30 March 2023
EMA/196210/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Pedmarqsi

International non-proprietary name: sodium thiosulfate

Procedure No. EMEA/H/C/005130/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ABR	auditory brainstem response
AE	adverse event
AFP	alpha-fetoprotein
ALT	alanine aminotransferase
ASHA	American Speech-Language-Hearing Association
AST	aspartate aminotransferase
BBB	blood-brain barrier
BSA	body surface area
CI	confidence interval
CIHL	cisplatin-induced hearing loss
CINECA	Consorzio Interuniversitario
CIS	cisplatin
CMH	Cochran-Mantel-Haenszel
CPPs	critical process parameters
CQAs	critical quality attributes
CR	complete remission
CRF	case report form
CSR	clinical study report
CTCAE	common terminology criteria for adverse events
DNA	deoxyribonucleic acid
DPOAE	distortion product otoacoustic emissions
EFS	event-free survival
EPA	Environmental Protection Agency
FTIR	Fourier transform infrared spectroscopy
GC	gas chromatography
GCP	good clinical practice
GFR	glomerular filtration rate
HB	hepatoblastoma
IC	ion chromatography
ICF	informed consent form
ICH	International Conference for Harmonisation
ICP-MS	inductively coupled plasma mass spectrometry

IEC	Independent Ethics Committee
IP	intraperitoneal
IR	infrared
ITT	intent-to-treat
IV	intravenous
mITT	modified intent-to-treat
MS	mass-spectromety
NE	not evaluable
NIOSH	National Institute for Occupational Safety and Health
OAE	otoacoustic emission
OLT	orthotopic liver transplantation
OS	overall survival
PD	progressive disease
Ph. Eur.	European Pharmacopoeia
PI	principal investigator
PLADO	cisplatin and doxorubicin
PP	per protocol
PR	partial response
PRETEXT	pre-treatment tumour extension
PTA	pure-tone audiometry
PVC	polyvinyl chloride
QbD	quality by design
QTPP	quality target product profile
RDE	remote data entry
RRR	rapid radiological review
RTECS	registry of toxic effects of chemical substances
SAE	serious adverse event
SAP	statistical analysis plan
SAR	serious adverse reaction
SC	subcutaneous
SD	standard deviation
SIOP	International Society of Paediatric Oncology
SIOPEL	International Childhood Liver Tumor Strategy Group

SOC	system organ class
SR-HB	standard-risk hepatoblastoma
STS	sodium thiosulfate
SUSAR	suspected unexpected serious adverse reaction
TAMC	total aerobic microbial count
TEOAE	transient evoked otoacoustic emissions
TYMC	total yeasts and moulds count
UPLC	ultra high-performance liquid chromatography
USP	United States Pharmacopoeia
UV	ultraviolet
XRPD	x-ray powder diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Fennec Pharmaceuticals (EU) Limited submitted on 6 February 2020 an application for a Paediatric Use marketing authorisation in accordance with Article 30 of Regulation (EC) No 1901/2006, to the European Medicines Agency (EMA) for Pedmarqsi, through the centralised procedure under Article 31 of Regulation (EC) No 1901/2006. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 26 July 2018.

The applicant applied for the following indication: prevention of ototoxicity induced by cisplatin (CIS) chemotherapy in patients 1 month to <18 years of age with localised, non-metastatic, solid tumours.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on paediatric requirements

Pursuant to Article 30 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0368/2019 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0368/2019 was completed.

The PDCO issued an opinion on compliance for the PIP P/0368/2019.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Scientific advice

The applicant did not seek scientific advice from the CHMP.

1.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Elita Poplavska Co-Rapporteur: Alexandre Moreau

The application was received by the EMA on	6 February 2020
The procedure started on	27 February 2020
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	21 May 2020
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	11 June 2020
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	2 June 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	11 June 2020
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	25 June 2020
The applicant submitted the responses to the CHMP consolidated List of Questions on	23 April 2021
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	2 June 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	10 June 2021
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	24 June 2021
The applicant submitted the responses to the CHMP List of Outstanding Issues on	15 November 2021
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	2 December 2021
SAG-Oncology experts were convened to address questions raised by the CHMP on The CHMP considered the views of the SAG as presented in the minutes of this meeting.	7 December 2021
The CHMP agreed on a second list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	16 December 2021
The applicant submitted the responses to the second CHMP List of Outstanding Issues on	9 September 2022
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the second List of Outstanding Issues to all CHMP and PRAC members on	28 September 2022
The CHMP agreed on a third list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	13 October 2022

The applicant submitted the responses to the third CHMP List of Outstanding Issues on	27 February 2023
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the third List of Outstanding Issues to all CHMP and PRAC members on	17 March 2023
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Pedmarqsi on	30 March 2023

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

This indication sought by the applicant is for the prevention of ototoxicity induced by cisplatin (CIS) chemotherapy in patients 1 month to < 18 years of age with localised, non-metastatic, solid tumours.

2.1.2. Epidemiology and risk factors

Ototoxicity resulting from dose dependent damage of cochlear outer hair cells (Laurell et al, 1991), is a common consequence of cisplatin chemotherapy among paediatric patients (Brock et al, 2012, Knight et al, 2017). The prevalence of any degree of ototoxicity is in range from 40% to 56%, and severe ototoxicity - from 7% to 22% (Knight et al, 2017). Sixty percent of children treated with cisplatin develop permanent hearing decrease (Knight et al, 2005, Punnett et al, 2004). Incidence and severity of ototoxicity is highest in children treated for medulloblastoma, neuroblastoma and osteosarcoma (Knight et al, 2005, Landier et al, 2014). Males and children below age of 15 might be affected more severely (Knight et all, 2005, Yancey et al, 2012). Younger age (<5 years) and a cumulative CIS dose of ≥400 mg/m^2 increase risk of hearing loss (Li et al, 2004, Yancey et al, 2012).

In children, cisplatin-induced ototoxicity has the potential to impact speech-language and social development, educational achievements, cognitive development, and quality of life (Gurney et al, 2007, Schreiber et al, 2014, Olivier et al, 2019). Contradictory studies have suggested that genetic factors might be associated with either increased or decreased susceptibility of patients to cisplatin ototoxicity (Rybak et al, 2019).

Approximately 60% of children treated with cisplatin-based regimens develop some degree of permanent hearing loss (Brock et al., 2012; Knight et al., 2005). Sensorineural hearing loss may be permanent and bilateral and usually first affects hearing at high frequencies then progresses to mid-range frequencies with continued drug exposure (McHaney et al., 1983; Neuwelt and Brock, 2010).

Ototoxicity appears soon after therapy with CIS and is likely to worsen after repeated doses (Berg et al, 1999; Hale et al, 1999; Li et al, 2004). Irreversible hearing loss, typically in the high frequency (4 to 8 kHz) and very high frequency (9 to 20 kHz) ranges, has been documented as early as following the first platinum chemotherapy dose. The hearing loss normally worsens, affecting progressively lower frequencies in a cumulative, dose-dependent fashion (Berg et al, 1999; Punnett et al, 2004; Bertolini et al, 2004).

Main Risk factors

All patients treated with ototoxic agents are at risk of developing ototoxic hearing loss, but the youngest paediatric patients are particularly sensitive due to the immaturity of their auditory system.

The primary risk factors for cisplatin-induced ototoxicity are young age and cumulative cisplatin dose (≥400 mg/m² (Li et al, 2004)). Contributing factors include dose schedule, pre-existing hearing loss, coexisting 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).

2.1.3. Aetiology and pathogenesis

The mechanisms underlying cisplatin ototoxicity are still not fully understood. It is known that cisplatin enters targeted cells in the cochlea through the action of several transporters. Once it enters the cochlea, cisplatin is retained for months to years. It can cause DNA damage, inhibit protein synthesis, and generate reactive oxygen species that can lead to inflammation and apoptosis of outer hair cells, resulting in permanent hearing loss (Rybak et al, 2019).

Cisplatin appears to target at least three major tissue areas in the cochlea: organ of Corti, spiral ganglion cells (SGCs), and lateral wall (stria vascularis and spiral ligament). Cisplatin damages both the outer hair cells (OHCs) and the SGCs (Rybak et al, 2019).

Sensorineural hearing loss may be permanent and bilateral and usually first affects hearing at high frequencies then progresses to mid-range frequencies with continued drug exposure (Brock et al, 2012).

The time of onset is variable and marked hearing loss can occur even after a single dose of platinum, likely due to first-pass high-dose perfusion of the vertebral arteries feeding the cochlea (Dickey et al., 2004; Dickey et al., 2005). Ototoxicity appears soon after therapy with cisplatin and is likely to worsen after repeated doses (Berg et al., 1999; Hale et al., 1999; Li et al., 2004).

2.1.4. Clinical presentation and diagnosis

Symptoms and grading of ototoxicity

Hearing loss starts with diminished high frequency hearing sensitivity, as high frequency regions within the cochlea appear to be more susceptible to cisplatin (McAlpine and Johnstone, 1990). With continued exposure to cisplatin, hearing loss tends to increase in severity and progressively spreads to affect hearing at lower frequencies associated with speech (Brock et al., 2012). With increasing cumulative drug exposure, there is progressive loss to include the lower frequencies (Brock et al., 1991). Loss of pure-tone sensitivity in the 2 to 4 kHz frequency range results in difficulty discriminating consonant sounds especially when identifying words in the presence of background noise. Hearing loss exceeding the 20 dB hearing level (HL) in speech frequencies impacts family and social interaction as well as work status (Doolittle et al., 2001).

In ototoxicity, adverse effects are graded by the degree of severity, and in the field of otolaryngology scales are used to describe severity. Scales relying on hearing change from baseline are difficult to apply in a young paediatric population because baseline cannot be properly measured. Instead, scales that measure Absolute Hearing levels (e.g. Brock, New SIOP-Boston Ototoxicity Scale) are used (Brock et al., 2012; Gurney and Bass, 2012).

The numeric ratings are based on the grading system developed by Brock (Brock et al., 1991). The Brock grading system is used to describe severity of the hearing loss and indicates the degree of expected disability.

For children who have a decrease in hearing related to treatment, audiological results are analysed and a numeric grade is assigned to describe the severity of the hearing loss. The numeric ratings are based on the grading system developed by Brock (Brock et al., 1991,**Table 1**). The Brock grading system accounts for the typical slope and configuration of ototoxic hearing loss, and it can be used to indicate the degree of disability or handicap that would be expected.

Table 1. Brock Grading Scale

Bilateral Hearing Loss	Grade	Designation
<40 dB at all frequencies	0	Minimal
≥40 dB at 8000 Hz only	1	Mild
≥40 dB at 4000 Hz and above	2	Moderate
≥40 dB at 2000 Hz and above	3	Marked
≥40 dB at 1000 Hz and above	4	Severe

Note: Results were obtained by pure-tone audiometry in both ears; the Brock Grade is derived from the "better" ear. Brock Grade 0 is not equivalent to normal hearing.

Normal hearing sensitivity for children is defined as hearing thresholds at or better than 15 dB hearing level across the entire speech spectrum 0.25 to 8 kHz. Threshold levels greater than 40dB indicate hearing loss that will cause disability.

Hearing loss at Grades 1, 2, 3, and 4 are considered clinically significant and have potential impact on communicative and educational development.

Children with Grade 1 hearing loss will require preferential classroom seating and educational monitoring. Children with high frequency hearing loss including 4 kHz (Grade 2) will likely have difficulty hearing and discriminating the high frequency consonant speech sounds and have difficulty understanding speech in noise or over distance and may require amplification or assistive listening devices, particularly during the early language-learning years. Children with hearing loss extending into the speech frequencies 2kHz and lower (Grades 3 and 4) will require hearing aids for speech and language development and for communication.

Diagnosis of hearing loss

Hearing loss can be detected by parents and health care professionals. However, this is clearly an underestimation of the real loss and its impact. Watkin and colleagues observed that parents experienced difficulties in identifying their children's hearing loss, even when the children were older (Watkin et al., 1990).

In cancer patients, platinum-induced ototoxicity typically occurs during or shortly after treatment. Medical Guidelines, such as the COG and SIOPEL Guidelines, recommend the follow-up of survivors even when asymptomatic (Grewal et al., 2010). SIOPEL Guidelines recommend to carefully monitor patients' hearing, with a method compatible with their age throughout treatment and thereafter (SIOPEL (2010) Guidelines for treating High Risk Hepatoblastoma). Survivors exposed to ototoxic therapy should undergo yearly evaluations with appropriate screening for cancer-related complications including a complete audiological evaluation. Frequency of evaluation should be increased if any change is noted. Outer hair cell function of patients treated with cisplatin can be tested in particular by otoacoustic emissions (Grewal et al., 2010) although behavioural testing and pure tone audiometry remain important for assessing the child's need for amplification.

2.1.5. Management

Currently, there is no approved treatment in the EU to prevent or reverse cisplatin induced ototoxicity.

Once ototoxicity is diagnosed through auditory monitoring, chemotherapy dose reductions or omissions maybe recommended, introducing alternative treatments. Although there is often no evidence base for the impact of dose reduction, omission or treatment alternatives on subsequent survival.

The management of patients suffering from ototoxicity is based on management of ototoxicity symptoms. This approach reduces negative consequences of hearing loss but does not restore normal hearing. Patients may benefit from hearing aids, speech-language therapy, and from learning other communication strategies (Brock et al., 2012; Whelan et al., 2011).

When hearing loss occurs, referring patients appropriately for hearing amplification is essential to prevent communication, social, and education set-backs. Implementation of amplification and other adaptive strategies may be required (Grewal et al., 2010). Amplification requires consideration of the severity and configuration of the hearing loss and age of the survivor. Hearing aids have been recommended in 30%–40% of survivors of childhood cancers who experience hearing loss (Grewal et al., 2010; Laverdiere et al., 2005).

2.2. About the product

Sodium thiosulfate (STS) is a detoxifying agent for antineoplastic treatment. The active substance is an inorganic salt containing 1 thiosulfate anion and 2 sodium ions.

STS is a well-known substance with established efficacy and safety profile. The mechanism by which STS reduces ototoxicity is not fully understood, but STS may act in several ways to protect cells from platinum toxicity:

- inactivate free (non-protein bound) CIS due to covalent binding of the molecule to platinum, formatting a stable Pt-thiosulfate complex and thereby inhibits cellular uptake and protein binding.
- reacts irreversibly with CIS to form Pt(S2O3)4 when the drugs are given simultaneously or in close approximation.
- may interfere with oxidative radical stress through increasing of glutathione levels and a positive effect on anti-oxidant enzymes, and in the inner ear STS concentrates in the perilymph or endolymph and may locally enhance chemoprotection against ototoxicity.

Sodium thiosulfate for infusion for the prevention of ototoxicity induced by cisplatin (CIS) chemotherapy in patients 1 month to < 18 years of age with localised, non-metastatic, solid tumours is administered as a 15-minute infusion, 6 hours after the completion of CIS administration, when CIS is infused for no longer than 6 hours. The proposed dose for sodium thiosulfate for infusion is based on body weight category and body surface area.

2.3. Quality aspects

2.3.1. Introduction

The finished product is presented as a solution for infusion containing 80 mg/mL of sodium thiosulfate as active substance.

Other ingredients are boric acid, sodium hydroxide, hydrochloric acid and water for injections.

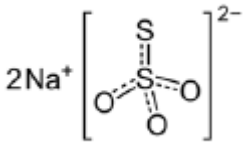
The product is available in type I, 100 mL, clear glass vials sealed with a chlorinated butyl rubber stopper and an aluminium flip-off overseal. Each vial contains 100 mL of solution for infusion.

2.3.2. Active substance

General information

Sodium thiosulfate is the chemical name of the active substance, it corresponds to the molecular formula $Na_2S_2O_3$. It has a relative molecular mass of 158.11 and the following structure:

Figure 1: active substance structure



The chemical structure of sodium thiosulfate anhydrous has been confirmed by IR, MS, Karl Fisher, thermal analysis, X-Ray powder diffraction (XRPD) and sodium identification.

The active substance consists of white, odourless crystals that are very soluble in water and practically insoluble in alcohol. It is mildly hygroscopic.

Sodium thiosulfate does not exhibit stereoisomerism due to the absence of chiral centres.

Polymorphism has not been observed for sodium thiosulfate. Batch data confirm the single crystalline form.

There is no monograph of sodium thiosulfate anhydrous in the European Pharmacopoeia; full information has been provided within the current Marketing Authorisation Application.

Manufacture, characterisation and process controls

Sodium thiosulfate is synthesised by one manufacturer in three simple steps, using commercially available well defined starting materials (sodium sulphite and sulphur) with acceptable specifications.

Quality by design (QbD) elements have been used for the development of the active substance manufacturing process.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised. The main inorganic impurities are sodium sulphate and sodium sulphite. Limits for their control are established both in the final active substance specification and finished product specification.

No discussion regarding potential genotoxic impurities is provided by the applicant. Considering that the main impurities are sulphite and sulphate, which are known to be non-genotoxic, and that sodium thiosulfate infusion is used for patients that are treated with cisplatin, this is accepted.

Acetone and methanol are used as solvents in the manufacturing process of active substance. They are controlled in the active substance specification with limits that are below ICH limits. During the procedure, upon request from CHMP, control of benzene has been included in the specification of the final active substance.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development prgramme. Changes introduced have been presented in sufficient detail and have

been justified. The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process.

The active substance is packaged into two low-density polyethylene (LDPE) bags, placed in a foil pouch which is then placed into a high-density polyethylene (HDPE) drum. The LDPE bag complies with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification includes tests for appearance (visual), identification (FTIR - Ph. Eur.), identification sodium (USP), Identification (IC), assay (IC), impurities (IC), water content (Karl Fisher), acetone, methanol, benzene (GC), elemental impurities (ICP-MS), total aerobic microbial count (TAMC – Ph. Eur.), total yeasts and moulds count (TYMC– Ph. Eur.), bacterial endotoxins (Ph. Eur.).

The acceptance criterion for the assay and residual solvents have been tightened during the procedure. The permissible limits for the content of residual sulphates and sulphites have been justified from a safety point of view as discussed in the non-clinical section.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines.

Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data for a number of commercial scale batches of the active substance, manufactured by the proposed manufacturer, are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from a number of commercial scale batches of active substance from the proposed manufacturer, stored in a package representative of the one proposed for marketing, for up to 12 months under long term (25ºC / 60% RH) and intermediate (30°C / 65% RH) conditions and for up to 6 months under accelerated (40ºC / 75% RH) conditions, according to the ICH guidelines, were provided. The following parameters were tested: appearance, assay, impurities, water content, bioburden and endotoxins. No significant changes/fluctuations or trends are observed during stability studies. No significant increase of impurities has been observed. An increase in the water content was observed, but the results were still within the acceptance limits. A forced degradation study of sodium thiosulfate has been performed.

The analytical methods used were the same as for release and were stability indicating.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 12 months stored below 25ºC in the proposed container to protect from light.

2.3.3. Finished medicinal product

Description of the product and Pharmaceutical development

Sodium thiosulfate 80 mg/mL solution for infusion is a sterile solution containing 80 mg of anhydrous sodium thiosulfate per mL. It does not require further dilution.

Characterisation of the active substance and excipients has been provided. The solubility of the active substance in different solvents is described. Physicochemical properties of the proposed formulation, such as pH, osmolality, oxygen sensitivity, moisture uptake and impact on dispensing/processing, which can affect formulation quality and manufacturability of product, are sufficiently discussed. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.3.1 of this report.

An overfill was implemented based on the fill weight control capability of the filler and to ensure compliance with the extractable volume specification of NLT 100 mL. This is accepted.

The primary packaging is Type I, 100 mL, clear glass vials sealed with a 32 mm chlorinated butyl rubber stopper (Daiko Fluorotec) and an aluminium flip-off overseal. The material complies with Ph.Eur. and EC requirements.

The pharmaceutical development of the finished product contains some QbD elements: the formulation and manufacturing process were developed and characterised in the context of the quality target product profile (QTPP), which is presented below, and critical quality attributes (CQAs).

However, no risk assessment on the CQAs of the finished product is performed; a traditional approach was utilised during formulation and manufacturing process development. Suitability of the proposed formulation with regards to the intended paediatric populations has been adequately addressed, see non-clinical discussion related to the composition of the finished product.

The formulation used during clinical studies has the same composition as that intended for marketing.

Table 2. Quality Target Product Profile of Sodium Thiosulfate for Infusion

QTPP Parameter	Drug Product Attribute	Target Profile
General Criteria	Dosage form and strength	100-mL vials of sodium thiosulfate (added as anhydrous form) solution containing 80mg/mL in nominally filled to 100 mL. The solution is ready for infusion without further dilution
	Attributes affecting the pharmacokinetic characteristics	Sodium Thiosulfate is completely in solution ready for infusion. Phlebitis or injection irritation/inflammation were not reported due to high pH and osmolarity. No incompatibility of the infusion solution with intravenous (IV) bags and infusion lines has been observed.
	Stability Criteria	Not less than 2 years when stored at 25°C/ 60% RH (Zone II conditions). Accelerated stability for 6 months at 40°C/ 75% RH with back-up storage of 30°C/65% RH.
	Container Closure System	A container closure system that will provide a sterile, stable solution with adequate protection from oxygen and suitable for marketing authorization. The identified primary degradation pathway is oxidation of the active. The final product is sterile-filled into USP Type I clear glass vial of 100 mL nominal capacity, closed with a 32 mm Flurotec stopper and secured with a 32mm aluminum flip-off cap.
Drug Product Quality Attributes	Specifications to assure safety and efficacy during the shelf life of the product	Over the shelf life of the product: • Appearance • Assay of active • pH • Impurities • Particulate matter • Sterility • Bacterial endotoxins

In view of the safety concerns linked to boron as excipient (i.e. risk of impaired fertility when administered to children, further discussed in the non-clinical section), alternative buffers were investigated. Several experiments were performed evaluating a range of phosphate buffer concentrations. However, formulation development work with phosphate buffer was suspended due to (1) particulate formation in the terminally sterilised formulation, (2) degradation of sodium thiosulfate and (3) poor buffer capacity; hence, indicating an inherent incompatibility between phosphate and sodium thiosulfate.

Due to the unfavorable results from the phosphate buffer study, additional data evaluating borate buffers were provided during the procedure. The chosen pH range was between 8.5 and 9, as sodium thiosulfate is most stable at this pH, and a range of concentrations were evaluated to establish the lowest minimum concentration of borate needed, in the effort of reducing patients' exposure to borate. After evaluation of the experimental data, it can be concluded that boric acid concentration of 4 mM equivalent to 0.25 mg/mL) is the lowest possible concentration without compromising the stability of the product (drop of pH value, higher levels of degradation products).

The toxicological risk associated with the amount of boron administered with sodium thiosulfate for infusion treatment to children (0.17- 0.22 mg/kg/day) is discussed in the clinical safety section of this report, where it is concluded that the benefit risk of the medicinal product remains positive for the proposed patient population.

The initially proposed sterilisation method for the formulation was sterile filtration/aseptic filling. However, its choice had not been adequately substantiated by the applicant, and as terminal sterilisation provides the highest sterility assurance for the finished product a Major Objection (MO) was raised by the CHMP questioning the choice of the sterilisation method. To address the MO, manufacture of the finished product by filtration followed by terminal sterilisation was proposed, ensuring a higher degree of sterility assurance.

Extractables studies of sterilising filters were performed: in the worst-case conditions there may be extractable compounds above the ICH M7 guidance for genotoxic impurities. However, considering the indication and the genotoxic co-therapy (cisplatin) the additional incremental risk from extractables is negligible. No further actions are required.

Suitability of the container closure system was assessed for protection of finished product from external factors such as light and oxidation. The compatibility of the proposed primary container and closure has been demonstrated by storing the vials in inverted position during stability. Furthermore, a glass delamination study and extractables study on stoppers were performed demonstrating the safety of the proposed primary packaging materials. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

The finished product is a sterile solution for infusion packaged in single-use vials which does not contain any antimicrobial preservative. Container closure integrity was demonstrated in by media fills and methylene blue dye integrity test.

Chemical and physical in-use stability has been demonstrated for 24 hours at controlled room temperature for product stored in standard IV bags (polyvinyl chloride, ethylene vinyl acetate and polyolephine intravenous bags). Additionally, compatibility of the finished product with the receiving bags, used during manufacturing process for storage of the filtered solution, has also been demonstrated.

Manufacture of the product and process controls

The finished product is manufactured by one finished product manufacturer. The manufacturing process consists of 4 main steps. The process is considered to be a standard manufacturing process as terminal sterilisation is performed at Ph. Eur. conditions.

A flow chart of the manufacturing process is presented indicating manufacturing steps, used materials and performed in process controls. Manufacturing equipment/used vessels and their capacity is described, sterilisation cycle of the container components is declared.

During the procedure the bioburden limit has been tightened before the pre-filter. The process is considered to be a standard manufacturing process as terminal sterilisation is performed at Ph. Eur. conditions. Holding time studies results demonstrate no change in key physical, chemical and microbial quality attributes, for both, unfiltered bulk and bulk after bioburden reduction filtration, and a total hold time has been defined.

Major steps of the manufacturing process have been validated by a number of studies. Process validation data for the aseptic manufacturing process were provided for a number of commercial scale batches at the beginning of the procedure, in response to a MO raised on the validation of the originally proposed non-standard manufacturing method. It has been demonstrated that the commercial manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance (visual), identification thiosulfate (IC), clarity and degree of opalescence of liquids (Ph. Eur.), degree of coloration of a liquid (Ph. Eur.), identification of sodium thiosulfate (FTIR), identification for sodium (Ph. Eur.), pH (Ph. Eur.), assay (IC), sulphite and sulphate (IC), sulfur (UPLC-UV), extractable volume (Ph. Eur.), particulate matter (Ph. Eur.), osmolality (Ph. Eur.), sterility (Ph. Eur.), bacterial endotoxin (Ph. Eur.) and elemental impurities (ICP-MS).

The proposed specification follows guidance recommendations. The limits for appearance, clarity and degree of opalescence of liquids, degree of coloration of a liquid, pH comply with the ones reported in section 3.2.P.5.4 (batch analysis data) and 3.2.P.8 (stability data). The limits for extractable volume, particulate matter and sterility are set according to the requirements of the Ph. Eur. The sulphur limit does not exceed the qualification threshold (as per ICH Q3B (R2), therefore the limit is justified. The limits for elemental impurities are based on requirements of ICH Q3D (option 2a). Three different types of identification tests are proposed covering the identification of thiosulfate and sodium, which is acceptable. Sulphate and sulphite limits exceed the qualification threshold of ICH Q3B. The applicant has submitted qualification data to justify the limits. This is acceptable.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data on a number of commercial scale batches of the finished product using a validated ICP-MS method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that the specified elemental impurities are included in the finished product specification. The information on the control of elemental impurities is satisfactory.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed (as requested) considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the

Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for a number of commercial scale commercial batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

An out of specification result (particles in solution) was reported for one batch of the finished product manufactured with sterile filtration/aseptic filling followed by terminal sterilsation, mishandling of the uncoated Type 1 glass vials was found to be the root cause, origin and a chemical identity of particles is confirmed, and corrective actions are implemented. All particles' related issues are sufficiently addressed.

Stability of the product

Stability data from a number of commercial scale batches of finished product stored in the inverted position, which is considered to be the worst-case scenario, for up to 18 months under long term conditions (25ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are representative to those proposed for marketing, as they were prepared by sterile filtration/aseptic filling following terminal sterilisation and were packed in the primary packaging proposed for marketing.

All parameters as per the finished product specification are tested during stability studies except identification and extractable volume. Particulate matter, sterility and bacterial endotoxins are tested periodically during stability studies but planned to be tested at least at the beginning and at the end of studies, this is acceptable.

All parameters have remained largely unchanged through long term and accelerated testing conditions except the out of specification results for appearance (particles in solution) for one batch observed at initial testing point. As discussed above, the route cause was found and it was concluded that it is not an aspect related to the stability of the finished product.

In addition, forced degradation studies were conducted.

Based on available stability data, the proposed shelf-life of 2 years, without any storage conditions, as stated in the SmPC (section 6.3) are acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.3.4. Discussion on chemical, and pharmaceutical aspects

The product is presented as a solution for infusion for paediatric use containing 80 mg/mL of sodium thiosulfate as active substance. Information on development, manufacture and control of the active

substance and finished product has been presented in a satisfactory manner. As requested by the CHMP, during the procedure the applicant has justified the choice of the formulation for the intended patient population, including the presence of borate (please see non-clinical discussion for safety considerations); and terminal sterilisation was added after sterile filtration/aseptic filling to ensure a higher degree of sterility of the finished product. Issues on potential particle formations have been adequately addressed. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

At the time of the CHMP opinion, a minor unresolved quality issue having no impact on the Benefit/Risk ratio of the product, which pertains to the use of Type I Plus glass vials in place of Type I glass vials. This point is put forward and agreed as a recommendation for future quality development.

2.3.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.3.6. Recommendation for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

The applicant is recommended to replace Type I glass vials with Type I Plus glass vials.

2.4. Non-clinical aspects

2.4.1. Introduction

Sodium thiosulfate (STS) is a water-soluble thiol compound and acts as a chemical reducing agent. STS is a well-known substance. It is approved and commercially available for the treatment of cyanide poisoning for many years in the EU and USA and has been used in oncology to prevent Cisplatin-induced nephrotoxicity and as an antidote for extravasation of various chemotherapy agents.

Non-clinical data submitted in support of this application are based primarily on published scientific literature on the safety and efficacy of STS.

2.4.2. Pharmacology

2.4.2.1. Primary pharmacodynamic studies

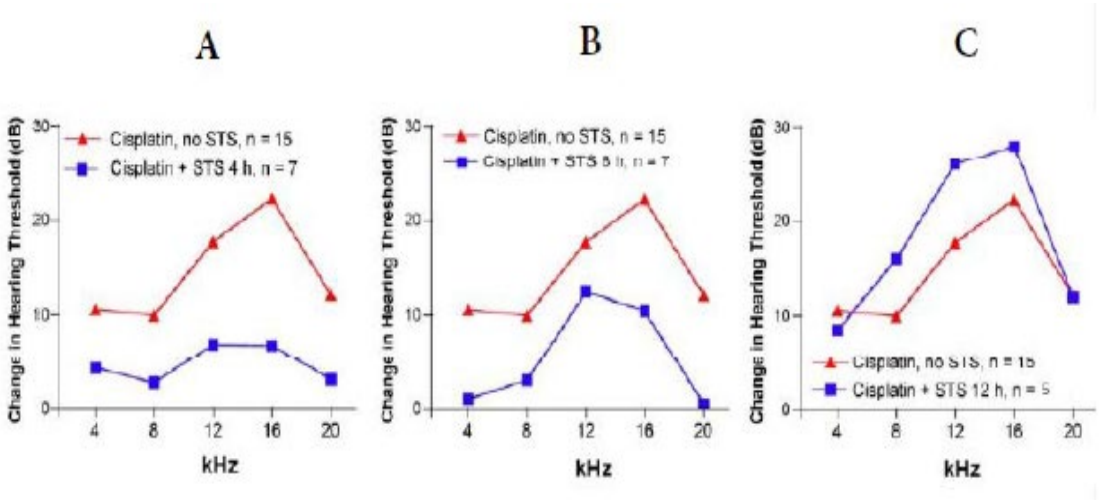
The effects of STS on platinum-induced ototoxicity have been assessed in several pharmacology studies from the literature in various species, including rat, hamster and guinea pig.

The potential for STS to protect against CIS-induced ototoxicity was investigated in adult female Long-Evans rats (Dickey et al, 2005) given single doses of CIS at 6 mg/kg (36 mg/m^2) via a retrograde carotid artery infusion (AI). At 4, 8, or 12 hours after CIS infusion, rats were given single IV doses of

saline or STS at 8 g/m^2. Auditory brainstem response (ABR) thresholds at 4 to 20 kHz were tested before and 7 days post-treatment.

When STS (8 g/m^2) was administered in rats 4 or 8 hours after cisplatin (IA, 6 mg/kg), significant hearing protection was achieved at every frequency (**Figure 2**, panels A and B), whereas no significant oto-protection was found when STS administration was delayed to 12 hours after cisplatin (**Figure 2.** STS Protects Against CIS-Induced Ototoxicity in Rats (Dickey et al, 2005, panel C).

Figure 2. **STS Protects Against CIS-Induced Ototoxicity in Rats (Dickey et al, 2005)**

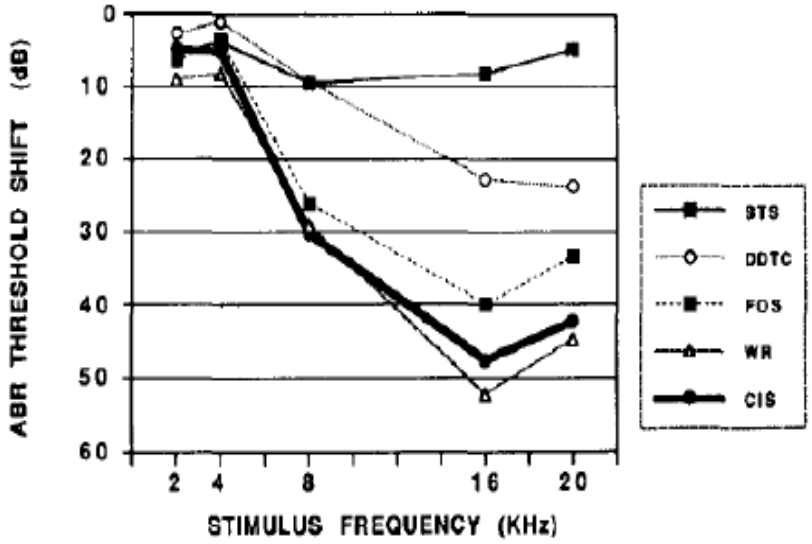


The efficacy of various agents, including STS, in ameliorating CIS-induced ototoxicity were investigated in the hamster (Church et al, 1995). Groups of 10 Syrian golden hamsters were given IP injections of CIS at 15 mg/m2 every other day for 5 doses either alone or in combination with:

- CIS plus STS (8 g/m2, IP) 30 minutes before each CIS dose
- CIS plus diethyldihydrothiocarbamate (DDTC) (1.5 g/m2, IP) 30 minutes after each CIS dose
- CIS plus fosfomycin (1.5 g/m2, IP) 30 minutes before each CIS dose
- CIS plus WR-2721 (90 mg/m2, IP) 30 minutes before each CIS dose.

The protective effect of STS against CIS-induced ototoxicity was assessed electro-physiologically by auditory brainstem responses (ABRs) and anatomically by cochlear histology 30 days after the last injection **(Figure 3).**

Figure 3. Mean ABR Threshold Shits as Function of Treatment Condition and Tone Burst Frequency (Church et al, 1995)



A subgroup of animals (n = 4/group) was chosen for examination by cochlear histology. Examination of the cochlear receptor membrane revealed extensive loss of OHC in the basal region following CIS treatment (56% of cochlear outer cell survival). By contrast, animals in the CIS + STS group showed greater OHC preservation (86% survival of OHCs).

These results were confirmed in a very similar study in hamsters (Kaltenbach et al, 1997), using the same design and the same doses as the study by Church et al (1995). Kaltenbach et al assessed ototoxicity 30 to 35 days after treatment by quantifying the extent of cochlear damage with the scanning electron microscope and with measures of the auditory brain stem response. When administered alone, CIS induced widespread loss of OHCs along much of the cochlea, especially in the basal and middle turns. STS provided the most effective protection against the ototoxic effects of CIS, yielding 91% survival of OHCs.

In guinea pigs, STS successfully protected against carboplatin-induced or CIS-induced ototoxicity when given systemically at 11.6 g/m^2 (Muldoon et al, 2000) or 14.64 g/m^2 (Neuwelt et al, 1996), or locally into the cochleae (Wang et al, 2003) but not when applied topically to the round window membrane (Wimmer et al, 2004). The maximum protection against carboplatin-induced cochlear damage was observed when STS was given at 2, 4, or 8 hours after carboplatin. No protection was observed if STS was given 24 hours after carboplatin.

When administered locally to the guinea pig, a continuous infusion of STS directly to the middle ear space (total dose received: 1.296 g) was better than a single daily dose of STS to the middle ear space (total dose received: 0.216 g) in reducing the ototoxicity of CIS (Stocks et al, 2004).

In albino guinea pigs, CIS (60 mg/m^2, intra-muscular (IM)) administered alone caused total outer hair cell (OHC) loss in the basal and second turns of the cochlea. Damage to the OHCs was mild when STS intra-peritoneal (IP) (8 g/m^2) was given concurrently but was more severe when STS dose was given 3 and 6 hours later, contrary to observations in other studies (Saito et al, 1997).

Another study to examine the efficacy of using STS to inhibit ototoxicity by CIS has been carried out in guinea pigs (Otto et al, 1988). In this study STS (12.8 g/m2) administered with CIS (12 mg/m^2)

consistently protected animals from hearing loss and yielded significant increases in amplitude when compared to baseline and saline controls (data not shown).

2.4.2.2. Secondary pharmacodynamic studies

STS has been used in combination with sodium nitrite to treat cyanide poisoning. Thiosulfate provides a source of exogenous sulfane sulphur to overcome the rate-limiting availability of endogenous sulphur for enzymatic conversion of cyanide to relatively nontoxic and readily excretable thiocyanate (Baskin et al, 1992). Thiosulfate serves as a sulphur donor for rhodanese, a mitochondrial sulphur-transferase that catalyses the conversion of cyanide to thiocyanate (Dollery, 1999).

Sodium thiosulfate has a protective effect against CIS nephrotoxicity in rats (Nagai et al, 1995). Protection against nephrotoxicity was due to the formation of inactive metabolites by a direct reaction between unchanged CIS and STS in the systemic circulation, resulting in a reduction in the amount of reactive CIS in the kidney.

In a study with mice given CIS 10.5 mg/m^2 IP once a day for five days, STS (3 g/m^2) given once a day over 9 days (beginning two days before CIS administration) reduced the incidence of increased serum alanine aminotransferase and hence could play a beneficial role for prevention of CIS hepatotoxicity (Liao et al, 2008) in combined use with other agents.

Sodium thiosulfate reduces the incidence of CIS-related retardation of wound healing in rats with intestinal anastomoses (Wile et al, 1993). All animals that had received CIS alone died in the postoperative period as a consequence of CIS toxicity. Rats given CIS (36 mg/m^2, IP) with STS (4.8 g/m^2, IV) had significantly higher tensile strength of the intestinal anastomoses than rats receiving CIS IV with STS.

Sodium thiosulfate can also protect against other types of toxicity associated with platinum-based chemotherapy; specifically, lethality in mice (Ishizawa et al, 1981), hematologic toxicity (Iwamoto et al, 1984; Neuwelt et al, 2004) and hepatotoxicity (Liao et al, 2008).

2.4.2.3. Safety pharmacology programme

Some safety pharmacology information has been identified in the literature but specific safety pharmacology studies for STS are not reported.

Effect on cardiovascular system

In the study by Dennis and Fletcher (1966), anesthetised and surgically instrumented dogs given an IV dose of STS at 30 g/m2 at a rate of 1 g/m^2/min had no effects on heart rate, blood pressure, or ECG parameters, but dogs given STS at 60 g/m^2 at a rate of 3 g/m^2/min experienced rapid increases in blood pressure and heart rate and had flattened or inverted T waves, all of which were considered secondary to a rapid rise in serum sodium concentration. The QRS complex amplitude also decreased without a change in QT interval. These effects resolved within 3 hours post dose.

In another study (Braverman et al, 1982) in which anesthetised dogs were given a single IV dose of STS at 3 g/m^2, blood pressure and heart rate remained constant during and after administration of STS. The STS dose was dissolved in 50 mL of saline for injection, which would have taken perhaps two minutes to inject; therefore, the rate of STS administration was approximately 1.5 g/m^2/min.

In a third study (Muldoon et al, 2000), STS was administered to four dogs by 15-minute IV infusion at either 20 g/m^2 (n = 2), 30 g/m2 (n = 1), or 40 g/m2 (n = 1); i.e., at rates of 1.3, 2.0, and 2.7 g/m^2/min. Continuous electrocardiograms (ECG; n = 4) and non-invasive blood pressure monitoring (n

= 2) were performed in the dogs during and after the STS infusion. No significant changes in blood pressure or heart rate were reported during or immediately after the infusion.

Effect on respiratory system

In the study by Dennis and Fletcher (1966), dogs given an IV dose of STS at 30 g/m^2 at a rate of 1 g/m^2/min had no effects on respiratory rate, pO2, pCO2, of blood pH. However, dogs given STS at 60 g/m^2 at a rate of 3 g/m^2/min experienced rapid decreases in arterial pO2 and pH, and increase in arterial pCO2, and became tachypnoeic. One dog that died shortly after STS administration had pronounced pulmonary oedema. Similar effects were produced in another dog by a single IV injection of sodium chloride at equimolar concentration.

In a study by Muldoon et al (2000), STS was administered IV to four dogs at either 20 g/m^2 (n = 2), 30 g/m^2 (n = 1), or 40 g/m^2 (n = 1). No significant changes were noted in blood gasses (pO2; pCO2).

Effect on renal system

Sodium thiosulfate has a long-known diuretic effect at high dose levels (Litwins et al, 1943), which appears to be solely attributable to the sodium ion, not to thiosulfate.

Sodium thiosulfate IV at 3 g/m^2 in anesthetised dogs produced a diuresis with a 50% increase in urine flow during the first ten minutes post dose; then the flow returned to baseline levels (Braverman et al, 1982). Renal blood flow increased from 225 to 275 mL/min, and then returned to baseline levels after 60 minutes.

In the dog study by Dennis and Fletcher (1966), single IV doses of STS at 60 g/m^2 caused the urinary bladder to fill overflowing within minutes of injection. In the four of five dogs that survived the STS injection for > 3 hours, marked diuresis occurred. Essentially identical diuresis occurred in dogs with single IV injections of sodium chloride at equimolar concentrations.

In a study by Muldoon et al (2000), STS was administered IV to four dogs at either 20 g/m^2 (n = 2), 30 g/m^2 (n = 1), or 40 g/m^2 (n = 1). Serum was collected for determination of STS concentrations, acid-base status, and sodium and potassium concentrations during the infusion, immediately after, and 30 minutes after infusion. Urine was collected between 5 and 20 minutes after STS infusion and assayed for STS. Mild to moderate hypernatremia (154 - 170 mEq/L) and mild hypokalaemia (2.26 - 3.46 mEq/L) occurred in all dogs and were more pronounced with increasing STS dose. No significant changes were noted in the publication on the acid-base balance (personal communication).

Effects on central nervous system (CNS)

In the study by Dennis and Fletcher (1966), an IV dose of STS at 60 g/m^2 produced muscular twitching that was probably due to changes in serum electrolytes but no clinical signs suggesting an effect on CNS function.

Potential neurotoxicity of STS with and without osmotic blood brain barrier disruption (BBBD) by mannitol infusion was studied in adult female Long Evans rats (Neuwelt et al, 1996). Groups of four rats were given STS at 11.6 g/m^2 by:

• Intracarotid infusion without mannitol infusion or immediately following mannitol infusion, or

• IV infusion immediately, 30 minutes, or 60 minutes after mannitol infusion.

Rats were observed for 2 hours after STS administration for signs of neurotoxicity. Sodium thiosulfate produced no discernible neurotoxic effects when administered without BBBD or when administered 30 or 60 minutes after BBBD, i.e., when the BBB was re-established. However, when given immediately after BBBD, STS produced neurotoxicity, including seizures. When given by intracarotid infusion, seizures occurred in three of four animals. When given by IV infusion, STS produced less neurotoxicity,

as one animal had a mild, focal seizure that did not require diazepam for control. Also, serum sodium and potassium levels did not change as a result of STS infusion.

2.4.2.4. Pharmacodynamic drug interactions

Interaction of STS with anti-tumour activity of platinum chemotherapy

Several studies have investigated the inhibition of the cytotoxic effect of CIS by STS *in vitro* and *in vivo*.

In vitro studies

In a mouse leukaemia cell line, STS had no effect on CIS-related cytotoxic effects at concentrations ≤ 15.5 µg /mL (0.0625 mM), but inhibited cytotoxicity by approximately 50% at 62 µg /mL (0.25 mM) when CIS and STS were mixed and added simultaneously (Viale et al, 1999).

Combinations of STS with CIS were also evaluated *in vitro* for CIS cytotoxicity to murine leukaemia cell line L1210 (Catino et al, 1986). The *in vitro* assay indicated that STS inhibits the cytotoxic effects of CIS in a concentration-dependent manner. The concentration of CIS required to kill 50% of L1210 cells was increased 40-fold (1.6 µg/mL to 65.2 µg/mL) at the highest concentration of STS evaluated (781 µg/mL, ~ 3 mM).

The *in vitro* cytotoxic dose-relation of CIS and STS was investigated in human tongue and oesophageal squamous carcinoma cell lines (Kovács et al, 2002). Cisplatin (0.2 - 10 µg/mL) was combined with STS (0 - 0.5 mg/mL, ~ 2 mM) in a panel of two tongue squamous cancer cell lines and an oesophageal cancer cell line as control and comparison. Any concentration of STS resulted in a measurable reduction of CIS cytotoxic effects. At the maximum dose of CIS and an STS/CIS ratio of 6:1, cytotoxic activity was still observed. An increase of CIS concentration led to higher cytotoxicity irrespective of STS concentration. It was concluded that an STS/CIS concentration ratio within the tumour of less than 6:1 may be acceptable without compromising the cytotoxic effects of CIS on tumour cells.

Neuwelt et al investigated the STS rescue of carboplatin cytotoxicity *in vitro* on LX-1 cells (Neuwelt et al, 1996). A time course experiment was performed to determine the time point after the addition of carboplatin when STS would no longer exert a tumour-protective effect. Treatment with STS anytime from 0 to 6 hours after the addition of carboplatin reduced the cytotoxicity of carboplatin by > 90%. At 8 hours after carboplatin, STS only partially inhibited cytotoxicity.

The time dependence for the effects of STS on CIS-induced cytotoxicity was also evaluated *in vitro* in four separate human tumour cells lines: U87 glioblastoma, SKOV3 ovarian carcinoma, DAOY medulloblastoma cells and B.5 LX-1 small cell lung cancer cells (SCLC) (Dickey et al, 2005). Sodium thiosulfate (2 mg/mL) was added 0, 2, 4, 6, or 8 hours after CIS (30-50 µM). Sodium thiosulfate (2 mg/mL, ~8 mM) decreased CIS-induced cytotoxicity on cancer cells when added either concurrently with CIS or up to 2 hours after CIS. Delayed administration of STS reduced its effect on CIS-induced cytotoxicity on cancer cells. If STS was administered 4 hours after CIS, its protective activity was reduced to 30 to 40% of the maximal protection seen with concurrent administration. When delayed until 6 hours post-CIS, STS showed no significant effect on CIS cytotoxic activity in any cell type tested. The magnitude of STS chemoprotection was dependent on CIS concentration, particularly in the 2- to 4-hours window.

Cell viability was assessed 48 hours after CIS administration to tumour cells in vitro. STS was administered at various time points after CIS (Dickey et al, 2005).

The effect of STS on CIS antitumour cytotoxicity was investigated for neuroblastoma in cells (Harned et al, 2008). The anti-neuroblastoma activity of CIS was determined with or without the addition of

STS at 0 or 6 hours after CIS in six neuroblastoma cell lines. A significant protection against CIS cytotoxicity was seen when the neuroblastoma cells were exposed to CIS directly combined with STS. However, when CIS was given first and STS exposure occurred 6 hours later, no effect on CIS cytotoxicity was observed.

In vivo studies

In vivo studies conducted in several animal models evaluated the impact of STS on tumour protection and the PK profile of cisplatin.

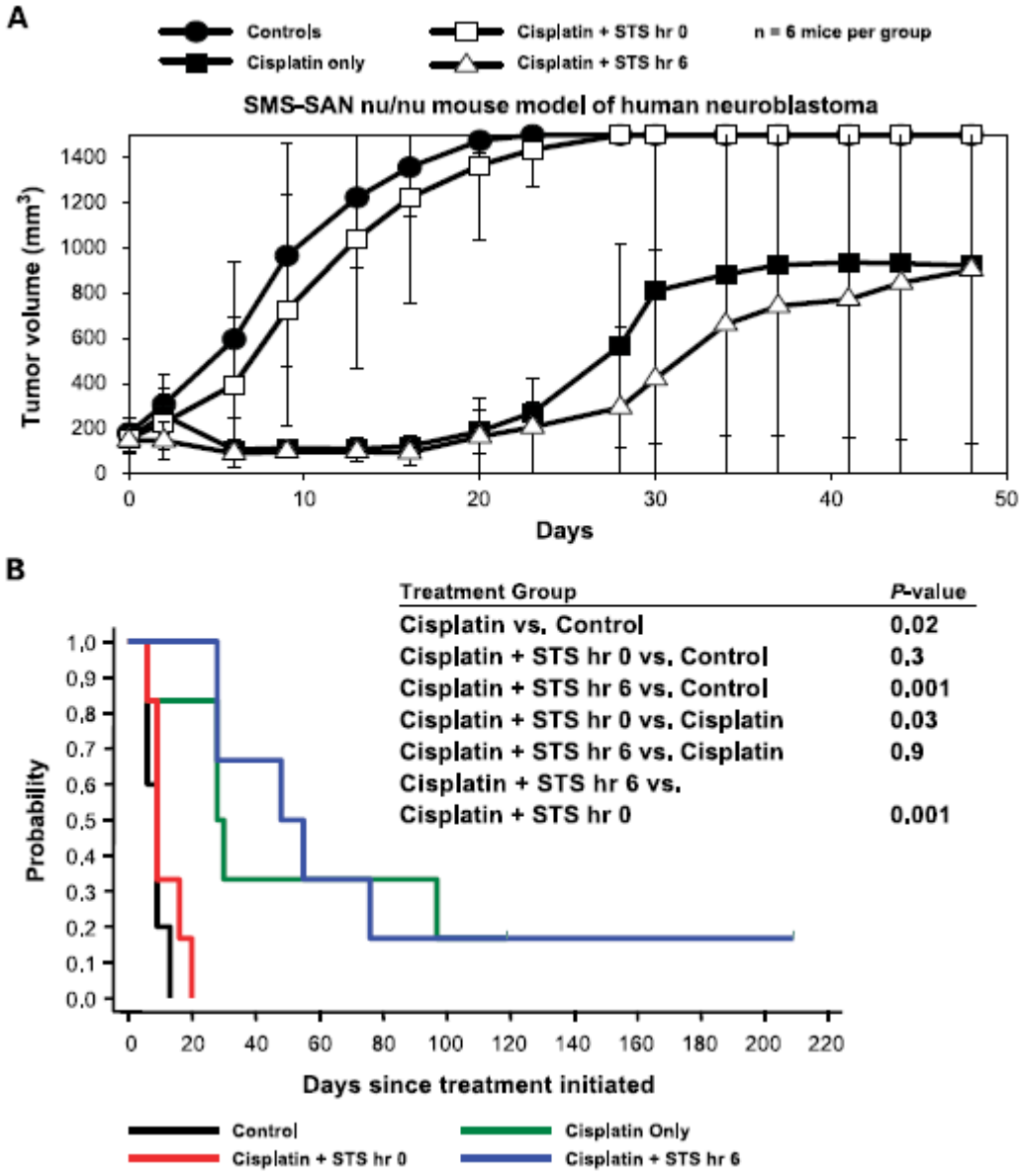
Muldoon et al investigated the effect of STS on tumour cells by using an in vivo nude rat model with SC tumours grown from the LX-1 human SCLC cell line (Muldoon et al, 2000). STS (IV, 8 g/m2) was provided at different times after chemotherapy to assess its potential impact vs. time.

Muldoon et al showed that STS may decrease the anticancer effects of carboplatin if STS was provided too early after chemotherapy. Treatment with STS at 2 hours and 6 hours after carboplatin significantly inhibited (p=0.012) the antitumour effect of the chemotherapy. The time delay to a measurable tumour of 6.4 ± 0.8 days (n = 8) if animals received STS 2 hours or 6 hours after chemotherapy was not significantly different from untreated animals (p=0.164). However, delaying STS administration to 8 hours after carboplatin/etoposide treatment did not significantly affect the chemotherapy. Administration of STS 8 hours after the combined carboplatin and etoposide phosphate treatment allowed significant prolongation of time to tumour detection (8.1 ± 0.7 days, n = 8, versus no treatment 5.5 ± 0.4 days, n = 20, p=0.0023) and did not significantly reduce the efficacy of chemotherapy (8.9 ± 0.6 days, p = 0.188, compared to 8.9 ± 0.6 days, n = 18, p=0.188 for chemotherapy alone).

Neuwelt et al (2004) evaluated the effect of a bone marrow chemoprotection regimen on the efficacy of chemotherapy against rat brain tumours. Nude rats with intracerebral human lung carcinoma xenografts were treated with carboplatin, melphalan, and etoposide phosphate delivered intra-arterially with osmotic BBBD (n = 8/group), which reduced intracerebral tumour volume from 29.1 ± 4.1 mm3 to 4.3 ± 1.0 mm3 (p<0.0001). This reduction in tumour volume was not affected (3.7 ± 0.6 mm3) by the chemoprotection regimen consisting of N-acetyl-L-cysteine (1000 mg/kg) 60 minutes before chemotherapy and STS (8 g/m2) 4 and 8 hours after chemotherapy, when the BBB was re-established. Sodium thiosulfate and N-acetyl-L-cysteine administered together protected against chemotherapy-induced bone marrow suppression, as improved white blood cell, granulocyte and platelet counts were observed in this group compared to chemotherapy alone. In this study, the lack of tumour protection by STS can also be explained because STS does not pass the BBB and the delay in administration allows restoration of the BBB.

Harned et al (2008) studied nude mice with SMS-SAN neuroblastoma xenografts treated with CIS 12 mg/m2/day IP (Harned et al, 2008). The results showed that giving STS 10.5 g/m2/day, IP at the same time as CIS negated the cytotoxic effects of the drug with tumour progression being identical with the control group. Whereas the CIS alone and the CIS and STS 10.5 g/m2/day at 6 hours groups both showed significantly improved progression free survival compared to controls (p=0.03 CIS alone, p=0.001 CIS plus STS at 6 hours). Therefore, STS delayed to 6 hours after CIS did not affect CIS antitumour activity. There was no statistically significant difference in outcomes between mice treated with CIS alone and the group treated with CIS followed by STS 6 hours later (p=0.9). This study showed that STS delayed to 6 hours after CIS in SMS-SAN xenografts in athymic nu/nu mice did not affect CIS antitumour activity (**Figure 4**).

Figure 4. Effect of STS and CIS on SC Human Neuroblastoma Xenograft Growth (Harned et al, 2008).



2.4.3. Pharmacokinetics

Absorption

In mice, STS 5.25 g/m^2 administered by intravenous (IV) injection produced maximum plasma concentrations (± sem) of 4.73 ± 0.14 mg/mL (Iwamoto et al, 1984). The plasma PK profile in mice showed first order kinetics, and an elimination half-life of 10 minutes was reported after the IV injection. After an intraperitoneal (IP) injection of 10.5 g/m2 STS the mean STS concentration was approximately 1.7 mg and 8.6 mg/mL at 1 and 15 minutes after STS administration, respectively (Harned et al, 2008). STS 5.25 g/m2 administered by subcutaneous (SC) injection produced maximum plasma concentration (± sem) of 1.10 ± 0.05 mg/mL (Iwamoto et al, 1984). Maximum plasma levels were reached 10 minutes after SC injection. The plasma PK profile showed a log-linear decline with an

estimated half-life of 27 minutes after SC injection. This was higher compared to the IV administration in this study and suggests flip-flop kinetics through rate limiting absorption from the SC injection site.

In rats, IV infusion of STS over 15 minutes at total doses of 6.0 g/m^2, 8.0 g/m^2, or 11.6 g/m^2 produced peak plasma concentrations at the end of infusion of approximately 2.8 mg/mL (n=2), 3.4 mg/ml (n=3), and 5.8 mg/mL (n = 4), respectively (Muldoon et al, 2000). STS 6 g/m^2 IP bolus injection produced a plasma concentration of approximately 0.3 mg/mL (n = 4) and 1.4 mg/mL at 15- and 30-minutes post dose, respectively (Muldoon et al, 2000). Sodium thiosulfate 11.6 g/m^2 IP bolus injection produced a plasma concentration of approximately 2.0 mg/mL (n = 1) at 15 minutes post dose (Muldoon et al, 2000).

In guinea pigs, IV infusions of STS over 15 minutes at a total dose of 11.6 g/m^2 produced a peak plasma concentration of approximately 6.7 mg/mL (n = 3) (Muldoon et al, 2000). STS dose of 14.64 g/m^2 over 15 minutes produced approximately 5.6 mg/mL STS in serum (n = 5) (Neuwelt et al, 1996). In another experiment, STS was injected IV to guinea pigs at 4 g/m2 (n = 7). Assuming first order elimination kinetics, a plasma half-life of 25.8 ± 3.0 minutes was calculated (Mengel et al, 1989). IP bolus injections of STS 11.6 g/m2 produced a plasma concentration of approximately 4.1 mg/mL (n = 2) at 15 minutes post dose (Muldoon et al, 2000).

In dogs, STS IV at 20 g/m^2, 30 g/m^2, or 40 g/m^2 produced peak plasma concentrations of 258 ± 37 mg/dL (n = 2), 404 mg/dL (n = 1), and 564 mg/dL (n = 1), respectively; i.e., approximately 2.6, 4.0, and 5.6 mg/mL, respectively (Muldoon et al, 2000).

In anesthetised dogs, STS IV at 3 g/m^2 produced a peak plasma concentration of 1.77 mg/mL (n = 5) at 2 minutes post dose (Braverman et al, 1982). After IV injection, the decline in STS in plasma over an hour showed two exponential phases, with an initial half-life of 3.4 minutes during the first 10 minutes followed by a half-life of 46.8 minutes.

Five gravid ewes received IV STS (50 mg/kg over 15 min, estimated to be 1.8 g/m^2 considering an average ewe of 41.4 kg; Simão, 2017) (Graeme et al, 1999). Serial plasma STS concentrations in ewes were measured over 135 minutes. The maximum concentration at the end of infusion was approximately 80 mg/mL after which the plasma profile showed a biphasic exponential decline in concentration with a distribution half-life (α) of 6.4 ± 1.9 minutes and a terminal half-life (β) of 39.2 ± 10.1 minutes (mean ± se). Area under the time-plasma STS concentration curve was calculated at 2758 ± 197 min.mg-1.L-1.

Distribution

In rats, STS distributed poorly into the CNS. Over a range of IV doses, STS concentrations were approximately 10-fold lower in cerebrospinal fluid (CSF) than plasma (Pollay and Kaplan, 1971).

In the guinea pig, high concentrations of STS (thiosulfate) reach scala tympani perilymph after administration of STS (824 mg/m^2, IV) (Videhult-Pierre et al, 2009). The highest concentrations were seen at the first sampling at about 10 minutes; the concentrations then gradually decreased. Sodium thiosulfate concentrations remain elevated longer in perilymph than blood.

The half-life of STS 250 mg/mL within perilymph was 44.4 minutes.

In one dog, STS was undetectable in the CSF at 4 hours after an IV dose (Muldoon et al, 2000). The average volume of distribution of STS is 3 L in dogs with an average body weight of 12.4 kg (n = 7), corresponding to 0.242 L/kg and 24.4% of body weight (Cardozo and Edelman, 1952).

Five control gravid ewes received IV sodium chloride solution, whereas five gravid ewes received IV STS (50 mg/kg over 15 minutes, estimated to be 1.8 g/m2 considering an average ewe of 41.4 kg; Simão, 2017) (Graeme et al, 1999). The maximum concentration at the end of infusion was

approximately 80 mg/mL after which the plasma profile showed a biphasic exponential decline in concentration with a distribution half-life (α) of 6.4 ± 1.9 minutes and a terminal half-life (β) of 39.2 ± 10.1 minutes (mean ± se). The volume of distribution for gravid ewes was 0.28 ± 0.03 L/kg (mean ± sem), which is in the range of extracellular fluid volume for adult mammals.

There was no difference in AUC for the fetuses from ewes treated with STS versus control fetuses: 236 ± 34 and 265 ± 23 min.mg-1.L-1, respectively. Hence, STS does not pass the placental barrier in meaningful amounts in sheep.

Metabolism

Thiosulfate is an endogenous compound, and its formation and degradation are part of the general and preserved metabolic sulphur pathways that include sulphur containing amino acids. STS is considered to be the principal, rapidly disappearing precursor of sulfate in mammals (Szczepkowski et al, 1961; Bilska-Wilkosz et al, 2017). The main route for thiosulfate metabolism does not involve CYP450 enzymes but instead occurs through thiosulfate sulphur transferase or thiosulfate reductase, resulting in sulphite. Subsequently, sulphite is converted by sulphite oxidase to sulfate. There are no breakdown products which are anticipated to be toxic or likely to cause any unpredictable off target effects. Studies have also shown that there are no cumulative effects (EPA, 2003). Orally administered STS (thiosulfate) that is absorbed from the gastrointestinal tract is excreted in the urine unchanged or after oxidation to sulfate (EPA, 2001).

In control rats with only endogenous sulphur metabolism, excretion in urine of sulfate and unchanged thiosulfate occurs in a ratio of 33-100 (Szczepkowski et al, 1961). After intravenous STS injection, urinary excretion occurs as sulfate or intact thiosulfate.

In rabbits, about a third of STS is excreted unchanged in the urine, the remainder as ethereal sulphates. When exogenous STS gets administered at increasing dose levels, the relative contribution of STS (thiosulfate) metabolism to sulfate is reduced, and that of direct excretion of STS as thiosulfate is increased (Litwins et al, 1943).

Excretion

Sodium thiosulfate is very rapidly excreted by the kidney in rats, guinea pigs and dogs (Neuwelt et al, 1996, Muldoon et al, 200).

Determination of the renal clearance of STS in dogs showed that the renal clearance of STS (thiosulfate) was directly related to the creatinine clearance and that 70% to 80% of that administered STS was recovered as thiosulfate in the urine (Gilman et al, 1946). Approximately 25% of administered STS was excreted in the urine during the first 30 minutes after administration and 41% within 90 minutes. By 60 minutes post-dose, the renal clearance of STS was approximately similar to that measured for creatinine, suggesting that renal clearance of STS at high plasma concentrations is similar to the glomerular filtration rate.

Pharmacokinetic drug interactions

<u>Sodium thiosulfate as an inhibitor of CYP450 (Study 2017-0301)</u>

The potential inhibitory capacity of STS towards major human CYP450 isoforms responsible for hepatic drug metabolism was assessed in using human liver microsomes. Sodium thiosulfate was evaluated in the range of the concentrations 0.1 to 300 mM (0.016 to 47.4 mg/mL). Sodium thiosulfate showed inhibition at low potency towards all isoforms (**Table 3**).

Table 3. IC50 values for CYP450 Inhibition of STS in Human Liver Microsomes, Study 2017-0301

	IC_{50}		IC_{50} Corrected for Sodium/Osmolality	
CYP450 Isoform	mM	(mg/mL)	mM	(mg/mL)
CYP1A2	107	16.9	180	28.5
CYP2B6	39.8	6.3	218	34.5
CYP2C8	85.4	13.5	95.4	15.1
CYP2C9	71.6	11.3	104	16.4
CYP2C19	57.8	9.1	89.2	14.1
CYP2D6	69.0	10.9	> 300	> 47.4
CYP3A4 midazolam	> 300	> 47.4	> 300	> 47.4
CYP3A4 testosterone	> 300	> 47.4	> 300	> 47.4

Sodium thiosulfate as an inductor of CYP450 (Study 2017-0305)

The potential of STS to induce cytochrome P450 isoforms CYP1A2, CYP2B6 and CYP3A4 was determined by comparing the mRNA expression of these isoforms after 72 hours incubation with STS or vehicle in three different batches of cryopreserved plateable human hepatocytes. STS was tested at the concentrations of 1, 10 and 25 mM. Incubation of hepatocytes from three donors with STS (1 to 25 mM) for 72 hours did not increase CYP1A2 or CYP3A4 mRNA expression in hepatocytes. For CYP2B6, no induction was observed for two donors, but in hepatocytes of a third donor 72-hour incubation at 10 and 25 mM STS resulted in 2.1- and 2.3- fold increased mRNA expression levels, respectively (approximately 27% of positive control phenobarbital). This was just above the thresholds set at 2.0-fold and 20%, respectively. Both concentrations showed similar effect with no further increase at the highest concentration.

2.4.4. Toxicology

The applicant relied on publicly available nonclinical safety data to characterise the toxicity/safety profile of STS following single-dose and repeat- dose administrations in various species. One of the main sources of information is the Registry of Toxic Effects of Chemical Substances (RTECS) published by the National Institute for Occupational Safety and Health (NIOSH).

2.4.4.1. Single dose toxicity

Single-dose toxicity findings from the literature are summarised in **Table 4.**

Table 4. Single-Dose Toxicity Studies with STS

				Test Article: Sodium thiosulfate	
Organism	**Test Type**	**Route**	**Reported Dose**	**Noteworthy Findings**	**Study Number**
Mouse	LD_{50}	IV	1600 mg/kg (3.57 g/m^2)	-	EPA, 2003 RTECS, 2011
Mouse	LD_{50}	IP	1000 mg/kg (15.6 g/m^2)	-	RTECS, 2011
Mouse	Maximum dose tolerated without signs of toxicity	IP	3200 mg/kg (9.6 g/m^2)	No signs of toxicity with doses up to 9.6 g/m^2	Howell and Taetle, 1980
Rat	LD_{50}	IV	> 2500 mg/kg (> 15 g/m^2)	Convulsions or effect on seizure threshold with doses > 15 g/m^2	EPA, 2003 RTECS, 2011
Rat	-	IV	11.6 g/m^2	No effect on sodium and potassium serum concentration not affected	Neuwelt et al, 1996
Rat	LD_{50}	Oral	> 5000 mg/kg (> 30 g/m^2)	-	EPA, 2003 RTECS, 2011
Rat	Maximum dose tolerated without signs of toxicity	IP	4.7 g/m^2	No signs of toxicity with doses up to 4.7 g/m^2	Bhagat and Lockett, 1960
Rabbit	Lethal dose	IV	4 g/kg (48 g/m^2)	-	EPA, 2003
Rabbit	Lowest published lethal dose	SC	4 g/kg (48 g/m^2)	-	RTECS, 2011
Dog	LD_{50}	IV	3 g/kg (60 g/m^2)	-	EPA, 2003 RTECS, 2011
Dog	-	IV	20 g/m^2, 30 g/m^2, and 40 g/m^2	Mild to moderate hypernatremia and mild hypokalaemia	Muldoon et al, 2000

2.4.4.2. Repeat dose toxicity

Studies have shown that excess thiosulfate from STS (beyond endogenous levels of thiosulfate) is rapidly cleared from the body by entering normal metabolic pathways and there are no cumulative effects *(*EPA, 2003*).*

Rats given daily 50 mg of STS by IM injection for 4 weeks (n=4) and 3 months (n=4) developed deleterious changes in various organs *(*Steger, 1953*).* Assuming rats weighed approximately 500g, this dose level was approximately 0.6 g/m^2. The thyroid gland and adrenal cortex showed changes in the capillary walls at 4 weeks. After 3 months the vessels of the kidneys displayed clear changes: the glomeruli were atrophic, hyaline, with markedly few cells, and the glomerulus capillaries were dilated and became permeable to plasma. The renal arterioles were partially dilated, and partially exhibited endothelial cell proliferation. An increased fluid permeation through the capillary walls and an increase in Kupffer cells was also observed in the liver.

No signs of toxicity were observed in hamsters given STS IP 8 g/m^2 every other day for a total of five injections, or in guinea pigs given IP doses of STS at 8 g/m^2 every 5 days for three doses *(*Saito, 1997*)* or at 12.8 g/m^2 daily for 8 days *(*EPA, 2003*).*

2.4.4.3. Genotoxicity

In bacterial reverse mutation assays (Ames assays), STS was not mutagenic in the absence of metabolic activation in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, or TA1538 or in the presence of metabolic activation in strains TA 98, TA1535, TA1537, TA1538 or *Escherichia coli* strain WP2 *(*Prival et al, 1991*).* In addition, STS at up to 1000 µM did not increase the frequency of sister chromatid exchanges (SCE) in human lymphocytes in vitro *(*Ohe et al, 1990*).* This is understandable since thiosulfate is regularly used in bacterial and cell culture media as a source of sulphur *(*EPA, 2003*).*

When STS (1 to 1000 µM) was added to the culture medium of human lymphocytes continuously treated with cisplatin (1 µM), STS produced a dose-related inhibition in the frequency of SCE induced by cisplatin *(*Ohe et al, 1990*)*. Also, when evaluated in Drosophila, STS exhibited antimutagenic

activity in the wing spot assay and completely inhibited cisplatin-induced mutagenesis and mitotic recombination (Katz, 1989). In Ames assays, co-administration of STS reduces the mutagenic effects several other chemicals *(*EPA, 2003).

2.4.4.4. Carcinogenicity

The applicant did not submit carcinogenicity studies with STS based on the fact that it will be administered periodically and only in conjunction with chemotherapy which is already carcinogenic and therefore any additional carcinogenic hazard presented by STS (if any) would be negligible in comparison. Furthermore, STS is generally recognised as safe when used as a food additive.

2.4.4.5. Reproductive and developmental toxicity

No nonclinical studies have been conducted to evaluate the potential effects of STS on fertility or reproductive function in animals of either sex but studies in various animal models on the effects of STS on reproductive toxicity and embryonic development have been described in the literature.

Animal studies do not indicate direct or indirect harmful effect with respect to reproductive toxicity (Food and Drug Research Labs, 1972; Food and Drug Research Labs, 1974).

STS is considered unlikely to affect the development of an embryo or fetus exposed via seminal fluid, as it is remains mainly extracellularly, and thus it is extremely unlikely that it would be found in semen.

Developmental toxicology studies of STS have been conducted in mice, rats, hamsters and rabbits (EPA, 2001; EPA, 2003).

In each species, there was no indication of any effect on nidation or on maternal or fetal survival, or incidences of visceral or skeletal abnormalities.

Sodium thiosulfate was shown as not embryotoxic or teratogenic in mice, rats, hamsters, or rabbits at maternal doses of up to 550, 400, 400 and 580 mg/kg/day (1650, 2400, 2000 and 6960 mg/m^2/day, STS administered as a water solution by oral intubation), *respectively (Food and Drug Research Labs, 1972; Food and Drug Research Labs, 1974)*.

In other studies, there were no teratogenic effects in offspring of hamsters treated during pregnancy with STS in doses similar to those given IV to treat cyanide poisoning in humans (Willhite, 1983).

2.4.4.6. Local tolerance

There are no reports of local (infusion site) reactions to i.v. injection of high concentrations of STS in the nonclinical published scientific literature, in view of presumed hypertonic formulations used for injection. In addition, no AE/SAE related to the site of administration were observed in the two clinical studies (See clinical safety section of this report).

2.4.4.7. Other toxicity studies

Excipients

No specific studies were submitted on excipients. However, the applicant submitted an assessment on boric acid toxicity which is a buffer component of the product and which can pose a risk to fertility. The assessment was based on the EMA guideline 'Questions and answers on boric acid and borates used as excipients in medicinal products for human use' (EMA/CHMP/619104/2013; October 2017) which sets

age-related thresholds. These are 1 mg/day for patients < 2 years old, 3 mg/day for patients 2 to < 12 years old, 7 mg/day for patients 12 to < 18 years old, and 10 mg/day for patients ≥ 18 years old. In addition, in cases of pregnancies and for exposures ≥ 7 mg, there is a potential risk for foetal development.

The STS formulation proposed for marketing contains 0.044 mg / mL of boron. Sodium Thiosulfate for Infusion is given between 6 and 30 times over a 6-month period depending on the cisplatin regimen being used, which is tumour dependent. When added to the tolerable daily intake of boron from the diet, over a 6-month period, the amount of boron administered to each child ranges from 0.17 to 0.22 mg/kg/day.

2.4.5. Ecotoxicity/environmental risk assessment

No environmental risk assessment (ERA) studies were submitted as STS is an industrial chemical, and its environmental effects are well characterised. Moreover, it is manufactured and/or imported in the EEA in 1000-10000 tonnes per year. Therefore, the additional exposure based on dosing children for the proposed indication is negligible compared to the European exposure from other sources, and STS for infusion is unlikely to pose a risk to the environment or to alter the concentration and distribution of the substance in the environment. As no increase in environmental exposure is expected, no further calculations or studies are required in accordance with the Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00 Rev. 1).

2.4.6. Discussion on non-clinical aspects

The non-clinical development prgramme to support the MAA for sodium thiosulfate 80 mg/mL solution for infusion is primarily based on bibliographical data, and further supported by two *in vitro* studies performed on behalf of the applicant to evaluate the ability of STS to inhibit or induce CYP450 isozymes.

Numerous studies *in vitro* and in animals have shown that STS can protect against ototoxicity associated with platinum-based chemotherapy. STS reduces ototoxicity even when administration is delayed for up to 8 hours after systemic platinum-based chemotherapy. Thus, STS has the potential to prevent chemotherapy-induced hearing loss.

The mechanism by which STS reduces ototoxicity is not fully understood, but STS may act in several ways to protect cells from platinum toxicity.

STS can inactivate free (non-protein bound) CIS due to covalent binding of the molecule to platinum, to form a stable Pt-thiosulfate complex (Sooriyaarachchi et al, 2016). This complex leads to a decrease of the intracellular penetration of CIS-pt and promotes its elimination. Cochlea cells have a strong metabolic activity and are sensitive to oxidative stress, STS has demonstrated in these studies an anti-oxidative stress effects by measuring the activities of the enzymes superoxide dismutase (SOD) and catalase (CAT). ROS were also measured using 5- (and-6) -carboxy-2 ’, 7’-difluorodihydrofluorescein diacetate. The action on oxidative stress was also evaluated by measuring the content of hydrogen peroxide. The STS would protect against oxidative stress by increasing the amounts of glutathione. In the inner ear STS concentrates in the perilymph or endolymph and may locally enhance chemoprotection against ototoxicity.

STS is used as an antidote for cyanide poisoning: source of sulphur (Dollery, 1999). It allows the reduction of the formation of calcium phosphate stones by a mechanism still unknown. It prevents vascular calcifications in the uremic rat (Pasch et al, 2008). STS also has a protective effect against CIS nephrotoxicity in rats (Nagai et al, 1995). The STS has demonstrated a power to prevent

hepatotoxicity (Liao et al, 2008) when used in combination with other agents. It also allows prevention of intestinal anastomosis in rats receiving CIS IV with STS. No non-clinical *in vitro* secondary pharmacological screening studies were conducted and published in scientific literature. However, given STS's inorganic nature and its rapid metabolism to endogenous constituents, there is no expectation that STS would be privy to enzyme interactions or receptor binding.

Administration of the STS 6 to 8 hours after the CIS-Pt seems adequate as proposed by the applicant to limit the toxicity of the CIS-Pt without affecting its anti-tumour power. *In vitro*, STS does not interfere with CIS cytotoxicity in cultured tumour cells when the start of incubation is delayed by 6 hours. *In vivo* in mice, STS does not interfere with CIS efficacy to decrease tumour burden, when STS administration is delayed by 6 hours.

The pharmacology and safety pharmacology associated with sodium thiosulfate has been extensively reported in the literature. The applicant has not performed any additional non-clinical studies except two *in vitro* studies investigating enzyme induction and inhibition by STS. Results from those studies have shown the potential for relevant pharmacokinetic drug-drug interaction is negligible as only a weak induction effect of STS was observed on activity of CYP2B6 in one assay. The clinical significance of this finding is not clear.

Toxicology data are also available from the literature. Because of the long history of STS patient use, which has defined clinical efficacy and safety of STS in children and adults, further toxicology/safety testing in animals to satisfy regulatory guidelines were not considered necessary. The main adverse effects of STS are due to hypernatremia and decrease in calcium with secondary diuresis and disturbances in acid-base balance, which affect the function of the cardiovascular, respiratory, and neuromuscular systems. It should be noted that the repeated toxicity study dates from 1953 and used the IM route in rats to assess the toxicology potential of the product which is not the human route used during clinical trials and for the marketing authorisation. Therefore, STS exposure cannot be accurately assessed with this study.

There is insufficient information from animal studies to assess the effects of intravenous infusion of sodium thiosulfate on fertility.

There is insufficient information from animal studies to assess developmental risks with intravenous infusion of sodium thiosulfate (see SmPC section 5.3). As a precautionary measure, it is preferable to avoid the use of sodium thiosulfate during pregnancy. Sodium thiosulfate is only intended to be administered in conjunction with cisplatin chemotherapy. Cisplatin is not used during pregnancy unless the clinician considers the risk in an individual patient to be clinically justified. Patients receiving cisplatin are warned of the need to use appropriate contraception during treatment and for 6 months following cisplatin treatment, as cisplatin is embryotoxic and fetotoxic (see SmPC section 4.6).

There are no studies regarding the excretion of STS into breast milk; however, breast milk is produced within alveolar cells and, since most thiosulfate remains extracellularly, it is unlikely that thiosulfate would be found in breast milk. In addition, STS will only be administered in conjunction with platinum-based chemotherapy, during which female patients are advised not to breastfeed an infant.

There are no clinical data available on the effects of sodium thiosulfate on fertility. There is insufficient information from animal studies to assess the effects of intravenous infusion of sodium thiosulfate on fertility. Exposure to boron through STS administration is unlikely to pose a risk to fertility as the intended intermittent use of the product would result in levels lower than those stipulated by relevant guidelines. Moreover, sodium thiosulfate is only intended to be administered in conjunction with cisplatin chemotherapy which is known to adversely affect fertility.

Long-term studies in animals have not been performed to evaluate the potential carcinogenicity of sodium thiosulfate. As STS will be administered in combination with chemotherapies which also have

carcinogenic potential the absence of carcinogenicity studies is considered acceptable (see SmPC section 5.3).

Sodium thiosulfate was not genotoxic in an *in vitro* bacterial reverse mutation assay (Ames test) with or without metabolic activation and was not clastogenic in an in vitro mammalian cell assay (sister chromatid exchange) using human peripheral lymphocytes.

There are no reports of local reactions to i.v. injections of high concentrations of STS in the non-clinical published scientific literature, and there were no reports of local reactions in the studies conducted. Due to the hypertonic formulation, administration through a central vein is recommended.

As no increase in environmental exposure is expected from the use of sodium thiosulfate for infusion in the claimed indication it is unlikely to represent a risk for the environment following its prescribed usage in paediatric patients.

Relevant information on non-clinical aspects is included in the SmPC.

2.4.7. Conclusion on the non-clinical aspects

There are no objections to an approval of Pedmarqsi from a non-clinical point of view.

2.5. Clinical aspects

2.5.1. Introduction

GCP aspects

The clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Study Identifier, Type of Study, Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects RD/ Treated	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
SIOPEL 6, Efficacy, 5.3.5.1	• Assess the efficacy of STS for reducing the hearing impairment caused by CIS chemotherapy • Monitor any potential impact of STS on response to CIS and survival • Assess the short- and long term tolerability of the combination of STS and CIS	Phase 3, multicenter, RD, controlled, OL	STS: dosing by weight of child: >10 kg: 20 g/m^2 ≥ 5 to ≤ 10 kg: 15 g/m^2 < 5 kg: 10 g/m^2 15-min IV infusion administered 6 hours after end of each CIS infusion CIS: >10 kg: 80 mg/m^2 ≥5 to ≤10 kg: 2.7 mg/kg <5 kg: 1.8 mg/kg 6-hour IV infusion administered: Pre-surgery: Days 1, 15, 29, and 43; if surgery delayed, then prior to surgery, and Days 57 and 71 Post-surgery: Within 21 days; 2 courses at an interval of 2 weeks	114/109 CIS+STS: 61/53[a] CIS Alone: 53/56[a]	Patients with newly diagnosed SR-HB	Up to 6 cycles; if surgery was delayed for any reason, 2 additional cycles may have been administered. Up to 5 years post dose of follow-up (or longer as clinically indicated and according to national guidelines)	Complete; Full

Study Identifier, Type of Study, Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects RD/ Treated	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
COG ACCL0431, Efficacy, 5.3.5.1	• Assess the efficacy of STS infusion (following CIS treatment), compared with CIS alone (Observation arm) for preventing hearing loss in children receiving CIS chemotherapy for the treatment of various cancer types • Compare changes in hearing thresholds for key frequencies • Compare the incidences of CIS-related Grade 3 and 4 nephrotoxicity and Grade 3 and 4 cytopenia • Monitor EFS and OS	Phase 3, multicenter, RD, controlled, OL	STS: 16 g/m^2 (or 533 mg/kg for children whose therapeutic protocol administered CIS on a per-kg basis due to young age or small body size) as 15-min IV infusion administered 6 hours after end of each CIS infusion CIS: >200 mg/m^2 (variable) infused over a duration of ≤6 hours according to the sites' disease-specific cancer treatment protocols in use at the time. Treatment regimens included additional chemotherapeutic agents (other than CIS) depending on tumor type. At least a 10-hour delay between any STS infusion and the beginning of the next CIS infusion.	125/123 CIS+STS: 61/59[b] Observation (CIS): 64/64[b]	Patients with newly diagnosed[c] GCT, HB, medulloblastoma, neuroblastoma, osteosarcoma, or any malignancy treated with CIS	STS was administered each day CIS was given, up to 6 cycles Up to 10 years of post-dose follow-up	Complete; Full

2.5.2. Clinical pharmacology

2.5.2.1. Pharmacokinetics

No pharmacokinetics (PK) studies were submitted by the applicant and the PK characterisation of sodium thiosulfate for infusion was based primarily on literature review.

A non-compartmental analysis of STS levels after a 15-minute intravenous infusion, was also based on literature data (Neuwelt et al, 1998; Neuwelt et al, 2006). This PK dataset included data only from 5 children (aged between 2.5-16 years) and 11 adult patients with malignant brain tumours, who received multiple 15-minute STS infusions after carboplatin chemotherapy on different occasions. On

all occasions serum levels were determined at the end of the 15-minute infusion, but follow-up sampling varied -the samples were taken at different timepoints.

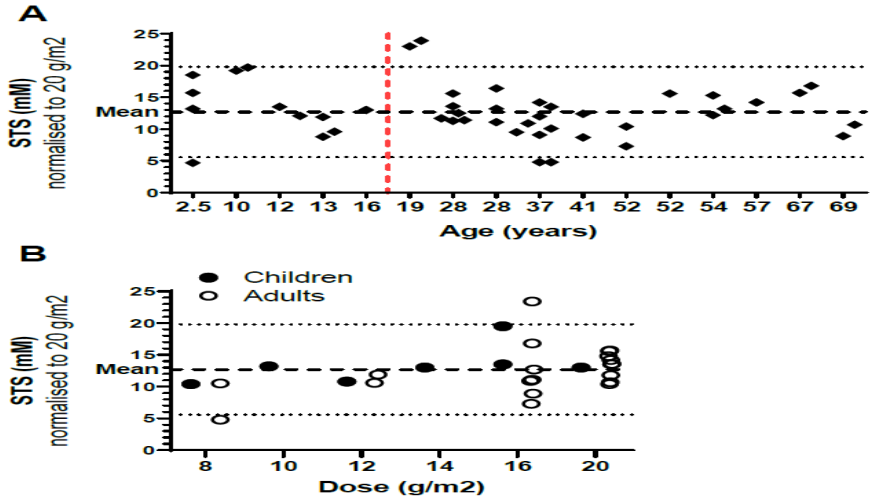
Apart from descriptive statistics, no formal statistics was performed in this study to compare groups or dose levels. The maximum concentration at the end of infusion and half-life were compared between the 5 paediatric and 11 adult subjects. Conclusions were drawn upon visual comparison of data. As in the majority of occasions samples were not collected beyond 30 minutes after the start of administration, i.e. 15 minutes after the end of infusion, the area under the curve in relation to dose or age was not evaluated.

Absorption

STS is poorly absorbed after oral administration and has to be administered intravenously (IV) (Farese et al, 2011). At the end of an IV infusion of STS, the plasma level of STS is maximal and declines rapidly thereafter with a half-life reported in the range of 20 to 50 minutes. Most studies appear to observe a biphasic decline and 2-compartmental PK, although a single phase has also been described. Irrespective of the shape of the decline in plasma concentration of STS, levels return to pre-dose levels within 3-6 hours after STS infusion.

Figure 5 depicts per dose level for each subject the mean STS concentration at the end of the infusion normalised to 20 g/m^2.

Figure 5. Comparison of STS Serum Levels in Children (n=5) and Adults (n=11) at the End of a 15-minute Infusion



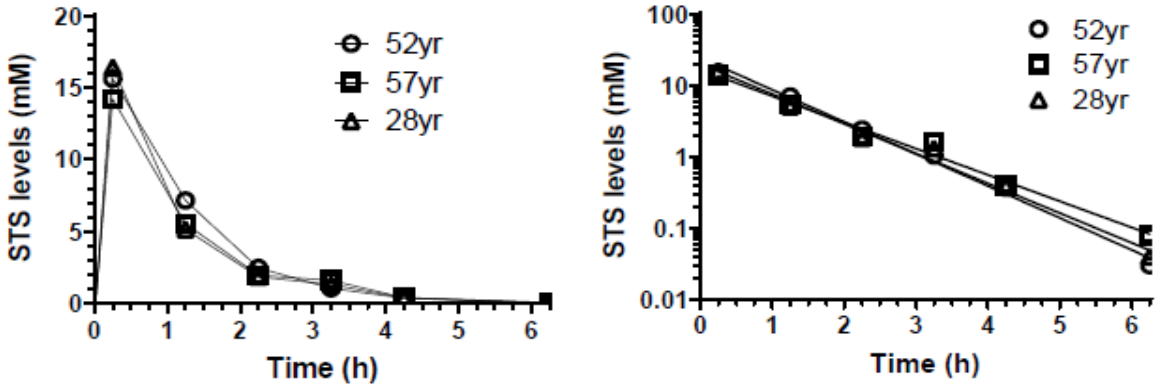
(A) Normalised STS peak serum levels for all administrations separately depicted for each subject. Subjects are indicated by age. The maximum exposure is similar across subjects and independent of age. The vertical red line marks the divide between children (< 19 years) and adult subjects.

(B) Normalised STS peak serum levels depicted per dose level. Each marker presents the mean result of one subject at that dose level. The normalised STS serum levels are similar across dose levels indicating dose proportionality. Moreover, STS peak levels were similar for adults (open circles) and children (<19 years, children closed circles) across dose levels.

After the end of the infusion, thiosulfate was rapidly cleared from plasma, and plasma STS levels declined more than 6-fold in 2 hours after the end of the infusion, returning to pre-dose levels in 4 to 6 hours (**Figure 6**). The terminal elimination phase follows first order kinetics. The terminal half-life was calculated at 46 minutes in adults (mean of 10 observations in 6 adults; median 47 minutes, range 37

– 52 minutes). The terminal elimination half-life could also be estimated in 2 children (12 and 16 years) at 50 minutes (2 observations at 39 and 60 minutes).

Figure 6. STS Serum Profile after 15-minute Infusion at 20 g/m²



STS (thiosulfate) serum level (in mM) – time profile me profile of three adults after infusion at a dose of 20 g/m² (n=3) are depicted at a linear and logarithmic scale.

Distribution

STS does not bind to human plasma proteins. As STS is an inorganic salt and thiosulfate anions should not readily cross membranes it is expected that distribution of STS largely confined to extracellular spaces. Therefore, its distribution appears largely confined to extracellular spaces. STS distribution volume was approximately 0.23 L/kg.

Non-clinical studies have shown that STS can enter cells at least partly through the sodium sulfate co-transporter 2 and cause intracellular effects such as the increase in anti-oxidant glutathione levels and inhibition of intracellular oxidative stress (Marutani et al, 2015; Bijarnia et al, 2015).A small proportion of STS entering cells in the cochlea and improving the intracellular anti-oxidant status is considered to contribute to the mechanism of action to prevent ototoxicity by STS.

Metabolism

Thiosulfate is an endogenous intermediate product of sulphur-containing amino acid metabolism. Thiosulfate metabolism does not involve CYP450 enzymes and is metabolised by thiosulfate sulphur transferase or thiosulfate reductase activity to sulphite (Hildebrandt and Manfred, 2008; Bilska-Wilkosz et al, 2017; Szczepkowski et al, 1961). There are no breakdown products that are anticipated to be toxic or likely to cause any unpredictable off target effects.

Elimination

STS is excreted through glomerular filtration. Under physiological conditions, endogenously produced thiosulfate is mainly metabolised to sulfate and the excretion of STS in urine is relatively low. However, after STS administration, several publications have reported high STS levels in urine and approximately 50% of the STS dose is retrieved unchanged in urine, most within the first 4 hours after administration (Neuwelt et al, 1998; Ivankovich et al, 1983; Farese et al, 2011). Newman et al (1946) demonstrated that STS renal clearance related well with inulin clearance as a measure for the glomerular filtration rate.

Excretion of endogenously produced thiosulfate in bile was very low and did not increase after STS administration (Ivankovich et al, 1983).

Dose-proportionality and time-dependency

Dose linearity was evaluated by graphical comparison of the maximum STS serum concentration for different dose levels (see **Figure 5**).

Normalised STS serum levels appeared to be similar across dose levels indicating dose proportionality after STS infusions.

Time-dependency has not been investigated. However, given the short elimination half-life of STS, and the STS dosing schedule no accumulation is expected.

Special populations

Impaired hepatic function

No specific clinical studies have been performed to evaluate the PK of STS in hepatically impaired subjects. As the main route of metabolism of STS is through thiosulfate sulphur transferase and thiosulfate reductase activity that are not confined to the liver, hepatic impairment is not expected to significatively impact PKs of STS.

Impaired renal function

Renal excretion of STS is an important route of elimination. Renal and non-renal clearance appear approximately equal in humans at the proposed dose level. A few publications have studied STS clearance in renally impaired subjects.

Newman et al (1946) studied clearance of thiosulfate in renally impaired subjects with a variety in renal disease including chronic glomerular nephritis, pyelonephritis; nephrosclerosis; coarctation of the aorta. STS and inulin were measured in plasma and urine and it was observed that STS (thiosulfate) renal clearance and inulin clearance correlated directly over a wide range of inulin clearance results (0 to 140 ml/min; n=73). Newman did not report other PK parameters.

Farese et al (2001) studied STS pharmacokinetics in 9 healthy volunteers and 10 haemodialysis patients on and off haemodialysis. Eight grams (32.25 mmol) STS was administered by IV infusion over 8 minutes.

In healthy volunteers, mean (± standard deviation (SD)) endogenous thiosulfate level in serum was 5.5 ± 1.8 uM. After infusion of STS, the mean maximum serum concentration was approximately 1.7 mM and rapidly declined thereafter, returning to the range of pre-dose endogenous levels within 180 minutes. The area under the plasma concentration curve (AUC) was 122 ± 37 mmol min/L with a corresponding clearance (CL) of 4.11 ± 0.77 mL/min/kg (284 ± 75 mL/min). Renal CL was high (1.86 ± 0.45 mL/min/kg) and represented 45% of total CL and reflected the glomerular filtration rate (GFR). Non-renal CL (2.25 mL/min/kg) accounted for 55% of the total CL.

In haemodialysis patients off haemodialysis, the total clearance was reduced to 2.04 ± 0.72 mL/min/kg with a corresponding AUC of 231 ± 68 mmol·min/L. The CL was essentially similar to the nonrenal CL observed in the healthy volunteers determined the PK of STS in renally impaired subjects requiring haemodialysis and showed that in the absence of renal function, the total STS clearance becomes essentially similar to the non-renal clearance in healthy subjects.

STS by IV infusion has been studied in haemodialysis patients to prevent the progression of or to reduce vascular calcification observed in end-stage renal disease with calciphylaxis (Mathews et al, 2011). Repeated administration of STS at a dose of 12.5 - 25 g three times per week after each

dialysis for up to 5 months appeared safe with nausea and vomiting reported as the main adverse effects (Mathews et al, 2011). No PK was reported in this study.

Pharmacokinetic Drug-Drug Interactions

STS does not bind to human plasma proteins (Kowalski and Rutstein, 1952).

In human liver microsomes, the IC50 of STS corrected for osmolality for CYP2C8, CYP2C9 and CYP2C19 were respectively 89.2 mM, 95.4 mM and 104 mM which were well above the anticipated STS maximum plasma levels of 13 mM at the end of a 15-minute infusion. Borderline induction of CYP2B6 was noted in cryopreserved hepatocytes of 1 of 3 donors after 72 hours incubation at 10 and 25mM STS (~2.2 fold and 27% of positive control; just above the respective thresholds of 2.0-fold and 20%).

Population PK model of STS

Using a PK model developed by Farese et al, 2011 as a starting point, and parameterised in terms of CL (as a sum of CLR (renal clearance) and CLNR (non-renal clearance)), V (distribution volume) and Kin (endogenous STS production rate), the structure of the PK model was adapted to account for growth and maturation of the renal clearance.

The Final STS popPK model consisted of a two-compartment model with first order elimination from the central compartment parameterised with CL (CLR and CLNR), Vc, Q and Vp, Kin, and considering a proportional residual error model. Covariates of interest (BSA, AGE, BW) were introduced earlier in the modelling step.

PK parameters were estimated with a good precision for both fixed and random effects (Relative standard Error (RSE) < 30%). CLR was fixed at value estimated by Farese et al at 1.36 mL/min/kg. The estimated typical Kin was 13.1 µM/min. CLNR was estimated at 4.52 L/h, Vc and Vp at 0.0689 L/kg and 0.166 L/kg respectively and Q at 96.8 L/h. RUV estimated at 35.2% as a proportional error term.

The developed STS PopPK model was used to perform simulations to predict thiosulfate concentration at the end of infusion (Cinf or Cmax) following a 15 minute i.v. infusion of 16 or 20 g/m2 STS or using the dosing regimen applied in the SIOPEL 6 study in the paediatric population with virtual subjects ranging from 2 months to 18 years or weighing from 5 to 75 kg.

Results from this simulation exercise showed that median Cinf remained similar across the age and weight range (data not shown). However, with a Residual unidentified variability (RUV) of 35.2%, a large fluctuation of Cinf is expected. When a BSA-based dose was applied within a weight band a proportional increase of Cinf, was shown also with an expected large fluctuation of Cinf (data not shown). Updating the PopPK model by considering CLNR a function of BSA or a function of BSA and a maturation factor showed again that that Cinf predictions increase in the respective weight bands (data not shown).

Other studies

Population PK model of unbound-cisplatin

The objective of the study was to simulate the PK of unbound cisplatin (pharmacological active form) in children based on a pop-PK model developed in adult cancer patients, since no PK evaluation of either cisplatin or STS was conducted during the SIOPEL 6 study.

In the popPK analysis by Urien and Lokiec (2004); age 21-76; n=43) the CL of unbound cisplatin was dependent on BSA and CLCr (Model 1), and resulted in a population mean of 35.5 L/h for clearance (CL) and 23.4 L for central distribution volume (V1).

In order to take into account adjustment for size (weight) in the children less than 1 year, an exponent on the ratio of children to adult equal for allometric scaling (Mahmood et al 2006) was investigated (Model 2).

Simulations were carried out to predict the systemic exposure (Cmax and AUC) based on BW. The simulations took into account the IIV (estimated and inflated), different subject weight (2-5, 5-10, 10-15 and 15-25 kg) and corresponding doses of cisplatin as defined in the SIOPEL 6 protocol. Results of these simulations for both models are summarised in **Table 5**.

Table 5. Summary of Median 5th and 95th Percentile Simulated PK Parameters of Unbound Cisplatin (IIV inflated for CL and V2)

Intersubject variability (CL=50 CV%, V_1=23.4 CV%; V_2=23.4 CV%)						
Weight	Dose	C_{max}*	AUC*	CL	V_{ss}	$t_{1/2,\beta}$
kg	mg/kg↑ or mg/m^2 ↑↑	µg/mL	mg·min/mL	L/h/m^2	L/m^2	h
CL scaled with BSA and CLCr and V_1 with BSA						
2-5	1.80↑ 1.71-1.89	0.840 0.433-1.38	0.403 0.171-0.864	14.9 6.94-35.0	57.0 38.1-92.7	3.59 1.91-7.68
5-10	2.70↑ 2.61-2.79	0.908 0.434-1.66	0.373 0.162-0.894	16.1 6.71-37.0	36.7 25.1-52.6	2.47 1.39-4.98
10-15	78.5↑↑ 72.6-85.0	0.805 0.385-1.54	0.309 0.140-0.691	19.4 8.68-43.0	29.4 21.9-40.2	1.90 1.17-3.49
15-25	79.4 ↑↑ 75.5-84.4	0.755 0.352-1.54	0.280 0.128-0.654	21.5 9.18-46.9	24.7 18.8-32.9	1.62 1.02-2.93
CL scaled with weight and CLCr and V_1 with BSA						
2-5	1.80↑ 1.71-1.89	1.48 0.924-2.23	1.38 0.555-3.18	4.36 1.89-10.8	57.5 36.8-92.7	10.1 4.39-23.3
5-10	2.70↑ 2.61-2.79	1.79 0.996-2.72	1.07 0.439-2.52	5.63 2.38-13.7	36.2 25.6-54.7	5.30 2.59-11.8
* Normalized to 100 mg/m^2 dose						

2.5.2.2. Pharmacodynamics

Mechanism of action

The mechanism of STS protection against ototoxicity is not fully understood but may include direct interaction between CIS and the thiol group in STS to form a non-toxic rapidly excreted non-toxic complex (Sooriyaarachchi et al, 2016), scavenging reactive oxygen species, and increasing levels of endogenous anti-oxidants.

Recent *in vitro* studies with mammalian blood plasma have demonstrated that cisplatin may react with thiosulfate to give complexes that may contain Pt—S bonds. Closely related studies have revealed that complexes with Pt—S bonds may also be formed in mammalian plasma when cisplatin and N-acetylcysteine, D-methionine or L-glutathione are added. To date, however, the chemistry of the thiosulfate complex (es) that are formed with cisplatin in blood plasma remains unclear.

Furthermore, similarly to kidneys, the cochlea may act to concentrate STS in perilymph or endolymph and enhance protection in the local environment.

In the clinical studies, STS was administered 6 hours after the end of infusion with CIS and hence direct interaction in plasma between free CIS and STS seems marginal compared to the overall free CIS exposure up to that time point.

Cisplatin can also increase oxidative stress and reduce protective anti-oxidant enzymes and it has been widely suggested that such effects are more relevant for the toxicity of CIS (Karasawa and Steyger, 2015). Indeed, a depletion in glutathione, changes in anti-oxidant enzymes and increased oxidative stress have been demonstrated in the cochlea after CIS treatment (Ravi et al, 1995; Campbell et al, 2003; Rybak et al, 2000). The normal function of the cochlea requires a high metabolic activity in areas such as the stria vascularis, spiral ligament, and spiral prominence (Sheth et al, 2017). The metabolic demand on the cochlea and accompanying leakage of electrons from the mitochondrial respiratory chain renders it very sensitive to hypoxic events, ischemia-reperfusion injuries and environmental stimuli (such as loud noise). This can also explain why the cochlea is particularly sensitive to toxicity of drugs, such as CIS, that can generate reactive oxygen species or inactivate anti-oxidant systems. Indeed, various anti-oxidant agents have been effective in animal models of CIS-induced ototoxicity (Hazlitt et al, 2018; Sheth et al, 2017; Karasawa and Steyger, 2015). Importantly, STS as an anion cannot readily diffuse through cell membranes and consequently distributes mainly in extracellular fluids. Marutani et al (2015) demonstrated that STS can enter cells, at least partially through the sodium sulfate cotransporter 2. This was also associated with an increase in anti-oxidant glutathione levels. Using renal and hepatic cell lines, Bijarnia et,(2015) demonstrated that these cells can consume STS leading to a reduction in oxalate-induced intracellular oxidative stress and cytotoxicity. In a rat model of vascular calcified kidney, treatment with STS resulted in improved renal glutathione levels, anti-oxidant enzymes and reduced oxidative stress (Mohan et al, 2017). Hence, an anti-oxidant effect of STS either as an oxygen radical scavenger or through improving anti-oxidant factors like intracellular glutathione levels in the cochlea, an organ with high sensitivity for oxidative injury, is likely the most relevant mechanism to prevent CIS-induced ototoxicity by delayed administration of STS.

Rodent and canine models suggest that CIS-induced ototoxicity is mediated by intracellular platinum activation (Siddik, 2003). In the chinchilla model, platinum causes degeneration of the outer cells of the spiral organ in the cochlea with a progressive loss of cells (Ding et al, 1999). Pathogenesis involves intracellular production of reactive oxygen species and free radicals that deplete cellular antioxidant defences (Hazlitt et al, 2018; Sheth et al, 2017; Evans and Halliwell, 1999; Dehne et al, 2001; Rybak et al, 2007).At high molar excess, STS binds to and inactivates electrophilic platinum compounds such as CIS and carboplatin in vitro (Dedon and Borch, 1987; Elferink et al, 1986). A study in rabbits showed that STS reduced bioactive CIS plasma levels within 5 minutes in a dose dependent manner reaching complete inactivation of CIS at a 400-fold molar ratio excess of STS (Iwamoto, 1985). However, bioactive CIS levels in plasma also decline rapidly after IV administration in the absence of STS. A 10-fold decline in free bioactive CIS was observed within 60 minutes after administration of CIS (Iwamoto, 1985).

Primary and secondary pharmacology

No studies to characterise the pharmacodynamic effects of STS were submitted.

2.5.3. Discussion on clinical pharmacology

The clinical pharmacology prgramme is entirely based on literature PK data (mainly on two publications: Neuwelt et al, 1998 and 2006).

Pharmacokinetics

Absorption, distribution, metabolism, and excretion (ADME) of STS have overall been adequately described based on literature data.

Sodium thiosulfate is poorly absorbed after oral administration and has to be administered intravenously. At the end of a sodium thiosulfate intravenous infusion, plasma levels of sodium thiosulfate are maximal and decline rapidly thereafter with a terminal elimination half-life of approximately 50 minutes. A return to pre-dose levels occurs within 3 to 6 hours after infusion. More than 95% of sodium thiosulfate excretion in urine occurs within the first 4 hours after administration. Hence, there is no plasma accumulation when sodium thiosulfate is administered on 2 consecutive days. Thiosulfate renal clearance compared well with inulin clearance as a measure for the GFR.

Sodium thiosulfate does not bind to human plasma proteins. Sodium thiosulfate is an inorganic salt and thiosulfate anions do not readily cross membranes. Hence, the volume of distribution appears largely confined to extracellular spaces and estimated at 0.23 L/kg in adults. In animals, sodium thiosulfate has been found to distribute to the cochlea. Distribution across the blood brain barrier or placenta appears absent or limited. Thiosulfate is an endogenous compound ubiquitously present in all cells and organs. Endogenous serum thiosulfate levels were 5.5 ± 1.8 µM in adult volunteers.

Metabolites of sodium thiosulfate have not been determined as part of clinical studies. Thiosulfate is an endogenous intermediate product of sulphur-containing amino acid metabolism. Thiosulfate metabolism does not involve CYP enzymes; it is metabolised through thiosulfate sulphur transferase and thiosulfate reductase activity to sulphite, which is rapidly oxidised to sulfate.

Excretion of endogenously produced thiosulfate in bile was very low and did not increase after sodium thiosulfate administration. No mass balance studies have been performed, but it is expected that non renal clearance will mainly result in renal excretion of sulphates. A small part of the sulphane sulphur of sodium thiosulfate may become part of endogenous cellular sulphur metabolism.

In haemodialysis patients, total clearance of sodium thiosulfate was 2.04 ± 0.72 mL/min/kg (off dialysis) compared to 4.11 ± 0.77 mL/min/kg in healthy volunteers. This clearance was essentially similar to the non renal clearance observed in the healthy volunteers (1.86 ± 0.45 mL/min/kg). In the absence of any glomerular filtration in haemodialysis patients, this only resulted in approximately a 25% increase in the maximum thiosulfate plasma levels and nearly a 2-fold increase in total exposure. The plasma concentration of thiosulfate is deemed to be the most important parameter associated with the efficacy of the product. Moreover, the most frequent adverse reactions are considered to be related to the sodium load with sodium thiosulfate administration and concurrent electrolyte imbalances. Non-clinical studies indicated that dose limiting acute effects were related to the sodium intake. Sodium thiosulfate is only intended to be administered in conjunction with cisplatin chemotherapy. Cisplatin is associated with renal toxicity (and contraindicated in patients with pre-existing renal impairment), renal function should be monitored in clinical practice with close monitoring of electrolyte balance, and sodium thiosulfate should not be given if serum sodium is > 145 mmol/litre at baseline.

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.

No information is available for use of sodium thiosulfate in patients with hepatic impairment. However, thiosulfate sulphur transferase/reductase activity is ubiquitous, including tissue like red blood cells, liver, kidney, intestine, muscle and brain. Therefore, the changes in thiosulfate pharmacokinetics in hepatically impaired patients are likely limited and without clinical significance.

Results of an *in vitro* study on the inhibition of cytochrome P450 (CYP) isoforms in microsomes did not reveal interaction close to the expected maximum plasma concentration for STS (Study 2017-0301). A borderline induction result for CYP2B6 was noted in cryopreserved hepatocytes of 1 donor (Study 2017-0305).

The chemical properties of STS and observations that STS does not distribute readily across membranes (i.e., low oral availability, low or no increased exposure in central nervous system or fetus in animal studies) and is excreted through glomerular filtration, make an interaction with membrane drug transporters unlikely.

The proposed commercial formulation (STS anhydrous) differs from the formulation (STS pentahydrate) used during the two clinical Phase 3 studies. The CHMP agreed that it is not essential to demonstrate bioequivalence between these formulations which differ in the amount of boric acid quantity (0.25 mg/mL and 0.3 mg/mL) as there were no concerns regarding the interaction between borate and STS.

STS PopPK model

The PopPK STS model included data from only 5 children, aged between 2.5 and 16 years. These children were treated at one or several occasions with STS dose ranging from 8 to 20 g/m^2, and account for n= 20 observations. Adult PK data consisted of n=81 observations from 11 patients.

The applicant considered that the PopPK model was able to adequately predict Cinf (Cmax end of infusion) considering different scenarios by simulations, and which is proposed as the main exposure metric driving STS efficacy (Neuwelt et al 1998). However, the PopPK model appeared to be over-parameterised, with no IIV terms and an estimated high RUV of 35.2%. In addition, Kin was estimated at 13.1 µM/min, approximately 12-times greater than the Kin estimated by Farese et al 2011.

Based on this the CHMP considered that this PopPK model whilst showing that the predicted sodium thiosulfate plasma levels at the end of infusion were consistent across the recommended dose levels for the indicated age and body weight ranges could not be used to support any claimed dosing regimens.

In SIOPEL 6, the 20 g/m^2 STS dose was further adjusted for children with <10 kg body weight (often children below the age of 1 year) because of renal maturation effects that can potentially affect thiosulfate excretion and/or sodium handling. For patients 5 to 10 kg, the STS dose was adjusted to 75% at 15 g/m^2. For patients <5 kg, the dose was adjusted to 50% at 10 g/m^2.

The proposed STS for infusion dosing (12.8 g/m2 for patients >10.0 kg, 9.6 g/m^2 for patients 5.0 to 10.0 kg, and 6.4 g/m^2 for patients <5.0 kg) is equivalent to the STS doses administered in SIOPEL 6 where dosing was based on the higher molecular mass of STS pentahydrate: 20 g/m2, 15 g/m^2, and 10 g/m^2, respectively. This dosing regimen is proposed given that there were no dose-limiting toxicities observed at these doses as well as to maximise the possibility for efficacy in the paediatric patient population that includes young children.

CIS PopPK model

The objective of the study was to simulate the PK of unbound cisplatin (pharmacological active form) in children based on a PopPK model developed in adult cancer patients, since no PK evaluation of cisplatin was conducted during the SIOPEL 6 study. Two PK models structure were investigated, Model 1 consisted of the initial PopPK model developed by Urien et al 2004, and Model 2 was an adaptation of Model 1 for children less than 1 year according to Mahmood et al 2005.

According to the applicant, the results of these simulations indicated that most of the unbound platinum was already distributed and/or eliminated from plasma when STS is administered 6 hours after the end of cisplatin 6 hours infusion. However, this is confirmed only with the simulation from Model 1. With Model 2, estimated terminal half-life were 10.1 h and 5.3 h, in virtual children of 2-5 kg and 5-10 kg, respectively.

According to the applicant CL should be scaled by BSA (Model 1) and not by BW, based on results from several literature papers (Urien et al 2004, de Jongh et al 2004 and Peng et al 1997) which suggest that CIS CL scales better to BSA than BW, particularly in children below 10 kg, while CL scaled by BW results in a clear underestimation,

By considering the applicant's hypothesis in patients weighting 2-5 kg and 5-10 kg, the % AUC12-∞ of remaining unbound cisplatin was approximately 13 % (7.4-21%) and 5.6%, at the time of STS infusion (6h after the end of CIS infusion)

Overall, these calculations provide sufficient reassurance that the delayed administration of STS would not result in reduces CIS efficacy, despite the lack of real observations performed in the target population.

Pharmacodynamics

The mechanism of sodium thiosulfate protection against ototoxicity 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 sodium thiosulfate to produce inactive platinum species.

Concurrent incubation of sodium thiosulfate with cisplatin decreased the *in vitro* cytotoxicity of cisplatin to tumour cells; delaying the addition of sodium thiosulfate to these cultures prevented the protective effect.

2.5.4. Conclusions on clinical pharmacology

Data derived from the literature show that the pharmacokinetic properties of sodium thiosulfate are sufficiently characterised in adults and can be reasonably extrapolated to the intended target paediatric population. The delayed sodium thiosulfate administration 6 hours after the cisplatin infusion and its recommended weight based and normalised to body surface area dose for the prevention of cisplatin-induced ototoxicity can be endorsed.

2.5.5. Clinical efficacy

2.5.5.1. Dose response study

No dose-finding studies carried out by the applicant.

Dose selection in the COG ACCL0431 and SIOPEL 6 studies was based on early clinical and nonclinical studies with STS in adults.

The applicant's proposed dose of STS in patients 1 month to < 18 years of age with localised, non-metastatic, solid tumours is based on STS doses administered in the SIOPEL 6 which included standard risk hepatoblastoma patients.

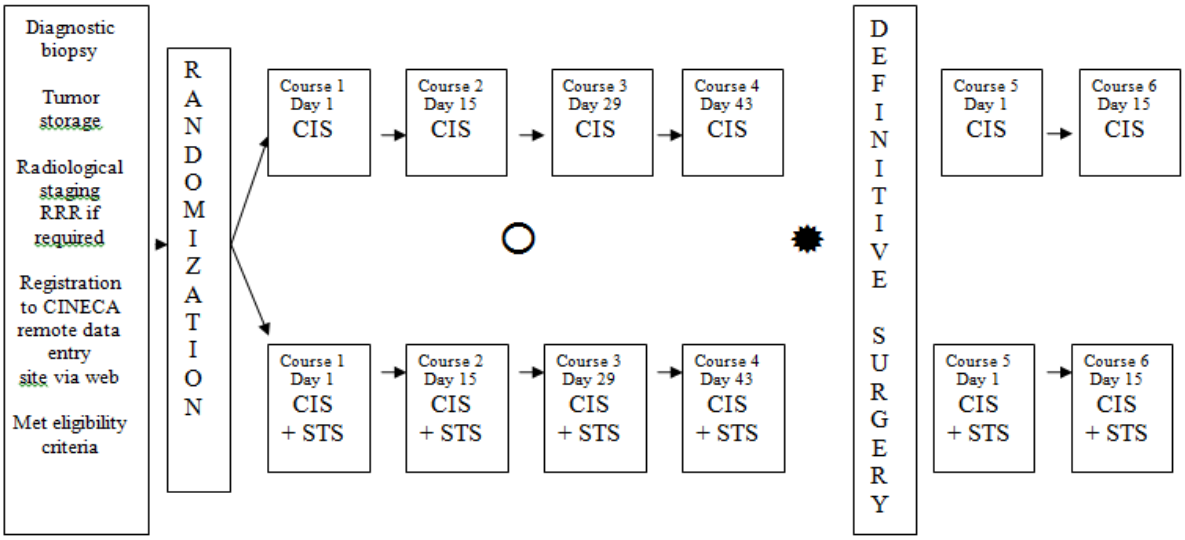
2.5.5.2. Main study

SIOPEL 6: A multi-center, open-label, randomized phase III trial of the efficacy of sodium thiosulfate in reducing ototoxicity in patients receiving cisplatin chemotherapy for standard-risk hepatoblastoma

Methods

Figure 7 provides a schematic of the overall study design.

Figure 7. SIOPEL 6 Study Schema



- **Study Participants**

Main inclusion criteria:

1. Age ≤18 years and > 1 month

2. Histologically confirmed newly diagnosed hepatoblastoma (HB).

3. Standard-risk HB:

    - Pre-treatment tumour extension (PRETEXT) I, II or III
    - Serum alpha-fetoprotein (AFP) > 100 µg/L
    - No additional PRETEXT criteria

Main exclusion criteria:

1. High risk HB

2. Serum AFP ≤100 µg/L.

3. Tumour involving all 4 hepatic sections (PRETEXT IV).

4. Additional PRETEXT criteria:

– Extrahepatic abdominal disease (E1, E1a, E2, E2a).

– Intraperitoneal hemorrhage or tumor rupture (H1).

– Distant metastases, any site (M1).

– Lymph node metastases (N1, N2).

– Involvement of the main portal vein (P2, P2a).

– Involvement of all 3 hepatic veins and/or the IVC (V3, V3a).

5. Hepatocellular carcinoma.

6. Abnormal renal function defined as calculated GFR < 75% of the lower limit of normal for age at diagnosis, which over 2 years of age is < 60 mL/min/1.73 m^2.

7. Recurrent disease.

- **Treatments**

Patients in SIOPEL 6 were randomised to receive either cisplatin + sodium thiosulfate or cisplatin alone (control). Treatment courses were as follows:

Cisplatin

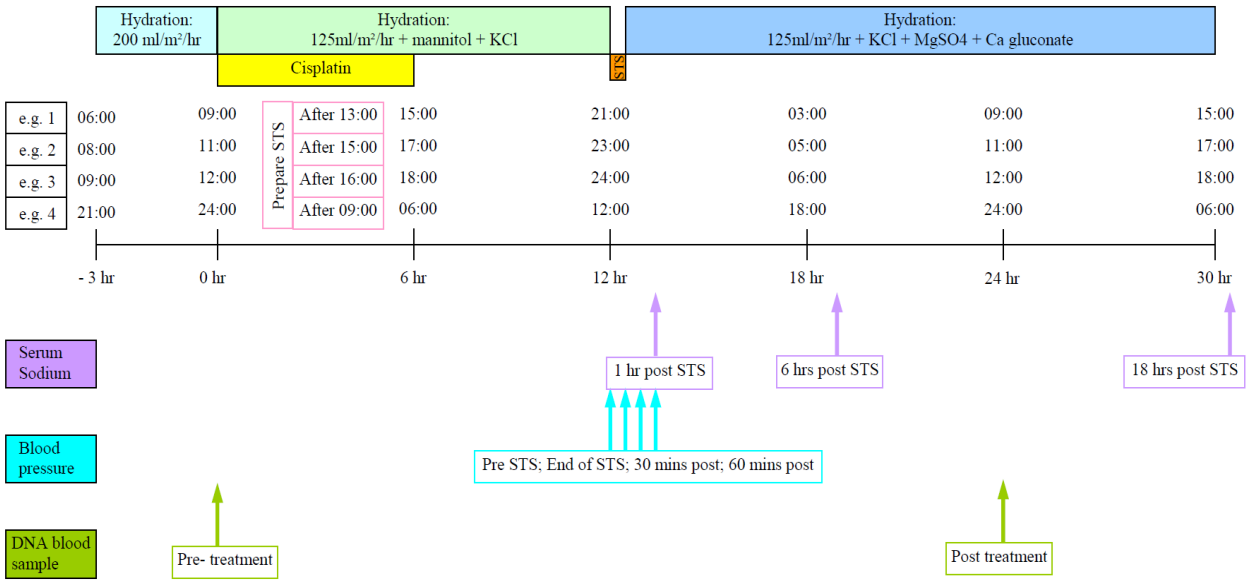
For children > 10 kg:	80 mg/m^2 intravenous infusion over 6 hours
For children ≥ 5 kg and ≤ 10 kg:	2.7 mg/kg intravenous infusion over 6 hours
For children < 5 kg:	1.8 mg/kg intravenous infusion over 6 hours

For children randomised to receive Sodium Thiosulfate

For children > 10 kg:	20 g/m^2 intravenous infusion over 15 minutes
For children ≥ 5 kg and ≤ 10 kg:	15 g/m^2 intravenous infusion over 15 minutes
For children < 5 kg:	10 g/m^2 intravenous infusion over 15 minutes

A summary of the treatment administration schedule including hydration, sodium monitoring, blood pressure monitoring, and DNA blood sampling with 4 example start times is presented in **Figure 8**.

Figure 8 Summary of Treatment Administration Schedule in SIOPEL 6 Study



Abbreviations: Ca=calcium; DNA=deoxyribonucleic acid; KCl=potassium chloride; MgSO4=magnesium sulfate; STS=sodium thiosulfate.

- **Objectives**

The primary objective of SIOPEL 6 was to assess the efficacy of STS for reducing the hearing impairment caused by CIS chemotherapy.

The secondary objectives were:

- To monitor any potential impact of STS on response to CIS and survival.
- To assess the short- and long-term tolerability of the combination of STS and CIS.
- To prospectively evaluate and validate biological, radiological and pathological features of SR-HB for future risk adapted management.
- To investigate the effect of STS on the formation of CIS-deoxyribonucleic acid (DNA) adducts.
- To prospectively collect patient DNA specifically for the analysis of possible genetic factors that may contribute to the development of treatment-related ototoxicity and nephrotoxicity.

- **Outcomes/endpoints**

The primary endpoint was the proportion of patients with Brock Grade ≥ 1 hearing loss, measured by pure tone audiometry (PTA), after end of study treatment or at an age of at least 3.5 years, whichever was later.

The secondary endpoints included:

- Response to preoperative chemotherapy.
- Complete resection.
- Complete remission.
- Event-free survival.
- Overall survival.

2 separate preoperative chemotherapy response criteria were used: the SIOPEL 6 criteria, and the post-hoc traditional SIOPEL criteria used in previous SIOPEL trials. The reason for both analyses is that to-date, there is no evidence that the rate of fall of AFP in HB, unlike in germ cell tumours, is of prognostic significance. The SIOPEL 6 criteria used a 1 log fall to align with COG study response criteria. However, SIOPEL 1 unpublished data (Shafford et al, presented at SIOPEL meetings) and subsequently Meyers et al (2016) presented preliminary data at the SIOPEL Spring meeting Barcelona April 2016, showing that the rate of fall of serum AFP in HB had no prognostic significance. Therefore, post-hoc response criteria were proposed to reflect conventional response assessment for HB. The criteria are defined below.

- SIOPEL 6 response criteria:

– Complete response (no evidence of disease and normal serum AFP value [for age]).

– Partial response: any tumour volume shrinkage associated with a decreasing serum AFP > 1 log fall below the original measurement

– Stable disease: no tumour volume change and no change in AFP, or decreasing serum AFP < 1 log fall from the original measurement

– Progressive disease: unequivocal increase in 1 or more dimensions and/or any unequivocal increase of the serum AFP concentration (three successive 1 to 2 weekly determinations) even without clinical (physical and/or radiological) evidence of tumour regrowth

• Traditional SIOPEL response criteria:

– Complete response: complete disappearance of tumour and normal AFP value for age

– Partial response was defined as any tumour volume shrinkage and any drop in AFP level (at least 3 consecutive reducing values, taken at weekly intervals)

– Stable disease: no tumour volume change and no increase in AFP

– Progressive disease: unequivocal increase in one or more dimensions. Any unequivocal increase of the serum AFP concentration (three weekly determinations) even without clinical (physical and/or radiological) evidence of tumour re-growth is considered progressive disease.

- **Sample size**

The hypothesis tested was a reduction of the rate of hearing loss (defined as Brock Grade ≥ 1) from 60% in the CIS alone arm to 35% in the CIS+STS arm. The test was a Chi-square test with significance level of 5% and power of 80%.

Based on these parameters, a total of 102 evaluable patients needed to be recruited. Approximately 10% of the randomised patients were expected to be unevaluable for the primary endpoint. Therefore, the sample size was augmented to 115 patients. This should have been attainable in 3.8 years with a yearly recruitment of 35 patients, and allowing for a run-in period of 6 months, during which sites were activated.

The baseline hearing loss in the CIS alone arm may not have been exactly 60%. The study did, however, have ≥ 80% power to detect an absolute reduction in hearing loss of 25% over a wide range of other baseline hearing loss values, as shown in the following table:

Hearing loss rates	Power
50 to 25	83%
55 to 30	81%
60 to 35	80%
65 to 40	80%
70 to 45	81%

- **Randomisation and Blinding (masking)**

Patients were randomised 1:1 to the CIS+STS arm or to the CIS alone arm. Randomisation was stratified by:

- Country
- Median age (above vs below 15 months)
- PRETEXT (I and II vs III)

This was an open-label study, however the audiologist carrying out central review for the primary endpoint was blinded.

- **Statistical methods**

Continuous variables (e.g., age) were summarised using descriptive statistics (the number of patients with available data, the mean, standard deviation [SD], median and minimum and maximum).

Categorical variables (e.g., race) were summarised using counts and percentages. Percentages were calculated using the total patients per treatment group.

Unless otherwise stated, any statistical tests performed use 2-sided tests at the 5% significance level. Secondary endpoint testing was not corrected for multiplicity.

A group-sequential design was chosen with 2 interim and 1 final evaluation, an alpha-spending function according to Lan DeMets (Lan KKG and DeMets DL, 1983) with O'Brien Fleming boundaries (O'Brien PC and Fleming TR, 1979). Early stopping for higher than expected difference was foreseen.

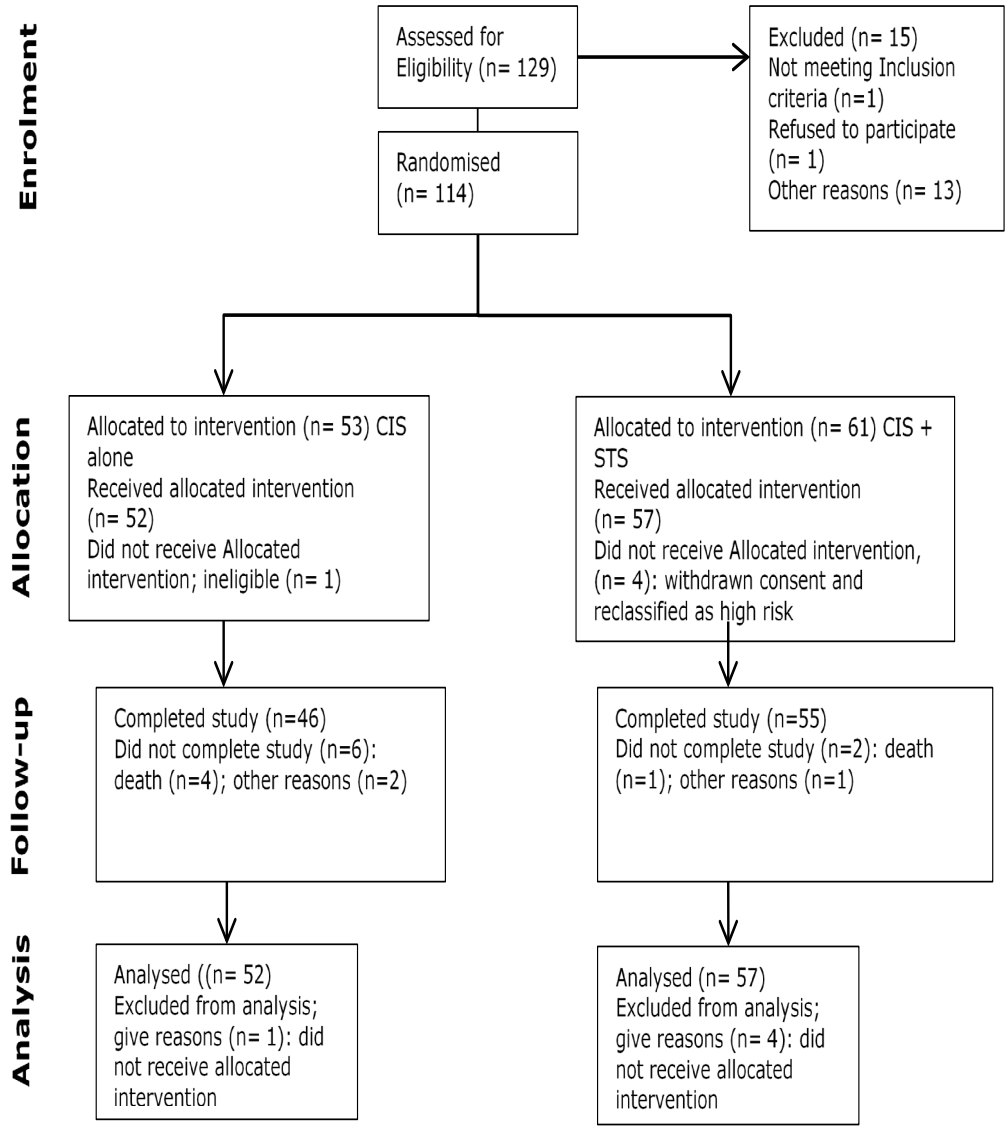
Hearing impairment defined as Brock Grade ≥ 1 hearing loss determined by PTA at age ≥3.5 years was the primary endpoint with hearing impairment rates calculated and compared between the 2 randomised treatment groups. The Brock Grade of the better ear was used for the analysis. The hypothesis tested was a reduction of the rate of hearing loss from 60% with CIS Alone to 35% with CIS+STS. The test was a Chi-square test with significance level of 0.045% and power of 80%. It was carried out in the ITT Population. The 8 patients without a hearing loss assessment were counted as a failure (i.e., had hearing loss) in this analysis.

Sensitivity analyses were carried out to explore the potential effects of strategies to impute of missing data using the complete mITT Population as well as the PP Population. The primary endpoint may have been missing due to any of the following: early death of the patient before the final hearing assessment could have been done at age ≥3.5 years; a lack of collaboration of a certain patient or his/her parents; or administrative or logistical reasons (lost to follow-up, family moving away, etc).

Results

- **Participant flow**

Figure 9. Patient Disposition in SIOPEL 6 Study



- **Recruitment**

The first patient was enrolled on 15 December 2007.

The last patient completed follow-up: 28 Feb 2018.

- **Conduct of the study**

The original SIOPEL 6 UK protocol was dated 10 May 2007; 4 UK protocol amendments were subsequently issued, and the final UK version of the protocol was dated 01 Feb 2015 (Version 5.0).

In addition, 2 international versions of the protocol were issued: International Version 4.0 was dated 01 May 2011, and International Version 5.0 was dated 15 Jul 2011.

Most amendments were administrative changes made to the Protocol Table of Contents; Study Committee; and Registration, randomisation, and Data Collection sections.

The following changes to the planned analyses were made:

Although the protocol called for a stratified randomisation by the minimisation method, a randomised permuted block design with block size 4 was used.

In response to FDA feedback, the primary efficacy analysis was changed from the mITT Population to the ITT Population in the final SAP. The ITT population comprised all 109 patients in the study, of which, 101 had a hearing assessment performed. The decision was made to impute the results of the 8 patients with a missing hearing assessment as "hearing impaired or failure."

The protocol specified that a "one-sided chi-square test" was to be done for the comparison of rates of hearing loss between the two randomised arms. This was a misnomer.

A total of 23 children (21.1%) had protocol deviations during the study, all of whom had deviations in treatment compliance. The proportion of children with protocol deviations was lower in the CIS+STS arm compared with the CIS Alone arm (6 patients [11.3%] vs 17 patients [30.4%], respectively). In both arms, the most common treatment compliance protocol deviations were due to insufficient response to CIS and resulted in a treatment switch to an alternative chemotherapy (CIS+STS arm: 5 patients and the CIS Alone arm: 8 patients).

- **Baseline data**

In SIOPEL 6, the CIS and CIS+STS arms were generally well balanced in terms of baseline demographic and disease characteristics (**Table 6** and **Table 7** respectively). Prior and concomitant Medications are summarised in **Table 8**.

Table 6. Summary of Patient Demographics (SIOPEL 6, ITT Population)

Variable	CIS Alone (N=52)	CIS+STS (N=57)	Total (N=109)
Age [a] (months)			
n	52	57	109
Mean (SD)	18.2 (15.0)	18.8 (16.7)	18.5 (15.8)
Median (min, max)	13.4 (3.0, 70.2)	12.8 (1.2, 98.6)	13.0 (1.2, 98.6)
Sex, n (%)			
Female	23 (44.2)	27 (47.4)	50 (45.9)
Male	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)
Height (cm)			
n	48	50	98
Mean (SD)	77.7 (12.3)	79.7 (14.6)	78.7 (13.5)
Median (min, max)	75.8 (58, 113)	77.0 (45, 126)	76.0 (45, 126)
Weight [b] (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)

Abbreviations: CIS=cisplatin; ITT=Intent-to-treat; max=maximum; min=minimum; SD=standard deviation; SIOPEL=International Childhood Liver Tumors Strategy Group; STS=sodium thiosulfate.

[a] Age was recorded at the time of diagnosis.

[b] 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 CIS and STS doses.

Table 7 Summary of Baseline Disease Characteristics (SIOPEL 6, ITT Population)

Variable	CIS Alone (N=52)	CIS+STS (N=57)	Total (N=109)
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)	374405.06 (565678.77)	496084.69 (888294.08)	438035.69 (750986.67)
Median	79251.50	181500.00	109872.00
(min, max)	187.0, 2632584.9	273.0, 5489165.0	187.0, 5489165.0
AFP Category, n (%)			
< 1000 ng/mL	4 (7.7)	4 (7.0)	8 (7.3)
1000 ng/mL to < 1000000 ng/mL	42 (80.8)	45 (78.9)	87 (79.8)
> 1000000 ng/mL	6 (11.5)	8 (14.0)	14 (12.8)
PRETEXT classification, n (%)			
I [a]	0	11 (19.3)	11 (10.1)
II [b]	31 (59.6)	30 (52.6)	61 (56.0)
III [c]	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)
Tumor focality, n (%)			
F0 (solitary tumor)	45 (86.5)	53 (93.0)	98 (89.9)
F1 (2 or more tumors [d])	7 (13.5)	4 (7.0)	11 (10.1)
Tumor rupture or intraperitoneal hemorrhage, n (%)			
H0 (no evidence of rupture or hemorrhage)	51 (98.1)	55 (96.5)	106 (97.2)
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)

Abbreviations: AFP=alpha-fetoprotein; CIS=cisplatin; GFR=glomerular filtration rate; ITT=Intent-to-treat; max=maximum; min=minimum; PRETEXT=Pretreatment Tumor Extension; SD=standard deviation; STS=sodium thiosulfate.

[a] One section of the liver was involved and 3 sections were free from disease.
[b] One or 2 sections of the liver were involved, but 2 adjoining sections were free from disease.
[c] Two or 3 sections of the liver were involved, and no 2 adjoining sections were free from disease.
[d] Regardless of nodule size or PRETEXT classification.

Table 8. Prior and Concomitant Medications (SIOPEL 6, ITT Population)

Parameter Category/Statistic	CIS Alone (N=56)	CIS+STS (N=53)
Other Chemotherapy Drug Administered		
Carboplatin	5 (8.9)	3 (5.7)
Doxorubicin	5 (8.9)	4 (7.5)
Irinotecan	0	1 (1.9)
Ototoxic medications administered [a]		
Aminoglycosides	2 (3.6)	2 (3.8)
Furosemide	0	0
Other	2 (3.6)	1 (1.9)

Abbreviations: CIS=cisplatin; PLADO=cisplatin (=platinol) and doxorubicin; STS=sodium thiosulfate.
[a] Ototoxic medications includes medications that are known to be ototoxic excluding chemotherapeutics.

- **Numbers analysed**

The primary endpoint of hearing impairment was initially planned (but not conducted) to be analysed for the mITT Population as follows:

- By checking if the STS was correctly timed (STS had to be started 6 hours after the end of the CIS infusion): if STS was started too late, the reduction of hearing impairment was expected to be lower.

- By taking into account whether STS was delivered in each cycle in patients randomised to CIS+STS. Again, if STS was not administered after

The primary analysis of all efficacy endpoints was performed using the ITT population. In addition, a per protocol analysis excluding significant protocol deviators was carried out for the primary analysis of hearing loss.

Numbers of patients included in each analysis set are presented in **Table 9**.

Table 9. Numbers Analysed in Each Analysis Set, SIOPEL 6 study

Population	Randomized Treatment		Actual Treatment		Total
	CIS Alone (N=53) n (%)	CIS+STS (N=61) n (%)	CIS Alone (N=56) n (%)	CIS+STS (N=53) n (%)	n (%)
ITT Population [a]	52 (98.1)	57 (93.4)	--	--	109 (84.5)
Safety Population [b]	--	--	56 (100)	53 (100)	109 (84.5)
PP Population [c]	52 (98.1)	53 (86.9)	--	--	105 (81.4)
mITT Population [d]	46 (86.8)	55 (90.2)	--	--	101 (78.3)

Abbreviations: CIS=cisplatin; ITT=Intent-to-treat; mITT=modified Intent-to-treat; PP=Per Protocol; STS=sodium thiosulfate.

- **Outcomes and estimation**

Primary endpoint

The primary objective of this study was to assess the efficacy of STS for reducing hearing impairment, defined as Brock Grade ≥ 1, caused by CIS chemotherapy and measured using audiologic evaluations. The proportion of children in the CIS+STS arm with hearing loss at age ≥ 3.5 years (20 children [35.1%]) was approximately one-half compared with the CIS Alone arm (35 children [67.3%]) (**Table 10**).

Table 10. Summary of Hearing Loss (SIOPEL 6, ITT Population)

Results	CIS Alone (N=52)	CIS+STS (N=57)
Yes, n (%)	35 (67.3)	20 (35.1)
No, n (%)	17 (32.7)	37 (64.9)
Relative Risk (95% CI) [a]		0.521 (0.349, 0.778)
P-value [a]		<0.001
Relative Risk (95% CI) [b]		0.519 (0.356, 0.755)
P-value [b]		<0.001

Abbreviations: CI=confidence interval; CIS=cisplatin; CMH=Cochran-Mantel-Haenszel; ITT=Intent-to-treat; PRETEXT=Pretreatment Tumor Extension; PTA=pure-tone audiometry; STS=sodium thiosulfate.
[a] P-value and relative risk from Chi-square test.
[b] P-value and relative risk from CMH test stratified by country group, PRETEXT group, and age group.
Note: Subjects without hearing loss assessment were included as a 'Yes' for hearing loss.
Note: Hearing impairment was defined as Brock ≥ 1 grade hearing loss determined by PTA at age ≥ 3.5 years.
Note: Treatment groups indicate treatments patients were randomized to during the study.

Secondary endpoints (PP population)

Event free survival

Event-free survival was calculated from the time of randomisation to the first of the following events: progression, relapse, second primary malignancy, or death (**Table 11**). Event-free survival of patients without an EFS event was censored at the time of last known follow-up visit.

Table 11. Summary of Event-Free Survival (Median 4.27-year Follow-up - SIOPEL 6, PP Population)

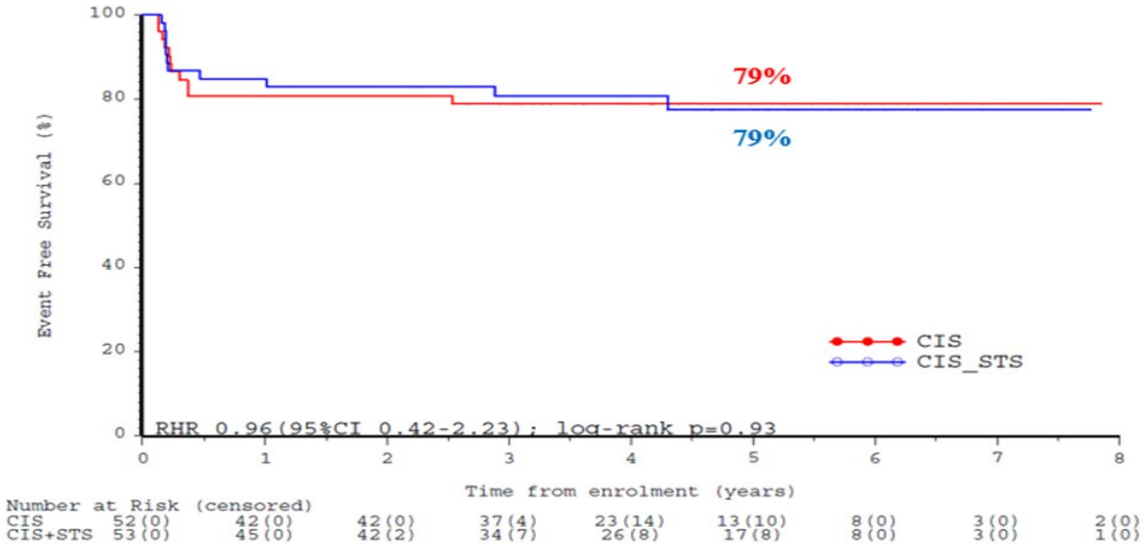
Parameter Category/Statistic	CIS Alone (N=52)	CIS+STS (N=53)
Number of patients censored, n (%)	41 (78.8)	42 (79.2)
Number of patients with event, n (%)	11 (21.2)	11 (20.8)
Treatment comparison (CIS+STS vs CIS Alone)		
Hazard ratio (95% CI)		0.96 (0.42, 2.23)
P-value (log-rank)		0.932
Hazard ratio (95% CI) [a]		1.07 (0.46, 2.51)
P-value (log-rank) [a]		0.775

Abbreviations: CI=confidence interval; CIS=cisplatin; PP=Per Protocol; PRETEXT=Pre-treatment Tumor Extension; STS=sodium thiosulfate.

[a] Hazard ratio and 95% CI were based on Cox proportional hazards model and includes treatment and randomization stratification of country group, PRETEXT group, and age group. The p-value was based on stratified log rank test.

Event-free survival was graphically compared between the randomised groups by Kaplan-Meier plots (**Figure 10**).

Figure 10. Event-Free Survival (SIOPEL 6, PP Population- Median 4.27-year Follow-up)



Abbreviations: CI=confidence interval; CIS=cisplatin; PP=Per Protocol; RHR=relative hazard ratio; SIOPEL=International Childhood Liver Tumors Strategy Group; STS=sodium thiosulfate.

Overall survival

Overall survival was calculated from the time of randomisation to death. Overall survival of alive patients was censored at the time of last known status of survival (**Table 12**).

Table 12. Summary of Overall Survival (Median 4.27-year Follow-up) (PP Population)

Parameter Category/Statistic	CIS Alone (N=52)	CIS+STS (N=53)
Number of patients who died, n (%)	4 (7.7)	2 (3.8)
Number of patients censored, n (%)	48 (92.3)	51 (96.2)
Treatment comparison (CIS+STS vs CIS Alone)		
Hazard ratio (95% CI)		0.48 (0.09, 2.61)
P-value (log-rank)		0.384

Abbreviations: CI=confidence interval; CIS=cisplatin; PP=Per Protocol; STS=sodium thiosulfate.
Note: Time to event was calculated from the time of randomization to death. Patients alive were censored at the time of last known Follow-up Visit.

Overall survival was graphically compared between the randomised groups by Kaplan-Meier plots (**Figure 11**).

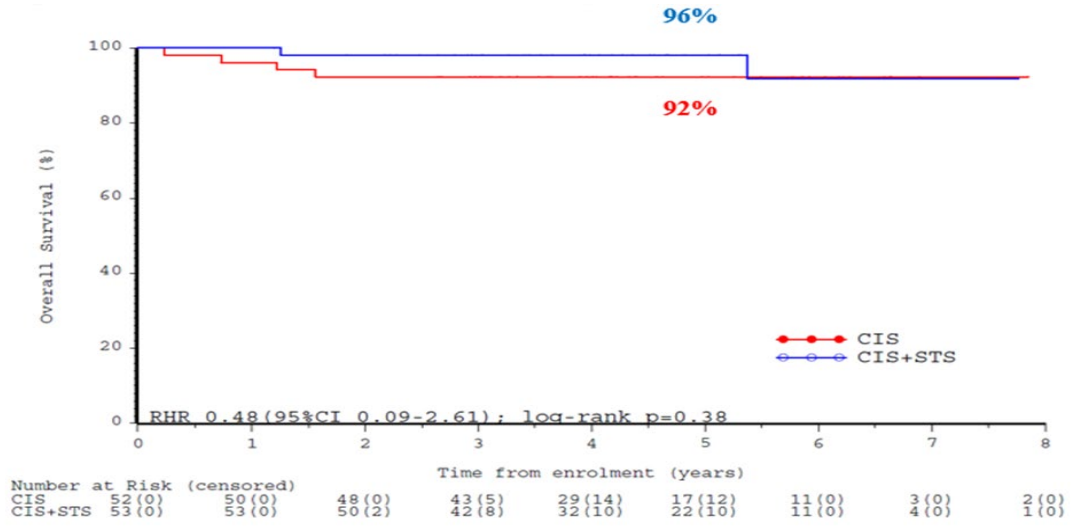
Response to Preoperative Chemotherapy

Responders to pre-operative chemotherapy was assessed as follows:

- Complete response (no evidence of disease and normal serum AFP value [for age]).
- Partial response (any tumour volume shrinkage associated with a decreasing serum AFP value, > 1 log below the original measurement).
- Stable disease (no tumour volume change and no change in AFP or decreasing serum AFP < 1 log fall from the original measurement).
- Progressive disease (unequivocal increase in 1 or more dimensions and/or any unequivocal increase of the serum AFP concentration [3 successive 1 to 2 weekly determinations] even without clinical [physical and/or radiological] evidence of tumour regrowth)

Results based on the pre-specified SIOPEL 6 criteria, and the post-hoc traditional SIOPEL criteria are summarised in **Error! Reference source not found.** and **Table 14** respectively.

Figure 11.Overall Survival (SIOPEL 6, PP Population- Median 4.27-year Follow-up)



Abbreviations: CI=confidence interval; CIS=cisplatin; PP-Per Protocol; RHR=relative hazard ratio;

Table 13 Summary of Response to Preoperative Chemotherapy using SIOPEL 6 Response Criteria (SIOPEL 6, PP Population)

Statistic	CIS Alone (N=52)	CIS+STS (N=53)
Last response after cycles 1 and 2, n (%)		
PR	28 (53.8)	21 (39.6)
Stable disease	24 (46.2)	32 (60.4)
Last response after cycles 3 and 4, n (%)		
PR	39 (75.0)	35 (66.0)
PD	5 (9.6)	5 (9.4)
Stable disease	5 (9.6)	10 (18.9)
Not evaluable	3 (5.8)	3 (5.7)
Responders (CR and PR) after 4 cycles [a], n (%)		
Responder	39 (75.0)	35 (66.0)
Non-responder	13 (25.0)	18 (34.0)
p-value [b]		0.393

Abbreviations: CIS=cisplatin; CR=complete response; PD=progressive disease; PP=Per Protocol; PR=partial response; SIOPEL=International Childhood Liver Tumors Strategy Group; STS=sodium thiosulfate.
[a] Responders includes both CR and PR; however, no CR was observed after 4 cycles.
[b] P-value from Fisher's Exact Test.
Note: Included last reported response prior to surgery.
Note: Treatment groups are treatments patients were randomized to receive and actually received.

Table 14. Summary of response to preoperative chemotherapy using traditional response criteria – Post hoc analysis ((SIOPEL 6, PP Population)

Statistic	CIS Alone (N=52)	CIS+STS (N=53)
Last response after cycles 1 and 2, n (%)		
PR	49 (94.2)	48 (90.6)
Stable disease	3 (5.8)	5 (9.4)
Last response after cycles 3 and 4, n (%)		
PR	46 (88.5)	46 (86.8)
PD	5 (9.6)	5 (9.4)
Not evaluable	1 (1.9)	2 (3.8)
Responders (CR and PR) after 4 cycles [a, n (%)]		
Responder	46 (88.5)	46 (86.8)
Non-responder	6 (11.5)	7 (13.2)
P-value [b]		>0.999

Abbreviations: CIS=cisplatin; CR=complete response; PD=progressive disease; PP=Per Protocol; PR=partial response; SIOPEL=International Childhood Liver Tumors Strategy Group; STS=sodium thiosulfate.
[a] Responders includes both CR and PR; however, no CR was observed after 4 cycles. Not evaluable were considered nonresponders.
[b] P-value from Fisher's Exact Test.

Complete Tumour Resection

The proportion of children with partial hepatectomy was similar between the CIS+STS (49 patients [92.5%]) compared with the CIS Alone arm (48 patients [92.3%]), and the proportion of children with liver transplantation was similar between arms as well (4 patents [7.7%] and 4 patients [7.5%]] respectively.)

Remission Status

In the PP population, there was no statistically significant difference in the proportion of children with CR at the end of treatment (as reported by the Investigator) in the CIS+STS arm (49 patients [92.5%]) compared with the CIS Alone arm (45 patients [86.5%]) (p=0.359). The proportion of children in PR was low and similar between the arms. In the CIS+STS arm, no child had PD, died from their disease, or died from other causes by the end of treatment. In the CIS Alone arm, 2 children (3.8%) had PD, 1 child (1.9%) died from disease, and 1 child (1.9%) died from other causes (surgical complications). See Section 7.3.1 for additional detail about the 4 deaths that occurred during Follow-Up. In both treatment arms, 2 children (3.8%) per arm switched from protocol treatment to further treatment that included PLADO.

The results of the complete remission assessment when performed by a Central Reviewer were generally similar for each category compared to those reported by the Investigator and also found no statistically significant difference between the 2 treatment arms (p=0.236), though the CIS+STS arm (49 patients [92.5%]) had more children with complete remission than the CIS Alone arm (44 patients [84.6%])

Alpha-fetoprotein Values

Alpha-fetoprotein values have been used as a tumour marker and are therefore included in the efficacy section. At baseline, the mean AFP log-transformed values were similar between the CIS+STS and CIS Alone arms (5.031 ng/mL and 4.874 ng/mL, respectively). In both the CIS+STS and the CIS Alone

arms, the mean change from baseline in AFP values were similar and statistically significant reductions were observed at post-course 1+2 (-0.635 ng/mL [p<0.001] and -0.817 ng/mL [p<0.001], respectively) and at post-course 3+4 (-1.467 ng/mL [p<0.001] and -1.956 ng/mL [p<0.001], respectively). In both the CIS+STS and the CIS Alone arms, the mean changes from baseline to end of treatment in AFP values were similar, and statistically significant reductions were observed (-3.792 ng/mL [p<0.001] and -3.714 ng/mL [p<0.001], respectively).

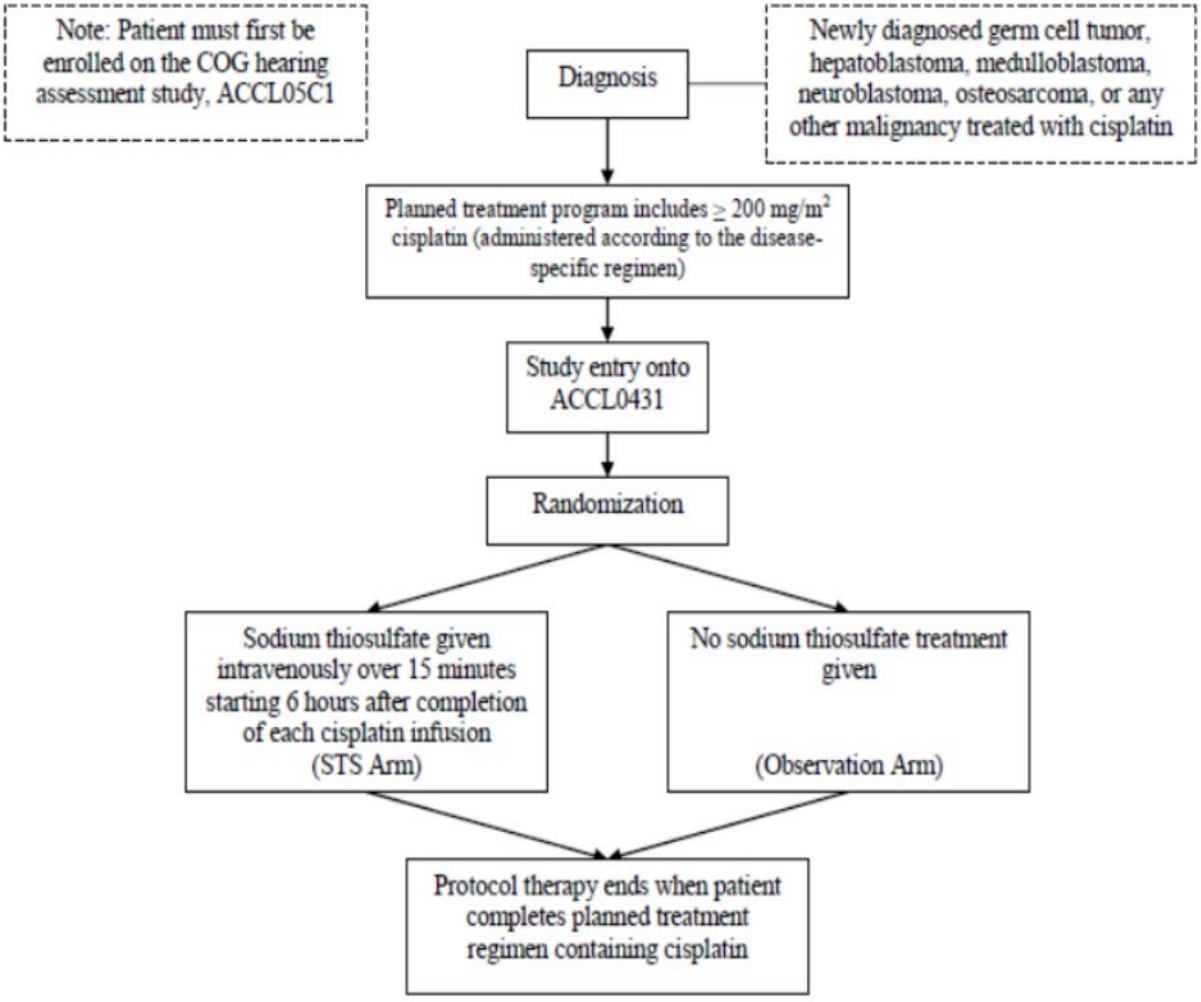
Disease relapse during follow-up

No statistically significant difference was observed in the proportion of children that were relapse free in the CIS+STS arm (48 children [90.6%]) and the CIS Alone arm (50 children [96.2%]) (p=0.437). A total of 5 children (9.4%) in the CIS+STS arm and 2 children (3.8%) in the CIS Alone arm had a disease relapse, with the majority of relapses occurring within the first year after surgery.

Study COG ACCL0431: A randomized phase 3 study of sodium thiosulfate for the prevention of cisplatin-induced ototoxicity in children

Figure 12 provides a schematic of the overall study design.

Figure 12. COG ACCL0431 Study Schema



Methods

- **Study participants**

Main inclusion criteria:

1. Age ≤18 years and ≥1 month

2. Histologically confirmed newly diagnosed germ cell tumour, HB, medulloblastoma, neuroblastoma, osteosarcoma, or other malignancy

3. Planned cumulative CIS dose of ≥ 200 mg/m^2, or more with an infusion duration of 6 hours or less

6. Performance status score ≥ 50 using Karnofsky scale (> 16 years) or Lansky scale (≤ 16 years).

7. No previous cisplatin or carboplatin treatment

8. Previous cranial irradiation was initially excluded but later permitted, provided hearing was normal, by a protocol amendment

9. Normal hearing

Main exclusion criteria

1. Females of childbearing 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.

2. Female patients who were lactating must have agreed to stop breastfeeding.

3. Children must not have been enrolled in any Children's Oncology Group (COG) therapeutic study for treatment of the underlying malignancy.

- **Treatments**

Patients were randomised 1:1 to one of the 2 following treatment groups: cisplatin alone administered according to the site specific protocols in use at the time or cisplatin at the same dose and STS administered IV exactly 6 hours after stop of cisplatin over 15 minutes at 16 g/m^2 (533 mg/kg for children whose therapeutic protocol administered CIS on a per kg basis due to young age or small body size).

Cisplatin was administered according to the sites' disease-specific cancer treatment protocols in use at the time, without specification by this study with regard to individual or cumulative CIS dose, schedule, infusion rate (up to a maximum infusion of 6 hours) or associated hydration/mannitol diuresis. However, when multiple daily doses of CIS were scheduled, there must have been at least a 10-hour delay between any STS infusion and the beginning of the next day's CIS infusion.

Sodium thiosulfate was administered by IV infusion over 15 minutes beginning 6 hours after the completion of each CIS infusion. Sodium thiosulfate was administered on each day that CIS was given. The STS dose was 16 g/m^2 (533 mg/kg for children whose therapeutic protocol administered CIS on a per kg basis due to young age or small body size) on each day it was given.

In study COG ACCL0431 the STS dose was 16 g/m^2 (533 mg/kg for children whose therapeutic protocol administered CIS on a per kg basis due to young age or small body size) as a 15-minute IV infusion. 1-5 daily doses per cycle, 1-6 cycles, 1-24 doses in total. The criterion to administer STS on multiple-day regimens was a pre-CIS serum sodium level ≤ 145 mEq/L (evaluated daily). If the pre-CIS serum sodium level was > 145 mEq/L, the STS dose for that day should have been withheld, but CIS for that day should have been given as scheduled. The following day, if the pre-CIS serum sodium

level had returned to ≤ 145 mEq/L, STS administration resumed without attempting to "make up" the dose that was withheld. When multiple daily doses of cisplatin are scheduled, there must be at least a 10-hour delay between any STS infusion and the beginning of the next day's cisplatin infusion.

- **Objectives**

The primary objective of ACCL0431 was to evaluate the efficacy of STS infusion (following CIS treatment), compared with CIS alone (Observation arm), for preventing hearing loss in children receiving CIS chemotherapy for the treatment of newly-diagnosed germ cell tumour, HB, medulloblastoma, neuroblastoma, osteosarcoma, or any other malignancy treated with CIS.

The secondary objectives were:

- To compare the mean change in hearing thresholds for key frequencies between the CIS+STS arm and the Observation arm
- To compare the incidences of CIS-related Grade 3 and 4 nephrotoxicity and Grade 3 and 4 cytopenia between the CIS+STS arm and the Observation arm
- To monitor event-free survival (EFS) and overall survival (OS) in the CIS+STS arm and the Observation arm
- To evaluate the association of 2 key gene mutations (thiopurine S-methyltransferase [TPMT] and catechol-O-methyltransferase [COMT]) with the development of CIHL

- **Outcomes/endpoints**

The primary endpoint was the proportional incidence of hearing loss between the CIS+STS arm and the observation arm.

Hearing loss was defined by comparing hearing sensitivity at the Follow-up evaluation (4 weeks following the last dose of CIS) relative to baseline measurements using American Speech-Language-Hearing Association (ASHA) criteria.

The secondary endpoints were:

- Mean change in hearing thresholds for key frequencies (500, 1000, 2000, 4000, and 8000 Hz) between the CIS+STS arm and the observation arm
- EFS and OS
- Association of 2 key gene mutations (TPMT and COMT) with the development of CIHL (due to an insufficient number of samples, this analysis was not conducted)

- **Sample size**

Sample size estimation was based on the primary analysis that compared the proportional incidence of hearing loss in the CIS+STS arm versus incidence in the observation arm. The incidence of hearing loss in the observation arm was assumed to be 45%, a somewhat more conservative figure than the 61% overall rate reported [Knight et al, 2005]. A treatment effect of STS with a 50% reduction in hearing loss for the CIS+STS arm was hypothesised; in other words a 22.5% hearing loss in the CIS+STS arm was assumed. Assuming a 1-sided significance level of 5% (as none of the considerable pilot data to date suggested STS would increase hearing loss), 54 children per arm were needed to achieve 80% power for detecting 22.5% hearing loss in the CIS+STS arm compared with 45% hearing loss in the observation arm. The numbers suggested that if the observation arm had hearing loss incidence of > 45%, then > 80% power would be achieved, when dosing with CIS+STS produced a 50% relative reduction in hearing loss. To accrue 108 patients evaluable for the primary analysis, the maximum accrual target was increased to 135 children to account for ineligible enrolments and

children who were found not evaluable for the primary hearing loss endpoint due to causes such as patient drop-outs, noncompliance of hearing tests, and incomplete/suboptimal hearing tests which were insufficient for determining the hearing loss status.

- **Randomisation and blinding (masking)**

Children were randomised to either receive STS or not to receive STS after each CIS dose. Randomisation was 1:1 and was stratified by prior cranial radiation (yes vs. no), age (< 5 versus ≥ 5 years), and duration of cisplatin infusion (< 2 versus ≥ 2 hours) in the 5 strata (**Table 15**).

Table 15 Summary of Randomisation Stratification (All Subjects, Study ACCL0431)

Parameter	Observation (N=64)	CIS+STS (N=61)	Total (N=125)
No cranial irradiation, n (%)			
< 5 years of age and < 2 hours CIS infusion duration	9 (14.1)	10 (16.4)	19 (15.2)
< 5 years of age and ≥ 2 hours CIS infusion duration	13 (20.3)	12 (19.7)	25 (20.0)
≥ 5 years of age and < 2 hours CIS infusion duration	20 (31.3)	20 (32.8)	40 (32.0)
≥ 5 years of age and ≥2 hours CIS infusion duration	17 (26.6)	15 (24.6)	32 (25.6)
Prior cranial irradiation, n (%)			
Regardless of age or CIS infusion duration	5 (7.8)	4 (6.6)	9 (7.2)

Abbreviations: CIS=cisplatin; STS=sodium thiosulfate.

Randomisation was blinded for central reviewers of audiometry data, but the study was open label for children and treating physicians.

Statistical methods

All analyses related to hearing loss (including mean change from baseline hearing loss) and frequencies were evaluated by adjusting for the treatment and stratification variables of prior cranial irradiation (yes/no), duration of CIS infusion (< 2 hours or ≥2 hours), and age (< 5 or ≥5 years) as covariates in the model.

In general, dropouts were not replaced, and missing data were not imputed.

No stopping rule was proposed for a positive effect (otoprotection observed). In the event of a beneficial effect on hearing loss, full accrual would permit a gain of maximal information on STS toxicity, as well as any possible negative or positive effect of STS on EFS and OS.

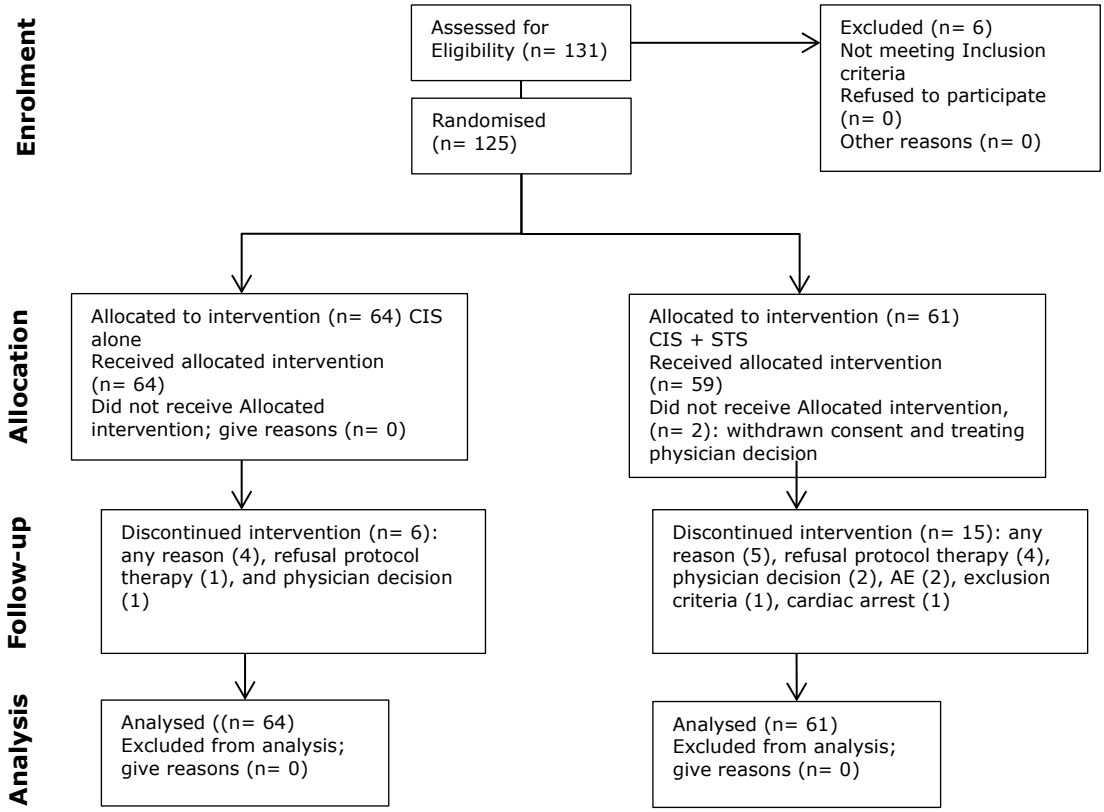
As there was very limited power for comparing EFS outcome between the 2 arms, the observed EFS and OS was informally monitored in a log-rank test between the 2 arms at each interim monitoring, for safety considerations. The term "informal monitoring" was used due to insufficient power and lack of precise estimates for EFS and OS to derive monitoring boundaries that give certain statistical properties. Instead, the comparison was made using a log-rank test and if such interim comparison suggested significantly worse EFS and OS for the CIS+STS arm at the level of 0.05, the data and the monitoring result were to be presented to the COG DSMC; upon recommendation by the DSMC, the Study Committee was to review the pertinent cases to assist in determining an appropriate response of action. The DSMC might also have stopped the study at any point based on their review of AEs and outcomes (including EFS and OS).

No multiple comparison adjustments were made for efficacy endpoints evaluated during this study.

Results

- **Participant flow**

Figure 13. Patient Disposition in Study ACCL0431



- **Recruitment**

The first patient was enrolled on 29 Oct 2008.

The last patient completed follow-up: 28 Feb 2018.

- **Conduct of the study**

The original ACCL0431 Protocol was dated 24 Jan 2008 and was subject to 3 global protocol amendments.

Protocol Amendment 1 was dated 31 Mar 2010 and expanded the inclusion criteria to allow enrolment of patents with prior cranial irradiation before study entry and those with other types of cancer instead of germ cell tumour, hepatoblastoma, medulloblastoma, neuroblastoma, or osteosarcoma which were stipulated in the original protocol.

Protocol Amendment 2 was dated 01 Jul 2011 and updated the Common Terminology Criteria for Adverse Events (CTCAE) from Version 3 to Version 4.

Protocol Amendment 3 was dated 10 Oct 2011 and included changes to increase the maximum enrolment from 120 to 135 children over 3.5 years (rather than 3 years).

Per COG policy, protocol deviations were not defined in the protocol or recorded by the individual COG sites. The physician responsible for the patient's management and care was stipulated to be the only individual authorised to decide if the patient should be removed from protocol therapy.

- **Baseline data**

Patient demographics and baseline disease characteristics are summarised in **Table 16**.

Table 16. **Patient Demographics and Baseline Characteristics in Study ACCL0431**

Variable	Observation N=64	CIS+STS 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)
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 tumor	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)

Variable	Observation N=64	CIS+STS N=61	Total N=125
Other	2 (3.1)	3 (4.9)	5 (4.0)
Atypical teratoid/rhabdoid tumor	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: CIS=cisplatin; ITT=Intent-to-treat; NOS=not otherwise specified; PNET=primitive neuroectodermal tumor; STS=sodium thiosulfate.

- **Numbers analysed**

Numbers analysed in each analysis set are presented in **Table 17**.

Table 17. **Analysis populations in Study ACCL0431**

Population	Observation (N=64)	CIS+STS (N=61)	Total (N=125)
ITT Population, n (%)	64 (100)	61 (100)	125 (100)
Safety Population, n (%)	64 (100)	59 (96.7)	123 (98.4)
Efficacy Population, n (%)	55 (85.9)	49 (80.3)	104 (83.2)

Abbreviations: CIS=cisplatin; ITT=Intent-to-treat; STS=sodium thiosulfate.

Of the children randomised to the CIS+STS arm 2 did not receive STS due to refusal of further protocol therapy by patient/parent/guardian or due to the physician determining it was in the patient's best interest and were excluded from both the safety and efficacy populations. A further 10 children in the CIS+STS arm were excluded from the efficacy population due to missing conventional hearing test data (missing Baseline and/or 4-week follow-up data)

All 64 children randomised to the observation arm received protocol therapy; and 9 children were excluded from the Efficacy Population due to missing conventional hearing test data.

- **Outcomes and estimation**

Primary Endpoint

The proportional incidence of hearing loss between the CIS+STS arm and the observation arm in the efficacy population is summarised in

Table 18.

Table 18. Summary of Hearing Loss in Study ACCL0431 (Efficacy population)

Results	Observation (N=55)	CIS+STS (N=49)	Odds ratio (95% CI) [a]	P-value [a]
n	55	49		
Yes, n (%)	31 (56.4)	14 (28.6)		
No, n (%)	24 (43.6)	35 (71.4)	0.274 (0.114, 0.660)	0.0039

Abbreviations: ASHA=American Speech-Language-Hearing Association; CI=confidence interval; CIS=cisplatin; STS=sodium thiosulfate.

[a] Based on logistic regression including treatment and stratification variables as covariates in the model.

Note: The hearing loss was assessed based on ASHA criteria via comparison of the baseline and 4-week follow-up evaluations. Children with missing baseline or 4-week follow-up evaluations were excluded from analyses.

Of the hearing tests performed to assess the primary endpoint of hearing loss, the majority of children in both the CIS+STS arm and the Observation arm were assessed by a decrease in hearing conventional frequency (13 patients [92.9%] and 28 patients [90.3%], respectively) and abnormal audiometry results (13 patients [92.9%] and 24 patients [77.4%], respectively). Fewer children had abnormal auditory brainstem response (ABR)/BAER results or ABR/BAER results worsening (1 patient [7.1%] each in the CIS+STS arm and 3 patients [9.7%] each in the observation arm), as these tests were only performed in very young children.

A sensitivity analysis for hearing loss was conducted in the ITT population **Table 19.**

Table 19. Summary of Hearing Loss in Study ACCL0431 (ITT Population)

Results	Observation (N=64)	CIS+STS (N=61)	Odds ratio (95% CI) [a]	P-value [a]
n	64	61		
Yes, n (%)	40 (62.5)	26 (42.6)		
No, n (%)	24 (37.5)	35 (57.4)	0.411 (0.191, 0.886)	0.0234

Abbreviations: ASHA=American Speech-Language-Hearing Association; CI=confidence interval; CIS=cisplatin; ITT=Intent-to-treat; STS=sodium thiosulfate.

[a] Based on logistic regression including treatment and stratification variables as covariates in the model.

Note: The hearing loss was assessed based on ASHA criteria via comparison of the baseline and 4-week follow-up evaluations. Children with missing baseline or 4-week follow-up evaluations were considered as having hearing loss in analyses.

A subgroup analysis by age in the efficacy population is presented in **Table 20**.

Table 20. Summary of Hearing Loss by Age Subgroup in Study ACCL0431 (Efficacy population)

	Observation (N=55)	CIS+STS (N=49)	Odds ratio (95% CI) [a]	P-value [a]
All				
n	55	49		
Yes, n (%)	31 (56.4)	14 (28.6)		
No, n (%)	24 (43.6)	35 (71.4)	0.310 (0.137, 0.701)	0.0049
< 5 years				
n	15	14		
Yes, n (%)	11 (73.3)	3 (21.4)		
No, n (%)	4 (26.7)	11 (78.6)	0.099 (0.018, 0.551)	0.0082
≥ 5 years				
n	40	35		
Yes, n (%)	20 (50.0)	11 (31.4)		
No, n (%)	20 (50.0)	24 (68.6)	0.458 (0.178, 1.180)	0.1058

Abbreviations: ASHA=American Speech-Language-Hearing Association; CI=confidence interval; CIS=cisplatin; STS=sodium thiosulfate.
[a] Based on logistic regression including only treatment in the model.
Note: The hearing loss was assessed based on ASHA criteria via comparison of the baseline and 4-week follow-up evaluations. Children with missing baseline or 4-week follow-up evaluations were excluded from analyses.

Secondary endpoints

Change in Hearing Thresholds

A secondary endpoint of the COG ACCL0431 study was the mean change in hearing thresholds for key frequencies between the CIS+STS arm and the observation arm **Table 21**.

Table 21. Summary of Mean Change from Baseline Hearing Loss in Study ACCL0431 (Efficacy Population)

	Reviewer 1		Reviewer 2	
	Observation (N=55)	CIS+STS (N=49)	Observation (N=55)	CIS+STS (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
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
1000 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
1000 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
4000 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
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
8000 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
8000 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

Abbreviations: CI=confidence interval; CIS=cisplatin; LS=least squares; SE=standard error; STS=sodium thiosulfate.
Note: Linear regression was used. Covariates included baseline values, stratum, and treatment. Missing values

Overall Response

Response was not prespecified in the SAP but data were provided by the applicant during the procedure. Complete response and partial response was 81.6% (95% CI 70.8%,92.5%) in the STS arm compared with 76.3% (65.4%, 87.1%) in the CIS arm. ORR treatment difference of 5.4% (95% CI -10%, 20.7%).

Event free survival

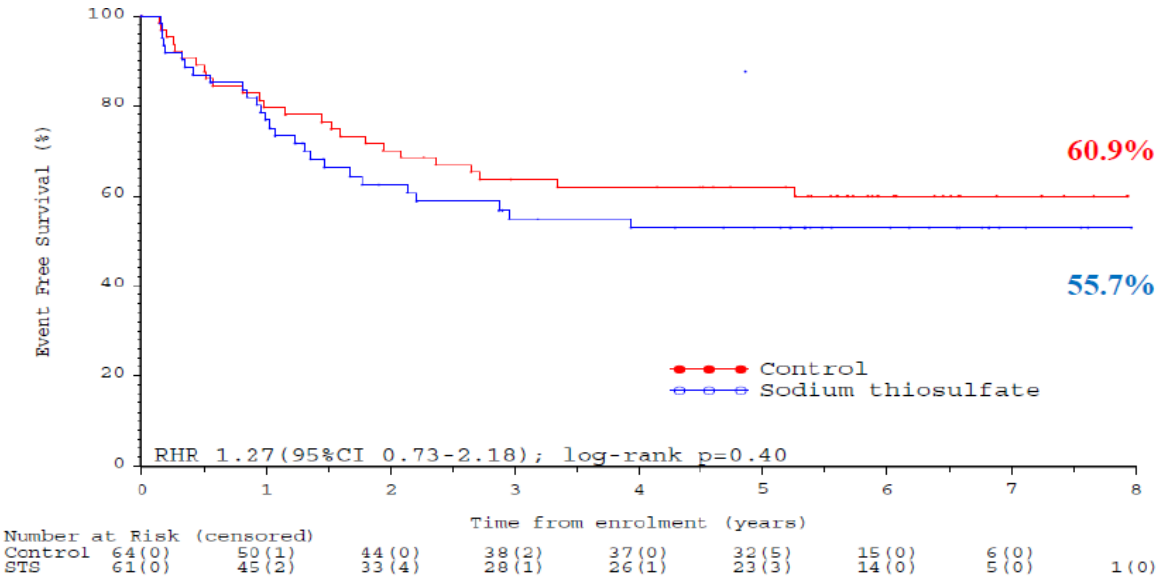
Event-free survival was monitored as a secondary endpoint. All 125 patients were considered in this analysis at a median follow-up of 5.33 years post-study entry years (interquartile range for duration of follow-up: 2.54 to 6.45 years) (**Table 22**). Event-free survival was graphically compared between the randomised groups by Kaplan-Meier plots (**Figure 14**).

Table 22. Summary of Event-free Survival in Study ACCL0431 (Median 5.33-year Follow-up) (ITT Population)

Parameter Category (Statistic)	Observation (N=64)	CIS+STS (N=61)
Number of patients with event *, n (%)	25 (39.1)	27 (44.3)
Number of patients censored, n (%)	39 (60.9)	34 (55.7)
Event-free survival (years)		
Minimum	0.8	0.6
25% (95% CI)	1.5 (0.5, 2.7)	1.0 (0.6, 1.8)
Median * (95% CI)	NE (3.3, NE)	NE (1.8, NE)
75% (95% CI)	NE (NE, NE)	NE (NE, NE)
Maximum	7.9	8.3
Treatment comparison (STS vs Observation)		
Hazard ratio		1.27
95% CI of hazard ratio		(0.73, 2.18)
Log-rank p-value		0.3964

Abbreviations: CI=confidence interval; CIS=cisplatin; ITT=Intent-to-treat; NE=not estimable; STS=sodium thiosulfate.
* The median and 75% estimates could not be calculated because fewer than 50% of patients in either arm experienced an event.
Note: The time to event was defined as the time to the first reported relapse or progression. Patients without relapse or progression were censored at the date of the last survival follow-up.

Figure 14 Event-free Survival in Study ACCL0431 (Overall population-Median 5.33-year Follow-up) (ITT Population)



Abbreviations: CI=confidence interval; ITT=Intent-to-treat; RHR=relative hazard ratio; STS=sodium thiosulfate.
Note: "Control" is the Observation arm.

Additional analyses were conducted in patients with localised **Figure 15**) and disseminated disease (**Figure 16**).

Figure 15. Event-free Survival in Study ACCL0431 (patients with localised disease, Median 5.61-year Follow-up; post-hoc analysis)

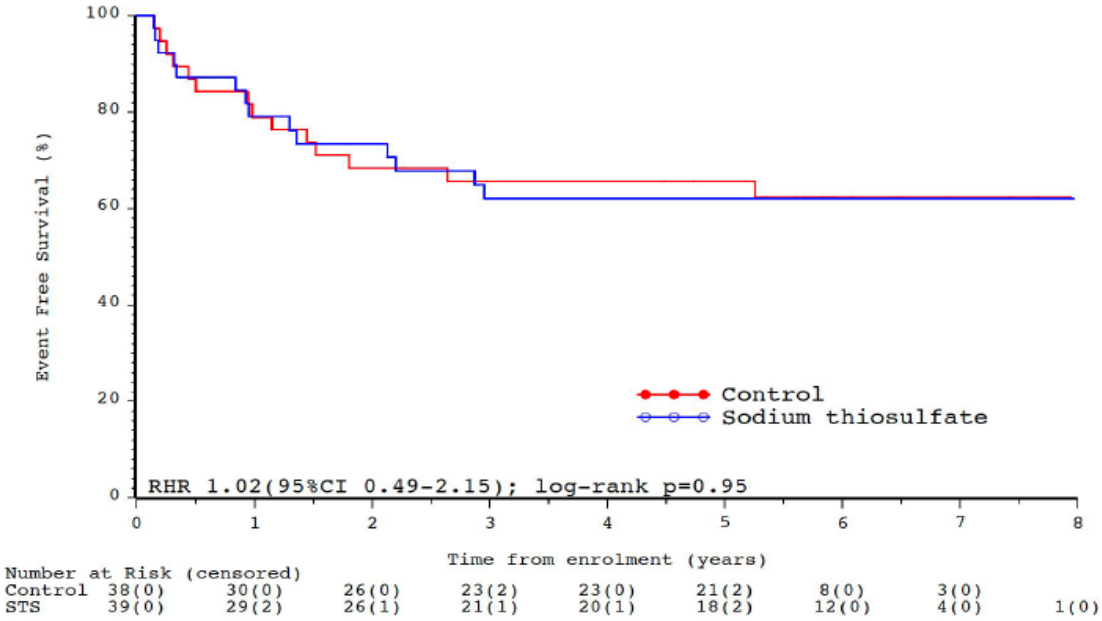
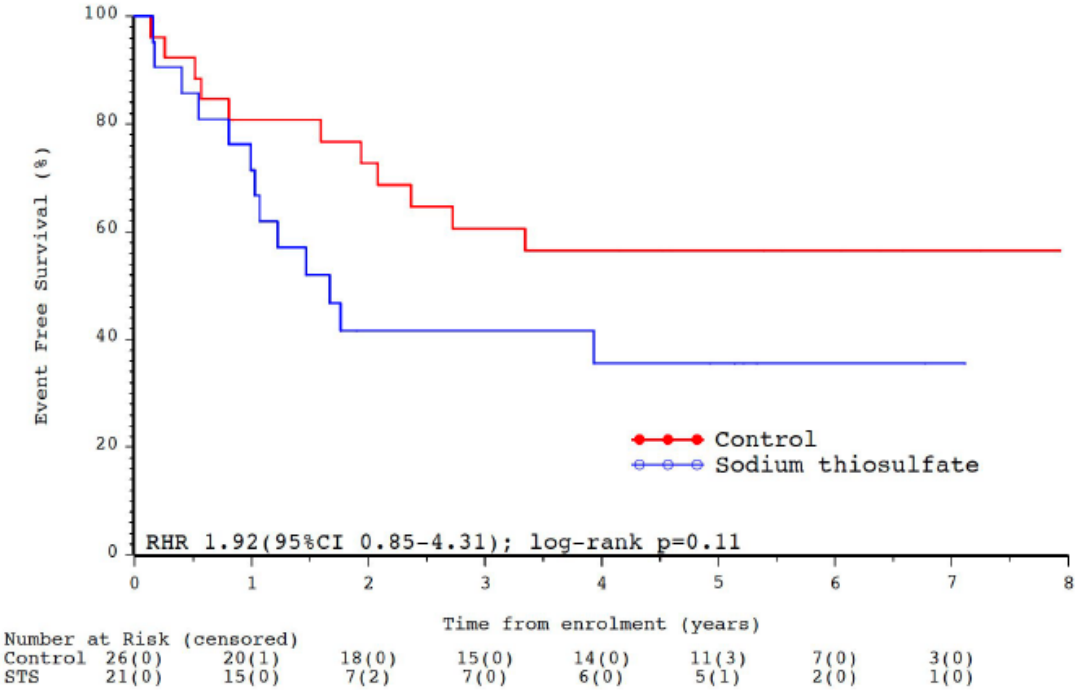


Figure 16 Event-free Survival in Study ACCL0431 (patients with disseminated disease, Median 4.52-year Follow-up; post-hoc analysis)



Overall survival

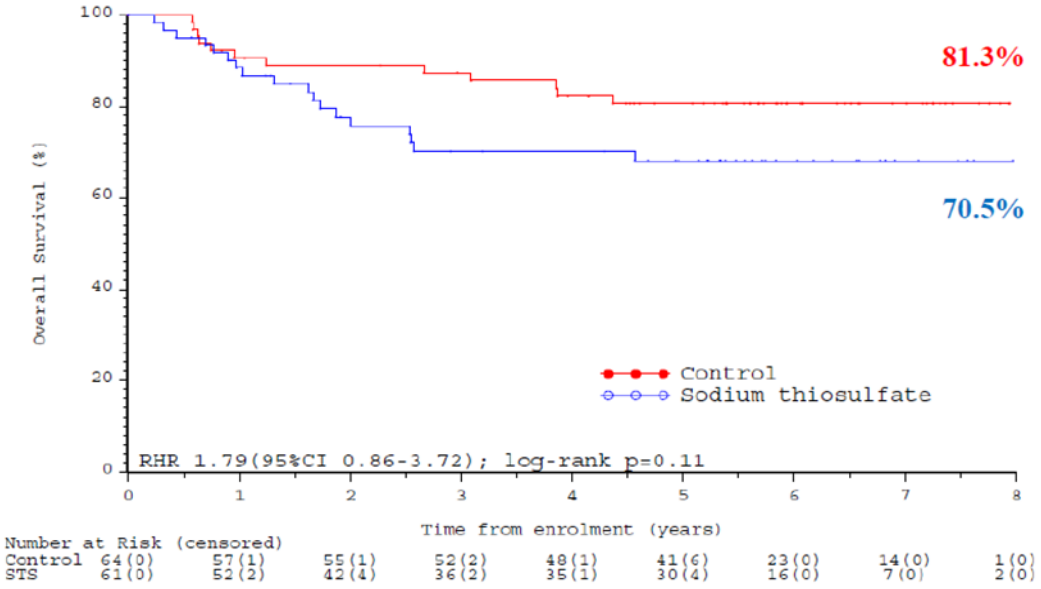
Overall survival was monitored as a secondary endpoint. All 125 patients were considered in this analysis at a median follow-up of 5.33 years post-study entry years (interquartile range for duration of follow-up: 2.54 to 6.45 years) (**Table 23**). Overall survival was graphically compared between the randomised groups by Kaplan-Meier plots (**Figure 17**).

Table 23. Summary of Overall Survival in Study ACCL0431 (Median 5.33-year Follow-up) (ITT Population)

Parameter Category (Statistic)	Observation (N=64)	CIS+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)
Overall survival (years)		
Minimum	0.8	0.6
25% * (95% CI)	NE (3.1, NE)	2.5 (1.3, NE)
Median * (95% CI)	NE	NE
75% * (95% CI)	NE	NE
Maximum	8.3	8.3
Treatment comparison (STS vs Observation)		
Hazard ratio		1.79
95% CI of hazard ratio		(0.86, 3.72)
Log-rank p-value		0.1132

Abbreviations: CI=confidence interval; CIS=cisplatin; ITT=Intent-to-treat; NE=not estimable; STS=sodium thiosulfate.
* The 25% estimate could not be calculated in the Observation arm because fewer than 25% of patients died. The median and 75% estimates could not be calculated because fewer than 50% of patients in either arm died.

Figure 17 Overall Survival in Study ACCL0431 (ITT Population Median 5.33-year Follow-up)



Abbreviations: CI=confidence interval; ITT=Intent-to-treat; RHR=relative hazard ratio; STS=sodium thiosulfate.
Note: "Control" is the Observation arm.

Additional analyses were conducted in patients with localised (**Figure 18**) and disseminated disease (**Figure 19**).

Figure 18. Overall Survival in Study ACCL0431 (patients with localised disease; Median 5.61-year Follow-up; post-hoc analysis*)*

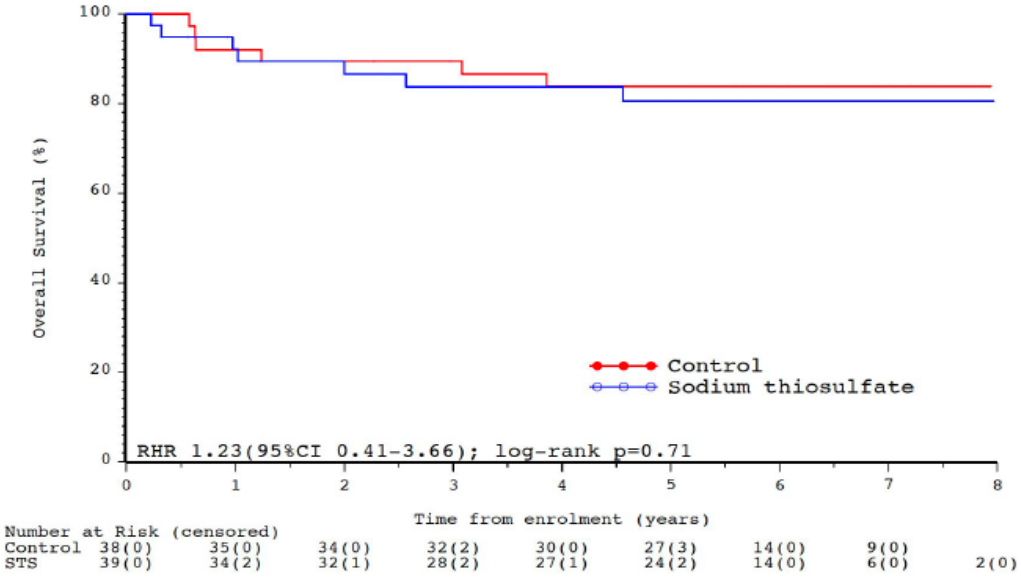
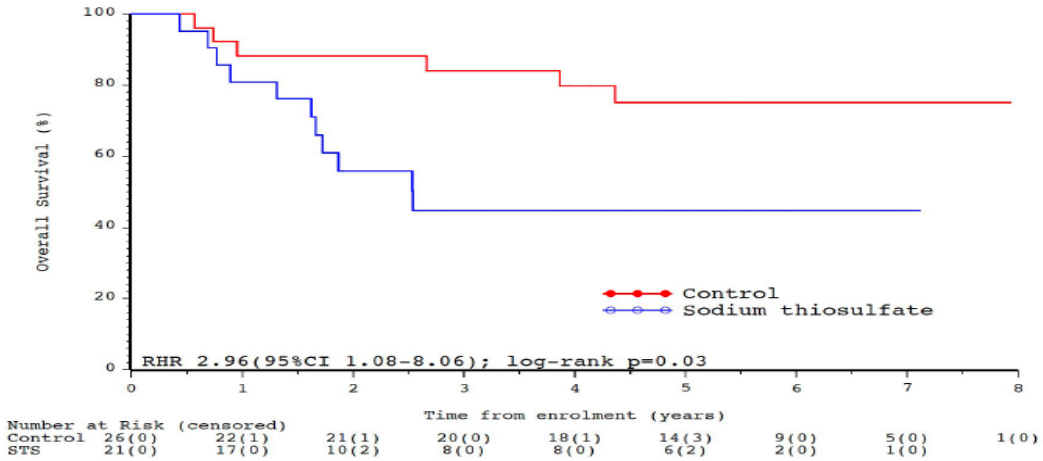


Figure 19 Overall Survival (patients with disseminated disease; Median 4.52-year Follow-up; post-hoc analysis*)*



The applicant conducted patient by patient analysis for predicted outcomes and prognosis indicators for participants with localised (**Table 24**) and disseminated disease (**Table 25**) at diagnosis to investigate possible explanation of lower OS in the latter subgroup. The applicant utilised the data from the choice of chemotherapy protocol used to treat the children e.g., protocols that are specifically used in poor prognosis or high-risk patients. Based on these data the applicant estimated number of patients with poor prognosis in each subgroup.

Table 24 Children with Poor Prognostic Risk Factors in Study ACCL0431, Safety Population, Localised Disease

	Observation (N=38)	CIS+STS (N=38)
Poor prognostic risk factors identified, n (%)	14 (36.8)	18 (46.2)
Response to chemotherapy, n (%)		
CR/PR	25 (65.8)	27 (69.2)
SD	6 (15.8)	4 (10.3)
PD	6 (15.8)	2 (5.1)
Not recorded	1 (2.6)	6 (15.4)

Abbreviations: CR=complete response; PD=progressive disease; PR=partial response; SD=stable disease; STS=sodium thiosulfate.

Table 25. Children with Poor Prognostic Risk Factors in Study ACCL0431, Safety Population, Disseminated Disease

	Observation (N=26)	CIS+STS (N=21)
Children with factors indicating a poor prognosis, n (%)	10 (38)	14 (67)
Response to chemotherapy, n (%)		
CR/PR	16 (61.5)	11 (52.4)
SD	4 (15.4)	2 (9.5)
PD	2 (7.7)	2 (9.5)
Not recorded	4 (15.4)	6 (28.6)

Abbreviations: CR=complete response; PD=progressive disease; PR=partial response; SD=stable disease; STS=sodium thiosulfate.

Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

- **Ancillary analyses**
- **Summary of main efficacy results**

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 26. Summary of Efficacy for trial SIOPEL 6

Title: SIOPEL 6 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			
Study identifier	EudraCT Number: 2007-002402-21 Sponsor Protocol Number: RG-09-205 Sponsor Name: University of Birmingham		
Design	Multicentre, open-label, randomized, controlled, Phase 3 study to assess the efficacy of STS in reducing ototoxicity in patients receiving CIS chemotherapy for SR-HB.		
	Duration:		Recruitment beginning in Dec 2007 and the last patient completing treatment on 14 Apr 2015 Follow up: Per protocol, up to 5 years (or longer as clinically indicated and according to national guidelines); actual median 4.27 years
Hypothesis	Superiority		
Treatments groups	CIS alone arm		• CIS by infusion over a duration of 6 hours: 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) Randomized: n=53
	CIS + STS arm		• CIS by infusion over a duration of 6 hours: 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) + • STS by a 15-minute infusion 6 hours after completion of CIS: 20 g/m2 (body weight >10 kg) 15 g/m2 (body weight ≥5 to ≤10 kg) 10 g/m2 (body weight <5 kg) Randomized: n=61
Endpoints and definitions	Primary endpoint	Hearing loss	Rate of Brock Grade (Brock et al, 1991) ≥1 hearing loss, measured by PTA, after end of study treatment or at an age of at least 3.5 years, whichever was later

	Secondary endpoint	Response to Preoperative Chemotherapy	Response to preoperative chemotherapy was assessed as follows: • Complete response (no evidence of disease and normal serum AFP value [for age]). • Partial response (any tumor volume shrinkage associated with a decreasing serum AFP value, > 1 log below the original measurement). • Stable disease (no tumor volume change and no change in AFP, or decreasing serum AFP < 1 log fall from the original measurement). • Progressive disease (unequivocal increase in 1 or more dimensions and/or any unequivocal increase of the serum AFP concentration [3 successive 1 to 2 weekly determinations] even without clinical [physical and/or radiological] evidence of tumor regrowth).
	Secondary endpoint	complete resection	Complete resection was total macroscopic removal of the tumor as reported by the surgeon and pathologist. In case of doubt, the lack of residual tumor was confirmed with imaging studies performed within 2 weeks after surgery.
	Secondary endpoint	complete remission	Complete remission was defined as lack of evidence of residual disease and normal (for age) AFP at the end of study treatment assessment. To establish CR, all of the following requirements must have been fulfilled: • No evidence of tumor intra-abdominally: • No evidence of metastases • Serum AFP level either normal or compatible with age for at least 4 weeks after normalization.
	Secondary endpoint	EFS	Event-free survival was calculated from the date of randomization to the first of the following events: progression, relapse, secondary primary malignancy, or death. The EFS of patients without an EFS event was censored at the time of last assessment for EFS.
	Secondary endpoint	OS	Overall survival was calculated from the date of randomization to death. The OS of alive patients was censored at the time last known alive.
Database lock	September 2017		

Results and Analysis

Analysis description	Primary Analysis
Analysis population and time point description	ITT population

Descriptive statistics and estimate variability Primary endpoint: Hearing loss	Treatment group	CIS Alone	CIS +STS
	Number of subject	52	57
	Hearing loss: Yes, n (%)	35 (67.3)	20 (35.1)
	Hearing loss: No, n(%)	17 (32.7)	37 (64.9)
	Relative Risk (95% CI) from Chi-square test.	0.521 (0.349, 0.778)	
	P-value from Chi-square test.	<0.001	
	Relative Risk (95% CI) from CMH test stratified by country group, PRETEXT group, and age group.	0.519 (0.356, 0.755)	
	P-value from CMH test stratified by country group, PRETEXT group, and age group.	<0.001	
Analysis population and time point description	PP population		
Descriptive statistics and estimate variability Secondary endpoint: Response to Preoperative Chemotherapy	Treatment group	CIS alone	CIS + STS
	Number of subject	52	53
	Responder	39 (75.0)	35 (66.0)
	Non responder	13 (25.0)	18 (34.0)
	p-value from Fisher's Exact Test.	0.393	
Descriptive statistics and estimate variability Secondary endpoint:	Treatment group	CIS alone	CIS + STS

Complete Tumor Resection	Partial hepatectomy, n (%)	48 (92.3)	49 (92.5)
	Liver transplantation, n (%)	4 (7.7)	4 (7.5)
	P-value from Fisher's Exact Test.	>0.999	
Descriptive statistics and estimate variability Secondary endpoint: Remission Status as assessed by central reviewer	Treatment group	CIS alone	CIS + STS
	Complete remission, n(%)	44 (84.6)	49 (92.5)
	Not complete remission, n (%)	8 (15.4)	4 (7.5)
	P-value from Fisher's Exact Test.	0.236	
Descriptive statistics and estimate variability Secondary endpoint: EFS	Treatment group	CIS alone	CIS + STS
	Number of patients censored, n (%)	41 (78.8)	42 (79.2)
	Number of patients with event, n (%)	11 (21.2)	11 (20.8)
	Hazard ratio (95% CI)	0.96 (0.42, 2.23)	
	P-value (log-rank)	0.932	
	Hazard ratio (95% CI) based on Cox proportional hazards model	1.07 (0.46, 2.51)	

Secondary endpoint: OS	Number of patients who died, n (%)	4 (7.7)	2 (3.8)
	Number of patients censored, n (%)	48 (92.3)	51 (96.2)
	Hazard ratio (95% CI)	0.48 (0.09, 2.61)	
	P-value (log-rank)	0.384	
Analysis population and time point description	mITT population		
Descriptive statistics and estimate variability Sensitivity analysis for primary endpoint	Treatment group	CIS Alone	CIS +STS
	Number of subject	46	55
	Hearing loss: Yes, n(%)	29 (63.0)	18 (32.7)
	Hearing loss: No, n(%)	17 (37.0)	37 (67.3)
	Relative Risk (95% CI) from Chi-square test.	0.519 (0.335, 0.805)	
	P-value from Chi-square test.	0.002	
	Relative Risk (95% CI) from CMH test stratified by country group, PRETEXT group, and age group.	0.516 (0.339, 0.787)	
	P-value from CMH test stratified by country group, PRETEXT group, and age group.	0.002	

Table 27. Summary of Efficacy for Trial COG ACCL0431

Study		Treatment Arm	Enrolled/Completed (Efficacy)
COG ACCL0431		CIS+STS	49/49 *
		Observation	55/55 *
Primary Endpoint (Efficacy Population)			
Proportion of Children with Hearing Impairment		**Observation**	**CIS+STS**
	Yes, n (%)	31 (56.4)	14 (28.6)
	No, n (%)	24 (43.6)	35 (71.4)
	Relative Risk (95% CI); p-value	--	0.274 (0.114, 0.660); p=0.0039

Secondary Endpoints												
Change in Hearing Thresholds from Baseline in dB (Efficacy Population)								**EFS (ITT Population)**		**OS (ITT Population)**		
Reviewer 1				**Reviewer 2**				**Patients with Events**				
Left Ear		Right Ear		Left Ear		Right Ear		CIS+STS n (%)	27 (44.3)	CIS+STS n (%)	18 (29.5)	
4000 Hz LS mean (SE)				4000 Hz LS mean (SE)				Observation n (%)	25 (39.1)	Observation n (%)	12 (18.8)	
CIS+STS	3.5 (4.38)	CIS+STS	4.1 (4.70)	CIS+STS	3.2 (4.37)	CIS+STS	4.0 (4.71)	**Patients Censored**				
Obsv.	10.7 (3.98)	Obsv.	11.2 (4.24)	Obsv.	11.2 (3.95)	Obsv.	11.2 (4.24)	CIS+STS n (%)	34 (55.7)	CIS+STS n (%)	43 (70.5)	
p=0.0395		p=0.0625		p=0.0221		p=0.0553		Observation n (%)	39 (60.9)	Observation n (%)	52 (81.3)	

Change in Hearing Thresholds from Baseline in dB (Efficacy Population)								**EFS (ITT Population)**	**OS (ITT Population)**
Reviewer 1				**Reviewer 2**				**Patients Censored**	
Left Ear		Right Ear		Left Ear		Right Ear			
8000 Hz LS mean (SE)				8000 Hz LS mean (SE)				p=0.3964	p=0.1132
CIS+STS	22.1 (4.18)	CIS+STS	23.0 (4.34)	CIS+STS	22.5 (4.17)	CIS+STS	23.2 (4.35)		
Obsv.	31.4 (3.87)	Obsv.	31.4 (4.05)	Obsv.	31.2 (3.85)	Obsv.	31.6 (4.06)		
p=0.0363		p=0.0662		p=0.0488		p=0.0707			

Abbreviations: CI=confidence interval; CIS=cisplatin; COG=Children's Oncology Group; CSR=clinical study report; EFS=event free survival; ITT=Intent-to-treat; LS=least squares; Obsv.=Observation; OS=overall survival; SE=standard error.
* Study completion was defined as completion of the Post-Treatment Hearing Assessment.

2.5.5.3. Clinical studies in special populations

Not applicable

2.5.5.4. In vitro biomarker test for patient selection for efficacy

Not applicable

2.5.5.5. Analysis performed across trials (pooled analyses and meta-analysis)

The OS, EFS and ORR data from the SIOPEL 6 and COG ACCL0431 studies were integrated and pooled analyses were performed using the ITT population from these trials.

Kaplan-Meier estimates for OS/EFS were presented by treatment group together with a summary of associated statistics including the 25th centile, median, and 75th centile survival time with two-sided

95% CIs, and the survival rate at 1, 2, 3, 4 and 5 years with corresponding two-sided 95% CIs. The between treatment comparisons were performed using the un-stratified log rank test.

The hazard ratios with corresponding two-sided 95% CIs between treatment groups were estimated using a Cox's Proportional Hazard model.

ORR was defined as the proportion of subjects having reached a best response of partial response (PR) or complete response (CR) according to investigator assigned response. Subjects with at least one response assessment were included in the analyses. The ORR by treatment group and the between group difference were calculated along with the Wald two- sided 95% CIs. In addition, the number and percentage of subjects with best response of CR, PR, stable disease (SD), progressive disease (PD) were also tabulated.

Subgroup analyses

The above-mentioned analyses were repeated for the following main subgroups:

1. Excluding subjects with Diagnosis of Other Tumour

2. Localised Disease

3. Localised Disease and Excluding subjects with Diagnosis of Other Tumour

4. Combinations of the above in the <5 years age group

Rationale for exclusion of subjects with Diagnosis of 'Other' Tumour

The pooled analysis consists of 5 principal paediatric tumour types: hepatoblastoma, germ cell tumour, medulloblastoma, neuroblastoma and osteosarcoma. The COG ACCL0431 study also included five patients with a disparate range of 'Other' tumours: one localised anaplastic astrocytoma (age 1.8y, CIS arm), one localised choroid plexus carcinoma (age 1.3y, CIS arm), one disseminated carcinoma NOS (age 14.2y, STS arm), and two localised ATRTs (age 1.7y and 1.1y, both in STS arm).

In the literature such patients are reported to have disparate survival rates:

- Localised choroid plexus carcinoma: 5-year survival 40-86% (Eppinger et al, 2016; Berger et al, 1998)
- Localised anaplastic astrocytoma: 5-year survival 27% (Cancer.net astrocytoma 2019)
- Disseminated carcinoma NOS: Median OS 6.7-15.4 months (Raghav et al, 2016)
- Localised atypical teratoid/rhabdoid tumour: for children under 3y, 4-year survival 26-52% (Reddy et al, 2020)

As these 5 patients are atypical of the overall pooled analysis group and have no matched control in the other treatment arm, it seemed appropriate to show results with and without these tumour types included.

Number of patients included in this analysis by treatment arm and for all subgroups analysed are summarised in **Table 28**.

Table 28. Pooled COG and SIOPEL– ITT Population and Dubgroups

	Siopel 6	COG	Total (n/%)
ITT Population	N= 109 - 57 (STS)	N= 125 - 61 (STS)	N= **234** - 118 (STS)

	- 52 (CIS)	- 64 (CIS)	- 116 (CIS)
Localised Disease	N=109 - 57 (STS) - 52 (CIS)	N=77 - 39 (STS) - 38 (CIS)	N=**186 (79.5%)** - 96 (STS) - 90 (CIS)
Age<5 Years	N=105 - 56 (STS) - 49 (CIS)	N=44 - 22 (STS) - 22 (CIS)	N= **149 (63.7%)** - 78 (STS) - 71 (CIS)
Localised Disease and Age<5 Years	N= 105 - 56 (STS) - 49 (CIS)	N=35 - 17 (STS) - 18 (CIS)	N=**140 (59.8%)** - 73 (STS) - 67 (CIS)
Localised Disease and Age≥5 Years	N= 4 - 1 (STS) - 3 (CIS)	N=42 - 22 (STS) - 20 (CIS)	N=**46 (19.7%)** - 23 (STS) - 23 (CIS)

Overall and event-free survival

A summary of the data from the pooled analysis for overall and event-free survival are presented in **Table 29** and **Table 30** including the subgroups: excluding 'Other' tumours (n=5), localised disease only, and localised disease excluding 'Other' tumours.

Table 29. Overall Survival Pooled COG and SIOPEL Analysis, ITT Population, All Subgroups

Analysis Group	Analysis Parameter	Observation	STS
Overall Survival (OS) (Table 1.1)	n	116	118
	Subjects with event n (%)	16 (13.8)	20 (16.9)
	Subjects censored n (%)	100 (86.2)	98 (83.1)
	Treatment comparison		
	Hazards Ratio	1.29	
	95% CI	(0.67, 2.53)	
	log-rank p-value	0.4464	
OS (excluding Diagnosis of 'Other' tumor) (Table 1.2)	n	114	115
	Subjects with event n (%)	16 (14.0)	17 (14.8)
	Subjects censored n (%)	98 (86.0)	98 (85.2)
	Treatment comparison		
	Hazards Ratio	1.08	
	95% CI	(0.55, 2.17)	
	log-rank p-value	0.8172	
OS - localized disease only (Table 1.3)	n	90	96
	Subjects with event n (%)	10 (11.1)	9 (9.4)
	Subjects censored n (%)	80 (88.9)	87 (90.6)
	Treatment comparison		
	Hazards Ratio	0.86	
	95% CI	(0.34, 2.13)	
	log-rank p-value	0.7364	
OS excluding 'Other' tumor - localized disease only (Table 1.4)	n	88	94
	Subjects with event n (%)	10 (11.4)	7 (7.4)
	Subjects censored n (%)	78 (88.6)	87 (92.6)
	Treatment comparison		
	Hazards Ratio	0.66	
	95% CI	(0.24, 1.71)	
	log-rank p-value	0.3872	

Table 30. Event-Free Survival, Pooled COG and SIOPEL Analysis, ITT Population, All Subgroups

Analysis Group	Analysis Parameter	Observation	STS
Event-free survival (EFS) (Table 2.1)	n	116	118
	Subjects with event n (%)	36 (31.0)	38 (32.2)
	Subjects censored n (%)	80 (69.0)	80 (67.8)
	Treatment comparison		
	Hazards Ratio	1.07	
	95% CI	(0.68, 1.70)	
	log-rank p-value	0.7666	
EFS (excluding Diagnosis of 'Other' tumor) (Table 2.2)	n	114	115
	Subjects with event n (%)	35 (30.7)	35 (30.4)
	Subjects censored n (%)	79 (69.3)	80 (69.6)
	Treatment comparison		
	Hazards Ratio	1.01	
	95% CI	(0.63, 1.62)	
	log-rank p-value	0.9534	
EFS - localized disease only (Table 2.3)	n	90	96
	Subjects with event n (%)	25 (27.8)	25 (26.0)
	Subjects censored n (%)	65 (72.2)	71 (74.0)
	Treatment comparison		
	Hazards Ratio	0.94	
	95% CI	(0.54, 1.65)	
	log-rank p-value	0.8322	
EFS excluding 'Other' tumor - localized disease only (Table 2.4)	n	88	94
	Subjects with event n (%)	24 (27.3)	23 (24.5)
	Subjects censored n (%)	64 (72.7)	71 (75.5)
	Treatment comparison		
	Hazards Ratio	0.90	
	95% CI	(0.50, 1.59)	
	log-rank p-value	0.7049	

Best Overall Response to Chemotherapy - pooled analysis, ITT population and localised disease subgroup

The ORR (95% CI) for the STS-treated patients was 91.5% (86.2%, 96.8%) compared with 86.5%% (80.1%, 92.8%) for the observation arm patients. The difference between the groups was 5.0% (-3.3%, 13.3%). For localised disease, the ORR was 93.4% (88.3%, 98.5%) for the STS-treated compared with 88.8%% (82.2%, 95.3%) for the observation arm patients and the difference between groups was 4.6% (-3.7%, 13.0%).

2.5.6. Discussion on clinical efficacy

To support the claimed indication, the applicant presented two datasets (one for localised tumour type SR-HB and one for various tumour types obtained from two phase III studies in paediatric populations). Both studies were designed and conducted by academic consortia for the purposes of establishing clinical practice guidelines for prevention of CIS-induced ototoxicity. Although the applicant did not sponsor these studies, it provided study medication and obtained rights to the data. Study results summarised in this marketing application represent the analyses conducted by the applicant.

Design and conduct of clinical studies

SIOPEL 6 was an open-label multicentre, randomised, controlled, Phase 3 study to assess the efficacy of STS in reducing ototoxicity in patients receiving CIS chemotherapy for standard risk hepatoblastoma

(SR-HB). A total of 114 patients were enrolled (109 treated and 101 were eligible for assessment of the primary endpoint).

Patients were randomised 1:1 to receive the dose of STS which is weight based and normalised to body surface area and administered for the prevention of CIS-induced ototoxicity, using the permuted block method, including Country, Median age (above vs below 15 months), PRETEXT (I and II vs III) as stratification factors.

The primary objective of SIOPEL 6 study was to assess the efficacy of STS to reduce the hearing impairment caused by cisplatin chemotherapy.

The primary endpoint for this study was any hearing loss defined as Brock grade 1 through 4 (centrally reviewed by blinded reviewers) at the end of treatment or at an age of ≥3.5 years, whichever was later. This primary endpoint is considered a highly clinically relevant endpoint in this setting.

The multiple secondary endpoints are endorsed, especially those regarding efficacy of cisplatin chemotherapy (OS, EFS) between the two arms, which are considered a highly clinically relevant endpoints in this setting.

The inclusion and exclusion criteria in SIOPEL 6 define a homogeneous patient population (children with a localised tumour type (standard risk hepatoblastoma)) considering the indication targeted by the PIP, i.e., prevention of platinum- induced ototoxic hearing loss for standard risk hepatoblastoma, and these criteria are acceptable. SR-HB is clearly defined childhood cancer- involving at the most three hepatic sectors (PRETEXT I-III) and alpha- fetoprotein (AFP)>100 ng/mL and treated with less toxic cisplatin monotherapy.

A total of 23 children (21.1%) had a total of 24 deviations protocol deviations during the study, all of whom had deviations in treatment compliance. Treatment compliance deviations could be expected for this type of protocol.

ACCL0431 was an open-label multicentre, randomised, controlled, Phase 3 study to assess the efficacy of STS in reducing ototoxicity in children receiving CIS chemotherapy (planned cumulative dose ≥ 200 mg/m²) for the treatment of newly diagnosed, different types of childhood cancers (hepatoblastoma, germ cell tumour, osteosarcoma, medulloblastoma, or other malignancy at any stage. A total of 125 patients were enrolled (125 treated and 104 were eligible for assessment of the primary endpoint).

Patients were randomised 1:1 to receive the dose of STS 16 g/m2 STS (or 533 mg/kg when CIS was dosed on a per-kg basis) 6 hours after the completion of a CIS infusion for the prevention of CIS-induced ototoxicity, using the permuted block method, including prior cranial irradiation (yes versus no; all prior cranial irradiation patients were in the same stratum), age (< 5 versus ≥ 5 years), and duration of CIS infusion (< 2 versus ≥ 2 hours) as stratification factors.

The primary endpoint was the proportional incidence of hearing loss between the CIS+STS arm and the Observation arm. Hearing loss was defined by comparing hearing sensitivity at the Follow-up evaluation (4 weeks following the last dose of CIS) relative to baseline measurements using American Speech-Language-Hearing Association (ASHA) criteria. The choice of the ASHA scale, to assess changes from the baseline, is not the most appropriate as it can be unreliable in young children.

The multiple secondary endpoints are endorsed, especially those regarding efficacy of cisplatin chemotherapy (OS, EFS), which are considered a highly clinically relevant endpoints in this setting.

The inclusion criteria in COG AACL0431 defines a heterogeneous patient population with localised and disseminated tumours that relate to a broader population (localised pooled with disseminated disease) than that which is the subject of the MAA application (localised, non-metastatic disease).

Protocol deviations were not defined in the protocol or recorded by the individual COG sites and therefore were not summarised in the clinical study report.

Efficacy data and additional analyses

SIOPEL 6

The pivotal study met its primary endpoint of the efficacy of STS as an oto-protectant i.e. the proportion of children with hearing loss at age ≥ 3.5 years in STS arm vs. observation group was 35.1% (n=20) vs. 67.3% (n=35) respectively (difference 32.2%, p<0.001). The odds ratio and 95% CI was 0.52 % (0.349, 0.778).

With a follow up of 4.27 years, EFS in observation group was 78.8. % and in STS arm was 79.2% (hazard ratio: 0.96; 95% CI: 0.42, 2.23; p=0.932); OS in observation group was 92.3% and in STS arm was 96.2% (hazard ratio: 0.48; 95% CI: 0.09, 2.61; p=0.384).

Response rates to preoperative chemotherapy were lower in CIS +STS group: non- responders after 4 cycles were higher in CIS-STS (18 children); the proportion of children with stable disease (no tumour volume change and no increase in AFP) after cycles 1 and 2 were 32 children in the CIS+STS arm and 24 children in the CIS alone arm; after cycles 3 and 4 CIS+STS arm had more children with stable disease (10 children) compared with the CIS alone arm (5 children). Results after 1 and 2 cycles were not intended to estimate the extent of response but rather to detect patients with an early progression. After 4 cycles, the proportion of responders to preoperative chemotherapy (using the pre-specified SIOPEL 6 criteria) was not statistically significantly different between the CIS+STS arm (35 children [66.0%]) and the CIS alone arm (39 children [75.0%]) (p=0.393). Same number, 5 patients in the CIS alone arm and 5 patients in the CIS+STS arm, had progressive disease after 3/4 cycles, suggesting an equal amount of lack of efficacy in the 2 arms. The data from SIOPEL 6, suggest that STS in children receiving cisplatin for SR-HB, does not compromise the anti-tumour efficacy of the chemotherapy or adversely impact oncological outcomes. However, it needs to be noted that sample size of the trial is relatively small and provided confidence intervals for EFS and OS estimates are rather wide.

In the final analysis, SIOPEL 6 included 114 randomised patients, of which 109 patients were evaluable, aged between >1 month and < 9 years old, with histologically confirmed SR-HB. The median age for children in the SIOPEL 6 study was 13.0 months and the mean weight was 10.24 kg. The population studied does not cover the entire population (patients from 1 month to < 18 years of age) indicated in the proposed indication, i.e., there no data on paediatric population from 98.6 months to 18 years of age due to the rarity of HB in this age group (the age of disease onset lies in infancy or early childhood (median age of occurrence is 1 year and 90% of HB presents before 5 years) (Orphanet)). Therefore, there is no known clinical benefit of STS in this age group from SIOPEL 6 study. COG ACCL0431 study provides STS data in other tumour types treated with platinum chemotherapy in an older paediatric population than that of the SIOPEL 6 study data (see below).

Demographic characteristics varied slightly across the treatment groups, most notably in terms of baseline PRETEXT classification, with only the CIS+STS arm including children with PRETEXT I classification (11 patients [19.3%]) and fewer patients in the CIS+STS arm with PRETEXT III classification than the CIS Alone arm (28.1% vs 40.4%, respectively). Imbalance was also noted in terms the median AFP level at diagnosis, with children in the CIS+STS arm having an approximately 3-fold higher median AFP level (181500.00 ng/mL) compared with the CIS alone arm (66031.50 ng/mL).

Despite these imbalances which could have suggested differential prognosis for the two treatment arms, this was not observed in terms of EFS and OS. Furthermore, similar numbers of children in each

arm had a complete surgical resection and an equal number of children in both arms required a liver transplant to achieve complete resection showing that surgical outcomes were equivalent between the groups.

Response to pre-operative chemotherapy was lower in the CIS+STS arm using the strict SIOPEL 6 response criteria, which required a 1 log fall in AFP to reach the criteria of partial response (PR). However, the response rates according to traditional SIOPEL criteria were equal in both arms and can be considered the true reflection of response, with the development of PD being equal in both arms. The additional sensitivity analyses clearly show that non-completion did not in any way alter the conclusions of the ITT analysis. It can be concluded that asymmetry between treatment arms did not alter the conclusions of the study results.

ACCL0431

In the overall population, the study met its primary endpoint of the efficacy of STS as an otoprotectant. In the ITT population (n=125) was 42.6% (n=26) versus 62.5%. (n=40) respectively (difference 19.9%, p=0.0234). The odds ratio and 95% CI was 0.41 (0.19, 0.88).

The youngest patients (children < 5 years of age) represent ~28% (29/104) of the efficacy population of the COG ACCL0431 study. At study entry, 75.8% (22/29) of patient had localised tumour versus 24.2% (7/29) with a disseminated disease. The median age of this group was 2.1 years (range 1.0-4.9 years) and the most common disease diagnoses were: medulloblastoma (n=13; 41.9%), neuroblastoma (n=7; 22.6%) and a total of 5 patients (16.1%) had hepatoblastoma.

Children ≥ 5 years represent 72% (75/104) of the efficacy population of the COG ACCL0431 study. At study entry, 56% (42/75) of patient had localised tumour versus 44% (33/75) with a disseminated disease. Median age was and the most common disease diagnoses were: GCT (n=17; 37%), osteosarcoma (n= 19; 41.3%), medulloblastoma (n=8; 17.4%), and neuroblastoma (n=8; 17.4%); 1 patient (2.2%) had hepatoblastoma.

The group of children less than 5 years of age is likely to derive the most benefit of STS on hearing loss induced by platinum: The proportion of children with hearing loss was 73.3% (95% CI 44.9, 92.2) in the control group vs. 21.4% (95% CI 4.7, 50.8) in the STS group. In this age group, the prevention of hearing loss by STS was similar in SIOPEL 6 and COG ACCL0431 and confirm that the action of STS is independent of tumour type.

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, there is no plausible clinical reason why STS would not reduce hearing loss in this older group of patients with localised disease.

In the COG ACCL0431 EFS and OS was monitored as secondary endpoints. At the median 5.33-year follow-up, 27 children (44.3%) in the CIS+STS arm and 25 children (39.1%) in the observation arm experienced an event during this study. Overall, at the median 5.33-year follow-up, a total of 18 children (29.5%) in the CIS+STS arm and 12 children (18.8%) in the Observation arm died during this study. These data demonstrate possible tumour protection and potential reduced OS in both treatment arms (18 death in the STS arm and 12 deaths in the Observational arm).

A clear effect of STS on EFS or OS was not observed in the patients categorised post hoc as having localised disease. In children categorised with localised disease, the response in COG ACCL0431 is similar between the arms, with CR/PR being the last recorded response to chemotherapy in 65.8% and 69.2% of Observation and CIS+STS arms, respectively. At the median 5.61 year follow up EFS was 63% STS group and 64% in control group (HR 0.98 95% CI 0.46-2.06) and OS 82% STS and 84% control (HR 0.81 95% CI 0,26-2.45). Differences in OS and EFS are observed in disseminated disease

subgroup with lower trend in the STS + CIS arm - EFS: HR 1.92 (95% CI 0.85-4.31) and OS: HR 2.96 (95% CI 1.08-8.06) (median 4.52 year follow -up).

A recent publication by Orgel et al (2022) presented updated OS data from the COG ACCL0431 study with a median follow up of 7.8 years. OS data in the solid tumour group remained stable – STS group 80% vs control group 84%, p = 0.67 while data from disseminated disease group still showed a detrimental effect: HR 2.74, 95% CI 1.01–7.44, p=0.040.

The applicant argues that the lower survival in patients categorised as having disseminated disease in COG ACCL0431 study was most likely due to an imbalance in tumour types and prognostic indicators present at randomisation rather than to the use of STS. To further support this suggestion that a disbalance in the prognostics factors has impacted the EFS and OS results in the disseminated disease group the applicant was asked to provide Cox regression analysis for the COG study with the treatment and prognostics factors as co-variates. However, due to limited data collected during the study, the applicant was unable to provide such analysis. Although the analysis could provide some assurance it is also noted that with the small sample size and heterogeneity in the data, including risk factors for developing cisplatin induced hearing loss (CIHL) include younger age (< 5 years) and higher cumulative cisplatin dose (> 200–400 mg/m2), as well as cranial irradiation involving the cochlea (Li et al, 2004, Freyer et al, 2017) this uncertainty would not be fully resolved.

Pooled analysis

The applicant provided pooled analyses of OS, EFS and ORR from SIOPEL 6 and COG ACCL043.

Results from the pooled analysis indicate that there are no significant differences in OS, EFS and ORR between cisplatin and cisplatin and STS groups in the target population.

Hazard ratios for an effect on OS across the groups range were 0.62 (0.18, 1.96) up to 1.29 (0.67, 2.53. Log-rank p values are not statistically different in any analysis group. Furthermore, in localised disease only (the indication requested by the applicant), the HR was 0.86 (0.34, 2.13), p=0.7364.

The hazard ratios for an effect on event-free survival across the groups range from 0.74 (0.38, 1.44) up to 1.07 (0.68, 1.70) and did not reach statistical significance in any of the groups. In localised disease only the HR was 0.94 (0.54, 1.65), p=0.8322.

For ORR 65.1% of STS-treated patients had a CR compared with 62.2% of Observation arm patients, with the PR responses being 26.4% and 24.3% respectively. The difference (95% CI) between the groups was 5.0% (-3.3%, 13.3%). For localised disease, the difference between groups was 4.6% (-3.7%, 13.0%).

While it is acknowledged that even with the pooled data the sample size remains small, this analysis provided further re-assurance that STS treatment does not interfere significantly with cisplatin treatment. Of note, the cisplatin renal and haematological toxicity observed was similar between the treatment arms in both studies (See Clinical Safety section of this report). This lends support to the notion that STS preferentially targets the auditory system. If STS 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.

As some uncertainty on the potential interaction between STS and cisplatin remains the CHMP considered whether a post-authorisation study could be conducted to address this. It was however concluded that the required study would not be feasible given the nature of the issue and the claimed indication which encompasses a broad range of tumour types.

Additional expert consultation

The Scientific Advisory Group in Oncology (SAG-O) was requested to provide their view on the following question:

While the mechanism of action of sodium thiosulfate is not fully understood, efficacy data show that this has an otoprotective effect when administered in the context of cisplatin therapy. The applicant claims that administering STS 6 hours after the completion of each CIS infusion should ensure a lack of a tumour protective effect. However, the clinical trials SIOPEN 6 and COG ACCL0431 are relatively small. Consequently, the precision of the estimates for ORR, EFS and OS in the studied population is low with wide confidence intervals.

The SAG is asked to provide its considerations on the risk that sodium thiosulfate might decrease the efficacy of cisplatin.

Response from the SAG

The experts acknowledged that cisplatin-induced ototoxicity in children is an important clinical issue for which there is need for efficacious treatments.

Available clinical data from studies SIOPEL and COG ACCL0431 have clearly demonstrated a positive effect of sodium thiosulfate (STS) on the prevention on hearing loss. The SAG noted the lack of data on tinnitus and vertigo which are important component of cisplatin-induced ototoxicity, acknowledging however that such data would have been difficult to collect in the mostly young paediatric population of the two trials.

The experts noted 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, especially as the timing of administration of STS in relation to cisplatin treatment is intended to reduce the possibility of inhibition of the cytotoxic effects of cisplatin.

The presented studies are based on a small number of patients with a rather broad range of clinical parameters as response, EFS and OS, which does not allow to draw definitive conclusions. The SAG noted that from the clinical data presented a negative effect of STS on the efficacy of cisplatin cannot be excluded in localised diseases, and that there is an uncertainty on the exact magnitude of this potential risk.

In the SIOPEL6 trial, which included a more homogeneous population with localised hepatoblastomas only, there was no negative signal observed in the clinical endpoints. In the COG ACCL0431 study, which included various tumour entities overall there was a slight detrimental effect observed in the STS arm. In the post-hoc analysis, which could be to some extent biased, there was no remarkable difference between both arms in the patients with localised tumours but a relevant worse outcome in the disseminated diseases. A potential explanation for this signal may be the imbalances in tumour types and prognostic indicators for disease progression in the COG ACCL0431 study as suggested by the applicant, but a detrimental effect of STS itself cannot be excluded in the disseminated diseases. No further investigations such as regression analyses have been done to evaluate the relevant parameters in worsening the clinical outcome.

Considering the uncertainties over this signal, the SAG considered this to be of limited clinical importance in localised tumours only, in relation to the observed benefits on hearing loss. In addition, the negative signal was based predominantly in patients with disseminated disease, which provides further re-assurance as the intended use of the product is only for localised, non-metastatic, solid tumours. For that population the advantage in preventing hearing loss outweighs the possible small risk of reduced efficacy of cisplatin following STS administration.

The SAG considered that whilst difficult, it would be important to collect further data in the post-authorisation setting, not only on the potential reduced efficacy of cisplatin with STS, but also on the incidence of neurotoxicity, side effects, more longitudinal data on hearing loss and its prevention and secondary malignancies.

2.5.7. Conclusions on the clinical efficacy

The review of the submitted clinical data supports the use of STS to prevent CIS-induced ototoxicity in patients with localised solid tumours. From the reported results STS seems to be more effective in the younger population who is also the one most vulnerable to the effects of hearing loss on their language development and future communication. The potential of sodium thiosulfate to decrease the efficacy of cisplatin cannot be completely ruled out, due to the small sample size of the clinical trials. Available data however suggest that such an effect would be of minimal clinical importance in the intended target population.

2.5.8. Clinical safety

2.5.8.1. Patient exposure

The safety database includes 112 subjects from two clinical studies exposed to STS.

Patients in the SIOPEL 6 study received a mean cumulative dose of 85.149 g/m^2 (**Table 31**). The median total duration of therapy (including PLADO courses) was similar between the CIS+STS arm (94.0 days [range: 63 to 158 days]) and the CIS Alone arm (94.5 days [range: 54 to 181 days]). The median duration of therapy prior to surgery was also similar between the CIS+STS arm (44.0 days [range: 15 to 88 days]) and the CIS Alone arm (43.0 days [range: 14 to 58 days]).

Table 31. **Summary of Cumulative Dosing in SIOPEL 6 including PLADO (Safety Population)**

Parameter/Statistic	**CIS Alone N=56**	**CIS+STS N=53**
Number of cycles		
n	56	53
Mean (SD)	5.8 (1.0)	5.9 (0.6)
Median (min, max)	6.0 (2, 10)	6.0 (4, 8)
CIS calculated dose (mg/m2)		
n	56	53
Mean (SD)	373.716 (104.246)	372.241 (99.459)
Median (min, max)	344.908 (107.51, 626.47)	334.236 (166.34, 617.64)
CIS actual dose (mg/m2)		
n	56	53
Mean (SD)	362.851 (98.871)	363.860 (96.607)
Median (min, max)	324.712 (105.51, 623.20)	317.833 (121.25, 594.43)
STS calculated dose (g/m2)		
n	53	
Mean (SD)	94.381 (20.882)	
Median (min, max)	90.000 (30.00, 120.69)	
STS actual dose (g/m2)		
n	53	
Mean (SD)	85.149 (24.390)	
Median (min, max)	83.284 (26.38, 121.30)	

Abbreviations: CIS=cisplatin; max=maximum; min=minimum; CSR=clinical study report; NA=not applicable; PLADO=cisplatin (=platinol) and doxorubicin; SD=standard deviation; STS=sodium thiosulfate.

In study COG ACCL0431 the mean cumulative dose of STS was 108.23 g/m^2 (**Table 32**). Across all reporting periods, children in the CIS+STS and Observation arms received mean cumulative CIS doses of 337.57 and 391.47 mg/m^2, respectively. Differences were observed in the mean number of CIS cycles received in each treatment arm (3.1 and 3.8 in the CIS+STS and Observation arms, respectively) as well as the mean number of days (7.6 and 9.0 in the CIS+STS and Observation arms, respectively).

Variability in the CIS dosing regimens was observed across the diagnosed tumour types. This variability 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.

Therefore, an imbalance in tumour types and/or prognostic factors could explain the difference between the arms in terms of cumulative CIS dose.

Table 32. Summary of Cumulative STS Dose (g/m^2) for All Patients in COG ACCL0431 ((Safety Population)

Statistic	**CIS+STS (N=59)**
All patients, n	59
Number of CIS cycles	
Mean (SD)	3.1 (1.4)
Median (Min, max)	3.0 (1, 6)
Total number of days STS administered	
Mean (SD)	7.3 (5.0)
Median (Min, max)	7.0 (1, 24)
Cumulative STS dose (g/m2)	
Mean (SD)	108.23 (80.24)
Median (min, max)	95.26 (13.21, 370.14)
Abbreviations: BSA=body surface area; CIS=cisplatin; CSR=clinical study report; max=maximum; min=minimum; SD=standard deviation; STS=sodium thiosulfate. Note: Cumulative STS dose for each patient is the sum of doses taken divided by the BSA ($0.007184 \times height^{0.725} \times weight^{0.425}$).	

Patients were analysed by weight group (<5kg, 5 to 10kg, >10kg). Differences of cumulative dose of cisplatin were observed between studies as well as between arms. In SIOPEL 6, mean cumulative CIS 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 CIS +STS arm compared to CIS arm (464.716 mg/m^2 vs 437.619 mg/m^2, respectively). In COG ACCL0431 study, mean cumulative CIS dose was higher in observation arm compared to CIS + STS arms (391 vs 337 mg/m² respectively) due to various tumours treated.

Number of patients was similar between the body weight subgroups in both studies. Of note, all patients enrolled in both studies were < 12 years of age.

In SIOPEL 6, STS dose reductions were made prior to treatment initiation and thus not due to SAE and were limited considering similar calculated and actual cumulative doses.

Follow-up phases were conducted in both studies according to the applicant, a 5-year-period in SIOPEL 6 and a 10-year-period in COG ACCL0431.

2.5.8.2. Adverse events

SIOPEL 6

Adverse events were recorded during and up to 30 days after chemotherapy during the Treatment Phase; SAEs were recorded during the Treatment Phase and Follow-up. An overview of AEs during both the Treatment and Follow-up Phases is provided in **Table 33**.

Table 33. **Overview of Adverse Events During Both Treatment and Follow-up Phases in SIOPEL 6 (Safety Population)**

Parameter	CIS Alone (N=56) n (%)	CIS+STS (N=53) n (%)	Total (N=109) n (%)
Patients with AEs	49 (87.5)	51 (96.2)	100 (91.7)
Patients with SAEs (including those leading to death)	19a (33.9)	21 (39.6)	40 (36.7)
Patients who required a dose alteration due to SAE	0	0	0
Patients who discontinued due to SAE	0	1 (1.9)	1 (0.9)
Patients with SAE resulting in death	1 (1.8)	0	1 (0.9)
Abbreviations: AE=adverse event; CIS=cisplatin; CSR=clinical study report; SAE=serious adverse event; STS=sodium thiosulfate. a One SAE in the CIS Alone arm occurred during Follow-up. Note: Information on dose alteration and discontinuation was only collected in conjunction with SAEs; the corresponding information on AEs was not collected.			

In both arms, AEs were most common in the SOCs of Gastrointestinal disorders, Investigations, and Metabolism and nutrition disorders. When comparing incidences between arms within the most common SOCs, children in the CIS+STS arm had a higher incidence of AEs compared with those in the CIS Alone arm: Gastrointestinal disorders (47 patients [88.7%] vs 33 patients [58.9%], respectively), Investigations (33 patients [62.3%] vs 29 patients [51.8%], respectively), and Metabolism and nutrition disorders (30 patients [56.6%] vs 21 patients [37.5%], respectively).

The 3 most frequently reported AEs by PT during the Treatment Phase were the same in both arms. In the CIS+STS arm compared with the CIS Alone arm, vomiting (45 patients [84.9%] vs 30 patients [53.6%], respectively) and nausea (21 patients [39.6%] vs 17 patients [30.4%], respectively) occurred at a higher incidence. Infection (22 patients [41.5%] vs 20 patients [35.7%]) occurred at a similar incidence in the CIS+STS arm and the CIS Alone arm, respectively.

The incidence of hypernatremia AEs was higher in the CIS+STS arm compared with the CIS Alone arm (14 patients [26.4%] vs 2 patients [3.6%], respectively).

Generally, the incidences of other most common AEs by PT were similar between the CIS+STS and the CIS Alone arms.

A total of 35 patients (66.0%) in the CIS+STS arm and 34 patients (60.7%) reported AEs with maximum severities of CTCAE Grade 3 or higher. In both arms, Grade 3 severity or higher AEs were most frequently reported in the SOCs of Investigations, Infections and infestations, and Blood and lymphatic system disorders.

The most frequently reported AEs by PT with maximum severity of CTCAE Grade 3 severity of higher were the same in both arms and occurred at similar incidences in the CIS+STS arm and the CIS Alone

arm: infection (14 patients [26.4%] and 15 patients [26.8%], respectively), neutrophil count decreased (12 patients [22.6%] and 9 patients [16.1%], respectively), and haemoglobin decreased (10 patients [18.9%] and 9 patients [16.1%], respectively), and febrile neutropenia (8 patients [15.1%] and 9 patients [16.1%], respectively).

Although the incidence of the most common AEs with a maximum severity of Grade 3 or higher were generally similar across the treatment arms, several AEs were reported more frequently in the CIS+STS arm than the CIS Alone arm that did not meet the 10% threshold. These included hypermagnesemia (5 patients [9.4%] vs 2 patients [3.6%], respectively), hypokalaemia (5 patients [9.4%] vs 0 patients, respectively), and hypophosphatemia (5 patients [9.4%] vs 0 patients, respectively), all of which occurred during the Treatment Phase.

During the Follow-up Phase, only SAEs were captured. No subjects in the CIS+STS arm experienced an SAE (fatal or non-fatal) during Follow-up. In the CIS Alone arm, 2 children (3.6%) experienced a non-fatal SAE of infection, 1 child (1.8%) experienced a non-fatal SAE of pain, and 1 child (1.8%) experienced a fatal SAE of death.

COG ACCL0431

An overview of AEs is presented in **Table 34**.

Table 34. Overview of Adverse Events in COG ACCL0431 (Safety Population)

Parameter	Observation (N=64) n (%)	CIS+STS (N=59) n (%)	Total (N=123) n (%)
Patients with at least 1 AE	57 (89.1)	55 (93.2)	112 (91.1)
Serious AEs a	ND	21 (35.6)	NA
Drug-related AEs b	NA	23 (39.0)	23 (39.0)
AEs graded CTCAE category 3 or higher	57 (89.1)	55 (93.2)	112 (91.1)
Deaths c	12 (18.8)	18 (30.5)	30 (24.4)
Abbreviations: AE=adverse event; CIS=cisplatin; CTCAE=Common Terminology Criteria for Adverse Events; NA=not applicable; ND=not defined; STS=sodium thiosulfate. a Serious AEs were reported only for the CIS+STS arm. B Drug-related included AEs that were considered Possible, Probable, or Definite in the case report form. c Eight patients were off Study ACCL0431 and subsequently died while enrolled into different COG studies.			

Adverse events during the reporting period were defined as those that occurred during the treatment cycle where children received the first through final doses of CIS+STS or CIS alone, excluding during the 4-week Follow-up Period.

The majority of children in both study arms experienced at least 1 AE during the reporting period (55 patients [93.2%] in the CIS+STS arm and 57 patients [89.1%] in the observation arm). In both arms, AEs were the most commonly reported in the SOCs of investigations, blood and lymphatic system disorders, metabolism and nutrition disorders, infections and infestations, and gastrointestinal disorders.

The 3 most frequently reported AEs by PT during the reporting period were the same in both arms and occurred at similar incidences in the CIS+STS arm and the Observation arm: neutrophil count decreased (49 patients [83.1%] vs. 51 patients [79.7%], respectively), white blood cell count decreased (38 patients [64.4%] vs. 42 patients [65.6%], respectively), and platelet count decreased (38 patients [64.4%] vs. 39 patients [60.9%], respectively).

The incidence of the most common AEs (frequency of ≥ 10% in either arm, by PT) were generally similar across the treatment arms; several AEs were reported more frequently in the CIS+STS arm than the Observation arm, including hypophosphatemia (12 patients [20.3%] vs 7 patients [10.9%]), hyponatremia (8 patients [13.6%] vs 4 patients [6.3%]), hypernatremia (7 patients [11.9%] vs 4 patients [6.3%]), and stomatitis (8 patients [13.6%] vs 4 patients [6.3%]).

The majority of AEs experienced by children during the reporting period were CTCAE Grade 3 or 4, and incidences of these events were similar between treatment arms (Grade 3: 51 patients [86.4%] and 54 patients [84.4%] of children in the CIS+STS and Observation arms, respectively, and Grade 4: 46 patients [78.0%] and 52 patients [81.3%], respectively). One child (1.7%), in the CIS+STS arm, experienced a CTCAE Grade 5 AE of death (cardiac arrest, which was considered unrelated to study medication by the Investigator. A summary of the most common AEs during the reporting period with severity of CTCAE Grade 3 or higher (frequency of ≥10% in either arm) in the Safety Population is presented in **Table 35**.

Table 35. Summary of Most Common AEs During the Reporting Period with Severity of CTCAE Grade 3 or Higher (Frequency of ⩾ 10% in Either Arm, by PT) in study COG ACCL0431 (Safety Population)

SOC **PT** a	**Observation (N=64) n (%)**	**CIS+STS (N=59) n (%)**	**Total (N=123) n (%)**
Any Grade 3 Severity b 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; CIS=cisplatin; CTCAE= Common terminology criteria for Adverse Events; MedDRA= Medical Dictionary for Regulatory Activities; PT=Preferred Term; SOC=system organ class; STS=sodium thiosulfate

[a] Based on MedDRA version 21.0

[b] Grading was based on CTCAE Version 4.0

During the Follow-up Period, 1 child (1.7%) in the CIS+STS arm experienced a Grade 3 AE of hypoacusis. In addition, 1 child (1.7%) in the CIS+STS arm and 1 child (1.6%) in the Observation arm each experienced a Grade 5 AE of death.

2.5.8.3. Serious adverse event/deaths/other significant events

SIOPEL 6

During the Treatment Phase, 21 children (39.6%) in the CIS+STS arm and 18 children (32.1%) in the CIS alone arm had non-fatal SAEs (**Table 36**).

Table 36. Most Common Non-fatal SAEs (Reported by ⩾ 2 Patients in Either Arm) During the Treatment Phase in SIOPEL 6 (Safety Population)

SOC PT	CIS Alone (N=56) n (%)	CIS+STS (N=53) n (%)	Total (N=109) n (%)
Patients with at least 1 SAE	18 (32.1)	21 (39.6)	39 (35.8)
Infections and infestations	5 (8.9)	7 (13.2)	12 (11.0)
Infection	5 (8.9)	7 (13.2)	12 (11.0)
Investigations	3 (5.4)	6 (11.3)	9 (8.3)
Neutrophil count decreased	1 (1.8)	6 (11.3)	7 (6.4)
General disorders and administration site conditions	3 (5.4)	5 (9.4)	8 (7.3)
Pyrexia	3 (5.4)	5 (9.4)	8 (7.3)
Injury, poisoning, and procedural complications	0	2 (3.8)	2 (1.8)
Procedural complication	0	2 (3.8)	2 (1.8)
Abbreviations: AE=adverse event; CIS=cisplatin; CSR=clinical study report; PT=preferred term; SAE=serious adverse event; SOC=system organ class; STS=sodium thiosulfate. Note: Most common SAEs are defined as ≥ 2 patients in either arm, rather than in the total column.			

Relatedness to STS (as determined by the Investigator) was captured for SAEs only. In the CIS+STS arm, 4 children (7.5%) overall experienced an SAE related to STS, as determined by the Investigator. . Two children (3.8%) experienced a drug-related AE of neutrophil count decreased, 1 child (1.9%) had a drug-related AE of infection, and 1 child (1.9%) had a drug-related AE of hypersensitivity.

In the CIS+STS arm 2 children died, both died due to tumour progression. In the CIS alone arm 4 children died: 2 children died due to tumour progression, 1 child due to surgical complications, and 1 child due to cardiac arrest. Of the 6 children who died, 5 had PRETEXT II disease.

Adverse events of special interest (AESIs) during the Treatment Phase are summarised for the Safety Population in. The overall number of patients experiencing AESIs was low and the incidence was similar between the arms.

Table 37. Summary of AESI Reported During the Treatment Phase in SIOPEL 6 (Safety Population)

SOC PT	CIS Alone (N=56) n (%)	CIS+STS (N=53) n (%)	Total (N=109) n (%)
Gastrointestinal disorders			
Vomiting	2 (3.6)	4 (7.5)	6 (5.5)
Nausea	3 (5.4)	2 (3.8)	5 (4.6)
Metabolism and nutrition disorders			
Hypomagnesemia	1 (1.8)	1 (1.9)	2 (1.8)
Hypernatremia	0	1 (1.9)	1 (0.9)
Abbreviations: AESI=adverse event of special interest; CIS=cisplatin; CSR=clinical study report; PT=preferred term; SOC=system organ class; STS=sodium thiosulfate. Note: Adverse events of special interest were defined as Grade 3 or higher vomiting, nausea, hypomagnesemia, or hypernatremia.			

COG ACCL0431

Serious AEs (fatal and non-fatal) were recorded only for patients in the CIS+STS arm (21 children [35.6%]). The most frequently reported SAEs at the PT level were febrile neutropenia (20.3%) and neutrophil count decreased (16.9%). A total of 6 children (10.2%) experienced SAEs that were considered related to STS; no individual PT was reported for more than 1 patient.

A total of 18 deaths (30.5%) occurred among children in the CIS+STS arm and 12 deaths (18.8%) occurred in the Observation arm. The majority of deaths were due to the child's underlying disease. No deaths in the CIS+STS arm were considered related to STS.

Adverse events of special interest during the Reporting Period are summarised for the Safety Population in. The incidences of AESIs were similar between the treatment arms. No Grade 3 severity or higher events of hypernatremia were reported.

Table 38. Summary of AESI Reported During the Reporting Period in COG ACCL0431 (Safety Population)

SOC PT	Observation (N=64) n (%)	CIS+STS (N=59) n (%)	Total (N=123) n (%)
Gastrointestinal disorders			
Vomiting	3 (4.7)	4 (6.8)	7 (5.7)
Nausea	3 (4.7)	5 (8.5)	8 (6.5)
Metabolism and nutrition disorders			
Hypomagnesemia	2 (3.1)	3 (5.1)	5 (4.1)
Abbreviations: AESI=adverse event of special interest; CIS=cisplatin; CSR=clinical study report; PT=preferred term; SOC=system organ class; STS=sodium thiosulfate. Note: Adverse events of special interest were defined as Grade 3 or higher vomiting, nausea, hypomagnesemia, or hypernatremia.			

Analysis of Adverse Events by Organ System

In the Cardiac disorders SOC in SIOPEL 6, 3 cases were reported including two in CIS+STS arm of arrhythmia and ventricular arrhythmia of Grade 1 in severity. In COG ACCL0431, one fatal case of cardiac arrest was reported 6 days after a cycle of CIS + doxorubicin +STS. Even if doxorubicin and cisplatin are known for cardiac toxicity, a causal role of STS-related hypokalaemia could not be excluded in this case.

In the Immune system disorders SOC, slightly more hypersensitivity AEs were reported in the CIS+STS arm compared to CIS alone in both studies (13.2% vs 10.7% in SIOPEL 6 and 8.5% vs 4.7% in COG ACCL0431). In SIOPEL 6, most of the 7 hypersensitivity cases reported in CIS-STS arm were of grade 1 severity and did not lead to study drug discontinuation except for one serious case in a 9-month-old patient. In COG ACCL0431 study, 5 cases were reported in CIS+STS arm, all of grade 1 to 2 and two which led to STS withdrawal. Two additional cases of allergic reactions which led to STS withdrawal were also reported and one of anaphylactic reaction attributed to platelet transfusion. In all cases, causal role of CIS cannot be excluded. Use of premedication was reported which allowed continuation of treatment.

As cisplatin is associated with renal and haematological toxicity (in addition to ototoxicity), the applicant was requested to present data on these which are summarised in **Table 39**.

Table 39. **Effect of STS on Cisplatin-Induced Renal and Haematological Toxicity, Studies SIOPEL 6 and COG ACCL0431 (Safety Population)**

Preferred Term	SIOPEL 6[b]		COG ACCL0431[a]	
	Observation n=56 n (%)	STS n=53 n (%)	Observation n=64 n (%)	STS 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
Hypophosphatemia	0	5 (9.4)	7 (10.9)	12 (20.3)
Hypomagnesemia	1 (1.8)	1 (1.9)	2 (3.1)	3 (5.1)
Hypokalemia	0	5 (9.4)	13 (20.3)	16 (27.1)
Hematological 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)
Hemoglobin decreased/Anemia	9 (16.1)	10 (18.9)	36 (56.3)	30 (50.8)

2.5.8.4. Laboratory findings

SIOPEL 6

In SIOPEL 6, mean changes in GFR from Baseline to the end of treatment were similar between the CIS+STS arm and the CIS Alone arm.

Mean changes in serum magnesium from Baseline to the end of treatment were statistically significant in the CIS+STS arm (-0.066 mmol/L [95% CI: -0.118, -0.014; p=0.015]), while those in the CIS Alone arm were not (0.009 mmol/L [95% CI: -0.055, 0.073; p = 0.780]). In both arms, mean changes from Baseline in serum magnesium levels to Follow-up were not statistically significant. The proportions of children in the CIS+STS arm and the CIS Alone arm who had abnormal serum magnesium (indicative of potential long-term clinical concern) were similar at the end of treatment (5 patients [9.4%] and 2 patients [3.6%], respectively) and at Follow-up (8 patients [15.1%] and 8 patients [14.3%], respectively). During the Treatment and Follow-up Phases, the incidence of hypermagnesemia AEs was higher in the CIS+STS arm (6 children [11.3%]) compared with the CIS Alone arm (3 children [5.4%]).

Children in the CIS+STS arm had a mean pre-course serum sodium level of 137.0 mmol/L, which increased to 143.1 mmol/L at 1 hour after STS dosing. At 6 hours and 18 hours after STS dosing, serum sodium levels returned to pre-STS values. During the Treatment and Follow-up Phases, the incidence of hypernatremia AEs was higher in the CIS+STS arm (14 children [26.4%]) compared with the CIS Alone arm (2 children [3.6%]). The majority of hypernatremia AEs were CTCAE Grade 1 in severity.

COG ACCL0431

In COG ACCL0431, mean and median serum sodium values were similar between arms. Across all reporting periods, no maximum serum sodium values were greater than 151 mmol/L in the CIS+STS arm or 146 mmol/L in the Observation arm. The remaining laboratory evaluations were not captured in the clinical database.

2.5.8.5. In vitro biomarker test for patient selection for safety

Not applicable.

2.5.8.6. Safety in special populations

Although the small sample sizes included in the SIOPEL 6 and COG ACCL0431 subgroups limit the interpretability of the data, no clinically meaningful differences in safety findings were observed between the age, gender, or weight subgroups that l. SIOPEL 6 and COG ACCL0431 did not enrol patients <1 month of age, as patients in this age group have less well-developed sodium homeostasis and the proposed indication is limited to the ages of 1 month to <18 years.

Clinical studies evaluating the PK of STS in patients with renal impairment have been reported in the literature (See Clinical Pharmacology Section in this report) and did not reveal any new safety However, STS is known to be substantially excreted by the kidney, and the risk of adverse effects related to STS may be greater in patients with impaired renal function.

No clinical studies have been conducted in patients with hepatic impairment. Metabolism of STS occurs through thiosulfate sulphur transferase and thiosulfate reductase activity and is independent of CYP450 and is not deemed to be affected by hepatic impairment.

2.5.8.7. Immunological events

Not applicable.

2.5.8.8. Safety related to drug-drug interactions and other interactions

No specific data on potential drug-drug interactions were gathered during studies SIOPEL 6 and COG ACCL0431. As claimed by the applicant, based on available data no clinically significant drug-drug interactions are expected for STS.

2.5.8.9. Discontinuation due to adverse events

In SIOPEL 6, 1 child (1.9%), in the CIS+STS arm, experienced a Grade 2 SAE of hypersensitivity that led to discontinuation of study medication. The event was noted 15 minutes after the end of STS infusion. The child experienced tachycardia and increased blood pressure was responsive to stimulus,

had no rash or respiratory distress, but initial blood gas showed metabolic acidosis. The child's heart rate responded appropriately after treatment with chlorpheniramine and saline.

No additional AEs led to study medication discontinuation in SIOPEL 6.

Discontinuations due to AEs were not systematically captured by the study sites in COG ACCL0431. Review of narratives for any patient who discontinued STS due to reasons related to an AE, or because the discontinuation occurred in close proximity to the occurrence of an AE (but was not specifically attributed to an AE) revealed that 1 child in the CIS+STS arm discontinued STS due to reasons related to an AE (PT of hypersensitivity) that was considered definitely related to STS by the investigator. In addition, 4 children in the CIS+STS arm discontinued STS in close proximity to an AE but not specifically due to an AE (2 children with PTs of chills [one AE considered probably and one AE considered possibly related to STS by the investigator], 1 child with PTs of stomatitis and pharyngeal stenosis [considered possibly related to STS by the investigator], and 1 child with PTs of anxiety, extrapyramidal disorder, and carpopedal spasm [considered possibly related to STS]

2.5.8.10. Post marketing experience

No post-marketing data on IV STS are available.

The applicant provided a review of scientific literature which described clinical studies testing STS in different indications (calciphylaxis, cyanide poisoning, malignant brain tumours, tumoral calcinosis, nephrogenic systemic fibrosis), different populations and different STS doses.

The most common AEs identified were hypotension, headache, and disorientation which are included in the product information of STS drug products currently marketed in other indications.

Dose dependency was also described in the literature for nausea, vomiting, hypernatremia, acidosis and blood pressure increased (Malbos et al, 2014; Neuwelt et al, 1998; Selk and Rodby, 2011) in association with STS use.

2.5.9. Discussion on clinical safety

This Marketing Authorisation Application is supported by 2 clinical studies which provide the basis of the safety data set. The safety data set was supplemented by an overview of results from published studies.

SIOPEL 6 study was a multicentre, open label, randomised Phase 3 trial which encompasses data from Safety Population of 53 patients in CIS+STS arm and 56 patients from the CIS alone arm. AEs were captured up to 30 days following the last chemotherapy administration and during the follow-up phase.

While most frequently reported AEs were reported with similar incidences in both treatment arms the following imbalances between the 2 treatment arms were noted: vomiting was reported in 84.9% patients in the CIS+STS arm vs 53.6% in the CIS alone group; nausea 39.6% vs 30.4% in the CIS+STS arm vs 53.6% in the CIS alone group, respectively. The reported events were transient and they were reported to stop soon after the sodium thiosulfate infusion had finished.

Hypernatremia was reported in 26.4% patients in the CIS+STS group vs 3.6 % in the CIS alone group, hypermagnesemia in 11.3% in the CIS+STS group vs 5.4% in the CIS alone group, hypokalaemia in 15.1% patients in the CIS+STS group vs 1.8% in the CIS alone group, hypophosphatemia in 15.1% patients in the CIS+STS group vs 1.8% in the CIS alone group.

COG ACCL0431 was a randomised, Phase 3 study in patients with other types of tumours offering safety population of 125 patients of which 59 were exposed to STS. In the SOC of Metabolism and

Nutritional disorders hypokalaemia was reported with notably higher incidence in the CIS+STS group (27.1% vs 20.3%), hypophosphatemia (20.3% vs 10.9%), hyponatremia (13.6% vs 6.3%), hypernatremia (11.9% vs 6.3%).

Gastrointestinal disorders and metabolic disorders (hypernatremia and hypomagnesemia) were defined as adverse events of special interest in SIOPEL 6. Safety data collected from both studies revealed substantially higher risk to hypernatremia in patients exposed to STS compared to control group. It is likely that increased frequency of nausea and vomiting in STS arms is largely associated with hypernatremia, due to the high sodium levels administered over a short time period. In addition to any prophylactic antiemetics administered prior to cisplatin administration, additional multi-agent antiemetics should be given in the 30 minutes prior to sodium thiosulfate administration.

In SIOPEL 6, in the CIS+STS arm the mean pre-course serum sodium level was 137.0 mmol/L, which increased at 1 hour after STS dosing (143.1 mmol/L) and returned back to pre-STS levels 6 hours after STS dosing (138.4 mmol/L) and 18 hours after STS dosing (136.4 mmol/L). During the treatment and follow-up phases, the incidence of hypernatremia was higher in the CIS+STS arm (14 children [26.4%]) vs the CIS alone arm (2 children [3.6%]). The majority of hypernatremia AEs were Grade 1. In COG ACCL0431, mean and medium sodium levels were similar between arms. Despite these small, transient increases in serum sodium levels, which appeared to be independent of age, body surface area, body weight it is recommended that electrolyte balance and blood pressure should be monitored carefully during STS treatment. However, as patients < 1 month of age have less well-developed sodium homeostasis, sodium thiosulfate should not be used in neonates.

In SIOPEL 6 the rate of SAEs and drug-related SAEs was relatively high in both arms, showing slightly higher incidence in CIS+STS arm (39.6% vs 32.1%). In study SIOPEL 6 CIS+STS arm 6 patients (11.3%) experienced severe neutropenia compared to 1 patient (1.8%) in CIS arm. Although, the difference between both arms seems significant, total numbers are too small to draw any definite conclusion especially as neutropenia is known to be caused by chemotherapy.

Hypersensitivity reactions were reported in clinical studies following the administration of sodium thiosulfate. Symptoms included rash, tachycardia, chills and dyspnoea. Sodium thiosulfate may contain a trace amount of sodium sulphite. It may rarely cause several hypersensitivity reactions and bronchospasm. Sulphite sensitivity is seen more frequently in asthmatic than in non-asthmatic people. Consequently, use of sodium thiosulfate is contraindicated in patients with a known hypersensitivity to the active substance (or any of the product’s excipients).

Antihistamines (e.g. diphenhydramine and steroids) should be immediately available to administer in the event of an allergic reaction. If the reaction is such that the patient is to continue with sodium thiosulfate after the next cisplatin administration, premedication with antihistamines should be given and the patient observed carefully.

Sodium thiosulfate is known to be substantially excreted by the kidney and the risk of adverse reactions of sodium thiosulfate may be greater in patients with impaired renal function. Because cisplatin chemotherapy is associated with renal toxicity, renal function should be monitored and caution applied with close monitoring of electrolytes if the GFR falls below 60 mL/min/1.73 m2.

Overall, cisplatin renal and haematological toxicity was similar between observation group and STS group in both studies supporting the hypothesis that STS does not interact with cisplatin if administered with a 6-hour interval. Sodium thiosulfate should not be given when cisplatin is infused for longer than 6 hours or if a subsequent cisplatin infusion is planned within 6 hours. The delayed administration prevents potential interference with cisplatin chemotherapy efficacy against the tumour (see also Clinical Efficacy section).

No other interaction studies have been performed. Relevant pharmacokinetic interactions are unlikely as administration of thiosulfate is infrequent, only in conjunction with cisplatin and thiosulfate is rapidly eliminated within hours after administration.

Follow-up of patients was conducted in both studies, a 5-year-period in SIOPEL 6 and a 10-year-period in COG ACCL0431. However, due to the limited number of patients within a vulnerable population, long-term safety is considered as missing information in the RMP and will need to be closely monitored in post-marketing setting.

Safety data from published literature demonstrated overall STS safety profile similar to that demonstrated in SIOPEL 6 and COG ACCL0431 trials. As the doses reported in the literature often greatly exceed the recommended dose for sodium thiosulfate, changes to blood pressure and acidosis are described as potential signs of overdose even though there is no specific antidote available. As hypertension has also been observed in clinical trials with STS for the claimed indication it has been included as an ADR in the SmPC of the product.

Additional expert consultations

See discussion on Clinical efficacy.

2.5.10. Conclusions on the clinical safety

Despite limitations due to the open design of both studies, data collection practices and relatively small sample sizes considering the indication and the intended use of the product the safety data base is considered acceptable to adequately characterise the safety profile of the product. Patients to be treated with sodium thiosulfate are under intensive monitoring due to the concomitant chemotherapy, and thus the recommendations included in the product information are considered sufficient to minimise the risks associated with its use.

2.6. Risk Management Plan

2.6.1. Safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	• Anaphylactic reactions • Medication errors
Missing information	• Long term safety

2.6.2. Pharmacovigilance plan

No additional pharmacovigilance activities are planned.

2.6.3. Risk minimisation measures

Table 40. Summary Table of Risk Minimisation Activities by Safety Concern

	Risk minimisation measures
Important potential risk Anaphylactic reactions	**Routine risk minimisation measures:** Please see • SmPC section 4.4 Special warnings and precautions for use • SmPC section 4.8 Undesirable effects • PL sections 2.2 Recommended Premedications and 2.3 Dosage Modifications for Adverse Reactions • PL section 4 Contraindications • PL section 5 Warnings and Precautions Routine risk minimisation activities recommending specific clinical measures to address the risk: None proposed Other routine risk minimisation measures beyond the Product Information: Legal status **Additional risk minimisation measures:** None proposed
Important potential risk Medication errors	**Routine risk minimisation measures:** Please see • SmPC section 4.2 Posology and method of administration • PL section 1 Indication and Usage • PL section 2 Dosage and Administration Routine risk minimisation activities recommending specific clinical measures to address the risk: None proposed Other routine risk minimisation measures beyond the Product Information: Legal status **Additional risk minimisation measures:** None proposed

2.6.4. Conclusion

The CHMP considers that the risk management plan version 0.91 is acceptable.

2.7. Pharmacovigilance

2.7.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.7.2. Periodic Safety Update Reports submission requirements

Based on the indication of Pedmarqsi compared to other authorised sodium thiosulfate containing

products, the PRAC is of the opinion that a separate entry in the EURD list for Pedmarqsi is needed, as it cannot follow the already existing entry for sodium thiosulfate. The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request the alignment of the new PSUR cycle with the international birth date (IBD). The IBD is 20.09.2022. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.8. Product information

2.8.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The target indication applied for by the applicant is for prevention of ototoxicity induced by cisplatin chemotherapy in patients 1 month to < 18 years of age with localised, non-metastatic, solid tumours.

3.1.2. Available therapies and unmet medical nee

Currently, there is no approved treatment in the EU to prevent or reverse cisplatin induced ototoxicity. Therefore, an unmet need exists for an effective and safe otoprotective agent for children treated with platinum-based chemotherapy.

3.1.3. Main clinical studies

In support of the claimed indication the applicant has provided two datasets, obtained from two phase III studies in paediatric populations, designed, sponsored, and conducted by academic consortia (SIOPEL and COG) for the purposes of establishing clinical practice guidelines for prevention of CIS-induced ototoxicity (International Childhood Liver Tumor Strategy Group [SIOPEL 6] and Children's Oncology Group [COG] ACCL0431).

The main safety and efficacy data in children were generated from a multicentre, randomised, open-label, pivotal Phase 3 clinical trial (SIOPEL 6) in paediatric patients [n=114] with confirmed SR-HB treated with cisplatin.

The applicant proposes Study ACCL0431 as a proof-of-concept of this STS effect in a heterogeneous population of paediatric cancers [n=125] inclusive of hepatoblastoma (HB). This study also enrolled significant proportion of adolescent patients, which the pivotal SIOPEL6 study was unable to do, due to the rarity of HB in this age group.

The primary efficacy endpoint, the proportion of children with hearing loss, was assessed by different criteria in each study, in keeping with the geographical regions of the consortia that conducted each study:

- SIOPEL 6 – positive ototoxicity was defined as hearing loss equal to or greater than Brock Grade 1 on the definitive audiologic evaluation at the end of treatment or at an age of ≥3.5 years, whichever was later.

- COG ACCL0431 – hearing loss was defined by ASHA scale defined by ASHA as ≥ 20 dB decrease from baseline in PTA threshold at one frequency, ≥ 10 dB decrease at 2 adjacent test frequencies, or loss of response at 3 consecutive test frequencies where responses were previously obtained.

In both studies, event free survival (EFS) and overall survival (OS) were secondary endpoints.

3.2. Favourable effects

SIOPEL 6

The pivotal study met its primary endpoint of the efficacy of STS regarding hearing loss i.e. the proportion of children with hearing loss at age ≥ 3.5 years in STS arm vs. observation group was 35.1% (n=20) vs. 67.3% (n=35) respectively with difference of 32.2%. The relative risk was 0.52 95% CI 0.349, 0.778, p<0.001.

The median age of children in STS arm was 13.8 months when they were treated with cisplatin and hearing was assessed 3 years later which shows long term hearing benefit.

ACCL0431

The study met its primary endpoint of the efficacy of STS regarding hearing loss. In the primary efficacy population the proportion of children in the CIS+STS arm with hearing loss was 14 patients (28.6%) vs the Observation arm - 31 patients (56.4%) with difference of 27.8%. The relative risk was 0.516 95% CI: 0.318- 0.839; p=0.0040.

3.3. Uncertainties and limitations about favourable effects

Clinical studies had small sample sizes which prevents interpretability of STS efficacy in children subgroups, e.g., based on age, chemotherapy regimen or underlying disease. Data in the older paediatric patients (above 9 years of age) data are limited. However, there is no plausible clinical reason why STS would not reduce hearing loss in this older group of patients with localised disease.

Given the complex regimen of administration due to the need to observe accurate timing of sodium thiosulphate administration relative to CIS chemotherapy there is a potential for medication errors that might lead to the loss of effectiveness for both products. Medication errors have been included in the Risk Management Plan as an important potential risk and this issue will be closely monitored through routine pharmacovigilance and reported in PSURs post-authorisation.

3.4. Unfavourable effects

The interaction of STS with cisplatin that could possibly lead to reduced effectiveness of the latter is the main potential risk associated with STS use.

Evidence of such a detrimental effect was observed in the COG ACLL0431 study in terms of EFS: HR 1.27; 95% CI: 0.73, 2.18; p=0.3964 and OS: HR 1.79; 95% CI: 0.86, 3.72; p=0.1132.

On the other hand this was not seen in the SIOPEL 6 study in which the HR for EFS was 0.96, 95% CI: 0.42, 2.23, p=0.932 and the OS HR 0.48, 95% CI: 0.09, 2.61, p=0.384.

Pooled analysis of the two trials and excluding certain types of tumours which are reported to have disparate survival rates was also provided. In this analysis, the HR for EFS and OS were: 1.01; 95% CI: 0.63-1.62; p=0.9534 and 1.08 95% CI: 0.55-2.17; p-value 0.8172, respectively.

Some AEs were reported with significantly higher incidence in the CIS+STS arm compared to the CIS alone arm, especially vomiting, hypernatremia, hypermagnesemia, hypokalaemia and hypophosphatemia, pyrexia and lower haemoglobin. In particular, AEs related to electrolyte imbalance can have clinically relevant consequences.

3.5. Uncertainties and limitations about unfavourable effects

Neither of the two studies are large enough to provide sufficient information that no detrimental effect on EFS and OS exists. In the pooled analysis excluding 'other tumour types' which allows assessing the potential effect on cisplatin efficacy across a larger sample size, no detrimental signal of concern is observed. In addition, available data suggest a potential reduced effect only in metastatic patients which are not included in the intended target population of Pedmarqsi which is limited to patients with localised, non-metastatic solid tumours only.

The timing of administration of STS (at 6 hours after the cisplatin infusion) in relation to cisplatin treatment is intended to reduce the possibility of inhibition of the cytotoxic effects of cisplatin. Moreover, it is notable that cisplatin renal and haematological toxicity is similar between observation groups and STS groups. These measures of cisplatin effects are considered more sensitive than the underpowered EFS and OS analyses. As there was no evident differences in ORR, no difference in the risk of cytopenias, and no difference in the risk of cisplatin-associated nephrotoxicity between the treatment arms, it can be concluded that STS exerts a tissue specific effect which allows it to act as on oto-protectant. This assumption is also supported by preclinical evidence.

3.6. Effects Table

Table 41. Effects Table for Pedmarqsi for the Prevention of Ototoxicity Induced by Cisplatin (CIS) Chemotherapy in Patients 1 Month to < 18 Years of Age with Localised, Non-Metastatic, Solid Tumors (data cut-off: 28 February 2018).

Effect	Short Description	Unit	CIS+STS	CIS	Uncertainties/ Strength of evidence	References
Favourable Effects						
Children with hearing loss at age ≥3.5 years	absolute hearing threshold at the age of ≥3.5 years, by pure tone audiometry, graded by Brock criteria	%	35.1	67.3	Relative risk: 0.521 95% CI 0.349 - 0.778, p<0.001	SIOPEL 6-study
Children with hearing loss at age	hearing loss defined by the ASHA criteria	%	43.6	71.4	Relative risk 0.516 95% CI: 0.318- 0.839; p=0.0040	COG ACCL0431 study
Unfavourable Effects						
OS EFS	In patients with localised and disseminated tumours, median follow up 5.33 years)	% %	70.5 55.7	81.3 60.9	hazard ratio: 1.79; 95% CI: 0.86- 3.72, p=0.11 hazard ratio: 1.27; 95% CI: 0.73- 2.18, p=0.3964 No differences observed in SIOPEL 6 study or in pooled analysis of SIOPEL 6 and COG ACCL0431	COG ACCL0431 study

Abbreviations: CIS: cisplatin; STS: sodium thiosulfate, ASHA: American Speech-Language-Hearing Association, CI: Confidence Interval; OS: Overall survival. EFS: Event free survival

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Although there were differences between SIOPEL 6 and ACCL0431 in terms of study designs and investigated populations the risk of having hearing loss was significantly lower in the CIS+STS arm compared with the CIS alone arm in both studies.

The prevention of hearing loss by STS was similar in SIOPEL 6 (hepatoblastoma only) and COG ACCL0431 (including hepatoblastoma, neuroblastoma, CNS tumours). These data indicate that the action of STS is independent of tumour type.

Overall, the qualitative safety profile of association of STS and cisplatin appears acceptable in the intended population. The main AE reported consist of gastro-intestinal disorders and electrolyte imbalance which necessitate close monitoring. Warnings included in the product information are considered sufficient to manage these risks.

3.7.2. Balance of benefits and risks

Available results show that STS is able to prevent a significant number of children from developing hearing loss related to their cisplatin-containing chemotherapy. Managing this toxicity is an important clinical issue especially as currently there are no treatment options available.

The safety profile of STS is well known as it has been in use for other indications. Clinical data submitted in support of this application did not identify any new safety issues associated with the use of STS in the claimed indication. The signal of reduced efficacy of cisplatin which was observed in study COG ACCL0431 was based on a small number of patients, which is justified given the claimed indication, and therefore difficult to draw definitive conclusions. Moreover, as STS is to be administered 6 hours after the end of infusion with CIS, the potential for a direct interaction in plasma between free CIS and STS would appear to be minimal. Even if a small negative effect on the efficacy of cisplatin when co-administrated with STS cannot be excluded in the context of mainly long-term cancer survivors, this is considered of limited clinical importance compared to the observed benefits on hearing loss.

On this basis, it is considered that the benefits of STS in the sought indication outweighs its risks.

3.8. Conclusions

The overall benefit/risk balance of Pedmarqsi is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by majority decision that the benefit-risk balance of Pedmarqsi is favourable in the following indication:

prevention of ototoxicity induced by cisplatin chemotherapy in patients 1 month to < 18 years of age with localised, non-metastatic, solid tumours.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription.

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0368/2019 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

Divergent position

Divergent position to the majority recommendation is appended to this report.

5. Appendix - Divergent position(s) to the majority recommendation

DIVERGENT POSITION DATED 30 March 2023

Pedmarqsi EMEA/H/C/005130/0000

The undersigned members of the CHMP did not agree with the CHMP's positive opinion recommending the granting of the marketing authorisation of Pedmarqsi 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 reason for divergent opinion was the following:

This indication is based on two trials:

- The SIOPEL-6 study (n=109), performed in patients with standard risk hepatoblastoma scheduled for definitive surgery.

- The COG ACLL0431 study (n=123), performed in patients with newly diagnosed germ cell tumour, hepatoblastoma, medulloblastoma, neuroblastoma, osteosarcoma, or another malignancy to be treated with cisplatin (CIS). Approximately 40% of patients had known metastases at baseline.

In both studies, patients were randomised to either CIS+STS or CIS alone.

For any tissue protective agent to be given alongside chemotherapy, a key risk is that tissue protection is accompanied by a reduction in the antitumoral efficacy of chemotherapy.

According to the prespecified analysis of responses to preoperative chemotherapy in the SIOPEL 6 study, the ORR was 66% in the CIS+STS arm versus 75% in the CIS arm. The EFS HR by stratified analysis was 1.07; (95% CI: 0.46, 2.51). The number of deaths in this small study was low (2 versus 4 patients in the CIS+STS and the CIS alone arm).

In the COG ACLL0431 study, the EFS HR was 1.27; (95% CI: 0.73, 2.18). The HR for OS was 1.79; (95% CI: 0.86, 3.72). In the subset of patients with localised disease at baseline, the OS HR was 1.23; (95% CI: 0.41, 3.66).

Notably, the indication for Pedmarqsi is limited to localised disease due to concerns about a tumour protective effect in disseminated disease. However, this limitation is data driven, as there is no pharmacological rationale why the impact of STS on CIS activity would differ depending on whether disease is localised or metastatic. Therefore, the overall OS result from this study is relevant, and granting an indication only for the curative setting does not mitigate the relevant uncertainty.

In summary, available data are compatible with a clinically significant detrimental effect of STS on cancer treatment outcome. Consequently, this risk has not been characterised with sufficient precision. This uncertainty precludes a conclusion of positive benefit/risk for Pedmarqsi.

Kristina Dunder

Armando Genazzani