.4), cisplatin exposure was slightly different between the cisplatin with STS arm and cisplatin without STS arm as measured by mean number of cycles (3.1 and 3.8 cycles, respectively) and mean cumulative actual dose (337.57 mg/m^2 versus 391.47 mg/m^2, respectively). As noted in the EMA assessment report,[29] cisplatin dosing regimens varied across the diagnosed tumour types and reflected the differences in each child's cancer treatment plan, which was dependent on the tumour type and staging, as well as the patient's age. In the cisplatin with STS arm, participants received

a mean cumulative STS dose of 108.23 g/m^2. Although the STS dosing regimen per protocol was fixed at 16 g/m^2, the number of STS doses was variable and dependent on the number of CIS cycles and the number of CIS administrations per cycle.[34]

As mentioned earlier, given the complex regimen of administration and the need to observe accurate timing of STS administration relative to cisplatin chemotherapy, the company's clarification response to question A22,[7] states that *'The 6-hour administration time separation was retrospectively checked for relapsed patients with disseminated disease (n=[redacted]) in the COG ACCL0431 study, and data returned for [redacted] patients confirmed the mean separation interval being [redacted] hours (range [redacted]-[redacted]).'* No further details were provided.

A summary of Grade ≥3 AEs occurring in ≥10% of children in either treatment arm is presented in

Table 21? In general, the majority of Grade ≥3 AEs experienced by patients during the treatment phase were similar in both arms. In addition, as noted in the US FDA assessment review,[34] the incidence of nausea (cisplatin with STS arm, 8.5% vs. cisplatin without STS group, 4.7%) and vomiting (cisplatin with STS arm, 6.8% vs. cisplatin without STS group, 4.7%) were much lower than those observed in SIOPEL 6; however, most events were Grade 3 or higher and 2 SAEs of nausea and 1 SAE of vomiting were reported in the cisplatin with STS arm. These differences between the trial was '*explained by the proactive collection of data on nausea and vomiting in the SIOPEL 6 CRF*.'[34]

Table 21: Summary of most common Grade 3 severity or higher AEs (frequency of ≥ 10% in either arm) - COG ACCL0431 safety population (reproduced with minor changes from CS, Table 26)

Preferred term	Cisplatin without STS (N=64) n (%)	Cisplatin with STS (N=59) n (%)	Total (N=123) n (%)
Any Grade 3 severity or higher AE	57 (89.1)	55 (93.2)	112 (91.1)
Investigations	57 (89.1)	54 (91.5)	111 (90.2)
Neutrophil count decreased	53 (82.8)	49 (83.1)	102 (82.9)
White blood cell count decreased	42 (65.6)	38 (64.4)	80 (65.0)
Platelet count decreased	39 (60.9)	38 (64.4)	77 (62.6)
Alanine aminotransferase increased	9 (14.1)	10 (16.9)	19 (15.4)
Lymphocyte count decreased	9 (14.1)	6 (10.2)	15 (12.2)
Blood and lymphatic system disorders	38 (59.4)	32 (54.2)	70 (56.9)
Anaemia	36 (56.3)	30 (50.8)	66 (53.7)
Febrile neutropenia	19 (29.7)	14 (23.7)	33 (26.8)
Metabolism and nutrition disorders	22 (34.4)	29 (49.2)	51 (41.5)
Hypokalaemia	13 (20.3)	16 (27.1)	29 (23.6)
Hypophosphatemia	7 (10.9)	12 (20.3)	19 (15.4)
Hyponatremia	4 (6.3)	7 (11.9)	11 (8.9)
Gastrointestinal disorders	8 (12.5)	12 (20.3)	20 (16.3)
Stomatitis	4 (6.3)	8 (13.6)	12 (9.8)

AE - adverse event; CS - company submission; STS – anhydrous sodium thiosulfate.

In COG ACCL0431, SAEs were only recorded for patients in the cisplatin with STS arm (21 children, 35.6%). The most common SAEs were febrile neutropenia (12 children, 20.3%), neutrophil count decreased (10 children, 16.9%), platelet count decreased and white blood cell count decreased (both eight children, 13.6%), and anaemia (seven children, 11.9%). A total of six children (10.2%) experienced SAEs that were determined to be related to STS. These were related to blood and lymphatic system disorders, investigations, and gastrointestinal.

The COG ACCL0431 trial did not specifically report discontinuations due to AEs; however, one patient in the cisplatin with STS arm discontinued due to reasons related to a Grade 2 hypersensitivity reaction (considered definitely related to STS),[34] and an additional four children discontinued STS in close proximity to an AE occurring but not specifically due to an AE (considered probably related to STS).[34]

In total, 30 deaths occurred in COG ACCL0431 (18 deaths in the cisplatin with STS arm and 12 deaths in the cisplatin without STS arm). The majority of deaths were due underlying disease and no deaths were considered related to STS.[29]

3.4 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

No indirect comparison was undertaken by the company to supplement the direct evidence as there are two trials that have evaluated the use of cisplatin plus STS compared with cisplatin-containing therapies for preventing ototoxicity in people aged 1 month to 17 years with localised solid tumours. The EAG agreed with this position.

3.5 Critique of the indirect comparison and/or multiple treatment comparison

No indirect comparison was undertaken by the company (see Section 3.3).

3.6 Additional work on clinical effectiveness undertaken by the EAG

As the company undertook a reasonably comprehensive SLR (no major limitations were noted) of STS for the prevention of cisplatin-induced ototoxicity in paediatric patients, no additional work was undertaken by the EAG.

3.7 Conclusions of the clinical effectiveness section

3.7.1 Completeness of the CS with regard to relevant clinical studies and relevant data within those studies

The clinical evidence in the CS is based on an SLR of STS for the prevention of cisplatin-induced ototoxicity in paediatric patients. The EAG is confident that all relevant controlled trials (published and unpublished) were included in the CS, including data from ongoing/planned studies. However, the EAG

is not entirely confident that all relevant non-controlled studies have been identified and whether any attempt was made by the company to contact authors to request potential additional unpublished data. Therefore, it is not entirely clear if all relevant data have been included in the CS.

3.7.2 Interpretation of treatment effects reported in the CS in relation to relevant population, interventions, comparator and outcomes

Although both studies (SIOPEL 6[30] and COG ACCL0431[31]) were open-label, multicentre, randomised, controlled studies evaluating the otoprotective effect of STS, the studies primarily differed with regard to patient population, cisplatin and STS dosing, and assessment of the primary efficacy endpoint.

The patient population in the SIOPEL 6 trial[30] comprised a homogeneous patient population of children with a localised tumour type (standard risk hepatoblastoma; mean age was 18.5 months). In contrast, the COG ACCL0431 included heterogeneous patient population with localised and disseminated disease with various tumour types (mean age was 9.2 years) that relates to a broader population than that reflected in the licensed application (localised, non-metastatic disease).[15]

In both studies, STS was administered via by a 15-minute IV infusion 6 hours after the completion of each cisplatin infusion. In the SIOPEL 6 trial,[30] participants received a mean cumulative STS dose of 85.15 g/m^2, whereas in the COG ACCL0431[31] study the mean cumulative STS dose was 108.23 g/m^2.[15] Differences in cumulative dose of cisplatin were also observed. For example, as stated in the EMA assessment report,[29] *"In SIOPEL 6, the mean cumulative cisplatin dose was similar between arms in patients under 10kg (297.986 mg/m^2 vs 296.608 mg/m^2, respectively) but higher in patients over 10kg in [cisplatin] + STS arm compared to [cisplatin] arm (464.716 mg/m^2 vs 437.619 mg/m^2, respectively). In COG ACCL0431 study, mean cumulative [cisplatin] dose was higher in observation arm compared to CIS + STS arms (391 vs 337 mg/m² respectively) due to various tumours treated."* The company's clarification response[7] (question B13) also provides data on the mean cumulative dose of cisplatin by treatment arm in COG ACCL0431 (localised only: [redacted] vs [redacted] mg/m²; p=[redacted], respectively), SIOPEL 6 (363.86 vs 362.85 mg/m²; p=[redacted], and the pooled analysis (localised only: [redacted] vs [redacted]; p=[redacted]) and shows that there are no statistically significant differences (p<0.05) between the treatment arms.

For the assessment of the primary endpoint different hearing loss grading scales were used in both studies: the ASHA scale was used in COG ACCL0431[31] and the Brock scale was used in SIOPEL 6.[30] As noted in the CS[1] (Section B.2.12,), the ASHA criteria do not assess the severity of the acquired hearing loss, only whether the patient's hearing levels meet a certain threshold, whereas the Brock scale is used to describe severity of the hearing loss and indicates the degree of expected disability. Acknowledging these differences, Clemens *et al*.[35] studied the concordance between ototoxicity grading

scales (including Brock, SIOP, Muenster and Chang scales) and concluded that there was generally good concordance between the ototoxicity grading scales; however, there was diversity in the severity definition and intermediate grades. Similarly, a recent re-evaluation of hearing outcomes in the COG ACCL0431 trial using the SIOP scale at the end of cisplatin therapy revealed a lower incidence of Grade ≥2 cisplatin-induced hearing loss in the cisplatin with STS arm compared with cisplatin without STS arm (see section 3.3.4.3). As such, careful consideration is needed in the type of hearing assessment and ototoxicity grading scale used when interpreting the incidence of hearing loss in studies.[36] Moreover, as the Brock grades use a cut-off of 40 dB HL, it is less sensitive to early ototoxicity and does not detect mild hearing loss that is communicatively and educationally important for developing children and adolescents.[37] In addition, the US FDA assessment review[34] states that *"Since the presence of normal hearing was not an inclusion criteria in this [SIOPEL 6] trial, the lack of baseline data contributes to uncertainty about whether a patient with an abnormal grade on the Brock scale at the end of the study, developed this abnormality during the study or had this abnormality at baseline. The presence of baseline hearing loss in some patients could confound the study results."* In their response to clarification question A19,[7] the company acknowledged, based on audiologists feedback in 2018 (n=10 from the USA [n=5] and UK [n=5]; no further details provided) that there is wide variability in the use of ototoxicity scales, with the ASHA scale being commonly used in the USA and the Brock ototoxicity grading scale commonly used in UK clinical practice for grading cisplatin-induced hearing loss. The company's clarification response[7] also states that the *"Great Ormond Street Hospital (GOSH) has been the leading centre in paediatric ototoxicity in the UK and use both the Brock and SIOP ototoxicity grading scales."*

3.7.3 Uncertainties surrounding the reliability of the clinical effectiveness

The main uncertainties in the clinical evidence, as noted in the CS, primarily relate to the small sample sizes in the SIOPEL 6 (n=114) and COG ACCL0431 (n=125) trials and the use of different hearing loss grading scales in both studies (as discussed in section 3.7.2 earlier). As such, the exact magnitude of observed benefit on outcomes or potential risk is unclear. In addition, there is no data available from these trials to inform on HRQoL or qualitative data from patients or carers who have experienced concurrent STS/cisplatin emetogenesis.[38]

Given the complex regimen of administration and the need to observe accurate timing of STS administration relative to cisplatin chemotherapy (i.e., a 15-minute intravenous STS infusion 6 hours after the completion of each cisplatin infusion), the EMA assessment report[29] raises concerns that the main potential risk associated with STS use is its interaction with cisplatin that could possibly lead to reduced effectiveness of cisplatin. The company's response to clarification question A22[7] states that: *"It is acknowledged, that the timing of Pedmarqsi administration is critical and this has the potential for errors which may impact efficacy. However clear labelling is provided in the SmPC and in the*

instructions for use included in the healthcare HCP section of the Patient Information Leaflet, to ensure that a gap of six hours is implemented between the end of Pedmarqsi infusion and the next cisplatin infusion." In addition, the EMA assessment report,[29] states *"that the exact mechanism of STS in preventing hearing loss remains unknown. Furthermore, the pharmacokinetic profile of STS has not been fully characterised and dose finding studies have not been conducted. The lack of such data is an important limitation".*

The generalisability of the results from both trials to clinical practice in England is also unclear. The COG ACCL0431 trial was conducted in North America in patients with various tumour types (localised and disseminated disease), whereas the SIOPEL study was conducted in patients with standard risk hepatoblastoma (localised disease) across 47 European centres including 14 from the UK. However, as suggested in the company's clarification response[7] (questions A14 and A19), both trials were considered by the company to be generalisable to cisplatin-treated paediatric localised cancers across England and Wales e.g. range of tumour types, cisplatin regimens/doses and timing of STS administration relative to the cisplatin infusion.

4 COST EFFECTIVENESS

This section presents a summary and critique of the company's health economic analyses of STS for the prevention of ototoxicity in children aged 1 month to 17 years with localised solid tumours treated with cisplatin-containing chemotherapy. Section 4.1 describes and critiques the company's review of existing economic evaluations. Section 4.2 describes the company's economic model and summarises the company's results. Sections 4.3 and 4.4 present the EAG's critical appraisal of the company's economic model and the additional exploratory analyses undertaken by the EAG, respectively. Section 4.5 presents a discussion of the company's economic analysis.

4.1 EAG's comment on company's review of cost-effectiveness evidence

The company conducted three systematic literature searches to identify published studies on: (i) cost-effectiveness of interventions for the prevention/management of patients with acquired hearing loss (CS, Appendix G); (ii) cost and resource use (CS, Appendix I), and (iii) HRQoL (CS, Appendix H).[1] The EAG's main focus in this section is the review of the published economic evaluations.

4.1.1 Summary and critique of the company's searches

The strategies for the identification and selection of relevant studies as part of the SLR for economic evaluation evidence are presented in CS Appendices G, H and I. The population of interest for economic evaluations was expanded to encompass acquired hearing loss in all age groups, with justification for this decision provided in Section G.1.1.1 of the CS Appendices.[1]

Searches of relevant bibliographic databases were performed on 25th October 2023. A range of relevant databases (Embase; MEDLINE; CRD HTA Database; CRD NHS Economic Evaluation Database EED; Sheffield Centre for Health and Related Research Health Utilities Database [ScHARRHUD]; EuroQol database; CENTRAL on the Cochrane Library) were systematically searched with the notable omission of EconLit, which could have yielded additional relevant results. This was supplemented by searches of Google Scholar, relevant trial registries and websites (ICTRP; the Tufts Medical Center Cost-Effectiveness Analysis (CEA) Registry; NICE; Research Papers in Economics; EQ-5D; CENTRAL; clinicaltrials.gov; WHO websites) and HTA body websites for the UK (NICE, Scottish Medicines Consortium, All Wales Medicines Strategy Group). As with the clinical effectiveness SLR, there is inconsistency in the CS reporting in that the search strategy outline stated that Embase was searched using Embase.com and MEDLINE was searched using PubMed (Section G.1.1), but the search strategy provided in CS Appendix G, Table 7 shows that one search strategy was used to search Embase.com for multiple databases (Embase, MEDLINE, CRD HTA and NHS EED). It is also unclear what strategy was used to search Google Scholar systematically for relevant evidence.

As mentioned with the clinical effectiveness SLR (see Section 3.1.1), the EAG advises that it is optimal to search each database with a strategy that incorporates the most appropriate subject headings for each individual database's index or thesaurus (most notably Emtree for Embase and MeSH for MEDLINE). Similarly, whilst the company has chosen appropriate and validated study design search filters for economic evaluations and HRQoL evidence (as confirmed in clarification response,[7] question A6 as being sourced from SIGN[39] and Arber *et al*.,[40] respectively), these filters are best used in the form adapted for each individual database. In this case, using a filter designed for Embase in a search on multiple databases risks missing potentially relevant evidence from MEDLINE or the other databases which index study types in a different way.

Overall, two search strategies have been reproduced in the CS:[1] Appendix G, Table 7 shows the search performed on Embase.com described above; Appendix G, Table 8 shows the search performed on CENTRAL. Neither of these tables report the search results line by line as is preferred for transparent reporting. CS Appendices H and I refer back to these search strategies. According to the PRISMA diagrams shown in CS Appendices Figure 2, Figure 3 and Figure 4, one search was performed on each platform and the results were then screened for three different topics: cost-effectiveness (Appendix G); HRQoL (Appendix H); and cost and health care resource identification, measurement and valuation (Appendix I).

According to the CS, the Centre for Reviews and Dissemination (CRD) HTA Database was searched. The EAG recommends searching the more up-to-date source, the International Network of Agencies for Health Technology Assessment (INAHTA) database. The company's clarification response[7] (question A9) stated that the company conducted a search of this platform on 23rd May 2024 to ensure comprehensiveness of coverage. This identified 11 results, none of which were eligible for inclusion against the criteria in the economic evaluation SLRs (full results and reasons for exclusion were given in Appendix Table 1 of the clarification letter).

As with the clinical SLR searches, for both the Embase.com search and the Cochrane Library search, a date limit of post-1978 was applied for searches with the reasonable justification that cisplatin was not used as part of chemotherapy until 1978.

Overall, there is a similar concern to that of the search strategy for the clinical SLR in conducting a combined search of multiple databases on one platform without tailoring the approach, especially to the use of subject headings and filters, as this approach risks missing results from the database(s) where the platform is left to map headings onto the different indexes with unpredictable results. The EAG also notes that the review did not include any previous NICE appraisal reports; however, previous NICE technology appraisals (TAs) and health technology evaluation (HTE) are used to inform the model.

4.1.2 Inclusion and exclusion criteria used in the study selection

The CS[1] states that the three SLRs were targeted at a broader population than the one defined in the final NICE scope[18] or in the marketing authorisation for STS. The population inclusion criteria comprised patients of all age groups with any acquired hearing loss (besides cisplatin-induced hearing loss), with the justification that these studies may be relevant to the target population and due to the lack of evidence in the specific population included in the licence. The company also noted that the population criteria were expanded further in the searches for economic evidence in grey literature to include patients with hearing loss of all causes (CS, Appendix G[1]).

For the review of economic evaluations, the outcomes of interest were defined as 'cost-effectiveness results such as ICER and QALYs', 'cost-utility results', 'cost-minimisation results' and 'cost-benefit results', without providing more details on other specific outcomes of interest from these types of studies, such as total and incremental costs and life-years gained (LYs). No restrictions were placed on the interventions or comparators. Studies were restricted to those published in English, and restrictions were placed at the searching stage for studies published between 1978 and 2023.

4.1.3 Summary and critique of company's review of existing economic evaluations

The CS states that the review of existing economic evaluations identified 4,161 citations, of which 13 cost-effectiveness studies in the prevention/management of acquired hearing loss were included (CS, Appendix G,[1] page 23). A summary of the ten full papers and three conference abstracts is provided in CS, Section B.3.1, Table 27 and CS Appendix G, Table 10. None of the included studies evaluated STS. Only two studies included children as part of their population,[41, 42] whilst another two studies are unclear about the population age included.[43, 44] Four studies reported on cost-effectiveness studies in a UK setting.[41, 44-46] None of the studies specifically stated that they included patients with drug-induced hearing loss. The types and severity levels of hearing loss included in the studies varied greatly, from mild to profound hearing loss.

Eleven studies evaluated some type of hearing implants (e.g., cochlear, bone conduction, or other type) or aids, whilst one study evaluated grommet insertion versus hearing aids in patients with otitis media,[41] and one study evaluated hypothetical novel regenerative hearing therapeutics in age-related hearing loss.[46]

The EAG agrees that expanding the population criteria in the review for economic studies to other forms of acquired hearing loss could have been beneficial in terms of identifying models applicable in the paediatric and adult settings. However, the review still retrieved a limited number of studies, and none of the identified studies directly relate to the population included in the decision problem for this appraisal. The EAG also notes that because of this expansion of the scope of the SLR, at least one of

the included studies relates to age-related hearing loss. Studies of this type of hearing loss are not particularly relevant to the current decision problem which relates to hearing loss acquired in children/adolescents.

Table 27 of the CS[1] indicates that the majority of previous studies included in the SLR have adopted a state transition (Markov) modelling approach,[42, 45-51] with three studies adopting a decision-analytic (decision-tree) structure.[41, 44, 52] The structure of one study was not clearly reported in the CS; however, the EAG was able to identify that it corresponded to a within-trial analysis,[53] whilst a further study was described as using 'influence diagrams and Monte Carlo simulations', but the EAG was unable to verify the approach adopted.[43] The CS does not report the definitions of health states used within the included state transition models. Where reported, the cycle length in the included studies varied from three months to one year, whilst the time horizons adopted varied from 24 months to lifetime.

The EAG notes that the quality assessment of only ten studies using the Drummond and Jefferson checklist is presented in CS Appendix G.2.3, Table 12.[1] At the FAC stage, the company clarified that the three remaining studies (Kiesewetter *et al.*[42, 44] and Hoch *et al.*)[52] correspond to the three conference abstracts included in the review, and therefore do not provide sufficient information for a full quality assessment. Furthermore, no consideration of the overall quality assessment of the 13 included studies is presented or discussed in the CS. Despite this discrepancy, the EAG is unaware of any relevant published economic evaluations which have been missed by the company's review.

4.2 Summary of the company's submitted economic evaluation

This section provides a detailed description of the methods and results of the company's health economic analysis. Following the clarification process, the company submitted a revised version of the economic model which included updated estimates of the cost-effectiveness of STS versus ECM in children aged ≥1 month to <18 years with cisplatin therapy-induced hearing loss. The updated model includes the correction of minor errors identified by the EAG in the company's original model which related to the implementation of formulae and the inclusion of elective stays in the costs of some AEs, the inclusion of the most recent life tables and the inclusion of the costs of antiemetics.[7] For brevity, this report describes the methods and results of the updated model.

4.2.1 Scope of the company's economic analysis

As part of their submission to NICE,[1] the company submitted an executable model programmed in Microsoft Excel.® The company's base case analysis compares STS versus ECM for cisplatin-treated patients aged ≥1 month to <18 years of age with localised, non-metastatic, solid tumours. The scope of the economic analysis is summarised in Table 22.

Table 22: Scope of the company's economic analyses

Population	Patients aged ≥1 month to < 18 years with localised, non-metastatic, solid tumours having cisplatin-containing chemotherapy
Time horizon	Lifetime
Intervention	Anhydrous sodium thiosulfate (Pedmarqsi™)
Comparator	Established clinical management without STS
Type of economic analysis	Cost-utility analysis
Outcome	Incremental cost per QALY gained
Perspective	NHS and PSS
Discount rate	3.5% per annum (1.5% for QALYs and costs explored in scenario analyses)
Price year	2021/2022 (except for drugs which are valued at 2024 prices)

NHS - National Health Service; PSS - Personal Social Services; QALY - quality-adjusted life year; STS - sodium thiosulfate

The economic analysis was undertaken from the perspective of the NHS and Personal Social Services (PSS) over a lifetime time horizon ([redacted] years). The model assesses the cost-effectiveness of STS versus ECM in terms of the incremental cost per QALY gained. Unit costs are valued at 2021/22 prices, except for drug acquisition costs which are valued at 2024 prices. Health outcomes and costs are discounted at a rate of 3.5% per annum in the base case analysis, with an alternative rate of 1.5% being explored as part of the company's scenario analyses (see Section 4.2.5).

Population

The population reflected in the company's economic model is based largely on the characteristics of the localised disease subgroup within the ITT population in the COG ACCL0431 trial. At model entry, patients are assumed to have a mean age of [redacted] years, mean weight of [redacted] kg, and [redacted]% were male.

In response to clarification question A14(a) regarding the generalisability of the regimens received by patients in COG ACCL0431 (conducted in North America) and SIOPEL 6 trials, the company stated that the chemotherapy regimens received in these trials were administered according to the sites' disease-specific cancer treatment protocols in use at the time of the study, and that *"cancer treatment protocols in paediatrics are determined by collaborative groups who share information globally due to the challenges of conducting research in this area"*, and for that reason the cisplatin and STS regimens and dosage are expected to reflect UK clinical practice.[7] The company also highlighted that the range of paediatric cancer types included in COG ACCL0431 is in line with the distribution observed in England and Wales for cisplatin-treated paediatric localised cancers,[17] and that SIOPEL 6 included 14 centres from the UK.

Interventions and comparators

The intervention evaluated within the economic analyses is anhydrous STS (Pedmarqsi) administered via IV infusion at 6 hours after each cisplatin-containing regimen received as part of patients' active

oncological therapy. This is in line with the SmPC for anhydrous STS and the final NICE scope.[15, 18] Within the base case, STS is assumed to be administered at a dose of 10.2 g/m^2 (or 341 mg/kg in younger or smaller children whose therapeutic protocol was on a per kg basis), in line with treatment schedule in COG ACCL0431.[1] The model does not include an explicit treatment discontinuation rule or maximum treatment duration, and drug acquisition costs are calculated independently of patients' health state. Treatment duration for patients receiving anhydrous STS is based on treatment exposure data from patients with localised disease in the anhydrous STS plus cisplatin (STS+CIS) treatment arm of COG ACCL0431.[1] Patients are assumed not to receive any further therapies to prevent ototoxicity after stopping treatment with STS or cisplatin. A scenario analysis using the treatment schedule and mean treatment duration data from SIOPEL 6 is presented by the company (see Section 4.2.5).

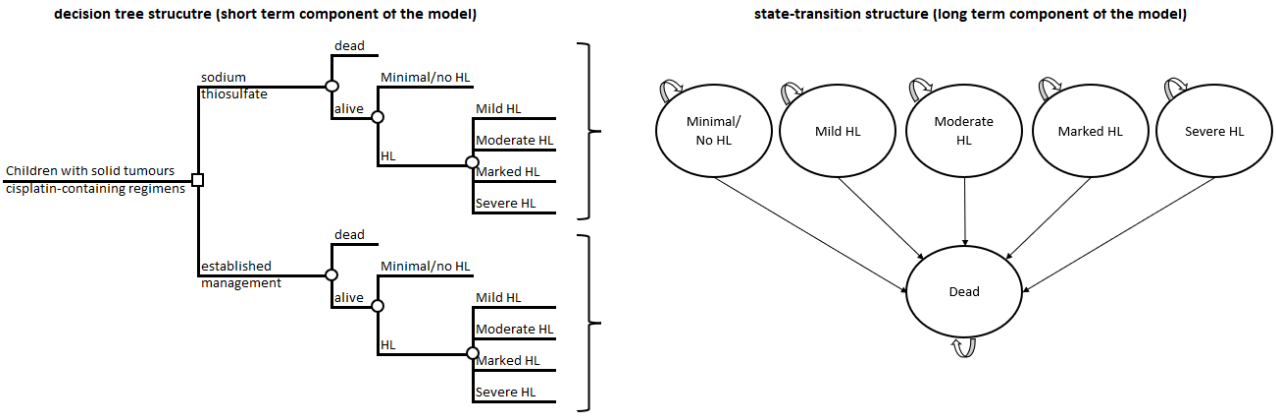
The company's analyses include ECM without STS as the comparator, which relates to patients receiving cisplatin-containing regimens as part of their active oncological therapy but no active therapy to prevent ototoxicity. The EAG notes, however, that details about dosage and treatment duration for the cisplatin regimens are not provided in the company's original model and CS, with the justification that *"the cost of cisplatin is not considered in the model on the basis that it is equal between each treatment arm"* (CS,[1] page 94). Following a request for clarification from the EAG (clarification response,[7] questions A14(a) and B13), the company shared an indirect assessment of the chemotherapy treatment protocols received in COG ACCL0431 based on frequency of cisplatin dosing, and data on the mean cumulative dose of cisplatin by treatment arm for localised disease patients in COG ACCL0431, SIOPEL 6, and in the pooled analysis. These data are presented later in Section 4.2.4.6.

4.2.2 Model structure

Section B.3.3.1 of the CS[1] describes the general structure of the company's economic model as a combination of a decision tree followed by a state-transition (Markov) model. Within this hybrid structure, the decision tree is used to capture 12-month health outcomes and costs for a cohort of patients from the point at which they start receiving treatment with a cisplatin-containing regimen and STS or cisplatin-containing chemotherapy only. The long-term state transition model structure is based on six health states: (i) minimal/no HL and alive, (ii) mild HL and alive, (iii) moderate HL and alive, (iv) marked HL and alive, (v) severe HL and alive; and (vi) dead (see

Figure 5).

Figure 5: Company's model structure (drawn by the EAG, adapted from CS Figures 8 and 9 and model)



CS - company submission; HL - hearing loss

The model logic operates as follows. All patients enter the decision tree in the minimal/no HL health state and receive treatment with either STS plus cisplatin or cisplatin alone. Health state occupancy as a result of the treatment received during the first year is determined by the combination of efficacy data from COG ACCL0431 and external data[1, 8, 20] (described further in Section 4.1.2.3). The model assumes that after the first year, patients cannot transition between the alive states, and can only transition to the death state. The probability of being alive at any time *t* in the first five years of the model is based on OS data from COG ACCL0431 (localised disease subgroup), and thereafter by applying a standardised mortality ratio (SMR) to the general population risk of death[54, 55] for an assumed period of time of 5 years. After 10 years, mortality risk is governed by life tables without the inclusion of an SMR. Further details on the evidence sources used to derive the risk of mortality are presented in Section 4.1.2.2. The model applies a structural constraint to ensure that the mortality risk for patients with solid tumours must be at least as high as that for the age- and sex-matched general population in England and Wales.[7]

HRQoL is assumed to be determined according to the patient's current health state, including negative impacts associated with the underlying cancer, and positive impacts associated with the receipt of hearing management treatments with cochlear implants. The utility values applied in the base case analysis are derived from external sources and are detailed in Section 4.1.2.5. Health utilities are adjusted by age.

The model includes costs associated with: (i) drug acquisition and administration; (ii) health state resource use for hearing loss management, including hearing assessments, hearing aids, cochlear implants, FM systems, and speech and language therapy; and (iii) treatments for depression and anxiety. These are detailed in Section 4.2.4.6. The company's revised base case analysis presented following the

clarification process also includes the costs of antiemetics that are given before STS administration to avoid nausea and sickness.[7]

The company's base case analysis does not explicitly include any costs or QALY losses associated with AEs - the model only includes the impact of STS treatment-related SAEs and insufficient events of this type were observed in the COG ACCL0431 trial (<2% in either arm). Scenario analyses using alternative sources of AEs are presented by the company (see Section 4.2.5). The company also presented scenario analyses including educational costs and productivity losses for parents and for patients when they reach working age based on a societal perspective. However, these are only briefly discussed in Section 4.2.5 since the inclusion of these costs are outside the NICE Reference Case.[22]

The incremental health gains, costs and cost-effectiveness for STS versus ECM are estimated over a lifetime horizon ([redacted] years in the base-case analysis) using an annual cycle length. In response to clarification question B4,[7] the company justified the choice of cycle length on the basis that cisplatin treatment is typically completed within this period, which is reflected in its mean treatment duration of [redacted] weeks or less in COG ACCL0431, depending on the population and treatment arm considered, and on the majority of costs and outcomes occurring in the first year of the model. The company also states that '*no additional accuracy can be achieved through applying a shorter cycle length.'* The company's model includes half-cycle correction.

4.2.3 Key assumptions employed in the company's model

The company's model employs the following key assumptions:

- The characteristics of patients in the COG ACCL0431 trial (e.g., start age, proportion of males, and mean weight) are assumed to represent those of patients who will potentially receive the treatment with STS in the NHS.
- The modelled comparison of STS versus ECM is assumed to be generalisable to patients between 1 month and 17 years of age who receive treatment containing cisplatin-based chemotherapy for solid tumours and are at risk of hearing loss, and would be eligible to receive STS.
- The model assumes that all ototoxicity effects from cisplatin-containing chemotherapy occur and are diagnosed within the first year after starting treatment.
- Treatment costs for STS are estimated from the mean treatment cumulative dose and number of visits/administrations per patient reported in COG ACCL0431 or SIOPEL 6 trials (base case and scenario analysis, respectively); the model implicitly assumes that these estimates already capture treatment discontinuation or dose suspensions/reductions which occurred in the trials.

- Treatment costs for cisplatin-containing chemotherapy regimens are assumed to be equivalent between treatment groups, and were therefore excluded from the model.
- Treatment with STS is assumed to have no impact on mortality; hence, the same mortality risk is applied to both treatment groups at any time *t*.
- In the first 5 years of the model, mortality risk is derived from OS data directly observed in the subgroup of patients with localised disease in COG ACCL0431 (base case analysis) and from the ITT population in SIOPEL 6 (scenario analysis). From years 6 to 10, OS for patients in both treatment groups is modelled by applying an SMR to general population life tables for England and Wales. After this 10-year timepoint, surviving patients are assumed to be "cured", irrespective of their treatment group and health state occupancy, and their subsequent mortality risk is assumed to be equivalent to that of the age- and sex-matched general population.
- The model includes a constraint to ensure that the modelled risk of death at any time *t* is at least as high as that for the general population in England and Wales.
- HRQoL is determined by the presence or absence of hearing loss and the severity level of hearing loss, and is assumed to be independent of treatment group. The use of cochlear implants by a proportion of patients in the marked and severe HL health states is associated with an HRQoL gain which is applied in every cycle of the model. Utility values are age-adjusted by age- and sex-matched general population values.
- Prior to the 10-year cure timepoint, HRQoL for patients in the model is assumed to include a disutility associated with their underlying cancer. After this period, patients are assumed to return to have a similar level of HRQoL to the general population who experience hearing loss, dependent on the hearing loss severity.
- In the base case analysis, the model assumes no vial sharing and full drug wastage is included in the estimates of drug cost. Other scenarios for drug wastage are explored in scenario analyses.
- The model includes annual costs associated with disease management which include long-term follow-up and monitoring of the hearing loss condition, and the use of different assistive technologies. These are assumed to be independent of treatment group but dependent on the patients' health state and/or age.
- All patients with any level of hearing loss are assumed to receive an FM system. In addition, half of all patients in the mild HL state are assumed to receive a hearing aid, whilst all patients in the moderate to severe states are assumed to receive either a hearing aid or a cochlear implant (proportions detailed in Section 4.2.4.6). All patients receiving these are assumed to receive two hearing aids or a bilateral cochlear implant.
- Only patients in the marked and severe HL states are assumed to receive speech and language sessions during their infancy, and only patients with severe HL still receive these at a lower frequency when adults.

- The model assumes that the same proportion of patients in the mild to severe HL states have depression and anxiety, with a comparatively lower proportion of patients affected in the minimal/no HL state.
- The model assumes that only treatment-related SAEs impact on additional costs and QALY losses related to AEs. However, because this type of event did not occur in 2% or more of patients in COG ACCL0431, these impacts are not included in the base case analysis.

4.2.4 Evidence used to inform the company's model parameters

The sources of evidence used to inform the company's model parameters are summarised in Table 23. These are discussed in detail in the subsequent sections.

Table 23: Summary of evidence used to inform the company's updated base case model

Parameter group	Parameter	Source
Patient characteristics	Age, proportion of males, weight, and age distribution	Based on characteristics of participants in the ITT population from the COG ACCL0431 trial (localised disease subgroup, clarification response questions B1 and B2)[1, 7]
Mortality	OS estimates for first 5 years	KM estimates of OS from localised disease subgroup in COG ACCL0431 (both treatment arms) used directly for both treatment groups[1]
	SMR (years 5-10)	Fidler *et al*.[54]
	General population mortality	National life tables for England and Wales (2020-22)[55]
Treatment efficacy	HL occurrence	COG ACCL0431 trial (overall efficacy population)[19]
	HL severity level	Orgel *et al.*[20] combined with Knight *et al.*[8]
HRQoL	Health state utility values	Treatment-independent utilities for alive health states based on Barton *et al.*,[56] Pogany *et al.*[57] and assumptions; utility decrements for cancer based on Chen *et al.*;[58] utility gains for use of cochlear implants taken from Barton *et al.*[56] and proportion of patients receiving them from audiologist market research report.[59] Scenario analysis explored the use of values from Gumbie *et al.*,[47] and the addition to the inclusion of the utility gains for hearing aids from Grutters *et al.*[60]
	Age adjustment	UK population norms from Hernandez Alava *et al*.[61]
AEs	AE frequencies	SAEs reported by ≥2% of patients in either arm of the COG ACCL0431 trial.[19] Scenario analysis explored use of SAEs reported by ≥2% of patients in SIOPEL 6,[16] use of Grade 3+ AEs reported by ≥10% of patients in the COG ACCL0431 trial,[1] and Grade 3+ in ≥5% of patients AEs for the localised disease subgroup of patients in COG ACCL0431 and in the pooled analysis with both trials.[7]
	AE disutilities and durations	Previous NICE appraisals,[62-66] other literature[45, 67-81] and clinical management websites.[82-84]

Drug acquisition costs	STS	Unit costs from the company; treatment schedule and mean duration from the COG ACCL0431 trial (subgroup population with localised disease only).[1]
	Cisplatin-containing chemotherapy	Not included.
	Costs of premedication (antiemetics)	Mean weight, and number of visits from the COG ACCL0431 trial (subgroup population with localised disease only);[1] dosage schedule from COG ACCL0431 protocol and Birmingham children's hospital guideline;[85, 86] unit costs from eMIT.[87]
Drug administration costs	-	Number of administrations from subgroup of localised patients in COG ACCL0431;[1] unit costs from PSSRU 2022[88] and assumptions.
Health state costs	Hearing assessments	Frequency of patients receiving intervention from Dionne *et al.*,[89] and audiologist expert opinion;[59] unit costs from NHS Reference Costs 2021/22[90] and age distribution of patients from COG ACCL0431.[19]
	Hearing aids	Proportion of patients receiving device from audiologist expert opinion[59] and assumption from NICE TA566;[91] unit costs from NHS Reference Costs 2021/22;[90] frequency of device replacement from Dionne *et al.*[89]
	Cochlear implant	Proportion of patients receiving implants from Chorozoglou *et al.;*[92]; unit costs from NHS Reference Costs 2021/22,[90] Cutler *et al.*,[45] Bond *et al.*[93] and NICE TA566.[91] Probability and frequency of device component replacement from Bond *et al.*[93] and NHS England Cochlear Implant Services.[94]
	FM systems	Proportion of patients receiving device from assumption based on clinical expert opinion;[59] frequency of replacement and unit costs taken from Dionne *et al.*,[89] costs converted to GBP and uplifted using the OECD PPP[95] index and OECD CPIs.[96]
	Speech and language therapy	Frequency of therapy visits based on Dionne *et al*.[89] and Smulders *et al.,*[97] unit costs from NHS Reference Costs 2021/22.[90]
	Depression and anxiety	Proportion of patients experiencing depression with or without HL from Gurney *et al*.[98]; unit costs from NICE resource impact statement,[99] uplifted to 2022 using NHSCII.[88]
AE management costs	-	Unit costs from NHS Reference Costs 2021/22,[90] eMIT,[87] previous NICE TAs,[65, 100] other literature,[70, 71, 74, 101-104] and assumptions

AE - adverse event; CPI - Consumer Price Index; eMIT - electronic Market Information Tool; HL - hearing loss; HRQoL - health-related quality of life; ITT - intention-to-treat; KM - Kaplan-Meier; NHSCII - NHS Cost Inflation Index; NICE - National Institute for Health and Care Excellence; OECD - Organisation for Economic Co-operation and Development; OS - overall survival; PPP - Purchasing Power Parities; PSSRU - Personal Social Services Research Unit; SAEs - serious adverse events; SMR - standardised mortality ratio; STS - sodium thiosulfate; TA - Technology Appraisal.

4.2.4.1 Patients' baseline characteristics

Patient characteristics are based on the subgroup of patients with localised disease within the ITT population in COG ACCL0431 (see clarification response,[7] questions B1 and B2). At model entry, patients are assumed to have a mean age of [redacted] years, a mean weight of [redacted] kg, and [redacted]% of

patients are assumed to be male.[1] These characteristics are used to determine the start age of the model and the time horizon, the general population mortality risks, the costs of antiemetic drugs, and to adjust utility values for increasing age. The model also includes the distribution of patients by age from the same population group, which is used to estimate the costs of hearing assessments. Details on drug and hearing assessment costs are provided in Section 4.1.2.6.

The EAG notes that although the CS states that the STS dosage is dependent on the patient's weight and BSA, these characteristics are not used for this purpose in the model. Instead, the model uses observed estimates of the mean dosage and the mean number of visits per patient to estimate drug costs (see Section 4.2.4.6).

4.2.4.2 Mortality

The model assumes that treatment with STS does not impact on OS; therefore, the same mortality risks are applied to both treatment groups. The company uses three separate approaches to estimate mortality risks over time. In the first five years of the modelled time horizon, KM estimates of OS from the subgroup of patients with localised disease in the COG ACCL0431 trial are used directly for both treatment groups; alternative estimates based on the SIOPEL 6 ITT population are explored in scenario analyses (see Table 24). The EAG notes that although the company's clarification response includes estimates of OS from the pooled analysis of data for localised patients in both trials, these were not included in the updated version of the model;[7] these are also shown in Table 24 for completeness.

Table 24: Company's survival estimates used in the model for years 1 to 5 (adapted from CS, Table 36 and clarification response, question A13 and additional data for pooled analysis with localised disease subgroup)

Year	Base-case (COG ACCL0431 – localised disease patients subgroup)	Scenario analysis (SIOPEL 6 ITT population)	Pooled analysis (localised disease patients, COG ACCL0431 and SIOPEL 6)*
1	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]

CS - Company's submission; ITT - intention-to-treat
** Presented in clarification response but not included in updated version of the model submitted*

In years 6 to 10, an increased risk of death related to the underlying cancer is modelled by applying a SMR of 9.1 to general population life tables for England and Wales (2020-22). The SMR estimate was sourced from Fidler *et al.*,[54] a population-based cohort study with 34,489 five year survivors from the British Childhood Cancer Survivor Study diagnosed with paediatric cancer under the age of 15 years from 1940 to 2006 in Britain which investigated the risk of late cause specific mortality after treatment.

After 10 years, patients are assumed to experience the same age- and sex-matched mortality risks as the general population, which corresponds to an implicit assumption of cure. The company justifies the application of a cure time point based on previous TAs in paediatric oncology indications (TA538).[1, 105] The company also mentions the same approach being preferred by the Appraisal Committee in a previous appraisal of adjuvant nivolumab for the treatment of invasive urothelial cancer at high risk of recurrence (TA817);[106] however, the EAG is unclear about the relevance of this appraisal to the population of interest of the current appraisal. This point is discussed in detail in Section 4.3.3.

4.2.4.3 Treatment efficacy

Treatment efficacy is captured using a piecewise approach in the 1-year decision tree model, based on: (i) the probability of developing hearing loss estimated from the overall efficacy population in the COG ACCL0431 trial;[19] and (ii) the probabilities of developing one of the four HL severity levels, based on combined data from studies reported by Orgel *et al.*[20] and Knight *et al.*[8] Orgel *et al.*[20] corresponds to a post-hoc analysis of the COG ACCL0431 trial data which re-evaluated its results for hearing outcomes using the SIOP ototoxicity scale, whilst Knight *et al*.[8] analysed audiologic data from 67 patients from 8 months to 23 years who received platinum chemotherapy in the US between June 2000 and December 2003 using the ASHA, CTCAE and Brock criteria to evaluate the incidence and severity of ototoxicity. The proportions of patients from the studies and the combined probabilities of transitioning to each of the HL states used in the model are shown in Table 6 and are described in detail below.

As the first step, the company calculated the probability of experiencing hearing loss in each treatment group, using count data from COG ACCL0431, in which the primary outcome is based on ASHA classification (see Section 2.3.4). Subsequently, the company estimated the proportion of patients who experience mild to severe HL by combining the proportion of patients having Grade 1 vs Grade ≥2 from Orgel *et al.*,[20] a reassessment of the COG ACCL0431 trial data using SIOP, and the proportion of patients who experienced Grades 2 to 4 (moderate to profound) from Knight *et al.*[8] based on the Brock system. The observed patient count data describing the proportion of patients in each study with HL occurrence and by HL severity level are presented in Tables 32 and 33 of the CS.

The model assumes that after people complete treatment with cisplatin and STS within the first year, any effects on hearing loss occurrence and severity levels experienced cannot be reverted or worsened, and therefore people cannot transition between the alive health states (minimal/no HL, mild HL, moderate HL, marked HL and severe HL) after the first year. The EAG's clinical advisors highlighted that potential late detection or late effects of hearing loss may be observed after that period. As such, the EAG asked the company to comment on the plausibility of the assumption of no improvement or worsening in HL state in the long-term model (see clarification response,[7] question B5). The company's response clarified that further declines in hearing are possible for a proportion of patients with hearing

loss; however, this was not included in the model due to a lack of robust evidence on the timing and rate of deterioration and an expectation that this would have a limited impact on the results given that the effect would apply to both treatment groups. The company also noted that Weissenstein *et al.*[107] suggest that *"only patients with some degree of hearing loss at the end of treatment are at risk of further deterioration"*, and therefore the inclusion of this impact is likely to have a greater impact in the ECM treatment group than the STS group. In addition, the company's response states that modelling the age-related decline in hearing loss was also considered, but was not included in the company's analyses due to similar challenges relating to lack of data, and because previous NICE appraisals in the area had also excluded these effects (NICE TA566 and HTE6).[91, 108]

Table 25: Proportions of patients experiencing HL and HL severity levels (adapted from CS, Tables 33 and 34, CS, Figure 10, and company's model)

	Base case						Scenario analysis*					
	STS			ECM			STS			ECM		
Model health states	**Proportion of patients with/no HL†**	**Proportion with HL severity levels‡**	**Combined proportion in health states**	**Proportion of patients with/no HL†**	**Proportion with HL severity levels‡**	**Combined proportion in health states**	**Proportion of patients with/no HL†**	**Proportion with HL severity levels‡**	**Combined proportion in health states**	**Proportion of patients with/no HL†**	**Proportion with HL severity levels‡**	**Combined proportion in health states**
Minimal/ No HL	0.7143	-	**0.7143**	0.4364	-	**0.4364**	0.6727	-	**0.6727**	0.3696	-	**0.3696**
Mild HL	0.2857	0.7778	**0.2222**	0.5636	0.4078	**0.2299**	0.3273	0.5556	**0.1818**	0.6304	0.4138	**0.2609**
Moderate HL		0.1806	**0.0516**		0.4812	**0.2712**		0.3333	**0.1091**		0.3793	**0.2391**
Marked HL		0.0139	**0.0040**		0.0370	**0.0209**		0.0556	**0.0182**		0.1724	**0.1087**
Severe HL		0.0278	**0.0079**		0.0740	**0.0417**		0.0556	**0.0182**		0.0345	**0.0217**

ASHA - American Speech-Language-Hearing Association; CS - Company's submission; ECM - established clinical management; HL - hearing loss; SIOP - International Society of Paediatric Oncology; STS - sodium thiosulfate.

** Using data from SIOPEL 6 mITT population for HL occurrence and HL severity levels.*

†Using count data from COG ACCL0431 (using ASHA classification system).

‡Using count data from Orgel et al. (reassessment of COG ACCL0431 using SIOP classification system) combined with Knight et al. (using Brock classification system).

Scenario analyses are presented by the company which use alternative sources for probability of developing hearing loss and for the proportion of patients experiencing each of the hearing loss severity levels such as SIOPEL 6 mITT population, Orgel *et al.* and Knight *et al*. In response to clarification question A19, the company presented the results of scenario analyses which included different combinations of data from these sources:

- COG ACCL0431 trial for HL occurrence, Orgel *et al.* and SIOPEL 6 mITT combined for HL severity;
- COG ACCL0431 trial for HL occurrence, and SIOPEL 6 mITT for HL severity;
- Orgel *et al.* for HL occurrence, Orgel *et al.* and Knight *et al.* combined for HL severity;
- Orgel *et al.* for HL occurrence, Orgel *et al.* and SIOPEL 6 mITT combined for HL severity;
- SIOPEL 6 mITT for HL occurrence and HL severity.

For brevity, only the proportions for the scenario which includes only data from SIOPEL 6 are displayed in Table 6. The results of these scenarios are presented in Section 4.2.7.

With respect to the different grading systems used in the trials and additional studies and their correspondence to the model health states,[7] the company's clarification response acknowledges the differences between thresholds in each classification system; however, it points out that Clemens *et al.*[35] suggest that there is good concordance between some of these scales, including Brock and the SIOP (κ = 0.840), and that Knight *et al.*[109] suggest a comparable sensitivity in detecting ototoxicity between SIOP and ASHA, whilst the sensitivity of the Brock scale would be slightly lower (see clarification response, questions A19 and B3). The company also states that: *"the ASHA criteria are not relevant for defining the severity-based health states in the model, and data from this scale are used once at the beginning of the model to answer the hearing loss yes/no aspect of the decision tree, based on the results of the COG ACCL0431 study."*[7] This issue is discussed in further detail in Section 4.3.3.

4.2.4.4 Treatment safety

Section B.3.4.4 of the CS[1] states that only SAEs considered treatment-related to STS with an incidence of at least 2% of patients in each of the arms of the COG ACCL0431 trial (safety overall population, including patients with metastases) were included in the base case analysis. The company provides the following justification: *"The focus is on Pedmarqsi treatment-related AEs as it is assumed that cisplatin-related AEs will be equal in both arms"*.[1] Because the COG ACCL0431 trial has not reported sufficient events to exceed this threshold, the base case analysis does not include any impacts on costs and QALYs related to the management of AEs. The CS also describes two scenario analyses performed using alternative AE incidence rates, which included:

- SAEs with ≥2% incidence in each of the SIOPEL 6 trial arms (a scenario where all clinical parameters are based on SIOPEL 6 clinical data);
- Grade 3+ AEs with an incidence of at least 10% of patients in each of the arms of COG ACCL0431 trial.

Although not included in the results of the scenario analyses, the model is structured to also allow for the inclusion of Grade 3+ AEs from the SIOPEL 6 trial. Table 26 presents the AE frequencies used in the model for each intervention in the base case and scenario analyses.

The EAG notes that the incidence rates reported in the CS taken from the COG ACCL0431 trial relate to the overall population, and have not been restricted to the subgroup of localised patients. In response to clarification question B24,[7] the company provided additional data on AEs for the localised disease subgroup of patients in COG ACCL0431 and in the pooled analysis requested by the EAG for: Grade 3+ AEs occurring in ≥5% of patients and treatment-related SAEs occurring in ≥2% of patients. The EAG notes that only the incidence for Grade 3+ AEs occurring in ≥5% of patients, which are also reported in Table 26, were included in updated version the model. This issue is discussed in more detail in Section 4.3.3.

Table 26: Adverse events incidence included in the economic model (adapted from CS, Table 44 and company's updated model)*

AE	Base case (COG ACCL0431 overall population, SAEs occurring in ≥ 2% of patients)		Scenario (SIOPEL 6, SAEs occurring in ≥ 2% of patients)†		Scenario (COG ACCL0431 overall population, Grade 3+ AEs occurring in ≥ 10% of patients)		Scenario (SIOPEL 6, Grade 3+ AEs occurring in ≥ 10% of patients)† - not presented in the CS		CR Scenario (COG ACCL0431 localised disease patients, Grade 3+ AEs occurring in ≥ 5% of patients)		CR Scenario (pooled COG and SIOPEL 6 localised disease patients, Grade 3+ AEs occurring in ≥ 5% of patients)	
	STS	ECM	STS	ECM	STS	ECM	STS	ECM	STS	ECM	STS	ECM
Neutrophil count decreased	0.0%	0.0%	3.8%	0.0%	83.1%	82.8%	22.6%	16.1%	[redacted]			
Haemoglobin decreased	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	18.9%	16.1%				
Infection	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	26.4%	26.8%				
Febrile neutropenia	0.0%	0.0%	0.0%	0.0%	23.7%	29.7%	15.1%	16.1%				
WBC count decreased	0.0%	0.0%	0.0%	0.0%	64.4%	65.6%	0.0%	0.0%				
Platelet count decreased	0.0%	0.0%	0.0%	0.0%	64.4%	60.9%	0.0%	0.0%				
ALT increased	0.0%	0.0%	0.0%	0.0%	16.9%	14.1%	0.0%	0.0%				
Lymphocyte count decreased	0.0%	0.0%	0.0%	0.0%	10.2%	14.1%	0.0%	0.0%				
Anaemia	0.0%	0.0%	0.0%	0.0%	50.8%	56.3%	0.0%	0.0%				
Hypokalaemia	0.0%	0.0%	0.0%	0.0%	27.1%	20.3%	0.0%	0.0%				
Hypophosphatemia	0.0%	0.0%	0.0%	0.0%	20.3%	10.9%	0.0%	0.0%				
Hyponatremia	0.0%	0.0%	0.0%	0.0%	11.9%	6.3%	0.0%	0.0%				
Stomatitis	0.0%	0.0%	0.0%	0.0%	13.6%	6.3%	0.0%	0.0%				
AST increased	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%				
GGT increased	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%				
Dehydration	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%				
Hypermagnesaemia	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%				
Hypocalcaemia	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%				
Hypomagnesaemia	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%				
Acidosis	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%				
Device related infection	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%				
Sepsis	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%				
Skin infection	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%				
Upper respiratory tract infection	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%				
Nausea	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%				
Vomiting	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%				
Colitis	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%				
Hypotension	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%				

AE - adverse event; ALT - alanine aminotransferase; AST - Aspartate aminotransferase; CR - clarification response; CS - company submission; ECM - established clinical management; GGT - gamma-glutamyltransferase; STS - sodium thiosulfate; WBC - white blood cell count

**For brevity, the incidence of hypersensitivity and decreased appetite, which had incidence zero across all scenarios, and for acoustic stimulation tests, which was assumed to have zero impact on costs and QALYs are omitted from this table.*

†SIOPEL 6 safety population includes patients with localised disease only

4.2.4.5 Health-related quality of life

The CS (Section B.3.5.1, page 89)[1] reports that HRQoL data were not collected in COG ACCL0431 or SIOPEL 6, and therefore the company undertook an SLR to identify existing HRQoL studies to inform the model. The methods and results of this SLR are reported in CS, Section B.3.5.3, and CS Appendix H. The targeted population and searches were the same as the SLR of economic studies (see Section 4.1); eligibility criteria are reported in CS, Appendix H, Table 13.

The company (CS, Appendix H, page 38 and Figure 3) states that 37 studies were included in the review, with nine studies presenting HRQoL data by hearing loss severity level.[43, 46, 47, 110-115] The EAG notes that an additional study identified by the company[47] also reports data for a specific hearing loss severity level (severe or profound). These studies present data based on the EuroQol 5-Dimension (EQ-5D), health utility index 3 (HUI3), Short-Form Six-Dimension (SF-6D) and other methods to measure HRQoL; however, only three studies included paediatric populations (Gumbie *et al.*, Verkleij *et al.* and Oostenbrink *et al.*).[47, 110, 111] The company reports that two of these studies based their utility estimates on Barton *et al.*,[56] which in turn, was selected by the company as the main source for the heath state utility values used in the model. The utility estimates used in the model are presented in

Table 27; these were based on a combination of sources, which are briefly described below.

The EAG also notes that there is a small discrepancy between CS Section B.3.5.3 and CS Appendix H in the numbers of included studies reported, whereby the CS reports 38 included studies, ten of which contained HRQoL data by hearing loss severity level, whilst the CS Appendix reported these as 37 and nine, respectively. The EAG believes this is a small typo and does not impact on the overall conclusions of the review.

Table 27: Utility values for health states (adapted from CS, Table 38)

	Base-case analysis	Sources	Scenario analysis	Sources
Health state utility estimates				
Minimal/no HL	0.92	Pogany *et al.*[57]	0.92	Pogany *et al.*[57]
Mild HL	0.80	Assumption	0.76	Based on disutilities estimated from utility values reported in Gumbie *et al.*,[47] applied to the estimate for the minimal/no HL state
Moderate HL	0.68	Barton *et al.*[56]	0.60	
Marked HL	0.62		0.54	
Severe HL	0.42		0.48	
Disutility estimates due to cancer				
Disutility due to cancer-related treatment (year 1)	-0.15	Chen *et al.*[58]	-0.15	Chen *et al.*[58]
Disutility due to cancer-related after treatment period (years 2+)	-0.07		-0.07	
Utility gains due to hearing management				
Mild HL	0.00	Barton *et al.*; [56] APEX market research[59]	0.06*	Grutters *et al.*;[60] APEX market research[59]
Moderate HL	0.00		0.12*	
Marked HL	0.01‡		0.12‡*	
Severe HL	0.10†		0.15†*	

CS - Company submission; HL - hearing loss.
‡Includes an utility gain of 0.18 for [redacted] of patients in the marked HL state related to the use of cochlear implants.
†Includes an utility gain of 0.18 for [redacted] of patients in the severe HL state related to the use of cochlear implants.
**Includes an utility gain of 0.12 applied to 50%, 100%, 94% and 48% of patients in the mild, moderate, marked and severe HL health states, respectively*

The utility value for patients who do not experience hearing loss ('minimal/no HL' state) was obtained from Pogany *et al.*,[57] which reports HRQoL using the HUI3 for a Canadian national retrospective cohort study with long-term survivors of cancer diagnosed during childhood and adolescence compared to controls. The company used the utility estimate of 0.92, which corresponds to the mean utility value for the study controls aged 5 to 12 years old. For the 'mild HL' health state, in the absence of data for this state, the company assumed a utility value which corresponds to the midpoint between the estimates for the 'minimal/no HL' and 'moderate HL' states. For the moderate, marked and severe HL states, utility values were taken from Barton *et al.,*[56] with the values corresponding to the reported estimates for 'moderate', 'severe', and the weighted mean of the two 'profound' severity levels, respectively.

The company justifies the choice of Pogany *et al.*[57] to inform the utility value for the 'minimal/no HL' state based on the unavailability of a HUI3 value that reflects the general population utility for the UK, and notes that the value used in the model (utility = 0.92) is similar to the EQ-5D utility value of 0.93 for the youngest age with data available for the UK (clarification response,[7] question B14(c)).

The company also notes that Barton *et al.*[56] reports utility estimates for the different hearing loss severity levels (moderate to profound) using the HUI3 instrument and that general population norms based on

the HUI3 are available for Canada but not the UK. The company also notes that the study included children in the UK with permanent bilateral hearing impairment >40 dB HL in the better hearing ear without detail of the underlying cause, and therefore these values are not specific to oncologic patients. Therefore, the company included an additional QALY loss related to underlying cancer status, which is applied to all alive health states for the first ten years of the model, corresponding to the cure time point described in Section 4.1.2.2. Two different estimates are applied in the model, both based in Chen *et al*:[58] a disutility of -0.15 is applied for the first year, whilst -0.07 is applied for the remaining 9 years. The same estimates are applied in the base case and in all scenario analyses, and correspond to, respectively, HUI3 proxy-report estimates for patients with mixed diagnosis, and HUI3 proxy-reported disutility for patients with retinoblastoma off treatment for 2-5 years, compared to non-cancer general paediatric populations. The EAG is unclear about the company's reasons for choosing these specific estimates.

The model also includes a QALY gain associated with the use of cochlear implants applied to a proportion of patients in the marked and severe HL health states, which is assumed to be accrued for the duration of the patient's remaining lifetime. The utility gain of 0.183 was obtained from Barton *et al.*[56] and corresponds to the health utility gain of children 5 years of age and older with cochlear implants with duration of use longer than 4 years, compared to patients without implants. The proportion of patients in the marked and severe HL states were obtained from consultation with specialists in managing ototoxicity in paediatric cancer patients from an audiologist market research report produced by a consultancy company.[59]

Utility values are adjusted using the age- and sex-matched EQ-5D-3L utility values for the UK general population from Hernandez Alava *et al.*[61] using a multiplicative approach. The EAG notes that two limitations of the approach used by the company are the unnavailability of EQ-5D-3L estimates for patients younger than 16 years old, which led to the assumption that in fact age adjustment starts from age 16, and that there are no values available for the UK general population using the HUI3. The use of a multiplicative approach for the age adjustment may reduce some of these limitations, and constitute the approach recommended in the NICE guidelines.[22]

The CS includes a scenario analysis which explores the use of alternative health state utilities based on estimates from Gumbie *et al.,*[47] in addition to the inclusion of the utility gains for hearing aids of 0.12 from Grutters *et al.,*[60] applied to 50%, 100%, 94% and 48% of patients in the mild, moderate, marked and severe HL health states, respectively (see Section 4.2.5).

QALY losses due to AEs

The model structure includes a once-only QALY loss associated with AEs at the first cycle. However, since the frequency data for the base case analysis was based on treatment-related SAEs occurring in ≥2% of patients in safety overall population of COG ACCL0431 (see Section 4.1.2.4), the base case model does not include any QALY losses related to the management of AEs. Nonetheless, the company's scenario analyses include exploration of alternative types or sources of AEs (e.g., Grade 3+ AEs or from SIOPEL 6), whereby the impacts of AE on QALYs for STS and the comparator are not zero. The disutility values associated with each AE and the corresponding durations are presented in Table 28. These were based on estimates from previous NICE appraisals,[62-66] other literature[45, 67-81] and other sources such as NHS and Medscape webpages.[82-84]

Table 28: Disutility values related to AEs and assumed durations used in the company's model (adapted from CS, Table 37 and company's updated model)

Adverse event	Utility loss	Duration (days)	Source / assumption
Neutrophil count decreased	0.007	40.1	Hudgens *et al.;*[67] NICE TA704;[62] NICE TA862[63]
Haemoglobin decreased	0.070	42.9	Assumed the same as anaemia
Infection	0.042	182.5	Cutler *et al.;*[45] assumed equal to 'wound infection'
Febrile Neutropenia	0.090	7.0	Nafees *et al.;*[68] AJMC 2023[69]
WBC count decreased	0.030	42.9	Hudgens *et al.;*[67] NICE TA704;[62] NICE TA862[63]
Platelet count decreased	0.110	58.3	Shao *et al.*;[70] NICE TA862[63]
ALT increased	0.050	28.0	Telford *et al.;*[71] duration assumed due to lack of data
Lymphocyte count decreased	0.200	4.1	Shao *et al.*;[70] McNamara *et al.*[72]
Anaemia	0.070	42.9	Shao *et al.*;[70] NICE TA704;[62] NICE TA862[63]
Hypokalaemia	0.030	13.0	Shao *et al.*;[70] Schlögl *et al.*[73]
Hypophosphatemia	0.080	3.3	NICE HST8;[64] Corona *et al.*[74]
Hyponatremia	0.521	2.0	Szymanski *et al.,*[75] duration based on assumption from Lee *et al.*[76]
Stomatitis	0.151	14.0	Lloyd *et al.;*[77] Plewa *et al.*[78]
AST increased	0.051	54.8	NICE TA898;[65] NICE TA789 [66]
GGT increased	0.051	54.8	Assumed equal to aspartate aminotransferase increased
Dehydration	0.048	2.0	Assumed equal to vomiting
Hypermagnesemia	0.030	13.0	Assumed equal to hyperkalaemia
Hypocalcaemia	0.003	7.0	Assumed equal to hypomagnesemia
Hypomagnesemia	0.003	7.0	NICE TA789 [66]
Acidosis	0.030	13.0	Assumed equal to hypokalaemia
Device related infection	0.060	8.5	Assumed equal to skin infection
Sepsis	0.200	14.0	Do *et al*.;[79] Medscape webpage on Bacterial Sepsis Treatment & Management[82]
Skin infection	0.060	8.5	Stein *et al*;[80] NHS web page on cellulitus[83]
Upper respiratory tract infection	0.060	10.5	Buendía *et al.*;[81] NHS web page on RTIs[84]
Nausea	0.048	10.5	NICE TA898;[65] NICE TA789[66]
Vomiting	0.048	2.0	NICE TA898;[65] NICE TA789 [66]
Colitis	0.110	3.0	NICE TA898[65]
Hypotension	0.030	183.4	NICE TA898[65]

AE - adverse event; AJMC - American Journal of Managed Care; ALT - alanine aminotransferase; AST - aspartate aminotransferase; CS – company's submission; GGT - gamma-glutamyl transferase; HST - Highly specialised technology; NICE - National Institute for Health and Care Excellence RTI - respiratory tract infections; WBC - white blood cell count.

**For brevity, the incidences for hypersensitivity and decreased appetite, which had incidence zero in all scenarios, and for acoustic stimulation tests, which was assumed to have zero impact on costs and QALYs, were omitted here.*

4.2.4.6 Resource use and unit costs

The model includes costs associated with: (i) drug acquisition and administration; (ii) premedication drugs (antiemetics); (iii) disease management associated with hearing loss management: (a) hearing assessments, (b) hearing aids, (c) cochlear implants, (d) FM systems, and (e) speech and language therapy; and (iv) management of depression and anxiety. Costs related to the active chemotherapy and to the management of AEs are not included in the base case analysis. Table 29 summarises the costs applied within the model.

Table 29: Summary of costs applied in the company's base case analysis by treatment group

Cost parameter	Intervention	Comparator
Drug acquisition costs (one-off cost)*	List price: [redacted] With PAS: [redacted]	£0.00
Drug administration costs (one-off cost)	[redacted]	£0.00
Cost of accompanying therapy (cisplatin, one-off cost)	Not included	Not included
Cost of premedication (antiemetics, one-off cost)	[redacted]	£0.00
Disease management – hearing assessments (per cycle)	**Patient's age: 0-17 years** mild/moderate HL: £207.78; marked/severe HL: £271.43 **Patient's age: ≥18 years** £33.02	
Disease management – hearing aids (per cycle)	**Patient's age: 0-17 years** Y1: £571.35; Y2+: £142.84 **Patient's age: ≥18 years** Y1:N/A; Y2+: £111.95	
Disease management – cochlear implants (per cycle)	Y1: £44,941.78 Y2-3: £377.98 + variable[*,**] Y4-10: £1,395.77 + variable[*,**] Y11+: £1,395.77 + variable[*,**]	
Disease management – FM systems (per cycle)	Y1: £2,450.04 Y2+: £160.42	
Disease management – speech and language therapy (per cycle)	**Patient's age: 0-17 years** mild/moderate HL: £0.00 marked/severe HL: £7,472.70 **Patient's age: ≥18 years** mild/moderate/marked HL: £0.00 Severe HL: £115.34	
Costs for treatment of depression and anxiety (per cycle)	£178.11	
AEs (once-only)	£0.00	£0.00

AE – adverse event; FM – frequency modulation; HL – hearing loss; PAS – Patient Access Scheme; Y – year.
**Drug acquisition costs do include wastage assumption that any partial vials used by patients cost a full vial.*

Drug acquisition costs

Drug acquisition and administration costs are modelled as a function of the mean number of doses of STS received in the localised disease subgroup of COG ACCL0431 and unit costs. The individual dosage of STS in the trial was dependent of the patient's BSA or weight; however, the model does not use these estimates directly. Instead, the mean number of vials of STS received and the mean number

of visits per patient from the CIS+STS arm of the trial are used to estimate the mean drug cost in the model. Based on its list price, the cost per 100ml vial containing 8.0g/100ml of STS is [redacted]. The company has an agreed PAS which takes the form of a simple price discount of [redacted]; the discounted cost per vial of STS is therefore [redacted]. The model assumes that patients require 6.79 visits and 1.87 vials of to receive STS per visit, based on the assumption that vial-sharing was not permitted. The annual acquisition cost of STS including the PAS is therefore estimated to be [redacted] ([redacted] at list price), which is applied as a one-off cost in the first cycle. The company presents scenario analyses with alternative vial-sharing and wastage assumptions and using dosage data from SIOPEL 6.

The model assumes that all drug regimens, including cisplatin-containing chemotherapy and STS, are received within the first year of the model (time-to-event data on treatment discontinuation, relative dose intensity [RDI] and dose reductions are not reported in the CS or used in the model). In their response to clarification question B12,[7] the company stated that in the COG ACCL0431 and SIOPEL 6 trials, all patients stopped treatment with STS once their cisplatin therapy stopped and no patients were still receiving treatment with STS at the end of the studies, and therefore patients who discontinued treatment were not censored unless follow-up hearing assessment data were not available. No explicit stopping rules or maximum treatment durations are included in the model. However, the company stated that STS *"must only be considered for use within its licensed indication, which includes only paediatric patients with localised, non-metastatic, solid tumours"* (clarification response,[7] question A4). It is unclear if patients who develop advanced or disseminated disease throughout their treatment with cisplatin would discontinue STS.

In the model, the comparator corresponds to 'established clinical management without anhydrous STS' (CS,[1] Section B.3.3.2), and therefore no treatment costs are included for the comparator. The costs of cisplatin (as monotherapy or in combination) were also not included for either treatment group in the model. The company justified this exclusion on the basis that the costs of chemotherapy treatment are assumed to be equal between the two treatment groups. In response to clarification question A14(b), the company included data on the number of patients in COG ACCL0431 who received each type of chemotherapy protocol by treatment arm and tumour type, indirectly obtained from the frequency of cisplatin dosing. Furthermore, the company provided information on the mean cumulative cisplatin dosage received by treatment arm for localised disease patients in COG ACCL0431, SIOPEL 6, and the pooled analysis of these studies (clarification response,[7] question B13); these data are reproduced in Table 30. The company noted that a statistically significant difference between the treatment arms was not observed, and used this finding to justify the decision to exclude these costs from the model.

Table 30: Cumulative dose of cisplatin by treatment arm, selected analysis with localised disease patients only (reproduced from clarification response, Table 21)

Cumulative dose of cisplatin (mg/m^2)	Pooled analysis (COG ACCL0431 and SIOPEL 6)		COG ACCL0431		SIOPEL 6	
	STS	ECM	STS	ECM	STS	ECM
Mean	[redacted]	[redacted]	[redacted]	[redacted]	363.86	362.85
Min	[redacted]	[redacted]	[redacted]	[redacted]	121.25	105.51
Max	[redacted]	[redacted]	[redacted]	[redacted]	594.43	623.20
SD	[redacted]	[redacted]	[redacted]	[redacted]	96.61	98.87
p-value	[redacted]		[redacted]		[redacted]	

ECM - established clinical management; Min: minimum; Max - maximum ; SD - standard deviation; STS - sodium thiosulfate.

The original version of the company's model did not include the costs of additional premedication for STS. The EAG's clinical advisors noted that patients receive antiemetics prior to each administration of STS to avoid or reduce nausea and sickness experienced whilst receiving the infusion. These regimens would be in addition to the antiemetics usually given alongside chemotherapy with cisplatin-containing regimens. In response to clarification question B17, the company stated that *"in practice it is unlikely that additional antiemetic medication would be required, given that patients would already be receiving multiple doses of antiemetic medication for their cisplatin infusion"* and clarified that the information on the use of specific antiemetic regimens before administration of STS was not recorded in the trials.[7] Nonetheless, the company included the costs of antiemetics as part of their revised base case analysis, which includes the administration of ondansetron, dexamethasone and metoclopramide 30 minutes before each STS administration. The regimens and dosage schedule included in the updated model are presented in Table 31; these were based on the COG ACCL0431 protocol and the Birmingham Children's Hospital guideline for the management of chemotherapy-induced nausea and vomiting.[85, 86] Unit costs were taken from electronic Market Information Tool (eMIT).[87] The mean number of doses per visit are calculated for the base case analysis using the mean weight of [redacted] kg and mean 6.79 visits observed in COG ACCL0431 (subgroup of localised patients).[7] The annual cost of antiemetics was estimated at [redacted], which is applied to the first cycle of the model. In a scenario analysis presented by the company using clinical data from SIOPEL 6 (see Section 4.2.5), the model assumes a mean weight of 10.24 kg and 5.28 visits which leads to estimates of annual costs of antiemetics of [redacted].

Table 31: Costs of premedication antiemetics used in the updated base case (adapted from CS, Table 40)

Regimen	Dose (mg/kg)	Pack size (mg)	Unit cost	Base-case (COG ACCL0431)			Scenario analysis (SIOPEL 6)			Sources
				Dose per visit	Total cost per visit	Total cost per cycle	Dose per visit	Total cost per visit	Total cost per cycle	
Ondansetron	0.15	40	£5.01[†]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	COG ACCL0431 protocol,[85] eMIT [87]
Dexamethasone	0.10	38	£17.01[‡]							
Metoclopramide	0.20	100	£1.60[§]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Birmingham Children's Hospital guideline,[86] eMIT [87]
Total	-	-	-	-	[redacted]	[redacted]	-	[redacted]	[redacted]	-

CS - company submission; eMIT - electronic Market Information Tool.
† Ondansetron 4mg/2ml solution for injection ampoules/ pack size 10.
‡ Dexamethasone 3.8mg/1ml solution for injection ampoules/ pack size 10.
§Metoclopramide 10mg/2ml solution for injection ampoules/ pack size 10.

Drug administration costs

Administration costs for STS were calculated assuming that each infusion lasting 15 minutes would require 30 minutes of nurse time. The estimated number of STS administrations was the same as in the drug acquisition costs (based on the subgroup of localised patients in COG ACCL0431), whilst the unit cost of £106.00 was taken from PSSRU,[88] assuming the hourly cost of a Band 8c hospital-based nurse. The annual administration cost of [redacted] is applied as a one-off cost in the first cycle of the model.

Disease management costs

Health care resource use related to disease management relates to the management of hearing loss over the patient's lifetime, and includes follow-up therapy and monitoring for patients and the use of assistive devices and systems to aid patients' communication skills and resources. These include: (a) hearing assessments; (b) hearing aids; (c) cochlear implants; (d) FM systems and (e) speech and language therapy. Each category is described in detail in the following sections. The model does not include the costs of other types of medical visits, or tests outside the assessment of the hearing loss. All disease management costs are assumed to be independent of treatment group and vary by disease severity and/or by age. The costs per cycle for each disease management category are summarised in Table 32. These costs are applied to each corresponding health state in every model cycle.

Table 32: Summary of health state resource use and costs per cycle used in the base-case analysis for disease management costs

Resource component	Health state (severity HL)	Percentage of patients receiving resource use	Resource use frequency (per cycle)			Unit costs			Total costs (per cycle)		
			0-5 years	6-17 years	≥18 years	0-5 years	6-17 years	≥18 years	0-5 years	6-17 years	≥18 years
Hearing assessment visits	Mild	100%	2.00	1.00	0.25	£144.14		£132.09	£207.78§		£33.02
	Moderate										
	Marked		3.00						£271.43§		
	Severe										
Hearing aid‡	Mild	50%	N/A			Devices: £289.88 Device fitting: £121.70 Follow-up: £159.77		Devices: £243.62 Device fitting: £128.08 Follow-up: £76.08	Y1: £571.35; Y2+: £142.84		Y1: N/A; Y2+: £111.95
	Moderate	100%									
	Marked	94%									
	Severe	48%									
Cochlear implant	Mild	0%	N/A			£0.00			£0.00		
	Moderate										
	Marked	6%				Initial implantation (one-off): £44,563.80; Device maintenance and programming: £377.98;† External processor replacement: £5,088.95;† Internal processor replacement: £17,933.80;† Re-implantation of internal electrode: £4,304.70 (<18 years old); £3,480.87 (≥18 years)			Y1: £44,941.78 Y2-3: £377.98 + variable⁂ Y4-10 : £1,395.77 + variable⁂ Y11+ : £1,395.77 + variable⁂		
	Severe	52%									
FM Systems*	Mild	100%	N/A			FM binaural system (one-off): £2,333.37; Maintenance/repairs: £116.67; Microphone replacement: £218.75		£0.00	Y1: £2,450.04; Y2+: £160.42		£0.00
	Moderate										
	Marked										
	Severe										
Speech and language therapy	Mild	100%	0.00			£143.21		£128.16	£0.00		
	Moderate										
	Marked		52.18		0.00				£7,472.70		£0.00
	Severe		52.18		0.90						£115.34

HL - hearing loss; N/A - not applicable; FM - frequency modulation.

§Based on the weighted frequency for 0-5 and 6-17 years-old for the corresponding severity level.

‡The model assumes a replacement frequency of 4 years for each pair of hearing aids, which is included in the estimated total annual costs.

** The model assumes a replacement frequency of 5 years for each set of bilateral cochlear implants and for FM systems, which is included in the estimated total annual costs.*

†The model assumes the costs are the same for child and adult patients.

⁂ The variable component of the costs correspond to the cost of fitting and replacing the internal processor of the cochlear implant, which is applied to the cycle probability of requiring an internal component replacement.

a) Hearing assessment costs

The model includes disease management costs associated with monitoring patients' hearing loss condition throughout their lifetime; these costs are applied in every cycle to all patients in the mild to severe HL heath states. Hearing assessment costs include visits for audiometry and hearing testing, and are assumed to be age-dependent and to vary by HL severity level whilst the patient is under 18 years of age.

The frequencies of audiology assessments per annual cycle were based on Dionne *et al.,*[89] a Canadian study which assessed the potential economic impact of implementing a genetic test to predict the likelihood that a cisplatin-treated paediatric patient will develop ototoxicity, and assumptions informed by audiologists interviewed by a consultancy company in 2018.[59] Unit costs were based on NHS Reference Costs 2021/22,[90] with the unit cost for under 18 years olds being estimated using the weighted mean based on the age distribution of patients from COG ACCL0431[19] and the costs of 'Audiometry and Hearing Assessment' for 4 years and under and for between 5 and 18 years ('Total HRGs' worksheet, codes CA73C and CA37B, unit costs of £151.16 and £139.41, respectively). The company used a similar approach for the frequencies to calculate the weighted annual cost for patients under 18 years old. This results in an annual cost of £207.78 for patients <18 years old in mild or moderate HL, and of £271.43 for patients in this age group with marked or severe HL. Adult patients, regardless of HL severity, are assumed to have a hearing assessment every 4 years, which is associated with an annual cost of £33.02.

The EAG notes that it is unclear why only the frequency of hearing assessments for patients 6-17 years was sourced from Dionne *et al.*, when this study reports frequencies by HL grade and by three age group categories (0-5, 6-11 and 12-18 years). It is also unclear how the frequency from this group was obtained from the data reported in the paper. This issue is discussed in Section 4.3.3. In response to clarification question B19[7] regarding the approach of applying a weighted cost for hearing assessments for all patients <18 year olds, instead of applying separate specific costs to each corresponding age group (<5 years and 5-18 years) in the model, the company justified using this approach given that the difference in cost between the age groups is minor, as is the impact on the ICER of applying corresponding specific costs to each age group (an increase of [redacted]).

b) Hearing loss management costs – hearing aids

The model includes costs associated with the use of three types of hearing devices: hearing aids, cochlear implants and FM systems. The costs of hearing aids are assumed to be age-dependent (<18 years old and ≥ 18 years old). The model assumes that 50% of patients experiencing mild HL[59] and every patient in the moderate, marked and severe HL health states who does not receive cochlear implants receive hearing aids (100%, 94% and 48% of patients, respectively) will receive a pair of

hearing aids and will use them for their lifetime. This approach was based on previous NICE appraisal of cochlear implants for children and adults with severe to profound deafness (TA566)[91] and was stated to avoid double-counting since it was assumed that patients would not receive both devices (clarification response,[7] question B18c).

The frequency at which these devices require replacement was assumed to be 4 years, based on Dione *et al.* [89] Unit costs were taken from NHS Reference Costs 2021/22,[90] and include the costs of the hearing aid devices (£289.88 for a pair if <18 years old and £243.62 for ≥ 18 years old, based on code AS07 and weighted average of codes AS05 and AS06, respectively), of the device fitting (£121.70 and £128.08 per patient <18 years and ≥ 18 years old, respectively, based on codes AS02 and AS01), and of follow-up (£159.77 and £76.08 per patient <18 years and ≥ 18 years old, respectively – based on codes AS09 and AS08). In the first year, the full cost of £571.35 is applied to patients in each mild to severe health state who receive hearing aids, and the annualised cost of a new device, fitting and a follow-up appointment is applied in every subsequent cycle (£142.84 whilst patient is <18 years and £111.95 after reaching adulthood).

The EAG notes that the model assumes that all patients will receive bilateral hearing aids; however, whilst the unit cost for the devices from the NHS Reference Costs was doubled for inclusion in the model, the costs associated with fitting and follow-up were not. In response to clarification question B20(a), the company clarified that: *"The NHS cost collection does not specify if the cost is per ear or per patient, therefore it was conservatively assumed that fitting a second hearing aid would add no additional cost compared to fitting a singular hearing aid."*[7] NICE Guideline NG98 (the NICE guideline for hearing loss in adults: assessment and management) seems to agree with this assumption, where it is noted that: *"there will be no difference in costs for fitting or follow-up appointments, as an individual will have the same number of appointments whether they are having 1 or 2 hearing aids fitted."*[116]

NG98 mentions that: *"all hearing aids consist of a microphone, an amplifier powered by a battery, a receiver, and a means to route the amplified sound into the ear canal."* and that *"there is variation across the UK in whether people with mild to moderate hearing losses receive hearing aid(s) and consider that the decision to fit should be based on need rather than on hearing thresholds."* [116] The EAG notes that the company's cost estimates for hearing aids does not include the cost of consumables such as batteries, and it is unclear if the proportions of patients experiencing mild or moderate HL assumed to receive hearing aids reflects this variation in current clinical practice in the UK. The cost estimates also do not account for any failure rates, where patients stop wearing their devices because of incompatibility or other reasons.

c) Hearing loss management costs – cochlear implants

In the model, only a proportion of patients in the marked and severe HL heath states are assumed to receive cochlear implants (6% and 52%, respectively), based on Chorozoglou *et al*.[92] The EAG notes that Chorozoglou *et al*. is an observational study of 110 adolescents (aged between 13 and 20 years) in England, where 1 of 18 (6%) children with severe HL received a single cochlear implant, whilst 12 of 23 (52%) children with profound HL received a single cochlear or bilateral cochlear implants.

The costs associated with cochlear implants are assumed to be disease severity-independent, and include the costs of the initial implantation of the bilateral cochlear implant, annual costs of maintenance and programming, costs of replacements of the external and internal components and their re-implantation (external processor and internal electrode – which are calculated separately). In the first year of the model, the full cost per patient of the initial implantation of £44,564 (including costs of pre-implantation clinical visits tests of £1,959.59, the cost of the bilateral devices of £36,147.15 and device fitting costs of £6,457.06) and the annual costs of device maintenance and programming of £377.98 are applied, with unit costs based on NHS Reference Costs 2021/22,[90] Bond *et al.*,[93] Cutler *et al.*,[45] and NICE TA566,[91] which were uplifted to 2022 values using the NHS Cost Inflation Index (NHSCII).[88]

Thereafter, the calculation includes warranty periods taken from Bond *et al*.[93] of 3 and 10 years for the external and internal components, respectively. During this period, the costs of new components are not considered, although the annual costs of device maintenance (£377.98, based on codes AS13 and AS11)[90] are still included for all patients with a cochlear implant, in addition to the cost of reimplanting an internal electrode for patients requiring an internal component replacement (unit costs of £4,304.70 whilst the patient is <18 years and £3,480.87 after reaching adulthood, based on Bond *et al*.[93] and uplifted to 2022). The probability of the internal component requiring replacement in each cycle of the model was also obtained from Bond *et al*.[93] (

Table 33).

Table 33: Probabilities of internal component of cochlear implants requiring replacement (reproduced from the company's updated version of the model)

Time since initial implantation (years)	Probability of internal component of cochlear implant requiring replacement
0	-
1	0.0020
2	0.0050
3	0.0050
4	0.0040
5	0.0041
6	0.0031
7	0.0041
8	0.0031
9	0.0021
10	0.0031
11	0.0031
12	0.0021
13	0.0031
14	0.0021
15	0.0031
16	0.0021
17	0.0032
18	0.0021
19	0.0032
20	0.0021
21	0.0032
22	0.0021
23	0.0032
24	0.0021
25	0.0022
26	0.0032
27	0.0032
28	0.0022
29	0.0022
30	0.0033
31	0.0022
32	0.0022
33	0.0033
34	0.0022
35	0.0022
36	0.0022
37	0.0022
38	0.0033
39	0.0022
40+	0.0022

After the warranty periods, the frequency of replacement of each component was assumed to be 5 years, based on document from NHS England Cochlear Implant Services.[94] The costs of replacing external and internal processors are based on unit costs of £5,088.95 and £17,933.80, respectively, taken from Bond *et al*.[93] and uplifted to 2022.[88] The costs of external processors are included as annualised costs

of £1,017.79 in every cycle, whilst the costs of the internal processors are applied in addition to the cost of reimplanting an internal electrode in full, to the cycle probability requiring an internal component replacement, also from Bond *et al*.[93]

The EAG notes that the Final Appraisal Determination (FAD) for NICE TA566 recommended the use of simultaneous bilateral cochlear implantation as an option for some groups of people with severe to profound deafness who do not receive adequate benefit from acoustic hearing aids, such as children.[91] The model assumes that all patients receiving cochlear implants incur the costs of a bilateral implant.

d) Hearing loss management costs – FM systems

The model also includes the costs of assistive devices such as FM systems, which are used to help people with hearing loss with listening in busy or noisy environments, such as classrooms. All patients in the model who experience hearing loss at any severity level are assumed to receive an FM system, based on clinical opinion from audiologists interviewed in 2018.[59] The costs of the device are the same regardless of age group and health state. Unit costs were taken from Dionne *et al.*,[89] which include the costs of the binaural system, the microphone replacement and annual cost of maintenance and repairs. These costs were converted to GBP and uplifted to 2023 using the Organisation for Economic Co-operation and Development (OECD) Purchasing Power Parities (PPP) index[96] and the OECD Consumer Price Indices (CPIs).[95]

The mean frequency of replacement of 5 years was based on Dione *et al.*[89] In the first year of the model, the full cost of £2,333.37 for the binaural system and the annual cost of maintenance/repairs of £116.67 are applied, resulting in a total cost of £2,450.04. In the subsequent years of the model, the annual cost of maintenance in addition to an annualised cost of microphone replacement of £43.75 is applied, leading to a total annual cost of £160.42. Patients are assumed to incur the costs of FM systems only until they reach 18 years old.

The EAG notes that, although the company has assumed that all children with any hearing loss severity would receive FM systems, in Dione *et al.*, these costs are included only for patients with hearing loss Grade 2+ (using the CTCAE grading system). In response to clarification question B18(b),[7] the company clarified that Dionne *et al.* was conducted from a Canadian perspective, whilst this assumption was based on report of market research interviews with UK audiologists, which stated that: "*most children have personal FM devices or other accessories"*, and that "*The new recommendations from the National Deaf Children's Society (NDCS) is that all children irrespective of their age, even babies, little ones, should have access to some FM systems."*[59]

e) Speech and language therapy costs

Health state resource use in the model also included the costs of speech and language therapy, which is assumed to be dependent on age group and HL severity level.[1] Patients with mild or moderate HL are assumed not to incur in any costs, whilst those with marked or severe HL are assumed to receive weekly sessions of speech and language therapy (52.18 sessions per year)[89] whilst under the age of 18 years. Those in the marked HL state are assumed to cease these sessions when they reach 18 years of age, and those in the severe health state have the number of sessions reduced to 0.9 sessions per year, based on Smulders *et al.*.[97]

Unit costs were taken from NHS Reference Costs 2021/22,[90] with the values per session of £143.21 and £128.16 corresponding to the cost of Community Health Services (Speech and Language Therapist, one to one) for children and adults, respectively. The total annual cost for marked and severe HL patients until 18 years-old corresponds to £7,472.70, whilst the cost for adult patients with severe HL corresponds to £115.34.

The EAG notes that the frequency of sessions for severe HL patients of 0.9 per year was based on the number of annual visits for speech therapy in patients who received bilateral cochlear implant before cochlear implantation (preoperative) from Smulders *et al*..[97] In response to clarification question B21,[7] the company stated that the choice for the lowest number of visits (preoperative) to be applied in the model was considered conservative. The EAG notes that Smulders *et al.* evaluated the results of the effectiveness and cost–utility of bilateral versus unilateral cochlear implants in adults, and therefore it is unclear if patients who have received the implants as children would still receive speech therapy sessions as adults, and at which frequency.

Costs of treatment for depression and anxiety

In the model, the costs of treatment for depression and anxiety are based on the proportion of patients who survived neuroblastoma, with hearing loss of all severities and without hearing loss, who reported having experienced depression from Gurney *et al.*[98] (25.58% and 14.89%, respectively). This study evaluated the quality of life of 137 patients enrolled to one of the COGs studies (CG3881 of CG3891), who had mean age at diagnosis was 1.4 years (SD: 1.7 years) and the mean age at interview was 12.1 years (SD: 2.2 years). Of the 137 patients selected, 25 (18.2%) reported depressive illness and 43 (31.4%) reported some degree of hearing loss with 11 (8.0%) of all patients in the study reporting both hearing loss and depressive illness. Thus, 11 of the 43 patients (25.6%) with hearing loss experienced depressive illness whilst 14 of the 94 patients (14.9%) without hearing loss experienced depressive illness. The CS reports that they did not include the proportion of patients in the study who reported experiencing anxiety to avoid double counting.[1] The EAG notes that the model does not include any

costs for treating anxiety alone, and that the model assumes that the rate of depressive illness is constant, regardless of the severity level of hearing loss.

Unit costs were based on the NICE resource impact statement: depression and anxiety disorder, which reported that 847,858 people were estimated to have depressive illness in England in 2015 with an associated total cost of £133,706,308, leading to a mean annual cost per person of treating depressive illness of £157.70.[99] This cost was uplifted to 2022 values using the NHS Cost Inflation Index (NHSCII)[88] which resulted in an annual cost of £178.11 per patient.

AE management costs

Costs related to the management of AEs in the base case analysis are based on the frequency of individual treatment-related SAEs with an observed incidence ≥2% in either the STS+CIS and CIS arms of the safety population of COG ACCL0431.[19] Since no SAEs were reported to meet this requirement, no costs associated with AEs were included in the base case.

Scenario analyses using SAEs frequencies from SIOPEL 6 and from Grade 3+ AEs with an observed incidence ≥10% in COG ACCL0431 were originally presented by the company with the results reported in Section B.3.12.3 of the CS.[1] At the clarification stage, the company included functionality in the model to also explore additional scenarios using the incidence of Grade 3+ AEs occurring in ≥5% of subgroup of localised disease patients in COG ACCL0431 and in the pooled analysis of COG ACCL0431 and SIOPEL 6. However, the company does not provide the full set of results for these analyses, and instead only reports the resulting ICER. The scenario analyses results are reported in Section 4.2.7.

The AE incidences used in the model for the base case and scenario analyses are presented in Table 26. Unit costs associated with treatment emergent AEs were taken from the NHS Reference Cost Collection for 2021/22[90] or from other literature.[70, 71, 74, 87, 101-104]

In response to clarification question B24, the company states that it considers it to be more appropriate to use the frequencies of SAEs related to STS treatment in the model, rather than all Grade 3+ AEs *"as the list of Grade 3+ AEs includes AEs which are related to cisplatin, and there is no reason to believe cisplatin-related AEs would differ between treatment arms".*[7] This issue is discussed further in Section 4.3.3.

Table 34: Adverse event costs assumed in the company's base-case and selected scenario analyses, STS and ECM*

AE	AE incidence (base case and scenario analyses)	Unit costs	Source of unit costs (HRG codes)	Base case (COG ACCL0431 overall population, SAEs occurring in ≥ 2% of patients)		Scenario (SIOPEL 6, SAEs occurring in ≥ 2% of patients)†		Scenario (COG ACCL0431 overall population, Grade 3+ AEs occurring in ≥ 10% of patients)		CR scenario (COG ACCL0431 localised disease patients, Grade 3+ AEs occurring in ≥ 5% of patients)		CR scenario (Pooled COG and SIOPEL 6 localised disease patients, Grade 3+ AEs occurring in ≥ 5% of patients)	
				STS	ECM	STS	ECM	STS	ECM	STS	ECM	STS	ECM
Neutrophil count decreased	See Table 26	£2,335.50	NHS RC 21/22[90] (SA35A – SA35E)	£0	£0	£88	£0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Haemoglobin decreased		£855.35	NHS RC 21/22[90] (SA04G – SA04L)			£0		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infection		£4,877.51	NHS RC 21/22[90] (WH07C – WH07D)					[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Febrile neutropenia		£ 7,769.19	NHS RC 21/22[90] (PM45A – PM45D)					[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WBC count decreased		£2,335.50	NHS RC 21/22[90] (SA35A – SA35E)					[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Platelet count decreased		£948.21	NHS RC 21/22[90] (SA12G – SA12K)					[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ALT increased		£ 1,850.20	Telford *et al.*[71]					[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lymphocyte count decreased		£1.079.47	Campone *et al.*[101]					[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia		£855.35	NHS RC 21/22[90] (SA04G – SA04L)					[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypokalaemia		£2,044.64	Shao *et al.*[70]					[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypophosphatemia		£2,044.64	Shao *et al.*[70]					[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hyponatremia		£1,873.79	Corona *et al.*[74]					[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stomatitis		£2,046.53	Wong *et al.*[102]					[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AST increased		£1,850.20	Assumption (TA898)[65]					[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GGT increased		£1,850.20	Assumption (TA551)[100]					[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dehydration		£1,362.60	Assumption					[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypermagnesaemia		£2,207.40	Assumption					[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypocalcaemia		£12.31	eMIT,[87] EMC,[103] Cleveland website 2022[104]					[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypomagnesaemia		£2,207.40	NHS RC 21/22[90]					[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acidosis		£2,816.26	NHS RC 21/22[90]					[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Device related infection		£964.05	NHS RC 21/22[90]					[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sepsis		£3,041.54	NHS RC 21/22[90]					[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Skin infection		£1,095.31	NHS RC 21/22[90]					[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AE	AE incidence (base case and scenario analyses)	Unit costs	Source of unit costs (HRG codes)	Base case (COG ACCL0431 overall population, SAEs occurring in ≥ 2% of patients)		Scenario (SIOPEL 6, SAEs occurring in ≥ 2% of patients)†		Scenario (COG ACCL0431 overall population, Grade 3+ AEs occurring in ≥ 10% of patients)		CR scenario (COG ACCL0431 localised disease patients, Grade 3+ AEs occurring in ≥ 5% of patients)		CR scenario (Pooled COG and SIOPEL 6 localised disease patients, Grade 3+ AEs occurring in ≥ 5% of patients)	
				STS	ECM	STS	ECM	STS	ECM	STS	ECM	STS	ECM
Upper respiratory tract infection		£706.26	NHS RC 21/22[90]							[redacted]	[redacted]	[redacted]	[redacted]
Nausea		£1,375.38	NHS RC 21/22[90]							[redacted]	[redacted]	[redacted]	[redacted]
Vomiting		£1,362.60	NHS RC 21/22[90]							[redacted]	[redacted]	[redacted]	[redacted]
Colitis		£1,735.73	NHS RC 21/22[90]							[redacted]	[redacted]	[redacted]	[redacted]
Hypotension		£764.27	NHS RC 21/22[90]							[redacted]	[redacted]	[redacted]	[redacted]
Total	-	-	-	**£0**	**£0**	**£88**	**£0**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AE - adverse event; ALT - alanine aminotransferase; AST - Aspartate aminotransferase; CR - clarification response; ECM - established clinical management; GGT - gamma-glutamyl transferase; HRG - Healthcare Resource Group; NHS RC - NHS Reference Costs; SAE - serious adverse event; STS - sodium thiosulfate; WBC - white blood cell count.

**For brevity, the incidences for hypersensitivity and decreased appetite, which had incidence zero in all scenarios, and for acoustic stimulation tests, which was assumed to have zero impact on costs and QALYs, were omitted here.*

4.2.5 Model evaluation methods

The CS presents the results of the original base case analyses in terms of incremental cost-effectiveness ratios (ICERs) using pairwise comparisons for STS versus established clinical management. The company's base case results were generated using the deterministic and probabilistic versions of the model; the probabilistic ICERs are based on 10,000 Monte Carlo simulations. The distributions used in the probabilistic sensitivity analysis (PSA) are summarised in Table 35. The EAG notes that the company's revised version of the model submitted following the clarification stage did not present probabilistic results. These results were instead generated by the EAG using the updated version of the model (see Section 4.2.7). The results of the company's deterministic sensitivity analyses (DSAs) are presented using a tornado plot and a summary table.

Table 35: Distributions used in company's PSA

Parameter / group	Distribution	EAG comments
Start age	*Gamma*	SE of 0.69 is applied which appears appropriate and is based on that observed in Children's Oncology Group
Proportion of males	*Beta*	SE assumed to be 20% of the mean
Percentage of patients experiencing HL	*Beta*	SE assumed to be 20% of the mean
Percentage of patients in each HL severity level	*Dirichlet*	-
Annual probability of mortality in years 1 to 5	*Beta*	SE assumed to be 20% of the mean
Post cancer survival SMR	*Gamma*	SE of 0.13 based on British Childhood Cancer Survivor Study[54]
Length of time to apply post cancer survival SMR	*Fixed*	In the original version of the model, this parameter was included in the PSA, but was removed in the updated version submitted at clarification stage.
Health state utility values	*Beta*	SEs for health state utility parameters based on data from Pogany *et al.*[57] (mild/no HL state) and Barton *et al.*[56] (base case) or Gumbie *et al.*[47] (scenario analysis). SE assumed to be 20% of the mean for disutilities associated with cancer. SEs for utility gains related to hearing devices estimated from Barton *et al.*[56] (base case) or Gumbie *et al.*[47] (scenario analysis).
AE rates	*Fixed/Beta*	SE assumed to be 20% of the mean (which are fixed at zero in the base-case but sampled at non-zero values in scenario analyses)
AE duration	*Gamma*	SE assumed to be 20% of the mean for the duration of the effects of AEs
AE QALY	*Beta*	SE assumed to be 20% of the mean in health state disutilities associated with treatment emergent adverse events
AE unit costs	*Gamma*	SE assumed to be 20% of the mean
Drug acquisition costs	*Fixed*	-

Parameter / group	Distribution	EAG comments
Drug administration costs	*Fixed*	The company has not included uncertainty for the unit costs or resource use
Percentage of patients requiring FM system	*Beta*	SE assumed to be 20% of the mean
Replacement frequency of FM system	*Gamma*	
Percentage of patients requiring hearing aids	*Beta*	
Replacement frequency of hearing aids	*Gamma*	
Percentage of patients requiring cochlear implants	*Beta*	
Replacement frequency of cochlear implants	*Gamma*	
Duration of warranty for elements of cochlear implant system	*Gamma*	
Frequency of audiology assessments	*Gamma*	
Annual number of speech & language therapy appointments	*Gamma*	
Unit costs	*Gamma*	

AE – adverse event; EAG – External Assessment Group; FM - frequency modulation; HL - hearing loss; OS – overall survival; SE – standard error; SMR – standardised mortality ratio; QALY – quality-adjusted life year

Scenario analyses

The CS (Section B.3.12.3, pages 130-132) also reports the results of scenario analyses which explore the impact of:

- Alternative economic perspectives – societal and payer but including education costs (Scenarios 1 and 2, respectively)
- Alternative discount rates of 1.5% for health outcomes and costs (Scenario 3)
- Alternative sources for clinical efficacy (HL incidence): SIOPEL 6 and Orgel *et al.* (Scenarios 4 and 5, respectively)
- Alternative sources for clinical efficacy (HL severity): Orgel *et al*. combined with SIOPEL 6 and SIOPEL 6 only (Scenarios 6 and 7, respectively)
- Alternative values for the SMR: 5.6 from Laverdiere *et al*. and 6.2 from Suh *et al*. (Scenarios 6 and 7, respectively)
- Alternative assumptions regarding wastage: no wastage (assumption of vial sharing allowed; Scenario 10), wastage included if ≥10% required (Scenario 11) and wastage included if ≥5% required (Scenario 12)
- Use of Grade 3+ AEs occurring in ≥10% of patients from COG ACCL0431 (Scenario 13)
- Use of alternative source of heath state utilities from Gumbie *et al.* (Scenario 14).

The results of these scenario analyses are reported in Section 4.2.7.

The EAG notes that the scenario analysis exploring the use of alternative health state utilities based on estimates from Gumbie *et al*.[47] (see

Table 27) also includes utility gains for hearing aids of 0.12 from Grutters *et al.,*[60] applied to 50%, 100%, 94% and 48% of patients in the mild, moderate, marked and severe HL health states, respectively (in addition to the utility gains from the use of cochlear implants).

The EAG also notes that Scenarios 1 and 2 include alternative non-Reference Case perspectives. The NICE Methods Manual[22] states in relation to measuring costs that *"The potential effect on resource costs and savings that would be expected from introducing the technology should be considered from the perspective of the NHS and personal social services. In exceptional circumstances for medicines, when requested by the Department of Health and Social Care in the remit for the evaluation, the scope will list requirements for adopting a broader perspective on costs."* In Scenarios 1 and 2 provided by the company, the cost of education resources (the proportion of patients with moderate to severe HL attending various types of schools) was based on Chorozoglou *et al.*[92] and the UK government school admissions website.[117] The societal perspective included productivity losses for parents of patients with different levels of HL, and for patients with HL when they reach working age, based on data from Chorozoglou *et al.*,[92] Dionne *et al.*[89] and the ONS.[118]

Scenarios 4 and 5 are run independently of Scenarios 6 and 7, i.e., changes are made to the source of HL incidence whilst the source of HL severity remains the same as the base case, and *vice versa*. At the clarification stage, the company presented additional scenario analyses regarding the alternative sources of data related to treatment efficacy, using the updated version of the model. These results are presented separately in Section 4.3.3, critical appraisal point 2(a).

4.2.6 Model validation and face validity check

Section B.3.15 of the CS[1] describes the company's model validation activities, which involved checking for errors and debugging in Visual Basic for Applications (VBA) coding for inconsistencies, assessing the plausibility of inputs and outputs by an economist not involved in the model development, and also testing the model on extreme values ("pressure testing"). The company also describes external validation activities involving interviews with clinical and HEOR experts (n=11 and n=1, respectively) regarding the model inputs, protocol and structure of the economic analysis. The results of the series of interviews with 10 audiologists conducted in 2018 were shared with the EAG as part of the supporting evidence presented by the company during clarification.[59]

The company mentions that the outputs of these activities were accounted for in the original version of the model.[1]

4.2.7 Company's cost effectiveness results

Company's central estimates of cost-effectiveness (deterministic and probabilistic)

The probabilistic and deterministic results presented in this section are based on the updated version of the company's model submitted at clarification response. Table 36 presents the central estimates of cost-effectiveness generated by the EAG using the company's model for the comparison of STS versus ECM. The probabilistic version of the updated model suggests that STS is expected to generate no additional life-years (LYs), 1.54 additional QALYs at additional costs of [redacted] compared to ECM; the corresponding ICER is [redacted] per QALY gained. The deterministic version of the company's base case analysis produces very similar results to the probabilistic analysis. The base case analysis suggests a decision modifier of 1.0, as suggested by the company in the CS (age = [redacted] years; [redacted] female; 16.89 discounted QALYs for the comparator group, which generates an absolute shortfall of [redacted] and proportional shortfall of [redacted] using the QALY shortfall calculator by Schneider *et al.*).[23]

Table 36: Company's central estimates of cost-effectiveness, STS versus ECM, generated by the EAG using the company's revised model

Options	LYGs*	QALYs	Cost	Inc. LYGs*	Inc. QALYs	Inc. Costs	ICER	DM
Probabilistic model (using 10,000 iterations)								
STS	59.77†	18.42	[redacted]	0.00	1.54	[redacted]	[redacted]	1.0
ECM	59.77†	16.88	£10,256	-	-	-	-	
Deterministic model								
STS	59.85	18.43	[redacted]	0.00	1.54	[redacted]	[redacted]	1.0
ECM	59.85	16.89	£10,187	-	-	-	-	

ECM – established clinical management; ICER – incremental cost-effectiveness ratio; Inc. – incremental; LYG – life year gained; QALY – quality-adjusted life year; STS – sodium thiosulfate.
** Undiscounted*
†Generated by the EAG by modifying the company's PSA sub-routine

Figure 6 presents the results of the company's PSA in the form of cost-effectiveness acceptability curves (CEACs) for STS and ECM. The probability that STS generates more net benefit than ECM at willingness-to-pay (WTP) thresholds of £20,000 and £30,000 per QALY gained is approximately [redacted] and [redacted], respectively.

Figure 6: CEACs, STS versus ECM (generated by the EAG using the company's model)

CEAC - Cost-effectiveness acceptability curve; EAG - external Assessment Group; ECM – established clinical management; STS – sodium thiosulfate.

Company's DSA results

Figure 7 presents the results of the company's DSAs in the form of a tornado plot. The EAG notes that the company has not presented revised results for the deterministic univariate sensitivity analyses following the clarification process. Instead, these results were generated by the EAG using the updated version of the model. The plot indicates that the ICER is particularly sensitive to the proportion of patients not experiencing HL in both the STS and ECM groups, and to a lesser degree, the mean number of STS visits (which drives the drug acquisition costs) and the probability of death in the first year of the model. Across the range of scenarios presented, the ICER ranges from [redacted] to [redacted] per QALY gained.

Figure 7: Tornado diagram, STS versus ECM (generated by the EAG using the company's model)

ECM – established clinical management; HL – hearing loss; ICER – incremental cost-effectiveness ratio; STS – sodium thiosulfate.

Company's scenario analyses

Table 37 presents the results of the company's scenario analyses using the deterministic version of the updated model. The EAG notes that whilst the CS reports the results for scenarios 1 to 14 using the probabilistic version of the model, the company has not presented revised results following the clarification process; these were generated by the EAG using the deterministic version of the updated model submitted. As shown in Table 37, the ICER is not sensitive to the lower values for SMR and when using the incidence of Grade 3+ AEs occurring in ≥10% of patients from COG ACCL0431 overall population. The ICER is significantly lower (<£20,000 per QALY gained) for the different perspective used in the model where the payer perspective is used with the addition of educational costs, using data from SIOPEL 6 mITT for clinical efficacy (HL occurrence), assuming no wastage for drug acquisition costs, and using discount rates of 1.5% for costs and health outcomes. Amongst the scenarios considered by the company, the highest ICER reported is [redacted] per QALY gained, for the alternative source for health state utilities from Gumbie *et al.*.[47] The EAG notes that the company also presented results for additional scenario analyses at the clarification response; however complete sets of results were not presented (only ICERs). The results for the scenarios which explores different efficacy data for HL occurrence and HL severity are presented in Section 4.3.3 (issue 2(a)).

Table 37: Scenario analysis results for STS versus EMC using the updated version of the model submitted at clarification response (generated by EAG using company's model, deterministic)

Scenario no.	Scenario description	Incremental results			ICER
		LYs	QALYs	Costs	
-	Deterministic base case	0.00	1.54	[redacted]	[redacted]
1	Perspective = societal	0.00	1.54		
2	Perspective = payer + education costs	0.00	1.54		
3	Discount rates = 1.5%	0.00	2.50		
4	Clinical efficacy source = SIOPEL 6 mITT[16]	0.00	1.75		
5	Clinical efficacy source = Orgel *et al*.[20]	0.00	1.42	[redacted]	[redacted]
6	Source for HL severity = Orgel *et al*.[20] + SIOPEL 6[16]	0.00	1.54		
7	Source for HL severity = SIOPEL 6[16]	0.00	1.33	[redacted]	[redacted]
8	Post-cancer SMR = 5.6 (Laverdiere *et al*.)[119]	0.00	1.54		
9	Post-cancer SMR = 6.2 (Suh *et al*.)[120]	0.00	1.54	[redacted]	[redacted]
10	Drug cost assumptions = no wastage	0.00	1.54		
11	Drug cost assumptions = 10% allowance	0.00	1.54		
12	Drug cost assumptions = 5% allowance	0.00	1.54		
13	Adverse events = Grade 3+ AEs occurring in ≥10% of patients from COG ACCL0431 overall population[19]	0.00	1.54		
14	Source for utilities = Gumbie *et al.*[47]	0.00	1.25	[redacted]	[redacted]

AE - adverse event; ECM – established clinical management; HL - hearing loss; ICER – incremental cost-effectiveness ratio; LY – life year; no. – number; OS – overall survival; QALY – quality-adjusted life year; SMR - standardised mortality ratio; STS – sodium thiosulfate.

4.3 Critique of company's submitted economic evaluation by the EAG

4.3.1 Methods for reviewing the company's economic evaluation and health economic model

The EAG adopted a number of approaches to explore, interrogate and critically appraise the company's submitted economic analyses and the underlying health economic model upon which these are based. These included:

- Scrutiny of the company's model by health economic modellers and discussion of issues identified amongst the members of the EAG.
- Double-programming of the deterministic version of the company's original model to fully assess the logic of the model structure, to draw out any unwritten assumptions and to identify any apparent errors in model implementation.
- Examination of the correspondence between the description of the model reported in the CS and the company's executable model.
- Replication of the base case results, PSA, DSAs and scenario analyses reported in the CS using the company's model.
- Where possible, checking of key parameter values used in the company's model against their original data sources.

- The use of expert clinical input to judge the credibility of the company's economic analyses and the assumptions underpinning the model.

Model verification by the EAG

During the process of checking the deterministic version of the company's original base case model in order to verify its implementation, the EAG has identified programming errors which were resolved by the company during the clarification process.[7] Additional programming errors in the updated version of the model submitted were identified by the EAG after the clarification stage; these are described in Section 4.3.3. The EAG believes the company's updated version of the model to be generally well programmed despite these errors, and that the version of the model used by the EAG after correcting these errors are appropriate for the decision problem.

Correspondence of the model inputs and the original sources of parameter values

Where possible, the EAG checked the model input values against their original sources including published sources and additional sources provided by the company such as the CSR of the COG ACCL0431 and SIOPEL 6 studies. The EAG did not identify any key remaining inconsistencies of relevance in the revised version of the company's model submitted following the clarification round. Nonetheless, the EAG notes that the frequency of speech and language therapy for patients under 18 years old in the marked or severe HL states is reported by Dionne *et al.* as corresponding to children diagnosed with ototoxicity between the ages of 0 and 5, which is younger than the targeted population's mean starting age in the model.

4.3.2 Adherence of the company's model to the NICE Reference Case

The extent to which the company's economic analyses adhere to the NICE Reference Case[22] is summarised in Table 38.

Table 38: Adherence of the company's economic analysis to the NICE Reference Case

Element	Reference case	EAG comments
Defining the decision problem	The scope developed by NICE	The company's economic analysis is generally in line with the final NICE scope.[18] The final scope defines the intervention as *"Anhydrous STS (Pedmarqsi)"* and the comparator as *"established clinical management without anhydrous STS"* (ECM). The company's economic analysis includes ECM as the sole comparator within the analysis.
Comparator(s)	As listed in the scope developed by NICE	
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	The base case economic analysis adopts a direct health perspective, including health effects on patients at risk of developing hearing loss after receiving cisplatin-containing therapy for solid tumours in terms of survival, experience of HL, severity level of hearing loss and safety. Health impacts on caregivers were not included in the analysis.
Perspective on costs	NHS and PSS	The base case analysis include costs borne by the NHS and PSS, although the company's scenario analyses explore broader perspectives including educational costs and productivity losses; these are outside of the NICE Reference Case[22] (see Section 4.2.5).
Type of economic evaluation	Cost-utility analysis with fully incremental analysis	The company's model adopts a cost-utility approach. Results are presented in terms of the incremental cost per QALY gained.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The model adopts a [redacted] years (lifetime) horizon. At the end of the time horizon, approximately [redacted] of patients are predicted to still be alive.
Synthesis of evidence on health effects	Based on systematic review	Transition probabilities between HL health states in the first year of the model were derived from the COG ACCL0431 trial (overall efficacy population)[19], Orgel *et al.*[20] and Knight *et al.*[8]. Based on the information provided in the CS and clarification response, alternative combinations of sources might be more suitable to inform treatment efficacy in the model (see Section 4.3.3, critical appraisal point 2).
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults.	Health utility values for states relating to HL severity levels (mild to severe) are based on external studies based on HUI3 data Barton *et al.*[56] and Pogany *et al.*[57] Utility decrements associated with underlying cancer, and utility gains associated with the use of hearing devices are derived from other sources.[56, 58] Utility values for AEs were taken from various sources in the literature.
Source of data for measurement of HRQoL	Reported directly by patients and/or carers	
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	

Element	Reference case	EAG comments
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	No additional equity weighting is applied to estimated QALY gains.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	The model includes relevant NHS and PSS costs, uplifted to current values using appropriate inflation indices, where applicable.
Discount rate	The same annual rate for both costs and health effects (currently 3.5%)	Costs and health outcomes are discounted at a rate of 3.5% per annum in the base case analysis.

EAG – External Assessment Group; NICE – National Institute for Health and Care Excellence; ICER – incremental cost-effectiveness ratio; QALY – quality-adjusted life year; NHS – National Health Service; PSS – Personal Social Services; AE – adverse event

4.3.3 Main issues identified from the EAG's critical appraisal

The main issues identified from the EAG's critical appraisal are summarised in Box 1. These are discussed in further detail in the subsequent sections.

Box 1: Summary of the main issues identified within the company's health economic model

(1) Model errors
(2) Concerns regarding efficacy data used in the model
(3) Concerns regarding company's approach to modelling mortality risks
(4) Concerns regarding health state utility values
(5) Concerns regarding resource use and cost assumptions
(6) Limitations regarding the approach for modelling AEs

(1) Model errors

Following the clarification round, the company submitted an updated version of their model which addresses some of the errors initially identified by the EAG (clarification response,[7] questions B10, B27, B28, B29 and B30), which impacted the company's base case. Whilst checking the updated version of the model submitted, the EAG has identified three further errors, which are summarised below:

a) *Incorrect calculation of the mean proportion of males.* The proportion of males used in the base case analysis is estimated as a weighted mean from the proportions of males in each treatment arm for the subgroup of patients with localised disease in the COG ACCL0431 trial ('[redacted]', which leads to a proportion of [redacted]). However, in the file containing the data for this subgroup which was shared with the EAG, named 'COG ACCL0431 localised only data.pdf', the number of males in both arms of the trial is available ([redacted] in a total of 77 patients in the subgroup), which leads to an estimated proportion of [redacted] males. The EAG considers this to be a very minor issue which will have a negligible impact on the ICER.

b) *Use of life tables for England and Wales.* In response to clarification question B10,[7] the company explained that the updated model uses general population life tables for England and Wales for the period 2020 to 2022.[55] The EAG believes that it would be more appropriate to use life tables for England only.[121]

c) Incorrect calculation of costs of internal component of cochlear implants. Part of the formulae in the trace worksheets, columns BF to BI (the 'INDEX)' component) that returns the probability of the internal component cochlear implants requiring replacement in each cycle of

the model is offset by one year. The EAG considers this to be a very minor issue which will have a negligible impact on the ICER.

The EAG notes that these errors have a minor impact on the results of the model. The EAG's exploratory analyses include the correction of these errors (see Section 4.4).

(2) Concerns regarding efficacy data used in the model

In the model, treatment efficacy is captured by two separate measures: (i) the probability of developing hearing loss (development of HL or no/minimal HL), and (ii) the probability of developing one of the four HL severity levels, conditional on having developed hearing loss. In the base case analysis, these probabilities are informed by three different sources: (a) the proportion of patients experiencing HL from observed count data for the overall efficacy population in the COG ACCL0431 trial[19] (the primary outcome of the trial); (b) the proportion of patients having Grade ≥1 or Grade ≥2 HL from Orgel *et al.,*[20] which corresponds to a *post hoc* analysis of the COG ACCL0431 trial, and (c) the proportion of patients who experienced Grades 2 to 4 HL from Knight *et al.*[8]

Using this approach, the final transition probabilities from the initial state of no/minimal HL state to each of the five alive health states (no/minimal, mild, moderate, marked and severe HL) uses a combination of one to three of these sources. For example, in the base case analysis these probabilities (shown in Table 25) are obtained for the STS treatment group as follows:

- Minimal/ no HL: proportion of patients who did not experience HL in the COG ACCL0431 trial = [redacted]
- Mild HL: proportion of patients who experienced HL in the COG ACCL0431 trial ([redacted]) multiplied by the proportion of patients with Grade 1 HL from Orgel *et al.* (0.778*)* = [redacted]
- Moderate HL: proportion of patients who experienced HL in the COG ACCL0431 trial ([redacted]) multiplied by the proportion of patients with Grade 2+ HL from Orgel *et al.* (0.222), multiplied by the proportion of patients in Grade 2 HL within Grades 2-4 from Knight *et al.* (0.813) = [redacted]
- Marked HL: proportion of patients who experienced HL in the COG ACCL0431 trial ([redacted]) multiplied by the proportion of patients with Grade 2+ HL from Orgel *et al.* (0.222), multiplied by the proportion of patients in Grade 3 HL within Grades 2-4 from Knight *et al.* (0.063) = [redacted]
- Severe HL: proportion of patients who experienced HL in the COG ACCL0431 trial ([redacted]) multiplied by the proportion of patients with Grade 2+ HL from Orgel *et al.* (0.222), multiplied by the proportion of patients in Grade 3 HL within Grades 2-4 from Knight *et al.* (0.125) = [redacted]

Although the EAG considers it necessary to use a stepwise approach to estimate the proportions of patients in each HL heath state (because the pivotal trial that informs the model does not capture the

different hearing loss severity levels), the EAG has some concerns regarding the overall approach adopted by the company to capture treatment efficacy of STS on hearing outcomes.

a) Use of evidence for treatment efficacy from different sources and HL grade systems

The primary endpoint in COG ACCL0431 was the proportional incidence of hearing loss based on the ASHA criteria for ototoxic hearing loss, which defines ototoxic change as a binary outcome (yes/no) based on threshold changes from baseline. The study did not capture the severity of hearing loss using other systems or measurements, which means that it is necessary to use external data to inform the different severity loss levels for those patients experiencing hearing loss in the model. Orgel *et al.*[20] is a reassessment of the COG ACCL0431 trial data which reports the proportion of patients with SIOP Grade ≥1 and with SIOP Grade ≥2 cisplatin-induced hearing loss for each treatment group, and therefore includes the same population as in the original trial. However, it does not discriminate between all HL levels. For this reason, the company used the data from Knight *et al*,[8] which reports data of 67 patients aged 8 months to 23 years evaluated using Brock's Grade system (1 to 4) who received platinum-based chemotherapy.

This stepwise approach creates a potential issue of data incongruence between the different sources, due to the use of different grading systems. The company clarified that *"no adjustments were made, or can be made with the data available, to account for differences between the different scales"* (clarification response,[7] question B7). In response to clarification question A19,[7] the company sought clinical expert opinion which suggested that *"there is a degree of variability in terms of scales used in UK clinical practice"* and that although ASHA is more commonly used in the USA, one of the leading centres in the UK in this area uses both the Brock and SIOP ototoxicity grading scales. This view was also confirmed by the EAG's clinical advisors. The company also presented evidence from Clemens *et al.*,[35] which suggests that there is generally good concordance between the scales, including between Brock and SIOP ($\kappa = 0.840$), and from Knight *et al.*[37] which suggests that the SIOP ototoxicity scale may be superior to the others, although the sensitivity between SIOP and ASHA in detecting any ototoxicity may be comparable (55% vs 56%), whilst the sensitivity for the Brock scale (40%) was lower. Clinical advisors to the EAG mentioned that SIOP was not available when the COG ACCL0431 trial was conducted, but it is now more commonly used in clinical practice than ASHA.

In order to address this potential issue, the company conducted additional scenario analyses using different combinations of data sources for HL occurrence and HL severity (clarification response,[7] question A19, reproduced in

Table 39).

Table 39: Results for base case and scenario analyses using different sources for efficacy, updated version of the model submitted at clarification (adapted from clarification response, Table 10)

Analysis	Source for HL occurrence (HL scale/criteria)	Source for HL severity (HL scale/criteria)	ICER
Base case	COG ACCL0431 (ASHA)	Orgel *et al.* (SIOP) combined with Knight *et al.* (Brock)	£[redacted]
Scenario 1	COG ACCL0431 (ASHA)	Orgel *et al.* (SIOP) combined with SIOPEL 6 (Brock)	£[redacted]
Scenario 2	Orgel *et al.* (SIOP)	Orgel *et al.* (SIOP) combined with Knight *et al.* (Brock)	£[redacted]
Scenario 3	Orgel *et al.* (SIOP)	Orgel *et al.* (SIOP) combined with SIOPEL 6 (Brock)	£[redacted]
Scenario 4	SIOPEL 6 (Brock)	SIOPEL 6 (Brock)	£[redacted]
Scenario 5	COG ACCL0431 (ASHA)	SIOPEL 6 (Brock)	£[redacted]

ASHA – American Speech-Language-Hearing Association; HL – hearing loss ;ICER – Incremental cost-effectiveness ratio; SIOP – International Society of Paediatric Oncology

The EAG considers the use of 3 sources as part of the base case analysis to be unnecessary and considers that using only data from Orgel *et al.*[20] and Knight *et al.*[8] may be more appropriate (scenario 2, which increases the ICER by approximately £2,916). The EAG also highlights that Orgel *et al*. still includes the same population as in COG ACCL0431, and its use could reduce potential biases from using data based on different scales/systems applied in the same underlying trial population. The EAG explores the use of efficacy data based on alternative combinations of sources as part of the exploratory analysis in Section 4.4.

b) Efficacy data not specific for localised disease subgroup

Data to inform efficacy (HL occurrence) in the base case analysis of the model were obtained from the overall efficacy population of the COG ACCL0431 trial, rather than the localised disease subgroup of patients, which is the target population for this appraisal (as per the licensed indication). Data from the localised disease subgroup of COG ACCL0431 are already used to inform other parameters in the model, such as mortality, baseline characteristics and drug costs. The EAG highlights that this issue is restricted to the base case analysis and the scenario analysis that use data from COG ACCL0431, but not to scenario analysis which explore the use of data of SIOPEL 6 to inform the model, since all patients in SIOPEL 6 have localised disease.

In response to clarification question B6,[7] the company stated that the efficacy of STS in preventing hearing loss is independent of the extent of disease and that it is a treatment for preventing hearing loss and not for the underlying cancer. The company also justifies including the efficacy data for the study overall population, including metastatic patients who would fall outside the licenced indication, due to

the study not being powered for an analysis in the subpopulation of localised patients. The company also argues that a subgroup analysis in localised patients would break randomisation, reduce the sample size and increase the uncertainty in the analysis.[7] The company's response to clarification question B6 stated that *"both ITT population (47/125 patients) and efficacy population (40/104 patients) included 38% of patients who were classified as having metastatic disease."* The EAG believes that the argument of the company is inconsistent, since data from this subgroup already inform survival, baseline characteristics (age, weight, proportion of males) and the costs of STS in the model. Therefore, choosing not to use efficacy data for the localised subgroup of patients creates a mismatch between the evidence used to inform the model.

The EAG cautions that the use of data for this subgroup would not be possible when adopting an alternative approach for efficacy data using Orgel *et al.*[20] and Knight *et al.*[8] only (see issue 1(a)), since Orgel *et al.* has not reported results for this subgroup. Nonetheless, alternative sources of efficacy data, including the localised disease subgroup in the COG ACCL0431 trial, were also considered in the EAG's exploratory analyses presented in Section 4.4.

(3) Concerns regarding company's approach to modelling mortality risks

The company's approach for modelling survival starts from the principle that STS does not impact on the patient's mortality risk, which is therefore assumed to be the same for both treatment groups. The OS results from COG ACCL0431 and SIOPEL 6 showed no statistically significant difference between STS+CIS and CIS treatment arms for this outcome. The model also assumes that mortality risks are the same regardless of whether patients experience HL, or the severity of HL, which the EAG considers appropriate given the nature of the condition.

The model includes three separate components to model survival: (i) use of observed OS data from combined treatment arms from the trial (localised disease subgroup) for the first five years given the limited follow-up data available; (ii) application of an SMR[54] to general population life tables for England and Wales for years 6 to 10, and (iii) direct use of general population life tables from year 11 onwards (thereby assuming full cure). The EAG agrees that the assumption of equivalent mortality between the treatment groups is reasonable, given the nature of the drug being appraised and considering the assumption that patients receive similar chemotherapy regimens in both groups. Nonetheless, the EAG has some concerns regarding the company's approach to handling mortality risks within the model.

a) No consideration of other approaches to model survival using OS data from the trials

The chosen approach to inform the mortality risks included the direct use of KM OS estimates from the subgroup of patients with localised disease in the COG ACCL0431 trial for 5 years, that is, the period

for which data were available. The EAG agrees that the use of estimates for localised patients only is appropriate, as the inclusion of metastatic patients would bias the estimates considered for the population of interest in this appraisal eligible to receive STS. However, the CS does not present any analyses which use parametric models fitted to the OS data from the trials; the company's justification for this was based on the immaturity of the data, with a median follow-up of 5.33 years in the COG ACCL0431 study and the small number of events. At the median follow-up, in the ITT population 18 deaths (29.5%) in the STS+CIS arm and 12 deaths (18.8%) in the CIS arm were observed, whilst in the localised disease subgroup [redacted] deaths ([redacted]%) in the STS+CIS arm and [redacted] deaths ([redacted]%) in the CIS arm were observed. The EAG considers that the approach undertaken by the company may be reasonable given the limitations of the available data, but that it would have been useful to explore predicted survival beyond the follow-up period, and potentially to avoid reliance on an SMR. However, with the low number of events in the trials, it is unclear if the use of parametric models would have presented a reasonable fit to the observed data.

b) *Use of SMR value from Fidler et al.*[54]

The CS[1] (Section 3.4.5) states that even though the use of parametric models to extrapolate OS data from the trials was not considered appropriate due to the limited follow-up and small number of events, patients would likely still have an increased rate of mortality compared with the general population. From years 6 to 10 in the model, an SMR of 9.1 taken from Fidler *et al.*[54] is applied to the mortality rates from the age and sex-matched general population from England and Wales. The value chosen corresponds to the estimate for all patients included in the study for all causes of death, except for deaths due to a mental disorder. The EAG notes that Fidler *et al.*[54] is a cohort study which included patients diagnosed with cancer under the age of 15 years from 1940 to 2006 in Britain. During the clarification stage, the EAG asked the company to provide further information regarding how this study relates to the target population for the current appraisal and COG ACCL0431 and SIOPEL 6 trials (clarification response,[7] question B11). The company highlighted that Fidler *et al.*[54] included a large UK cohort of patients with paediatric cancer, including a broad range of solid cancer tumour types and with age of diagnosis under 15 years, that has a degree of concordance with the COG ACCL04321 study. The company noted, however, that there may be less concordance between Fidler *et al.*[54] and SIOPEL 6, since SIOPEL 6 included only younger patients with hepatoblastoma.[7]

The EAG notes, however, that the reasons for choosing the SMR estimate from Fidler *et al.*[54] for the overall population and all causes of death (including recurrence or progression, subsequent primary neoplasm or non-neoplastic causes, but excluding mental health-related causes) are unclear. In the study, SMR estimates were also available by major cause of death groups, by age of diagnosis or by follow-up period. For example, the estimated SMR for patients diagnosed at 5-9 years old is 10.5 (95%

CI 10.0-11.1), whilst the estimates for all causes of death by follow-up period are presented in Table 40.

Table 40: SMR estimates reported in Fidler *et al.*,[54] all causes of death, by follow-up period

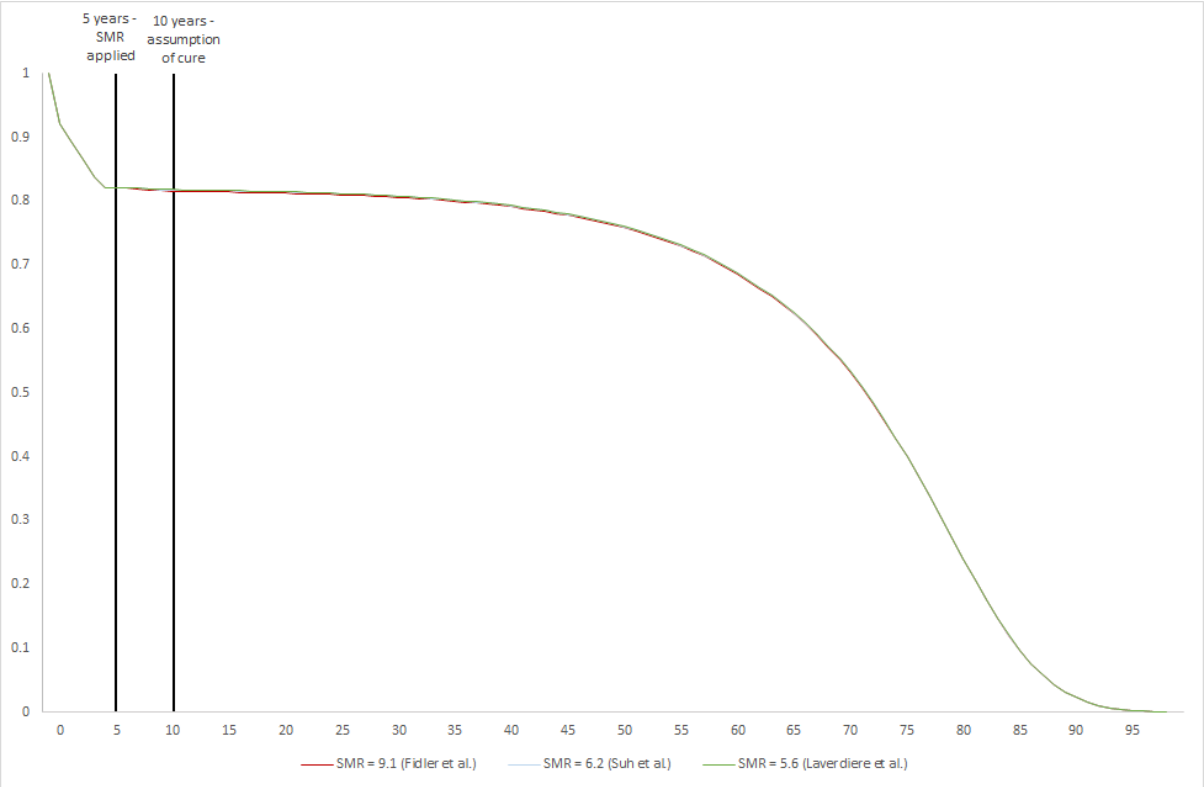
Follow-up (years)	SMR	95% CI
5-19	19.9	19.2 – 20.6
20-29	5.4	4.9 – 5.8
30-39	4.2	3.8 – 4.6
40-49	3.3	2.9 – 3.7
50-59	2.4	2.0 – 2.9
≥60	2.3	1.3 – 3.7

SMR – standardised mortality ratio

The company has also presented alternative sources for the post-cancer SMR identified from targeted literature searches conducted by the company (clarification response,[7] question B11): Laverdiere *et al.*[119] reported a SMR estimate of 5.6 based on data from neuroblastoma survivors diagnosed in 1970–1986 in United States and Canada; and Suh *et al.*[120] reports a SMR estimate of 6.2 from five-year cancer survivors diagnosed in 1970–1999 in North America. The company noted that both estimates are lower than the estimate from Fidler *et al.*[54] and the use of lower SMR values reduce the ICER, and therefore their current approach was considered conservative and more appropriate because Fidler *et al.*[54] included patients from the UK.[7] The EAG believes that there is uncertainty around which SMR estimate would be more appropriate for use in the model, and whether the use of a single value only in addition to an assumption of cure at 10 years corresponds to the best approach. The EAG notes that changing SMR values alone with similar values (such as from Fidler *et al.*,[54] Laverdiere *et al.*[119] and Suh *et al.*[120] which all report SMRs of between 5 and 10), without changing the assumption of cure at 10 years, have a very limited impact on survival and on the ICER. The use of SMR estimates from Laverdiere *et al.*[119] and Suh *et al.*[120] decrease the ICER by £61 and £51, respectively.

Figure 8 shows the predicted survival in the model using the SMR estimates from the three studies.

Figure 8: Model estimates of survival using different SMR estimates (generated by the EAG using the company's updated version of the model)*



SMR – Standardised mortality ratio

** All survival estimates include the assumption of cure after 10 years*

Alternative estimates for the SMR, including the use of values by follow-up period, combined with changes in the timepoint of the assumption of cure (see critical appraisal point 3[c]), are explored in Section 4.4.

c) Assumption of cure timepoint

The model assumes that after 10 years, surviving patients experience the same mortality risk as the general population in England and Wales of the same age, which corresponds to an assumption of cure. The CS[1] justified this assumption on the basis that a similar assumption was used in TA538[105] a previous NICE appraisal of dinutuximab beta for high-risk neuroblastoma patients aged 12 months and over, and in TA817,[106] an appraisal of nivolumab in invasive urothelial cancer at high risk of recurrence. The EAG notes that the population in TA817 was an adult population and therefore it is unclear about its direct relevance to the population of interest in the current appraisal.

One of the EAG's clinical advisors stated that the risk of death in this population of paediatric patients with solid tumours remains higher than that of the general population even after 40 years. They referred to a study of 34,230 eligible 5-year or greater cancer survivors from US with various types of cancers

who were diagnosed before the age of 21 years and between 1970 and 1999 (Dixon *et al.*,[122]). This study suggests that cancer survivors have an elevated risk of death compared with the general US population of comparable age, sex, and calendar-year (SMR: 5.6, 95% CI: 5.4–5.7), with higher risks estimated at 5–9 years from diagnosis (SMR: 18.1, 95% CI: 17.3–18.9) which subsequently decrease and plateau from 20 years from diagnosis onwards (SMR 20 years: 3.9, 95% CI: 3.6–4.2; SMR ≥40 years: 4.0, 95% CI: 3.5–4.5).

In their response to clarification question B9,[7] the company disagreed with the EAG's view, suggesting that Dixon *et al.* is not an appropriate source for the model, because it includes patients diagnosed at older ages (18 to 21 years) than the targeted population of this appraisal, and that the overall SMR reported in the study was lower than in Fidler *et al.*. The company also stated that its base case is considered conservative, and that applying an SMR of 9.1 at 40 years would not be considered appropriate. The company also reiterated that the 10-year cure point is in line with approaches adopted in TA538[105] and TA817[106] (originally mentioned in the CS) and with literature retrieved by a targeted literature search performed by the company: Brosa *et al.*[123] reported patients with high-grade, non-metastatic, resectable osteosarcoma were assumed to have a mortality rate equivalent to the general population from 12.25 years, whilst Aerts *et al.*[124] and Oldenburg *et al.*[125] reported 11.2- and 12-year relapse time periods, respectively. The EAG notes that Brosa *et al.*[123] is an economic evaluation, rather than an empirical clinical study, and that it is unclear why the specific timepoint of 12.25 years was chosen in this particular study. The EAG believes that there is uncertainty around whether the assumption of full cure is appropriate, and if so, the timepoint at which this should be applied. The EAG's exploratory analysis includes scenarios around both aspects (the cure timepoint and the use of multiple SMRs as an alternative to the cure assumption); these are reported in Section 4.4.

(4) Concerns regarding health state utility values

The model uses health state utility values derived from HUI3. The NICE Methods Manual[22] recommends the use of the EQ-5D-3L for adults, but does not specify a preferred approach for measuring and valuing health in paediatric populations. Utility values derived from HUI3 were also used in the previous NICE appraisal of cochlear implants for children and adults with severe to profound deafness (TA566).[91]

The EAG notes that the health state utilities for marked and severe HL in the base case analysis include an additional utility gain related to the use of cochlear implants, but not for hearing aids. This approach is justified by the company as being due to the utility values for moderate to severe HL health states taken from Barton *et al.*[56] being assumed to already account for the impact of hearing aids (clarification response B14e).[7] At the factual accuracy check stage,[126] the company shared additional information with the EAG where one of the authors of the study (via personal communication) confirms that the

study compared '*children whose hearing loss was managed with cochlear implants and children whose hearing loss was managed in any other way*', with '*any other way'* corresponding to management with '*acoustic hearing aids*', 'any other assistive devices' or 'none', but there is a *'strong likelihood*' that the majority of patients would have received hearing aids since it was the standard practice in the NHS at the time of the study. The EAG also notes that the model assumes the same utility gain for cochlear implants regardless of age, hearing loss severity and duration of use of the devices. This issue was discussed in NICE NG98[116] (Appendix N) and was deemed as a simplification in the model, which was agreed by the NICE Guideline Development Group. NG98 states that there was no evidence to support different estimates of utility gain for people with different degrees of hearing loss.[116] Although these issues may be considered areas of remaining uncertainty in the model, the EAG is unable to provide an estimate of the likely impact in the results, and therefore the EAG has not explored changes to these assumptions used in the model related to health state utility gains from use of hearing devices as part of the exploratory analysis.

(5) Concerns regarding resource use and cost assumptions

The EAG has several concerns regarding the resource use and cost assumptions used in the company's model.

(i) Drug acquisition costs

The estimated drug acquisition costs for STS are implicitly assumed to include any discontinuations and dose reductions, since they are based on the mean cumulative dosage and mean number of visits observed in COG ACCL0431 (or SIOPEL 6 if considering scenario analysis). In their response to clarification question A17,[7] the company reported the number of patients in COG ACCL0431 who discontinued protocol therapy by type of reason for discontinuation. [redacted] patients ([redacted]) in the STS+CIS arm and [redacted] patients ([redacted]) in the CIS arm discontinued the treatment protocol in the ITT population, whilst in the localised only subgroup there were [redacted] and [redacted] discontinuations, respectively. The main reasons for discontinuation were '*Premature discontinuation of cisplatin therapy for any reason'*, '*Refusal of further protocol therapy by patient/parent/guardian*' and physician's determination. However, there were [redacted] discontinuations in the ITT population ([redacted] in the localised disease subgroup) in the STS+CIS arm that were due to AEs or STS-unrelated death. In SIOPEL 6, where all patients had localised disease, 2 (3.5%) and 6 (11.5%) patients randomised to STS+CIS and CIS arms, respectively, did not complete the study by not completing the post-treatment hearing assessment, but the reasons for non-completion are unclear.

The company also states in their response to clarification question A17 that *"No dose alterations were required due to AEs."*[7] In response to clarification question A18, the company stated that dose alterations were not permitted in COG ACCL0431 but dose suspensions could occur in cases of AEs

hypernatraemia or allergic reaction, whilst in SIOPEL 6, an experience of metabolic, vascular, neurological or other, presumed to be related toxicity of CTCAE Grade 3+ would lead to treatment termination, but five dose reductions occurred by physicians' decision (not due to a serious AE).

It is unclear at which point in therapy these discontinuations or dose alterations happened and if the data on the dosage received in both COG ACCL0431 and SIOPEL 6 account for these factors. However, the EAG believes that in the absence of time-to-discontinuation data from the trials or any additional data to clarify the proportion of patients discontinuing STS and timing of discontinuation, the current assumption employed in the model appears reasonable.

(ii) Non-inclusion of the costs of cisplatin-containing regimens

The model assumes that the cumulative dose of cisplatin in the chemotherapy regimens received by patients is similar between treatment groups, and therefore the costs of cisplatin were excluded from the analyses. In response to clarification question B13,[7] the company presented data on the mean cumulative dosage of cisplatin by treatment arm for localised patients in COG ACCL0431, SIOPEL 6, and the pooled analysis with the two studies requested by the EAG (see Table 9). For the three analyses, the mean cumulative dose was similar between the two groups, but was numerically higher in the treatment arm that received only cisplatin-containing regimens. The EAG notes that the inclusion of the costs of cisplatin in the base case would favour the STS group; however, since patients could have received combined chemotherapy regimens according to the protocols available to their underlying type of cancer, it is difficult to predict the impact of the inclusion of the costs of the chemotherapy regimens without more details on the regimens, schedule and dosage of each regimen component received. Therefore, the EAG believes that the exclusion of the chemotherapy costs seems appropriate given the evidence presented by the company.

(iii) Frequency of hearing assessments

As discussed in Section 4.2.4.6, the frequency of audiology assessments used in the model was based on Dionne *et al.*,[89] and on assumptions informed by audiologists interviewed by a consultancy company in 2018.[59] It is unclear why the company used assumptions for the majority of these frequencies, when Dionne *et al.* reports the frequencies by HL grades across the three age group categories (0-5, 6-11 and 12-18 years old). The EAG explored the use of all frequencies from Dionne *et al.*[89] where available, and notes the impact of this change on the ICER is small.

(iv) Assumptions regarding hearing assessment and speech and language therapy costs

The company's model assumes that patients in the mild and moderate HL states will not undergo any speech and language therapy throughout their lifetime, whilst patients in the marked and severe HL states will continue to receive weekly sessions until they reach 18 years of age, and after that age the

number of annual sessions reduces dramatically or ceases. The EAG notes that Dionne *et al.*[89] reports weekly speech therapy only for patients diagnosed with Grade 3/4 HL between the ages of 0 and 5, which is younger than the mean starting age in the model. For children aged 6 years-old and higher, the study reports weekly sessions with 'Hearing Resource Teacher' and speech language pathologist 'as needed', which may correspond to different resources than used by the company in the model. The results of the interviews with audiologists presented by the company suggest that the frequency for patients with marked and severe HL might be overestimated, since the views from the healthcare professionals were that "[redacted][59] The EAG's exploratory analyses include alternative frequencies of language and speech therapies for patients in the mild to severe HL states, as informed by the audiologists' report provided by the company.

(v) Inclusion of FM costs for all patients

The model assumes that all patients who experience hearing loss will receive an FM system, regardless of severity level, and that the system will be used for the patients' lifetime, including periodic replacement. The EAG considers that these assumptions may overestimate the costs of these systems, since it seems unlikely that all patients with mild HL would require them, or that all patients would continue to use them throughout all of their adulthood. Dione *et al.*[89] included the costs of FM systems in their study only for patients with grade 2 or higher HL. In response to clarification question B18,[7] the company mentions that the audiologists interviewed[59] stated that most children have personal FM devices or other accessories, and that one expert commented that *"all children irrespective of their age, even babies, little ones, should have access to some FM systems."* The EAG notes that this report mentions that in the UK, FM systems are provided in classrooms and funded by local education authorities, and that [redacted] The EAG's exploratory analyses include scenarios which include alternative assumptions regarding the costs of FMs, such as applying these costs only to patients who receive hearing aids or cochlear implants, and removing the cost when patients reach adulthood.

(vi) Inclusion of costs of depression and anxiety

The model includes the costs of 'depression and anxiety' based on the incidence of depression by the status of hearing loss (no HL or with HL) reported in Gurney *et al.*[98] The company uses the observed count data from the study; however, the study reports that: *"Substantive differences by hearing loss were not observed for problems with writing skills, behavioural concerns, anxiety, or depression (Table 3)."*[98] In response to clarification question B23,[7] the company reiterated their view that costs related to depression should be included in the model, and that in the study more patients with hearing loss were

reported to experience depression compared to those without, and that other literature indicates that hearing loss can contribute to anxiety and depressive symptoms amongst cancer survivors. The EAG explores the removal of the costs of depression as part of exploratory analysis.

(6) Limitations regarding the approach for modelling AEs

The company's base case model includes the impact of STS treatment-related SAEs reported in ≥2% of either arm in the full safety population from the COG ACCL0431 trial. Because the observed frequency of events was <2% in both groups, the model does not include any impacts associated with AEs on patients' HRQoL or costs. The EAG believes that the company's model may underestimate the negative impact of treatment-related AEs on HRQoL and costs because the base case analysis only considers SAEs. In their response to clarification question B24,[7] the company stated: *"it is more appropriate to use the latter [treatment-related SAEs], as the list of Grade 3+ AEs includes AEs which are related to cisplatin, and there is no reason to believe cisplatin-related AEs would differ between treatment arms. This position is supported by the fact that the overall incidence of AEs was similar between the two arms, as shown in Section B.2.10.2 of the CS."* The company also highlighted that a scenario analysis using the incidence of Grade 3+ AEs with a cut-off of ≥10% from the full safety population had been already presented in the CS. The company's updated model also includes the data for Grade 3+ AEs with a cut-off of ≥5% from the localised disease subgroup in the COG ACCL0431 trial and in the pooled analysis with COG ACCL0431 and SIOPEL 6 patients, as requested by the EAG. The company has also provided separate additional data for SAEs occurring in ≥2% of patients for the localised disease subgroup of patients in COG ACCL0431 and in pooled analysis as part of the clarification response; however, these rates of SAEs have not been included in the updated version of the model. The updated base case analysis retains the use of only treatment-related SAEs for the overall population in the COG ACCL0431 trial, and therefore no impact of AEs on costs and HRQoL is included.

The EAG believes that the impact of Grade 3+ AEs should be included as part of the base case analysis in order to better capture the impact of these events on HRQoL and costs. However, their impact on the results is limited (increasing the ICER by £328 or less, depending on the selected cut-off and the source of AE frequency data). The EAG also believes that the AE incidence data should align with the population data for the localised disease subgroup, which is used in the base case analysis for the baseline characteristics, survival and drug costs. The company has included data on SAEs for this group of patients as part of their clarification response, but it has not included the functionality to explore this data within the updated model. In addition, no evidence has been provided regarding the AEs reported being related exclusively to cisplatin. Hence, the use of Grade 3+ AEs reported in ≥10% and ≥5% patients are considered as part of the EAG's exploratory analyses.

4.4 Exploratory analyses undertaken by the EAG

4.4.1 EAG exploratory analysis – methods

The EAG undertook exploratory analyses (EAs) using the updated version of the company's model submitted at the clarification stage to address the key points identified within the critical appraisal (Section 4.3.3). All EAs were undertaken using the deterministic version of the model. The EAG's preferred analysis was also undertaken using the probabilistic version of the model. All analyses presented in this section reflect the PAS price of STS. The EAG's preferred analysis is comprised of 9 sets of amendments to the company's model.

EAG's preferred analysis

EA1: Correction of errors

(a) *Use of life tables for England.* The model was amended to include general population life tables for England only (2020-2022).[121]

(b) *Mean proportion of males.* The model was amended to include the mean proportion of males using the count data from both treatment arms in the COG ACCL0431 trial, thus replacing [redacted] with [redacted].

(c) *Costs of internal component of cochlear implants*. The EAG corrected the model to ensure that the formula in columns BF to BI returns the correct probability of the internal component cochlear implants requiring replacement in each cycle of the model, by amending the 'INDEX' component in its multiple occurrences to use the values in column D instead of C as the row number.

All subsequent exploratory analyses include the error corrections included in EA1.

EA2: Use approach for SMR

The EAG preferred the approach where multiple SMR estimates are applied to estimate the mortality risks for the population in the model, using SMR estimates by follow-up period, as reported by Fidler *et al.* (see Table 40). Within this exploratory analysis, the assumption of cure at 10 years was maintained.

EA3: Use of alternative approach for cure time point

In this exploratory analysis, the EAG explored removing the assumption of cure at 10 years from the model, by setting the period of application of the SMR after the first five years of the model to 200 years. The EAG notes that this exploratory analysis keeps the original SMR estimate of 9.1 from the company's base case, applied to all cycles after year 5.

EA4: Disease management costs (hearing assessments and speech and language therapies)

The EAG preferred to use the frequencies of hearing assessments reported by Dionne *et al*.[89] (Table 41) for all age groups and HL health states. The EAG amended the model to include the flexibility to apply different frequencies to allow for changes in the mean initial age of the population. The EAG notes that since the model structure includes the same frequency for patients in mild and moderate HL states for 0-5 years and all HL states for 6-18 years, the EAG obtained the correspondent frequencies by using the average between the corresponding groups. The resulting frequencies used in the model are presented in Table 42. The EAG notes that the frequency of hearing assessments for patients ≥18 years old (0.25 assessments per year) was maintained, since Dionne *et al*.[89] does not include data for adults. In this analysis, the EAG also preferred to use the frequencies of annual speech and language therapy sessions from the company's audiologists report[59] (

Table 43).

Table 41: Frequencies of annual hearing assessments reported by Dionne *et al*.

HL health state	Current age in the model	Age group at diagnosis		
		0-5 years	6-11 years	12-18 years
Grade 1 HL	0-5 years	2.50	0.00	0.00
	6-11 years	1.00	1.00	0.00
	12-18 years	1.00	1.00	1.00
Grade 2 HL	0-5 years	3.00	0.00	0.00
	6-11 years	1.50	1.00	0.00
	12-18 years	1.00	1.00	1.00
Grade 3 and 4 HL	0-5 years	3.00	0.00	0.00
	6-11 years	2.00	2.00	0.00
	12-18 years	1.00	1.00	1.00

HL- hearing loss

Table 42: Comparison of frequencies of annual hearing assessments - company's base case versus EAG's alternative approach

HL health state	Current age in the model	Company's base case	EAG's alternative approach (by initial age group)		
			0-5 years	6-11 years	12-17 years
Mild and Moderate HL	0-5 years	2	2.75	0	0.00
	6-17 years	1	1.07	1.17	0.50
	≥ 18 years	0.25	0.25		
Marked and Severe HL	0-5 years	3	3	0	0.00
	6-17 years	1	1.07	1.17	0.50
	≥ 18 years	0.25	0.25		

HL- hearing loss

Table 43: Frequencies of speech and language therapies from the audiologists report[59]

Health state	Number of therapy sessions per year
Mild HL	[redacted]
Moderate HL	[redacted]
Marked HL	[redacted]
Profound HL*	[redacted]

HL- hearing loss
**The EAG notes that the frequency for profound HL mentioned in the report was used for the severe HL heath state in the model.*

EA5: Alternative approach for disease management costs (FM systems)

In this exploratory analysis, the EAG amended the model to include the costs of FM systems only for patients who receive hearing aids or cochlear implants ([redacted] mild HL, [redacted] moderate HL, [redacted] marked HL and [redacted] severe HL), instead of 100% for all HL states.

EA6: Exclusion of costs for treatment of depression

In this analysis, the EAG explored the impact of removing all costs associated with treatment of depression from the model, by setting the switch variable for 'include HL-induced depression costs and disutilities' to 'No'.

EA7: Alternative approach for AEs incidence

In this exploratory analysis, the EAG explored the approach used in the company's scenario analysis whereby the AEs incidence was based on safety data for Grade 3+ AEs occurring in ≥10% of patients from the COG ACCL0431 trial.

EA8: Use of efficacy data for HL incidence from the COG ACCL0431 trial for localised disease subgroup instead of overall population

In this analysis, the EAG amended the model to use the count data from the localised disease subgroup analysis from COG ACCL0431[7] to inform the probabilities of developing HL or Minimal/No HL (see Table 14). This aligns the data on HL incidence used in the model with the licenced indication for STS, however, it inevitably uses data from a smaller sample size population to inform the model which may increase uncertainty. The EAG notes that in this analysis, data from Orgel *et. al.*[20] combined to Knight *et al.*[8] are still used to estimate HL severity in the model.

EA9: EAG's preferred analysis

This analysis combines EAs 1-8. Results are presented using both the deterministic and probabilistic versions of the model (EA9a and EA9b, respectively).

Additional sensitivity analyses

The following additional sensitivity analyses (ASAs) were conducted using the deterministic versions of the EAG's preferred analyses (EA9a), to explore the impact of the assumption of cure and the chosen timepoint from which it is applied, alternative costs assumptions and for AEs incidence, and use of alternative data sources for treatment efficacy (HL incidence and HL severity).

ASA1: **Use of alternative cure timepoints**

Within this additional analysis, the model was re-run restoring the inclusion of the cure assumption, using alternative timepoints: (a) 10 years, (b) 15 years and (c) 20 years.

ASA 2: Exclusion of the costs for FM systems

In this sensitivity analysis, the EAG removed all costs associated with FM systems by setting the proportions of patients who receive them in each health states to zero.

ASA 3: Inclusion of the costs of treatment of depression

In this sensitivity analysis, the EAG reinstated the costs associated with the treatment of depression, using the estimates from the company's base case model.

ASA 4: Alternative approach for AEs incidence

Within this additional analysis, the model was re-run using the AE incidence rates for Grade 3+ AEs occurring in ≥5% of patients based on data from the COG ACCL0431 study.

ASA5: Use of alternative sources of efficacy data (HL incidence and HL severity)

Based on the studies available, it is not possible to estimate both HL incidence and severity in the target population using a single source. This leads to some uncertainty around the magnitude of treatment benefit for STS. In order to provide the NICE appraisal committee with a more comprehensive set of analyses exploring the uncertainty related to the treatment benefit in terms of prevention of hearing loss and HL severity, in this additional analysis the EAG explored the individual impact use of alternative combinations of sources of efficacy data, as follows:

(a) Pooled data from COG ACCL0431 and SIOPEL 6 (localised disease patients only)[7] to inform HL incidence and Orgel *et al.*[20] combined with Knight *et al.*[8] for HL severity. The EAG notes that, as discussed in Section 3.3.3.2, the use of the pooled data from the two trials may not be ideal due to study differences such as patient population and study design; therefore, the EAG opted not to include it as part of the EAG preferred analysis;

(b) Pooled data from COG ACCL0431 and SIOPEL 6 (localised disease patients only)[7] to inform HL incidence and Knight *et al.*[8] for HL severity, as an extreme scenario where it is assumed that the benefit of STS therapy is restricted to avoiding the development of HL but not its severity;

(c) Orgel *et al.*[20] to inform HL incidence and Orgel *et al.*[20] combined with Knight *et al.*[8] for HL severity. The EAG notes that this analysis includes data which are not specific to patients with localised disease, but attempts to reduce the number of different grade systems and to reduce potential biases from using data based on different scales/systems applied in the same underlying trial population (see Section 4.3, issue [2]).

(d) Data from COG ACCL0431 (overall efficacy population from the trial, including localised and metastatic disease patients)[19] to inform HL incidence and Orgel *et al.*[20] combined with Knight *et al.*[8] for HL severity. The EAG notes that this additional scenario corresponds to the efficacy sources used in the company's base-case.

4.4.2 EAG exploratory analysis – results

Table 44 presents the results of the EAG's preferred analyses for the comparison of STS versus ECM. Individual changes are applied in EA2-8 relative to the error corrections identified in EA1; all individual changes are combined in EA9. The results indicate that fixing the remaining errors in the company's base case leads to an estimated ICER for STS versus ECM of [redacted] per QALY gained. Changing preferences around the SMR estimates whilst keeping the cure assumption, using alternative frequencies for hearing assessments and speech and language therapies, changing the proportion of patients who receive FM systems and the source of AE incidence, and removing the costs of depression (EA2, EA4, EA5, EA6 and EA7) do not have a substantial impact on the ICER. However, removing the cure assumption and using data from the subgroup of patients with localised disease in COG ACCL0431 to estimate HL incidence are key drivers of the ICER (EA3, and EA8). Under the EAG's preferred scenario, the ICER for STS versus ECM is estimated to be [redacted] (deterministic) and [redacted] (probabilistic) per QALY gained.

Table 44: EAG preferred analysis results

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER	DM
Company's revised base case (deterministic)								
STS	59.85	18.43	[redacted]	0.00	1.54	[redacted]	[redacted]	**1.0**
ECM	59.85	16.89	£10,187	-	-	-	-	
EA1: Correction of errors								
STS	59.89	18.43	[redacted]	0.00	1.54	[redacted]	[redacted]	**1.0**
ECM	59.89	16.89	£10,189	-	-	-	-	
EA2: Use of alternative values for SMR (multiple SMRs) from Fidler et al‡								
STS	59.45	18.32	[redacted]	0.00	1.53	[redacted]	[redacted]	**1.0**
ECM	59.45	16.79	£10,152	-	-	-	-	
EA3: Exclusion of cure assumption†								
STS	40.54	15.43	[redacted]	0.00	1.36	[redacted]	[redacted]	**1.0**
ECM	40.54	14.07	£9,181	-	-	-	-	
EA4: Alternative sources for frequencies of hearing assessments and speech and language therapies								
STS	59.89	18.43	[redacted]	0.00	1.54	[redacted]	[redacted]	**1.0**
ECM	59.89	16.89	£9,811	-	-	-	-	
EA5: Costs of FM systems only applied to patients with hearing aids or cochlear implants								
STS	59.89	18.43	[redacted]	0.00	1.54	[redacted]	[redacted]	**1.0**
ECM	59.89	16.89	£9,941	-	-	-	-	
EA6: Exclusion of costs of depression								
STS	59.89	18.43	[redacted]	0.00	1.54	[redacted]	[redacted]	**1.0**
ECM	59.89	16.89	£7,963	-	-	-	-	
EA7: Inclusion of Grade 3+ AEs occurring in ≥10% of patients								
STS	59.89	18.41	[redacted]	0.00	1.54	[redacted]	[redacted]	**1.0**
ECM	59.89	16.87	£17,998	-	-	-	-	
EA8: Alternative source of efficacy for HL (COG ACCL0431 data for localised patients + Orgel *et al.* + Knight *et al.*)								
STS	59.89	18.41	[redacted]	0.00	1.31	[redacted]	[redacted]	**1.0**
ECM	59.89	17.10	£9,449	-	-	-	-	
EA9a: EAG preferred analysis (deterministic)								
STS	48.17	15.95	[redacted]	0.00	1.20	[redacted]	[redacted]	**1.0**
ECM	48.17	14.75	£14,332	-	-	-	-	
EA9b: EAG preferred analysis (probabilistic)								
STS	58.28	15.92	[redacted]	0.00	1.19	[redacted]	[redacted]	**1.0**
ECM	58.28	14.73	£17,754	-	-	-	-	

DM - decision modifier; EA - exploratory analysis; ECM - established clinical management; ICER - incremental cost-effectiveness ratio; Inc. - incremental; LYG - life year gained; QALY - quality-adjusted life year; STS - sodium thiosulfate.
** Undiscounted*
‡ Does not include removing the assumption of cure at 10 years
†In this analysis, the original SMR value from Fidler is kept throughout the model

Table 45 presents the results of the EAG's additional sensitivity analysis for STS versus ECM. As shown in the table, including an extreme assumption of no impact of STS treatment on HL severity has the greatest individual impact on the ICER, which increased to [redacted] per QALY gained; however, the EAG cautious that this scenario correspond to a very pessimistic scenario. Using data for HL occurrence from COG ACCL0431 overall population (original approach in company's base-case -

ASA5d) or from pooled data from the trials for the subgroup of localised patients (ASA5a), and reinstating the cure assumption at 10 years (ASA1a) and have a moderate impact on the ICER (decreasing the EAG's preferred ICER to [redacted], [redacted] and [redacted] per QALY gained, respectively). The remaining additional scenario analysis have modest impact on the results, with ICERs ranging from [redacted] to [redacted] per QALY gained.

Table 45: EAG additional sensitivity analysis results

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER	DM
EA10a: EAG preferred analysis (deterministic)								
STS	48.17	15.95	[redacted]	0.00	1.20	[redacted]	[redacted]	**1.0**
ECM	48.17	14.75	£14,332	-	-	-	-	
ASA1a: Inclusion of cure timepoint at 10 years								
STS	59.45	18.28	[redacted]	0.00	1.30	[redacted]	[redacted]	**1.0**
ECM	59.45	16.98	£14,497	-	-	-	-	
ASA1b: Inclusion of cure timepoint at 15 years								
STS	57.83	17.73	[redacted]	0.00	1.28	[redacted]	[redacted]	**1.0**
ECM	57.83	16.45	£14,457	-	-	-	-	
ASA1c: Inclusion of cure timepoint at 20 years								
STS	56.34	17.27	[redacted]	0.00	1.26	[redacted]	[redacted]	**1.0**
ECM	56.34	16.02	£14,423	-	-	-	-	
ASA2: Exclusion of FM systems costs								
STS	48.17	15.95	[redacted]	0.00	1.20	[redacted]	[redacted]	**1.0**
ECM	48.17	14.75	£13,448	-	-	-	-	
ASA3: Re-inclusion of costs of depression								
STS	48.17	15.95	[redacted]	0.00	1.20	[redacted]	[redacted]	**1.0**
ECM	48.17	14.75	£16,077	-	-	-	-	
ASA4: Use of Grade 3+ AEs occurring in ≥5% of patients								
STS	48.17	15.97	[redacted]	0.00	1.20	[redacted]	[redacted]	**1.0**
ECM	48.17	14.77	£6,523	-	-	-	-	
ASA5a: Alternative source of efficacy for HL (Pooled analysis for localised patients + Orgel *et al.* + Knight *et al.*)								
STS	48.17	15.67	[redacted]	0.00	1.39	[redacted]	[redacted]	**1.0**
ECM	48.17	14.27	£15,828	-	-	-	-	
ASA5b: Alternative source of efficacy for HL (Pooled analysis for localised patients + Knight *et al.*)								
STS	48.17	15.29	[redacted]	0.00	0.98	[redacted]	[redacted]	**1.0**
ECM	48.17	14.31	£15,646	-	-	-	-	
ASA5c: Alternative source of efficacy for HL (Orgel *et al.* + Knight *et al.*)								
STS	48.17	16.28	[redacted]	0.00	1.30	[redacted]	[redacted]	**1.0**
ECM	48.17	14.98	£13,604	-	-	-	-	
ASA5d: Alternative source of efficacy for HL (COG ACCL0431 overall population + Orgel *et al.* + Knight *et al.)*								
STS	48.17	15.96	[redacted]	0.00	1.41	[redacted]	[redacted]	**1.0**
ECM	48.17	14.55	£14,946	-	-	-	-	

DM - decision modifier; EA - exploratory analysis; ECM - established clinical management; ICER - incremental cost-effectiveness ratio; Inc. - incremental; LYG - life year gained; QALY - quality-adjusted life year; STS - sodium thiosulfate.
** Undiscounted*

4.5 Discussion

The model submitted by the company was implemented to a reasonable standard although it was associated with some minor errors, which were identified and corrected by the EAG in their exploratory analyses. The EAG, in addition, preferred alternative assumptions to those used by the company which markedly increased the ICER. The factors having the greatest impact on the cost-effectiveness of STS relative to ECM are the assumption that surviving patients experience the same age- and sex-matched mortality risks as the general population after 10 years and the uncertainty regarding the most appropriate sources for efficacy of STS in terms of hearing loss incidence and disease severity.

5 OVERALL CONCLUSIONS

In general, the efficacy (e.g., incidence of hearing loss) and safety of anhydrous STS for preventing ototoxicity caused by cisplatin chemotherapy in people aged 1 month to 17 years with localised solid tumours (i.e. licensed population) was positively demonstrated (compared with cisplatin without STS) in the key studies included in the CS. Safety was largely comparable to cisplatin therapy, with some increases in nausea, vomiting, hypernatremia, hypophosphatemia, hypokalemia, and hypermagnesemia. However, there are a number of limitations and uncertainties in the evidence base which warrant caution in its interpretation. Due to the small sample sizes, slight imbalances of relevant prognostic factors, use of different hearing loss grading scales, lack of statistical power to detect a difference between study groups specific to the licensed population, treatment effects (including the exact magnitude) are uncertain and may be confounded. The key uncertainties relate to complex regimen of administration and the need to observe accurate timing of STS administration relative to cisplatin chemotherapy and the generalisability of the trial results to England. In addition, there is no data available from the STS trials to inform on HRQoL or qualitative data from patients or carers who have experienced concurrent STS/cisplatin emetogenesis.[38]

The EAG considers that the company's economic analysing comparing STS to ECM is relevant to people aged ≥1 month to < 18 years with localised, non-metastatic, solid tumours receiving cisplatin-containing chemotherapy. The deterministic version of the company's revised base case model suggests that STS is expected to generate an additional 1.54 QALYs when compared to ECM, at an additional cost of [redacted] per patient and corresponding ICER of [redacted] per QALY gained.

The key differences between the company's base case and the EAG's preferred analysis included using data from the subgroup of patients with localised disease from COG ACCL0431 to estimate HL incidence, removing the assumption of full cure from the underlying cancer at 10 years, and applying multiple SMR estimates which decreased by time of follow-up period. Other changes implemented by the EAG included the exclusion of costs of depression for all patients and of FM systems for patients who do not receive hearing aids or cochlear implants, assuming different frequencies for hearing assessment and speech and language therapies visits and including the impact on HRQoL and costs from Grade 3+ AEs occurring in ≥10% of patients from the COG ACCL0431 trial.

Overall, the EAG's additional analyses indicate that the ICER for comparing is likely to be higher than estimated by the company and particularly sensitive to: the exclusion of the cure assumption, and the source of data for HL incidence (localised disease subgroup of patients from the COG ACCL0431 trial or pooled analysis with the two trials for the localised disease subgroup, instead of overall efficacy population from the COG ACCL0431 trial). The model is also sensitive at a lesser degree to the use of

multiple SMR estimates after the fifth year of the model, when combined with the exclusion of the cure assumption. The ICER for the EAG's preferred scenario is [redacted] per QALY gained for STS versus ECM when using the deterministic version of the model, and [redacted] when using the outputs of the PSA. The EAG notes that the use of data from the localised disease subgroup of the COG ACCL0431 trial to estimate HL incidence better aligns the efficacy data to the population within the licenced indication for STS. However, it may increase uncertainty due to the smaller sample size population of this trial subgroup.

6 REFERENCES

1. Norgine. Anhydrous sodium thiosulfate (Pedmarqsi) for preventing ototoxicity caused by cisplatin chemotherapy in people aged 1 month to 17 years with localised solid tumours [ID1001]

Company evidence submission.; 2024.

2. Pamela A Mudd, Joel W Jones, F Robert Glatz, Kathleen C M Campbell, Leonard P Rybak. Ototoxicity. Medscape; 2024. https://emedicine.medscape.com/article/857679-overview?form=fpf#a5 (Accessed 10/06/2024).
3. Chattaraj A, Syed MP, Low CA, Owonikoko TK. Cisplatin-Induced Ototoxicity: A Concise Review of the Burden, Prevention, and Interception Strategies. *JCO Oncology Practice* 2023;19:278-83.
4. Tanna RJ, Lin JW, O. DJ. Sensorineural Hearing Loss. 2023. https://www.ncbi.nlm.nih.gov/books/NBK565860/ (Accessed 25/06/2024).
5. Desai A, Das D. Hear Me Out: Mitigating Cisplatin-Induced Ototoxicity. *JCO Oncology Practice* 2023;19:284-5.
6. Li C-M, Zhang X, Hoffman HJ, Cotch MF, Themann CL, Wilson MR. Hearing Impairment Associated With Depression in US Adults, National Health and Nutrition Examination Survey 2005–2010. *JAMA otolaryngology-- head & neck surgery* 2014;140:293-302.
7. Norgine. Anhydrous sodium thiosulfate (Pedmarqsi) for preventing ototoxicity caused by cisplatin chemotherapy in people aged 1 month to 17 years with localised solid tumours [ID1001]

Clarification Response.; 2024.

8. Knight KRG, Kraemer DF, Neuwelt EA. Ototoxicity in Children Receiving Platinum Chemotherapy: Underestimating a Commonly Occurring Toxicity That May Influence Academic and Social Development. *Journal of Clinical Oncology* 2005;23:8588-96.
9. Whelan K, Stratton K, Kawashima T, Leisenring W, Hayashi S, Waterbor J*, et al.* Auditory complications in childhood cancer survivors: A report from the childhood cancer survivor study. *Pediatric Blood & Cancer* 2011;57:126-34.
10. Brock P, Rajput K, Edwards L, Meijer A, Simpkin P, Hoetink A*, et al.* Cisplatin Ototoxicity in Children. In: *Hearing Loss - From Multidisciplinary Teamwork to Public Health*: IntechOpen; 2021.
11. Brock PR, Knight KR, Freyer DR, Campbell KCM, Steyger PS, Blakley BW*, et al.* Platinum-Induced Ototoxicity in Children: A Consensus Review on Mechanisms, Predisposition, and Protection, Including a New International Society of Pediatric Oncology Boston Ototoxicity Scale. *Journal of Clinical Oncology* 2012;30:2408-17.
12. Minasian LM, Frazier AL, Sung L, O'Mara A, Kelaghan J, Chang KW*, et al.* Prevention of cisplatin-induced hearing loss in children: Informing the design of future clinical trials. *Cancer Medicine* 2018;7:2951-9.
13. GBD 2019 Hearing Loss Collaborators. Hearing loss prevalence and years lived with disability, 1990-2019: findings from the Global Burden of Disease Study 2019. *Lancet* 2021;397:996–1009.
14. The National Deaf Children's Society (NDCS), The Royal National Institute for Deaf People (RNID). Anhydrous sodium thiosulfate (Pedmarqsi) for preventing ototoxicity caused by cisplatin chemotherapy in people aged 1 month to 17 years with localised solid tumours. [ID1001]. Patient Organisation Submission. In; 2024: 16.
15. Medicines and Healthcare products Regulatory Agency (MHRA). Pedmarqsi 80 mg/mL solution for infusion - Summary of Product Characteristics (SmPC); 2024.
16. Norgine. SIOPEL CSR [data on file] A MULTICENTER, OPEN-LABEL, RANDOMIZED PHASE III TRIAL OF THE EFFICACY OF SODIUM THIOSULFATE IN REDUCING OTOTOXICITY IN PATIENTS RECEIVING CISPLATIN CHEMOTHERAPY FOR STANDARD-RISK HEPATOBLASTOMA. In; 2019.
17. National Disease Registration Service (NDRS). Children, teenagers and young adults UK cancer statistics report 2021, Appendix and downloads. In: NDRS; 2021.

18. National Institute for Health and Care Excellence (NICE). Anhydrous sodium thiosulfate (Pedmarqsi) for preventing ototoxicity caused by cisplatin chemotherapy in people aged 1 month to 17 years with localised solid tumours. Final scope.; 2024.
19. Norgine. ACCL0431 CSR [Data on file] RANDOMIZED PHASE 3 STUDY OF SODIUM THIOSULFATE (IND #72877, NSC #45624) FOR THE PREVENTION OF CISPLATIN-INDUCED OTOTOXICITY IN CHILDREN. In; 2019.
20. Orgel E, Knight KR, Villaluna D, Krailo M, Esbenshade AJ, Sung L*, et al.* Reevaluation of sodium thiosulfate otoprotection using the consensus International Society of Paediatric Oncology Ototoxicity Scale: A report from the Children's Oncology Group study ACCL0431. *Pediatric Blood & Cancer* 2023;70:e30550.
21. British Society of Audiology. Pure-tone air-conduction and boneconduction threshold audiometry with and without masking. Recommended Procedure. Bathgate, UK; 2018.
22. National Institute for Health and Care Excellence (NICE). NICE health technology evaluations: the manual. NICE process and methods [PMG36]. 2022.
23. Schneider P, McNamara S, Love-Koh J, Doran T, Gutacker N. QALY Shortfall Calculator. 2021.
24. Tanaka R, Sullivan M, Canpolat C, Johnston R, Ataseven E, Ates DC*, et al.* Named Patient Program use of PEDMARK to reduce the risk of cisplatin-induced ototoxicity in pediatric patients with varied solid tumors. Paper presented at: Pediatric Blood & Cancer.
25. Cabi EU, Tacyildiz N, Ataseven E, Sivrice AC, Sevinir B, Brock P*, et al.* PEDMARK reduced the risk of cisplatin-induced ototoxicity in pediatric patients with hepatoblastoma, seen in a Turkish compassionate use treatment protocol. PEDIATRIC BLOOD & CANCER, abstract no. 148, p. S572-S3.
26. National Institute for Health and Care Excellence (NICE). Single technology appraisal and highly specialised technologies evaluation: User guide for company evidence submission template. NICE process and methods [PMG24]. 2022. https://www.nice.org.uk/process/pmg24 (Accessed
27. Centre for Reviews and Dissemination (CRD). Systematic reviews: CRD's guidance for undertaking reviews in health care. University of York; 2009. https://www.york.ac.uk/crd/guidance/ (Accessed
28. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ*, et al.* Cochrane Handbook for Systematic Reviews of Interventions version 6.4 (updated August 2023). Cochrane; 2023. www.training.cochrane.org/handbook (Accessed
29. European Medicines Agency (EMA). Assessment report - Pedmarqsi; 2023.
30. Brock PR, Maibach R, Childs M, Rajput K, Roebuck D, Sullivan MJ*, et al.* Sodium Thiosulfate for Protection from Cisplatin-Induced Hearing Loss. *New England Journal of Medicine* 2018;378:2376-85.
31. Freyer DR, Chen L, Krailo MD, Knight K, Villaluna D, Bliss B*, et al.* Effects of sodium thiosulfate versus observation on development of cisplatin-induced hearing loss in children with cancer (ACCL0431): a multicentre, randomised, controlled, open-label, phase 3 trial. *The Lancet Oncology* 2017;18:63-74.
32. ClinicalTrials.gov. Cisplatin With or Without Sodium Thiosulfate in Treating Young Patients With Stage I, II, or III Childhood Liver Cancer (SIOPEL6).
33. ClinicalTrials.gov. Sodium Thiosulfate in Preventing Hearing Loss in Young Patients Receiving Cisplatin for Newly Diagnosed Germ Cell Tumor, Hepatoblastoma, Medulloblastoma, Neuroblastoma, Osteosarcoma, or Other Malignancy.
34. US Food and Drug Administration (FDA). Center for Drug Evaluation and Research. Application Number: 212937Orig1s000. Multi-disciplinary review. 2022. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2023/212937Orig1s000TOC.cfm (Accessed
35. Clemens E, Brooks B, de Vries ACH, van Grotel M, van den Heuvel-Eibrink MM, Carleton B. A comparison of the Muenster, SIOP Boston, Brock, Chang and CTCAEv4.03 ototoxicity grading scales applied to 3,799 audiograms of childhood cancer patients treated with platinum-based chemotherapy. *PLoS ONE* 2019;14:e0210646.

36. Meijer AJM, Diepstraten FA, Ansari M, Bouffet E, Bleyer A, Fresneau B*, et al.* Use of Sodium Thiosulfate as an Otoprotectant in Patients With Cancer Treated With Platinum Compounds: A Review of the Literature. *Journal of Clinical Oncology* 2024; 10.1200/JCO.23.02353:JCO.23.02353.
37. Knight KR, Chen L, Freyer D, Aplenc R, Bancroft M, Bliss B*, et al.* Group-Wide, Prospective Study of Ototoxicity Assessment in Children Receiving Cisplatin Chemotherapy (ACCL05C1): A Report From the Children's Oncology Group. *Journal of Clinical Oncology* 2017;35:440-5.
38. Meijer AJ, Diepstraten FA, van den Heuvel-Eibrink MM, Bleyer A. Prevention of cisplatin-induced hearing loss in children: achievements and challenges for evidence-based implementation of sodium Thiosulfate. *Frontiers in Oncology* 2024;14:1336714.
39. Scottish Intercollegiate Guideline Network (SIGN). Search filters. https://www.sign.ac.uk/what-we-do/methodology/search-filters/ (Accessed
40. Arber M, Garcia S, Veale T, Glanville J. Sensitivity of a search filter designed to identify studies reporting health state utility values | Cochrane Colloquium Abstracts. *Cochrane Colloquium Abstracts*;2015 Vienna.
41. Mohiuddin S, Payne K, Fenwick E, O'Brien K, Bruce I. A model-based cost-effectiveness analysis of a grommets-led care pathway for children with cleft palate affected by otitis media with effusion. *The European Journal of Health Economics* 2015;16:573-87.
42. Kiesewetter K, Dejaco T, Hoch A, Scandurra F, Rose-Eichberger K, Schwarz*, et al.* EE83 Cost-Effectiveness Analysis of an Active Transcutaneous Bone Conduction Implant for Patients With Conductive or Mixed Hearing Loss or Single-Sided Deafness in Turkey. *Value in Health* 2022;25:S69.
43. Montes F, Peñaranda A, Correa S, Peñaranda D, García J-M, Aparicio ML*, et al.* Cochlear Implants Versus Hearing Aids in a Middle-Income Country: Costs, Productivity, and Quality of Life. *Otology & Neurotology* 2017;38.
44. Kiesewetter K, Dejaco T, Scandurra F, Rose-Eichberger K, Hoch A, Schwarz*, et al.* MT9 Cost-Utility of Bone Conduction Implants for Conductive or Mixed Hearing Loss or Single-Sided Deafness: A Decision Analysis. *Value in Health* 2022;25:S379.
45. Cutler H, Gumbie M, Olin E, Parkinson B, Bowman R, Quadri H*, et al.* The cost-effectiveness of unilateral cochlear implants in UK adults. *The European Journal of Health Economics* 2022;23:763-79.
46. Landry EC, Scholte M, Su MP, Horstink Y, Mandavia R, Rovers MM*, et al.* Early Health Economic Modeling of Novel Therapeutics in Age-Related Hearing Loss. *Front Neurosci,* 2022.
47. Gumbie M, Parkinson B, Dillon H, Bowman R, Song R, Cutler H. Cost-Effectiveness of Screening Preschool Children for Hearing Loss in Australia. *Ear & Hearing* 2022;43:1067-78.
48. Skarzynski PH, Ciesla K, Lorens A, Wojcik J, Skarzynski H. Cost-Utility Analysis of Bilateral Cochlear Implantation in Adults With Severe to Profound Sensorineural Hearing Loss in Poland. *Otology & Neurotology* 2021;42.
49. Seebacher J, Muigg F, Kühn H, Weichbold V, Galvan O, Zorowka P*, et al.* Cost-utility Analysis of Cochlear Implantation in Adults With Single-sided Deafness: Austrian and German Perspective. *Otology & Neurotology* 2021;42.
50. Kosaner Kliess M, Kluibenschaedl M, Zoehrer R, Schlick B, Scandurra F, Urban M. Cost-Utility of Partially Implantable Active Middle Ear Implants for Sensorineural Hearing Loss: A Decision Analysis. *Value in Health* 2017;20:1092-9.
51. Joore MA, van der Stel H, Peters HJM, Boas GM, Anteunis LJC. The Cost-effectiveness of Hearing-Aid Fitting in the Netherlands. *Archives of Otolaryngology–Head & Neck Surgery* 2003;129:297-304.
52. Hoch A, Kiesewetter K, Dejaco T, Scandurra F, Rose-Eichberger K, Schwarz*, et al.* EE157 Cost-Utility of Active Middle Ear Implants for Sensorineural Hearing Loss. *Value in Health* 2022;25:S83.
53. Palmer CS, Niparko JK, Wyatt JR, Rothman M, de Lissovoy G. A Prospective Study of the Cost-Utility of the Multichannel Cochlear Implant. *Archives of Otolaryngology–Head & Neck Surgery* 1999;125:1221-8.

54. Fidler MM, Reulen RC, Winter DL, Kelly J, Jenkinson HC, Skinner R*, et al.* Long term cause specific mortality among 34 489 five year survivors of childhood cancer in Great Britain: population based cohort study. *BMJ* 2016;354:i4351.
55. Office for National Statistics. National life tables: England and Wales 2020-2022. In; 2024.
56. Barton GR, Stacey PC, Fortnum HM, Summerfield AQ. Hearing-Impaired Children in the United Kingdom, IV: Cost-Effectiveness of Pediatric Cochlear Implantation. *Ear & Hearing* 2006;27:575-88.
57. Pogany L, Barr RD, Shaw A, Speechley KN, Barrera M, Maunsell E. Health Status in Survivors of Cancer in Childhood and Adolescence. *Quality of Life Research* 2006;15:143-57.
58. Chen P, Hudson MM, Li M, Huang IC. Health utilities in pediatric cancer patients and survivors: a systematic review and meta-analysis for clinical implementation. *Quality of Life Research* 2022;31:343-74.
59. Apex Healthcare Consulting. Managing ototoxicity in paediatric cancer patients and assessment of PEDMARK from an audiology perspective: audiologist market research report for Fennec Pharmaceuticals. In; 2018.
60. Grutters JPC, Joore MA, van der Horst F, Verschuure H, Dreschler WA, Anteunis LJC. Choosing between measures: comparison of EQ-5D, HUI2 and HUI3 in persons with hearing complaints. *Quality of Life Research* 2007;16:1439-49.
61. Hernández-Alava M, Pudney S, Wailoo A. Estimating EQ-5D by age and sex for the UK. Report by the Decision Support Unit. 2022.
62. National Institute for Health and Care Excellence (NICE). Trastuzumab deruxtecan for treating HER2-positive unresectable or metastatic breast cancer after 2 or more anti-HER2 therapies no. TA704; 2021.
63. National Institute for Health and Care Excellence (NICE). Trastuzumab deruxtecan for treating HER2-positive unresectable or metastatic breast cancer after 1 or more anti-HER2 treatments no. TA862; 2023.
64. National Institute for Health and Care Excellence (NICE). Burosumab for treating X-linked hypophosphataemia in children and young people no. HST8; 2018.
65. National Institute for Health and Care Excellence (NICE). Dabrafenib plus trametinib for treating BRAF V600 mutation-positive advanced non-small-cell lung cancer (TA989). Technology appraisal guidance. 2023.
66. National Institute for Health and Care Excellence (NICE). Tepotinib for treating advanced non-small-cell lung cancer with MET gene alterations (TA789). Technology appraisal guidance.; 2022.
67. Hudgens S, Briggs A, Velikova G, Forsythe A, McCutcheon S, Kind P. Impact of Treatment with Eribulin (Eri) or Capecitabine (Cap) for Metastatic Breast Cancer (Mbc) on Eq–5D Utility Derived from Eortc Qlq–C30. *Annals of Oncology* 2014;25:iv360.
68. Nafees B, Stafford M, Gavriel S, Bhalla S, Watkins J. Health state utilities for non small cell lung cancer. *Health and Quality of Life Outcomes* 2008;6:84.
69. Guidelines in the Management of Febrile Neutropenia for Clinical Practice. *American Journal of Managed Care (AJMC)* 2017.
70. Shao T, Zhao M, Tang W. Cost-effectiveness analysis of sintilimab vs. placebo in combination with chemotherapy as first-line therapy for local advanced or metastatic oesophageal squamous cell carcinoma. *Frontiers in Oncology* 2022;12.
71. Telford C, Bertranou E, Large S, Phelps H, Ekman M, Livings C. Cost-Effectiveness Analysis of Fulvestrant 500 mg in Endocrine Therapy-Naïve Postmenopausal Women with Hormone Receptor-Positive Advanced Breast Cancer in the UK. *PharmacoEconomics Open* 2019;3:559-70.
72. McNamara MG, Fitzpatrick F, Smyth E, Humphries H, Breathnach OS, Grogan L. Lymphopenia and duration of hospital stay in patients with cancer and febrile neutropenia secondary to chemotherapy. *Journal of Clinical Oncology* 2008;26:20590-.
73. Schlögl M, Käch I, Beeler PE, Pape H-C, Neuhaus V. Trauma patients with hypokalemia have an increased risk of morbidity and mortality. *Surgery in Practice and Science* 2021;7:100041.

74. Corona G, Giuliani C, Parenti G, Colombo GL, Sforza A, Maggi M*, et al.* The Economic Burden of Hyponatremia: Systematic Review and Meta-Analysis. *The American Journal of Medicine* 2016;129:823-35.e4.
75. Szymanski T. Is comprehensive medication review cost-effective for patients admitted to hospital? 2020; 10.25560/101598.
76. Lee JJY, Kilonzo K, Nistico A, Yeates K. Management of hyponatremia. *CMAJ* 2014;186:E281-E6.
77. Lloyd A, Nafees B, Narewska J, Dewilde S, Watkins J. Health state utilities for metastatic breast cancer. *British Journal of Cancer* 2006;95:683-90.
78. Plewa MC, Chatterjee K. Recurrent Aphthous Stomatitis. In: *StatPearls*Treasure Island (FL): StatPearls Publishing; 2024.
79. Do N, Thielen FW. Cost-Effectiveness of Venetoclax Plus Obinutuzumab Versus Chlorambucil Plus Obinutuzumab for the First-Line Treatment of Adult Patients With Chronic Lymphocytic Leukemia: An Extended Societal View. *Value in Health* 2023;26:477-86.
80. Stein EM, Yang M, Guerin A, Gao W, Galebach P, Xiang CQ*, et al.* Assessing utility values for treatment-related health states of acute myeloid leukemia in the United States. *Health and Quality of Life Outcomes* 2018;16:193.
81. Buendía JA, Patiño DG. Cost-utility of vitamin D supplementation to prevent acute respiratory infections in children. *Cost Effectiveness and Resource Allocation : C/E* 2023;21:23.
82. Bokhari A. Bacterial Sepsis Treatment & Management: Approach Considerations, Surgical Intervention, Consultations. 2023.
83. NHS England. Cellulitis. 2017. https://www.nhs.uk/conditions/cellulitis/ (Accessed
84. NHS England. Respiratory tract infections (RTIs). 2017. https://www.nhs.uk/conditions/respiratory-tract-infection/ (Accessed
85. Norgine. Clinical Study Protocol: COG ACCL0431 [Data on file]; 2008.
86. Birmingham Childrens Hospital. GUIDELINE FOR THE MANAGEMENT OF CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING. In; 2016.
87. Department of Health and Social Care. Drugs and pharmaceutical electronic market information tool (eMIT). In. GOV.UK; 2023.
88. Pssru. Unit Costs of Health and Social Care 2022: Manual; 2022.
89. Dionne F, Mitton C, Rassekh R, Brooks B, Ross C, Hayden M*, et al.* Economic impact of a genetic test for cisplatin-induced ototoxicity. *The Pharmacogenomics Journal* 2012;12:205-13.
90. NHS England. National Cost Collection for the NHS. 2021/22 National Cost Collection data. In; 2023.
91. National Institute for Health and Care Excellence (NICE). Cochlear implants for children and adults with severe to profound deafness (TA566). Technology appraisal guidance. 2019.
92. Chorozoglou M, Mahon M, Pimperton H, Worsfold S, Kennedy CR. Societal costs of permanent childhood hearing loss at teen age: a cross-sectional cohort follow-up study of universal newborn hearing screening. *BMJ Paediatrics Open* 2018;2:e000228.
93. Bond M, Mealing S, Anderson R, Elston J, Weiner G, Taylor RS*, et al.* The effectiveness and cost-effectiveness of cochlear implants for severe to profound deafness in children and adults: a systematic review and economic model. *Health Technology Assessment* 2009;13:1-330.
94. NHS England. Schedule 2 - The services. Cochlear implant implantation services (adults and children); 2023.
95. Organisation for Economic Co-operation and Development (OECD). Purchasing power parities (PPP) (indicator); 2024.
96. Organisation for Economic Co-operation and Development (OECD). Consumer price indices (CPIs) - Complete database : Consumer prices - Annual inflation, All items non-food non-energy. In; 2024.
97. Smulders YE, van Zon A, Stegeman I, van Zanten GA, Rinia AB, Stokroos RJ*, et al.* Cost–Utility of Bilateral Versus Unilateral Cochlear Implantation in Adults: A Randomized Controlled Trial. *Otology & Neurotology* 2015;37:38.
98. Gurney JG, Tersak JM, Ness KK, Landier W, Matthay KK, Schmidt ML. Hearing Loss, Quality of Life, and Academic Problems in Long-term Neuroblastoma Survivors: A Report From the Children's Oncology Group. *Pediatrics* 2007;120:e1229-e36.

99. National Institute for Health and Care Excellence (NICE). INDICATOR DEVELOPMENT PROGRAMME (QOF) Resource impact statement: Depression and anxiety disorder. In; 2015.
100. National Institute for Health and Care Excellence (NICE). Lenvatinib for untreated advanced hepatocellular carcinoma [TA551]. Technology appraisal guidance.; 2018.
101. Campone M, Yang H, Faust E, Kageleiry A, Signorovitch JE, Zhang J, *et al.* Cost of adverse events during treatment with everolimus plus exemestane or single-agent chemotherapy in patients with advanced breast cancer in Western Europe. *Journal of Medical Economics* 2014;17:837-45.
102. Wong W, Yim YM, Kim A, Cloutier M, Gauthier-Loiselle M, Gagnon-Sanschagrin P, *et al.* Assessment of costs associated with adverse events in patients with cancer. *PLOS ONE* 2018;13:e0196007.
103. Eletronic Medicines Compendium (EMC). Calvive 1000 Effervescent Tablets (formerly Sandocal Tablets). In; 2023.
104. Cleveland Clinic. Hypocalcemia.; 2022. https://my.clevelandclinic.org/health/diseases/23143-hypocalcemia (Accessed
105. National Institute for Health and Care Excellence (NICE). Dinutuximab beta for treating neuroblastoma (TA538). Technology appraisal guidance. 2018.
106. National Institute for Health and Care Excellence (NICE). Nivolumab for adjuvant treatment of invasive urothelial cancer at high risk of recurrence (TA817). Technology appraisal guidance.; 2022.
107. Weissenstein A, Deuster D, Knief A, Zehnhoff-Dinnesen AA, Schmidt C-M. Progressive hearing loss after completion of cisplatin chemotherapy is common and more pronounced in children without spontaneous otoacoustic emissions before chemotherapy. *International Journal of Pediatric Otorhinolaryngology* 2012;76:131-6.
108. National Institute for Health and Care Excellence (NICE). Genedrive MT-RNR1 ID Kit for detecting a genetic variant to guide antibiotic use and prevent hearing loss in babies: early value assessment no. HTE6; 2023.
109. Bass JK, Knight KR, Yock TI, Chang KW, Cipkala D, Grewal SS. Evaluation and Management of Hearing Loss in Survivors of Childhood and Adolescent Cancers: a Report from the Children's Oncology Group. *Pediatric blood & cancer* 2016;63:1152-62.
110. Verkleij ML, Heijnsdijk EAM, Bussé AML, Carr G, Goedegebure A, Mackey AR, *et al.* Cost-Effectiveness of Neonatal Hearing Screening Programs: A Micro-Simulation Modeling Analysis. *Ear & Hearing* 2021;42:909-16.
111. Oostenbrink R, A Moll H, Essink-Bot M-L. The EQ-5D and the Health Utilities Index for permanent sequelae after meningitis. *Journal of Clinical Epidemiology* 2002;55:791-9.
112. McDool E, Mukuria C, Brazier J. A Comparison of the SF-6Dv2 and SF-6D UK Utility Values in a Mixed Patient and Healthy Population. *PharmacoEconomics* 2021;39:929-40.
113. Baek MK, Kim YS, Kim EY, Kim AJ, Choi W-J. Health-Related Quality of Life in Korean Adults with Hearing Impairment: The Korea National Health and Nutrition Examination Survey 2010 to 2012. *PLOS ONE* 2016;11:e0163999.
114. Maes IHL, Joore MA, Cima RFF, Vlaeyen JW, Anteunis LJC. Assessment of Health State in Patients With Tinnitus: A Comparison of the EQ-5D and HUI Mark III. *Ear and Hearing* 2011;32.
115. Simpson AN, Simpson KN, Dubno JR. Health-related quality of life in older adults: Effects of hearing loss and common chronic conditions. *Healthy Aging Res* 2015;4.
116. National Institute for Health and Care Excellence (NICE). Hearing loss in adults: assessment and management. 2018.
117. UK Government. School admissions. https://www.gov.uk/schools-admissions/school-starting-age (Accessed
118. Office for National Statistics. Employee earnings in the UK. In.
119. Laverdière C, Liu Q, Yasui Y, Nathan PC, Gurney JG, Stovall M, *et al.* Long-term Outcomes in Survivors of Neuroblastoma: A Report From the Childhood Cancer Survivor Study. *JNCI: Journal of the National Cancer Institute* 2009;101:1131-40.
120. Suh E, Stratton KL, Leisenring WM, Nathan PC, Ford JS, Freyer DR, *et al.* Late mortality and chronic health conditions in long-term survivors of early-adolescent and young adult cancers:

a retrospective cohort analysis from the Childhood Cancer Survivor Study. *The Lancet Oncology* 2020;21:421-35.
121. Office for National Statistics. National life tables: England 2020-2022. In; 2024.
122. Dixon SB, Liu Q, Chow EJ, Oeffinger KC, Nathan PC, Howell RM*, et al.* Specific causes of excess late mortality and association with modifiable risk factors among survivors of childhood cancer: a report from the Childhood Cancer Survivor Study cohort. *The Lancet* 2023;401:1447-57.
123. Brosa M, García del Muro X, Mora J, Villacampa A, Pozo-Rubio T, Cubells L*, et al.* Orphan drugs revisited: cost–effectiveness analysis of the addition of mifamurtide to the conventional treatment of osteosarcoma. *Expert Review of Pharmacoeconomics & Outcomes Research* 2015;15:331-40.
124. Aerts I, Pacquement H, Doz F, Mosseri V, Desjardins L, Sastre X*, et al.* Outcome of second malignancies after retinoblastoma: a retrospective analysis of 25 patients treated at the Institut Curie. *European Journal of Cancer* 2004;40:1522-9.
125. Oldenburg J, Wahlqvist R, Fosså SD. Late relapse of germ cell tumors. *World Journal of Urology* 2009;27:493-500.
126. Norgine. Anhydrous sodium thiosulfate (Pedmarqsi) for preventing ototoxicity caused by cisplatin chemotherapy in people aged 1 month to 17 years with localised solid tumours [ID1001]. EAG report – factual accuracy check and confidential information check.; 2024.

Single Technology Appraisal

Anhydrous sodium thiosulfate (Pedmarqsi) for preventing ototoxicity caused by cisplatin chemotherapy in people aged 1 month to 17 years with localised solid tumours [ID1001]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on 08 July 2024** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as 'confidential' should be highlighted in turquoise and all information submitted as 'depersonalised data' in pink.

Issue 1 Double counting utility gain associated with hearing aids

Description of problem	Description of proposed amendment	Justification for amendment
Section 4.3.3., Page 117, Issue (4) "*The EAG notes that it is unclear why the health state utilities for marked and severe HL in the base case analysis include a utility gain only related to the use of cochlear implants, but not for hearing aids, since the model assumes that patients cannot receive both devices.*" The EAG's preferred analysis included a utility gain of 0.12 related specifically to the use of hearing aids. This utility benefit was applied to the proportions of patients in each health state who received hearing aids. The Company acknowledges that hearing aid use is associated with a gain in utility. However, the utility values in the model (derived from Barton *et al*. 2006) already account for the utility gain associated with	The Company proposes removing the quoted text from Section 4.3.3, Page 118, Issue (4) referring to the utility gain from hearing aids, and proposes that the EAG does not apply an additional utility benefit for hearing aids in its preferred analysis (i.e. the EA4 scenario should not be included in the EAG's preferred analysis). In addition, all mention of including a utility gain for hearing aids should be removed across the report.	As described in the Company's response to the EAG's clarification question B14e, it is not appropriate to apply an additional utility gain associated with hearing aids to the health state utility values sourced from Barton *et al.* 2006 (used in the Company's base case). In the Barton *et al*. study, it is stated that "*the incremental cost is the additional cost of providing implants* ***over and above the cost of management with acoustic hearing aids***" suggesting that the patients who did not receive cochlear implants in the study received hearing aids instead. As the cost-effectiveness analysis by Barton *et al.* considers the incremental costs of cochlear implants versus hearing aids, it is appropriate to assume that the incremental utilities are also reflective of cochlear implants versus hearing aids i.e. the utility values reported for 'Severe (AHL 71–95 dB)', 'Profound (AHL 96–105 dB)', and 'Profound (AHL 105 dB)' hearing loss are for patients receiving hearing aids. If this was not the case, the cost-effectiveness analysis conducted by Barton *et al.* would not be valid because ICER calculations rely on comparing the incremental costs and effects compared to the same baseline (in this

hearing aid use. Therefore, it is inappropriate to apply a utility gain of 0.12 to the utility values sourced from Barton *et al*. 2006 as it would mean double-counting of the utility benefit associated with hearing aids. This issue is also discussed in the following sections of the EAG report: 1.1, 1.2, 1.5, 4.4.1 (EA4 and ASA6 ASA7), 4.4.2, and 5.		case, the baseline includes the use of hearing aids in patients not receiving cochlear implants). To avoid any doubt, the Company contacted the authors of the study, who confirmed that it would be appropriate to interpret the utility data from the study for children without cochlear implants as **including** the utility gain associated with hearing aids. The assumption – that patients in Barton *et al.* who did not receive cochlear implants were fitted with hearing aids – also aligns with feedback from the Company's interviews with audiologists; all 10 audiologists (including 5 from the UK) agreed that **all** patients with moderate hearing loss would receive hearing aids in clinical practice. As the patients in the Barton *et al.* study had at least moderate hearing loss, it is appropriate to assume that those who did not receive cochlear implants were fitted with hearing aids. Furthermore, using the EAGs approach results in utility values of 0.86, 0.80 and 0.74 for the mild HL, moderate HL and marked HL health states respectively, after the utility gain of cochlear implants and hearing aids is applied. The Company believe these values to be implausibly high, lack face validity, and underestimate the impact that hearing loss has on the quality of life

		of children. This also does not align with feedback from a UK audiovestibular physician who suggested that the health state utility values used in the model for the four hearing loss health states were appropriate. Finally, in the report, the EAG appear not to have considered the Company's response to clarification question B14e, regarding the potential issue of double counting utility gains, nor has the EAG provided a clear rationale in the report for why their preferred approach includes a utility gain for hearing aid use. In summary, the Company is concerned that by utilising the utility values from Barton *et al.* and applying an additional utility benefit associated with hearing aids, the EAG is double-counting the utility benefit of hearing aids, thereby overestimating the quality of life of patients with hearing loss in the model. Based on this, the Company considers that Issue 4 should therefore be excluded from the EAG report.

Issue 2 It is not appropriate to use efficacy data from the localised disease subgroup of COG ACCL0431

Description of problem	Description of proposed amendment	Justification for amendment
Section 4.4.1., Page 125, Scenario EA9 "***Use of efficacy data for HL incidence from COG ACCL0431 trial for localised disease subgroup instead of overall population*** *In this analysis, the EAG amended the model to use the count data from the localised disease subgroup analysis from COG ACCL0431 to inform the probabilities of developing HL or Minimal/No HL (see Table 14). This aligns the data on HL incidence used in the model with the licenced indication for STS, however, it inevitably uses data from a smaller sample size population to inform the model*". The EAG's scenario described above using hearing loss efficacy data from the localised disease subgroup of the COG ACCL0431	The Company proposes that the discussion of Scenario EA9 should be removed from the report and the use of subgroup data from the localised disease subgroup should not be used to inform efficacy data in the EAG's preferred analysis.	As discussed in the Company's response to the EAG's clarification question B6, it is inappropriate to use data from the localised subgroup of patients from the COG ACCL0431 trial to inform hearing loss efficacy in the economic model for a number of reasons. Firstly, Pedmarqsi's mechanism of action is directed at cisplatin-induced ototoxicity and is independent of the underlying cancer stage. The efficacy results from the subgroup of patients with localised disease in COG ACCL0431 should therefore be viewed as supportive and validate the overall treatment effect of Pedmarqsi, as opposed to being the analysis on which to base the cost-effectiveness analysis. Additionally, as noted in the response to clarification question B6, the COG ACCL0431 trial did not consider localised/metastatic disease status as a stratification variable. Therefore, subgroup analysis based on this categorisation would break the randomisation of the trial, which strongly suggests that subgrouping data to

trial is not appropriate and should not be included in the EAG preferred analysis. This issue is also discussed in the following sections of the EAG report: 1.1, 1.5, 1.6, 4.3.3 (2b), 4.4.2 (Scenario EA9, EA10), and 5.		localised only patients would not be robust or appropriate. Furthermore, the COG ACCL0431 trial was not powered for an analysis of hearing loss in localised disease only patients, with [redacted] children treated with Pedmarqsi in the efficacy population reporting localised disease. Also, restricting the overall trial population to the subgroup of localised patients only further reduces an already limited sample size and therefore increases the uncertainty in the analysis of treatment effect on hearing loss. For example, both the ITT population and efficacy population included 38% of patients who were classified as having metastatic disease (47/125 patients and 40/104 patients, respectively). The approach preferred by the EAG is also inconsistent with the critique raised in Issue 1 of the EAG report, which states: *"Sample sizes in the SIOPEL 6 and COG ACCL0431 trials were small and may lead to uncertainty in estimated treatment effects".* Therefore, it is unclear why the EAG would advocate for the use of a method which unnecessarily reduces the patient numbers in COG ACCL0431.

		Given these reasons, the Company suggest that Scenario EA9 should be removed from the report.

Issue 3 The pooled analyses used in the EAG scenario analyses were not conducted appropriately

Description of problem	Description of proposed amendment	Justification for amendment
Section 4.4.2., Page 126, ASA5a, ASA5b, and ASA7 *"Within this additional analysis, the EAG explored the use of alternative combinations of sources of efficacy data, as follows:* *(a) Pooled data from COG ACCL0431 and SIOPEL 6 (localised disease patients only) to inform HL incidence and Orgel et al. combined with Knight et al. for HL severity… the use of the pooled data from the two trials may not be ideal due to study differences such as patient population and study design; therefore the EAG opted not to include it as part of the EAG preferred analysis;*	If the EAG choose to present scenarios using the pooled data from COG ACCL0431 and SIOPEL 6 (localised disease patients only), then the pooled data should be used for all relevant inputs of the model to ensure the sources used for the model inputs are consistent and aligned throughout. This includes using pooled analysis data for the proportion of male, mortality, baseline age, age distribution, mean weight, dosing inputs and adverse event rates. In addition, mITT data should be used for HL incidence, not the ITT data currently used in the EAG's pooled analysis. Applying data from the pooled analysis (localised only patients) for all the relevant model inputs, including the pooled mITT data for HL	As stated in the Company's response to clarification question A13, it is not appropriate to assess the efficacy of Pedmarqsi in the subpopulation of patients with localised disease from COG ACCL0431 either alone, or in a pooled analysis with the SIOPEL 6 trial. The reasons for this are also summarised in Issue 2 above. Despite this, the Company notes that if such a scenario is to be presented, then all relevant model inputs should be sourced from the pooled localised population to match the efficacy source. These data were provided by the Company in response to the clarification question A13. Currently the EAG's pooled analysis only applies pooled data for the hearing loss efficacy input, which is not appropriate as it lacks consistency. Additionally, the Company notes that the EAG's pooled analysis applies efficacy data from the pooled ITT population, rather than the pooled efficacy/mITT population. The Company believes that the pooled data from the efficacy or mITT

(b) *Pooled data from COG ACCL0431 and SIOPEL 6 (localised disease patients only) to inform HL incidence and Knight et al. for HL severity, as an extreme scenario where it is assumed that the benefit of STS therapy is restricted to avoiding the development of HL but not its severity;"* In the EAG's scenarios described above, pooled data are not applied to other relevant inputs in the model (only included for HL incidence); with data from the pooled ITT population used instead of efficacy/mITT. Therefore, the modelling approach adopted by the EAG is not appropriate. This issue is also discussed in the following sections of the EAG report: 1.2, 1.5 (Issue 4), 1.6, 4.4.2, and 5.	incidence, results in an ICER of [redacted]. The Company has provided a version of the model with this scenario along with this response form (see "Company Scenario 4" on the "EAG flags" sheet of the model).	population should be used to inform the efficacy data in this scenario analysis, as this aligns with the population in which the primary efficacy endpoint was measured in COG ACCL0431.

Issue 4 Typographical errors

Description of problem	Description of proposed amendment	Justification for amendment
The Company note that Pedmarqsi has been abbreviated to STS throughout the EAG report. As mentioned in Section B.1.1 of the CS, the submission focuses on a novel form of anhydrous sodium thiosulfate (STS), Pedmarqsi, which is specifically formulated for use in children. Given the specific and novel formulation of Pedmarqsi, and to ensure clarity throughout the appraisal the product is referred to as Pedmarqsi.	The Company request that all mentions of "STS" are amended to "anhydrous sodium thiosulfate (Pedmarqsi)" as per the NICE website.	Aligns with the wording used on the NICE website and recognises the differences between Pedmarqsi and other formulations of STS, as noted in response to clarification question A2.
Section 1.5, page 15: *"The revised deterministic version of the company's base case model suggests that STS is expected to generate an additional [redacted] QALYs when compared to ECM, at an additional cost of [redacted] per patient; the corresponding ICER is estimated to be [redacted] per QALY gained."*	Please amend the text as follows: *"The revised deterministic version of the company's base case model suggests that STS is expected to generate an additional [redacted] QALYs when compared to ECM, at an additional cost of [redacted] per patient; the corresponding ICER is estimated to be [redacted] per QALY gained."*	Typographical error.
Section 3.3.3.1, page 50: *"The odds ratio (OR) was statistically significant and indicated that the odds of experiencing hearing loss in the cisplatin with STS group was lower than the odds in the cisplatin without STS group in both the ITT population (p=[redacted]) and the mITT population (p=[redacted])."*	Please amend the text as follows: *"The odds ratio (OR) was statistically significant and indicated that the odds of experiencing hearing loss in the cisplatin with STS group was lower than the odds in the cisplatin without STS group in both the ITT population (p=[redacted]) and the mITT population (p[redacted])."*	Typographical error.

Section 4.2.3, page 70: *"All patients with any level of hearing loss are assumed to receive an FM system. In addition, half of all patients in the mild HL state are assumed to receive a hearing aid, whilst all patients in the moderate to severe states are assumed to receive either a hearing aid or a cochlear implant (proportions detailed in Section 4.1.2.6). All patients receiving these are assumed to two receive hearing aids or a bilateral cochlear implant."*	Please amend the text as follows: *"All patients with any level of hearing loss are assumed to receive an FM system. In addition, half of all patients in the mild HL state are assumed to receive a hearing aid, whilst all patients in the moderate to severe states are assumed to receive either a hearing aid or a cochlear implant (proportions detailed **in Section 4.2.4.6**). All patients receiving these are assumed to **receive two** hearing aids or a bilateral cochlear implant."*	Typographical error – Section 4.1.2.6 does not exist.
Section 4.2.3, page 71: *"The model assumes that the same proportion of patients in the moderate to severe HL states have depression and anxiety, with a comparatively lower proportion of patients affected in the mild HL state."*	Please amend the text as follows: *"The model assumes that the same proportion of patients in the **mild** to severe HL states have depression and anxiety, with a comparatively lower proportion of patients affected in the **minimal/no** HL state."*	Typographical error.
Section 4.2.4.1, page 73: *"The EAG notes that although the CS states that the STS dosage is dependent on the patient's weight and BSA, these characteristics are not used for this purpose in the model, Instead, the model uses observed estimates of the mean dosage and the mean number of visits per patient to estimate drug costs (see Section 4.1.2.6)."*	Please amend the text as follows: *"The EAG notes that although the CS states that the STS dosage is dependent on the patient's weight and BSA, these characteristics are not used for this purpose in the model. Instead, the model uses observed estimates of the mean dosage and the mean number of visits per patient to estimate drug costs (**Section 4.2.4.6**)."*	Typographical error – Section 4.1.2.6 does not exist.
Section 4.2.4, Table 25, page 76: The Company note that Table 25 of the EAG report provides a summary of the proportion of	For ease of reference, Table 25 has been amended and is available in the Appendix.	Typographical error.

patients experiencing HL and HL severity levels. However, in this table, there is an error whereby the EAG have incorrectly reported the proportion of patients in the base case receiving treatment with ECM with mild HL.		
Section 4.2.4.6, Table 29, page 84; Table 32, page 89; page 96 The total costs for speech and language therapy for patients in the Marked/Severe HL health states is quoted as "£7,466.97."	As noted, this value is not correct across multiple tables. Please amend the value as follows: "£7,4**72.70**"	Typographical error.
Section 4.2.4.6, page 93: *"During this period, the costs of new components are not considered, although the annual costs of device maintenance (£378, based on codes AS13 and AS11) are still included for all patients with a cochlear implant, in addition to the cost of reimplanting an internal electrode for patients requiring an internal component replacement (unit costs of £4,304.70 whilst the patient is <18 years and £111.95 after reaching adulthood, based on Bond et al. and uplifted to 2022)"*	Please amend the text as follows: *"During this period, the costs of new components are not considered, although the annual costs of device maintenance (£378, based on codes AS13 and AS11) are still included for all patients with a cochlear implant, in addition to the cost of reimplanting an internal electrode for patients requiring an internal component replacement (unit costs of £4,304.70 whilst the patient is <18 years and £**3,480.87** after reaching adulthood, based on Bond et al. and uplifted to 2022)".*	Typographical error.
Section 4.2.4.6, Table 34, page 97: The Company note that Table 34 of the EAG report provides a summary of adverse event (AE) costs in the Company's base case and selected scenario analyses. For brevity, the EAG have removed the incidences for hypersensitivity and	For ease of reference, Table 34 has been amended and is available in the Appendix.	Typographical error.

decreased appetite (as these were zero in all scenarios) and for acoustic stimulation tests (as these were assumed to have zero impact on costs and QALYs). However, in this table, although these AEs were omitted, there is an error whereby the EAG have incorrectly kept the associated costs of the omitted AEs in the scenario columns of the table. In addition, the unit costs for febrile neutropenia and ALT increased are incorrect.		
Section 4.2.5, page 101; Section 4.2.7, page 105; Section 4.2.7, Table 37, page 106: *"Grade 3+ AEs occurring in >10% of patients from COG ACCL0431".*	Please amend the text as follows: *"Grade 3+ AEs occurring in* **≥***10% of patients from COG ACCL0431".*	Typographical error.
Section 4.2.7, page 103: *"The probabilistic version of the updated model suggests that STS is expected to generate no additional life-years (LYs), 1.54 additional QALYs at additional costs of [redacted] compared to ECM; the corresponding ICER is [redacted] per QALY gained."*	Please amend the text as follows: *"The probabilistic version of the updated model suggests that STS is expected to generate no additional life-years (LYs), 1.54 additional QALYs at additional costs of [redacted] compared to ECM; the corresponding ICER is [redacted] per QALY gained."*	Typographical error.
Section 4.2.7, page 103: *"The base case analysis suggests a decision modifier of 1.0, as suggested by the company in the CS (age = [redacted] years; [redacted] female; 16.89 discounted QALYs for the comparator group)."*	Please amend the text as follows: *"The base case analysis suggests a decision modifier of 1.0, as suggested by the company in the CS (age = [redacted] years; [redacted] female; 1****5.44*** *discounted QALYs for the comparator group)."*	Typographical error.

Section 4.2.7, Table 36, page 103: The Company note that Table 36 of the EAG report provides the Company's central estimates of cost-effectiveness. However, in this table, there are typographical errors whereby the EAG have incorrectly reported several of the estimates.	For ease of reference, Table 36 has been amended and is available in the Appendix.	Typographical error.
Section 4.2.7, page 103: *"The probability that STS generates more net benefit than ECM at willingness-to-pay (WTP) thresholds of £20,000 and £30,000 per QALY gained is approximately [redacted] and [redacted], respectively."*	Please amend the text as follows: *"The probability that STS generates more net benefit than ECM at willingness-to-pay (WTP) thresholds of £20,000 and £30,000 per QALY gained is approximately [redacted] and [redacted], respectively."*	Typographical error.
Section 4.3.1, page 106: *"Additional programming errors in the updated version of the model submitted were identified by the EAG after the clarification stage; these are described in Section 4.3.4."*	Please amend the text as follows: *"Additional programming errors in the updated version of the model submitted were identified by the EAG after the clarification stage; these are described* ***in Section 4.3.3.****"*	Typographical error – Section 4.3.4 does not exist.
Section 4.3.2, Table 38, page 108: *"The model adopts a [redacted] years (lifetime) horizon."*	Please amend the text as follows: *"The model adopts a [redacted] years (lifetime) horizon."*	Typographical error.
Section 4.3.3, page 119: *"In their response to clarification question A17, the company reported the number of patients in COG ACCL0431 who discontinued protocol therapy by type of reason for discontinuation. [redacted]*	Please amend the text as follows: *"In their response to clarification question A17, the company reported the number of patients in COG ACCL0431 who discontinued protocol therapy by type of reason for discontinuation. [redacted] patients ([redacted]) in*	Typographical error.

patients ([redacted]) in the STS+CIS arm and [redacted] patients ([redacted]) in the CIS arm discontinued the treatment protocol in the ITT population, whilst in the localised only subgroup there were [redacted] and [redacted] discontinuations, respectively."	*the STS+CIS arm and [redacted] patients ([redacted]) in the CIS arm discontinued the treatment protocol in the ITT population, whilst in the localised only subgroup there were [redacted] and [redacted] discontinuations, respectively."*	
Section 4.3.3, page 120: *"As discussed in Section 4.1.2.6, the frequency of audiology assessments used in the model was based on Dionne et al., and on assumptions informed by audiologists interviewed by a consultancy company in 2018."*	Please amend the text as follows: *"As discussed **in Section 4.2.4.6**, the frequency of audiology assessments used in the model was based on Dionne et al., and on assumptions informed by audiologists interviewed by a consultancy company in 2018."*	Typographical error – Section 4.1.2.6 does not exist.
Section 4.2.2, page 69: *"The incremental health gains, costs and cost-effectiveness for STS versus are estimated over a lifetime horizon ([redacted] years in the base-case analysis) using an annual cycle length."*	Please amend the text as follows: *"The incremental health gains, costs and cost-effectiveness **for cisplatin with Pedmarqsi versus cisplatin without Pedmarqsi** are estimated over a lifetime horizon ([redacted] years in the base-case analysis) using an annual cycle length."*	Typographical error.

Issue 5 Inaccuracies

Description of problem	Description of proposed amendment	Justification for amendment
Section 2.1, page 21: *"This support may include additional educational support, the use of frequency modulation (FM) systems in classrooms by school-age children, the use of hearing aids by patients with moderate or severe hearing loss,*	Please amend the text as follows: *"This support may include additional educational support, the use of frequency modulation (FM) systems in classrooms by school-age children, the use of hearing aids by patients with moderate or severe hearing loss, or the use of bilateral cochlear*	As stated in NICE TA566, and in Section 2.2 of the EAG report, cochlear implants are offered to children with severe to profound hearing loss.

or the use of bilateral cochlear implants in patients suffering from profound hearing loss."	*implants in patients suffering from* ***severe to*** *profound hearing loss."*	
Section 3.1.1, page 34: *"It is unclear from the company's clarification response to question A10 how this relevant material was missed in the literature search, although the date of the conference is close to the dates when the searches were conducted, so it is possible that it had not been indexed at the time of the search and therefore could not have been retrieved."*	Please amend the text as follows: *"****The Company provided reasoning as to why this conference abstract was excluded in clarification response A10e: "it should be noted that the study did not meet the eligibility criteria for the clinical SLR (defined in Appendix Table 3, Appendix D.1.2 of the CS) because the study included patients with an age range of 3-19 years and did not report results in the subgroup of patients aged 18 or younger.""***	The Company have provided reasoning as to why the conference abstract by Tanaka *et al.* was excluded from the SLR in clarification response A10e.
Section 3.1.2, page 36: *"Moreover, the study reported by Tanaka et al., was not identified by the company searches"*	The Company request the removal of this sentence.	As noted in the clarification response A10e, the conference abstract by Tanaka *et al*. was identified, but did not meet the SLR eligibility criteria detailed in Appendix D of the Company submission.
Section 3.2.3, page 43, Section 3.7.2, page 60: *"In their response to clarification question A19, the company acknowledged, based on audiologists feedback in 2018 (no further details provided including the number of participants interviewed other than 'data on file') that there is wide variability in the use of ototoxicity scales, with the ASHA scale being commonly used in the USA and the Brock*	Please amend the text as follows: *"In their response to clarification question A19, the company acknowledged, based on audiologists feedback in 2018 (****n=10 from the USA [n=5] and UK [n=5]****) that there is wide variability in the use of ototoxicity scales, with the ASHA scale being commonly used in the USA and the Brock ototoxicity grading scale commonly used in UK clinical practice for grading cisplatin-induced hearing loss."*	As stated in Section 3.15.2 of the CS, "a series of interviews were conducted in 2018 with 10 audiologists from the USA (n=5) and UK (n=5) to validate inputs for early economic modelling".

ototoxicity grading scale commonly used in UK clinical practice for grading cisplatin-induced hearing loss."		
Section 4.1.3, page 65: *"The EAG identified a discrepancy in CS Appendix G.2.3, Table 12, whereby the quality assessment of only ten studies using the Drummond and Jefferson checklist is presented, with no justification for the omission of the results for the three remaining studies (Kiesewetter et al. and Hoch et al.)."*	The Company requests the removal of this text.	As stated in Appendix G.2.3 of the Company submission, "a quality assessment of the ten journal articles" identified was conducted. The studies by Kiesewetter *et al*. and Hoch *et al.* are conference abstracts, not journal articles, and therefore do not provide sufficient information to merit a full quality assessment.
Section 4.2.3, page 71: *"SAEs reported by ≥2% of patients in either arm of COG ACCL0431 trial. Scenario analysis explored use of SAEs reported by ≥2% of patients in SIOPEL 6, use of Grade 3+ AEs reported by ≥10% of patients in COG ACCL0431 trial, and Grade 3+ in ≥5% of patients AEs and SAEs in ≥2% of patients using data for the localised disease subgroup of patients in COG ACCL0431 and in the pooled analysis with both trials."*	Please amend the text as follows: *"SAEs reported by ≥2% of patients in either arm of COG ACCL0431 trial. Scenario analysis explored use of SAEs reported by ≥2% of patients in SIOPEL 6, use of Grade 3+ AEs reported by ≥10% of patients in COG ACCL0431 trial, and Grade 3+ in ≥5% of patients AEs* ***~~and SAEs in ≥2% of patients~~*** *using data for the localised disease subgroup of patients in COG ACCL0431 and in the pooled analysis with both trials."*	The incidence for SAEs occurring in ≥2% of patients using data for the localised disease subgroup of patients in COG ACCL0431 and in the pooled analysis was not provided in the company's updated base case model.
Section 4.2.4, page 72: *"Frequency of therapy visits based on Smulders et al. unit costs from NHS Reference Costs 2021/22."*	Please amend the text as follows: *"Frequency of therapy visits based on* ***Dionne et al. and*** *Smulders et al.; unit costs from NHS Reference Costs 2021/22."*	As stated in Section B.3.6.2.3 of the CS, the number of sessions per person, per cycle were sourced from Dionne et al. 2012 and Smulders et al. 2016.

Section 4.2.4, page 77: *"In response to clarification question A19, the company presented the results of scenario analyses which included different combinations of data from these sources:* • *COG ACCL0431 trial for HL occurrence, Orgel et al. and SIOPEL 6 mITT combined for HL severity;* • *COG ACCL0431 trial for HL occurrence, and SIOPEL 6 mITT for HL severity;* • *Orgel et al. for HL occurrence, Orgel et al. and Knight et al. combined for HL severity;* • *Orgel et al. for HL occurrence, Orgel et al. and SIOPEL 6 mITT combined for HL severity;SIOPEL 6 mITT for HL occurrence and HL severity."*	Please amend the text as follows: *"In response to clarification question A19, the company presented the results of scenario analyses which included different combinations of data from these sources:* • ***COG ACCL0431 trial for HL occurrence, Orgel et al. and Knight et al. combined for HL severity**;* • *COG ACCL0431 trial for HL occurrence, Orgel et al. and SIOPEL 6 mITT combined for HL severity;* • *COG ACCL0431 trial for HL occurrence, and SIOPEL 6 mITT for HL severity;* • *Orgel et al. for HL occurrence, Orgel et al. and Knight et al. combined for HL severity;* • *Orgel et al. for HL occurrence, Orgel et al. and SIOPEL 6 mITT combined for HL severity;* • *SIOPEL 6 mITT for HL occurrence and HL severity."*	In response to clarification question A19, the company presented the results of **six** scenario analyses.
Section 4.2.4.6, page 96: "The EAG notes that the frequency of sessions for severe HL patients of 0.9 per year was based on the number of annual visits for speech therapy in patients who received bilateral cochlear implant before cochlear implantation (preoperative) from Smulders *et al*. It is unclear why the company has not chosen the frequency of sessions for post-surgery patients (10.2 sessions in the first	Please amend the text as follows: "The EAG notes that the frequency of sessions for severe HL patients of 0.9 per year was based on the number of annual visits for speech therapy in patients who received bilateral cochlear implant before cochlear implantation (preoperative) from Smulders *et al*. **In response to clarification question B21, the Company noted that a conservative approach of using the lowest**	The Company provided clarification regarding the number of visits as part of clarification question B21.

year, and 1.2 sessions in the second year), since around 52% of patients in the severe state will have received cochlear implants."	**number of visits (preoperative) was applied in the model."**	

Issue 6 Confidential mark-up

Location of incorrect marking	Description of incorrect marking	Amended marking
Section 2.3.1, page 28	Unpublished baseline patient characteristics to be marked as confidential.	*"In addition, the baseline characteristics of patients included in the two studies (age range from 1.2 months to 18 years, weights ranging from 2.6 kg to [redacted] kg [the EAG could not verify the upper limit as data were not reported in the CSR and published studies] and tumour types with similar effects on the prevention of hearing loss) suggests that STS is effective across a heterogenous paediatric patient population (clarification response, question A3)."*
Section 3.3.3.1, Table 17, page 51	Unpublished COG ACCL0431 and SIOPEL 6 pooled mITT population numbers to be marked as confidential.	**mITT** **Cisplatin without STS (N=[redacted])** / **Cisplatin with STS (N=[redacted])**
Section 3.3.5.2, page 57	Unpublished intervention and comparator administration times and doses for patients in SIOPEL 6 and COG	*"As mentioned earlier, given the complex regimen of administration and the need to observe accurate timing of STS administration relative to cisplatin chemotherapy, the company's clarification response to question A22, states that 'The 6-hour administration time separation was*

	ACCL0431 to be marked as confidential.	*retrospectively checked for relapsed patients with disseminated disease (n=[redacted]) in the COG ACCL0431 study, and data returned for [redacted] patients confirmed the mean separation interval being [redacted] hours (range [redacted]-[redacted]).'"*
Section 4.2.7, page 103	Publication of QALY shortfall data would allow back-calculation of confidential model results and so is to be marked as confidential.	*Please note the values below need to be updated in the EAG report (see typographical errors section); however, values quoted as per the EAG report to illustrate required confidential marking.* *"The base case analysis suggests a decision modifier of 1.0, as suggested by the company in the CS (age = [redacted] years; [redacted] female; [redacted] discounted QALYs for the comparator group)."*
Section 4.3.3, page 119	Unpublished COG ACCL0431 patient disposition (localised only) to be marked as confidential.	*"However, there were 3 discontinuations in the ITT population ([redacted] in the localised disease subgroup) in the STS+CIS arm that were due to AEs or STS-unrelated death."*

(Please add further lines to the table as necessary)

Appendix

Table 25: Proportions of patients experiencing HL and HL severity levels (adapted from CS, Tables 33 and 34, CS, Figure 10, and company's model)

	Base case					
	STS			ECM		
Model health states	**Proportion of patients with/no HL†**	**Proportion with HL severity levels‡**	**Combined proportion in health states**	**Proportion of patients with/no HL†**	**Proportion with HL severity levels‡**	**Combined proportion in health states**
Minimal/no HL	0.7143	-	0.7143	0.4364	-	0.4364
Mild HL	0.2857	0.7778	0.2222	0.5636	**0.4078**	0.2299
Moderate HL		0.1806	0.0516		0.4812	0.2712
Marked HL		0.0139	0.0040		0.0370	0.0209
Severe HL		0.0278	0.0079		0.0740	0.0417

Table 34: Adverse event costs assumed in the company's base-case and selected scenario analyses, STS and ECM

AE	AE incidence (base case and scenario analyses)	Unit costs	Source of unit costs (HRG codes)	Base case (COG ACCL0431 overall population, SAEs occurring in ≥ 2% of patients)		Scenario (SIOPEL 6, SAEs occurring in ≥ 2% of patients)†		Scenario (COG ACCL0431 overall population, Grade 3+ AEs occurring in ≥ 10% of patients)		CR scenario (COG ACCL0431 localised disease patients, Grade 3+ AEs occurring in ≥ 5% of patients)		CR scenario (Pooled COG and SIOPEL 6 localised disease patients, Grade 3+ AEs occurring in ≥ 5% of patients)	
				STS	ECM	STS	ECM	STS	ECM	STS	ECM	STS	ECM
Neutrophil count decreased	See Table 26	£2,335.50	NHS RC 21/22[90] (SA35A – SA35E)	£0	£0	£88	£0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Haemoglobin decreased		£855.35	NHS RC 21/22[90] (SA04G – SA04L)			£0		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infection		£4,877.51	NHS RC 21/22[90] (WH07C – WH07D)					[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AE	AE incidence (base case and scenario analyses)	Unit costs	Source of unit costs (HRG codes)	Base case (COG ACCL0431 overall population, SAEs occurring in ≥ 2% of patients)		Scenario (SIOPEL 6, SAEs occurring in ≥ 2% of patients)†		Scenario (COG ACCL0431 overall population, Grade 3+ AEs occurring in ≥ 10% of patients)		CR scenario (COG ACCL0431 localised disease patients, Grade 3+ AEs occurring in ≥ 5% of patients)		CR scenario (Pooled COG and SIOPEL 6 localised disease patients, Grade 3+ AEs occurring in ≥ 5% of patients)	
				STS	ECM	STS	ECM	STS	ECM	STS	ECM	STS	ECM
Febrile neutropenia		£**7,769.19**	NHS RC 21/22[90] (PM45A – PM45D)										
WBC count decreased		£2,335.50	NHS RC 21/22[90] (SA35A – SA35E)										
Platelet count decreased		£948.21	NHS RC 21/22[90] (SA12G – SA12K)										
ALT increased		£**1,850.20**	Telford *et al.*[71]										
Lymphocyte count decreased		£1.079.47	Campone *et al.*[101]										
Anaemia		£855.35	NHS RC 21/22[90] (SA04G – SA04L)										
Hypokalaemia		£2,044.64	Shao *et al.*[70]										
Hypophosphatemia		£2,044.64	Shao *et al.*[70]										
Hyponatremia		£1,873.79	Corona *et al.*[74]										
Stomatitis		£2,046.53	Wong *et al.*[102]										
AST increased		£1,850.20	Assumption (TA898)[65]										
GGT increased		£1,850.20	Assumption (TA551)[100]										
Dehydration		£1,362.60	Assumption										
Hypermagnesaemia		£2,207.40	Assumption										
Hypocalcaemia		£12.31	eMIT,[87] EMC,[103] Cleveland website 2022[104]										
Hypomagnesaemia		£2,207.40	NHS RC 21/22[90]										
Acidosis		£2,816.26	NHS RC 21/22[90]										
Device related infection		£964.05	NHS RC 21/22[90]										
Sepsis		£3,041.54	NHS RC 21/22[90]										
Skin infection		£1,095.31	NHS RC 21/22[90]										

AE	AE incidence (base case and scenario analyses)	Unit costs	Source of unit costs (HRG codes)	Base case (COG ACCL0431 overall population, SAEs occurring in ≥ 2% of patients)		Scenario (SIOPEL 6, SAEs occurring in ≥ 2% of patients)†		Scenario (COG ACCL0431 overall population, Grade 3+ AEs occurring in ≥ 10% of patients)		CR scenario (COG ACCL0431 localised disease patients, Grade 3+ AEs occurring in ≥ 5% of patients)		CR scenario (Pooled COG and SIOPEL 6 localised disease patients, Grade 3+ AEs occurring in ≥ 5% of patients)	
				STS	ECM	STS	ECM	STS	ECM	STS	ECM	STS	ECM
Upper respiratory tract infection		£706.26	NHS RC 21/22[90]										
Nausea		£1,375.38	NHS RC 21/22[90]										
Vomiting		£1,362.60	NHS RC 21/22[90]										
Colitis		£1,735.73	NHS RC 21/22[90]										
Hypotension		£764.27	NHS RC 21/22[90]										
Total	-	-	-	**£0**	**£0**	**£88**	**£0**						

Table 36: Company's central estimates of cost-effectiveness, STS versus ECM, generated by the EAG using the company's revised model

Options	LYGs*	QALYs	Cost	Inc. LYGs*	Inc. QALYs	Inc. Costs	ICER	DM
Probabilistic model (using 10,000 iterations)								
STS	59.77†	18.4**0**		0.00	1.5**3**			1.0
ECM	59.77†	16.8**7**		-	-	-	-	
Deterministic model								
STS	59.85	18.43		0.00	1.54			1.0
ECM	59.85	16.89		-	-	-	-	