CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212937Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-disciplinary Review and Evaluation

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant, which do not necessarily reflect the positions of the FDA.

Application Type	NDA, Resubmission Class 2
Application Number(s)	212937
Priority or Standard	n/a *(Original application: Priority)*
Submit Date(s)	March 23, 2022 *(Original application: February 10, 2020)*
Received Date(s)	March 23, 2022 *(Original application: February 10, 2020)*
PDUFA Goal Date	September 23, 2022 *(Original application; Complete Response Issued on August 10, 2020)*
Division/Office	OOD/DO2
Review Completion Date	September 20, 2022
Established Name	sodium thiosulfate injection
(Proposed) Trade Name	Pedmark
Pharmacologic Class	None
Code name	ADH300001
Applicant	Fennec Pharmaceuticals, Inc.
Formulation(s)	injection

<table>
<tr><td>Dosing Regimen</td><td>Administered as an intravenous infusion over 15 minutes following cisplatin infusions that are 1 to 6 hours in duration, starting 6 hours after the completion of each cisplatin infusion. For multiday cisplatin regimens, administer PEDMARK 6 hours after completion of each cisplatin infusion and at least 10 hours before the next cisplatin infusion. Do not administer PEDMARK if the next cisplatin infusion is scheduled to begin in less than 10 hours

The recommended dose is based on surface area according to actual body weight:

<table>
<tr><td>Actual Body Weight</td><td>PEDMARK Dose</td></tr>
<tr><td>Less than 5 kg</td><td>10 g/m^2</td></tr>
<tr><td>5 to 10 kg</td><td>15 g/m^2</td></tr>
<tr><td>Greater than 10 kg</td><td>20 g/m^2</td></tr>
</table>
</td></tr>
<tr><td>Applicant Proposed Indication(s)/Population(s)</td><td>PEDMARK is indicated to reduce the risk of ototoxicity associated with cisplatin in pediatric patients 1 month of age and older with localized, non-metastatic solid tumors

(Original application: Prevention of ototoxicity induced by cisplatin (CIS) chemotherapy in patients 1 month to <18 years of age with localized, non-metastatic solid tumors)</td></tr>
<tr><td>Recommendation on Regulatory Action</td><td>Traditional Approval</td></tr>
<tr><td>Recommended Indication(s)/Population(s) (if applicable)</td><td>PEDMARK is indicated to reduce the risk of ototoxicity associated with cisplatin in pediatric patients 1 month of age and older with localized, non-metastatic solid tumors.</td></tr>
</table>

Table of Contents

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

Table of Tables

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

Table of Figures

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

REVIEWERS OF MULTI-DISCIPLINARY REVIEW AND EVALUATION

Regulatory Project Manager	Maritsa Stephenson *(Original application: Anuja Patel)*
Pharmacology/Toxicology Reviewer(s)	Sachia Khasar
Pharmacology/Toxicology Team Leader(s)	Claudia Miller *(Original application: Whitney Helms)*
Clinical Pharmacology Reviewer(s)	Wentao Fu Youwei Bi
Clinical Pharmacology Team Leader(s)	Jeanne Fourie Zirkelbach Jiang Liu
Clinical Reviewer	Amy Barone
Clinical Team Leader	Amy Barone
Associate Director for Safety (if applicable)	Shaily Arora *(original application)*
Safety Team Analysts	Peter Schotland, Jizu Zhi *(original application)*
Statistical Reviewer	Abhishek Bhattacharjee *(original application)*
Statistical Team Leader	Joyce Cheng
Associate Director for Labeling (ADL)	Barb Scepura Stacy Shord *(original application)*

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

Cross-Disciplinary Team Leader	Amy Barone
Division Director (DHOT)	John Leighton
Division Director (OCP)	Atik Rhaman
Acting Deputy Division Director (OB)	Yuan-Li Shen
Deputy Division Director (OOD) (signatory authority)	Martha Donoghue *(Original application: Division Director Harpreet Singh)*

GLOSSARY

Abbreviation or Specialist Term	Explanation
AdEERS	Adverse Event Expedited Reporting System
AE	Adverse event
AFP	Alpha-fetoprotein
ASHA	American Speech-Language-Hearing Association
AST	Aspartate aminotransferase
BBBD	Blood brain barrier disruption
BSA	Body surface area
CI	Confidence interval
CIS	Cisplatin
CMH	Cochran-Mantel-Haenszel
CNS	Central nervous system
COG	Children's Oncology Group
COMT	Catechol-O-methyltransferase
CR	Complete response
CRF	Case Report Form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome
DSMC	Data Safety Monitoring Committee
EFS	Event-free survival
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GCT	Germ cell tumor
GFR	Glomerular filtration rate

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

Abbreviation or Specialist Term	Explanation
HB	Hepatoblastoma
ICH	International Council for Harmonisation
IM	Intramuscular
IP	Intraperitoneal
ITT	Intent-to-treat
IV	Intravenous(ly)
mITT	Modified Intent-to-treat
NCI	National Cancer Institute
NDA	New Drug Application
ODAC	Oncologic Drug Advisory Committee
OLT	Orthotopic liver transplantation
OS	Overall survival
pCO_2	Partial pressure of carbon dioxide
PD	Progressive disease
PI	Principal Investigator
PLADO	Cisplatin (=platinol) and doxorubicin
pO_2	Partial pressure of oxygen
PP	Per Protocol
PR	Partial response
PRETEXT	Pre-treatment Tumor Extension
PT	Preferred term
PTA	Pure-tone audiometry
SAE	Serious adverse event
SAP	Statistical analysis plan
SAR	Serious adverse reaction
SD	Standard deviation

Abbreviation or Specialist Term	Explanation
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
TPMT	Thiopurine S-methyltransferase
US	United States
USP	United States Pharmacopoeia

1 EXECUTIVE SUMMARY

1.1 PRODUCT INTRODUCTION

Sodium thiosulfate (PEDMARK) is intended to prevent cisplatin-induced irreversible damage to hair cells in the cochlea. The mechanism of sodium thiosulfate (STS) protection against ototoxicity is not fully understood but is thought to act directly with cisplatin to produce an inactive platinum species and exert intracellular effects such as increasing antioxidant glutathione levels and inhibiting intracellular oxidative stress. Both activities may contribute to the ability of sodium thiosulfate to reduce the risk of ototoxicity.

The original application was received on February 10, 2020, but the FDA issued a complete response (CR) on August 10, 2020 due to deficiencies identified during the pre-license inspection of the manufacturing facility for the STS drug product. On May 27, 2021, Fennec submitted a Class 2 NDA Resubmission intended to provide a complete response to the deficiencies outlined in the CR Letter. Deficiencies were again identified as part of the re-inspection of the manufacturing facility and a CR letter was issued on November 26, 2021. On March 23, 2022, Fennec submitted a Class 2 NDA resubmission (current application); all previously identified CR deficiencies have been resolved (see the Integrated Quality Review for full details). A summary of high level deficiencies and resolution of these deficiencies is included in Section 4.2 (Product Quality) of this integrated review.

The original proposed indication for NDA 212937 was:

> *PEDMARK is indicated for the prevention of ototoxicity induced by cisplatin (CIS) chemotherapy in patients 1 month to <18 years of age with localized, non-metastatic, solid tumors.*

The recommended indication is:

> *PEDMARK is indicated to reduce the risk of ototoxicity associated with cisplatin in pediatric patients 1 month of age and older with localized, non-metastatic solid tumors.*
>
> *Limitations of Use: The safety and efficacy of PEDMARK have not been established when administered following cisplatin infusions longer than 6 hours. PEDMARK may not reduce the risk of ototoxicity when administered following longer cisplatin infusions, because irreversible ototoxicity may have already occurred.*

A statement regarding nonsubstitutability of PEDMARK for other approved STS products was included in product labeling. The review team determined that PEDMARK is not substitutable with the other approved sodium thiosulfate products [Sodium Thiosulfate Injection (NDA 203923), approved for sequential use with sodium nitrite for treatment of acute cyanide poisoning that is judged to be serious or life-threatening; or Nithiodote (NDA 201444), approved for the treatment of acute cyanide poisoning that is judged to be serious or life-threatening] due to the risks of serious adverse reactions related to excessive exposure to boric acid and inadvertent use of sodium nitrate which is copackaged with sodium thiosulfate in Nithiodote. See Section 19.6 of this review for additional information.

The recommended dose of PEDMARK is based on surface area according to actual body weight.

Actual body Weight	**PEDMARK Dose**
Less than 5 kg	10 g/m^2
5 to 10 kg	15 g/m^2
Greater than 10 kg	20 g/m^2

PEDMARK™ (b) (4)

PEDMARK is administered as an intravenous infusion over 15 minutes, following cisplatin infusions that are 1 to 6 hours in duration, starting 6 hours after the completion of each cisplatin infusion. Dosage recommendations in approved product labeling contain instructions (b) (4)

Note: For the purposes of this review, the words metastatic and disseminated are used interchangeably. The words non-metastatic and localized are also used interchangeably.

1.2 CONCLUSIONS ON THE SUBSTANTIAL EVIDENCE OF EFFECTIVENESS

The clinical, nonclinical and clinical pharmacology data support traditional approval of sodium thiosulfate (STS) to reduce the risk of ototoxicity associated with cisplatin (CIS) in pediatric patients 1 month of age and older with localized, non-metastatic solid tumors.

The clinical data supporting traditional approval is based on the efficacy and safety data from two adequate and well controlled, randomized, multicenter trials: SIOPEL 6 and COG ACCL0431. The primary efficacy outcome for both studies was the proportion of children with hearing loss confirmed by blinded independent review; this was assessed by different criteria in each study. In SIOPEL 6, hearing loss was defined as Brock Grade ≥1 hearing loss; hearing was assessed using pure tone audiometry after study treatment or at an age of at least 3.5 years, whichever was later. In COG ACCL0431, hearing loss was assessed by American Speech-Language-Hearing Association (ASHA) criteria; hearing was assessed at baseline and 4 weeks after the final course of cisplatin. ASHA criteria define hearing loss as (a) 20 dB decrease at any one test frequency, (b) 10 dB decrease at any two adjacent test frequencies, or (c) loss of response at three consecutive test frequencies where responses were previously obtained.

- In SIOPEL 6, a total 114 patients with standard-risk hepatoblastoma were randomized, 61 patients to the STS+cisplatin arm and 53 patients to the cisplatin alone arm. The incidence of hearing loss was lower in the patients who received STS (n=24, 39%) compared to those who did not (n=36, 68%); unadjusted relative risk: 0.58 (95% CI: 0.40, 0.83), adjusted relative risk based on stratification factors [country, age (above vs below 15 months), and PRETEXT (I and II vs III)]: 0.58 (95% CI: 0.41, 0.81).
- In COG ACCL0431, a total of 125 patients with solid tumors who were receiving a chemotherapy regimen that included a cumulative cisplatin dose of 200 mg/m^2 or higher were randomized; however, the efficacy population used to support regulatory approval was restricted to patients with localized solid tumors and comprised 77 patients (39 randomized to the STS+cisplatin arm and 38 randomized to the cisplatin alone arm). The incidence of hearing loss was lower in patients who received STS (n=17, 44%) compared to those who did not (n=22, 58%); unadjusted relative risk: 0.75 (95% CI: 0.48, 1.18); adjusted relative risk based on stratification factors (prior cranial radiation versus without prior cranial radiation, age less than or greater than or equal to 5 years, durations of cisplatin infusion less than or greater than or equal to 2 hours): 0.84 (95% CI: 0.53, 1.35).

The efficacy population of COG ACCL0431 was restricted to patients with localized tumors based on concerns relating to a potential detriment in survival in patients with metastatic disease as described below. Interpretation of the efficacy results of COG ACCL0431 are complicated by the reduction in sample size and loss of randomization resulting from this adjustment to the efficacy population. Nevertheless, both trials showed evidence of a decreased incidence of hearing loss in favor of the CIS+STS arm.

Review of this application also included an assessment of the theoretical risk that STS could impact the anti-tumor efficacy of cisplatin. Key endpoints used for this assessment were event-free survival (EFS) and overall survival (OS), which were evaluated in both studies, although neither study was powered for this comparison. SIOPEL 6 showed no apparent difference between arms for EFS and OS; however, COG ACCL0431 showed a potential detriment in both endpoints for the CIS+STS arm. Exploratory post-hoc analyses of EFS and OS in COG ACCL0431 suggested that the potential detriment in EFS and OS may have been driven by patients with metastatic disease. After extensive review, the review team concluded that this potential detriment in patients with metastatic disease is likely to be due to an imbalance in prognostic risk factors rather than an effect of STS treatment; however, due to the lack of conclusive

evidence to rule out a potential detriment in EFS and OS with use of STS in pediatric patients with metastatic solid tumors, the FDA concurred with the Applicant's proposal to limit the indication to patients with non-metastatic disease and that the totality of the evidence supports the use of STS after CIS to prevent ototoxicity in pediatric patients with localized, non-metastatic solid tumors.

The safety profile of STS was generally consistent between studies despite differences in patient populations, CIS dosing, and STS dosing. The primary safety concerns attributable to STS in the indicated patient population are hypersensitivity reactions, nausea, vomiting, and adverse reactions related to electrolyte changes (e.g. hypernatremia and hypokalemia).

Based on these two randomized studies, the clinical data is supportive of traditional approval of sodium thiosulfate to reduce the risk of ototoxicity associated with cisplatin in pediatric patients 1 month of age and older with localized, non-metastatic solid tumors.

1.3 BENEFIT-RISK ASSESSMENT (BRA)

Benefit-Risk Summary and Assessment

The clinical data are supportive of traditional approval of STS to reduce the risk of ototoxicity associated with cisplatin in pediatric patients 1 month of age and older with localized, non-metastatic solid tumors.

Cisplatin causes irreversible, high-frequency, bilateral hearing loss in 50-60% of patients who receive it for treatment. In the US, approximately 5000 children are treated with cisplatin per year for various tumor types; cisplatin is the most common cause of hearing loss in children. Permanent hearing loss caused by cisplatin-induced ototoxicity may have serious communication, educational, and social consequences with detrimental effects on speech, language, and social development, in particular for young children who have an immature auditory system. Sodium thiosulfate is thought to act directly with cisplatin to produce an inactive platinum species and also by exerting intracellular effects such as increasing antioxidant glutathione levels and inhibiting intracellular oxidative stress.

Support for this application is based on the efficacy and safety data from two multicenter trials (SIOPEL 6 and COG ACCL0431) where patients were randomized (1:1) to receive cisplatin-based chemotherapy with or without STS. The primary efficacy outcome for both studies was the proportion of children with hearing loss confirmed by blinded independent review; this was assessed by different criteria in each study. In SIOPEL 6, hearing loss was defined as a Brock Grade ≥1 and was assessed using pure tone audiometry after study treatment or at an age of at least 3.5 years, whichever was later. In COG ACCL0431, hearing loss was assessed by American Speech-Language-Hearing Association (ASHA) criteria; hearing was assessed at baseline and 4 weeks after the final course of cisplatin. The patient populations differed between studies; children with a localized tumor type (standard-risk hepatoblastoma) were enrolled in SIOPEL 6 whereas children with various tumor types (both localized and metastatic) were enrolled in COG ACCL0431.

Efficacy

Treatment with sodium thiosulfate after cisplatin resulted in a clinically meaningful decrease in the incidence of hearing loss compared to those who were not treated with sodium thiosulfate.

1) In SIOPEL 6, a total 114 patients with standard-risk hepatoblastoma were randomized, 61 patients to the STS+cisplatin arm and 53 patients to the cisplatin alone arm. The incidence of hearing loss was lower in the patients who received STS (n=24, 39%) compared to those who did not (n=36, 68%); unadjusted relative risk 0.58 (95% CI: 0.40, 0.83), adjusted relative risk based on stratification factors 0.58 (95% CI: 0.41, 0.81).
2) In COG ACCL0431, a total of 125 patients with solid tumors who were receiving a chemotherapy regimen that included a cumulative cisplatin dose of 200 mg/m^2 or higher were randomized; the efficacy population used to support regulatory approval (patients with localized solid tumors) included 77 patients where 39 were randomized to the STS+cisplatin arm and 38 to the cisplatin alone arm. The incidence of hearing loss was lower in the patients who received STS (n=17, 44%) compared to those who did not (n=22, 58%); unadjusted relative risk 0.75 (95% CI: 0.48, 1.18), adjusted relative risk based on stratification factors 0.84 (95% CI: 0.53, 1.35).

The efficacy population in COG ACCL0431 was restricted to patients with localized tumors based on concerns relating to potential detriment in survival in patients with metastatic disease as described below. Interpretation of the efficacy results of COG ACCL0431 are complicated by the reduction in sample size and loss of randomization resulting from this adjustment to the efficacy population. Nevertheless, both trials showed evidence of a decreased incidence of hearing loss in favor of the CIS+STS arm.

Review of this application also included an assessment of the theoretical risk that STS could impact the anti-tumor efficacy of cisplatin. Key endpoints used for this assessment were event-free survival (EFS) and overall survival (OS), which were evaluated in both studies, although neither study was powered for this comparison. SIOPEL 6 showed no apparent difference between arms for EFS and OS; however, COG ACCL0431 showed a potential detriment in both EFS and OS for the CIS+STS arm. A post-hoc exploratory evaluation of EFS and OS according to the extent of disease at the time of enrollment in COG ACCL0431 was conducted, categorizing patients with a binary assignment to groups of

localized or disseminated disease. In children with localized, non-metastatic, solid tumors, treatment was STS was not associated with a reduction in EFS or OS. These results are supported by those from SIOPEL 6, which limited enrollment topatients had localized, non-metastatic disease (i.e., standard-risk hepatoblastoma). In COG ACCL0431 in patients characterized with disseminated disease, there was a disparity in the OS between the groups; however, after extensive review, this is thought to be due to an imbalance in prognostic risk factors not to an effect from STS treatment.

Safety

The safety assessment was based upon all patients who received least 1 dose of STS in SIOPEL 6 (n=53) and COG ACCL0431 (n=59). The primary safety concerns attributable to STS in the indicated patient population are the potential for hypersensitivity reactions, nausea, vomiting, and adverse reactions related to electrolyte changes (i.e., hypernatremia and hypokalemia).

In SIOPEL 6, serious adverse reactions occurred in 40% of patients who received STS in combination with cisplatin-based chemotherapy. Serious adverse reactions in > 5% of patients who received STS included infection, decreased neutrophil count, and pyrexia. STS was permanently discontinued due to an adverse reaction in 1 patient (Grade 2 hypersensitivity). The most common adverse reactions (≥ 25% with difference between arms of >5% compared to cisplatin alone) were vomiting, , nausea, hemoglobin decreased, and hypernatremia.

In COG AACL0431, serious adverse reactions occurred in 36% of patients who received PEDMARK in combination with cisplatin-based chemotherapy. Serious adverse reactions in > 5% of patients who received PEDMARK included febrile neutropenia, decreased neutrophil count, decreased platelet count, decreased white blood cell count, anemia, stomatitis, infections, decreased lymphocyte count, and increased alanine aminotransferase (ALT). Discontinuations due to AEs were not systematically collected; however, 1 (1.7%) patient in the CIS+STS arm discontinued STS due an AE of hypersensitivity. The most common adverse reaction (≥25% with difference between arms of >5% compared to cisplatin alone) was hypokalemia.

Based on these two randomized studies, traditional approval is recommended for sodium thiosulfate to reduce the risk of ototoxicity associated with cisplatin in pediatric patients 1 month of age and older with localized, non-metastatic solid tumors.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Cisplatin is the most common cause of ototoxicity in children. Approximately 5,000 children in US receive cisplatin annually for solid tumors such as germ cell tumors, osteosarcoma, medulloblastoma, neuroblastoma, and hepatoblastoma. Cisplatin causes irreversible, high-frequency, bilateral hearing loss in 50-60% of patients. Permanent hearing loss caused by cisplatin-induced ototoxicity may have serious communication, educational, and social consequences with detrimental effects on speech, language, and social development, in particular for young children who have an immature auditory system.	Cisplatin-induced hearing loss is a serious condition that has significant morbidity for pediatric patients.
Current Treatment Options	There are no drugs approved for the prevention or treatment of cisplatin-inducted ototoxicity.	Safe and effective treatments for this highly morbid condition are needed.

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Therapeutic options are limited to reducing cisplatin dose, switching therapy, or managing hearing loss with assistive technology, speech-language therapy, etc.	
Benefit	The efficacy and safety data are supported by two randomized, multicenter trials: SIOPEL 6 and COG ACCL0431. The primary efficacy outcome for both studies was the was the proportion of children with hearing loss confirmed by blinded independent review; this was assessed by different criteria in each study. In SIOPEL 6, a total 114 patients with standard-risk hepatoblastoma were randomized. The incidence of hearing loss was lower in the patients who received STS (n=24, 39%) compared to those who did not (n=36, 68%); unadjusted relative risk 0.58 (95% CI: 0.40, 0.83), adjusted relative risk based on stratification factors, 0.58 (95% CI: 0.41, 0.81). In COG ACCL0431, a total of 125 patients with solid tumors who were receiving a chemotherapy regime that included a cumulative cisplatin dose of 200 mg/m2 or higher were randomized; the efficacy population used to support regulatory approval (patients with localized solid tumors) included 77 patients. The incidence of hearing	Substantial evidence of effectiveness was demonstrated for sodium thiosulfate in the patient population being indicated. The efficacy population of COG ACCL0431 was restricted to patients with localized tumors based on a potential detriment in survival in patients with metastatic disease described below. Interpretation of the efficacy results of COG ACCL0431 are complicated by the reduction in sample size and loss of randomization resulting from this adjustment to the efficacy population. Nevertheless, both showed evidence of a decreased incidence of hearing loss in favor of the CIS+STS arm.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	loss was lower in the patients who received STS (n=17, 44%) compared to those who did not (n=22, 58%); unadjusted relative risk 0.75 (95% CI: 0.48, 1.18), adjusted relative risk based on stratification factors, 0.84 (95% CI: 0.53, 1.35).	
Risk and Risk Management	There is a theoretical risk that STS could impact the anti-tumor efficacy of cisplatin Neither study was powered to detect a difference in event-free survival (EFS) or overall survival (OS); however, given the risk, post-hoc analyses were done for both studies. SIOPEL6 showed no apparent difference between arms for EFS and OS; however, COG ACCL0431 showed a potential detriment in both endpoints on the CIS+STS arm. Exploratory post-hoc analyses of EFS and OS in COG ACCL0431 suggested that the potential detriment in both may have been driven by patients with metastatic disease. After extensive review, this potential detriment in patients with metastatic disease was thought to be due to an imbalance in prognostic factors, not due to effect from STS. The primary safety concerns attributable to STS in the indicated patient population are hypersensitivity reactions, nausea, vomiting, and adverse reactions related to electrolyte changes (e.g.	The safety profile of sodium thiosulfate based on the clinical data is acceptable in the intended population.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	hypernatremia and hypokalemia). These concerns are consistent with the known safety profile of sodium thiosulfate.	

1.4 PATIENT EXPERIENCE DATA

Patient Experience Data Relevant to this Application (check all that apply)

□	The patient experience data that was submitted as part of the application, include:			Section where discussed, if applicable
	□	Clinical outcome assessment (COA) data, such as		[e.g., Section 6.1 Study endpoints]
		□	Patient reported outcome (PRO)	
		□	Observer reported outcome (ObsRO)	
		□	Clinician reported outcome (ClinRO)	
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		[e.g., Section 2.1 Analysis of Condition]
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify)		
☐	Patient experience data that was not submitted in the application, but was considered in this review.			
X	**Patient experience data was not submitted as part of this application.**			

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

X

Amy Barone

Cross-Disciplinary Team Leader

1.

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

2 THERAPEUTIC CONTEXT

2.1 ANALYSIS OF CONDITION

The Applicant's Position:

Chemotherapeutic agents containing the heavy metal platinum have demonstrated efficacy in the treatment of a variety of malignant neoplasms in adults and children, and have been the standard of care in cancer therapy for 40 years (Macdonald et al, 1994; Kelland 2007). Cisplatin (CIS), the first-line platinum chemotherapeutic agent, treats many childhood cancers, such as nervous system cancers (medulloblastomas and neuroblastomas), liver tumors, bone and soft tissue sarcomas, and germ cell tumors (GCTs). Other platinum compounds are used less often because of suspected lower efficacy and other dose-related toxicities (Lokich, 2001). Cisplatin is the most ototoxic of all platinum-based drugs, including carboplatin and oxaliplatin, when used at standard doses (Park, 1996).

Cisplatin is the most common cause of ototoxicity in children (Langer et al, 2013; Arslan et al, 1999). Depending on data sources, the incidence of platinum-induced ototoxicity in children with diverse types of cancers varies from 4% to 95% (Li et al, 2004; Landier et al, 2014; Katzenstein et al, 2009; Skinner et al, 1990; Yancey et al, 2012; Knight et al, 2005; and Knight et al, 2007). Unfortunately, at commonly used doses and administration schedules, CIS frequently causes ototoxicity through progressive loss of outer and inner hair cells in the organ of Corti. The exact mechanism is still not understood, but the release of reactive oxygen species and depletion of antioxidants in the microenvironment contribute to this process (Blakley et al, 2002; Ryback and Somani, 1999; Ryback et al, 1999). Recent research suggests that CIS accumulates in the cochlea with long-term retention, making the inner ear uniquely susceptible to CIS-induced damage (Breglio et al 2017). Irreversible hearing loss, typically in the high frequency (4000 to 8000 Hz) and very high frequency (9000 to 20000 Hz) ranges, has been documented as early as following the first platinum chemotherapy dose, 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 CIS, and is likely to worsen after repeated doses (Berg et al, 1999; Hale et al, 1999; Li et al, 2004). This worsening hearing loss affects progressively lower frequencies in a cumulative, dose-dependent fashion (Berg et al, 1999; Punnett et al, 2004; Bertolini et al, 2004).

Factors that significantly increase a child's risk for moderate to severe hearing loss include age <5 years at treatment and a cumulative CIS dose of ≥400 mg/m^2 (Li et al, 2004).

Cisplatin-induced hearing loss is often clinically significant, especially in young children who are critically dependent upon normal hearing for cognitive, psychosocial, and speech development (Gilmer-Knight et al, 2005; Fausti et al, 1993; Hindley 1997). In older children, both educational and behavioral effects studies showed impaired functional status, cognitive status, depressive symptomatology, and disability (Brock et al, 2012).

The FDA's Assessment:

FDA agrees with the Applicant's overall assessment of hearing loss in children that is associated with cisplatin treatment.

2.2 ANALYSIS OF CURRENT TREATMENT OPTIONS

The Applicant's Position:

Fennec Pharmaceuticals, Inc (Fennec) is unaware of any drug approved for the prevention or treatment of CIS-induced ototoxicity. Current therapeutic options are limited to reducing the CIS dose (or switching to a different platinum-based chemotherapy, both of which risk decreased tumor efficacy), or managing the hearing loss. This management includes hearing assistive technology, speech-language therapy, and other communication strategies (Whelan et al, 2011; Brock et al, 2012). While such interventions must be considered to help patients communicate, these management options cannot restore normal hearing.

As such, there is clearly a need for safe and effective treatments targeted at prevention of CIS-induced ototoxicity.

The FDA's Assessment:

FDA agrees with the Applicant's assessment of current treatment options to reduce the risk of hearing loss associated with cisplatin. There are no FDA approved drugs to reduce the risk of hearing loss associated with cisplatin or due to any cause.

3 REGULATORY BACKGROUND

3.1 U.S. REGULATORY ACTIONS AND MARKETING HISTORY

The Applicant's Position:

PEDMARK is being developed for prevention of ototoxicity induced by CIS chemotherapy in patients 1 month to <18 years of age with localized, non-metastatic solid tumors. The New Drug Application (NDA) has been submitted to the Division of Oncology 1 in the Office of New Drugs; no other review division within the Office of New Drugs was involved prior to the submission, and, thus, all of the applicable United States (US) regulatory history is provided in Section 3.2 below. Fennec was recently notified that the review of the NDA is being moved to the Division of Oncology 2.

The FDA's Assessment:

FDA agrees with the Applicant's assessment. The review of the NDA was transferred to DO2 based on the proposed indicated population of pediatric patients with solid tumors. DO2 is responsible for managing drug development for pediatric solid tumors.

PEDMARK is not approved in any country. Sodium thiosulfate is commercially available in the US and in Europe for the treatment of cyanide poisoning. In Belgium and Italy, sodium thiosulfate is also commercially available for the prevention of nephrotoxicity associated with cisplatin.

3.2 SUMMARY OF PRESUBMISSION/SUBMISSION REGULATORY ACTIVITY

The Applicant's Position:

Clinical advice was sought from the Food and Drug Administration (FDA) during a Type C meeting in March 2011 and during a meeting of the Pediatric Subcommittee of Oncologic Drug Advisory Committee (ODAC) in November 2011. In response to a request for Breakthrough Therapy Designation, the FDA provided additional suggestions for PEDMARK clinical development in August 2014. Agency advice from FDA was also provided through a Type C

clinical meeting request and written responses (January 2018), a pre-NDA meeting (December 2018) focused on clinical, nonclinical, and regulatory aspects of the NDA, and a pre-NDA chemistry, manufacturing, and controls meeting (September 2019). In the US, PEDMARK has received Orphan designation (March 2004), Breakthrough Therapy Designation (March 2018), and Fast-Track designation (March 2018).

Key discussions and agreements during these US agency interactions are summarized in Table 1.

Table 1: Summary of Key Agreements/Discussions with FDA

Correspondence	Key Agreements/Discussions with FDA	Implementation of Advice
FDA Clinical Type C Meeting Minutes (March 2011)	Fennec is required to convincingly demonstrate that STS does not reduce the efficacy of CIS. Pooling data from SIOPEL 6 and COG ACCL0431 was not recommended.	Tumor response and survival evaluated (Module 2.5, Section 4.5). No pooling was conducted.
Pediatric Subcommittee of ODAC Meeting (November 2011)	Fennec discussed the COG ACCL0431 study design and efficacy evaluations. The subcommittee agreed that this study would support proof of concept with adequate follow up. Possible tumor protection is a critical component of the safety profile of STS, and that it should be thoroughly investigated prior to drug approval.	Tumor response and survival evaluated (Module 2.5,Section 4.5).
Breakthrough Therapy Designation Request Denial - Additional Responses from FDA Clinical Pharmacology Reviewer (August 2014)	The PK of STS should be adequately characterized at the proposed dose. Evaluation of the in vitro ability of STS and its major metabolite(s) to act as substrates, inhibitors, or inducers of CYP enzymes, transporters, and conjugating enzymes should be conducted. Fennec should evaluate the impact of CIS doses, body size, and other demographic covariates on STS exposure and resulting efficacy and safety of STS in the proposed indication.	PK and exposure response considering BSA, age, renal maturation, and weight were characterized through STS (thiosulfate) exposure modeling and sodium analysis (Module 2.5, Section 3; Section 3.1.2.1; Section 3.3). Evaluation of DDIs, including induction/inhibition of CYP isoforms evaluated (Module 2.5, Section 3.1.2.2; Section 3.1.3.1).

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

Table 1: Summary of Key Agreements/Discussions with FDA

Correspondence	Key Agreements/Discussions with FDA	Implementation of Advice
FDA Clinical Type C Meeting Written Responses (January 2018)	The available nonclinical data in the literature were sufficient to support the PEDMARK NDA for prevention of ototoxicity induced by CIS in pediatric patients with SR-HB. Fennec's approach to evaluate STS dose and duration of treatment using PK modeling of serum STS and sodium concentration based on data from Neuwelt et al, 1998 was sufficient. Together with a summary of published data, the agency also agreed on the plans for in vitro evaluation of DDIs through CYP induction and inhibition studies. SIOPEL 6 and COG ACCL0431 and further published STS clinical results provided sufficient efficacy and safety data to allow the filing of the PEDMARK NDA for the prevention of ototoxicity induced by CIS chemotherapy in pediatric patients with SR-HB. Further evaluation of OS would be conducted on the COG ACCL0431 study data to examine the observation of decreased survival in the disseminated subgroup of the CIS+STS arm.	Nonclinical literature summarized (Module 2.4). PK and exposure response considering BSA, age, renal maturation, and weight were characterized through STS (thiosulfate) exposure modeling and sodium analysis (Module 2.5, Section 3; Section 3.1.2.1; Section 3.3). Evaluation of DDIs, including induction/inhibition of CYP isoforms evaluated (Module 2.5, Section 3.1.2.2; Section 3.1.3.1). SIOPEL and COG data were summarized in addition to summary of available applicable literature. Tumor response and survival evaluated (Module 2.5, Section 4.5).

Table 1: Summary of Key Agreements/Discussions with FDA

Correspondence	Key Agreements/Discussions with FDA	Implementation of Advice
FDA Pre-NDA Meeting Minutes (December 2018)	The available nonclinical data in the literature were sufficient to support the PEDMARK NDA for prevention of ototoxicity induced by CIS in pediatric patients with SR-HB. Given that no novel excipients are used in the proposed STS formulation and any impurities will be qualified in accordance with ICH Q3 limits, no additional GLP toxicity studies of STS impurities were required. The proposed approach for the literature review was generally acceptable. Evaluation of serum sodium levels after STS administration was an adequate surrogate to evaluate safety at the recommended STS dose; however, it can be confounded by endogenous sodium and may not be reliable. Given that no STS PK samples were collected from SIOPEL 6 or COG ACCL0431, the use of STS PK literature to develop a popPK model and incorporation of growth and maturation models was acceptable to predict STS exposure. The proposed approach of descriptive efficacy and safety data per weight category was acceptable. The CYP inhibition and induction studies conducted were sufficient for the FDA to review the potential of drug-drug interaction with STS in the NDA. The review of safety and efficacy can be based on the individual studies (SIOPEL 6 and COG ACCL0431) rather than pooled data.	Nonclinical literature summarized (Module 2.4) Clinical literature reviewed (Module 2.5, Section 1.2.2). PK and exposure response considering BSA, age, renal maturation, and weight were characterized through STS (thiosulfate) exposure modeling and sodium analysis (Module 2.5, Section 3; Section 3.1.2.1; Section 3.3). Efficacy and safety data were evaluated by weight category (Module 2.5, Section 4.6; Section 5.9.1). Evaluation of DDIs, including induction/inhibition of CYP isoforms evaluated (Module 2.5, Section 3.1.2.2; Section 3.1.3.1). No pooling was conducted.

FDA Pre-NDA Meeting Minutes (December 2018) *(continued)*	Because SR-HB is obsolete in terms of classifying and reviewing patients for treatment, the Agency agreed with the proposed indication: STS for injection for the prevention of ototoxicity induced by CIS chemotherapy in patients 1 month to <18 years of age with localized, non-metastatic HB. (b) (4) The effect of differing CIS regimens and prognosis on OS in each treatment group in the COG ACCL0431 study should be explored. To satisfy the Integrated Summary of Effectiveness and Integrated Summary of Safety requirements (21CFR 314.50(d)(5)(v) and 21 CFR 314.50(d)(5)(vi)(a),respectively), data summarized within the Module 2 documents (Summary of Clinical Efficacy [2.7.3] and Summary of Clinical Safety [2.7.4], respectively) will be sufficient. For SIOPEL 6 and COG ACCL0431, full narratives are provided for patients in the CIS+STS arm who (1) experienced an SAE or (2) discontinued STS due to an AE (depending on information available). In addition, full narratives are provided for patients who died during the study due to a cause other than progression of disease regardless of treatment group. Data from the SIOPEL 6 and COG ACCL0431 studies are acceptable in SDTM and ADaM formats. The SAS programs used to create all analysis datasets are provided. The legacy datasets transferred from COG and SIOPEL were converted to CDISC format. Supporting documentation is provided (define.xml version 2.0, SDTM and ADaM reviewer guides and SAS programs in .txt format). The Agency agreed to the plan for the NDA rolling submission.	An evaluation of prognostic factors that affect survival was conducted (Module 2.5, Section 4.5). Module 2.7.3 and 2.7.4 include all data summaries. No Integrated Summary of Effectiveness or Integrated Summary of Safety were submitted. Full narratives for these events are provided in the respective CSRs. SDTM and ADaM datasets, SAS programs, and supporting documentation is provided. The first part of the rolling submission for this NDA submitted in December 2018. No Pediatric Study Plan or Risk Evaluation and Mitigation Strategy have been submitted.

Table 1: Summary of Key Agreements/Discussions with FDA

Correspondence	Key Agreements/Discussions with FDA	Implementation of Advice
	No Pediatric Study Plan or Risk Evaluation and Mitigation Strategy are required for the submission of the NDA.	

Abbreviations: ADaM=Analysis Data Model; AE=adverse event; BSA=body surface area; CDISC=clinical data interchange standards consortium; CIS=cisplatin; COG=Children's Oncology Group; CSR=clinical study report; CYP=cytochrome P450; DDI=drug-drug interaction; FDA=Food and Drug Administration; GLP=Good Laboratory Practice; ICH=International Council for Harmonisation; NDA=New Drug Application; ODAC= Oncological Drug Advisory Committee; OS=overall survival; PK=pharmacokinetics; popPK=population PK; SAE=serious adverse event; SAS=Statistical Analysis System; SIOPEL=International Childhood Liver Tumor Strategy Group; SDTM=Study Data Tabulation Model; SR-HB=standard risk hepatoblastoma; STS=sodium thiosulfate.

PEDMARK™ (b) (4)

The FDA's Assessment:

FDA agrees with the pre-submission regulatory activity stated by the Applicant above.

The original application was received on February 10, 2020. A complete response (CR) was issued on August 10, 2020 due to deficiencies identified during the pre-license inspection of the manufacturing facility of STS. On May 27, 2021, Fennec submitted a Class 2 NDA Resubmission intended to provide a complete response to the deficiencies outlined in the CR Letter. Deficiencies were again identified as part of the re-inspection of manufacturing facility and a CR letter was issued on November 26, 2021.

4 SIGNIFICANT ISSUES FROM OTHER REVIEW DISCIPLINES PERTINENT TO CLINICAL CONCLUSIONS ON EFFICACY AND SAFETY

4.1 OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI)

No clinical sites were inspected for this NDA. FDA determined that OSI inspections were not needed given that the safety profile is well known, it is a supportive care drug, and that that results of the two trials conducted independently and at different regions are similar.

4.2 PRODUCT QUALITY

During the review of the original NDA submission, major deficiencies identified in the manufacturing inspections included multiple quality event deviations (b) (4) Potential risk was linked to actual data that could impact product quality. Additionally, the observations were identical or similar to previous inspection observations; changes the site had agreed to incorporate into their manufacturing processes to address the identified deficiencies had not been implemented.

As part of this application, Fennec withdrew the prior facility and replaced it with Berkshire

PEDMARK™ (b) (4)

Sterile Manufacturing (BSM) as the drug product manufacturer. A pre-approval inspection was conducted at BSM. Office of Pharmaceutical Manufacturing Assessment (OPMA) evaluated the inspection outcome (b) (4) and deemed the manufacturing process and facilities information as adequate.

Office of Product Quality (OPQ) recommends **APPROVAL** of this application**,** stating that, "Based on our evaluation of the available information, the Applicant provided sufficient information to support an approval recommendation from the product quality perspective. The Applicant provided adequate information on the proposed drug product to ensure the identity, strength, purity, and strength of the proposed drug product. The overall manufacturing inspection recommendation is approval for all the facilities associated with this application. The proposed labeling and labels include adequate information to meet the regulatory requirements."

Other Issues Reviewed as Part of the Original Submission

The CMC team asked the nonclinical team whether there was toxicological justification for several extractables and for two impurities with specifications above the thresholds discussed in ICH Q3A and B: (b) (4) (b) (4) These data provide sufficient coverage for the safety of the (b) (4) at the proposed specifications without the need for additional toxicology studies.

The Applicant identified the following extractables at levels above a calculated analytical evaluation threshold (AET). The Applicant based the AET on the threshold of toxicological concern for genotoxic impurities discussed in ICH M7, of (b) (4) µg/day for drugs given for less than 1 month. The Applicant then established an AET with the expectations that most patients would receive no more than two vials of STS/day on cisplatin dosing days, with one stopper (device)/vial and each stopper weighing 2 g with the calculation as follows:

AET (µg/g) = (b) (4) µg/day x 1 day/2 vials x 1 vial/device x 1 device/2.0 g = (b) (4) µg/g.

PEDMARK™ (b) (4)

Extractables that exceeded the (b) (4) µg/g threshold were limited to (b) (4) The Applicant based this threshold on a 2 vial maximum as most pediatric patients receive less than or equal to 2 vials maximum; however based on the maximum dose described in the label, up to 3 vials/dose may be needed.

Table 2: Extractable Levels

(b) (4)

While STS is not a genotoxic drug, for the proposed indication it is given only in combination with cisplatin, which is genotoxic. The Applicant did not provide any justification for the levels of these potential extractables. As these levels represent worse-case scenario extractions, it is unclear whether patients would receive (b) (4) at these levels. (b) (4)

(b) (4) In addition, levels up to (b) (4) mg were detected in previously approved STS injectable projects. Given these high levels in previously approved products and the use of this product in combination with cisplatin, there is not a clear safety risk for the proposed level of (b) (4)

(b) (4) in another intravenous drug based on the methods for establishing exposure limits in ICH Q3C/D. In a repeat-dose oral toxicity study, after 28-day exposure in rats at 25, 250, and 500 mg/kg/day (b) (4) the liver was the main target organ of toxicity at doses of 250 and 500 mg/kg/day. The NOAEL was 25 mg/kg/day. Based on the NOAEL of 25 mg/kg from the repeat-dose toxicity study with (b) (4) in rats, the acceptable daily intake (ADI) for (b) (4) was calculated to be 250 µg/day with the following factors based on lifetime exposure:

(b) (4)

PEDMARK™ (b) (4)

(b) (4)

The worst case scenario for (b) (4) presented by the Applicant would exceed the (b) (4) however, this dose is still over 800x lower than the NOAEL determined in the rat study and dosing with STS is limited in the currently proposed indication.

For the (b) (4) is likely an extractable in a wide array of parenteral products (solutions or lyophilized products), it was (b) (4) in the last few years. As a result, while there is some evidence that independent laboratories may be attempting to screen (b) (4) for their genotoxic potential, FDA was unable to find any toxicology data to support the safety of (b) (4) at any level. The actual genotoxic potential for patient exposure to (b) (4) following PEDMARK infusion is unclear. However, despite the lack of information on the genotoxic potential of (b) (4), given that patients will receive STS only in conjunction with cisplatin, which is genotoxic, the potential risk is not expected to be greater than with cisplatin alone.

4.3 CLINICAL MICROBIOLOGY

Not applicable.

4.4 DEVICES AND COMPANION DIAGNOSTIC ISSUES

Not applicable.

5 NONCLINICAL PHARMACOLOGY/TOXICOLOGY

5.1 EXECUTIVE SUMMARY

Fennec Pharmaceuticals has submitted NDA 212937 under the 505(b)(2) pathway for sodium thiosulfate (STS) for the prevention of ototoxicity induced by cisplatin chemotherapy in patients 1 month to <18 years of age with localized, non-metastatic, solid tumors. STS is an inorganic salt with reducing agent properties, currently approved as an antidote used sequentially with sodium nitrite for acute cyanide poisoning. STS has been investigated clinically for over 100 years. Because Fennec submitted the application under the 505(b)(2) pathway, the Applicant submitted very limited nonclinical data and instead relies primarily on literature reports for the pharmacology/toxicology information needed to support approval in the current indication. Currently STS does not have an established pharmacological class; due to remaining uncertainties regarding the mechanism of its activity in several indications and its general characteristics as a reactive chemical compound/target no EPC is currently proposed.

While STS is an anion that does not diffuse across cell membranes, the Applicant cited data from Marutani et al., (2015) showing that it can enter cells by transport through the sodium sulfate cotransporter 2. Pharmacology studies suggest that STS neutralizes cisplatin by covalently binding to electrophilic platinum compounds, making an inactive easily excretable product; this neutralization may occur primarily extracellularly but can also occur intracellularly. STS also has an established role in decreasing oxidative stress in cells. The mechanism of cisplatin-induced hearing loss is not fully elucidated but appears to be due to uptake and accumulation of cisplatin into cochlear hair cells by various transporters where it may lead to cell death through DNA damage and excessive generation of reactive oxygen species (ROS) and inflammation.

The Applicant submitted multiple literature reports in several species, including hamsters, guinea pigs, and rats, showing that the addition of STS to cisplatin treatment resulted in protection from hearing loss. Investigators observed this protection in animals when STS was

given systemically (intraperitoneally or intravenously) or by direct cochlear perfusion, but not when given locally by infusion in the round window membrane. When administered concurrently with cisplatin, STS reduces not only the general toxicity (including nephrotoxicity) but also the antitumor activity of cisplatin (Elferink, et al. (1986); Wimmer, et al. (2004), however, the cited studies showed that delayed administration of STS between 2 and 8 hours retained the otoprotective effect without significantly reducing antitumor activity; waiting longer than 12 hours post-cisplatin to administer STS resulted in a loss of the otoprotective activity.

A study of the pharmacokinetic interaction of STS co-administration with carboplatin or cisplatin showed no significant effects on the plasma pharmacokinetics of free platinum in the guinea pig ototoxicity model. STS has the potential to inhibit CYP2C8, CYP2C9, and CYP2C19, but very low potential to induce CYP enzymes.

Administration of single intravenous (IV) STS doses of up to 30 g/m^2 to anesthetized dogs showed no effect on heart rate or blood pressure, however, doses ≥ 60 g/m^2 led to muscular twitching and profound electrolyte and hemodynamic changes, cardiovascular, and respiratory changes (including hypoxemia and metabolic acidosis) that proved fatal to 3 of 5 dogs within 24 hours of dosing. The cardiovascular and respiratory effects appeared to be secondary to a rapid rise in sodium. In addition, the 60 g/m^2 dose in dogs resulted in urinary bladder filling to overflowing within minutes of the injection, with marked diuresis in the 4/5 dogs that survived to the 3-hour time point after injection. In rats given a single IV STS dose of 116. g/m^2 immediately after mannitol (to disrupt the blood-brain-barrier) there were seizures, consistent with the muscular twitching in dogs at the 60 g/m^2 dose level; no seizures occurred in the absence of mannitol. This data suggests that in patients with a compromised blood-brain-barrier, there may be a potential for STS-related seizures.

There are no chronic toxicology studies investigating the safety of IV-administered STS. Thiosulfate is an endogenous molecule and there is a long history of human use of STS both at high IV doses as a drug, at least acutely, and at low concentrations as a food additive. In addition, for the current indication STS is given on a limited basis on the same schedule as

cisplatin (1-6 days/21-28-day cycle for up to 8 cycles) and only in combination with cisplatin. Given these considerations and the intended submission under the 505(b)(2) pathway, FDA did not request chronic toxicology by the IV route of administration. In addition to the single dose studies already discussed, the Applicant cited data from limited repeated dose studies of STS given by IP injection to guinea pigs or hamsters for up to 8 daily doses with no clear evidence of toxicity. In rats (4/group) given intramuscular (IM) sodium thiosulfate at a dose of 0.6 g/m^2 for 4 weeks there were pathological findings of changes in the capillary walls of the thyroid and adrenal cortex. Following 3 months of treatment with STS, the vessels of the kidneys displayed atrophy of the glomeruli and dilation of the glomerular capillaries, which were permeable to plasma. Increased permeability of liver capillary walls and an increase in Küppfer cells was also present in this study. Overall this study suggested some potential for damage to capillaries and renal toxicity with long term daily administration of high doses of STS, though the relevance of these findings to STS given by the intended route the intended dose intensity is limited.

STS showed no genotoxic potential in Ames and micronucleus assays. Carcinogenicity studies by the IV route of administration have not been conducted and are not necessary to support the safety of a drug intended for use in patients with advanced cancer in combination with cisplatin. Oral administration of STS was not embryotoxic or teratogenic in embryofetal development studies in mice, rats, hamsters, or rabbits. The highest dose in any of these studies was in the rabbit, 6 g/m^2 (~half the highest clinical dose of 12.6 g/m^2 based on BSA). In addition, STS has poor bioavailability, suggesting that the exposure in animals was significantly lower than in humans and making the relevance of this animal data for the current indication questionable. In one cited study hamsters did receive a single daily (multiple injections over 10 hours) STS dose of 9 g/m^2 during organogenesis and there were no reported developmental effects. A pharmacokinetic study in gravid ewes suggests that there is no significant transfer of STS across the placenta. While the available embryofetal development data are of questionable relevance given the intended clinical dose of 12.8 g/m2 and the IV route of administration, STS is given only in combination with cisplatin in the intended patient population. As cisplatin is a genotoxic drug with embryotoxic and teratogenic effects in animals, no additional developmental studies with STS are warranted. The label includes references to the cisplatin label for relevant pregnancy considerations. Based on the available data, there was no clear need for the “Females and Males of Reproductive Potential” section of the label specifically for STS; this section was therefore removed and there are no

recommendations for use of contraception for STS alone. There are no outstanding nonclinical issues for this 505(b)(2) application that would prevent the approval of PEDMARK for the prevention of cisplatin-mediated ototoxicity.

Refer to Section 20.6 for the pharmacology/toxicology review of boric acid levels and proposed non-substitutability statement in the label during the resubmission.

5.2 REFERENCED NDAS, BLAS, DMFS

The Applicant's Position:

There are no referenced NDAs, BLAs, or DMFs related to nonclinical pharmacology or toxicology for the PEDMARK NDA.

5.3 PHARMACOLOGY

The Applicant's Position:

Primary pharmacology

Effects of sodium thiosulfate on platinum-induced ototoxicity

Numerous studies in vitro and in animals have shown that sodium thiosulfate (STS) can protect against ototoxicity associated with platinum-based chemotherapy (Otto et al, 1988; Church et al, 1995; Kaltenbach et al, 1997; Saito et al, 1997; Muldoon et al, 2000; Wang et al, 2003; Stocks et al, 2004). Importantly, STS has been shown to inhibit ototoxicity even when administration is delayed for up to 8 hours after systemic platinum-based chemotherapy administration in rats (Dickey et al, 2005) and guinea pigs (Neuwelt et al, 1996).

Sodium thiosulfate was the most effective of several drugs tested as a protectant against CIS-induced ototoxicity in hamsters and provided a nearly complete protection (Church et al, 1995; Kaltenbach et al, 1997).

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). 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 loss in the basal and second turns of the cochlea. Damage to the outer hair cell s was mild when STS intra-peritoneal (IP) (8 g/m^2) was given concurrently, but was severe when STS dose was given 3 and 6 hours later (Saito et al, 1997). Otto et al (1988) confirmed the strong protective effect of STS IP against CIS-induced ototoxicity in guinea pigs: STS (12.8 g/m^2) 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.

In guinea pigs, STS blocked carboplatin-induced ototoxicity when administered IP 2 hours after carboplatin (Neuwelt et al, 1996). Protection against carboplatin-induced cochlear damage was observed when STS (14.64 g/m^2) was given at 2, 4, or 8 hours after carboplatin (192 mg/m^2); however, there was no protection if STS was given 24 hours after carboplatin.

In rats, STS intravenous (IV) protected against CIS-induced ototoxicity, even when STS 8 g/m^2 was given 8 hours after CIS (36 mg/m^2) (Dickey et al, 2005).

Mechanism(s) of Action

Several mechanisms of STS protection may be responsible for its effects, including conversion of the alkylating drug into a non-cytotoxic compound by thiol group binding of the electrophilic platinum to form a rapidly excreted complex, scavenging reactive oxygen species, and increasing levels of reducing agent. Furthermore, the cochlea may act similarly to the kidney to concentrate STS in perilymph or endolymph and enhance protection in the local environment (Dorr, 1991).

Within 4 hours after the end of CIS administration, free active platinum has largely disappeared from the circulation; however, it has recently been reported for mice and humans that platinum can accumulate and remain in the cochlea for many months after the last CIS treatment, making the cochlea uniquely susceptible to CIS-induced damage (Breglio et al, 2017). 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 defenses (Hazlitt et al, 2018; Sheth et al, 2017; Evans and Halliwell, 1999; Dehne et al, 2001; Rybak et al, 2007).

Cisplatin can react directly with STS to form the four-coordinate Pt (II) species [Pt(S2O3)4]6- with Pt-S bonds (Sooriyaarachchi et al, 2016). The Pt-thiosulfate complex is formed rapidly in extracellular fluid and this complex is cleared from plasma without cellular uptake and binding to intracellular macromolecules (Uozumi et al, 1984). At high molar excess, STS binds to and

inactivates the electrophilic platinum compounds CIS and carboplatin in vitro (Dedon and Borch, 1987; Elferink et al, 1986). Upon simultaneous administration of STS with CIS in guinea pigs, it was noted that a Pt-thiosulfate complex formed in plasma can still distribute through the blood cochlear barrier and that prevention of ototoxicity is probably related to the inhibition of cellular uptake of free CIS or the binding of CIS to intracellular macromolecules (Saito et al, 1997). A study in rabbits, where plasma samples were analyzed by a bioassay specific for bioactive CIS, showed that STS reduced bioactive CIS within 5 minutes in a dose dependent manner reaching complete inactivation of CIS at a 400-fold molar ratio for STS (Iwamoto, 1985). Results also indicated that CIS did not subsequently return to its active form.

However, the study also showed that bioactive CIS in plasma declined rapidly after IV administration also in the absence of STS. A 10 fold decline in free bioactive CIS was observed within 60 minutes after administration of CIS. In the clinical studies, STS was administered 6 hours after the end of infusion with CIS and hence the direct interaction between free CIS and STS appears 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 ototoxicity 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).

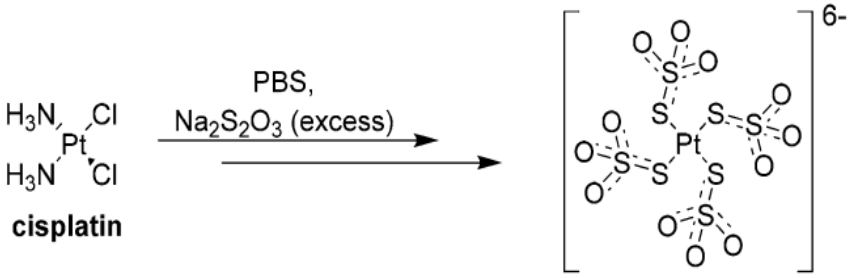
Importantly, while STS as an anion cannot diffuse through cell membranes and consequently distributes mainly in extracellular fluid, Marutani et al (2015) demonstrated that STS does enter cells, at least partially through the sodium sulfate cotransporter 2. This was also associated with an increase in anti-oxidant glutathione levels. Using renal and hepatic cell lines, Bijarnia et al (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 induced by 28-day adenine treatment, simultaneous oral treatment with STS resulted in improved renal glutathione levels, anti-oxidant enzymes and reduced oxidative stress (Mohan et al, 2017). While specific publications that measure oxidative stress and anti-oxidant factors in the cochlea after CIS with or without STS have not been found, it seems likely that a positive effect of STS on

intracellular glutathione levels and other anti-oxidant enzymes can contribute to the prevention of CIS-induced ototoxicity.

The FDA's Assessment:

FDA reviewed the cited papers and generally agrees with the Applicant's summary. The thiosulfate portion of STS can form covalent bonds with cisplatin and the normally slow kinetics of the reaction are increased in the presence of high (relative to cisplatin) concentrations of STS (Elferink, et al. 1986). The formation of a Pt−STS complex has been characterized as a four-coordinate Pt(II) species, $[Pt(S_2O_3)_4]^{6-}$, that occurs through the external sulfur of STS (Figure 1). This complex is inactive and excreted renally.

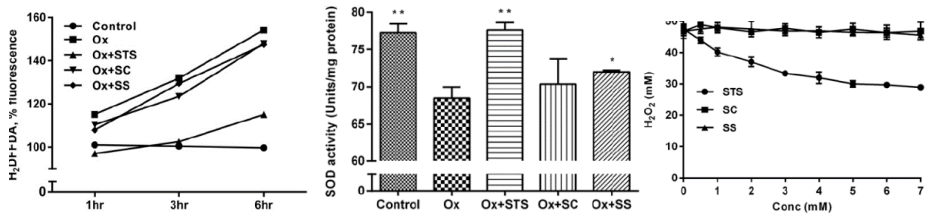
Figure 1: Depiction of a Cisplatin Complex with STS as Observed by X-ray Crystallography



(Excerpted from Hazlitt, et al. 2018)

While STS is an anion that does not diffuse across cell membranes, the Applicant cited data from Marutani et al. (2015) showing that it can transported across cells by the sodium sulfate cotransporter 2. In addition, Bijarnia et al. (2015) showed that incubation of LLC-PK1 (proximal tubule kidney cell line) with STS (but not sodium chloride (SC) or sodium sulfate (SS)) was able to reduce oxalate-induced intracellular oxidative stress and H_2O_2 release as well as stabilizing levels of superoxide dismutase (SOD) (Figure 2). Other authors showed similar anti-oxidant activity for STS including its ability to react with GSSG (oxidized glutathione) to produce reduced glutathione in the presence of hydroxyl radicals or peroxides ((Sen, et al. (2008), Lee, et al. (2016)) and a potential to produce hydrogen sulfide by reaction with trans-sulfuration enzymes.

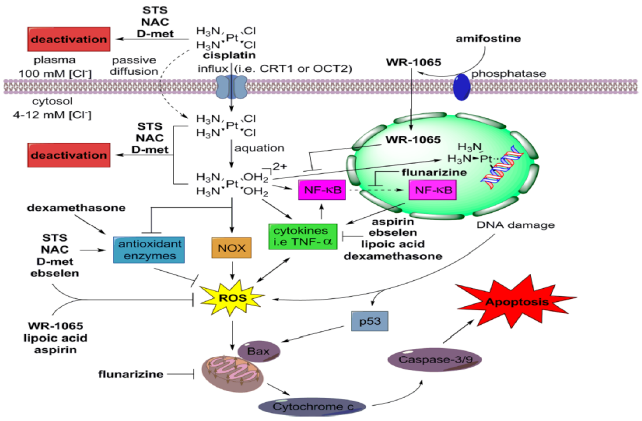
Figure 2: STS Effects on Oxidative Stress Markers



(Adapted from Bijarnia et al., 2015)

Although the cellular and molecular mechanisms by which cisplatin causes ototoxicity are not fully understood, scientists postulate that cisplatin-induced hearing loss is due to uptake of cisplatin into cochlear hair cells by various transporters such as copper transporter 1 (CTR1) or, in the case of inner-ear hair cells, organic cation transporters (OCT1−3). Cisplatin can accumulate in the perilymph and cochlear cells, where it may lead to cell death by cisplatin-mediated DNA damage and activation of apoptosis through DNA-damage induced pathways and to the excessive generation of reactive oxygen species (ROS); the ROS can also trigger cell death and stimulation of cochlear inflammation including the release of proinflammatory cytokines such as TNF-α, IL-1β, and IL-6. STS can, therefore, also potentially reduce cisplatin-induced ototoxicity through its roles in quenching ROS (e.g., H_2O_2) and preserving the activity of antioxidant enzymes (e.g., SOD), as well as by forming biologically inactive complexes with cisplatin to effectively reduce exposure to active cisplatin (Hazlitt et al (2018) (Figure 3)).

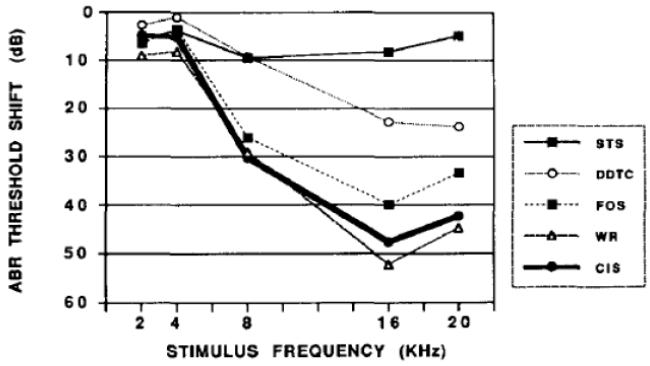
Figure 3: Schematic of Cisplatin-Induced Ototoxicity and the Mechanistic Pathways of Otoprotective Clinical Candidates



(Excerpted from Hazlitt et al. 2018)

The Applicant cited the study of Church et al (1995) investigating the effects of sodium thiosulfate (STS), diethyldithiocarbamate (DDTC), WR-2721 (WR), or Fosfomycin (FOS) against cisplatin-induced ototoxicity. Hamsters received a series of 5 cisplatin injections (3 mg/kg once every other day, intraperitoneally (i.p.)) either alone or in combination with 1600 mg/kg STS, 300 mg/kg DDTC, 18 mg/kg WR, or 300 mg/kg FOS (n = 10/group). Injections of both cisplatin and each of the other drugs were within of each other. Ototoxicity was assessed electrophysiologically by auditory brainstem responses (ABRs) and anatomically by cochlear histology. Five animals in the cisplatin + FOS and two each in the cisplatin + WR and cisplatin alone groups died during the study. All the animals in the cisplatin + STS and cisplatin + DDTC groups survived. As shown in Figure 4, STS provided the most auditory protection, followed by DDTC. Thus, it appears that the agents that were protective against ototoxicity were also protective against mortality.

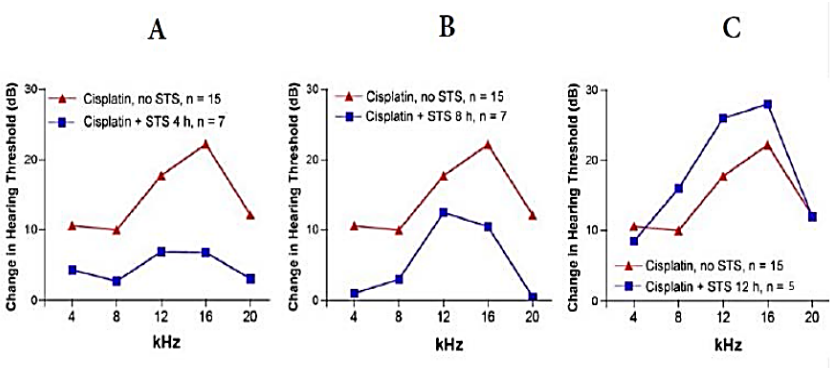
Figure 4: Effect of Treatment with STS, DDTC, WR, or FOS on ABR Threshold Shifts as Function of Treatment condition and tone burst frequency.



(Excerpted from Church, et al. 1995)

The Applicant also cited a study by Dickey, et al (2005) that evaluated the potential for STS to protect against cisplatin-induced ototoxicity in adult female Long-Evans rats given a single dose of cisplatin at 6 mg/kg (36 mg/m^2). At 4, 8, or 12 hours after cisplatin infusion, rats received a single IV dose of saline or STS at 8 g/m^2. Investigators tested auditory brainstem response thresholds at 4 to 20 kHz before and 7 days post-treatment. At the 7 -day post-dose timepoint, cisplatin significantly increased hearing thresholds at each frequency, however, STS given at 4 or 8 hours after cisplatin, decreased the cisplatin-induced increase in hearing threshold at all frequencies, suggesting that STS (8 g/m^2, IV) was otoprotective at the tested frequencies if given between 4 and 8 hours after cisplatin. STS given 12 hours post-cisplatin had a significantly diminished otoprotective effect.

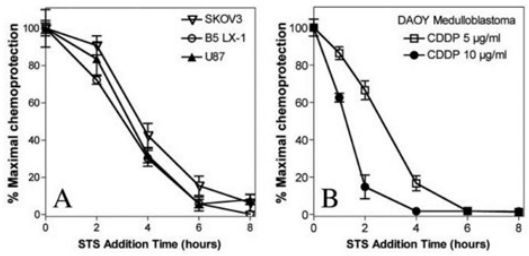
Figure 5: Effect of STS on Cisplatin-Induced Ototoxicity in Rats



(Excerpted from Dickey, et al., 2005)

The authors went on to examine effects of STS on cisplatin-mediated cell death using multiple human tumor cell lines (LX-1 SCLC, SKOV3, B5 LX-1, U87, and DAOY). When investigators added STS to cells within 1 hour of cisplatin treatment, STS prevented cell death. By 6 hours post cisplatin treatment, this protection was generally lost.

Figure 6: In Vitro Protection from Cisplatin Toxicity by STS in Tumor Cell Lines



(Excerpted from Dickey, et al., 2005)

Secondary Pharmacology

The Applicant's Position:

Sodium thiosulfate can protect against other types of toxicity associated with platinum-based chemotherapy; specifically, lethality in mice (Ishizawa et al, 1981), nephrotoxicity (Taniguchi and Baba, 1982; Iwamoto et al, 1984; Poore et al, 1984; Nagai et al, 1995), hematologic toxicity (Iwamoto et al, 1984; Neuwelt et al, 2004), hepatotoxicity (Liao et al, 2008) and CIS-impaired wound healing (Wile et al, 1993). In animal models, STS was shown to reduce kidney stone formation and prevent vascular calcifications (Asplin et al, 2009; Pasch et al, 2008).

The FDA's Assessment:

FDA did not review the additional studies on prevention of cisplatin-mediated impairment of wound healing, hepatotoxicity, and kidney stone formation in detail as they are not critical for the currently proposed indication. In general, the effects described by the Applicant do not appear to be secondary pharmacology, but rather related to the primary activity of STS described above.

Safety Pharmacology

The Applicant's Position:

Central Nervous System

An IV dose of STS at 60 mg/m^2 produced muscular twitching that was probably due to changes in serum electrolytes but no clinical signs suggesting an effect on central nervous system (CNS) function (Ref).

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). Sodium thiosulfate at a dose of 11.6 g/m^{2}produced no discernable neurotoxic effects when administered without BBBD or when administered 30 or 60 minutes after BBBD, ie, when the BBB was re-established. However, when given immediately after BBBD, STS produced neurotoxicity, including seizures. The results suggest that STS may produce CNS effects when large doses are given to patients with a compromised BBB, but that CNS effects are unlikely when the BBB is intact.

Cardiovascular System

Anesthetized and surgically instrumented 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 heart rate, blood pressure, or electrocardiogram 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 (Dennis and Fletcher, 1966). The QRS complex amplitude also decreased without a change in QT interval. These effects resolved within 3 hours post dose. The authors attributed the cardiovascular effects to sodium overload from STS. In addition, the increased blood pressure and tachycardia are also an appropriate adaptive response to hypoxia. Similarly, profound hypoxia can contribute to the flattened or inverted T waves as these typically reflect myocardial ischemia.

In another study, blood pressure and heart rate remained constant during and after administration of a single IV dose of STS at 3 g/m^{2}to anesthetized dogs (the STS dose would have taken perhaps two minutes to inject; therefore, the rate of STS administration was approximately 1.5 g/m^2/min) (Braverman et al, 1982).

In a third study, no changes in blood pressure or heart rate were reported during or immediately after 15-minute IV STS infusions at rates of 1.3, 2.0, and 2.7 g/m^2/min (Muldoon et al, 2000; personal communication).

Respiratory System

Dogs given an IV dose of STS at 30 g/m^2 at a rate of 1 g/m^2/min had no effects respiratory rate, partial pressure of oxygen [pO_2]; partial pressure of carbon dioxide [pCO_2], of blood pH (Dennis and Fletcher, 1966). However, dogs given STS at 60 g/m^2 at a rate of 3 g/m^2/min experienced rapid decreases in arterial pO_2 and pH, and increase in arterial pCO_2, and became tachypneic. One dog that died shortly after STS administration had pronounced pulmonary edema. Similar effects were produced in another dog by a single IV injection of sodium chloride at equimolar concentration. Respiratory effects observed with STS were considered secondary to a rapid rise in serum sodium concentration. In surviving dogs, these effects resolved within 3 hours post dose.

No significant changes were noted in blood gasses (pO_2; pCO_2) in dogs administered IV STS at either 20 g/m^2, 30 g/m^2, or 40 g/m^2 (Muldoon et al, 2000; personal communication).

Renal System

Sodium thiosulfate IV at 3 g/m^2 in anesthetized dogs produced a diuresis with a 50% increase in urine flow during the first ten minutes; 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.

Single IV doses of STS 60 g/m^2 caused the urinary bladder to fill to overflowing within minutes of injection. In the four of five dogs that survived the STS injection for > 3 hours, marked diuresis occurred (Ref).

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 hypokalemia (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).

The FDA's Assessment:

FDA generally agrees with the Applicant's position. Dr. Kimberly Benson previously reviewed the majority of the safety pharmacology data cited by the Applicant and her assessment is summarized here. In anesthetized dogs given single IV STS doses of up to 30 g/m^2, STS showed no effect on heart rate or blood pressure, however, at 60 g/m^2 STS led to muscular twitching and profound electrolyte and hemodynamic changes, cardiovascular, respiratory (including hypoxemia and metabolic acidosis), and electrolyte changes that proved fatal to 1/5 dogs shortly after dosing and to 2/5 more within 24 hours of dosing. The cardiovascular and respiratory effects appeared to be secondary to a rapid rise in sodium as they were also present in dogs that received equimolar doses of sodium and included increased blood pressure, tachycardia, flattening of T waves and frequent T-wave inversions as well as QRS voltage decrease but no change in the QT interval. In addition, dogs at the 60 g/m^2 dose had urinary bladder filling to overflowing within minutes of the injection, with marked diuresis in the 4/5 dogs that survived to the 3 hour time point after injection. A low dose of 3 g/m^2 caused up to 50% increase in urinary flow in anesthetized dogs. The effects resolved within 3 hours post-dose. In female Long-Evans rats, there were no neurotoxic effects following IV STS (11.6 g/m^2) without mannitol or 30 and 60 minutes after mannitol, but when STS was given immediately after mannitol (to disrupt the blood-brain-barrier), STS produced seizures, consistent with the muscular twitching in dogs at the 60 g/m^2 dose level. These data suggest that while STS is unlikely, under most circumstances, to be neurotoxic, in patients with a compromised blood-brain-barrier, there may a potential for STS-related seizures.

5.4 ADME/PK

The Applicant's Position:

Sodium thiosulfate is poorly absorbed after oral administration and has to be administered IV. Plasma levels of STS are maximal at the end of infusion and decline rapidly thereafter with a half-life of approximately 20 to 50 minutes. A return to pre-dose levels occurs within 3 to 6 hours after infusion. More than 95% of STS excretion in urine occurs within the first 4 hours after administration. Hence, there is no plasma accumulation when STS is administered on 2 consecutive days.

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. In animals, STS 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.

Metabolites of STS have not been determined. Thiosulfate is an endogenous intermediate product of sulfur-containing amino acid metabolism. Thiosulfate metabolism does not involve cytochrome P450 (CYP) enzymes; it is metabolized through thiosulfate sulfur transferase and thiosulfate reductase activity to sulfite, which is rapidly oxidized to sulfate.

No mass balance studies have been performed, but it is expected that non-renal clearance will mainly result in renal excretion of sulfates. A small part of the sulfane sulfur of STS may become part of endogenous cellular sulfur metabolism.

The FDA's Assessment:

FDA reviewed the cited data and generally agrees with the Applicant's assessment; however, the Applicant did include clinical data showing that sulfite and sulfate are metabolites of STS and that this metabolism (along with incorporation into endogenous sulphur compounds) is responsible for the clearance of up to 50% of the administered dose. (b) (4)

5.5 TOXICOLOGY

5.5.1 General Toxicology

The Applicant's Position:

Although no formal Good Laboratory Practices-compliant toxicology studies were discovered with STS, toxicity data for STS were reported in various literature studies. Single IV doses of STS are well tolerated at high dose levels in all species tested, with IV 50% lethal dose values reported to be 3.6 g/m^2 in mice, > 15 g/m^2 in rats, and 60 g/m^2 in dogs (EPA, 2003; RTECS, 2011). The adverse effects of STS are due to hypernatremia and secondary diuresis and disturbances in electrolyte and acid-base balance, which affect the function of the cardiovascular, respiratory, and neuromuscular systems. For example, while rats tolerated single IV doses of STS at 11.6 g/m^2, single IV doses above 15 g/m^2 cause behavioral toxic effects in the rat (convulsions or effect on seizure threshold) (RTECS, 2011).

The toxicity of single IV doses of STS may be a function not only of total dose but also of administration rate. For example, dogs tolerated single IV doses of STS at 30 g/m^2 given by 30-minute infusion (ie, at a rate of 1 g/m^2/min) (Dennis and Fletcher, 1966) and at 20 g/m^2 (n = 2), 30 g/m^2 (n = 1), or 40 g/m^2 (n = 1) given by 15-minute infusion (ie, at rates of 1.3, 2.0, and 2.7 g/m^2/min) (Muldoon et al, 2000) However, dogs did not tolerate single IV doses of STS at 60 g/m^2 given by 20-minute infusion (ie, at a rate of 3 g/m^2/min); indeed, one of five dogs died shortly after infusion ended, and two more dogs died within 24 hours of dosing (Dennis and Fletcher, 1966). At the higher infusion rate and total dose, there were hemodynamic, cardiovascular, respiratory and electrolyte changes that were attributed to the sodium ion in STS, because essentially identical effects occurred with single IV doses of sodium chloride at equimolar concentrations and rates.

Repeated IP doses of STS at high dose levels also are well tolerated. For example, there were no adverse effects when STS was administered IP to hamsters at 8 g/m^2 every other day for 5 doses, to guinea pigs at 8 g/m^2 every 5 days for 3 doses, or to guinea pigs at 12.8 g/m^2 daily for 8 days.

Taken together, the publicly available nonclinical information indicates that STS has low toxicity when administered IV.

The FDA's Assessment:

FDA confirmed the cited data regarding the single dose IV studies as the IV route is the intended route of administration for STS in the current indication. The same studies are discussed in the safety pharmacology section of this review.

While FDA agrees that publicly available nonclinical data suggest low toxicity of acute treatment of animals with STS by IV route (the proposed route of administration of STS clinically), the Applicant also cited literature showing that chronic intramuscular treatment of 4 rats/group with 0.6 g/m^2 STS daily for 4 weeks or 3 months resulted in vascular wall lesions in the thyroid and adrenal glands and, only after 3-months, in renal atrophy of the glomeruli and dilation of the glomerular capillaries, which became permeable to plasma. This study suggests some potential vascular and renal toxicity with long-term repeated high dose administration by this route. Finally, in more limited repeat-dose cited studies by intraperitoneal injection of STS in guinea pigs (12.8 g/m^2 daily for 8 days) or hamsters (8 g/m^2 every other day for 5 injections) there was no evidence of STS-mediated target organ toxicity.

5.5.2 Genetic Toxicology

The Applicant's Position:

Sodium thiosulfate is considered not to pose a genotoxic hazard to patients. 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 in human lymphocytes in vitro (Ohe et al, 1990). These results are not surprising, as thiosulfate is regularly used in bacterial and cell culture media as a source of sulfur (EPA, 2003).

The FDA's Assessment:

FDA agrees that the available data do not suggest a genotoxic risk from treatment with STS. The study by Prival et al. (1991) was previously reviewed by Drs. Mellon and Delatte; these data were from a study published by the U.S. Food and Drug Administration which reports that sodium thiosulfate pentahydrate tested negative for mutagenic potential in the bacterial reverse mutation assay (Ames test) using *S. typhimurium* strains TA98, TA100, TA1535, TA1537, TA1538, and *E. coli* strain WP2 (with or without S9 metabolic activation).

5.5.3 Carcinogenicity

The Applicant's Position:

Long-term studies in animals have not been performed to evaluate the potential carcinogenicity of STS.

The FDA's Assessment:

FDA agrees. Consistent with the principles in ICH S9, animal carcinogenicity studies are not typically expected to support the approval of a drug intended for the treatment of patients with advanced cancer and as the intended use of STS in the current indication is only in combination with the cytotoxic and genotoxic drug, cisplatin, carcinogenicity studies are not necessary.

5.5.4 Reproductive and Developmental Toxicology

The Applicant's Position:

Fertility

Nonclinical studies have not been conducted to evaluate the potential effects of STS on fertility or reproductive function in animals of either sex; however, STS is considered unlikely to add to the adverse effects associated with platinum-based chemotherapy itself.

Embryo-Fetal Development

In animal studies, STS was not embryotoxic or teratogenic in pregnant mice, rats, hamsters, or rabbits at maternal doses of up to 550, 400, 400, and 580 mg/kg/day (1.65, 2.4, 2.0, and 6.96 g/m^2/day), respectively, when STS was administered as an aqueous solution by oral intubation. Additionally, an IV pharmacokinetic (PK) study in gravid ewes indicated that STS does not cross the placenta.

Based on studies conducted in pregnant mice, rats, hamsters, and rabbits, STS is considered unlikely to affect embryofetal development in a female patient who is pregnant or to add to the risk of adverse effects on embryofetal development associated with platinum-based chemotherapy itself.

Pre- and Post-natal Development

There is no information about the potential effect of STS on postnatal development.

Sodium thiosulfate will be administered only in conjunction with platinum-based chemotherapy, which is generally cytotoxic and has the potential to affect development of multiple organ systems; therefore, any additional risk presented by STS is unlikely to be clinically meaningful.

The FDA's Assessment:

The Applicant did not conduct studies examining the potential for reproductive toxicity of STS, but relied instead on published literature. Fertility and pre-and postnatal development studies are not recommended to support a drug intended for the treatment of patients with advanced cancer. In addition, as the intended use of STS in the current indication is only in combination with the cytotoxic and genotoxic drug, cisplatin, FDA would not request additional embryo-fetal development studies.

The Applicant does cite previously conducted embryo-fetal development studies. FDA previously reviewed the cited literature regarding the potential for STS-mediated embryo-fetal developmental effects of STS. Relevant conclusions from the FDA review of these studies by Drs. Mellon and Delatte are consistent with the Applicant's conclusions and are included here.

> In animal studies, there are no teratogenic effects in offspring of hamsters treated during pregnancy with sodium thiosulfate in doses similar to those given intravenously to treat cyanide poisoning in humans (Willhite, 1983). In other studies, sodium thiosulfate was not embryotoxic or teratogenic in mice, rats, hamsters, or rabbits at maternal doses of up to 550, 400, 400 and 580 mg/kg/day, respectively (Food and Drug Research Labs,1972;Food and Drug Research Labs, 1974).

FDA notes that the embryofetal development studies conducted by FDA were investigating the toxicity following oral administration of STS. While animals received doses up to approximately half of the highest clinical dose for STS for the treatment of ototoxicity, the Applicant states that STS has poor oral bioavailability, suggesting that these studies may result in exposures that are significantly lower than the clinical exposure by the IV route of administration.

In the cited Wilhite 1983 study, previously reviewed by Dr. Delatte, hamsters received IP STS as a divided dose of 1800 mg/kg (~9 g/m^2; given 300 mg/kg every 2 hours over a 10 hour period) as a single agent or in combination with acetonitrile (methyl cyanide); STS alone did not have an

effect on development. Finally, the Applicant cites data from Graeme et al. (1999) in which five gravid ewes received IV STS (~1.8 g/m^2). Despite large increases in maternal thiosulfate levels following treatment, fetuses showed no clear increase plasma thiosulfate, suggesting that STS does not cross the placenta.

5.5.5 Other Toxicology Studies

The Applicant's Position:

Adverse effects at the STS injection site have not been reported in animals, and considerable clinical experience confirms that STS is well tolerated at the injection sites.

Studies have shown that excess STS beyond endogenous levels of thiosulfate is rapidly cleared from the body and there are no cumulative effects (EPA, 2003). In addition, no breakdown products which are anticipated to be toxic or likely to cause any unpredictable off target effects have been reported in the literature.

Impurities (b) (4) and solvents in the drug substance are fully controlled. Potential impurities and degradants of the drug product have been investigated and characterized (see Section 3.2.P.5).

The FDA's Assessment:

FDA agrees that injection site reactions are not predicted based on the available nonclinical data.

The Applicant is referring to impurity and degradant information in Section 3.2.P.5 of the NDA submission rather than a discussion in this document. See section 4.2 of this document for FDA's assessment of the safety of impurities at levels above the ICH Q3A/B thresholds.

G. Sachia Khasar, PhD	**Whitney S. Helms, PhD**
Primary Reviewer	Supervisor

6 CLINICAL PHARMACOLOGY

6.1 EXECUTIVE SUMMARY

The FDA's Assessment:

The Applicant seeks approval for sodium thiosulfate (STS) (b) (4) injection (PEDMARK) for the prevention of ototoxicity induced by cisplatin (CIS) chemotherapy in patients 1 month to <18 years of age with localized, non-metastatic, solid tumors. The clinical data to support the proposed indication are from two randomized, open-label Study SIOPEL 6 and Study COG ACCL0431. Patients were randomized 1:1 to receive either STS over 15 minutes intravenous infusion 6 hours after each CIS dose (CIS+STS) or chemotherapy that included CIS, without subsequent STS (CIS Alone). In the CIS+STS arm in Study SIOPEL 6, doses of STS were dependent on the child's weight (children > 10 kg received an equivalent of 12.8 g/m^2 PEDMARK, children ≥ 5 to ≤ 10 kg received an equivalent of 9.6 g/m^2 PEDMARK, and children < 5 kg received an equivalent of 6.4 g/m^2 PEDMARK). In the CIS+STS arm in Study COG ACCL0431, an equivalent of 10.2 g/m^2 PEDMARK was administered by intravenous infusion over 15 minutes. The proposed recommended dosing regimens are the same as these in Study SIOPEL 6. No pharmacokinetics (PK) data were collected in Study SIOPEL 6 or Study COG ACCL0431. In support of the proposed dosing regimens, population PK modeling and simulation approaches were applied to extrapolate PK across different weight and age groups. The Office of Clinical Pharmacology Division of Cancer Pharmacology II and Division of Pharmacometrics have reviewed the information contained in NDA 212937. This NDA is approvable from a clinical pharmacology perspective.

The key review questions focus on appropriateness of PEDMARK dose, recommendations PEDMARK dose in patients with renal impairment.

6.2 SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

6.2.1 Pharmacology and Clinical Pharmacokinetics

The Applicant's Position:

Sodium thiosulfate plasma or serum level (thiosulfate) is maximal at the end of infusion and declines rapidly thereafter, with a half-life reported mostly in the range of 20 to 50 minutes (Module 2.7.2, Section 2.2). 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 (thiosulfate), levels return to pre-dose values within 3 to 6 hours after STS infusion. Hence, there was no accumulation of STS in plasma if STS was administered on 2 consecutive days (Neuwelt et al, 1998).

Maximum plasma levels increase in a dose proportional manner over a dose range of 8 to 20 g/m^2 administered by a 15-minute IV infusion (Module 2.7.2, Section 2.2.2; Neuwelt et al, 1998).

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 extracellular spaces (Ivancevich, 1983; Farese et al, 2011).

Nevertheless, STS has the ability to enter cells at least partly through the sodium sulfate co-transporter 2, and causes intracellular effects such as the increase in antioxidant 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 antioxidant status is considered to contribute to the mechanism of action of ototoxicity prevention by STS. Because CIS has shown to accumulate in the cochlea with long-term retention, the ability of STS to enter the cochlea to reduce oxidative stress allows prevention of CIS-induced damage (Breglio et al 2017).

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

Sodium thiosulfate (thiosulfate) is excreted through glomerular filtration. After administration, STS (thiosulfate) levels in urine are high, and approximately 50% of the STS dose is excreted unchanged in urine, nearly all within the first 4 hours after administration (Neuwelt et al, 1998;

Ivankovich et al, 1983; Farese et al, 2011). Newman (1946) demonstrated that STS renal clearance correlated with inulin clearance as a measure for the glomerular filtration rate (GFR).

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

The FDA's Assessment:

FDA agrees with the Applicant's characterization of sodium thiosulfate or thiosulfate clinical pharmacokinetics. Nine published studies were relied on as a bridge to support characterization of the clinical PK and ADME . The studies were reviewed by the review team and found scientifically relevant to the proposed product, because they use the same active moiety (sodium thiosulfate) as contained in the Sponsor's drug product, and the doses tested are scientifically relevant to the proposed recommended dosage. The list of the nine published studies are provided below.

1. Population PK modeling and simulation: Farese et al, 2011; Neuwelt et al, 1998; Neuwelt et al, 2006; Doolittle et al, 2001
2. Distribution: Kowalski et al, 1952 for Plasma Protein Binding
3. Metabolism: Hildebrandt et al, 2008; Bilska-Wilkosz et al, 2017; Szczepkowski et al, 1961
4. Excretion: Neuwelt et al, 1998; Ivankovich et al, 1983; Farese et al, 2011
5. PK in hemodialysis patients: Farese et al, 2011

Please refer to the Section 5.3 for FDA's assessment of the mechanism of action of sodium thiosulfate in the prevention of ototoxicity induced by CIS.

6.2.2 General Dosing and Therapeutic Individualization

General Dosing

The Applicant's Position:

Two studies (International Childhood Liver Tumor Strategy Group [SIOPEL] 6 and Children's Oncology Group [COG] ACCL0431) were conducted to demonstrate the efficacy and safety of STS in pediatric patients treated with CIS. SIOPEL 6 was designed to administer 20 g/m^2 STS (adjusted for body weights <10kg) 6 hours after completion of a 6-hour CIS infusion, which were to be administered every 2 weeks for up to 6 cycles in patients with standard risk hepatoblastoma (SR-HB). COG ACCL0431 was designed to administer 16 g/m^2 STS (or 533 mg/kg when CIS was dosed on a per-kg basis) 6 hours after the completion of a CIS infusion in

patients with various tumor types. In the COG ACCL0431 study, the CIS dosing regimen was determined by each site's disease-specific cancer treatment protocols in use at the time, but the durations of CIS infusions were generally between 1 to 6 hours with up to 5 daily administrations per cycle. Together, these studies administered STS as single administrations in conjunction with CIS treatment cycles based on the disease-specific treatment regimen for the patient (e.g., up to 5 daily administrations per cycle for up to 6 cycles) for approximately a 3- to 6-month period).

Because no PK analysis was performed for either study, the following approach was taken to support the PEDMARK dosing recommendations:

As STS has been applied clinically for almost a century, available literature has been used to describe the PK characteristics of IV administered STS.

Sodium thiosulfate plasma data of 45 administrations from 16 individual patients (aged 2.5 to 69 years) has been made available to Fennec by authors from other academic studies investigating STS administration to prevent ototoxicity in brain cancer patients (Neuwelt et al, 1998; Doolittle et al, 2001; Neuwelt et al, 2006). Data were obtained after IV administration by a 15-minute infusion, the same duration of infusion as used in SIOPEL 6 and COG ACCL0431. Various STS dose levels up to 20 g/m^2 were used. Using these data, Fennec performed a non-compartmental analysis and developed a population pharmacokinetic (popPK) model to evaluate potential maturation and growth effects on STS exposure when extrapolating to smaller children.

Administration of STS is associated with a high sodium load and results in a transient increase in serum sodium levels. Because of the potential for adverse effects due to increases in serum sodium (eg, nausea and vomiting) and because renal maturation effects during the first year after birth may influence sodium handling, serum sodium levels were monitored in SIOPEL 6. For these reasons, the STS dose in SIOPEL 6 was also adjusted for children <10kg of body weight. To confirm the consistency of STS dosing over different cycles and between body weight (based dose) groups in SIOPEL 6, a non-compartmental analysis was performed on the increase in sodium serum levels.

SIOPEL 6 and COG ACCL0431 confirmed that STS treatment at 16 to 20 g/m^2 resulted in statistically significant reductions in ototoxicity in patients with various types of solid tumors treated with CIS (Module 2.5, Section 4.4) while not affecting the anti-tumor efficacy of CIS in patients with localized, non-metastatic solid tumors (Module 2.5, Section 4.5). The studies also confirmed that the main and most frequently reported adverse events (AEs) attributable to STS were vomiting, nausea, and AEs related to electrolyte changes (ie, hypernatremia, hypokalemia, and hypophosphatemia) (Module 2.5, Section 5.8). None of these were considered dose limiting at a dose level of 16 or 20 g/m^2.

Depending on the tumor type, CIS administration may occur over multiple days per cycle followed each time by an STS infusion (as was done in the CIS+STS arm of COG ACCL0431). At the end of an IV infusion of STS, the plasma level of STS (thiosulfate) is maximal and declines rapidly thereafter with a half-life reported in the range of 20 to 50 minutes. Levels return to pre-dose levels within 3 to 6 hours after STS infusion (Module 2.7.2, Section 3.1). Therefore, the negligible amount of STS remaining at 6 hours after completion of an STS infusion would not be expected to interact with a subsequent CIS infusion.

Growth and maturation in pediatric patients need to be considered for the dose recommendation. The dose level of STS was normalized to body surface ara (BSA) in clinical studies, including SIOPEL 6 and COG ACCL0431, and literature (Neuwelt et al, 2006; Doolittle et al, 2001; Neuwelt et al, 1998). SIOPEL 6 included children of 1.2 months to 8.2 years and COG ACCL0431 between 1 and 18 years. Efficacy and safety outcomes were similar and independent of the ages or weights of the children, or the absolute doses of STS. Dose normalization to BSA is further supported by results from a non-compartmental analysis in patients >2.5 years where comparable maximum thiosulfate exposure levels and similar plasma half-lives were observed between adults and children (Module 2.5, Section 3.1.2.1). Similarly, popPK modelling and simulation of STS (thiosulfate) plasma levels after BSA-normalized STS dosing showed consistent exposure over wide age (1 to 18 years) and weight (>10 kg) ranges.

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 STS dosing scheme normalized to BSA and adjusted for body weight did not affect the efficacy of otoprotection or AEs in this study, both when analyzing different groups based on body weight (Module 2.5, Section 4.6 and Section 5.9.1). These clinical findings are supported by results from the popPK model for STS plasma levels incorporating renal glomerular maturation (Module 2.5, Section 3.1.2.1); simulation results showed consistent STS exposure over the different body weight and STS dose groups. Further support is also observed in the results from the analysis of the transient increase in serum sodium levels following STS administration (Module 2.5, Section 3.1.2.1). Results similarly showed that the small transient increase in sodium after STS administration was consistent and independent of body weight and dose groups.

(b) (4) the STS doses administered in SIOPEL 6 where dosing was based on the higher molecular mass of STS pentahydrate: 20 g/m^2, 15 g/m^2, and 10 g/m^2, respectively. This dosing regimen is considered effective and tolerable in a pediatric population with localized, non-metastatic solid tumors, as supported by the 2 clinical

studies (SIOPEL 6 and COG ACCL0341), literature, and available PK analyses. In addition, the results support delayed administration of PEDMARK with varying CIS treatment regimens (ie, number of cycles, days per cycle, and daily CIS doses) for a range of tumor types. Finally, (b) (4) there were no dose-limiting toxicities observed at these doses as well as to maximize the possibility for efficacy in the pediatric patient population that includes young children.

(b) (4)

The FDA's Assessment:

(b) (4) The efficacy and safety results from trial SIOPEL6 support the proposed dosage in patients with weight between 5-10 kg and >10 kg. The PopPK model predicted the proposed dosage would produce Cmax in patients weighing 5 to 10kg that is comparable to that in patients weighing more than 10kg. The predicted Cmax in patients weighing less than 5kg is 16% and 36% lower than the predicted Cmax in patients weighing more than 10kg based on popPK simulation.

In Study SIOPEL 6, CIS and STS were administrated once every treatment cycle of two weeks (Q2W) for patients (age range 1 month to less than 18 years) with histologically confirmed newly diagnosed hepatoblastoma. In Study COG ACCL0341, CIS and STS were administered

more frequently than once per treatment cycle in some patients . For example, patients with germ cell tumors (GCTs) received up to 5 doses of CIS (20 to 40 mg/m^2) and STS (equivalent of 10.2 g/m^2 STS anhydrous injection) per cycle. The average number of doses of STS was 2.5 per cycle. To understand the effect of multiple STS administrations per cycle on the safety and efficacy of CIS, the Applicant conducted an exploratory analysis in patients by STS dose < 3 versus ≥ 3 per cycle as a response to FDA's information request. No meaningful differences were observed in the safety (Table 4) and efficacy (hearing loss, event-free survival, or overall survival) between the patients with the number of STS doses < 3 and ≥ 3 per cycle.

Table 4: Summary of the (b) (4) adverse drug reactions (b) (4) by number of STS doses per Cycle (COG ACCL0431, Safety Population)

SOC PT	CIS+STS Arm		
	<3 STS Doses per Cycle (n=34)	≥3 STS Doses per Cycle (n=25)	Total (N=59)
Gastrointestinal disorders			
Vomiting	1 (2.9)	3 (12.0)	4 (6.8)
Nausea	4 (11.8)	1 (4.0)	5 (8.5)
Metabolism and nutrition disorders			
Hypernatremia	6 (17.6)	1 (4.0)	7 (11.9)
Hypokalemia	11 (32.4)	5 (20.0)	16 (27.1)
Hypophosphatemia	8 (23.5)	4 (16.0)	12 (20.3)
Immune system disorders			
Hypersensitivity	3 (8.8)	2 (8.0)	5 (8.5)

Abbreviations: ADR=adverse drug reaction; CIS=cisplatin; COG=Children's Oncology Group; PT=preferred term; SOC=system organ class; STS=sodium thiosulfate.

Sources: Table 13 of Response to Clinical Pharmacology Information Request: NDA 212937 (17 April 2020)

Therapeutic Individualization

The Applicant's Position:

Pharmacokinetics Related to Intrinsic Factors

Age

Non-compartmental analysis of STS serum data obtained from 5 pediatric patients (mean age: 11 years; range: 2.5 to 16 years) and 11 adult patients (mean age: 46 years; range: 19 to 69 years) treated for brain tumors (Neuwelt et al, 1998; Neuwelt et al, 2006) indicated that the maximum STS plasma levels and the rate of decline thereafter were not influenced by age (Module 2.7.2, Section 2.2.2). These data support a nominal dose level based on BSA over a wide age range.

A 2-compartmental popPK model was developed based on data from these patients and from literature (Farese et al, 2011) to further investigate the influence of growth and renal maturation (Module 2.7.2, Section 2.2.3.1). Covariates were implemented in the model according to the following published relationships: lean body mass for the volume of distribution (of the central and peripheral compartments) (Peters et al, 2011) and BSA for renal clearance and an age-related adjustment for renal maturation (Tod et al, 2001). Two models were employed: one with constant non-renal clearance that best fit data in the available age range, and an additional one that scaled non-renal clearance to BSA to capture growth for very young children below 2.5 years.

The predicted maximum exposure at 20 g/m^2 STS for a virtual pediatric population was similar to levels at the end-of-infusion published for adults (Neuwelt et al, 1998). In the age range above 2 years and body weight above 20 kg, the results were independent of the PK model used for non-renal clearance (Module 2.7.2, Section 2.2.3.2). In the PK model with constant non-renal clearance, maximum predicted exposure remained constant until the dose level was decreased by 25% (to 15 g/m^2) for children between 5.0 and 10.0 kg. This predicted exposure was still in the effective range of a dose of 16 g/m^2 that showed otoprotective effects in COG ACCL0431 for children aged 1 to 18 years. If the PK model with a growth-dependent non-renal clearance was used, the predicted maximum exposure in thiosulfate gradually increased for children below 20 kg, which is then corrected by the dose level adjustments for children <10 kg (to 75%) and <5 kg (to 50%).

The above PK exposure analyses for STS regard the exposure to thiosulfate as it relates to efficacy for the prevention of ototoxicity. Thiosulfate exhibits a relatively low toxicity profile, and acute toxicity and dose-limiting effects in animals have been attributed to the sodium load if a high IV dose of STS is administered rapidly. In SIOPEL 6, sodium levels were monitored, and

the transient increase in sodium was generally considered of limited clinical significance (Module 2.5, Section 5.6.1). Nevertheless, these sodium data can also be used to analyze the consistency of dosing and exposure of STS. The maximum increase in serum sodium levels after STS administration was similar for children with a body weight >10 kg receiving 20 g/m^2 compared with those with a body weight of 5 to10 kg receiving 15 g/m^2, across all cycles (Module 2.7.2, Section 2.2.4). In addition, the transient increase in sodium for individual children remained within the same range and was independent of age, weight, BSA, or total daily STS dose.

Cytochrome P450 Induction and Inhibition

Metabolism of STS is independent of CYP. Two standard in vitro studies were performed to evaluate the potential effect of STS on the inhibition and induction of CYP isoforms (Module 2.6.4, Section 7 and Module 2.6.5). In human liver microsomes, the half-maximal inhibitory concentration (IC_{50}) of STS corrected for osmolality effects for CYP2C8, CYP2C9, and CYP2C19 were 89.2 mM, 95.4 mM, and 104 mM, respectively, 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 from 1 of 3 donors after 72 hours incubation at 10 and 25 mM STS (approximately 2.2-fold and 27% of positive control; just above the respective thresholds of 2.0-fold and 20%).

Pharmacokinetics in Renal Impairment

Approximately 50% of STS (thiosulfate) is cleared through glomerular filtration; hence, renal clearance of STS decreases in patients with renal disease (Newman et al, 1946; Farese et al, 2001). In patients requiring hemodialysis, the total clearance declined approximately 50% and became similar to the non-renal (metabolic) clearance in healthy subjects. The maximum STS plasma levels increased approximately 25% (Module 2.7.2, Section 2.2.7). Sodium thiosulfate has also been administered safely to hemodialysis patients at a dose of 12.5 to 25 g, 3 times per week after each dialysis and for up to 5 months (Mathews et al, 2011).

PEDMARK is administered only after CIS treatment. Children receiving chemotherapy for cancer are routinely and carefully monitored for renal function. As a precaution to prevent CIS-induced nephrotoxicity, patients receive saline fluid hydration treatment with high chloride content before and after CIS administration to stimulate glomerular filtration and urinary flow. It is likely that under these conditions, glomerular filtration and excretion of STS is maintained, even when the tumor or chemotherapy has reduced renal function below normal values for the child's age.

Pharmacokinetics in Hepatic Impairment

Metabolism of STS occurs through thiosulfate sulfur transferase and thiosulfate reductase activity and is independent of CYP. Hence, STS metabolism is not confined to the liver; thus, the clinical impact on the STS PK in patients with hepatic impairment is likely limited.

Pharmacokinetics Related to Extrinsic Factors

Drug-drug Interactions

Sodium thiosulfate does not bind to human plasma proteins (Kowalski et al, 1952). The chemical properties of STS and observations that STS does not distribute readily across membranes (ie, 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. Results of in vitro studies did not reveal inhibition of CYP isoforms in microsomes close to the expected maximum plasma concentration for STS; only a borderline induction result for CYP2B6 was noted in cryopreserved hepatocytes from 1 donor (Module 2.5, Section 3.1.2.2).

For the overall risk assessment for PK drug-drug interactions, the STS PK profile and treatment schedule also need to be taken in to account. The duration of STS exposure during administration is limited and returns to pre-dose values within 3 to 6 hours after administration. High plasma levels are even more limited, given its half-life of 20 to 50 minutes. Furthermore, STS treatment is not chronically administered and is confined to a limited number of intermittent, single administrations generally over a 3- to 6-month period in conjunction with CIS treatment cycles. Even when given on consecutive days, plasma levels do not accumulate.

Therefore, given the in vitro results, STS chemical characteristics, PK profile, metabolism, and treatment schedule, clinically relevant PK drug-drug interactions would not be expected for STS. The potential for pharmacodynamic interaction of STS to interfere with CIS anti-tumor efficacy is considered elsewhere (Module 2.5, Section 3.2, Section 3.3, Section 3.4, and Section 4.5).

The FDA's Assessment:

Simulation results based on the final popPK model and sensitivity analyses suggest that the recommended dosage would produce comparable exposure across the proposed weight bands for approval. (b) (4) In SIOPEL 6, the dose of sodium thiosulfate at the recommended dosage resulted in an average transient increase in serum sodium levels approximately 5 to 7 mmol/L. Maximum increase in serum sodium was generally observed at 1

hour after infusion and levels had returned to baseline by 18 h or 24 h after administration. The transient increase in sodium for individual pediatric patients remained within the same range and was independent of weight (See Section 19.4 for more details).
FDA agrees with the Applicant that the thiosulfate clearance decreases by approximately 50% and Cmax increases approximately 25% in patients requiring hemodialysis compared with healthy subjects with normal renal function (See Section 19.4 for more details). See Section 6.3.2.3 for evaluation of the dosing regimen in patients with renal impairment. No dose adjustment is recommended for patients with renal impairment or end-stage renal disease.

FDA agrees with the Applicant that hepatic impairment has limited impact on the thiosulfate PK as thiosulfate metabolism is modulated by thiosulfate sulfur transferase and thiosulfate reductase activity.

FDA agrees with the Applicant that clinically relevant drug-drug interactions (DDI) are unlikely for sodium thiosulfate at the proposed dosing regimen (See Section 6.3.2.4 for more details).

Outstanding Issues

The Applicant's Position:

None.

The FDA's Assessment:

FDA agrees.

6.3 COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

6.3.1 General Pharmacology and Pharmacokinetic Characteristics

The Applicant's Position:

PEDMARK is a clear and colorless sterile solution of STS anhydrous provided as a sterile solution in single use, United States Pharmacopoeia (USP) (b) (4) 100 mL, clear glass vials that contain STS at 80 mg/mL, water for injection (USP), boric acid (b) (4), and sodium hydroxide and hydrochloric acid for pH adjustment. The active ingredient, STS, is an inorganic salt that contains one thiosulfate anion and two sodium ions. Compared to commercially available STS drug products, PEDMARK has used drug substance STS anhydrous instead of STS pentahydrate and has lowered the boric acid concentration.

Given the high solubility of STS and the IV route of administration, no further specific formulation development was needed.

An overview of the absorption, distribution, metabolism, and elimination properties of PEDMARK is provided in Section 5.4 for nonclinical pharmacology/toxicology and Section 6.2.1 for clinical pharmacology and PK.

The FDA's Assessment: Refer to FDA's assessment in Section 6.2.1 for clinical PK and pharmacology.

6.3.2 Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

The Applicant's Position:

Yes. In SIOPEL 6, the 20 g/m^2 STS dose was 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 STS dosing scheme normalized to BSA and adjusted for body weight did not affect the efficacy of otoprotection or AEs in this study, both when analyzing different groups based on body weight. Results from the popPK model and simulations incorporating maturation and growth effects support the use of a nominal STS dose level normalized to BSA as well as the proposed dose adjustments to 75% at a body weight of 5.0 to 10.0 kg and to 50% at a body weight below 5.0 kg. This dose regimen is expected to result in effective thiosulfate exposure levels as supported by simulation using popPK models irrespective of the functional relationship between growth (body size) and non-renal clearance. Only in the case of children with a body weight below 5.0 kg, the assumption of constant non-renal clearance would result in a potential underexposure. However, the same non-renal clearance in infants and adults seems highly unlikely and when growth aspects are incorporated in the popPK model, simulated STS (thiosulfate) exposure at the end of infusion is within the same effective range for all children.

In SIOPEL 6 and COG ACCL0431, STS was administered 6 hours after the end of the CIS infusion. Cisplatin plasma levels were not determined in the clinical studies; however, a CIS population PK model from adults was used to extrapolate and predict exposures in children. Analyses showed that when STS is administered after a 6 hour delay, a direct interaction of STS with CIS causing interference with tumoricidal effects is unlikely. This is because (i) CIS

reactivity requires immediate pharmacodynamic initiation of tumoricidal effect following administration; (ii) only unbound CIS is active against tumor cells and protein binding is a major route of inactivation; (iii) unbound CIS levels rapidly decline by a factor of at least 10-fold after the end of the CIS infusion; (iv) persisting unbound platinum levels are likely to include platinum species without significant cytotoxic activity due to CIS metabolism. Hence, any remaining platinum levels 6 hours after CIS administration are considered insignificant compared to the total CIS exposure. Only in (newborn) children below 5 kg body weight, remaining platinum exposure may be above 10% because renal function is still developing in newborns during the first months. To what extent this fraction would still be active CIS or clinically significant is unknown.

Overall, the CIS data in the literature and the popPK model extrapolation support the delayed treatment of STS by 6 hours after the end of CIS as suggested by non-clinical studies and employed in clinical studies SIOPEL 6 and COG ACCL0431.

The FDA's Assessment:

FDA agrees with the proposed dosing regimen based on the clinical pharmacology information and the popPK simulations. FDA recommends not to administer PEDMARK if the time before starting the next cisplatin dose is less than 10 hours away, when cisplatin is to be administered on multiple consecutive days. FDA agrees that the predicted unbound plasma platinum levels 6 hours after CIS administration are low compared to the total CIS exposure (Table 5). The 6-hour delay of PEDMARK treatment after cisplatin chemotherapy can prevent interaction of sodium thiosulfate with the unbound cisplatin in plasma.

Table 5. Predicted Cisplatin Pharmacokinetics by Unbound Platinum in Children Mean (5th - 95th Percentile) prediction of 1000 virtual subjects per category

Weight	Dose	CL	V_{total}	Half-life	AUC0-∞ exposure	% AUC12-∞ remaining*
Kg		L/h/m²	L/m²	H	µg·min/mL to 100mg/m²	+12h to ∞ total AUC
2 – 5	1.8 mg/kg	16 12 - 20	58 46-75	Alpha: 0.05 h Beta: 3.5 h	394 297-510	13% 7.4 - 21%
5 – 10	2.7 mg/kg	16 13 - 21	37 31 – 44	Alpha: 0.10 h Beta: 2.4 h	376 289 – 477	5.6% 3.0 - 9.1%
10-15	78 mg/m²	20 15 - 25	30 27 – 33	Alpha: 0.13 h Beta: 1.9 h	314 240 – 394	2.5% 1.3 - 4.1%
15-25	80 mg/m²	22 17 - 28	25 22 – 28	Alpha: 0.17 h Beta: 1.6 h	283 219 – 358	1.2% 0.6 - 2.0%

** Residual unbound platinum exposure in plasma beyond 12 h after the start of CIS treatment (6 hour after the end of infusion; AUC12-∞) relative to the total exposure (AUC0-∞).*

Source: Table 10 of Section 2.7.2 Summary of Clinical Pharmacology Studies

Based on the 20 to 50 minute half-life of thiosulfate in plasma, a negligible amount of sodium thiosulfate remains in plasma 10 hours after completion of a sodium thiosulfate infusion. Therefore, subsequent cisplatin infusions administered no sooner than 10 hours after the completion of a PEDMARK infusion may avoid an interaction between thiosulfate and unbound cisplatin in plasma.

FDA identified that the proposed popPK model for STS has limitations in predicting the exposure with the proposed dosing regimen in young pediatric patients, as the developed model is based on a limited dataset of five pediatric subjects and eleven adults. Although the model fits the observed data well, the model is not able to describe the PK in pediatric patients at a younger ages (<6 months). Because of these uncertainties, sensitivity analysis was also conducted to test the robustness of the model simulations when the non-renal clearance is related to the body size, or when the non-renal clearance also follows the maturation function.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

The Applicant's Position:

Yes. The proposed PEDMARK dose normalized to BSA and adjusted for body weight when administered 6 hours after the end of each CIS infusion (up to 6 hours duration) is considered effective and tolerable in a pediatric population with localized, non-metastatic solid tumors, as supported by the 2 clinical studies (SIOPEL 6 and COG ACCL0341), literature, and available PK analyses. In addition, the results support delayed administration of PEDMARK with varying CIS treatment regimens (ie, number of cycles, days per cycle, and daily CIS doses) for a range of tumor types.

The FDA's Assessment:

FDA agrees.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

The Applicant's Position:

No. Based on the assessment of intrinsic factors (ie, age, weight (SIOPEL 6 only), and gender), no dose adjustment or change in regimen is required.

No clinically meaningful differences in safety findings were observed between the age, gender, or weight subgroups within each study that would necessitate changes to the dosing recommendations in the proposed label.

SIOPEL 6 and COG ACCL0431 did not enroll patients <1 month of age, as patients in this age group have less well-developed sodium homeostasis; therefore, the safety of PEDMARK in this age group is unknown, 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. No new safety concerns were identified in these studies. 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.

The FDA's Assessment:

The proposed dosing regimen considered body weight and body surface area. Simulation results based on the final popPK model and sensitivity analyses suggest that at the recommended dosage, the geometric mean (±SD) maximum concentration (Cmax) was 13 ± 1.2 mM in pediatric patients with cancer. The predicted Cmax in patients weighing 5 to 10kg is comparable to the predicted Cmax in patients weighing more than 10kg (9.5% lower to 3% higher); the predicted Cmax in patients weighing less than 5kg is between 16% and 36% lower than the predicted Cmax in patients weighing more than 10kg.

FDA agrees with the Applicant that no initial dose adjustment is needed for renal impairment. In the worst-case scenario, the Cmax of thiosulfate increased about 25% in patients requiring hemodialysis (off-hemodialysis). The Cmax of thiosulfate in patients with renal impairment is expected to lower than the Cmax of thiosulfate (IV injection equivalence of STS anhydrous 6.4 g/m^2 in children) indicated for acute cyanide poisoning. The labeling includes serum sodium and electrolytes monitoring for patients with glomerular filtration rate below 60 mL/min/1.73m^2. In addition, the labeling recommend that PEDMARK is not administrated for patient with serum sodium > 145 mmol/liter.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

The Applicant's Position:

Dosing recommendations and the rationale for the recommendation is provided in Section 6.3.1, General Pharmacology and Pharmacokinetic Characteristics.

There have been no food effect studies with STS.

Sodium thiosulfate does not bind to human plasma proteins (Kowalski et al, 1952). The chemical properties of STS and observations that STS does not distribute readily across membranes (ie, 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. Results of in vitro studies did not reveal inhibition of CYP isoforms in microsomes close to the expected maximum plasma concentration for STS; only a borderline induction result for CYP2B6 was noted in cryopreserved hepatocytes from 1 donor (Module 2.5, Section 3.1.2.2).

For the overall risk assessment for PK drug-drug interactions, the STS PK profile and treatment schedule also need to be taken in to account. The duration of STS exposure during administration is limited and returns to pre-dose values within 3 to 6 hours after administration. High plasma levels are even more limited, given its half-life of 20 to 50 minutes. Furthermore, STS treatment is not chronically administered and is confined to a limited number of intermittent, single administrations generally over a 3- to 6-month period in conjunction with CIS treatment cycles. Even when given on consecutive days, plasma levels do not accumulate.

Therefore, given the in vitro results, STS chemical characteristics, PK profile, metabolism, and treatment schedule, clinically relevant PK drug-drug interactions would not be expected for STS. The potential for pharmacodynamic interaction of STS to interfere with CIS anti-tumor efficacy is considered elsewhere (Module 2.5, Section 3.2, Section 3.3, Section 3.4, and Section 4.5).

The FDA's Assessment:

Food does not affect the absorption of STS, as it is administered by IV infusion.

FDA agrees with the Applicant that clinically relevant drug-drug interactions (DDI) are unlikely for STS at the proposed dosing regimen based on following:

1. The DDI potential of STS as an inhibitor of major CYP enzymes is unlikely based on AUCR calculations using static mechanistic models (FDA guidance for industry *In Vitro Drug Interaction Studies – Cytochrome P450 Enzyme and Transporter- Mediated Drug-Drug Interactions*). The predicted AUCR ratio for CYP2C19 is higher than the 1.25 cut-off value at Cmax. However, a clinically relevant DDI between STS and a CYP2C19 substrate is unlikely, as there is a very short time period for STS plasma concentration around Cmax in a treatment cycle (thiosulfate half-life is 20 to 50 minutes and STS is administrated not more than 5 days daily in a given treatment cycle).

Table 6 AUCR calculations of major CYP enzymes

CYP Enzymes	IC_{50} (mM)	Probe Substrate	f_m	ACUR (Cmax = 13.3 mM; K_i = ½ IC_{50})
CYP1A2	180		1	1.15
CYP2C8	96.4	Repaglinide	0.71	1.18
CYP2C9	104	Celecoxib	0.89	1.22
CYP2C19	89.2	S-mephenytoin	0.91	1.26

2. In vitro, sodium thiosulfate is an inducer of CYP2B6 but not of CYP1A2 or CYP3A4.

Induction of CYP2B6 was noted in cryopreserved hepatocytes from 1 of 3 donors after a 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%). The clinical DDI potential of STS as an inducer of CYP2B6 is low as the thiosulfate half-life is 20 to 50 minutes and STS is administrated not more than 5 days daily in a given treatment cycle.

3. The DDI potential of STS as a substrate of major CYP enzymes is unlikely as CYP isozymes are not involved in thiosulfate metabolism.

X	X
Wentao Fu Clinical Pharmacology Primary Reviewer	Jeanne Fourie Zirkelbach Team Leader
X	X
Youwei Bi Pharmacometrics Primary Reviewer	Jiang Liu Team Leader

7 SOURCES OF CLINICAL DATA

7.1 TABLE OF CLINICAL STUDIES

The Applicant's Position:

Table 7: Efficacy and Safety 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	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
			Post-surgery: Within 21 days; 2 courses at an interval of 2 weeks				

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

Abbreviations: ASAP=as soon as possible; BSA=body surface area; CIS=cisplatin; EFS=event-free survival; GCT=germ cell tumor; HB=hepatoblastoma; IV=intravenous(ly); OL=open-label; OS=overall survival; RD=Randomized; SR-HB=standard-risk hepatoblastoma; STS=sodium thiosulfate

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

[a] Five SIOPEL 6 randomized patients withdrew prior to treatment. Of the 109 patients remaining, 4 children randomized to the CIS+STS arm never received STS. These patients were assigned to the CIS Alone arm for the Safety Population (CIS Alone=56; CIS+STS=53) but remained in the CIS+STS arm for the ITT Population (CIS Alone=52; CIS+STS=57).

[b] Two COG ACCL0431 patients randomized to the CIS+STS arm did not receive STS and were excluded from both the Safety and Efficacy Populations (Observation=64; CIS+STS=59).

[c] "Newly diagnosed" meant previously untreated and not currently receiving cancer treatment for the diagnosis that made the child eligible for the study.

The FDA's Assessment:

FDA agrees with the Applicant's descriptions of the studies as outlined in Table 7.

8 STATISTICAL AND CLINICAL EVALUATION

8.1 REVIEW OF RELEVANT INDIVIDUAL TRIALS USED TO SUPPORT EFFICACY

The Applicant's Description:

The efficacy evaluation for this submission is based on SIOPEL 6 and COG ACCL0431.

SIOPEL 6 and COG ACCL0431 were designed and conducted by academic consortia for the purposes of establishing clinical practice guidelines for prevention of CIS-induced ototoxicity. In addition to being conducted in accordance with Good Clinical Practice (GCP), these studies were considered adequate and well-controlled studies as defined by 21CFR314.126 and form the primary evidence of efficacy of STS supporting this application. Both studies were open-label, multicenter, randomized, controlled studies evaluating the otoprotective effect of STS. The studies differed with regard to patient population, CIS and STS dosing, and assessment of the primary efficacy endpoint, as described below.

The patient populations differed between studies; children with a localized tumor type (SR-HB) were enrolled in SIOPEL 6 while children with various tumor types (both localized and disseminated) were enrolled in COG ACCL0431. As such, the demographics and Baseline disease characteristics differed between studies.

The dosing and administration of STS also differed between the studies (Table 8); though, importantly, in both studies, STS administration was within the desired 6- to 12-hour window relative to CIS administration. In both studies, STS was administered via a 15-minute IV infusion, beginning 6 hours after completion of each CIS infusion, as is the proposed STS dosing regimen for marketing. The dose of STS used in both studies was normalized to BSA, and, in both studies, adjusted based on the weight of the child for low-weight children.

The dosing regimen for CIS differed between disease types, with varying regimens of CIS being administered over 1 to 6 hours (Table 8). In SIOPEL 6, CIS dosing was weight based and administered as a 6-hour IV infusion. Four courses of CIS were given pre-surgery and 2 additional courses were given post-surgery. In COG ACCL0431, CIS 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, or associated hydration/mannitol diuresis; eligibility criteria required CIS infusion durations up to a maximum duration of 6 hours and an intended cumulative dose of $\geq$200 mg/m^2. When multiple daily doses of CIS were scheduled in COG ACCL0431, there must have been at least a 10-hour delay between any STS infusion and the beginning of the next day's CIS infusion.

The primary efficacy endpoint in SIOPEL 6 and COG ACCL0431 was the proportion of children with hearing loss; this was assessed by different criteria in each study, as described in Table 8, which is in keeping with the geographical regions of the consortia that conducted each study.

In both studies, all audiologic data were centrally reviewed by blinded reviewers. Hearing assessments in both studies included the following measurements:

Measurement of bilateral pure tone air conduction thresholds at 8000, 6000, 4000, 2000, 1000, and 500 Hz (Brock Grade specifies to start with the high frequencies)

Otoscopy

Immittance evaluation (Brock allows for tympanometry as well)

Where available, measurement of otoacoustic emissions including transient evoked otoacoustic emissions and distortion product otoacoustic emissions

For children too young to cooperate with standard audiometric measurements, brainstem auditory evoked response should have been obtained instead

Additionally, American Speech Language Hearing Association (ASHA) specified that ultra-high frequency audiometry (bilateral pure tone air conduction thresholds at 9000 to 16000 Hz) was performed where available.

Regardless of the differences in study designs, populations, and efficacy evaluations between the studies, the efficacy of STS as an otoprotectant was consistent across studies, as described below.

Table 8: Key Design Elements of Phase 3 Studies in the STS Clinical Program

Study Name	SIOPEL 6	COG ACCL0431
Design	Multi-center, Open-label, Randomized, Controlled	Multi-center, Open-label, Randomized, Controlled
Regions	52 sites in 12 countries (United Kingdom, Ireland, Belgium, Denmark, France, Italy, Switzerland, Spain, Australia, New Zealand, United States, and Japan)	38 COG hospitals in the US and Canada
Tumor Type/Eligibility Criteria	• Histologically confirmed newly diagnosed HB • Standard-risk HB: PRETEXT I, II or III; Serum AFP >100 µg/L; No additional PRETEXT criteria • Children were not eligible if they had: o Previous chemotherapy o Hepatocellular carcinoma o Treatment starting more than 15 days from written biopsy report o Abnormal renal function o Recurrent disease o A previous hypersensitivity to STS	• Newly diagnosed[a] with any histologically confirmed GCT, HB, medulloblastoma, neuroblastoma, osteosarcoma, or other malignancy to be treated with CIS dose of ≥200 mg/m^2 (infused over ≤6 hours). This may have been the child's first or subsequent malignancy. • Receipt of prior CIS or carboplatin was not allowed, but other types of prior chemotherapy were permitted, including on a current treatment regimen to which CIS would be added • Normal audiometry results prior to enrollment • Performance status score ≥50 (Karnofsky criteria for >16 years; Lansky criteria for ≤16 years) • Serum sodium levels within a normal range, adequate hematological function, and adequate renal function

Table 8: Key Design Elements of Phase 3 Studies in the STS Clinical Program

Study Name	SIOPEL 6	COG ACCL0431
Treatment Groups (Randomization)	CIS (CIS Alone) vs CIS+STS (1:1)	CIS (Observation arm) vs CIS+STS (1:1)
Stratification Factors	• Country • Median age >15 months, <15 months • PRETEXT stage	• Prior cranial radiation • Without prior cranial radiation: o Age <5 years, ≥5 years o Duration of CIS infusion (<2 hours versus ≥2 hours)
Treatment	• CIS by infusion over a duration of 6 hours: 80 mg/m^2 (body weight >10 kg) 2.7 mg/kg (body weight ≥5 to ≤10 kg) 1.8 mg/kg (body weight <5 kg) • STS by a 15-minute infusion 6 hours after completion of CIS: 20 g/m^2 (body weight >10 kg) 15 g/m^2 (body weight ≥5 to ≤10 kg) 10 g/m^2 (body weight <5 kg)	• CIS: Eligibility required CIS treatment to be ≥200 mg/m^2 (variable) infused over a duration of ≤6 hours • STS: 16 g/m^2 by a 15-minute infusion 6 hours after completion of CIS (or 533 mg/kg for children whose therapeutic protocol administered CIS on a per-kg basis due to young age or small body size)

Table 8: Key Design Elements of Phase 3 Studies in the STS Clinical Program

Study Name	SIOPEL 6	COG ACCL0431
Treatment Regimen	• Pre-operative: 4 courses of CIS with or without STS on Days 1, 15, 29, and 43 • Post-operative: 2 courses of CIS with or without STS as soon as possible (but within 21 days of surgery completion) on Days 1 and 15. If surgery was delayed, 2 courses may also have been given prior to surgery, on Days 57 and 71 • Prior to surgery, patients with PD after 2 or more courses of CIS (with or without STS) were considered treatment failures and stopped STS treatment • Further chemotherapy treatment recommendations were provided, including treatment with PLADO	• 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 (except cumulative dose intended must be ≥200 mg/m^2), schedule, infusion rate (up to a maximum infusion of 6 hours) or associated hydration/mannitol diuresis • Treatment regimens in use included additional chemotherapeutic agents (other than CIS) depending on tumor type • 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
Duration of Follow-up	Per protocol, up to 5 years (or longer as clinically indicated and according to national guidelines); actual median 4.27 years	Per protocol, 10 years from the date that the patient started the study; actual median 5.33 years
Number of Patients Randomized	114 (CIS Alone=53; CIS+STS=61)[b]	125 (Observation [CIS]=64; CIS+STS=61)[c]

Table 8: Key Design Elements of Phase 3 Studies in the STS Clinical Program

Study Name	SIOPEL 6	COG ACCL0431
Age range[d]/ Gender (M/F)	1.2 months to 8.2 years (59 M/50 F)	1 to 18 years (76 M/47 F)
Primary Endpoint	Rate of Brock Grade (Brock et al, 1991) ≥1 hearing loss, measured by PTA, after[e] end of study treatment or at an age of at least 3.5 years, whichever was later	Proportional incidence of hearing loss between the CIS+STS arm and the Observation arm, as defined by comparison of ASHA criteria (ASHA, 1994) at Baseline and the 4-week follow-up evaluation
Secondary Endpoints	Response to preoperative chemotherapy, complete resection, complete remission, EFS, OS	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

Abbreviations: AFP=alpha fetoprotein ; CIS=cisplatin; ASHA= American Speech Language Hearing Association; COG=Children's Oncology Group; EFS=event-free survival; GCT=germ cell tumor; HB=hepatoblastoma; ITT=Intent-to-Treat; PRETEXT=pre-treatment tumor extension; OS=overall survival; PD=progressive disease; PLADO=CIS (=platinol) and doxorubicin; PTA=pure-tone audiometry; SIOPEL=International Childhood Liver Tumor Strategy Group; SR-HB=standard-risk hepatoblastoma; STS=sodium thiosulfate.

[a] "Newly diagnosed" meant previously untreated and not currently receiving cancer treatment for the diagnosis that made the child eligible for the study.

[b] Five SIOPEL 6 randomized patients withdrew prior to treatment. Of the 109 patients remaining, 4 children randomized to the CIS+STS arm never received STS. These patients were assigned to the CIS Alone arm for the Safety Population (CIS=56; CIS+STS=53) but remained in the CIS+STS arm for the ITT Population (CIS=52; CIS+STS=57).

[c] Two COG ACCL0431 patients randomized to the CIS+STS arm did not receive STS and were excluded from both the Safety and Efficacy Populations (Observation=64; CIS+STS=59).

[d] Age was recorded at the time of diagnosis. The age range presented is based on the Safety Population.

[e] All children had a definitive hearing evaluation when they completed treatment and were aged 3.5 years or older. If the child was old enough, the evaluation was done within 6 to 12 weeks after the last CIS dose.

The FDA's Assessment:

FDA generally agrees with the Applicant's description of the studies; more detailed assessment is described below by study.

8.1.1 SIOPEL 6

Trial Design

The Applicant's Description:

A comparison of the SIOPEL 6 and COG ACCL0431 trial designs was provided in Section 8.1, including a comparison of key design elements in Table 8.

The FDA's Assessment:

FDA agrees with the Applicant's description of the studies as outlined in Table 8.

Study Endpoints

The Applicant's Description:

A comparison of the SIOPEL 6 and COG ACCL0431 study endpoints is provided in Section 8.1.

In SIOPEL 6, Brock grading (0 to 4, minimal to severe) was performed yearly until a reliable result (ie, a hearing test that could be centrally reviewed) was obtained through pure-tone audiometry (PTA) (age ≥3.5 years) (Module 2.7.3, Section 1.3.1.2.2). Though specified, children in SIOPEL 6 were often too young to have reliable Brock Grade assessments performed at Baseline. After the initial Baseline evaluation before the start of treatment, interim audiometry was recommended after every second cycle of CIS. In children younger than 3.5 years of age, interim audiometry was strongly recommended. All children had a definitive evaluation when they completed treatment and were aged 3.5 years or older. If the child was old enough, the evaluation was done within 6 to 12 weeks after the last CIS dose. If the children had hearing loss ≥Brock Grade 1 on the definitive audiologic evaluation, that was considered as positive for ototoxicity.

The FDA's Assessment:

FDA agrees with the Applicant's description of the Brock grading as the endpoint to assess hearing for patients in SIOPEL 6. See Table 9 below for description of Brock grades. Because Brock grades use a cutoff of 40 dB HL, mild hearing loss may not be detected. All audiological data were centrally reviewed.

Statistical Analysis Plan and Amendments

The Applicant's Description:

Analysis Populations

In SIOPEL 6, the primary efficacy analysis was conducted on the Intent-to-Treat (ITT) Population, which comprised all randomized patients except those for whom informed consent was withdrawn prior to start of study treatment, and those for whom study treatment would have been inappropriate because they had to be considered "high risk," regardless of whether or not study drug was administered. The Per-Protocol (PP) Population comprised all patients in the ITT Population who had received at least 1 dose of STS (if randomized to the CIS+STS arm); this population was used for evaluation of the secondary endpoints of response to preoperative chemotherapy, complete resection, complete remission, event-free survival (EFS), and overall survial (OS).

Analysis of Efficacy Endpoints

Primary Analysis

In SIOPEL 6, the primary endpoint was hearing impairment defined as Brock Grade ≥1 hearing loss determined by PTA at age ≥3.5 years. The Brock Grade of the better ear was used for the analysis (as shown in Table 9). Hearing impairment rates were calculated and compared between the 2 randomized treatment groups. 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 non-stratified Chi-square test with significance level of 5% and power of 80%. It was carried out in the ITT Population. Patients without a hearing loss assessment were counted as a failure (ie, had hearing loss) in this analysis. In response to FDA feedback, the primary efficacy analysis was changed from the Modified Intent-to-Treat (mITT) Population, which included patients in the ITT Population with a definitive hearing evaluation, to the ITT Population in the final statistical analysis plan (SAP). The ITT Population comprised all 109 patients in the study, and 101 patients 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 non-stratified Chi-square test was chosen to avoid any loss of power incurred by a stratified analysis. Patients without a hearing loss assessment were counted as a failure (ie, had hearing loss) in this analysis. A Cochran Mantel Haenszel (CMH) test stratified by factors used for the randomization was also performed.

In addition, the relative risk of hearing loss in the CIS+STS arm compared with the CIS Alone arm was also calculated, and shown with an exact 95% confidence interval (CI)

(2.5% confidence limit to 97.5% confidence limit). Multiple sensitivity analyses were conducted to assess the robustness of the primary efficacy results.

Table 9: 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

PTA=pure-tone audiometry

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

Source: Brock et al, 1991

Secondary Analyses

Multiple secondary endpoints were evaluated, as shown in Table 8. Event-free survival and OS was assessed and the methods of analysis are summarized below.

In SIOPEL 6, EFS was calculated from the time of randomization to the first of the following events: progression, relapse, second primary malignancy, or death. Event-free survival of patients without an event was censored at the time of last known follow-up visit. Overall survival was calculated from the time of randomization to death. Overall survival of alive patients was censored at the time of last known alive. Event-free survival and OS were graphically compared between the randomized groups by Kaplan-Meier plots. A log-rank test was calculated, stratified by the stratification factors used for randomization. The hazard ratio between the 2 groups was calculated by stratified Cox regression and was presented together with its asymmetrical 95% CI.

The statistical analyses for the remaining secondary endpoints conducted in SIOPEL 6 are summarized briefly below; full details can be found in SIOPEL 6 clinical study report (CSR) Section 4.6.3.2.3.

Response to preoperative chemotherapy: The percentage of responders (complete response [CR] and partial response [PR]) was compared between the groups with a Chi-square test or Fisher's exact test (if the statistical assumptions for the Chi-square test were not fulfilled).

Complete resection: Resection was reported as percentage of partial hepatectomy versus orthotopic liver transplantation (OLT) and was presented overall and by randomized group. The percentage of OLT was compared between the groups with a Chi-square test or Fisher's exact test (if the statistical assumptions for the Chi-square test were not fulfilled).

Remission status: Complete remission was defined as lack of evidence of residual disease and normal (for age) alpha fetoprotein (AFP) at the end of study treatment. The percentages of complete remission, PR, progressive disease (PD), death, and not evaluable were presented overall and by randomized group. The percentage of complete remission was compared between the groups with a Chi-square test or Fisher's exact test (if the statistical assumptions for the Chi square test were not fulfilled).

The FDA's Assessment:

FDA generally agrees with the Applicant's description of the efficacy endpoints. For the primary endpoint of hearing loss, the analysis was based on hearing loss assessments conducted within 6-12 weeks after the last dose for children 3.5 years or older. The Applicant's CSR noted that the last patient reached 3.5 years of age in September 2017, so all patients should have had the opportunity to complete their definitive evaluation. However, there may have been cases when patients died or were lost to follow up prior to this final definitive hearing assessment, resulting in missing assessments. As mentioned by the Applicant, patients with missing assessments were imputed as having hearing loss in the primary analysis.

FDA also has the following comments regarding the Applicant's description of the analysis population and efficacy analysis methods:

1) The Applicant's ITT population comprised all randomized patients except those for whom informed consent was withdrawn prior to start of study treatment, and those for whom study treatment would have been inappropriate because they had to be considered "high

risk," regardless of whether or not study drug was administered. FDA does not agree with this definition and considers the ITT population to include all randomized patients. FDA will present the primary analysis results in this population with the excluded patients imputed as hearing loss.

2) The test for the primary analysis of hearing impairment was conducted at a nominal significance level of 5% (one-sided). There were two interim analyses for the primary endpoint and alpha was adjusted using a Lan-DeMets O'Brien Fleming alpha spending function: the first was after 34 patients were evaluable for the primary endpoint at a nominal alpha level of 0.00069 (one-sided) and the second was after 68 patients were evaluable at a nominal alpha level of 0.016 (one-sided), leaving a nominal alpha level of 0.045 (one-sided) for the final analysis. There was no multiplicity plan specified for the secondary endpoints, so they are considered exploratory only. Since the regulatory standard is to control type-1 error at a level of 5% (two-sided), all p-values reported for this study should be interpreted as nominal only.
3) The SAP pre-specified that the minimization method would be used for randomization. However, the Applicant noted in the CSR that the database provider (CINECA) used a randomized permuted block design with block size 4 instead, contrary to what was pre-specified in the protocol/SAP. Thus, while the SAP pre-specified a re-randomization test, this ultimately was not used due to the change in randomization scheme.

Protocol Amendments

The Applicant's Description:

Most amendments to the SIOPEL 6 protocol did not impact the study endpoints or assessments, safety meaurements, or analyses.

Those amendments impacting the safety assessments are described below.

Protocol Amendment 1

- Added Bedside Nursing Worksheet and Figure 12.1 (Summary schema of treatment, hydration, sodium monitoring, blood pressure monitoring, and deoxyribonucleic acid blood sampling with 4 example start times);
- Serum sodium monitoring time changed from 24 to 18 hours;

- The text "Additionally, if the serum sodium is 146 to 150 mmol/L at 1 hour, the individual clinician looking after the patient may decide whether or not to give mannitol" was added;
- Information was added regarding the use of anti-emetics.

Protocol Amendment 3

1. The cardioprotectant dexrazoxane was removed as a permitted concomitant medication in accordance with updated guidance from European Medicines Agency and clarification was added regarding the requirement for careful monitoring of cardiotoxicity;
2. The section on AE reporting was revised to add definitions; reference to events that were not to be regarded as serious adverse events (SAEs) were removed and replaced with "expected SARs (serious adverse reactions [SAR] which are expected can be reported on an 'expected SAR' form)";
3. The endpoints hypomagnesemia and renal toxicity were removed as events not collected as unexpected;
4. A section on monitoring pregnancies for potential SAEs was added;
5. The AE reporting period text changed from "occurring during therapy and until 30 days after the 'end of treatment visit"' to "from the date of commencement of protocol defined treatment until 30 days after the administration of the last treatment."

The FDA's Assessment:

The FDA agrees with the description of protocol amendments presented in this section. In addition, FDA acknowledges that clarification of the central audiology review procedures was added as part of Protocol amendment 1.

The SAP version 1.1 was amended to include the ITT population for primary efficacy analysis instead of the modified ITT (mITT) population and added a re-randomization test to account for the minimization method used for randomization. However, as mentioned above, FDA does not agree with the Applicant's definition of ITT population; and the ITT population should include all randomized patients. Additionally, the re-randomization test was not used as the randomization scheme did not follow protocol.

8.1.2 SIOPEL 6 Study Results

Compliance with Good Clinical Practices

The Applicant's Position:

This study was conducted in accordance with the current version of the applicable regulatory and International Council for Harmonisation (ICH)- GCP requirements, the ethical principles that have their origin in the principles of the Declaration of Helsinki, and the local laws of the countries involved.

The FDA's Assessment:

The FDA acknowledges the Applicant's statement of compliance with GCP in the SIOPEL 6 Clinical Study Report.

Financial Disclosure

The Applicant's Position:

All financial interests/arrangements with clinical investigators have been adequately addressed as recommended in the FDA Guidance for Clinical Investigators, Industry, and FDA Staff, Financial Disclosure by Clinical Investigators (2013); please see Section 19.2.

The FDA's Assessment:

In accordance with 21 CFR 54, the Applicant submitted a financial disclosure certification document in module 1.3.4. The document includes a list of all investigators who participated in SIOPEL 6.

Patient Disposition

The Applicant's Position:

A total of 129 children were registered and 114 children were randomized in the study (61 patients in the CIS+STS arm and 53 patients in the CIS Alone arm) (SIOPEL 6 CSR Table 14.1.2.3). Of the 15 patients registered but not randomized, 13 patients were not randomized due to other (unspecified) reasons, 1 patient was due to withdrawal of parental consent, and 1 patient was due to ineligibility (SIOPEL 6 CSR Listing 16.2.1.1). Of the 114 patients randomized, 5 patients withdrew prior to treatment (2 patients due to withdrawal of parental consent, 2 patients due to reclassification as high risk, and 1 due to ineligibility) (SIOPEL 6 CSR Listing 16.2.2.1).

Study completion was defined as completion of the post-treatment hearing assessment. Therefore, patient disposition for study completion was based on the ITT Population. Of the 109 children in the ITT Population, 101 (92.7%) completed the study and 8 (7.3%) did not complete the study. The proportion of children who completed the study was higher in the CIS+STS arm than the CIS Alone arm (55 of 57 patients [96.5%] vs 46 of 52 patients [88.5%], respectively). In the CIS+STS arm, 1 child (1.8%) did not complete the post-treatment hearing assessment due to death and 1 child (1.8%) due to other reasons. In the CIS Alone arm, 4 children (7.7%) did not complete the post-treatment hearing assessment due to death and 2 children (3.8%) due to other reasons (SIOPEL 6 CSR Table 14.1.2.2).

The FDA's Assessment:

The FDA generally agrees with the Applicant's description of patient disposition. Of 109 patients in the Applicant's ITT Population, 4 who were randomized to the CIS+STS arm did not receive STS and were analyzed in the CIS arm. As described above in Section 8.1.1, the Applicant's ITT population excluded 5 randomized patients who withdrew prior to treatment. However, FDA considers the ITT population to include all 114 randomized patients. In FDA's analysis of the primary endpoint of hearing loss, the 5 patients excluded from the Applicant's ITT population and the 8 patients who did not complete the study (missing hearing assessment) were counted as having hearing loss (i.e., that the treatment failed) for the primary analysis.

Protocol Violations/Deviations

The Applicant's Position:

A total of 23 children (21.1%) had protocol deviations during the study, all of whom had deviations in treatment compliance (for treatment compliance, see SIOPEL 6 CSR Section 5.4). 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) (Table 14.1.3). 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) (SIOPEL 6 CSR Listing 16.2.2.1).

The FDA's Assessment:

The FDA generally agrees with Applicant's description of protocol violations. Note that if the 5 patients randomized but not treated were considered protocol deviations in the 114 patient ITT population, then a total of 28 patients (24.6%) had protocol deviations. The reasons for protocol deviations/violations do not appear to be a significant cause of bias influencing the study results.

Table of Demographic Characteristics

The Applicant's Position:

Demographic characteristics were generally balanced between the CIS+STS and CIS Alone arms (Table 10).

Table 10: Summary of Patient Demographics (Safety Population; SIOPEL 6)

Variable	CIS Alone N=56	CIS+STS N=53	Total N=109
Age [a](months)			
N	56	53	109
Mean (SD)	18.1 (14.6)	18.9 (17.2)	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)

Variable	CIS Alone N=56	CIS+STS N=53	Total N=109
Sex, n (%)			
Female	25 (44.6)	25 (47.2)	50 (45.9)
Male	31 (55.4)	28 (52.8)	59 (54.1)
Race, n (%)			
White	36 (64.3)	28 (52.8)	64 (58.7)
Missing	6 (10.7)	11 (20.8)	17 (15.6)
Asian	7 (12.5)	6 (11.3)	13 (11.9)
Other	5 (8.9)	8 (15.1)	13 (11.9)
Black or African American	2 (3.6)	0	2 (1.8)
Height (cm)			
N	52	46	98
Mean (SD)	77 (11.9)	79.6 (15.1)	78.7 (13.5)
Median (Min, max)	76.0 (58, 113)	76.0 (45, 126)	76..0 (45, 126)
Weight [b] (kg)			
N	56	53	109
Mean (SD)	10.33 (3.19)	10.15 (3.85)	10.24 (3.51)
Median (Min, max)	9.55 (4.8, 20.7)	8.96 (2.6, 25.8)	9.30 (2.6, 25.8)

Abbreviations: CIS=cisplatin; CSR=clinical study report; max=maximum; min=minimum; SD=standard deviation; 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.

Source: SIOPEL 6 CSR Table 14.1.4.1.

The FDA's Assessment:

The FDA agrees with the demographic data as presented in Table 11 for the safety population. FDA also agrees with the demographic data for the ITT population efficacy population as presented in the SIOPEL 6 Clinical Study Report (see Table 11 below), note, race is missing for 6 patients in the CIS arm and 11 patients in the CIS+STS arm. This may be due to some EU countries not allowing the collection of race information. Demographic data were similar when considering all 114 randomized patients comprising the FDA's ITT population.

Table 11 Summary of Patient Demographics in the Efficacy Population, SIOPEL 6

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; 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.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The Applicant's Position:

Baseline disease characteristics were generally balanced between the CIS+STS and CIS Alone arms, with the exception of imbalances in the median AFP level and Pre-treatment Tumor Extension (PRETEXT) classification (see SIOPEL 6 CSR Table 14.1.4.1). The mean GFR for all patients in the Safety Set was 130.3 mL/min/1.73 m^2 and was similar in both treatment arms.

The majority of children had no caudate lobe involvement (89 patients [81.7%]), solitary tumor (98 patients [89.9%]), no evidence of tumor rupture (106 patients [97.2%]), no distant or lymph node metastases (107 patients [98.2%]) (though 2 patients [1.8%] had an uncertain status), and no portal vein involvement (91 patients [83.5%]). All patients with Baseline characteristics of multiple tumors, uncertain tumor rupture, uncertain distant metastases and uncertain lymph node metastases achieved complete remission at the end of treatment and none developed PD or had a relapse (see SIOPEL 6 CSR Listing 16.2.4.2, Listing 16.2.6.4, and Listing 16.2.6.6).

Diagnostic AFP levels >1000000 ng/mL have been shown to be a prognostic factor in hepatoblastoma (HB) outcome, and AFP levels between 1000 ng/ml and 1000000 ng/ml have been shown to have no prognostic value (Meyers et al, 2017). There was a slight imbalance in 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). Overall, 14 children (12.8%) had an AFP level of > 1000000 ng/mL, including 8 patients (14.0%) in the CIS+STS arm and 6 patients (11.5%) in the CIS Alone arm.

Overall, 8 children (7.3%) had an AFP level of < 1000 ng/mL, including 4 patients (7.0%) in the CIS+STS arm and 4 patients (7.7%) in the CIS Alone arm.

There was a slight imbalance in 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), although this was consistent with the method of randomization (SIOPEL 6 CSR Section 3.5.3). There was no noticeable trend in children with PRETEXT III classification and death; of the 6 children who died during the study, 5 had a PRETEXT II classification at Baseline (SIOPEL 6 CSR Listing 16.2.4.2 and Listing 16.2.7.6).

The FDA's Assessment:

The FDA agrees with the description of baseline characteristics described above for the **safety population** with the exception of the AFP level at diagnosis. The FDA reviewers calculate the median AFP at diagnosis as 192,682.1 ng/mL (range 273-5,489,165) for the CIS+STS arm and 77,090 ng/mL (range 187-2,632,584.7). This discrepancy does not directly impact the interpretation of the results.

For the **efficacy population**, see Table 12 below. Baseline disease characteristics were generally balanced between treatment arms and similar to the Applicant's summary of the safety population. Baseline characteristic data in all 114 randomized patients comprising the FDA's ITT population were similar to what was seen in the Applicant's ITT population .

Table 12 Baseline Disease Characteristics for the ITT Population, SIOPEL 6

Variable	CIS Alone (N=52)	CIS+STS (N=57)	Total (N=109)
GFR (mL/min/1.73 m^2)			
N	49	57	106

Variable	CIS Alone (N=52)	CIS+STS (N=57)	Total (N=109)
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)

Variable	CIS Alone (N=52)	CIS+STS (N=57)	Total (N=109)
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)
Beckwith Wiedemann			
Yes	2 (3.8)	1 (1.8)	3 (2.8)
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

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The Applicant's Position:

Cisplatin and STS were administered under the supervision of Investigators or attending staff, who monitored compliance. The mean CIS percent compliance (excluding PLADO) for the CIS+STS and CIS Alone arms were high and similar (97.55% and 97.28%, respectively) (Module 2.7.4, Section 1.2.3.1). The mean STS percent compliance in the CIS+STS arm was 94.79%. The mean CIS percent compliance (including PLADO) for the CIS+STS and CIS Alone arms was also high and similar (97.65% and 97.36%, respectively) (SIOPEL 6 CSR Table 14.3.1). The mean percent STS compliance in the CIS+STS arm (including PLADO) was 89.74%.

Concomitant medication use was not recorded comprehensively. The case report form (CRF) asked for "any other chemotherapy" and for "ototoxic medication," eg, aminoglycoside antibiotics, but not for other medication in general. In the CIS+STS and CIS Alone arms, the use of other chemotherapies was similar for carboplatin, doxorubicin, and irinotecan and the use of other ototoxic medications was similar as well (SIOPEL 6 CSR Table 14.3.1).

The FDA's Assessment:

The FDA reviewers calculated a discrepancy in treatment compliance, however, the difference is within a percent and does not impact the interpretation of the results.

Regarding concomitant medication, FDA agrees with the description above. Specifically, FDA acknowledges that ototoxic mediations were generally prohibited as defined by the protocol and if used, were well balanced between arms (see Table 13).

Table 13 Ototoxic Concomitant Medications by Treatment Received (SIOPEL 6)

Ototoxic Drug	CIS Alone (n=56)	CIS+STS (n=53)	Total (n=109)
Gentamicin	1 (1.8)*	2 (3.8)	3 (2.8)
Vancomycin	1 (1.8)*	0	1 (0.9)
Teicoplanin	1 (1.8)*	1 (1.9)*	2 (1.8)

*Patients who had hearing loss as defined by the primary endpoint

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

The Applicant's Position:

Hearing Loss

Primary Analysis

The primary objective of this study, to assess the efficacy of STS for reducing hearing impairment caused by CIS chemotherapy, was met. Hearing loss was defined by a Brock Grade ≥ 1 measured using audiologic evaluations (Module 2.7.3, Section 1.3.1.2.2). 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 14). The risk of having hearing loss was statistically significantly lower in the CIS+STS arm compared with the CIS Alone arm (relative risk: 0.521, 95% CI: 0.349, 0.778; p<0.001), corresponding to a clinically meaningful 48% lower risk after STS treatment. The results favoring CIS+STS over CIS Alone were similar using a CMH test stratified by country group, PRETEXT group, and age group (relative risk: 0.519, 95% CI: 0.356, 0.755; p<0.001).

Table 14: 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) (1)		0.521 (0.349, 0.778)
p-value (1)		<0.001
Relative Risk (95% CI) (2)		0.519 (0.356, 0.755)
p-value (2)		<0.001

Abbreviations: CI=confidence interval; CIS=cisplatin; CMH=Cochran-Mantel-Haenszel; ITT=Intent-to-treat; PRETEXT=Pretreatment Extent of Disease; PTA=pure-tone audiometry; SIOPEL=International Childhood Liver Tumors Strategy Group; STS=sodium thiosulfate.

(1) Relative risk and p-value from Chi-square test.

(2) Relative risk and p-value 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 subjects were randomized to and actually received during the study.

Source: SIOPEL 6 CSR Table 14.2.1.1

Sensitivity Analyses

Results of all sensitivity analyses supported the results of the primary analysis and demonstrated a statistically significantly lower risk of hearing loss in the CIS+STS arm compared with the CIS Alone arm; see SIOPEL 6 CSR Section 6.2.1.1.2 for details. These findings demonstrate that the results for the primary analysis are robust.

The FDA's Assessment:

FDA acknowledges the Applicant's assessment of the primary endpoint of hearing loss in the 109 patient ITT population but notes that all reported p-values are nominal as the overall type-1 error was not controlled at 0.05 (two-sided) and no claims of statistical significance should be made. As previously discussed, FDA considers the ITT population to include all 114 randomized patients.

The primary efficacy results based on the 114 patient ITT population are provided below. Patients with missing hearing assessment were imputed as hearing loss. The relative risk along with Wald 95% confidence intervals are provided. The unadjusted relative risk (95% CI) is based on unstratified chi-squared test and the adjusted relative risk (95% CI) is based on CMH test based stratified by country group, age group and PRETEXT group.

Table 15: Hearing Loss in SIOPEL 6 (ITT population)

Results (Patient experienced hearing loss, Y/N)	**CIS Alone (N=53)**	**CIS + STS (N=61)**
Yes, n (%)	36 (68%)	24 (39%)
No, n (%)	17 (32%)	37 (61%)
Unadjusted Relative Risk (95% CI)	0.58 (0.40, 0.83)	
Adjusted Relative Risk (95% CI)	0.58 (0.41, 0.81)	

Results were generally consistent across exploratory subgroup analyses as shown in the table below.

Table 16: Subgroup Analysis of Hearing Loss (ITT population)

Variable	**CIS**	**CIS + STS**	**Relative Risk (95% CI)**
Age Group			
< 15 months	22/30 (73%)	15/33 (45%)	0.62 (0.4, 0.95)
≥ 15 months	14/23 (61%)	9/28 (32%)	0.53 (0.28, 0.99)
Sex			
Male	21/30 (70%)	17/33 (52%)	0.74 (0.49, 1.1)
Female	15/23 (65%)	7/28 (25%)	0.38 (0.19, 0.78)
Race			
White	22/33 (67%)	17/36 (47%)	0.71 (0.46, 1.08)
Asian	6/7 (86%)	3/6 (50%)	0.58 (0.25, 1.37)
Black	2/2 (100%)	--	--
Other	3/5 (60%)	1/8 (13%)	0.21 (0.03, 1.49)

Country group			
Great Britain	14/21 (67%)	10/20 (50%)	0.75 (0.44, 1.28)
France	13/16 (81%)	8/23 (35%)	0.43 (0.23, 0.79)
Other	9/16 (56%)	6/18 (33%)	0.59 (0.27, 1.3)
PRETEXT			
I or II	21/31 (68%)	14/43 (33%)	0.48 (0.29, 0.79)
III	15/22 (68%)	10/18 (56%)	0.81 (0.49, 1.35)

There were a total of 13 patients in the 114 patient ITT population with missing hearing assessments: 7 patients on the CIS alone arm compared to 6 patients on the CIS+STS arm. In the primary analysis, these patients were included as failure/hearing impaired. The Applicant conducted a sensitivity analysis in the modified ITT (mITT) population made up of the 101 patients in the ITT population with definite hearing assessment. Results in the mITT population were consistent with those in the ITT population as shown in the table below.

Table 17: Hearing Loss in SIOPEL6 (modified ITT population)

Results (Patient experienced hearing loss, Y/N)	**CIS Alone (N=46)**	**CIS + STS (N=55)**
Yes, n (%)	29 (63%)	18 (33%)
No, n (%)	17 (37%)	37 (67%)
Unadjusted Relative Risk (95% CI)	0.52 (0.33, 0.81)	
Adjusted Relative Risk (95% CI)	0.52 (0.34, 0.79)	

FDA conducted an additional sensitivity analysis based on the unlikely worst case scenario. Under the worst case scenario, instead of imputing a missing hearing assessment as a failure,

missing assessments in the control arm of CIS alone were imputed as success/no hearing loss and missing assessments in the CIS+STS treatment arm were imputed as failure. The following table summarizes the results based on the worst case scenario.

Table 18: Sensitivity Analysis - Worst Case Scenario for SIOPEL 6

Results (Patient experienced hearing loss, Y/N)	**CIS Alone (N=53)**	**CIS + STS (N=61)**
Yes, n (%)	29 (55%)	24 (39%)
No, n (%)	24 (45%)	37 (61%)
Unadjusted Relative Risk (95% CI)	0.72 (0.48, 1.07)	
Adjusted Relative Risk (95% CI)	0.74 (0.50, 1.08)	

The results of the primary endpoint of hearing loss in the 114 patient ITT population in SIOPEL 6 appear to be robust across the sensitivity analyses considered and FDA agrees that the totality of the evidence supports a decreased incidence of hearing loss in the CIS+STS arm; however, FDA acknowledges several weaknesses to the study design and interpretation of the data.

The Brock grading scale does not require baseline audiologic evaluation. Part of the Applicant's explanation for the choice to use a grading system such as the Brock scale is that the majority of young children in this study would likely use different baseline tests as compared to the tests used at 3.5 years of age. Therefore, even if baseline testing was conducted, comparing change from baseline using two different tests is not feasible; however, the lack of a baseline assessment eliminates the ability to determine the degree of change that occurred after drug exposure. Since the presence of normal hearing was not an inclusion criteria in this trial, the lack of baseline data contributes to uncertainty about whether a patient with an abnormal grade on the Brock scale at the end of the study developed this abnormality during the study or had this abnormality at

baseline. The presence of baseline hearing loss in some patients could confound the study results.

Additionally the Brock scale is focused on identifying functional difficulties, which is part of the Applicant's rationale for using the better ear for assessment as well as lack of baseline testing. The Brock scale is less sensitive in identifying ototoxic hearing loss than the ASHA criteria (described below for COG ACCL0431 study) because of the use of absolute threshold criteria and reliance on the assessment of the better ear. The Brock scale would not identify all mild hearing loss since the threshold is ≥40 dB. The Brock scale allows for a patient to have ≥40 dB HL in one ear but would not be positive for ototoxicity if the better ear hearing threshold was <40 dB hearing loss.

Despite these limitations, FDA determined that the totality of the data support a clinical benefit for patients and acknowledge that some of the uncertainty introduced by this design is mitigated in part by randomization.

Data Quality and Integrity

The Applicant's Position:

The data submitted are of sufficient quality and integrity.

The FDA's Assessment:

See FDA Assessment above of primary efficacy analysis.

Efficacy Results – Secondary and other relevant endpoints

The Applicant's Position:

Response to Preoperative Chemotherapy

Using SIOPEL 6 response criteria for the PP Population, the proportion of children with a PR at the last response evaluation after cycles 1 and 2 were 21 children (39.6%) in the CIS+STS arm and 28 children (53.8%) in the CIS Alone arm (Table 19). The proportion of children with stable disease after cycles 1 and 2 were 32 children (60.4%) in the CIS+STS arm and 24 children (46.2%) in the CIS Alone arm. Neither treatment arm had children with PD after cycles 1 and 2.

For the last response evaluation after cycles 3 and 4, the proportion of children with PR in the CIS+STS arm was 35 children (66.0%) and was 39 children (75.0%) in the CIS Alone arm. The CIS+STS arm had more children with stable disease (10 children [18.9%]) compared with the CIS Alone arm (5 children [9.6%]). A similar proportion of children had PD between the CIS+STS arm and the CIS Alone arm (5 children [9.4%] vs 5 children [9.6%], respectively).

After 4 cycles, the proportion of responders (defined as CR and PR, but no patients achieved CR after 4 cycles) were not significantly different between the CIS+STS arm (35 children [66.0%]) and the CIS Alone arm (39 children [75.0%]) (p=0.393). The proportion of children with PD was similar in the CIS+STS and CIS Alone arms (SIOPEL 6 CSR Listing 16.2.6.2). Compared with the PP Population, the responses in the CIS+STS and CIS Alone arms to preoperative chemotherapy using the SIOPEL 6 response criteria were similar in the ITT Population (SIOPEL 6 CSR Table 14.2.2.2).

Table 19: 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 (%)		

Statistic	CIS Alone (N=52)	CIS+STS (N=53)
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.

Source: SIOPEL 6 CSR Table 14.2.2.1.

Complete Tumor Resection

For the PP Population, there was no statistically significant difference in the percentage of partial hepatectomy vs OLT (p>0.999) (Table 20). Complete tumor resection results using the ITT Population were similar to the PP Population (SIOPEL 6 CSR Table 14.2.3.2).

Table 20: Summary of Complete Tumor Resection (SIOPEL 6, PP Population)

Statistic	CIS Alone (N=52)	CIS+STS (N=53)
Partial hepatectomy, n (%)	48 (92.3)	49 (92.5)
Liver transplantation, n (%)	4 (7.7)	4 (7.5)
P-value (1)		>0.999

Abbreviations: CIS=cisplatin; PP=Per Protocol; SIOPEL=International Childhood Liver Tumors Strategy Group; STS=sodium thiosulfate.

(1) P-value from Fisher's Exact Test.

Note: Treatment groups are treatments patients were randomized to receive and actually received.

Source: SIOPEL 6 CSR Table 14.2.3.1.

Remission Status

For the PP Population, there was no statistically significant difference in the proportion of children with complete remission 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) (Table 21).

The results of the complete remission assessment when performed by a Central Reviewer were generally similar for each category 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%]). Remission assessment results using the ITT Population were similar to the PP Population (SIOPEL 6 CSR Table 14.2.4.2).

Table 21: Summary of Remission Status at End of Treatment (SIOPEL 6, PP Population)

Statistic	CIS Alone (N=52)	CIS+STS (N=53)
Status as Reported by Investigator, n (%)		
Complete remission	45 (86.5)	49 (92.5)
Partial remission	1 (1.9)	2 (3.8)
Progressive disease	2 (3.8)	0
Died from disease	1 (1.9)	0
Died from other causes	1 (1.9)	0
Withdrawn from protocol	2 (3.8)	2 (3.8)
Complete remission	45 (86.5)	49 (92.5)
Not complete remission	7 (13.5)	4 (7.5)
P-value(1)		0.359
Status as Assessed by Central Reviewer, n (%)		
Complete remission	44 (84.6)	49 (92.5)
Partial remission	4 (7.7)	4 (7.5)
Progressive disease	2 (3.8)	0
Not Evaluable	1 (1.9)	0
Died from other causes	1 (1.9)	0
Complete remission	44 (84.6)	49 (92.5)
Not complete remission	8 (15.4)	4 (7.5)
P-value(1)		0.236

Statistic	CIS Alone (N=52)	CIS+STS (N=53)

Abbreviations: CIS=cisplatin; PP=Per Protocol; SIOPEL=International Childhood Liver Tumors Strategy Group; STS=sodium thiosulfate.

(1) P-value from Fisher's Exact Test.

Note: Treatment groups are treatments patients were randomized to receive and actually received.

Note: Patients that were withdrawn from the protocol switched from protocol-defined treatment to other treatments.

Source: SIOPEL 6 CSR Table 14.2.4.1.

Duration of Follow-up

Overall, the median duration of follow-up for the PP Population was 4.27 years (interquartile range: 3.11 to 5.82 years), and was similar between the CIS+STS arm (4.55 years) and CIS Alone arm (4.17 years) (Table 22).

Table 22: Summary of Duration of Follow-up (Years) (SIOPEL 6, PP Population)

Statistic	CIS Alone (N=52)	CIS+STS (N=53)	Total (N=105)
Minimum	0.23	1.21	0.23
25%	3.10	3.27	3.11
Median	4.17	4.55	4.27
75%	5.81	5.82	5.82
Maximum	8.54	9.23	9.23

Abbreviations: CIS=cisplatin; PP=Per Protocol; SIOPEL=International Childhood Liver Tumors Strategy Group; STS=sodium thiosulfate.

Note: Duration of follow-up was derived based on the last survival follow-up date.

Source: SIOPEL 6 CSR Table 14.1.8.

Event-free Survival

For the PP Population, the proportion of children that had an event (defined as disease progression, relapse, secondary primary malignancy, or death) was similar between the CIS+STS arm (11 patients [20.8%]) and the CIS Alone arm (11 patients [21.2%]) (Table 23).

There was no statistically significant difference between the proportion of children that were censored at the time of their last known Follow-up Visit (ie, EFS) between the CIS+STS arm (42 patients [79.2%]) and the CIS Alone arm (41 patients [78.8%]) (hazard ratio: 0.96; 95% CI: 0.42, 2.23; p=0.932) (Table 23 and Figure 8).

Event-free survival results in the ITT Population were similar to those in the PP Population (SIOPEL 6 CSR Table 14.2.6.2 and Figure 1.2).

Table 23: 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 [Reference Group])		
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

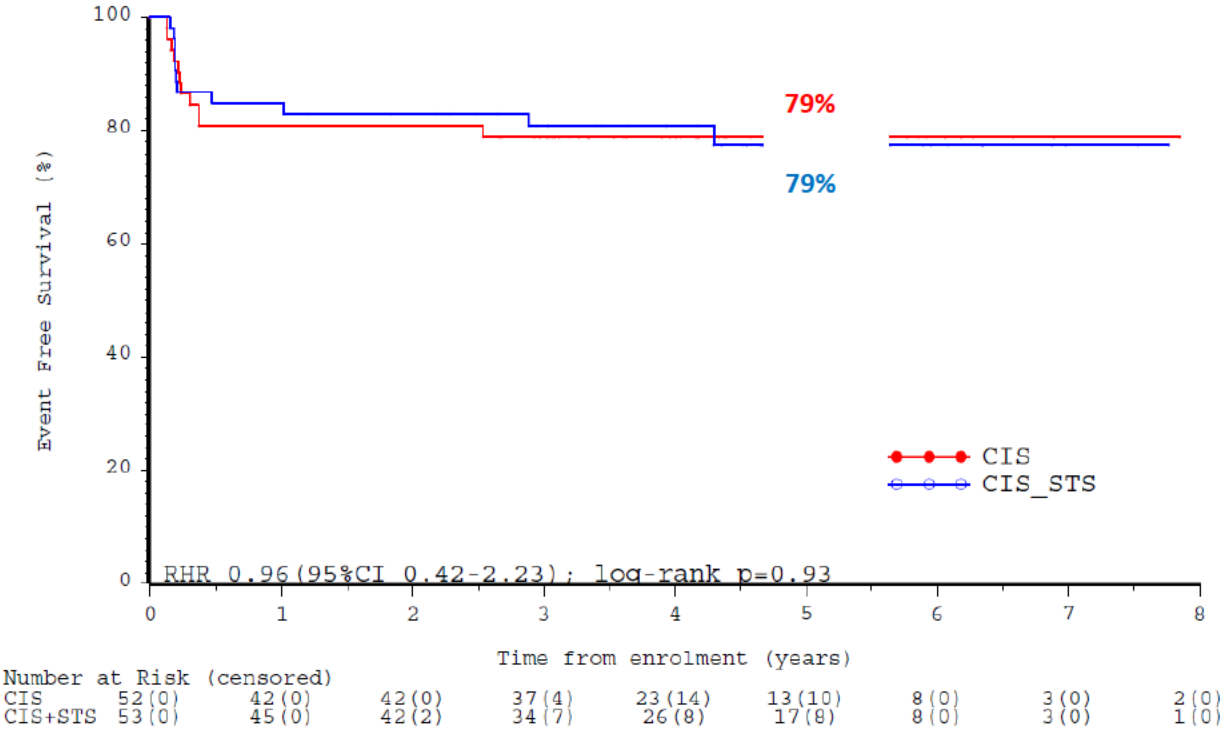
Abbreviations: CI=confidence interval; CIS=cisplatin; PP=Per Protocol; PRETEXT=Pre-treatment Tumor Extension; SIOPEL=International Childhood Liver Tumors Strategy Group; STS=sodium thiosulfate.

[a] Hazard ratio and 95% CI was 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.

Note: Time to event was calculated from the time of randomization to the first of the following events: progression, relapse, second primary malignancy or death. Patients without an event were censored at the time of last known Follow-up Visit.

Source: SIOPEL 6 CSR Table 14.2.6.1.

Figure 8: Event-free Survival (SIOPEL 6, PP Population)



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

Note: The provided EFS percentages of censored patients are from 5 years after study entry.

Note: For the calculation of the EFS relative hazard ratio, the CIS Alone arm was the reference group.

Sources: SIOPEL 6 CSR Figure 1.1 and Table 13.

Overall Survival

For the PP Population, there was no statistically significant difference in the proportion of children who died during the study in the CIS+STS arm (2 patients [3.8%]) and in the CIS Alone arm (4 patients [7.7%]) (hazard ratio: 0.48; 95% CI: 0.09, 2.61; p=0.384) (Table 24 and

Figure 3). For additional detail about deaths during the SIOPEL 6 study, see Module 2.7.4, Section 2.1.2.1.

Overall survival results in the ITT Population were similar to those in the PP Population (SIOPEL 6 CSR Table 14.2.7.2 and Figure 2.2).

Table 24: Summary of Overall Survival (Median 4.27-year Follow-up) (SIOPEL 6, PP Population)

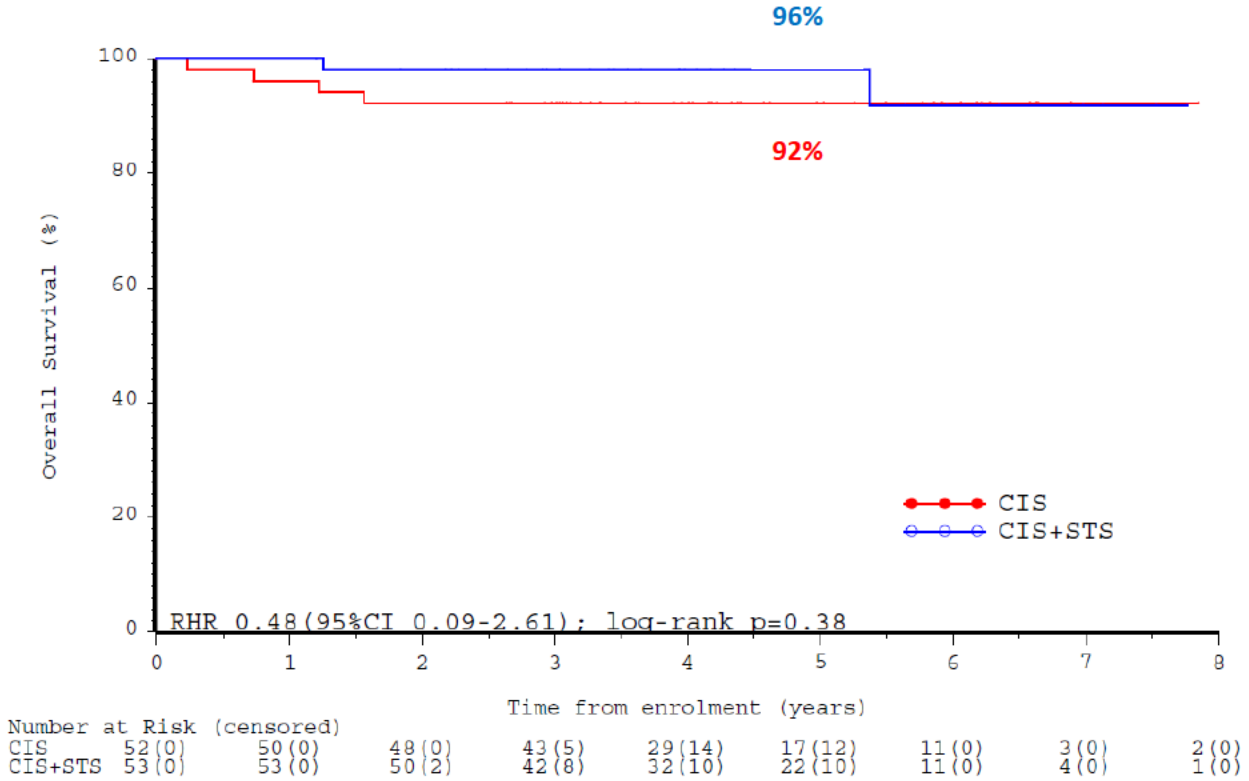
Parameter **Category/Statistic**	**CIS Alone (N=52)**	**CIS+STS (N=53)**
Number of patients who died, n (%)	4 (7.7)	2 (3.8)
Number of patients censored, n (%)	48 (92.3)	51 (96.2)
Treatment comparison (CIS+STS vs CIS Alone [Reference Group])		
Hazard ratio (95% CI)		0.48 (0.09, 2.61)
P-value (log-rank)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

Abbreviations: CI=confidence interval; CIS=cisplatin; PP=Per Protocol; SIOPEL=International Childhood Liver Tumors Strategy Group; 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.

Source: SIOPEL 6 CSR Table 14.2.7.1.

Figure 9: Overall Survival (SIOPEL 6, PP Population)



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

Note: The provided OS percentages of censored patients are from 5 years after study entry.

Note: For the calculation of the OS relative hazard ratio, the CIS Alone arm was the reference group.

Sources: SIOPEL 6 CSR Figure 2.1 and Table 14.

Alpha-fetoprotein Values

Alpha-fetoprotein values have been used as a tumor marker. In the PP Population, the mean AFP log-transformed values at baseline were similar between the CIS+STS and CIS Alone arms (5.031 ng/mL and 4.874 ng/mL, respectively) (Table 25).

Alpha-fetoprotein results in the ITT Population were similar to those in the PP Population (SIOPEL 6 CSR Table 14.3.5.1).

Table 25: Summary of Change in Log AFP from Baseline to End of Treatment and End of Follow-up (SIOPEL 6, PP Population)

Parameter **Category/Statistic**	**CIS Alone (N=52)**	**CIS+STS (N=53)**
Baseline AFP (log-transformed, ng/mL)		
N	52	53
Mean (SD)	4.897 (1.071)	5.031 (1.082)
Median (min, max)	5.029 (2.11, 6.42)	5.384 (2.20, 6.50)
After Course 2 Change from Baseline AFP		
N	52	53
Mean (SD)	-0.817 (0.496)	-0.635 (0.644)
Median (min, max)	-0.740 (-2.05, 0.00)	-0.650 (-2.48, 1.04)
95% CI (lower, upper)	-0.955, -0.679	-0.812, -0.457
P-value [a]	<0.001	<0.001
After Course 4 Change from Baseline AFP		
N	50	51
Mean (SD)	-1.956 (1.035)	-1.467 (0.769)
Median (min, max)	-1.890 (-4.28, 1.17)	-1.498 (-3.56, 0.08)
95% CI (lower, upper)	-2.250, -1.661	-1.683, -1.250
P-value [a]	<0.001	<0.001

Parameter Category/Statistic	CIS Alone (N=52)	CIS+STS (N=53)
End of Treatment Change from Baseline AFP		
N	49	53
Mean (SD)	-3.714 (1.149)	-3.792 (1.098)
Median (min, max)	-4.070 (-5.39, -0.66)	-4.013 (-5.66, -1.14)
95% CI (lower, upper)	-4.044, -3.384	-4.095, -3.490
P-value [a]	<0.001	<0.001

Abbreviations: AFP=alpha-fetoprotein; CI=confidence interval; CIS=cisplatin; max=maximum; min=minimum; PP=Per Protocol; SD=standard deviation; SIOPEL=International Childhood Liver Tumors Strategy Group; STS=sodium thiosulfate.

[a] P-value was from a paired t-test on mean change from baseline.

Source: SIOPEL 6 CSR Table 14.3.5.3.

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 (Table 26).

Disease relapse results in the ITT Population were similar to those in the PP Population (SIOPEL 6 CSR Table 14.2.8.2).

Table 26: Summary of Disease Relapse During Follow-up (SIOPEL 6, PP Population)

Parameter	CIS Alone (N=52) n (%)	CIS+STS (N=53) n (%)
Disease Status		
No Relapse	50 (96.2)	48 (90.6)
Relapse [a]	2 (3.8)	5 (9.4)
P-value [b]		0.437
Years from Surgery to Relapse		
Less than 1 Year	1 (1.9)	3 (5.7)
2 to 3 Years	1 (1.9)	1 (1.9)
3 to 4 Years	0	1 (1.9)

Abbreviations: CIS=cisplatin; PP=Per Protocol; SIOPEL=International Childhood Liver Tumors Strategy Group; STS=sodium thiosulfate.

[a] If the relapse date was missing, the patient contact date was used.

[b] P-value from Fischer's exact test.

Source: SIOPEL 6 CSR Table 14.2.8.1.

The FDA's Assessment:

The Applicant's Per-Protocol (PP) Population comprised all patients in the ITT Population who had received at least 1 dose of STS (if randomized to the CIS+STS arm); this population was used for evaluation of the secondary endpoints of response to preoperative chemotherapy, complete resection, complete remission, event-free survival (EFS), and overall survival (OS).

With the exception of EFS and OS, FDA did not independently verify the secondary endpoint analysis since this trial was not designed to demonstrate anti-tumor activity. FDA notes that all secondary endpoint analyses are exploratory as no alpha was allocated to these endpoints. Thus, all p-values presented in relation to these endpoints should be considered nominal only

and no claims of statistical significance should be made.

Though SIOPEL6 was not powered for EFS or OS, FDA considered the results of these analyses to help address the theoretical concern that STS could interact with CIS and decrease anti-tumor activity. In general, FDA agrees with the Applicant's reported results for of EFS and OS in the PP population. FDA considers the 114 patient ITT population to be the more relevant population for analysis of EFS and OS but notes that no EFS or OS data was available for the 5 randomized patients the Applicant excluded who withdrew prior to treatment. In the Applicant's 109 patient ITT population, the EFS HR comparing CIS+STS arm with CIS alone was 0.89 (95% CI: 0.39, 2.05) and the OS HR comparing CIS+STS arm with CIS alone was 0.44 (95% CI: 0.08, 2.41). Though there are limitations to these analyses due to small sample size, the results appear to show that there was no apparent difference between the two groups with respect to EFS or OS.

Dose/Dose Response

The Applicant's Position:

SIOPEL 6 confirmed that STS treatment at 16 to 20 g/m^2 resulted in statistically significant reductions in ototoxicity in patients with various types of solid tumors treated with CIS (Module 2.5, Section 4.4) while not affecting the anti-tumor efficacy of CIS in patients with localized, non-metastatic solid tumors (Module 2.5, Section 4.5).

The FDA's Assessment:

A consistent body-surface-area dose was used for this study; therefore FDA cannot determine if a there is dose-response related to the magnitude of prevention of hearing loss.

Durability of Response

The Applicant's Position:

All data related to the effect of STS over time in SIOPEL 6 is presented earlier in this section.

The FDA's Assessment:

This study was not designed to assess tumor response. Regarding persistence of effect of STS efficacy on hearing, see below (not relevant).

Persistence of Effect

The Applicant's Position:

Sodium thiosulfate was only given during chemotherapy treatment and audiometry was performed yearly until a reliable result (ie, a hearing test that could be centrally reviewed) was obtained through PTA (age ≥ 3.5 years). Thus, persistence of STS efficacy over time is not relevant.

The FDA's Assessment:

Not applicable.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

The Applicant's Position:

No patient-reporated outcome endpoints were included in the SIOPEL 6 study.

The FDA's Assessment:

Not applicable.

Additional Analyses Conducted on the Individual Trial

The Applicant's Position:

No additional analyses were conducted for the SIOPEL 6 study.

The FDA's Assessment:

Not applicable.

8.1.3 COG ACCL0431

Trial Design

The Applicant's Description:

A comparison of the SIOPEL 6 and COG ACCL0431 trial designs was provided in Section 8.1, including a comparison of key design elements in Table 8 .

The FDA's Assessment:

FDA agrees with the Applicant's description of the studies as outlined in Table 8.

Study Endpoints

The Applicant's Description:

A comparison of the SIOPEL 6 and COG ACCL0431 study endpoints is provided in Section 8.1.

In COG ACCL0431, ASHA (1994) criteria were used, which required audiological assessments at Baseline (prior to the first dose of CIS), at monitoring (within 8 days or, preferably, 72 hours prior to each CIS course), and at Follow up (at both 4 weeks and 1 year after final CIS course). Patients in follow up were to complete audiograms at 4 weeks and 1 year as per COG ACCL0431 Protocol, Section 7.1.

The FDA's Assessment:

FDA agrees with the Applicant's description of the endpoints and has the following additional detail.

The primary endpoint was defined by ASHA criteria via comparison of the baseline and 4-week follow-up evaluations. Based on ASHA guidelines hearing loss is defined as the presence of any of these conditions:

(a) 20 dB decrease at any one test frequency,

(b) 10 dB decrease at any two adjacent test frequencies, or

(c) loss of response at three consecutive test frequencies where responses were previously obtained

*Results must be confirmed by repeat testing.

Audiological testing included: (a) measurement of bilateral pure tone air conduction thresholds at 0.5 to 8 kHz; (b) otoscopy by audiologist or other healthcare professional; (c) immittance evaluation; and (d) measurement of evoked OAEs, if available. For patients too young to cooperate with standard audiometric measurements, brainstem auditory evoked response (BAER) should have been obtained instead. Additionally, ultra-high frequency (UHF) audiometry was performed for patients 5 years of age or older at institutions where that modality was available. Measurements of UHF were of bilateral pure tone air conduction thresholds at 9 to 16 kHz.

Statistical Analysis Plan and Amendments

The Applicant's Description:

Analysis Populations

In COG ACCL0431, the primary efficacy analysis was conducted on the Efficacy Population, which comprised all children in the ITT Population who had both Baseline and 4-week follow-up hearing assessments. The ITT Population comprised all children who were randomized; this population was used for the anti-tumor efficacy data evaluation (ie, EFS and OS).

Analysis of Efficacy Endpoints

Primary Analysis

In COG ACCL0431, for the primary analysis comparing the proportional incidence of hearing loss between the CIS+STS arm and the Observation arm, hearing loss was treated as a dichotomous variable (as defined by ASHA criteria via comparison of the Baseline and 4-week follow-up evaluations). A logistic regression model was used to evaluate if there was any

association between STS treatment and hearing loss when adjusting for the stratification variables. The odds ratio with associated 95% CI and p-value for the between-treatment comparison was estimated based on the model.

Similar analyses were performed for hearing loss by age group (<5 or ≥5 years) based on logistic regression including only the treatment as a fixed effect in the model. The odds ratio with associated 95% CI and p-value for the between-treatment comparison was estimated.

A sensitivity analysis was performed using the ITT Population. Children without hearing data were considered as hearing loss in the ITT analysis.

Secondary Analyses

Multiple secondary endpoints were evaluated, as shown in Table 8. Event-free survival and OS was assessed and the methods of analysis are summarized below.

In COG ACCL0431, for analyses on survival outcomes, with an estimated number of 65 eligible patients per arm, there was minimal power for a formal comparison of EFS between the 2 arms. The heterogeneous patient population further complicated the problem of estimating the power. Since the actual proportion for children with each tumor type could have been influenced by many factors such as competing COG disease-specific studies and different treatments by cancer type, the assumed 3-year EFS could only be approximate. Per COG ACCL0431 Protocol Amendment 1, the study also expanded enrollment to children with other rare tumors; the number of enrollments with each of the other diagnoses was even more difficult to speculate. These uncertainties and small number of patients per arm made calculations based on disease-stratified comparison impractical. Therefore, the observed ("pooled") EFS from the mixture of patients between the 2 arms was calculated. Since it was very difficult to predict the types and number of patients with other, rarer tumors who might have been enrolled, and since the power discussion was mostly for illustration, the sample size estimates for the "pooled" EFS were based on the 5 major tumor types only (see COG ACCL0431 SAP, Section 9.1). Per COG ACCL0431 Protocol Amendment 3, with approximately 130 eligible patients expected to be enrolled, there was only enough power (~84%) if the CIS+STS arm had much worse EFS; the power for detecting a smaller change in EFS would have been minimal. Therefore, a formal comparison of EFS/OS was not proposed between the 2 arms; instead, EFS and OS were monitored for the CIS+STS arm and the Observation Arm during the study.

For the secondary objective on monitoring EFS and OS, Kaplan-Meier curves (and corresponding 95% CI) of EFS/OS for the 2 arms were estimated. As exploratory analyses, EFS and OS between the 2 arms were compared using log rank tests. These analyses were performed at each scheduled interim monitoring period during accrual and in follow up after accrual was completed. Exploratory analyses of EFS/OS outcomes using Cox models with randomization stratification as covariates were performed.

The statistical analyses for the remaining secondary endpoints conducted in COG ACCL0431 are summarized briefly below; full details can be found in COG ACCL0431 CSR, Section 4.5.3.2.3.

Mean change in hearing thresholds for key frequencies: hearing threshold was treated as a continuous variable and the mean change in hearing thresholds (from Baseline to the 4-week follow-up evaluation) was compared between the 2 arms for 5 key frequencies (500, 1000, 2000, 4000, and 8000 Hz). Linear regression analyses were used to assess whether STS treatment reduced the mean change in hearing thresholds when adjusting for stratification variables. Analyses were performed individually for each key frequency; no multiple comparison adjustment was made for these analyses. Hearing data were collected and reviewed by 2 different blinded central reviewers.

The FDA's Assessment:

FDA notes that the sample size for COG ACCL0431 was planned to be 108 which would allow for 80% power to detect a treatment effect of 22.5% hearing loss in the CIS+STS arm compared to 45% hearing loss in the CIS only (observation) arm at a one-sided significance level of 0.05. Since the regulatory standard is to control type-1 error at a two-sided level of 0.05, the p-value for the primary analysis for this study should be interpreted as nominal only. FDA also notes that no multiplicity plan was specified for the secondary endpoints, so they are considered exploratory and any p-values reported are nominal only.

Additionally, FDA does not agree with the Applicant's definition of the efficacy population. For regulatory purposes, FDA defines the efficacy population as all patients enrolled and randomized in the trial who had non-metastatic disease. This population will be used to assess the primary endpoint for this review and to support labeling.

Protocol Amendments

The Applicant's Description:

The significant amendments made to the COG ACCL0431 are described below.

Protocol Amendment 1

Protocol Amendment 1 was dated 31 Mar 2010. Based on the date of the amendment, 38 children were enrolled prior to this amendment (both first patient first visit and first patient

first dose were 29 Oct 2008). This amendment was significant and included the changes summarized in the following subsections:

Expansion of Eligibility Criteria to Widen Patient Pool

Cranial Irradiation Prior to COG ACCL0431 Enrollment

COG ACCL0431 was originally written to exclude children with cranial irradiation prior to COG ACCL0431 enrollment, so that CIS would be the only treatment-related ototoxic exposure. One consequence of this was that most children with medulloblastoma were unable to enroll in COG ACCL0431 because those patients generally received their irradiation prior to administration of CIS. It was believed that accrual would be enhanced by including those children, provided they had normal hearing documented following irradiation (prior to study enrollment). It was anticipated that STS would provide its putative otoprotection from CIS, whether or not children had received prior irradiation. Thus, these children were expected to be equally evaluable for the primary study endpoint. With the addition of children with prior cranial irradiation, the randomization stratification was modified to include a separate stratum for them. As these enrollments were expected to be "older" medulloblastoma patients and only a minority of the future enrollments, randomization for them was not further stratified by age or CIS duration, unlike randomization for children without prior cranial irradiation. See Protocol Section 3.1.6, Section 3.2.4.2, Section 3.2.6.4, Section 3.3, Section 4.0, Section 4.4.2, Section 4.5.5, Section 7.1, and Section 9.1 for further information.

Any Newly Diagnosed Malignancy Treated with Cisplatin

COG ACCL0431 was originally written to include only children with GCTs, HB, medulloblastoma, neuroblastoma, or osteosarcoma. One consequence of this was that children with other, less common malignancies also treated with CIS (eg, nasopharyngeal carcinoma and gastrointestinal cancers) were excluded. While individually rare, in aggregate, these patients would enhance accrual if allowed to be eligible. The original rationale for limiting eligible children to the 5 diagnostic categories previously mentioned was to estimate pooled EFS for purposes of monitoring the randomized children, as described in Protocol Section 9.0. However, monitoring of EFS involved comparison of 1 dosing arm with the other (CIS+STS versus Observation), not with historical or expected values. Randomization was expected to distribute children with other malignancies approximately evenly between the 2 dosing arms (note that the study was not designed to stratify by diagnosis). It was acknowledged that for each rare tumor type, it may not have been possible to achieve optimal balance between the 2 randomized arms. However, because of the small number of such patients, the imbalance was not expected to have significant impact on the observed survival outcomes for the 2 dosing arms. These added children were expected to experience similar otoprotective effect of STS as patients with the original 5 diagnoses, and therefore were to be equally evaluable for the primary endpoint. See

Protocol Abstract, Experimental Design Schema, Section 1.1, Section 2.10, Section 3.2.2.1, Section 4.0, Section 9.1, and Section 9.2 for further information.

Addition of Optional Biology Study

As described in Protocol Section 2.9, an optional biology study was added to confirm the prior finding [Ross et al, 2009] that genetic variants in thiopurine S methyltransferase (TPMT) and catechol-O-methyltransferase (COMT) predispose to CIS-induced hearing loss, and to explore whether the effect of STS, if any, varied in children with and without genetic variants in TPMT and COMT. Due to an insufficient number of samples, however, this optional biology study was not included in the final analyses for COG ACCL0431.

Protocol Amendment 3

Protocol Amendment 3 was dated 10 Oct 2011. Based on the date of the amendment, 107 children were enrolled prior to this amendment. This amendment included a status change to "reactivation" and included changes to increase the maximum enrollment from 120 to 135 children over 3.5 years (rather than 3 years) (see Protocol Abstract and Sections 9.1, 9.2, 9.4, and Informed Consent).

The FDA's Assessment:

The FDA agrees with the description of protocol amendments presented in this section.

8.1.4 COG ACCL0431 Study Results

Compliance with Good Clinical Practices

The Applicant's Position:

This study was conducted in accordance with the current version of the applicable regulatory and ICH GCP requirements, the ethical principles that have their origin in the principles of the Declaration of Helsinki, and the local laws of the countries involved.

The FDA's Assessment:

The FDA acknowledges the Applicant's statement of compliance with GCP in the COG ACCL0431 Clinical Study Report.

Financial Disclosure

The Applicant's Position:

All financial interests/arrangements with clinical investigators have been adequately addressed as recommended in the FDA Guidance for Clinical Investigators, Industry, and FDA Staff, Financial Disclosure by Clinical Investigators (2013); see Section 19.2.

The FDA's Assessment:

In accordance with 21 CFR 54, the Applicant submitted a financial disclosure certification document in module 1.3.4. The document includes a list of all investigators who participated in COG ACCL04331.

Patient Disposition

The Applicant's Position:

A total of 131 children were enrolled in the study (Freyer et al, 2017). Six children were determined to be ineligible, and a total of 125 children were randomized to either the CIS+STS arm or the Observation arm (COG ACCL0431 CSR Table 14.1.4).

Two children in the CIS+STS arm did not receive any STS (COG ACCL0431 CSR Table 14.1.1). Of the remaining 123 children on the study, 102 of these children completed their chemotherapy regimen as planned; the number of children who completed chemotherapy was higher in the Observation arm (57 patients [89.1%]) than the CIS+STS arm (45 patients [76.3%]), and the 21 remaining children went off protocol therapy for other reasons including discontinuation of CIS therapy, refusal of protocol therapy by patient/parent/guardian, or because the physician determined it was in the patient's best interest. The patients continued to be followed-up after going off protocol therapy and remained in the study (COG ACCL0431 CSR Table 14.1.4).

The FDA's Assessment:

FDA agrees with the Applicant's description of patient disposition.

Protocol Violations/Deviations

The Applicant's Position:

Per COG policy, Protocol deviations were not defined in the protocol or recorded by the individual COG sites and therefore could not be summarized in this report. According to COG Policy 7.25 and in accordance with CTMB audit guidelines, deviations made in the best interest of the patient were not graded as deviations if they were well documented in the patient's medical record. Protocol deviations that were made in the interest of patient management were not subject to review and interpretation by a physician auditor (ie, COG Study Chair) or the COG quality coordinator. The physician responsible for the patient's management and care was stipulated to be the only individual authorized to decide if the patient should be removed from protocol therapy. Children's Oncology Group reviewed patient eligibility criteria and identified patients who were an eligibility deviation at the time of study entry (ineligible) or at the time of randomization (not evaluable).

The FDA's Assessment: The FDA agrees with Applicant's description of protocol violations.

Table of Demographic Characteristics

The Applicant's Position:

Demographics and baseline disease characteristics were balanced between the 2 arms overall (Table 27) and by age group (COG ACCL0431 CSR Table 14.1.3.2).

Table 27: Patient Demographics and Baseline Disease Characteristics (COG ACCL0431, ITT Population)

Variable	Observation (N=64)	CIS+STS (N=61)	Total (N=125)
Age (years), n (%)			

Variable	Observation (N=64)	CIS+STS (N=61)	Total (N=125)
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 (%)			
GCT	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)

Variable	Observation (N=64)	CIS+STS (N=61)	Total (N=125)
Medulloblastoma	14 (21.9)	10 (16.4)	24 (19.2)
Supratentorial PNET	0	2 (3.3)	2 (1.6)
Neuroblastoma	12 (18.8)	14 (23.0)	26 (20.8)
Hepatoblastoma	5 (7.8)	2 (3.3)	7 (5.6)
Other	2 (3.1)	3 (4.9)	5 (4.0)
Atypical teratoid/rhabdoid 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; COG=Children's Oncology Group; ITT=Intent-to-treat; GCT=germ cell tumor; max=maximum; min=minimum; NOS=not otherwise specified; PNET=primitive neuroectodermal tumor; STS=sodium thiosulfate.

Source: COG ACCL0431 CSR Table 14.1.3.1.

The FDA's Assessment:

The FDA agrees with the Applicant's description of the demographics for the ITT population; however, see Table 28 below for a comparison of demographics of those in the ITT population with non-metastatic disease (the relevant efficacy population). Note that the arms are not completely balanced with respect to certain demographics and baseline characteristics because

randomization has been broken due to the fact that metastatic vs. non-metastatic disease was not a stratification factor.

Table 28 Patient Demographics and Baseline Disease Characteristics (COG ACCL0431, ITT Population, non-metastatic only)

Variable	Observation (N=38)	CIS+STS (N=39)	Total (N=77)
Age (years), n (%)			
N	38	39	77
Mean (SD)	8.6 (6.1)	8.6 (6.0)	8.6 (6.0)
Median (min, max)	7.1 (1.2, 17.7)	9.5 (1.1, 17.9)	8 (1.1, 17.9)
< 5, n (%)	15 (39.5)	16 (41)	31 (40.3)
≥ 5, n (%)	23 (60.5)	23 (59)	46 (59.7)
Sex, n (%)			
Male	25 (65.8)	22 (56.4)	47 (61)
Female	13 (34.2)	17 (43.6)	30 (39)
Race, n (%)			
White	24 (63.2)	24 (61.5)	48 (62.3)
Black	7 (18.4)	4 (10.3)	11 (14.3)
Asian	1 (2.6)	1 (2.6)	2 (2.6)
American Indian or Alaska Native	0	1 (2.6)	1 (1.3)
Native Hawaiian or other Pacific Islander	1 (2.6)	1 (2.6)	2 (2.6)
Unknown	5 (13.2)	8 (20.5)	13 (16.9)
Ethnicity, n (%)			
Not Hispanic or Latino	30 (78.9)	28 (71.8)	58 (75.3)

Variable	Observation (N=38)	CIS+STS (N=39)	Total (N=77)
Hispanic or Latino	5 (13.2)	10 (25.6)	15 (19.5)
Unknown	3 (7.9)	1 (2.6)	4 (5.2)
Diagnosis, n (%)			
GCT	9 (23.7)	9 (23.1)	18 (23.4)
Osteosarcoma	10 (26.3)	10 (25.6)	20 (26)
Medulloblastoma	12 (31.6)	9 (23.1)	21 (27.3)
Neuroblastoma	1 (2.6)	7 (17.9)	8 (10.4)
Hepatoblastoma	4 (10.5)	2 (5.1)	6 (7.8)
Other	2 (5.3)	2 (5.1)	4 (5.2)
Prior cranial irradiation	2 (5.3)	3 (7.7)	5 (6.5)

Abbreviations: CIS=cisplatin; COG=Children's Oncology Group; ITT=Intent-to-treat; GCT=germ cell tumor; max=maximum; min=minimum; NOS=not otherwise specified; PNET=primitive neuroectodermal tumor; STS=sodium thiosulfate.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The Applicant's Position:

Other baseline characteristics are discussed in the demographics section above.

The FDA's Assessment:

The FDA agrees.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The Applicant's Position:

Study medication was administered at the site, under the supervision of the Investigator or attending staff, and by trained personnel who recorded the dosing on the CRF.

The FDA's Assessment:

No consistent collection of data on specific concomitant medications was captured in the database. Antiemetics were indicated to prevent nausea and vomiting due to STS. Concurrent administration of loop diuretics (e.g., ethacrynic acid, furosemide, and bumetanide) and/or aminoglycosides with CIS were to be avoided, if possible, because concurrent usage could have increased the risk of ototoxicity. If concurrent administration of these agents with CIS was indicated, administration information was recorded on standardized report forms but this was not included in the submission.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

The Applicant's Position:

Hearing Loss

Primary Analysis

The primary objective of this study, to assess the efficacy of STS for preventing hearing loss caused by CIS chemotherapy, was met.

Following the last dose of CIS, the proportion of children in the CIS+STS arm with hearing loss (14 patients [28.6%]) was approximately one-half of the proportion in the Observation arm (31 patients [56.4%]) (Table 29). The odds of having hearing loss as defined by the ASHA criteria were statistically significantly lower in the CIS+STS arm compared with the Observation arm (odds ratio: 0.274; 95% CI: 0.114, 0.660; p=0.0039), when adjusted for the stratification variables of prior cranial irradiation (yes versus no); age subgroup (< 5 years or ≥ 5 years), and duration of CIS infusion (< 2 versus ≥ 2 hours).

Table 29: Summary of Hearing Loss (COG ACCL0431, Efficacy Population)

Results	Observation (N=55)	CIS+STS (N=49)
N	55	49
Yes, n (%)	31 (56.4)	14 (28.6)
No, n (%)	24 (43.6)	35 (71.4)
Odds ratio (95% CI) (1)		0.274 (0.114, 0.660)
P-value (1)		0.0039

Abbreviations: ASHA=American Speech-Language-Hearing Association; CI=confidence interval; CIS=cisplatin; COG=Children's Oncology Group; STS=sodium thiosulfate.

(1) 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.

Source: COG ACCL0431 CSR Table 14.2.1.1.

Sensitivity Analysis

Results of the sensitivity analysis supported the results of the primary analysis and demonstrated a statistically significantly lower risk of hearing loss in the CIS+STS arm compared with the CIS Alone arm; see COG ACCL0431 CSR, Section 6.2.1.1.2 for details.

The FDA's Assessment:

FDA acknowledges the Applicant's assessment of the primary endpoint of hearing loss in their defined efficacy population but notes that all reported p-values are nominal as the overall type-1 error was not controlled at 0.05 (two-sided) and no claims of statistical significance should be made. Also, as noted above, for regulatory purposes, FDA does not agree with the efficacy

population.

The FDA considers the population for efficacy to be patients in the ITT population with non-metastatic disease. The FDA evaluated the primary efficacy endpoint of hearing loss based on 77 patients in the ITT population with non-metastatic disease. Among these 77 patients with non-metastatic disease, 5 patients in the CIS alone arm and 8 patients in the CIS + STS arm had missing hearing assessments. Patient with missing hearing assessment were imputed as hearing impaired or failure for the primary efficacy analysis. The following table provides the primary efficacy results with relative risks and Wald 95% confidence intervals. The unadjusted relative risk (95% CI) is based on unstratified chi-squared test and the adjusted relative risk (95% CI) is based on CMH test based stratified by prior cranial irradiation, age group, and duration of CIS infusion.

Table 30: Hearing Loss in COG ACCL0431 for patients with non-metastatic disease (ITT population)

Results (Patient experienced hearing loss, Y/N)	**CIS Alone (N=38)**	**CIS + STS (N=39)**
Yes, n (%)	22 (58%)	17 (44%)
No, n (%)	16 (42%)	22 (56%)
Unadjusted Relative Risk (95% CI)	0.75 (0.48, 1.18)	
Adjusted Relative Risk (95% CI)	0.84 (0.53, 1.35)	

Additionally, the efficacy results from subgroup analysis involving patients in the ITT population with non-metastatic disease were generally consistent except for age group >=5 years. However, FDA notes that these results are based on post-hoc exploratory analyses with small subgroup sizes and the margin of error was high.

Table 31: Hearing Loss by Subgroup for patients with localized disease (ITT population)

Variables	CIS Alone	CIS + STS	Relative Risk (95% CI)
Age Group			
<5 years	13/15 (87%)	7/16 (44%)	0.5 (0.28, 0.91)
>=5 years	9/23 (39%)	10/23 (43%)	1.11 (0.56, 2.22)
Sex			
Female	7/13 (54%)	6/17 (35%)	0.66 (0.29, 1.48)
Male	15/25 (60%)	11/22 (50%)	0.83 (0.49, 1.41)
Race			
White	14/24 (58%)	10/24 (42%)	0.71 (0.4, 1.28)
Black	4/7 (57%)	1/4 (25%)	0.44 (0.07, 2.69)
Others	4/7 (57%)	6/11 (55%)	0.95 (0.41, 2.21)

The following table provides the efficacy results based on patients in the efficacy population, as defined by the Applicant, excluding any patient with missing hearing assessment, who have non-metastatic disease. There were a total of 13 patients with missing hearing assessment (5 patients on the CIS alone arm and 8 patients on the CIS+STS arm).

Table 32: Hearing Loss in COG ACCL0431 for patients with non-metastatic disease (efficacy population)

Results (Patient experienced hearing loss, Y/N)	**CIS Alone (N=33)**	**CIS + STS (N=31)**
Yes, n (%)	17 (52%)	9 (29%)
No, n (%)	16 (48%)	22 (71%)
Unadjusted Relative Risk (95% CI)	0.56 (0.30, 1.07)	
Adjusted Relative Risk (95% CI)	0.64 (0.32, 1.21)	

An additional sensitivity analysis was done considering the unlikely worst case scenario, where each missing hearing assessment in the CIS + STS arm is imputed as hearing impaired and each missing hearing assessment in the CIS alone arm is imputed as no hearing impairment. The adjusted and unadjusted relative risk are provided in the following table-

Table 33: Sensitivity Analysis - Worst Case Scenario for COG ACCL0431

Results (Patient experienced hearing loss, Y/N)	**CIS Alone (N=38)**	**CIS + STS (N=39)**
Yes, n (%)	17 (45%)	17 (44%)
No, n (%)	21 (55%)	22 (56%)
Unadjusted Relative Risk (95% CI)	0.97 (0.59, 1.61)	
Adjusted Relative Risk (95% CI)	1.07 (0.64, 1.79)	

FDA notes that these results should be interpreted within the context of the totality of the evidence given the post-hoc restriction of sample size to the non-metastatic patient population. Thus, while there appears to be a lower incidence of hearing loss in the CIS+STS arm compared to CIS alone, the true treatment effect is hard to quantify. Sensitivity analyses show that the unadjusted relative risk of hearing loss varies from 0.56 (95% CI: 0.30, 1.07) in the best case to 0.97 (95% CI: 0.59, 1.61) in the worst case. While adjusted relative risks estimated using a stratified CMH test were also provided, FDA notes that these stratified analyses may be limited by small sample sizes both overall and within strata, as well as heterogeneity of tumor types in the population.

Data Quality and Integrity

The Applicant's Position:

The data submitted are of high quality and integrity.

The FDA's Assessment:

FDA agrees that the data quality and integrity are acceptable.

Efficacy Results – Secondary and other relevant endpoints

The Applicant's Position:

Change in Hearing Thresholds

For both the left and right ears, there were no significant differences in the change in hearing threshold from baseline to 4 weeks after CIS treatment for the lower frequencies (≤ 2000 Hz) between the CIS+STS arm and the Observation arm, based on either independent reviewer's assessment (Table 344). Greater differences were observed for the CIS+STS arm compared with the Observation arm at the higher frequencies (≥ 4000 Hz) for both the left and right ears for both reviewers, with less hearing loss observed for the CIS+STS arm than the Observation arm at the higher frequencies. This finding is in keeping with high frequency hearing loss reported following platinum chemotherapy (Dickey et al, 2004; Dickey et al, 2005).

Table 34: Summary of Mean Change from Baseline Hearing Loss (COG 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

	Reviewer 1		Reviewer 2	
	Observation (N=55)	**CIS+STS (N=49)**	**Observation (N=55)**	**CIS+STS (N=49)**
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

	Reviewer 1		Reviewer 2	
	Observation (N=55)	**CIS+STS (N=49)**	**Observation (N=55)**	**CIS+STS (N=49)**
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
4000 Hz – Right Ear, n	43	36	43	36
LS mean (SE)	11.2 (4.24)	4.1 (4.70)	11.2 (4.24)	4.0 (4.71)
LS mean treatment difference	--	-7.0	--	-7.3
P-value	--	0.0625	--	0.0553
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

	Reviewer 1		Reviewer 2	
	Observation (N=55)	**CIS+STS (N=49)**	**Observation (N=55)**	**CIS+STS (N=49)**
P-value	--	0.0662	--	0.0707

Abbreviations: CI=confidence interval; CIS=cisplatin; COG=Children's Oncology Group; LS=least squares; SE=standard error; STS=sodium thiosulfate.

Note: Linear regression was used. Covariates included baseline values, stratum, and treatment. Observations with missing values were excluded from the model.

Sources: COG ACCL0431 CSR Table 14.2.4.1 and COG ACCL0431 CSR Table 14.2.4.2.

Duration of Follow-up

A summary of the duration of follow-up in years is presented for the ITT Population in Table 35.

Table 35: Summary of Duration of Follow-up (Years) (COG ACCL0431, ITT Population)

Statistic	**Observation (N=64)**	**CIS+STS (N=61)**	**Total (N=125)**
Minimum	0.57	0.23	0.23
25%	4.05	1.66	2.54
Median	5.60	4.95	5.33
75%	6.58	6.03	6.45
Maximum	8.27	8.28	8.28

Abbreviations: CIS=cisplatin; COG=Children's Oncology Group; ITT=Intent-to-treat; STS=sodium thiosulfate.

Note: Duration of follow-up was derived based on the last survival follow-up date.

Source: COG ACCL0431 CSR Table 14.1.3.3.

Event-free Survival

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 (Table 21).

Results of an exploratory analysis showed that there was no statistically significant difference in EFS between the CIS+STS arm and the Observation arm (hazard ratio: 1.27; 95% CI: 0.73, 2.18; p=0.3964) (Table 36 and Figure 10).

Results of a sensitivity analysis of EFS using stratification factors at randomization in a stratified log-rank test showed similar results (hazard ratio: 1.32; 95% CI: 0.76, 2.29; p=0.3263) (COG ACCL0431 CSR Table 14.2.2.2). Interpretation of these results is limited by the heterogeneity of the population.

Table 36: Summary of Event-free Survival (Median 5.33-year Follow-up) (COG ACCL0431, ITT Population)

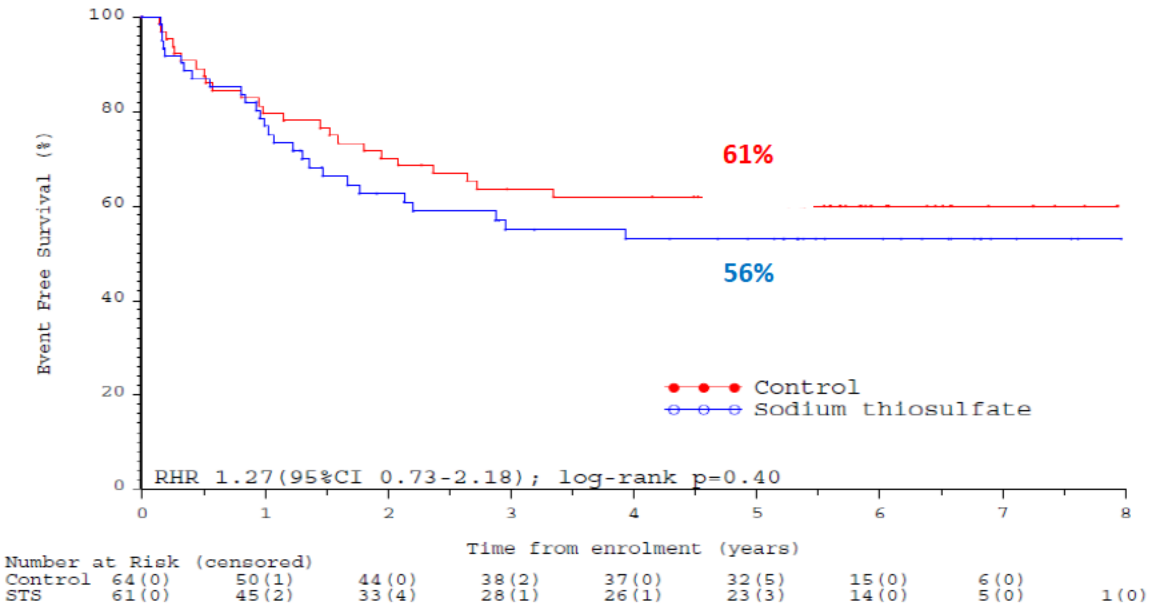
Parameter Category (Statistic)	Observation (N=64)	CIS+STS (N=61)
Number of patients with event, n (%)	25 (39.1)	27 (44.3)
Number of patients censored, n (%)	39 (60.9)	34 (55.7)
Treatment comparison (CIS+STS vs Observation [Reference Group])		
Hazard ratio		1.27
95% CI of hazard ratio		(0.73, 2.18)
Log-rank p-value		0.3964

Abbreviations: CI=confidence interval; CIS=cisplatin; COG=Children's Oncology Group; ITT=Intent-to-treat; STS=sodium thiosulfate.

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.

Source: COG ACCL0431 CSR Table 14.2.2.1.

Figure 10: Event-free Survival (Median 5.33-year Follow-up) (COG ACCL0431, ITT Population)



Abbreviations: CI=confidence interval; COG=Children's Oncology Group; EFS=event-free survival; ITT=Intent-to-treat; RHR=relative hazard ratio; STS=sodium thiosulfate.

Note: "Control" is the Observation arm.

Note: The provided EFS percentages of censored patients are from 5 years after study entry.

Note: For the calculation of the EFS relative hazard ratio, the Observation arm was the reference group.

Sources: COG ACCL0431 CSR Figure 2.1 and Table 21.

Overall Survival

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 (Table 22).

Results of an exploratory analysis showed that there was no statistically significant difference in OS between the CIS+STS arm and the Observation arm (hazard ratio: 1.79; 95% CI: 0.86, 3.72; p=0.1132) (Table 22 and Figure 5). Interpretation of these results is limited by the heterogeneity of the population. Results of a sensitivity analysis of OS using stratification factors at randomization in a stratified log-rank test showed similar results (COG ACCL0431 CSR Table 14.2.3.2).

Of the 30 children who died during this study, 28 of these children died due to their underlying disease: 16 in the CIS+STS arm and 12 in the Observation arm (Module 2.7.4, Section 2.1.2.2).

Of these, 13 of 16 deaths in the CIS+STS arm and 9 of 12 deaths in the Observation arm were related to progression of the disease, rather than to side effects of treatment.

Two children, both in the CIS+STS arm, died due to causes other than their underlying disease. Neither of these deaths was considered by the Investigator to be related to study medication.

Table 37: Summary of Overall Survival (Median 5.33-year Follow-up) (COG ACCL0431, ITT Population)

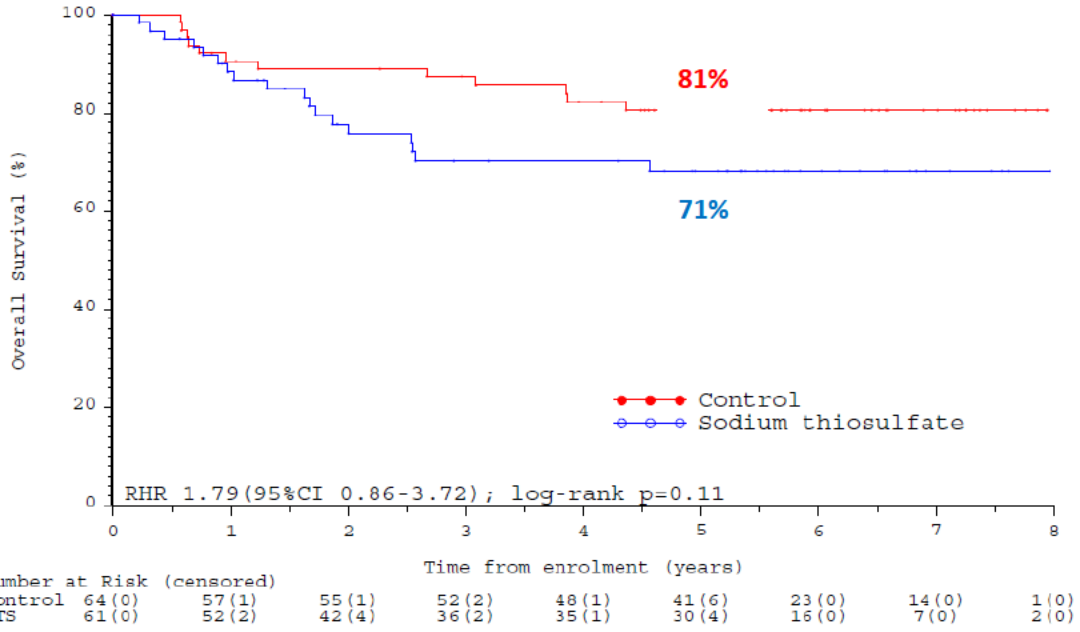
Parameter Category (Statistic)	**Observation (N=64)**	**CIS+STS (N=61)**
Number of patients who died [(1)], n (%)	12 (18.8)	18 (29.5)
Number of patients censored, n (%)	52 (81.3)	43 (70.5)
Treatment comparison (CIS+STS vs Observation [Reference Group])		
Hazard ratio		1.79
95% CI of hazard ratio		(0.86, 3.72)
Log-rank p-value		0.1132

Abbreviations: CI=confidence interval; CIS=cisplatin; COG=Children's Oncology Group; ITT=Intent-to-treat; STS=sodium thiosulfate.

(1) 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.

Source: COG ACCL0431 CSR Table 14.2.3.1.

Figure 11: Overall Survival (Median 5.33-year Follow-up) (COG ACCL0431, ITT Population)



Abbreviations: CI=confidence interval; COG=Children's Oncology Group; ITT=Intent-to-treat; OS=overall survival; RHR=relative hazard ratio; STS=sodium thiosulfate.

Note: "Control" is the Observation arm.

Note: The provided OS percentages of censored patients are from 5 years after study entry.

Note: For the calculation of the OS relative hazard ratio, the Observation arm was the reference group.

Sources: COG ACCL0431 CSR Figure 1.1 and Table 22.

The FDA's Assessment:

FDA notes that all secondary endpoint analyses are exploratory as no alpha was allocated to these endpoints. Thus, all p-values presented in relation to these endpoints should be considered nominal only and no claims of statistical significance should be made. FDA acknowledges the Applicant's analyses of change in hearing thresholds as presented in the efficacy population. However these data were not verified by FDA and are considered

exploratory. FDA also acknowledges that the study was not powered for EFS or OS and these analyses were exploratory. However, results for both endpoints suggested a potential detriment in the ITT population consisting of patients with metastatic and non-metastatic disease. FDA was particularly concerned about the potential detriment in OS. The study investigators shared this concern, and this is discussed further in the section on additional analyses conducted.

Dose/Dose Response

The Applicant's Position:

COG ACCL0431 confirmed that STS treatment at 16 to 20 g/m^2 resulted in statistically significant reductions in ototoxicity in patients with various types of solid tumors treated with CIS (Module 2.5, Section 4.4) while not affecting the anti-tumor efficacy of CIS in patients with localized, non-metastatic solid tumors (Module 2.5, Section 4.5).

The FDA's Assessment:

FDA agrees with the Applicant's position.

Durability of Response

The Applicant's Position:

All data related to the effect of STS over time in COG ACCL0431 is presented earlier in this section.

The FDA's Assessment:

This study was not designed to assess tumor response. Regarding persistence of effect of STS efficacy on hearing, see below (not relevant).

Persistence of Effect

The Applicant's Position:

Because STS was only given during chemotherapy treatment and hearing was assessed up to 1 year later, persistence of STS efficacy over time is not relevant.

The FDA's Assessment:

Not applicable.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

The Applicant's Position:

No patient-reported outcome endpoints were included in the COG ACCL0431 study.

The FDA's Assessment:

Not applicable.

Additional Analyses Conducted on the Individual Trial

The Applicant's Position:

A post-hoc analysis of EFS and OS in patients categorized with localized and disseminated disease (as determined post-hoc) was conducted by Fennec to address the findings published by COG in Freyer et al, 2017.

The protocol for COG ACCL0431 noted that, with the planned number of children at 65 per treatment arm, there would be minimal power for a formal comparison of EFS, with the heterogeneous patient population further complicating estimates of power. The statistical plan noted that the study had 84% power to detect a difference in EFS only if the Observation arm had a 3-year EFS of 59% with the STS arm being 34% and that such estimates would be highly dependent on the precise mix of tumor types of the patients who actually entered into the study. In the end, the difference between the groups was far less than this estimate, the OS was higher than expected, and there was no statistical difference in EFS or OS between the CIS+STS arm and the Observation arm (Module 2.7.3, Section 2.2.3.4 and Section 2.2.3.5).

Nevertheless, the study Investigators were concerned about a trend towards lower OS in the CIS+STS group and undertook a post-hoc evaluation of EFS and OS according to the extent of disease at the time of enrollment, classifying patients with a binary assignment to groups of localized or disseminated disease. The results of the post-hoc analysis (Freyer et al, 2017) suggested that, in patients categorized with disseminated disease, use of STS might be associated with reduced OS, although the publication noted that underlying diversity of patient tumor type, tumor biology, and staging were not taken into account during randomization and the study was only powered adequately for the primary hearing loss endpoint.

The following post-hoc analysis conducted by Fennec examines the results of the COG ACCL0431 study in patients categorized with localized and disseminated tumors to determine the possible explanations for the observed disparity in OS between the groups. Of note, 1 child (Patient (b) (6)) in the CIS+STS treatment arm had missing data for disease group and could not be categorized by localized or disseminated disease (Module 5.3.5.3 Table 12.1.1 and COG ACCL0431 CSR Listing 16.2.4.1). As such, 124 of the 125 randomized children in the COG ACCL0431 study were evaluated for this post-hoc analysis (77 children categorized with localized disease and 47 children categorized with disseminated disease).

Data are presented below for EFS and OS.

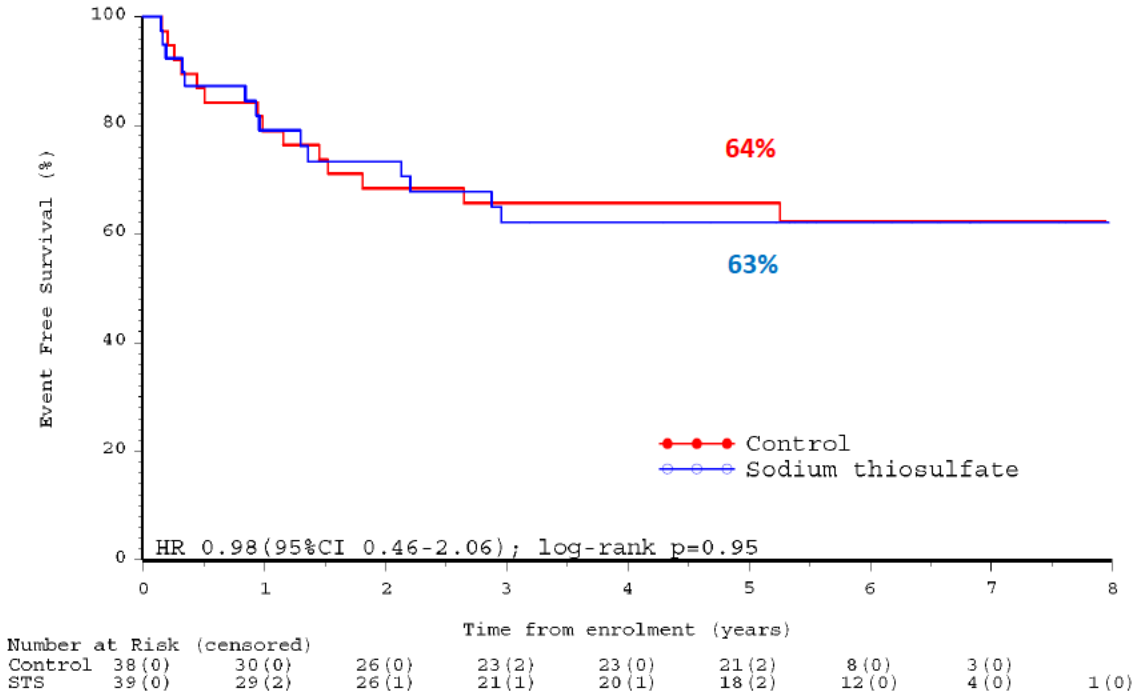
Post-hoc Analysis in Localized Disease

Fennec conducted a post-hoc analysis of EFS and OS by localized disease subgroup (determined post-hoc) with a median follow-up of 5.61 years (Module 5.3.5.3 Table 16.1). Results were similar to those with a median of 3.5 years follow-up, as published by Freyer et al 2017. Fennec further investigated efficacy and survival in the localized disease group to support the efficacy of STS and the effect of STS on anti-tumor efficacy of CIS.

Event-free Survival (Localized Disease)

Fourteen children categorized with localized disease in each arm experienced an event (Figure 12 and Module 5.3.5.3 Table 13.1). In children categorized with localized disease, a between group comparison showed no statistical difference in EFS between the arms (hazard ratio: 0.98; 95% CI: 0.46, 2.06 [p=0.9483]).

Figure 12: Event-free Survival (Median 5.61-year Follow-up) (COG ACCL0431, ITT Population, Localized Disease)



Abbreviations: CI=confidence interval; COG=Children's Oncology Group; EFS=event-free survival; HR=hazard ratio; ITT=Intent-to-treat; STS=sodium thiosulfate.

Note: The provided EFS percentages of censored patients are from 5 years after study entry.

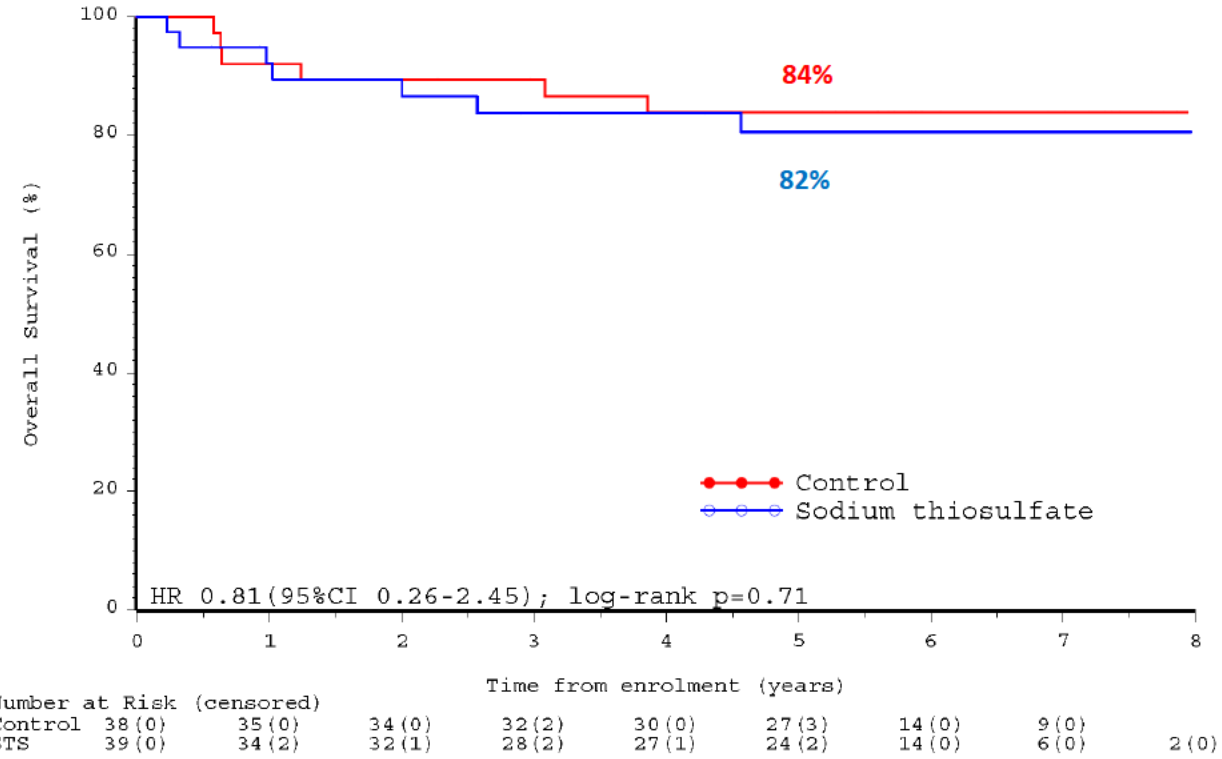
Note: For the calculation of the EFS hazard ratio, the Observation arm was the reference group.

Sources: Module 5.3.5.3 Figure 2.1 and Module 5.3.5.3 Table 13.1.

Overall Survival (Localized Disease)

Thirteen children categorized with localized disease died during the study: 6 children (15.8%) in the Observation arm and 7 children (17.9%) in the CIS+STS arm (Module 5.3.5.3 Table 14.1). All deaths were considered due to disease progression with the exception of 1 death in the CIS+STS arm (Patient (b) (6)) (see COG ACCL0431 CSR Section 6.2.1.2.3 for additional detail), which was a cardiac arrest during the night, considered not related to STS. In children categorized with localized disease, a between-group comparison showed no statistical difference in OS between the arms (hazard ratio: 0.81; 95% CI: 0.26, 2.45 [p=0.7105]) (Figure 13).

Figure 13: Overall Survival (Median 5.61-year Follow-up) (COG ACCL0431, ITT Population, Localized Disease)



Abbreviations: CI=confidence interval; COG=Children's Oncology Group; HR=hazard ratio; ITT=Intent-to-treat; OS=overall survival; STS=sodium thiosulfate.

Note: The provided OS percentages of censored patients are from 5 years after study entry.

Note: For the calculation of the OS hazard ratio, the Observation arm was the reference group.

Sources: Module 5.3.5.3 Figure 3.1 and Module 5.3.5.3 Table 14.1.

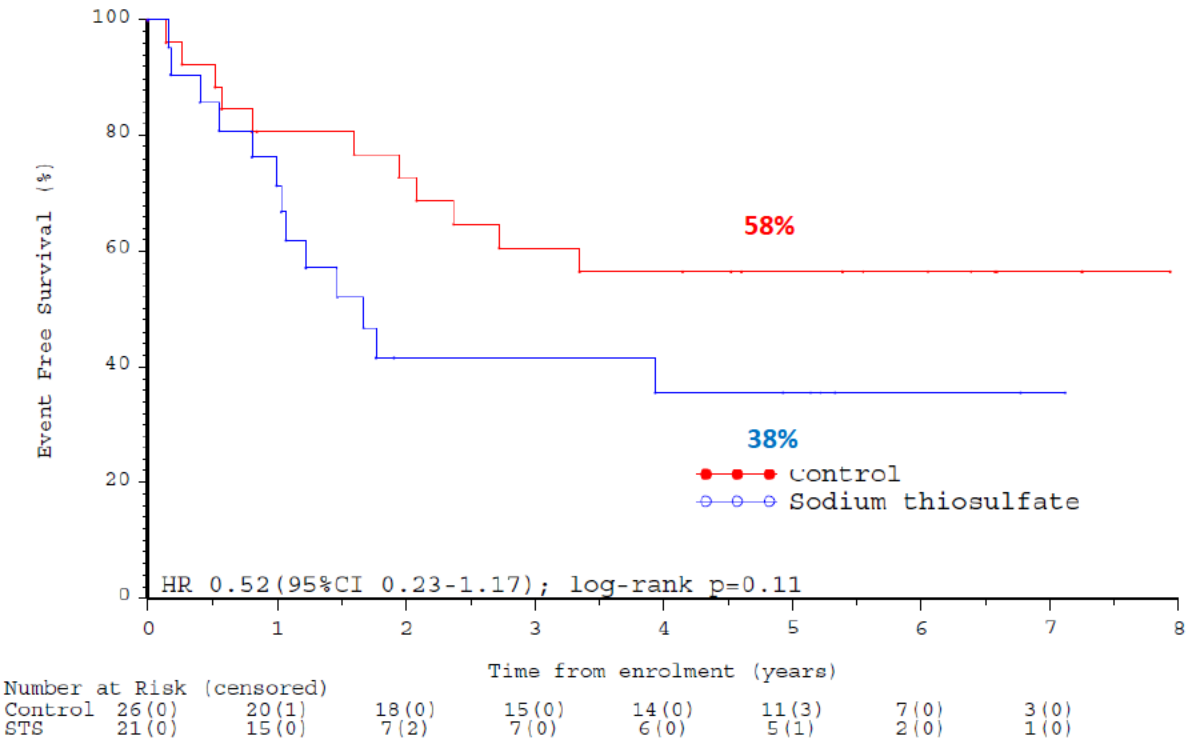
Post-Hoc Analysis in Disseminated Disease

Fennec conducted a post-hoc analysis of EFS and OS by disseminated disease subgroup (determined post-hoc) with a median follow-up of 4.52 years (Module 5.3.5.3 Table 16.2). Results were similar to those with a median of 3.5 years follow-up, as published by Freyer et al 2017. Fennec further investigated efficacy and survival in the disseminated disease group to evaluate the efficacy of STS and the effect of STS on anti-tumor efficacy of CIS.

Event-free Survival (Disseminated Disease)

Thirteen children in the CIS+STS arm and 11 children categorized with disseminated disease in the Observation arm experienced an event (Module 5.3.5.3 Table 13.2 and Figure 14). Minimum and maximum EFS results were 1.5 to 7.1 years and 0.8 to 7.9 years in the CIS+STS and Observation arms, respectively. In children categorized with disseminated disease, a between group comparison of OS showed a hazard ratio of 0.52 in favor of the Observation arm (95% CI: 0.23, 1.17; p=0.1089) showing no statistically significant difference between the groups. However, Figure 14 below suggests a trend towards a reduced EFS in the CIS+STS arm.

Figure 14: Event-free Survival (Median 4.52-year Follow-up)
(COG ACCL0431, ITT Population, Disseminated Disease)



Abbreviations: CI=confidence interval; COG=Children's Oncology Group; EFS=event-free survival; HR=hazard ratio; ITT=Intent-to-treat; STS=sodium thiosulfate.

Note: The provided EFS percentages of censored patients are from 5 years after study entry.

Note: For the calculation of the EFS hazard ratio, the Observation arm was the reference group.

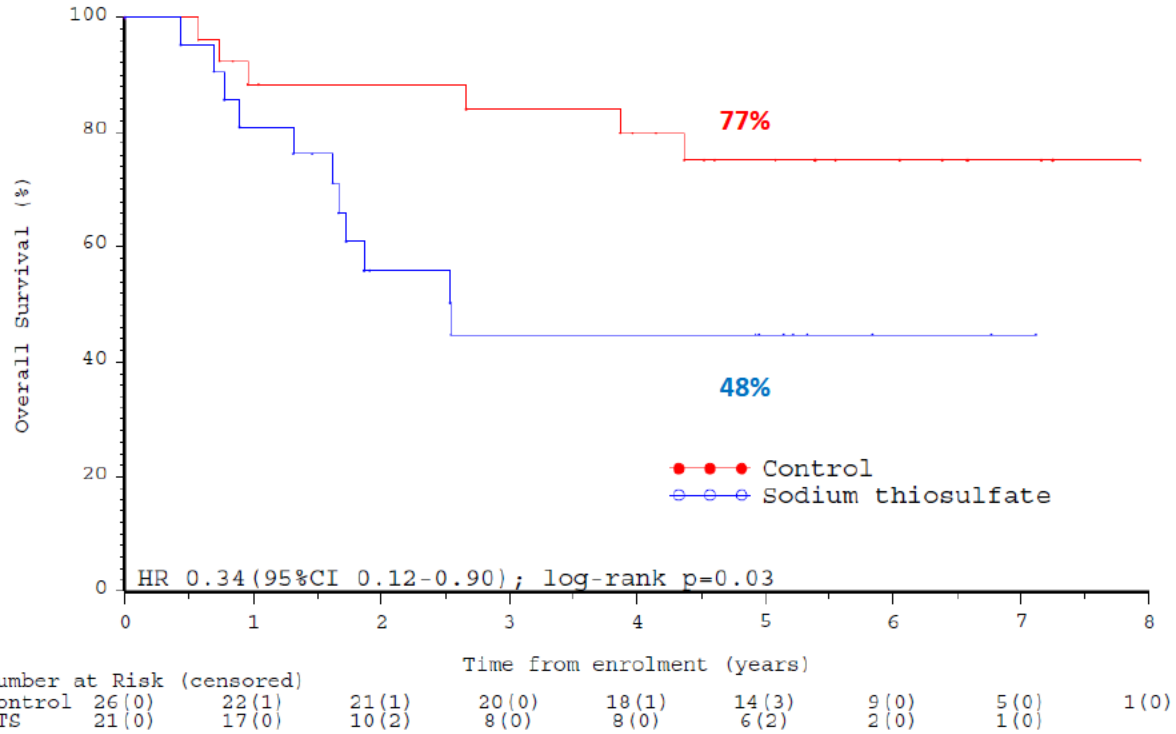
Sources: Module 5.3.5.3 Figure 2.2 and Module 5.3.5.3 Table 13.2.

Overall Survival (Disseminated Disease)

A total of 17 children categorized with disseminated disease died during the study; 6 children (23.1%) in the Observation arm and 11 children (52.4%) in the CIS+STS arm (Module 5.3.5.3 Table 14.2). In the Observation arm, all deaths were considered due to disease progression. In the CIS+STS arm, 10 deaths were due to disease progression and 1 was related to the child's participation in another trial at the time of disease relapse, during which he developed a consumptive coagulopathy as a result of experimental use of Vorinostat (Patient (b) (6)).

In children categorized with disseminated disease, a between group comparison showed a difference in OS between the arms (hazard ratio: 0.34; 95% CI: 0.12, 0.90 [p=0.0265]) (Figure 15).

Figure 15: Overall Survival (Median 4.52-year Follow-up) (COG ACCL0431, ITT Population, Disseminated Disease)



Abbreviations: CI=confidence interval; COG=Children's Oncology Group; HR=hazard ratio; ITT=Intent-to-treat; OS=overall survival; STS=sodium thiosulfate.

Note: The provided OS percentages of censored patients are from 5 years after study entry.

Note: For the calculation of the OS hazard ratio, the Observation arm was the reference group.

Sources: Module 5.3.5.3 Figure 3.2 and Module 5.3.5.3 Table 14.2.

The FDA's Assessment:

FDA acknowledges the Applicant's rationale for conducting additional post-hoc analyses for survival given the theoretical concern for STS interference with anti-tumor activity of cisplatin. FDA again notes that this study was not designed to assess secondary endpoints of EFS and OS and the results should be interpreted with caution. However, FDA shares the study

investigators' concern that results of the EFS and OS analyses suggest a potential detriment in these endpoints and agrees that additional analyses should be considered.

As noted by the Applicant, the localized and disseminated disease (non-metastatic and metastatic) subgroups were determined post-hoc. Thus, FDA notes that randomization was not stratified by these groups which may lead to some imbalances between arms within the subgroups. Additionally, sample size in these subgroups is small. Given these limitations, results from the post-hoc exploratory analyses of EFS and OS by localized and disseminated disease subgroups appear to suggest that the potential detriment seen for both endpoints may be driven by the disseminated disease subgroup. For this reason and others, the Applicant proposed to limit the indication to patients with non-metastatic/localized disease and FDA agreed.

For discussion regarding possible explanation for decreased OS in patients with metastatic disease, see Section 8.1.5 (Assessment of Efficacy Across Trial, secondary endpoints).

8.1.5 Assessment of Efficacy Across Trials

Primary Endpoints

The Applicant's Position:

SIOPEL 6 and COG ACCL0431 were each designed with adequate statistical power to evaluate the primary endpoint of their respective studies, ie, to assess the effectiveness of STS as an otoprotectant. Though both studies were open-label, all audiologic data were centrally reviewed by blinded reviewers in each study. Due to the different study populations, control arms, and hearing assessment scales (Brock grading or ASHA) utilized in the Phase 3 studies, it is not possible to directly compare results of the 2 studies. That said, the extent of reduction in ototoxicity with STS was remarkably similar in the 2 studies.

Within each study, treatment with STS 6 hours after the end of CIS infusion resulted in statistically significant and clinically relevant reductions (approximately 50%) in the proportion of children with CIS-induced hearing loss whether evaluated using the Brock Grading scale (as in SIOPEL 6) or the ASHA criteria (as in COG ACCL0431) (Table 23). Replication of this finding across both studies demonstrates the efficacy of STS in the prevention of CIS-induced ototoxicity in patients with SR-HB as well as other solid tumor types.

In SIOPEL 6, the risk of having hearing loss at ages ≥3.5 years was statistically significantly lower in the CIS+STS arm compared with the CIS Alone arm (relative risk: 0.521, 95% CI: 0.349, 0.778; p<0.001), corresponding to a clinically meaningful 48% lower risk after STS treatment.

In COG ACCL0431, the odds of having hearing loss 4 weeks after the last course of CIS, as defined by the ASHA criteria, were statistically significantly lower in the CIS+STS arm compared with the Observation arm (odds ratio: 0.274; 95% CI: 0.114, 0.660; p=0.0039). The greatest difference between groups was observed for children <5 years of age. Results of a post-hoc analysis categorizing patients by localized and disseminated disease showed similar reductions in hearing loss regardless of the extent of disease (Module 2.7.3, Section 2.2.3.7.1.2 [localized] and Section 2.2.3.7.2.2 [disseminated]).

Multiple sensitivity analyses within each study support the robustness of these primary efficacy results (Module 2.7.3, Section 2.1.3.1.2 [SIOPEL 6] and Module 2.7.3, Section 2.2.3.1.2 [COG ACCL0431]).

Table 38: Summary of Hearing Loss in Phase 3 Studies of STS

Results	SIOPEL 6 ITT Population		COG ACCL0431 Efficacy Population	
	CIS Alone (N=52)	CIS+STS (N=57)	Observation (N=55)	CIS+STS (N=49)
Yes, n (%)	35 (67.3)	20 (35.1)	31 (56.4)	14 (28.6)
No, n (%)	17 (32.7)	37 (64.9)	24 (43.6)	35 (71.4)
Relative Risk (95% CI)		0.521 (0.349, 0.778)		0.516 (0.318, 0.839)
P-value [a]		<0.001		0.0040
Odds Ratio [b] (95% CI)		0.254 (0.111, 0.579)		0.274 (0.114, 0.660)
P-value [b]		0.001		0.0039

Abbreviations: ASHA=American Speech-Language-Hearing Association; CI=confidence interval; CIS=cisplatin; CMH=Cochran-Mantel-Haenszel; COG=Children's Oncology Group; ITT=Intent-to-treat; OR=odds ratio; PRETEXT=Pre-treatment Tumor Extension; PTA=pure tone audiometry; RR=relative risk; SIOPEL=International Childhood Liver Tumor Strategy Group; STS=sodium thiosulfate.

[a] In SIOPEL 6, relative risk was calculated non-stratified. In COG ACCL0431, relative risk was calculated using a CMH test including stratification variable.

[b] In SIOPEL 6 and COG ACCL0431, the odds ratio was based on logistic regression including treatment and stratification variable as a covariate in the model.

Note: In SIOPEL 6, patients without hearing loss assessment were included as a 'Yes' for hearing loss. Hearing impairment was defined as Brock Grade ≥1 hearing loss determined by PTA at age ≥3.5 years.

Note: In COG ACCL0431, 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.

Sources: Module 5.3.5.3 Table 8.1 and Module 5.3.5.3 Table 8.10.

In addition to the evaluation of the primary efficacy endpoint, a secondary endpoint in COG ACCL0431 provides further support for the effectiveness of STS as an otoprotectant. This secondary endpoint was the mean change in hearing thresholds for key frequencies (500, 1000,

2000, 4000, and 8000 Hz) between the CIS+STS arm and the Observation arm. The effect of STS at various hearing thresholds was not evaluated in SIOPEL 6.

For both the left and right ears in COG ACCL0431, there were no significant differences in the change in hearing threshold from Baseline to 4 weeks after CIS treatment for the lower frequencies (≤2000 Hz) between the CIS+STS arm and the Observation arm, based on either independent reviewer's assessment (Module 2.7.3, In-text Table 21). Greater differences were observed for the CIS+STS arm compared with the Observation arm at the higher frequencies (≥4000 Hz) for both the left and right ears for both reviewers, with less hearing loss observed for the CIS+STS arm than the Observation arm at the higher frequencies. This finding is in keeping with high frequency hearing loss reported following platinum chemotherapy (Dickey et al, 2004; Dickey et al, 2005).

The FDA's Assessment:

FDA reiterates that, though both SIOPEL 6 and COG ACCL0431 were designed with adequate power for their respective primary endpoints, the type-1 error was controlled at a level of 0.05 (one-sided). Since the regulatory standard is to control type-1 error at a level of 0.05 (two-sided), the p-values associated with the primary endpoint in these studies were interpreted as nominal only and no claims of statistical significance should be made. Furthermore, FDA did not agree with the analysis populations in these studies, and the regulatory decision was based on FDA's analysis of the primary endpoint of each study in their respective re-defined populations.

FDA's analysis of the primary endpoint of hearing loss in SIOPEL 6 was based on the 114 patient ITT population which includes 5 randomized patients the Applicant originally excluded who withdrew prior to treatment. In this population, the unadjusted relative risk was 0.58 (95% CI: 0.40, 0.83) and the adjusted relative risk was 0.58 (95% CI: 0.41, 0.81), both in the direction of a lower incidence of hearing loss in the CIS+STS arm. Results were robust across various sensitivity analyses. However, as noted in Section 8.1.2, limits to the interpretation of the data include the inability of the Brock scale to identify mild hearing loss and a slight imbalance in missing data. These factors could potentially bias the study results in favor of the STS arm, however, given the totality of the evidence, FDA agrees that the results are clinically meaningful.

FDA's analysis of the primary endpoint of hearing loss in COG ACCL0431 was based on the 77 patients in the ITT population with non-metastatic disease. In this population, the unadjusted relative risk was 0.75 (95% CI: 0.48, 1.18) and the adjusted relative risk was 0.84 (95% CI: 0.53, 1.35), both in the direction of a lower incidence of hearing loss in the CIS+STS arm. Since the study was not designed to assess hearing loss in the non-metastatic subgroup, the sample size is small and these results should be interpreted with caution. Sensitivity analyses suggested that the unadjusted relative risk of hearing loss could vary from 0.56 (95% CI: 0.30, 1.07) in the best case to 0.97 (95% CI: 0.59, 1.61) in the worst case.

FDA did not independently confirm the secondary endpoint of mean change in hearing thresholds for key frequencies in COG ACCL0431 and considers these results to be exploratory.

Secondary and Other Endpoints

The Applicant's Position:

When evaluating the effectiveness of STS as an otoprotectant, it was equally important to ensure that STS did not negatively impact the anti-tumor efficacy of CIS. The timing of administration of STS relative to CIS dosing was optimized in each study to minimize any potential of STS to affect the anti-tumor efficacy of CIS.

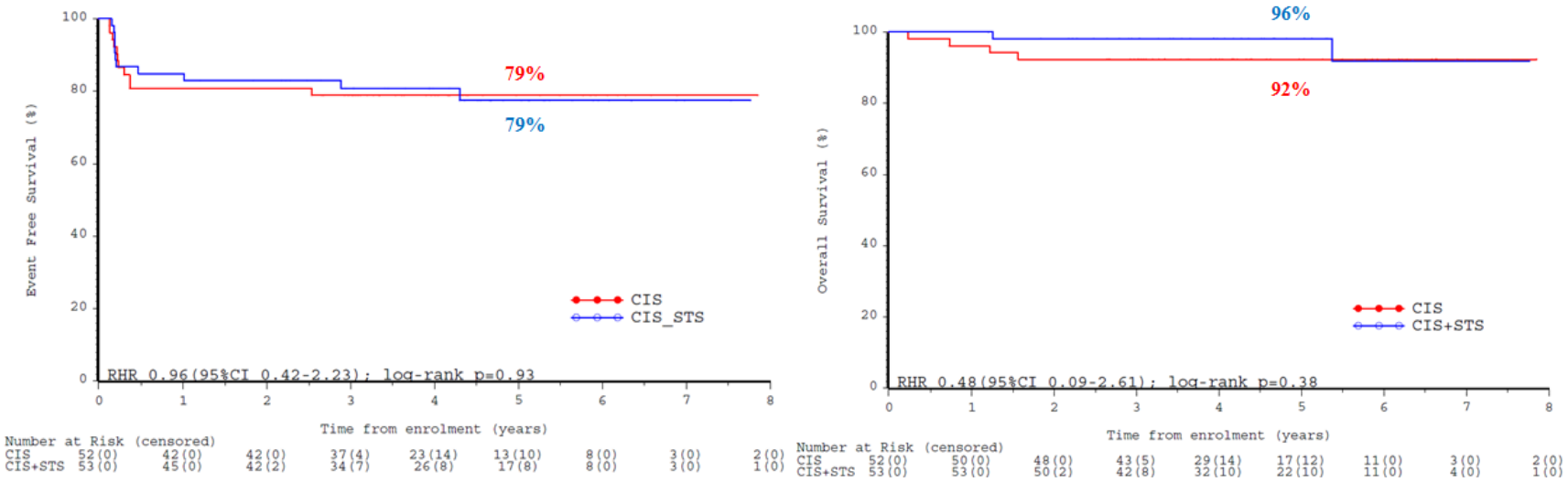
In addition to optimizing the timing of administration of CIS and STS relative to one another, multiple endpoints were evaluated in each study to assess the potential effect of STS on CIS anti-tumor efficacy. Event-free and OS were evaluated in both studies, though neither study was powered for this comparison. Specifically, it should be noted that in COG ACCL0431 (which enrolled children with various tumor types), the protocol proactively stated that there would be minimal power for a formal comparison of EFS, with the heterogeneous patient population further complicating estimates of power.

Both studies showed that there was no statistically significant difference in EFS or OS for the CIS+STS arm compared with the CIS Alone arm (SIOPEL 6) or with the Observation arm (COG ACCL0431) (Figure). This finding supports that treatment with STS does not negatively affect the anti-tumor efficacy of CIS.

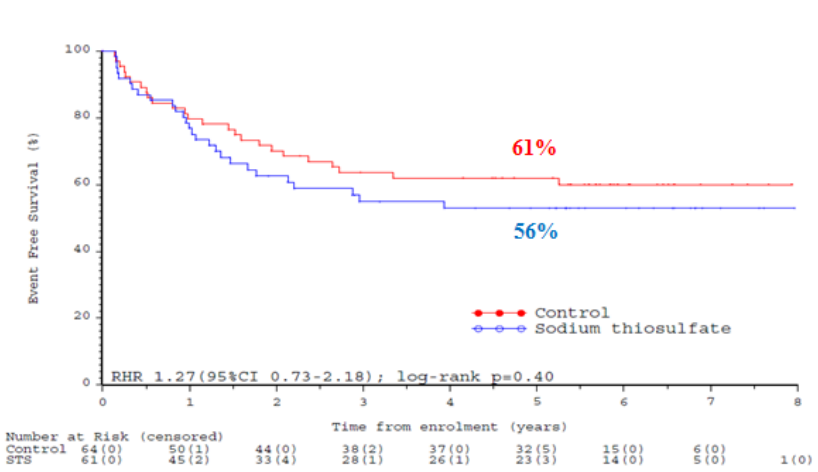
Figure 16: Event-free and Overall Survival in SIOPEL 6 and COG ACCL0431

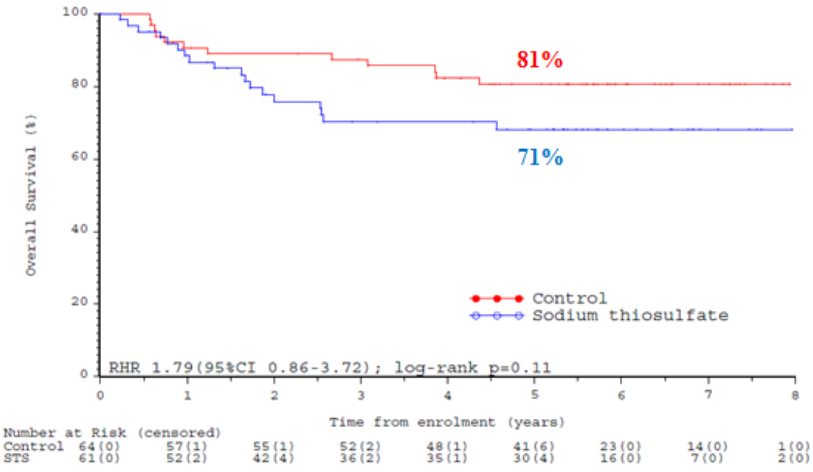
Event-free Survival **Overall Survival**

SIOPEL 6 (Median 4.27-year Follow-up)



COG ACCL0431 (Median 5.33-year Follow-up)





Abbreviations: CI=confidence interval; COG=Children's Oncology Group; EFS=event-free survival; ITT=Intent-to-treat; OS=overall survival; RHR=relative hazard ratio; SIOPEL=International Childhood Liver Tumor Strategy Group; STS=sodium thiosulfate.

Note: "Control" is the Observation arm.

Note: The provided EFS and OS percentages of censored patients are from 5 years after study entry.

Note: For the calculation of the EFS and OS relative hazard ratio, the CIS arm (in SIOPEL 6) and Control/Observation arm (in COG ACCL0431) was the reference group.

Sources: SIOPEL 6 CSR Figure 1.1, SIOPEL 6 CSR Figure 2.1, COG ACCL0431 CSR Figure 1.1, COG ACCL0431 CSR Figure 2.1.

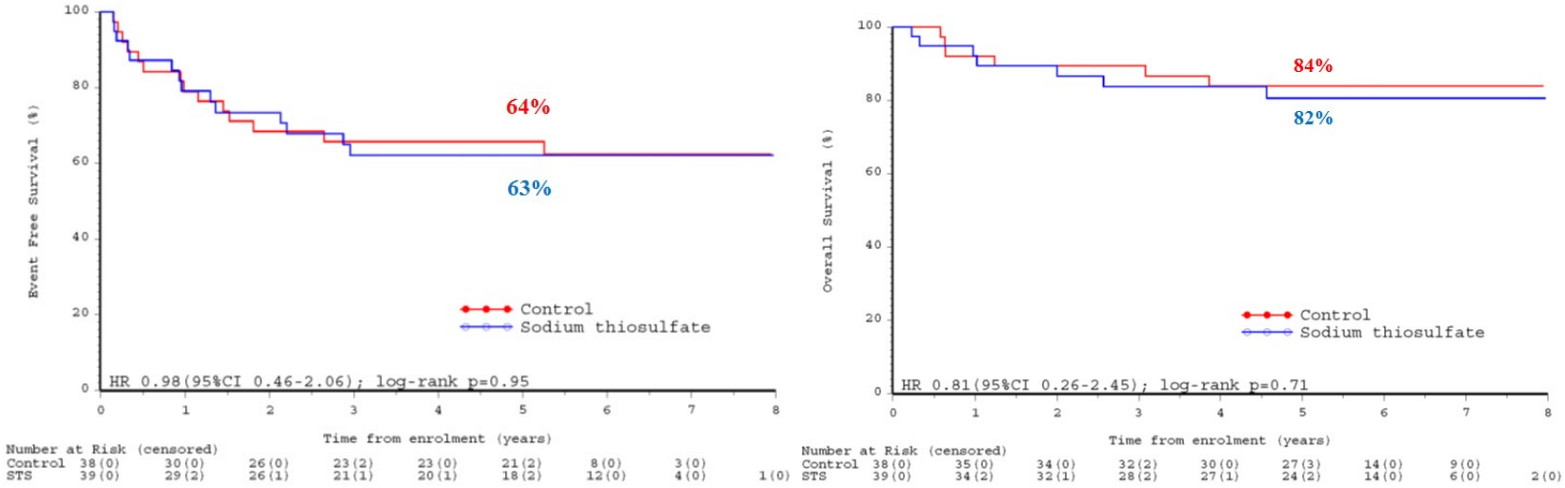
Nevertheless, the COG ACCL0431 study Investigators were concerned about a trend towards lower OS in the CIS+STS group and undertook a post-hoc evaluation of EFS and OS according to the extent of disease at the time of enrollment, classifying patients with a binary assignment to groups of localized or disseminated disease. The results of the post-hoc analysis (Freyer et al, 2017) suggested that, in patients categorized with disseminated disease, use of STS might be associated with reduced EFS and OS, although the publication noted that underlying diversity of patient tumor type, tumor biology, and staging were not taken into account during randomization and the study was only powered adequately for the primary hearing loss endpoint.

To address these published results, Fennec conducted its own post-hoc analysis of EFS and OS for patients categorized by localized and disseminated disease subgroup (determined post-hoc) with a median follow up of 5.61 years and 4.52 years, respectively (see 17). Results were similar to those with a median of 3.5 years follow up, as published by Freyer et al, 2017. No difference was observed in EFS or OS in patients with localized disease, as assessed for SR-HB in SIOPEL 6 (upper panel; Figure 7) and for various tumor types by post-hoc designation in COG ACCL0431 (upper panel; 7). This evaluation reiterates the overall conclusion that treatment with STS does not negatively affect the anti-tumor efficacy of CIS in patients with localized, non-metastatic, solid tumors, the population for which STS is proposed in this application.

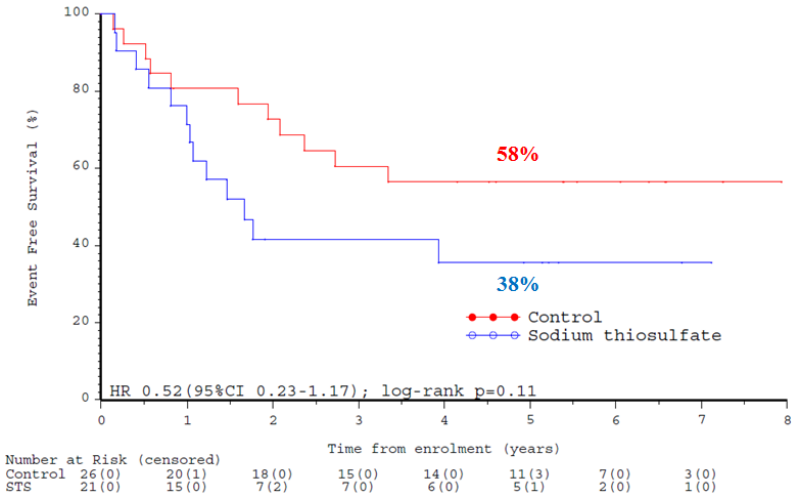
Figure 17: Event-free and Overall Survival in COG ACCL0431 (By Post-hoc Categorization of Localized or Disseminated Disease)

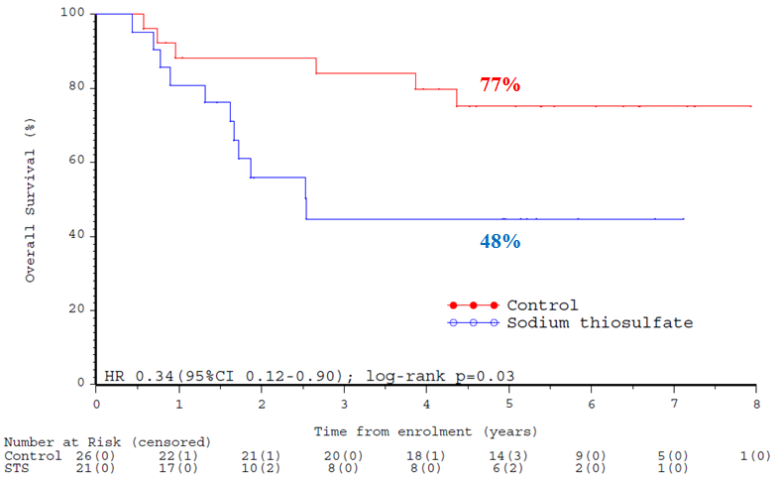
Event-free Survival **Overall Survival**

COG ACCL0431 (Localized; Median 5.61-year Follow-up)



COG ACCL0431 (Disseminated; Median 4.52-year Follow-up)





Abbreviations: CI=confidence interval; COG=Children's Oncology Group; HR=hazard ratio; ITT=Intent-to-treat; OS=overall survival; STS=sodium thiosulfate.

Note: The provided EFS and OS percentages of censored patients are from 5 years after study entry.

Note: For the calculation of the EFS and OS hazard ratio, the CIS arm (in SIOPEL 6) and Control/Observation arm (in COG ACCL0431) was the reference group.

Sources: Module 5.3.5.3 Figure 2.1, Figure 2.2, Figure 3.1, and Figure 3.2.

To further investigate the disparity in OS in patients categorized with disseminated disease in COG ACCL0431 (lower panel; Figure 17), Fennec undertook a patient-by-patient analysis of results in children with disseminated tumors to determine the possible explanations for this finding. This effort focused on the predicted OS for each specific tumor type, EFS/OS published for the chemotherapy regimens the children received in COG ACCL0431, and the individual prognostic indicators derived from the data set provided by COG to Fennec.

Table 24 Column 3 shows the predicted 3-year EFS rates from the COG statistical plan (which did not discriminate between localized and disseminated disease), which predicted EFS of 59% and long-term EFS (OS) of 48%. In reality, the EFS was similar to what was predicted at 58.4% (73/125 censored).

In the literature, OS rates for the common tumor types in COG ACCL0431 vary according to various prognostic indicators present at the time of diagnosis and the common ranges are summarized in Column 4, Table 39. The OS for all children categorized with mixed disseminated disease in COG ACCL0431 was within that expected in the literature at 64% (Column 5, Table 39) as was that observed in the CIS+STS arm of 48% (Column 7, Table 39). However, OS in the Observation arm was higher than would be predicted for a group of children categorized with mixed, disseminated disease at 77% (Column 6, Table 3939) and very close to what was observed for children categorized with localized disease (84.2%).

Table 39: Predicted vs Observed Survival Rates in COG ACCL0431, ITT Population (Median 4.52-year Follow-up)

Disease type	Age Range in COG ACCL0431 (years)	Expected 3-year EFS from COG ACCL0431[a] (All Patients)	Expected 5-year OS Disseminated Disease (literature)	Observed OS in Disseminated Disease in COG ACCL0431		
				All Patients % (n/N)	Observation Arm % (n/N)	CIS+STS Arm % (n/N)
GCTs	10.7 to 17.8	75%	40% to 83%[b]	93% (13/14)	100% (7/7)	86% (6/7)
Medulloblastomas	2.3 to 12.4	55%	20% to 89%[c]	60% (3/5)	100% (2/2)	33% (1/3)
Neuroblastomas	1.4 to 15.4	45%	46% to 68%[d]	59% (10/17)	64% (7/11)	50% (3/6)
Osteosarcomas	3.3 to 15.4	70%	29% to 31%[e]	33% (3/9)	60% (3/5)	0% (0/4)
Overall	1.1 to 17.8	59%	~34% to 68%[f]	64% (30/47)	77% (20/26)	48% (11/21) [g]

Abbreviations: CIS=cisplatin; COG=Children's Oncology Group; CSR=clinical study report; EFS=event-free survival; GCT=Germ cell tumor; NOS=not otherwise specified; OS=overall survival; STS=sodium thiosulfate.

[a] Statistical considerations in the COG ACCL0431 protocol: Observation arm all patients (localized and disseminated) 3-year EFS: 59%, 3-year long term EFS: 48%.

[b] MaGIC study results for children ≥ 11 years with Stage IV (metastatic disease) (Frazier et al, 2015).

[c] Von Bueren et al, 2016.

[d] National Cancer Institute, OS children age 1 to 14 years and 10 to 21 years

[e] Kager et al, 2003 and Boye et al, 2014.

[f] Assuming an even preponderance of tumor types

[g] One additional death occurred in the CIS+STS arm, the child had disseminated carcinoma (NOS), and a poor prognosis.

Source: COG ACCL0431 CSR Listing 16.2.8.1.

When comparing the observed survival rates in COG ACCL0431 to the predicted survival rates in the literature, the clear outlier was the OS in the Observation arm, which was higher than would be predicted for a group of children with mixed, disseminated tumors at 77% and very close to what was observed for children with localized disease (84.2%) (right-hand panels in Figure 17). As a result of this finding, Fennec conducted a by-patient review of prognostic factors for children with disseminated disease to determine if there was an imbalance between the groups prior to randomization.

Table 25 below summarizes the number of children identified with poor prognostic risk indicators at diagnosis and the response to chemotherapy recorded for patients with disseminated disease. These results clearly suggest that the most likely explanation for the difference is an imbalance in prognostic indicators relating to the underlying tumor types in the 2 arms with 67% (14 of 21) children in the CIS+STS arm having identified poor prognostic indicators compared to 38% (10 of 26) in the Observation arm. These prognostic indicators were not controlled for during randomization and were not stratification variables and the study was not sufficiently large such that the variability in prognostic indicators would be taken care of during randomization without stratification since the study was powered for the hearing loss endpoint only.

Table 40: Children with Factors Indicating a Poor Prognosis (COG 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)
Stable disease	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; STS=sodium thiosulfate.

Sources: COG ACCL0431 CSR Listing 16.2.4.1, Module 2.7.3, In-text Table 33, Table 35, Table 38, Table 40, and Table 42.

To examine whether the STS treatment regimens used in COG ACCL0431 somehow interfered with the anti-tumor efficacy of CIS (and thereby would affect the safety profile of the proposed use of STS), the patterns of CIS and STS dosing were evaluated with respect to children categorized with localized vs disseminated disease and survival status. If STS was the reason for the differences observed in survival, this would be most likely to be seen in children who were given cycles of 5 days of 20 mg/m^2 CIS with 5 days of 16 g/m^2 of STS since this scenario represents the greatest risk of an interaction between the 2 agents, and yet it was the group who received less than 3 days of CIS and STS per cycle that contained the preponderance of children who died (7 of 9) compared with 4 of 12 deaths in those receiving >3 doses of CIS and STS per cycle. Furthermore, receiving fewer doses of STS (<8 doses) was also associated with a lower likelihood of survival during the study compared to those who received >8 doses of STS. The likelihood of dying was not associated with the cumulative dose of STS received. The recorded response to chemotherapy is similar between the arms, although analysis is hampered by a larger number of unrecorded responses in the CIS+STS arm. The slightly lower proportion of PR/CR in the CIS+STS arm compared with the Observation arm is not unexpected given the poor prognostic risk factors identified in the CIS+STS arm.

In conclusion, the reason for the observed disparity in OS between the groups categorized with disseminated disease in COG ACCL0431 is most likely due to an imbalance in tumor types and prognostic indicators at randomization rather than to the use of STS. The characteristics of the tumors in COG ACCL0431 have a far greater potential to affect survival than the use of STS. Thus the Observation arm, containing by chance some children with a better prognosis from the outset, did better than expected from the published literature with an overall 5-year survival rate of 77% despite disseminated disease at diagnosis, whereas more children in the CIS+STS arm, by chance, had poor prognostic indicators from the outset and had survival rates (48%) in keeping with the literature for disseminated disease at diagnosis across a mixed group of solid tumors.

In addition to the EFS and OS assessed in both SIOPEL 6 and COG ACCL0431, additional endpoints were evaluated in SIOPEL 6 to address the potential effect of STS treatment on the anti-tumor efficacy of CIS, including response to preoperative chemotherapy, complete tumor resection, remission status, and AFP values (used as a tumor marker). These endpoints were not evaluated in COG ACCL0431. Although not powered for these analyses, results for each of these endpoints showed that there were no statistically significant differences between the CIS+STS arm and the CIS Alone arm, as detailed below, supporting that treatment with STS 6 hours after the end of each CIS infusion did not affect the anti-tumor efficacy of CIS.

With regard to the response to preoperative chemotherapy, after 4 cycles, the proportion of responders (defined as CR and PR, but no patients achieved CR after 4 cycles) were not significantly different between the CIS+STS arm (35 children [66.0%]) and the CIS Alone arm

(39 children [75.0%]) (p=0.393) (Module 2.7.3, In-text Table 8). The proportion of children with PD was similar in the CIS+STS and CIS Alone arms (SIOPEL 6 CSR, Listing 16.2.6.2).

There was no statistically significant difference in the percentage of children with partial hepatectomy vs OLT (p>0.999) (Module 2.7.3, In-text Table 10).

There was no statistically significant difference in the proportion of children with complete remission 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) (Module 2.7.3, In-text Table 11). 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).

In both the CIS+STS and the CIS Alone arms, the mean change from Baseline in log-transformed AFP values were similar and statistically significant reductions were observed after course 2 (-0.635 ng/mL [p<0.001] and -0.817 ng/mL [p<0.001], respectively) and after course 4 (-1.467 ng/mL [p<0.001] and -1.956 ng/mL [p<0.001], respectively) (Module 2.7.3, In-text Table 15). In both the CIS+STS and the CIS Alone arms, the mean changes from Baseline to end of treatment in log-transformed 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).

Taken together, the results of the evaluation of EFS and OS in both studies and the additional evaluations of response to preoperative chemotherapy, complete tumor resection, remission status, and AFP values (used as a tumor marker) in SIOPEL 6, support that treatment with STS did not negatively impact the anti-tumor effectiveness of CIS chemotherapy (with infusion times of 1 to 6 hours) in children with localized, non-metastatic, solid tumors.

The FDA's Assessment:

FDA acknowledges that neither study was designed to assess EFS or OS, so the results should be interpreted with caution. Given the theoretical risk of STS interference with anti-tumor activity, FDA agrees with the due diligence conducted by the study sponsors of COG ACCL0431 and the Applicant's independent analysis to attempt to analyze the potential risk of decreased OS.

Results for EFS and OS in the SIOPEL6 study showed no apparent difference between arms for either endpoint. However, as noted previously, FDA shared the study investigators' concern that there could be a potential detriment in EFS and OS in the ITT population (consisting of metastatic and non-metastatic patients) for the COG ACCL0431 study. The post-hoc exploratory

analysis of OS in COG ACCL0431 by subgroups defined by extent of disease suggested that this difference was potentially driven by patients with metastatic disease. Note that extent of disease (metastatic or non-metastatic) was determined post-hoc and was not a stratification factor and sample size in each subgroup was small, so these results should be considered with these limitations in mind.

The Applicant provides further evidence that the potential detriment in OS seen in patients with metastatic/disseminated disease in COG ACCL0431 could be due to heterogeneity in the patient population due to the enrollment of diverse tumor types without controlling for certain prognostic factors at randomization. FDA acknowledges that enrollment on COG ACCL0431 did not account for important prognostic variables (e.g. age, histology, stage, biologic features, prior therapy, tumor location, ability resect, tumor size, etc.) and that an imbalance in prognostic factors could be driving the potential detriment in OS observed in patients with metastatic disease. However, FDA considers the analyses conducted to support this explanation to be exploratory and also notes that the selection of factors indicating a poor prognosis could be subjective.

The Applicant also examined STS treatment regimens and notes that, in general, patients receiving more STS did not appear to account for more deaths than those who received less STS. FDA also considers these analyses to be exploratory and does not believe any conclusions should be made due to the very limited data available.

Analyses of additional secondary endpoints in SIOPEL6 and COG ACCL0431 (other than EFS and OS) were not verified by FDA, results are considered exploratory, and any p-values reported are nominal only.

Notwithstanding the limitations of the data with respect to elucidating whether STS has a potential adverse impact on the antitumor effect of cisplatin in pediatric patients with metastatic cancers, FDA agrees that limiting the indication to patients with non-metastatic disease will help alleviate these concerns.

Subpopulations

The Applicant's Position:

The SIOPEL 6 and COG ACCL0431 studies had small sample sizes (Module 2.7.3, In-text Table 51) which limits the interpretation of data by subgroups. Overall, the results of the

subgroup analyses in each study showed that there was no clinically meaningful association of gender, age group, or weight with the otoprotective effect of STS that would necessitate changes to the dosing recommendations in the proposed label.

Nevertheless, in the pre-specified analysis of COG ACCL0431 by age group, the greatest difference between the CIS+STS arm and the Observation arm was observed for children <5 years of age (3 patients [21.4%] vs 11 patients [73.3%], respectively) compared with children ≥5 years of age (11 patients [31.4%] vs 20 patients [50.0%], respectively) (Module 2.7.3, Section 3.3.2.2). Children <5 years old are known to be at increased risk for moderate to severe hearing loss (Li et al, 2004).

The FDA's Assessment:

The FDA generally agrees with the Applicant's position on subpopulations. Refer to the respective efficacy sections above for results from FDA's exploratory subgroup analyses for SIOPEL6 and COG ACCL0431 in the relevant re-defined analysis populations. No conclusions should be drawn regarding hearing loss by age group in COG ACCL0431.

Additional Efficacy Considerations

The FDA's Assessment:

n/a

8.1.6 Integrated Assessment of Effectiveness

The Applicant's Position:

The totality of evidence from the STS clinical development program and available literature demonstrates that PEDMARK is effective when administered for the prevention of ototoxicity induced by CIS chemotherapy in patients 1 month to <18 years of age with localized, non-metastatic, solid tumors.

Effective Otoprotectant

Both SIOPEL 6 and COG ACCL0431 showed that treatment with STS administered via a 15-minute IV infusion 6 hours after the end of CIS infusion resulted in statistically significant and clinically relevant reductions (approximately 50%) in the proportion of children with CIS-induced hearing loss compared with patients not receiving STS, whether evaluated using the Brock Grading scale (35.1% vs 67.3%; as in SIOPEL 6) or the ASHA criteria (28.6% vs 56.4%; as in COG ACCL0431). Replication of this finding across both studies demonstrates the efficacy of STS in the prevention of CIS-induced ototoxicity in patients with a range of tumor

types. Prevention of ototoxicity after STS treatment was particularly seen in children <5 years of age (21.4% vs 73.3%; as in COG ACCL0431), who are most vulnerable to the effects of hearing loss on their language development and future communication.

Although these results are straightforward, their impact should not be minimized given the very good chances for long-term survival in these children. In the context of the impact of hearing loss in children, the clinical relevance of the results obtained from SIOPEL 6 and COG ACCL0431 are obvious. Use of PEDMARK in children undergoing CIS treatment for various types of localized, non-metastatic solid tumors can reduce the risk of hearing loss by 50%. Such a reduction is especially meaningful in this patient population as it can improve the chances that these children will not have to suffer the challenges of profound and irreversible hearing loss on top of those challenges already associated with their disease.

No Impact on Anti-tumor Efficacy of Cisplatin

When evaluating the effectiveness of STS as an otoprotectant, it was equally important to ensure that STS did not negatively impact the anti-tumor efficacy of CIS. Multiple endpoints were evaluated in SIOPEL 6 and COG ACCL0431 to assess the potential effect of STS on anti-tumor efficacy of CIS. The key endpoints used for this assessment were EFS and OS, which were evaluated in both studies, though neither study was powered for this comparison. Both studies showed that there was no statistically significant difference in EFS or OS for the CIS+STS arm compared with the CIS Alone arm (SIOPEL 6) or with the Observation arm (COG ACCL0431); though in COG ACCL0431, a trend for disparity in OS was observed between the arms.

A post-hoc evaluation of EFS and OS according to the extent of disease at the time of enrollment in COG ACCL0431 was conducted, categorizing patients with a binary assignment to groups of localized or disseminated disease. In children with localized, non-metastatic, solid tumors,

PEDMARK administered 6 hours after completion of a 1- to 6-hour CIS infusion no association with a reduction in EFS or OS, indicating that treatment does not negatively impact the anti-tumor efficacy of CIS chemotherapy. These results are confirmed by those from SIOPEL 6, where all patients had localized, non-metastatic disease (SR-HB). In COG ACCL0431 in patients characterized with disseminated disease, there was a disparity in the OS between the groups due to an imbalance in prognostic risk factors.

Furthermore, based on the known PK profile of CIS, unbound active platinum levels are no longer detected at 6 hours after the end of CIS infusion, or only low residual platinum exposure remains likely consisting of inactive platinum species. Therefore, the 6-hour delay in STS administration prevents a pharmacodynamic drug-interaction interference with the anti-tumor efficacy of CIS. Based on the half-life of STS in plasma, a negligible amount of STS would remain 6 hours after completion of an STS infusion and would not be expected to interact with a subsequent CIS infusion.

Taken together, the results of the evaluation of EFS and OS in both studies, the additional evaluations of response to preoperative chemotherapy, complete tumor resection, remission status, and AFP values (used as a tumor marker) in SIOPEL 6, and the known PK profile of CIS and STS, support that treatment with STS did not affect the anti-tumor efficacy of CIS in patients with localized, non-metastatic solid tumors.

In context with the efficacy of PEDMARK, these results are meaningful as they enable parents and physicians to be confident about the use of PEDMARK as part of the child's CIS treatment regimen without concern for an impact on survival.

The FDA's Assessment:

The clinical data from SIOPEL 6 and COG ACCL0431 are supportive of traditional approval of sodium thiosulfate to reduce the risk of ototoxicity associated with cisplatin in pediatric patients 1 month of age and older with localized, non-metastatic solid tumors. FDA recognizes limitations of both studies including issues with type-1 error control and the definition of the patient populations Neither SIOPEL 6 nor COG ACCL0431 controlled type-1 error at a level of 0.05 (two-sided). Thus, p-values associated with the primary endpoint of hearing loss in these studies were interpreted as nominal only and no claims of statistical significance should be made. Furthermore, as noted in Sections 8.1.3 and 8.1.4, FDA does not agree with the definition of the patient population to support regulatory decision making in either study (For SIOPEL 6: Applicant excluded 5 randomized patients who withdrew prior to treatment, while FDA uses all randomized patients; COG ACCL0431: Applicant uses all patients who had a baseline and 4-week post-CIS follow-up assessment, while FDA uses all patients with localized disease irrespective of missing assessments). FDA analyses of the primary endpoints in each respective study showed evidence of a decreased incidence of hearing loss in favor of the CIS+STS arm. Because the efficacy population of COG ACCL0431 was restricted to patients with localized tumors based on concerns relating to a possibly detriment in survival in patients with metastatic disease, interpretation of the efficacy results are complicated by the reduction in sample size and loss of randomization resulting from this adjustment to the efficacy population. Nevertheless, both trials showed evidence of a decreased incidence of hearing loss in favor of the CIS+STS arm. No conclusions should be drawn regarding hearing loss by age group in COG ACCL0431 as this was an exploratory subgroup analysis with limited sample size.

FDA also considered the risk of STS impacting the anti-tumor activity efficacy of CIS in the context of a trend for decreased survival in the STS+CIS arm in COG ACCL0431. No secondary endpoint analyses were verified outside of those for EFS and OS. In COG ACCL0431, results of

the EFS and OS analyses showed a trend in detriment in both endpoints, although the study was not powered for either analysis. The Applicant provided several possible explanations for this trend including an imbalance of prognostic factors. Multiple exploratory analyses suggest that the survival difference is driven by patients with metastatic disease. This is supported by SIOPEL 6, where a detriment in overall survival was not observed in a more homogenous population of patients with localized hepatoblastoma, although FDA notes that neither study was powered for survival analyses and that these findings could be due to chance, particularly given that there is no known plausible biologic rationale for a difference in the mechanism of action of STS in patients with metastatic disease.

However, despite these limitations, FDA agrees that limiting the indication to patients with non-metastatic disease was warranted to help alleviate these concerns and that the totality of the evidence supports the use of STS after CIS to prevent ototoxicity in pediatric patients with localized solid tumors.

8.2 REVIEW OF SAFETY

The Applicant's Position:

Sodium thiosulfate has been safely used for over 100 years as a therapeutic agent, and medical uses of STS have been well documented since 1895 (EPA, 2003). However, the majority of support for the safety of PEDMARK in the proposed indication was derived from the 2 confirmative Phase 3 studies, SIOPEL 6 and COG ACCL0431, with additional support from the published literature. SIOPEL 6 and COG ACCL0431 enrolled patients who comprise the intended target population for PEDMARK. Data are presented from a total of 232 patients with a variety of solid tumor types of whom 112 received at least 1 dose of STS in addition to CIS and 120 received CIS without STS.

Although the patient populations and CIS and STS dosing differed between SIOPEL 6 and COG ACCL0431 (Table 4), the safety profile of STS administration was generally consistent. The primary safety concerns attributable to STS in the indicated patient population are the potential for hypersensitivity reactions, nausea, vomiting, and AEs related to electrolyte changes (ie, hypernatremia, hypokalemia, and hypophosphatemia). These events are included as ADRs for the proposed label. All of these events are transitory and manageable considering the support that is typically already standard for a pediatric patient population receiving CIS chemotherapy.

Due to the open-label study designs for SIOPEL 6 and COG ACCL0431 and the nature of the data provided by these academic consortium-led studies, there are expected limitations of the safety analyses conducted. Both studies were designed and conducted for the purposes of establishing clinical practice guidelines for prevention of CIS-induced ototoxicity. As such, these studies were conducted in a "real-world" setting; thus, the safety results can be easily generalized to clinical practice.

The FDA's Assessment:

FDA agrees with the Applicant's assessment.

8.2.1 Safety Review Approach

The Applicant's Position:

Safety findings are based primarily on the key safety results from 2 confirmative Phase 3 studies (SIOPEL 6 and COG ACCL0431) that enrolled patients who comprise the intended target population for PEDMARK.

In SIOPEL 6, AEs were recorded during and up to 30 days after chemotherapy during the Treatment Phase; SAEs were recorded during the Treatment Phase and Follow-up. Serious AEs were reported in accordance with the local reporting requirements and to the main Research Ethics Committee. Fatal or life-threatening suspected unexpected serious adverse reactions (SUSARs) were also reported to the MHRA. An independent Data Monitoring Committee (DMC) reviewed all SAEs. The following AEs were termed Targeted Acute Toxicity AEs and were specifically analyzed: allergic reaction/hypersensitivity, febrile neutropenia, infection, hypomagnesemia, hypernatremia, vomiting, nausea, left ventricular systolic dysfunction, and hypertension.

In COG ACCL0431, AEs were recorded for all patients during the Reporting Period (defined as the treatment cycle where children received the first through final doses of CIS and/or STS excluding the 4-week Follow-up Period) and through last Follow-up. Serious AEs were to be reported only for patients in the CIS+STS arm during the Reporting Period, unless a death or secondary malignancy occurred. Serious AEs of death or secondary malignancy were to be reported through last Follow-up for patients in the Observation and CIS+STS arms. Serious AEs, deaths, and secondary malignancies for patients in the CIS+STS arm were to be reported using Adverse Event Expedited Reporting System (AdEERs). Serious AEs were only captured in the clinical database for those patients with SAEs who also had AdEERs forms. However, there were a few exceptions. The COG Data Safety Monitoring Committee (DSMC) monitored the safety of the study including intermittent assessments of tumor response. The following hematological toxicity AEs were specifically evaluated: neutrophil count decreased, platelet

count decreased, and anemia. The following nephrotoxicity AEs were also specifically evaluated: acidosis, creatinine increased, GFR decreased, hypokalemia, hypomagnesemia, and hypophosphatemia.

For this submission, the following AEs of special interest were analyzed for both studies: Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or higher events of hypomagnesemia, hypernatremia, vomiting, and nausea.

In both studies, clinical laboratory assessments (sodium, magnesium [SIOPEL 6 only], and GFR [SIOPEL 6 only]), vital sign measurements, echocardiograms (SIOPEL 6 only), and physical examination results were measured at protocol-specified time points. However, for COG ACCL0431, vital signs, physical findings, and other observations related to safety were assessed but these data were not captured in the clinical database or analyzed; AEs related to abnormal vital signs or physical examinations were summarized.

Analyses of EFS, OS, and other measures of tumor response were evaluated; these data were analyzed as efficacy endpoints (Module 2.5, Section 4.2.3).

Based on the safety findings in SIOPEL 6 and COG ACCL0431, adverse drug reactions (ADRs) were identified (AEs with an incidence that was ≥10% higher in the CIS+STS arm compared with the CIS Alone arm in either SIOPEL 6 or COG ACCL0431 or those identified by medical review) and included in the proposed PEDMARK labeling.

The FDA's Assessment:

FDA agrees with the Applicant's description of the collection of safety data from the two trials (SIOPEL-6 and ACCL0431) that support the safety profile for this application. FDA emphasizes that there are key limitations to the interpretation of the safety data; these limitations are listed below:

1) AEs start and stop dates were not collected for either study
2) For SIOPEL
   a) Information on dose alteration and discontinuation was only collected in conjunction with SAEs; the corresponding information on AEs was not collected.
3) For ACCL0431,
   a) AEs leading to discontinuation were not systematically collected
   b) SAEs were only captured for the CIS+STS arm
   c)Serum sodium was the only lab captured
   d) Vital signs and physical findings but were not captured in the clinical database or analyzed; they were summarized where available.

8.2.2 Review of the Safety Database

Overall Exposure

The Applicant's Position:

SIOPEL 6

Of the 129 children registered, a total of 114 children from 12 countries were randomized in SIOPEL 6. Five randomized patients withdrew prior to treatment. Therefore, 109 children were included in the Safety Population, including 53 children in the CIS+STS arm and 56 children in the CIS Alone arm. Four children randomized to the CIS+STS arm never received STS and were thus assigned to the CIS Alone arm in the Safety Population (ie, as treated).

The median total duration of therapy (including CIS [=platinol] and doxorubicin [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]) (Module 2.7.4, Section 1.2.2.1). Cisplatin exposure was similar between the CIS+STS and CIS Alone arms, as measured by mean number of cycles (5.9 and 5.8 cycles, respectively) and mean cumulative actual dose (363.860 mg/m^2 vs 362.851 mg/m^2, respectively). When analyzed by weight group (<5kg, 5 to 10kg, >10kg), the number of cycles was similar between the arms, while mean cumulative actual CIS doses were more variable.

In the CIS+STS arm, the overall mean cumulative actual STS dose was 85.149 g/m^2, which differed by weight group (28.446 g/m^2 [1 child <5kg], 75.555 g/m^2 [5 to 10kg], and 100.537 g/m^2 [>10kg]).

COG ACCL0431

Of the 131 patients enrolled in the study from sites in the US and Canada, Fennec was provided data from the 125 children who were randomized to either the CIS+STS arm or the Observation arm. Two children randomized to the CIS+STS arm did not receive STS and were not included in the Safety Population. Of the 123 total patients, 59 children were in the CIS+STS arm and 64 children were in the Observation arm.

Children in the CIS+STS and Observation arms received mean cumulative CIS doses of 337.57 and 391.47 mg/m^2, respectively (Module 2.7.4, Section 1.2.2.2). Differences were observed between arms in the mean number of CIS cycles (3.1 and 3.8 in the CIS+STS and Observation arms, respectively) as well as the mean number of administration days (7.6 and 9.0, respectively). Variability in the CIS dosing regimens was observed across the diagnosed tumor types. This variability reflected the differences in each child's cancer treatment plan, which was dependent on the tumor type and staging, as well as the patient's age.

Children in the CIS+STS arm received a mean cumulative STS dose of 108.23 g/m^2. Although the STS dosing regimen per protocol was fixed at 16 g/m^2, the number of STS doses was variable and dependent on the number of CIS cycles and the number of CIS administrations per cycle.

The FDA's Assessment:

FDA agrees with the Applicant's assessment of exposure. See Section 5 for more detail.

Table 41 SIOPEL 6 Analysis Population

Population	Randomized Treatment		Actual Treatment		Total n (%)
	CIS Alone (N=53) n (%)	CIS+STS (N=61) n (%)	CIS Alone (N=56) n (%)	CIS+STS (N=53) 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.

[a] The following patients were ineligible for randomization: (b) (6) (ineligible), (b) (6) (due to parental refusal), (b) (6) and (b) (6) reclassified as high risk). These patients were excluded from the ITT Population.

[b] Patients (b) (6) were randomized to the CIS+STS arm but did not receive any STS. They were assigned to CIS Alone arm.

[c] Patients (b) (6) were randomized to the CIS+STS arm, but never received STS, and were excluded from the PP Population.

[d] Patients (b) (6) did not have hearing loss data, and were excluded from mITT Population.

Table 42 ACCL0431 Analysis Population

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.

Relevant characteristics of the safety population:

The Applicant's Position:

Demographics and Baseline disease characteristics differed between SIOPEL 6 and COG ACCL0431, as was expected based on the different patient populations enrolled in each study (children with SR-HB in SIOPEL 6 and children with various tumor types in COG ACCL0431). As described below, the children evaluated in these studies are considered representative of the target population for marketed STS (ie, patients 1 month to <18 years of age receiving CIS chemotherapy).

In SIOPEL 6, children between 1 month and 18 years old with standard-risk HB were eligible, as defined by PRETEXT I, II, or III (indicating the number of sections involved by tumor), serum AFP >100 µg/L, and no vascular invasion/no extra-hepatic or metastatic disease (Table 4). A total of 114 patients (61 patients in the CIS+STS arm and 53 patients in the CIS Alone arm) from 12 countries were randomized into the study (Module 2.7.3, Section 2.1.2.1). Overall, the median age was 13.0 months (range: 1.2 to 98.6 months [8.2 years]) and the majority of children were male (59 patients [54.1%]) and White (64 patients [58.7%]) (Module 2.7.3, Section 2.1.2.2.1). Baseline disease characteristics were generally balanced between the 2 arms (Module 2.7.3, Section 2.1.2.2.2), with the exception of a slight imbalance in the PRETEXT classification. Only the CIS+STS arm included 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), though this was consistent with the method of randomization (SIOPEL 6 CSR, Section 3.5.3).

In contrast, in COG ACCL0431, a heterogeneous population of children between 1 year and 18 years old receiving CIS chemotherapy for the treatment of various tumor types were eligible (Table 4). A total of 125 patients (61 patients in the CIS+STS arm and 64 patients in the Observation arm) were randomized into the study (Module 2.7.3, Section 2.2.1). Overall, the

median age was 9.5 years (range: 1 to 18 years) (Module 2.7.3, Section 2.2.2). The majority of children in the study were ≥5 years of age (81 patients [64.8%]); male (76 patients [60.8%]); White (81 patients [64.8%]); and Not Hispanic or Latino (87 patients [69.6%]). The most common disease diagnoses were: GCT (32 patients [25.6%]), osteosarcoma (29 patients [23.2%]), medulloblastoma (26 patients [20.8%]), and neuroblastoma (26 patients [20.8%]); a total of 7 patients (5.6%) had HB. Unlike in SIOPEL 6, children in COG ACCL0431 could have had metastases (ie, disseminated disease) at study entry, though the majority (77 patients [61.6%]) did not. Importantly, COG ACCL0431 did not take the differing prognostic factors by tumor type into consideration when randomizing children to treatment, since the study was designed to evaluate hearing loss rather than tumor efficacy. The effect of these prognostic factors on the anti-tumor efficacy of CIS was evaluated and results are presented in Module 2.5, Section 4.5.

The FDA's Assessment:

The Applicant's description of the baseline characteristics for both studies is based on the ITT population, not the safety populations.

For SIOPEL 6, four patients randomized to the CIS+STS arm in the ITT population did not receive STS and are included in the CIS alone arm for the safety population. The demographics and characteristics pertinent to the interpretation of the primary endpoint of hearing loss (e.g. weight, age) are balanced between arms.

For COG ACCL0431, 2 children randomized to the CIS+STS arm did not receive STS due to parent refusal or physician determined it was in the patient's best interest. The demographics and characteristics pertinent to interpretation of the primary endpoint of hearing loss (e.g. weight, age, prior radiation, tumor type, presence of metastatic disease) were generally balance between arms. Prognostic factors (e.g. tumor stage, histology, biologic features, prior therapy, tumor location, ability to resect, etc.) were not stratified for or included in the eligibility criteria.

Adequacy of the safety database:

The Applicant's Position:

Due to the nature of the open-label study designs for SIOPEL 6 and COG ACCL0431 and the data provided by these academic consortium-led studies, there are expected limitations of the safety analyses conducted. Both studies were designed and conducted for the purposes of establishing clinical practice guidelines for prevention of CIS-induced ototoxicity. As such, these studies were conducted in a "real-world" setting; thus, the safety results can be easily generalized to clinical practice.

There are similarities and differences between the SIOPEL 6 and COG ACCL0431 study designs. Key limitations of the study designs (eg, open-label) and differences between the studies (eg, patient population, CIS and STS exposure [Table 4]) could affect interpretation of the safety profile across the indicated patient population.

The STS (pentahydrate) formulation used in SIOPEL 6 and COG ACCL0431 differs from the formulation of STS (anhydrous) (b) (4) intended for marketing. However, the STS solutions prepared and administered in the clinical studies and publications are considered representative for PEDMARK since all formulations were based on a solution of STS dissolved in water with a boric acid (b) (4) and no further specific requirements. Both the clinical study formulations and PEDMARK use the same infusion volume, molar amount of dissolved STS, and rate of infusion. Therefore, there is no reason to expect an impact on the safety profile of PEDMARK in the intended patient population.

Data collection practices for these academic consortium-led studies could also limit the interpretation of safety data. For example, AE start and stop dates and times were not collected in the clinical database for either study, which restricted the understanding of AE duration as well as what AEs were concurrent. Furthermore, collection of AE relatedness to STS or other concomitant medications was also limited. In SIOPEL 6, relatedness to STS was only captured for SAEs. In COG ACCL0431, relatedness to STS was captured for all AEs. Additional information about the timing of AEs and relatedness to STS or other medications was included on some SAE reporting forms for those patients with SAEs. Where those details were provided, additional insights could be drawn. Finally, in COG ACCL0431, AEs leading to discontinuation were not systematically collected in the CRF and therefore were not reliably identified in the clinical database. However, AE data were manually reviewed for any patient who discontinued STS due to reasons related to an AE, per entry on the disposition CRF or because the discontinuation occurred in close proximity to the occurrence of an AE (but was not specifically attributed to an AE).

Although additional support on the safety of STS comes from the published literature, the amount of safety information on use of STS in the indicated patient population (ie, use of STS in combination with platinum-based chemotherapy) was very limited and most events were

attributable to the chemotherapy or underlying disease (Module 2.7.4, Section 7.2.2). The majority of the available published information on the safety of STS comes from its use in different patient populations (eg, cyanide poisoning, calcific uremic arteriolopathy [calciphylaxis], tumoral calcinosis, vascular calcifications, and nephrogenic systemic fibrosis). Relevant safety findings in these indications were considered based on their relevance to the proposed indication.

The FDA's Assessment:

See FDA Assessment in Section 8.2.1, Safety Review Approach for comment on key limitations of the safety data collection. The focus of this review from the FDA perspective is on the review of the datasets from the two trials supporting the application.

8.2.3 Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The Applicant's Position:

The limitations of the safety database are presented under "Adequacy of the safety database." Fennec is not aware of any issues or concerns regarding the data quality or quality of the overall submission that would have an effect on the safety review.

The global clinical development program supporting the efficacy and safety of PEDMARK in the proposed indication included 2 confirmatory Phase 3 clinical studies (SIOPEL 6 and COG ACCL0431).

SIOPEL 6 and COG ACCL0431 were designed and conducted by academic consortia for the purposes of establishing clinical practice guidelines for prevention of CIS-induced ototoxicity. These studies were conducted in accordance with GCP; the results of COG ACCL0431 were published by Freyer et al, 2017 and results of SIOPEL 6 were published by Brock et al, 2018. Although they did not sponsor these studies, Fennec provided study medication (STS) and obtained rights to the data. Study results summarized in this marketing application represent the analyses conducted by Fennec, which are provided in ICH-compliant CSRs.

As agreed with the Agency at the pre- NDA meeting (see Module 2.5, Table 2), Fennec did not conduct any integrated analyses based on pooled study data given the different patient populations (ie, SR-HB in SIOPEL 6 and various cancer types in COG ACCL0431), study designs, and dosing evaluated.

The FDA's Assessment:

FDA agrees with the Applicant's assessment.

Categorization of Adverse Event

The Applicant's Position:

In both SIOPEL 6 and COG ACCL0431, AEs were collected and assessed using the National Cancer Institute (NCI) CTCAE (V3.0 [SIOPEL 6]; V4.0 [COG ACCL0431]). For analysis, AEs were mapped to MedDRA Version 21.0 system organ classification (SOC) and preferred term (PT). Adverse events were evaluated by CTCAE grade, Investigator assigned relationship to STS (evaluated only for SAEs in SIOPEL 6), seriousness, and those leading to discontinuation. Deaths were also analyzed regardless of whether they were the result of an AE.

In SIOPEL 6, AEs were recorded during and up to 30 days after chemotherapy during the Treatment Phase; SAEs were recorded during the Treatment Phase and Follow-up. Serious AEs were reported in accordance with the local reporting requirements and to the main Research Ethics Committee. Fatal or life-threatening SUSARs were also reported to the MHRA. An independent Data Monitoring Committee (DMC) reviewed all SAEs. The following AEs were termed Targeted Acute Toxicity AEs and were specifically analyzed: allergic reaction/hypersensitivity, febrile neutropenia, infection, hypomagnesemia, hypernatremia, vomiting, nausea, left ventricular systolic dysfunction, and hypertension.

In COG ACCL0431, AEs were recorded for all patients during the Reporting Period (defined as the treatment cycle where children received the first through final doses of CIS and/or STS excluding the 4-week Follow-up Period) and through last Follow-up. Serious AEs were to be reported only for patients in the CIS+STS arm during the Reporting Period, unless a death or secondary malignancy occurred. Serious AEs of death or secondary malignancy were to be reported through last Follow-up for patients in the Observation and CIS+STS arms. Serious AEs, deaths, and secondary malignancies for patients in the CIS+STS arm were to be reported using AdEERs. Serious AEs were only captured in the clinical database for those patients with SAEs who also had AdEERs forms. However, there were a few exceptions. The COG DSMC monitored the safety of the study including intermittent assessments of tumor response. The following hematological toxicity AEs were specifically evaluated: neutrophil count decreased, platelet count decreased, and anemia. The following nephrotoxicity AEs were also specifically evaluated: acidosis, creatinine increased, GFR decreased, hypokalemia, hypomagnesemia, and hypophosphatemia.

The FDA's Assessment:

FDA agrees with the Applicant's assessment.

Routine Clinical Tests

The Applicant's Position:

In both studies, clinical laboratory assessments (sodium, magnesium [SIOPEL 6 only], and GFR [SIOPEL 6 only]), vital sign measurements, echocardiograms (SIOPEL 6 only), and physical examination results were measured at protocol-specified time points. However, for COG ACCL0431, vital signs, physical findings, and other observations related to safety were assessed but these data were not captured in the clinical database or analyzed; AEs related to abnormal vital signs or physical examinations were summarized.

Analyses of EFS, OS, and other measures of tumor response were evaluated; these data were analyzed as efficacy endpoints (Module 2.5, Section 4.2.3).

Although vital signs, physical findings, and other observations related to safety were assessed per the Protocol (see COG ACCL0431 CSR Table 2), these data were not captured in the clinical database or analyzed. However, AEs related to abnormal vital signs or physical examinations were summarized.

The FDA's Assessment:

FDA agrees with the Applicant's assessment.

8.2.4 Safety Results

Deaths

The Applicant's Position:

SIOPEL 6

Overall, a total of 6 children (5.5%) died during the study, including 5 who had PRETEXT II disease (Module 2.7.4, Section 2.1.2.1). Of these, 2 children in the CIS Alone arm died by the end of treatment and 4 children died during Follow-up (2 children in each arm). Both children in the CIS+STS arm died due to tumor progression. Of the 4 children in the CIS Alone arm who died, 2 children died due to tumor progression, 1 child died due to surgical complications, and

1 child due to cardiac arrest (after receiving additional alternative chemotherapy for progression).

COG ACCL0431

Overall in both arms of the study, 30 children died, including 18 children (30.5%) in the CIS+STS arm and 12 children (18.8%) in the Observation arm (Module 2.7.4, Section 2.1.2.2). The majority of deaths were due to the child's underlying disease. No deaths in the CIS+STS arm were considered related to STS.

The FDA's Assessment:

The FDA generally agrees with the Applicant's description of deaths in the SIOPEL 6 trial. Of the 6 deaths, 4 patients were in the CIS alone arm (7.1%) and 2 were in the CIS + STS arm (3.8%). Narratives were provided for the two children (both in the CIS alone arm) who did not die due to disease progression (cardiac arrest and surgery). The patient who died due to cardiac arrest was an 11 month old male (originally diagnosed with hepatoblastoma (b) (6) who went on to receive carboplatin and doxorubicin (b) (6) followed by paclitaxel (b) (6) after progressing on upfront cisplatin/resection therapy; the investigator considered the cardiac arrest and death (b) (6) possibly related to paclitaxel. The patient who died due to a surgical complication was a 9 month old female (b) (6) who died during partial hepatectomy (b) (6) after two courses of pre-operative CIS; no further information is available. These two deaths occurred in patients who did not receive STS and the deaths overall are generally well-balanced between arms.

The FDA generally agrees with the Applicant's description of deaths in the COG trial. A broader discussion of the higher death rate for patients in the CIS+STS arm is included in the efficacy section. One patient death not due to progressive disease was associated with an AE while on treatment (CIS+STS arm). A detailed narrative was provided for this patient in the application. The patient was an 8 year old male with osteosarcoma who experienced cardiac arrest and died 6 days after a cycle of chemotherapy (cisplatin and doxorubicin). The death was confounded by several factors including recent history of febrile neutropenia, pancytopenia, and *C.difficile* pseudomembranous colitis.

Serious Adverse Events

The Applicant's Position:

SIOPEL 6

Twenty-one children (39.6%) in the CIS+STS arm and 18 children (32.1%) in the CIS Alone arm had non-fatal SAEs during the Treatment Phase (Module 2.7.4, Section 2.1.3.1). In both CIS+STS and CIS Alone arms, the PTs of infection (13.2% and 8.9%, respectively) and pyrexia (9.4% and 5.4%, respectively) were among the most frequently reported SAEs. In addition, 2 other SAEs were reported by more than 1 patient in the CIS+STS arm (neutrophil count decreased and procedural complications). The incidence of SAEs of neutrophil count decreased was numerically higher in the CIS+STS arm (6 children [11.3%]) compared with the CIS Alone arm (1 child [1.8%]), but there is no plausible mechanism by which this could be caused by STS.

No patients required a dose alteration due to an SAE. Relatedness to STS as determined by the Investigator was only captured for SAEs. In the CIS+STS arm, 4 children (7.5%) overall experienced an SAE determined by the Investigator as being related to STS, which included neutrophil count decreased, infection, and hypersensitivity. This drug-related CTCAE Grade 2 SAE of hypersensitivity also led to discontinuation of study medication and was considered as a SUSAR (Patient (b) (6). The event was noted 15 minutes after the end of STS infusion and the child had a tachycardia of 180 bpm and a systolic blood pressure of 130 mmHg. The child 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.

COG ACCL0431

Serious AEs (fatal and non-fatal) were recorded only for patients in the CIS+STS arm (21 children [35.6%]) (Module 2.7.4, Section 2.1.3.2). 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.

The FDA's Assessment:

Regarding SIOPEL 6, FDA agrees with the characterization of SAEs. FDA additionally notes that 5 patients (9%) had an SAE of pyrexia in the CIS+STS arm compared to 3 in the CIS alone arm (5%).

Regarding COG ACCL0431, FDA agrees with the total number of patients who had a SAE and that the most commonly reported SAE was febrile neutropenia in 12 patients (20%). Other SAEs reported in more than one patient included neutrophil count decreased in 11 patients (19%), white blood cell and platelet count decreased in 8 patients each (14%), anemia in 7 patients (12%), stomatitis in 5 patients (8%), lymphocyte count decrease in 4 patients (7%), ALT increased in 3 patients (5%), and diarrhea, colitis, nausea, UTI, decreased appetite, dehydration,

and syncope in 2 patients each (3.4%).

One patient in COG ACCL0431 was reported to have a secondary malignancy of AML that was reported to AdEERS but not captured as an SAE. The patient was a 2 year old male with localized neuroblastoma who received one dose of STS. This case is confounded by treatment with etoposide which is known to be associated with secondary AML. The patient was alive and cancer-free 7 years after study entry.

Dropouts and/or Discontinuations Due to Adverse Effects

The Applicant's Position:

SIOPEL 6

During the Treatment Phase, 1 child (1.9%), in the CIS+STS arm, experienced a Grade 2 SAE of hypersensitivity that led to discontinuation of study medication (SIOPEL 6 CSR Table 14.3.9.4). This event is discussed in the SAE section above.

No additional AEs led to study medication discontinuation (SIOPEL 6 CSR Listing 16.2.7.5).

COG ACCL0431

Discontinuations due to AEs were not systematically collected in the CRF and therefore were not reliably identified in the clinical database. However, 1 child in the CIS+STS arm discontinued STS due to reasons related to an AE of hypersensitivity (considered definitely related to STS by the Investigator), and 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 [1 AE considered probably and 1 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]) (Module 2.7.4, Section 2.1.4.1.2).

The FDA's Assessment:

FDA agrees with the assessment of treatment discontinuations due to treatment-emergent adverse events.

Dose Interruption/Reduction Due to Adverse Effects

The Applicant's Position:

Dose reductions are described only for the SIOPEL 6 and COG ACCL0431 studies.

SIOPEL 6

No patients required a dose alteration due to an SAE.

COG ACCL0431

The overall incidence of AEs, total number of AEs, and total number of STS administrations were summarized by cumulative and mean daily STS dosing quartiles (Module 2.7.4, Section 2.1.1.2.5). As expected, the total number of STS administrations and the average number of STS administrations per patient increased across STS dose quartiles. However, there was no correlation between the average number of AEs per patient and the cumulative STS dosing quartile. No STS dose-related trends in the PTs of nausea, vomiting, hypernatremia, hypokalemia, hypophosphatemia, and hypersensitivity were observed.

The FDA's Assessment:

Regarding SIOPEL 6, FDA notes that dose alterations and discontinuations were only collected in conjunction with SAEs. Based on the dataset, it appears that there were two event of STS interruption and CIS delay (due to infection and neutrophil count decreased). According to the narrative for the patient with neutrophil count decreased (191), surgery was delayed due to low neutrophil count but patient received all planned doses of CIS and STS. According to the narrative for the patient with infection (135), the patient did not receive the final dose of STS (received 5 of 6) due to Grade 3 infection; CIS still given.

Dose reductions and interruptions were not captured for ACCL0431.

Significant Adverse Events

The Applicant's Position:

Adverse events of special interest were identified as Grade 3 severity or higher events in the PTs of nausea, vomiting, hypomagnesemia, and hypernatremia for both SIOPEL 6 and COG ACCL0431.

SIOPEL 6

Adverse events of special interest during the Treatment Phase are summarized for the Safety Population in Table 43. The overall number of patients experiencing AESIs was low and the incidence was similar between the arms.

Table 43: Summary of AESI Reported During the Treatment Phase (Safety Population; SIOPEL 6)

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.

Source: SIOPEL 6 CSR Table 14.3.9.12.2.

COG ACCL0431

Adverse events of special interest during the Reporting Period are summarized for the Safety Population in Table 44. The incidences of AESIs were similar between the treatment arms. No Grade 3 severity or higher events of hypernatremia were reported.

Table 44: Summary of AESI Reported During the Reporting Period (Safety Population; COG ACCL0431)

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)

SOC PT	Observation (N=64) n (%)	CIS+STS (N=59) n (%)	Total (N=123) n (%)

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.

Source: COG ACCL0431 CSR Table 14.3.1.2.

The FDA's Assessment:

FDA agrees with the Applicant's assessment of the predefined adverse events of special interest. The overall numbers were low and balanced between arms.

Treatment Emergent Adverse Events and Adverse Reactions

The Applicant's Position:

SIOPEL 6

Overview of Adverse Events

An overview of AEs during both the Treatment and Follow-up Phases is provided in 45. Overall during both the Treatment and Follow-up Phases, the incidences of AEs, SAEs, SAEs requiring dose alteration, discontinuations due to SAEs, and SAEs resulting in death were similar between the 2 treatment arms. The majority of these events occurred during the Treatment Phase and are summarized further below. During the Follow-up Phase, only SAEs and deaths were captured, which included 2 non-fatal SAEs and 1 fatal SAE in the CIS Alone arm and no events in the CIS+STS arm.

Table 45: Overview of Adverse Events during both the Treatment and Follow-up Phases (Safety Population; SIOPEL 6)

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)	19[(1)] (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; SIOPEL=International Childhood Liver Tumor Strategy Group; STS=sodium thiosulfate.

Note: Information on dose alteration and discontinuation was only collected in conjunction with SAEs; the corresponding information on AEs was not collected.

(1) One SAE in the CIS Alone arm occurred during Follow-up.

Source: SIOPEL 6 CSR Table 14.3.3.1.

Most Common Adverse Events during the Treatment Phase

The most common AEs by PT (frequency of ≥10% in either arm) during the Treatment Phase are summarized in Table 46. The 3 most frequently reported AEs by PT were the same in both arms (nausea, vomiting, and infection). In the CIS+STS arm compared with the CIS Alone arm, vomiting (84.9% vs 53.6%, respectively) and nausea (39.6% vs 30.4%, respectively) occurred at higher incidences. In the CIS+STS arm compared with the CIS Alone arm, infection (41.5% vs 35.7%, respectively) occurred at a similar incidence. Generally, the incidences of other most common AEs by PT were similar between the CIS+STS and the CIS Alone arms.

Table 46: Summary of the Most Common AEs (PT Frequency of ≥10% in Either Arm) During the Treatment Phase (Safety Population; SIOPEL 6)

SOC PT	CIS Alone (N=56) n (%)	CIS+STS (N=53) n (%)	Total (N=109) n (%)
Patients with at least 1 AE	49 (87.5)	51 (96.2)	100 (91.7)
Gastrointestinal disorders	**33 (58.9)**	**47 (88.7)**	**80 (73.4)**
Vomiting	30 (53.6)	45 (84.9)	75 (68.8)
Nausea	17 (30.4)	21 (39.6)	38 (34.9)
Diarrhea	6 (10.7)	5 (9.4)	11 (10.1)
Investigations	**29 (51.8)**	**33 (62.3)**	**62 (56.9)**
Hemoglobin decreased	16 (28.6)	18 (34.0)	34 (31.2)
Neutrophil count decreased	12 (21.4)	12 (22.6)	24 (22.0)
Acoustic stimulation tests	12 (21.4)	11 (20.8)	23 (21.1)
AST increased	10 (17.9)	9 (17.0)	19 (17.4)
ALT increased	12 (21.4)	6 (11.3)	18 (16.5)
GGT increased	7 (12.5)	4 (7.5)	11 (10.1)
Metabolism and nutrition disorders	**21 (37.5)**	**30 (56.6)**	**51 (46.8)**
Hypomagnesemia	16 (28.6)	17 (32.1)	33 (30.3)
Hypernatremia	2 (3.6)	14 (26.4)	16 (14.7)
Hypermagnesemia	3 (5.4)	6 (11.3)	9 (8.3)
Hypokalemia	1 (1.8)	8 (15.1)	9 (8.3)
Hypophosphatemia	1 (1.8)	8 (15.1)	9 (8.3)
Infections and infestations	**21 (37.5)**	**23 (43.4)**	**44 (40.4)**
Infection	20 (35.7)	22 (41.5)	42 (38.5)
Blood and lymphatic system disorders	**12 (21.4)**	**10 (18.9)**	**22 (20.2)**
Febrile neutropenia	11 (19.6)	8 (15.1)	19 (17.4)

SOC PT	CIS Alone (N=56) n (%)	CIS+STS (N=53) n (%)	Total (N=109) n (%)
General disorders and administrative site conditions	**8 (14.3)**	**11 (20.8)**	**19 (17.4)**
Pyrexia	5 (8.9)	8 (15.1)	13 (11.9)
Immune system disorders	**6 (10.7)**	**7 (13.2)**	**13 (11.9)**
Hypersensitivity	6 (10.7)	7 (13.2)	13 (11.9)

Abbreviations: AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CIS=cisplatin; CSR=clinical study report; GGT=gamma-glutamyl transferase; PT=preferred term; SAE=serious adverse event; SIOPEL=International Childhood Liver Tumor Strategy Group; SOC=system organ class; STS=sodium thiosulfate.

Note: In the Follow-up Period, only SAEs were collected.

Note: AEs were only recorded in the Treatment Phase up 30 days after the end of treatment.

Source: SIOPEL 6 CSR Table 14.3.9.9.2

Adverse Events by CTCAE Grade During the Treatment Phase

The majority of AEs experienced by patients during the Treatment Phase were CTCAE Grade 3 or higher and occurred at similar incidences in the CIS+STS and CIS Alone arms (66.0% vs 60.7%, respectively) (Module 2.7.4, Section 2.1.1.1.3). The incidences of AESIs (Grade 3 severity or higher AEs of nausea, vomiting, hypomagnesemia, and hypernatremia) were generally similar between the treatment arms (Module 2.7.4, Section 2.1.4.2.1).

COG ACCL0431

Overview of Adverse Events

An overview of AEs is presented in Table 47. Details of these events are described further below.

Table 47: Overview of AEs (Safety Population; COG ACCL0431)

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)
SAEs[1]	ND	21 (35.6)	NA
Drug-related AEs[2]	NA	23 (39.0)	23 (39.0)
AEs graded CTCAE category 3 or higher	57 (89.1)	55 (93.2)	112 (91.1)
Deaths[3]	12 (18.8)	18 (30.5)	30 (24.4)

Abbreviations: AE=adverse event; CIS=cisplatin; COG=Children's Oncology Group; CRF=Case Report Form; CSR=clinical study report; CTCAE=Common Terminology Criteria for Adverse Events; NA=not applicable; ND=not defined; SAE=serious AE; SAP=statistical analysis plan; STS=sodium thiosulfate.

[1] As described in the SAP, SAEs were reported only for the CIS+STS arm.

[2] Relationship was to the STS treatment; "drug-related" included AEs that were considered Possible, Probable, or Definite in the CRF.

[3] Eight patients were off Study ACCL0431 and subsequently died while enrolled into different COG studies.

Sources: COG ACCL0431 CSR Table 14.3.1.1, Table 14.3.1.2, Table 14.3.1.3, Table 14.3.1.4, and Table 14.1.5.

Most Common Adverse Events During the Reporting Period

The most common AEs by PT (frequency of ≥10% in either arm) during the Treatment Phase are summarized in Table 48. The 3 most frequently reported AEs by PT occurred at similar incidences in the CIS+STS and Observation arms: neutrophil count decreased (83.1% vs. 79.7%, respectively), white blood cell count decreased (64.4% vs. 65.6%, respectively), and

platelet count decreased (64.4% vs. 60.9%, respectively). These events are commonly known to be associated with chemotherapy.

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.

Table 48: Summary of the Most Common AEs (Frequency of ≥10% in Either Arm, by PT) During the Reporting Period (Safety Population; COG ACCL0431)

SOC PT	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)
Investigations	**57 (89.1)**	**54 (91.5)**	**111 (90.2)**
Neutrophil count decreased	51 (79.7)	49 (83.1)	100 (81.3)
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)**
Anemia	36 (56.3)	30 (50.8)	66 (53.7)
Febrile neutropenia	19 (29.7)	14 (23.7)	33 (26.8)
Metabolism and nutrition disorders	**23 (35.9)**	**32 (54.2)**	**55 (44.7)**
Hypokalemia	13 (20.3)	16 (27.1)	29 (23.6)
Hypophosphatemia	7 (10.9)	12 (20.3)	19 (15.4)
Hyponatremia	4 (6.3)	8 (13.6)	12 (9.8)
Hypernatremia	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; COG=Children's Oncology Group; CSR=clinical study report; CTCAE= Common Terminology Criteria for Adverse Events; PT=preferred term; SOC=system organ class; STS=sodium thiosulfate.

Source: COG ACCL0431 CSR Table 14.3.1.1.

Adverse Events by CTCAE Grade During the Reporting Period

The majority of AEs experienced by patients during the reporting period were CTCAE Grade 3 or higher and occurred at similar incidences in the CIS+STS and Observation arms (93.2% vs 89.1%, respectively) (Module 2.7.4, Section 2.1.1.2.3). The incidences of AESIs (Grade 3 severity or higher AEs of nausea, vomiting, hypomagnesemia, and hypernatremia) were also similar between the treatment arms (Module 2.7.4, Section 2.1.4.2.2).

The FDA's Assessment:

Regarding SIOPEL 6, FDA agrees with the incidence of common AEs as described by the Applicant. In addition, FDA emphasizes that the incidence of electrolyte imbalances was higher in the CIS+STS arm compared to CIS alone (>5%): hypernatremia 14 patients (26.4%) compared to 2 patients (3.6%), hypokalemia and hypophosphatemia with 8 patients (15%) each compared to 1 (1.8%), and hypermagnesemia in 6 patients (11%) vs 3 patients (5%).

Regarding COG ACCL0431, FDA agrees with the incidence of common AEs as described by the Applicant with the exception of neutrophil count decreased in the observation arm (FDA calculated 53 events (83%) compared to Applicant's 51 events (80%); this does not impact the risk profile of the study. Similar to the SIOPEL-6 trial, the incidence of electrolyte imbalances was higher in the CIS+STS arm compared to the observation arm of CIS alone (>5%): hypernatremia in 7 patients (12%) vs. 4 patients (6%); hypokalemia in 16 patients (27%) vs. 13 patients (20%); and hypophosphatemia in 12 patients (20%) vs. 7 patients (11%). Stomatitis was also reported at a higher incidence in patients who received STS [8 patients (14%) vs. 4 patients (6%)].

Laboratory Findings

The Applicant's Position:

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 (Module 2.7.4, Section 3.1).

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.

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 the CIS Alone arms 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%]).

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 >151 mmol/L in the CIS+STS arm or >146 mmol/L in the Observation arm (Module 2.7.4, Section 3.2). The remaining laboratory evaluations were not captured in the clinical database.

The FDA's Assessment:

In both the COG ACCL0431 and the SIOPEL 6 studies, laboratory results that were captured in the datasets were not graded by CTCAE criteria unless they were reported as AEs; the standard variable ATOXGR was not available for laboratory analysis and review. FDA acknowledges the Applicant's assessments but cannot draw conclusions based on the laboratory data provided. See sections above for review of laboratory findings that were reported as AEs.

Vital Signs

The Applicant's Position:

SIOPEL 6

Overall, there were no clinically relevant mean changes in vital signs over the course of the study (see SIOPEL 6 CSR, Section 7.5.1).

In the CIS+STS arm, the mean systolic BP was similar at pre-course 1 (101.8 mmHg) and pre-course 6 (104.3 mmHg). In the CIS Alone arm, the mean systolic BP was similar at pre-course 1 (100.7 mmHg) and pre-course 6 (98.0 mmHg) (SIOPEL 6 CSR, Table 14.3.4.1).

Across all courses, in the CIS+STS arm, the mean pre-course systolic BP was 102.1 mmHg, rose 5.8 mmHg at 30 minutes post-course (p<0.001), and returned to a pre-course level at 60 minutes post-course (-0.3 mmHg change from pre-course [p=0.771]) (SIOPEL 6 CSR, Table 14.3.4.2).

COG ACCL0431

Although vital signs were assessed per the Protocol (see COG ACCL0431 CSR Table 2), these data were not systematically collected in the CRF and therefore were not reliably identified in the clinical database. However, AEs related to abnormal vital signs were summarized (see COG ACCL0431 CSR Section 7.5).

Adverse events in the PT of hypotension were reported in 2 patients (3.4%) in the CIS+STS arm, and 1 patient (1.6%) in the Observation arm (COG ACCL0431 CSR Table 14.3.1.1). An AE in the PT of hypertension was reported in 1 patient (1.7%) in the CIS+STS arm (COG ACCL0431 CSR Table 14.3.1.1).

The FDA's Assessment:

FDA agrees with the Applicant's assessment.

Electrocardiograms

The Applicant's Position:

***SIOPEL* 6**

Echocardiograms were not a mandatory assessment, but were only performed if clinically indicated (ie, after doxorubicin treatment) (SIOPEL 6 CSR, Section 7.5.2 and Table 2).

The CIS+STS and the CIS Alone arms had no notable differences in mean percent shortening fractions at the end of treatment (35.871% and 37.334%, respectively) and at Follow-up (34.138% and 34.744%, respectively) (SIOPEL 6 CSR Table 14.3.4.1). The CIS+STS and the CIS Alone arms also had no notable differences in mean percent ejection fractions at the end of treatment (67.426% and 68.942%, respectively) and at Follow-up (69.786% and 63.744%, respectively).

Overall, 3 patients experienced AEs in the SOC Cardiac disorders during the Treatment Phase. In the CIS+STS arm, 1 patient each (1.9%) experienced arrhythmia and ventricular arrhythmia; both AEs were Grade 1 in severity (SIOPEL 6 CSR Table 14.3.9.6.1). In the CIS Alone arm, 1 patient (1.8%) experienced a Grade 1 AE of left ventricular dysfunction.

COG ACCL0431

Cardiac function was not reported in the clinician database for this study.

Adverse events in the PT of hypotension were reported in 2 patients (3.4%) in the CIS+STS arm, and 1 patient (1.6%) in the Observation arm (COG ACCL0431 CSR Table 14.3.1.1). An AE in the PT of hypertension was reported in 1 patient (1.7%) in the CIS+STS arm (COG ACCL0431 CSR Table 14.3.1.1).

The FDA's Assessment:

FDA agrees with the Applicant's assessment.

QT

The Applicant's Position:

Pursuant to 21 CFR 314.90, Fennec Pharmaceuticals, Inc. has requested a waiver of the Thorough QTc data requirements for approval of PEDMARK (sodium thiosulfate injection), for IV use. Available data adequately establish the cardiac conduction safety of sodium thiosulfate for the intended use, in the intended patient population; therefore, no further data are required to support approval of PEDMARK.

Sodium thiosulfate has been used clinically for nearly a century. Moreover PEDMARK treatment is confined to a limited number of distinct administrations and will not be indicated for chronic use. Furthermore, PEDMARK is only administered to cancer patients receiving CIS treatment. Therefore, STS at the studied and proposed dose regimen is not considered to increase the risk for cardiotoxicity in these conditions.

The FDA's Assessment:

FDA agrees with the Applicant's assessment and request for waiver.

Immunogenicity

The Applicant's Position:

Not applicable.

The FDA's Assessment:

FDA agrees.

8.2.5 Analysis of Submission-Specific Safety Issues

The Applicant's Position:

Adverse events of special interest were identified as Grade 3 severity or higher events in the PTs of nausea, vomiting, hypomagnesemia, and hypernatremia for both SIOPEL 6 and COG ACCL0431. These AEs are discussed in Section 8.2.4.

The FDA's Assessment:

FDA agrees with the Applicant's assessment. See Section 82.4.

8.2.6 Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

The Applicant's Position:

There were no clinical outcome assessments or patient-reported outcomes in the studies.

The FDA's Assessment:

FDA agrees.

8.2.7 Safety Analyses by Demographic Subgroups

The Applicant's Position:

Overall, SIOPEL 6 and COG ACCL0431 were smaller studies (N=109 and N=104 patients, respectively), which can limit the interpretation of data by subgroups with small sample sizes. Demographics, exposure, incidence of AEs, and serum sodium levels were evaluated by the subgroups of gender and age for each study. Due to differences in median age between the SIOPEL 6 and COG ACCL0431 patient populations, the age cutoffs evaluated were different for each study. Evaluations of magnesium and GFR levels (by subgroups) were conducted for SIOPEL 6 only.

In addition to gender and age subgroup analyses, data were evaluated by weight subgroup (≤10 kg and >10 kg) in SIOPEL 6 only. The weight subgroup analysis was not conducted for COG ACCL0431 because only 1 child treated with STS was ≤10 kg.

Overall in SIOPEL 6, demographics and incidence of AEs were balanced across the age, gender, and weight subgroups. As expected, the total cumulative CIS doses over all cycles were higher in the ≥24 months subgroup compared with the <24 months subgroup, regardless of whether treatment included or excluded PLADO, due to weight/BSA-based dose calculations. Total cumulative STS doses over all cycles were also higher in the ≥24 months subgroup compared with the <24 months subgroup, for the same reason. Adverse events were more common in children in the <24 months age group, regardless of treatment arm, and SAEs were more common in children weighing >10 kg in the CIS Alone arm, compared with the other weight subgroup and treatment arm. The incidences of AESIs were similar across subgroups and treatment arms. There were no notable differences across subgroups and treatment arms for GFR, magnesium, and sodium.

Overall in COG ACCL0431, demographics were mostly balanced across the age subgroups and treatment arms; however, the percentage of females was lower in both age subgroups. Baseline disease characteristics reflected the specific tumor type expected to be associated with the age of the child. The total cumulative CIS administered doses over all cycles was higher in the ≥5 years

subgroup compared with the <5 years subgroup, which was expected based on the size of the child and prescribed chemotherapy regimen. Mean STS doses and dosing days in the ≥5 years subgroup were higher because more doses of CIS were required for tumor types that occur in older children and because older/larger children received larger doses of STS (calculated as g/m^2). The incidence of AEs (of all grades) and SAEs were similar across age subgroups, with slightly higher incidences of AEs, SAEs, and drug-related AEs in females compared with males. The incidence of death was generally similar across the age subgroups regardless of treatment; however, among patients in the <5 years subgroup, a higher number of patients in the CIS+STS arm died (9 patients) than in the CIS Alone arm (3 patients), which is most likely related to the underlying prognostic factors of tumors which occur in younger children. Among children in the ≥5 years subgroup, the incidences of AESIs of nausea and vomiting were higher in the CIS+STS arm compared with the Observation arm. There were no noticeable differences in sodium level across subgroups and treatment arms.

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 would necessitate changes to the dosing recommendations in the proposed label. SIOPEL 6 and COG ACCL0431 did not enroll patients <1 month of age, as patients in this age group have less well-developed sodium homeostasis (Module 2.7.2, Section 2.2.7); therefore, the safety of PEDMARK in this age group is unknown, and the proposed indication is limited to the ages of 1 month to <18 years.

No new safety concerns were identified in clinical studies evaluating the PK of STS in patients with renal impairment in the literature. 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.

The FDA's Assessment:

FDA did not conduct separate safety analyses by demographic subgroups.

8.2.8 Specific Safety Studies/Clinical Trials

The Applicant's Position:

No separate studies were conducted to evaluate a specific safety concern.

The FDA's Assessment:

Not applicable.

8.2.9 Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The Applicant's Position:

No carcinogenicity studies have been conducted with STS. As the ICH S1A guidance noted 23 years ago, "since carcinogenicity studies are time consuming and resource intensive, they should only be performed when human exposure warrants the need for information from life-time studies in animals in order to assess carcinogenic potential."

Fennec does not plan to conduct a carcinogenicity study with STS because:

- Patients will not be exposed to STS on a chronic basis or "frequently in an intermittent manner in the treatment of a chronic or recurrent condition," as described in the ICH S1A guidance. While STS will be administered in an intermittent manner (ie, typically for 5 days/month and for up to six months in conjunction with platinum chemotherapy), cancer is not a chronic or recurrent condition of the sort given as examples in the ICH S1A guidance (allergic rhinitis, depression, or anxiety).
- There is no cause for concern that STS might pose a carcinogenic hazard to patients because it does not pose a genotoxic hazard and is generally recognized as safe by the FDA when used in food.
- Sodium thiosulfate will be administered only in conjunction with platinum-based chemotherapy, which already presents a carcinogenic hazard to patients. Therefore, the additional carcinogenic hazard presented by STS (if any) would be negligible in comparison.

The FDA's Assessment:

FDA agrees with the Applicant's assessment.

Human Reproduction and Pregnancy

The Applicant's Position:

There are no adequate and well-controlled studies in pregnant women. No pregnancies were reported in either SIOPEL 6 or COG ACCL0431.

There are no reported epidemiological studies of congenital anomalies in infants born to women treated with sodium thiosulfate during pregnancy.

Sodium thiosulfate was not embryotoxic or teratogenic in pregnant mice, rats, hamsters, or rabbits at maternal doses of up to 550, 400, 400, and 580 mg/kg/day (1.65, 2.4, 2.0, and 6.96 g/m^2/day), respectively, when STS was administered as an aqueous solution by oral intubation (Module 2.6.6 Section 6.3). Additionally, a PK study in gravid ewes indicated that IV STS does not cross the placenta (Module 2.6.4 Section 4.4).

Based on all available information, PEDMARK is considered unlikely to affect embryofetal development in a female patient who is pregnant. Importantly, PEDMARK is only intended to be

administered in conjunction with CIS chemotherapy, which already presents a risk of adversely affecting embryofetal development in a pregnant female patient.

There are no studies regarding the excretion of STS into breast milk in humans or animals; however, breast milk is produced within alveolar cells and, since thiosulfate remains extracellularly, it is extremely unlikely that thiosulfate would be found in breast milk (Module 2.6.6 Section 6.3.3). In addition, PEDMARK is only intended to be administered in conjunction with CIS chemotherapy, during which female patients are advised not to breastfeed an infant.

The FDA's Assessment:

See Section 5 for FDA comments.

Pediatrics and Assessment of Effects on Growth

The Applicant's Position:

As the proposed indication for PEDMARK™ (b) (4) is in patients 1 month to <18 years of age, all of the data included in Section 8.2, Review of Safety, addresses safety in pediatric patients.

The FDA's Assessment:

FDA agrees with the Applicant's assessment and refers to Section 8.2. FDA is not aware of any in vitro, in vivo or clinical data that suggest sodium thiosulfate may interfere with pediatric growth or development.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The Applicant's Position:

There is limited information about the effects of large doses of STS administered IV in humans.

Drug abuse potential, withdrawal, and rebound are not applicable for STS.

The FDA's Assessment:

FDA agrees with the Applicant's assessment.

8.2.10 Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The Applicant's Position:

PEDMARK is not approved for human use; therefore, no postmarketing information is available for this product.

The following adverse events (AEs), potentially relevant to the use of PEDMARK, have been reported in the medical literature in association with STS administration used for other indications. These AEs were not reported in the context of controlled trials; therefore, frequency of occurrence cannot be assessed.

Cardiovascular System: hypertension, hypotension

Laboratory Investigations: hypocalcemia

Metabolic and Nutritional Disorders: metabolic acidosis

The FDA's Assessment:

FDA does not object to including the proposed terms as safety concerns identified through the post-marketing experience. Terms reported on other labels for sodium thiosulfate were not based on controlled trials and are confounded by different indications and comorbidities.

Expectations on Safety in the Postmarket Setting

The Applicant's Position:

Potential safety concerns beyond the risks conveyed in the proposed labeling are not expected. Routine pharmacovigilance will be conducted to monitor for unexpected adverse events.

The FDA's Assessment:

FDA agrees with the Applicant's assessment.

8.2.11 Integrated Assessment of Safety

The Applicant's Position:

The totality of evidence from the STS clinical development program and available literature demonstrates that PEDMARK has a favorable safety profile for the proposed indication. Fennec's conclusions from the review of safety is provided in Section 8.2.

To provide context for the safety of PEDMARK in the proposed indication, the following subsections provide critical evaluations of these safety concerns as well as overviews of other key elements in the safety profile of STS.

Adverse Drug Reactions

As an inorganic salt in solution, a (b) (4) dose of PEDMARK delivers a sodium load of 162 mmol/m^2. In animal toxicity studies, sodium-related effects have been the dose-limiting factor for STS. Adverse events of hypernatremia were frequently reported in STS-treated patients in SIOPEL 6 (26.4% and 3.6% of patients in the CIS+STS and CIS Alone arms, respectively). No seizures and no ocular problems from sudden high sodium levels translating

into sudden high blood pressure levels were observed. In COG ACCL0431, the overall incidence of hypernatremia was lower than observed in SIOPEL 6, but AEs of hypernatremia were still more frequently reported in patients who received STS (11.9% and 6.3% of patients in the CIS+STS and Observation arms, respectively). No events of hypernatremia were serious in either study, and the majority had a maximum severity of CTCAE Grade 1. In SIOPEL 6, sodium levels were recorded over time, and results showed that increases in sodium levels at 1 hour after STS infusion were transitory and well tolerated. Analysis of modeling and simulation using the proposed PEDMARK dosing showed that the increase in sodium was independent of body weight-dependent dose class, age, or total daily STS dose. Results did not indicate that under- or overdosing occurred in relation to (renal) sodium handling by subjects across the proposed pediatric age range. However, due to the potential for hypernatremia, electrolyte balance should be monitored carefully and PEDMARK should not be given if serum sodium is >145 mmol/L.

Patients receiving CIS are treated with large volumes of fluid and electrolytes (to reduce renal toxicity), sometimes resulting in transient electrolyte imbalances. Other AEs related to electrolyte changes (ie, hypokalemia and hypophosphatemia) were also frequently reported in SIOPEL 6 and COG ACCL0431. In SIOPEL 6, hypokalemia and hypophosphatemia were reported more often in patients treated with STS (15.1% and 1.8% of patients in the CIS+STS and CIS Alone arms, respectively, for both PTs). In COG ACCL0431, hypophosphatemia was also reported more often in patients treated with STS (20.3% and 10.9% of patients the CIS+STS and Observation arms, respectively), while the incidence of hypokalemia was generally similar between arms (27.1% and 20.3% of patients in the CIS+STS and Observation arms, respectively). Nearly all events in both studies were non-serious and considered unlikely related or unrelated to STS. As these patients are already monitored closely for sodium, potassium, and magnesium levels, no additional monitoring of these electrolytes should be required with the use of PEDMARK.

In SIOPEL 6, nausea and vomiting were among the most frequently reported AEs and were more likely to be observed in STS-treated patients. In the CIS+STS arm, 39.6% of patients reported nausea and 84.9% of patients reported vomiting compared with 30.4% and 53.6%, respectively, in the CIS Alone arm. Based on observations from the Investigators, transient increases in incidence and severity of nausea and vomiting during the infusion of STS were probably due to the high sodium levels administered over a short time period; nausea and vomiting tended to stop soon after the STS infusion had finished. In SIOPEL 6, no AEs of nausea or vomiting were serious and the majority had a maximum severity of CTCAE Grade 2 or lower. In COG ACCL0431, the incidences of nausea (8.5% and 4.7% of patients in the CIS+STS and Observation arms, respectively) and vomiting (6.8% and 4.7%, respectively) were much lower than those observed in SIOPEL 6; however, most events were Grade 3 or higher and 2 SAEs of nausea and 1 SAE of vomiting were reported in the CIS+STS arm. The higher incidences of

nausea and vomiting AEs in SIOPEL 6 compared with COG ACCL0431 in both treatment arms are explained by the proactive collection of data on nausea and vomiting in the SIOPEL 6 CRF. Events of nausea and vomiting are manageable with appropriate pre-medication. Children receiving chemotherapy known to cause nausea and vomiting, such as CIS, receive prophylactic anti-emetics. Additional multi-agent anti-emetics should be given in the 30 minutes prior to the administration of PEDMARK.

Although not frequently reported, hypersensitivity reactions were observed in SIOPEL 6 and COG ACCL0431 and were more likely to be reported in STS-treated patients. In SIOPEL 6, the hypersensitivity AEs were reported in 13.2% of patients in the CIS+STS arm and 10.7% of patients in the CIS Alone arm. In COG ACCL0431, the incidence was 8.5% in the CIS+STS arm and 4.7% in the Observation arm. With the exception of 1 SAE of hypersensitivity leading to discontinuation (also considered a SUSAR) that was reported in the CIS+STS arm of SIOPEL 6, no other AEs of hypersensitivity were considered serious. Other non-serious AEs of hypersensitivity were reported in both studies; although incidences were generally similar across arms. Nonetheless, the potential for hypersensitivity reactions is included as an ADR. In addition, because PEDMARK may contain trace amounts of sodium sulfite, hypersensitivity reactions due to sulfite are possible. Such events are manageable with appropriate observation and treatment.

Other Serious Adverse Events and Death

In SIOPEL 6, the overall incidence of non-fatal SAEs during the Treatment Phase was similar between the CIS+STS arm (39.6%) and the CIS Alone arm (32.1%). In COG ACCL0431, SAEs were only collected for patients in the CIS+STS arm, but the overall incidence of SAEs (fatal and non-fatal) in the CIS+STS arm was similar to that observed in SIOPEL 6 (35.6%). The most frequently reported SAEs observed in both studies (eg, febrile neutropenia, anemia, neutrophil count decreased, infection, pyrexia) are commonly known to be associated with chemotherapy and are not plausibly associated with the known mechanism of action of STS.

As expected for a pediatric oncology study, deaths were reported in both studies (6 deaths in SIOPEL 6 [2 deaths in the CIS+STS arm and 4 deaths in the CIS Alone arm]; 30 deaths in COG ACCL0431 [18 deaths in the CIS+STS arm and 12 deaths in the Observation arm]). The majority were due to tumor progression occurring during long-term follow up. No deaths were considered related to STS by the Investigators.

Although not powered for the analysis, both studies evaluated survival during treatment and long-term follow up (SIOPEL 6 median 4.27 years; COG ACCL0431 median 5.33 years). No differences in EFS or OS for the CIS+STS arm compared with the CIS Alone/Observation arm were observed for patients with a localized tumor type (SR-HB; SIOPEL 6) or for patients in COG ACCL0431 categorized post-hoc as having localized disease (various tumor types). For patients in COG ACCL0431 categorized post-hoc with disseminated disease, OS favored the

Observation arm; however, the OS for patients in the Observation arm was higher than that predicted for children with mixed disseminated disease based on the literature and very similar to the OS observed in children categorized as having localized disease. A detailed review concluded that the most likely explanation for the difference between the 2 arms in patients with disseminated disease was an imbalance in tumor types and prognostic indicators at randomization rather than the use of STS. The characteristics of the tumors in COG ACCL0431 have a far greater potential to affect survival than the use of STS.

For all of these reasons, deaths due to disease may be expected given the patient population in pediatric oncology, but STS treatment administered 6 hours after completion of CIS infusions does not negatively affect the anti-tumor efficacy of CIS.

Potential for AEs in Patients with Impaired Renal Function or Insufficiency

Evaluation of long-term GFR/creatinine clearance in SIOPEL 6 showed that there was no deterioration in renal function and results were similar between treatment arms. Children receiving chemotherapy for cancer are routinely and carefully monitored for renal function. As a precaution to prevent CIS accumulation in the kidney and CIS-induced nephrotoxicity, patients receive saline fluid hydration treatment with high chloride content before and after CIS administration to stimulate glomerular filtration and urinary flow. It is likely that, under these conditions, glomerular filtration and excretion of STS is maintained, even when the tumor or chemotherapy has affected renal function. However, because STS is known to be substantially excreted by the kidney, the risk of AEs may be greater in patients with impaired renal function. In children with moderate to severe renal insufficiency, PEDMARK should be used with caution and careful monitoring.

Renal function and its maturation in infants are important to the control of sodium hemostasis. PEDMARK is contraindicated in neonates under the age of 1 month due to the potential risk of hypernatremia considering the immaturity of a neonate's renal system. In the PIP, a waiver was granted for preterm and term newborn infants from birth to <1 month of age.

Other Safety Information for Sodium Thiosulfate from Published Literature

In addition to the ADRs, adverse effects associated with STS administration that were reported in the medical literature or in labels from other marketed STS products used for other indications were reviewed. The following events were judged to be relevant to the indicated patient population for PEDMARK based on medical plausibility and occurrence in SIOPEL 6 or COG ACCL0431. These AEs were not reported in the context of controlled studies or with consistent monitoring and reporting methodologies. Therefore, frequency of occurrence of these AEs cannot be assessed.

Cardiovascular System: hypertension, hypotension

Laboratory Investigations: hypocalcemia

Metabolic and Nutritional Disorders: metabolic acidosis

The FDA's Assessment:

FDA agrees with the Applicant's integrated assessment of safety. Overall, the safety profile of STS is consistent with the known safety profile of other STS products. No new safety issues were identified.

9 SUMMARY AND CONCLUSIONS

9.1 STATISTICAL ISSUES

The FDA's Assessment:

Because the primary analyses of hearing loss for both SIOPEL6 and COG ACCL0431 were not controlled for type-1 error at a level of 0.05 (two-sided), no claims of statistical significance should be made. Additionally, FDA does not agree with the analysis populations in either study, and the regulatory decision was based on FDA's analysis of the primary endpoint of each study in their respective re-defined populations.

Though neither study was powered for EFS or OS, SIOPEL 6 showed no apparent difference between arms for either endpoint while COG ACCL0431 showed a potential detriment in both endpoints. Exploratory post-hoc analyses of EFS and OS in COG ACCL0431 suggested that the potential detriment in both may have been driven by patients with metastatic disease. FDA noted that extent of disease (metastatic or non-metastatic), determined post-hoc, was not a stratification factor and sample size in each subgroup was small, so these results should be considered with these limitations in mind. The indication was limited to patients with non-metastatic disease, which helps alleviate concerns of a potential survival detriment.

9.2 CONCLUSIONS AND RECOMMENDATIONS

The FDA's Assessment:

The clinical and statistical reviewers agree that the data from SIOPEL 6 and COG ACCL0431 support traditional approval for this NDA..

X	X
Primary Statistical Reviewer	Joyce Chen Statistical Team Leader
X	X
Amy Barone Primary Clinical Reviewer	Amy Barone Clinical Team Leader

10 ADVISORY COMMITTEE MEETING AND OTHER EXTERNAL CONSULTATIONS

The FDA's Assessment:

The review team opted not to seek advice at an Advisory Committee meeting and did not consult other external subject matter experts during review of this application because it did not raise significant efficacy or safety issues for the proposed indication that would require external input.

11 PEDIATRICS

The Applicant's Position:

The proposed indication for PEDMARK™ [redacted] (b) (4) is prevention of ototoxicity induced by CIS chemotherapy in patients 1 month to <18 years of age with localized, non-metastatic solid tumors. Thus, all clinical study data included in this document is for pediatric patients.

PEDMARK was granted orphan status and thus there is no requirement for a PSP.

The FDA's Assessment:

FDA agrees with the Applicant's assessment. PEDMARK was granted orphan designation for the proposed application and is not a molecularly targeted drug under development for treatment of an adult cancer; therefore this application is not subject to FDARA provisions and is exempt from PREA requirements.

12 LABELING RECOMMENDATIONS

The Applicant's Position:

Fennec provided a draft labeling with the NDA.

The FDA's Assessment:

The table below summarizes changes to the proposed prescribing information made by FDA.

See the final approved prescribing information for PEDMARK (sodium thiosulfate injection) accompanying the approval letter for more information. At the time of the CR, labeling negotiations were ongoing.

Section	Applicant's Proposed Labeling	FDA Proposed Labeling
General	Proposed a product title of PEDMARK (b) (4) PEDMARK is indicated to reduce the risk of ototoxicity associated with cisplatin- (b) (4) in pediatric patients ider with localized, non metastatic solid tumors	(b) (4) Removed unnecessary description for brevity.
Highlights	…	Modified based on changes made to the full prescribing information.
Full Prescribing Information		
Indications and Usage	(b) (4)	Revised indication statement based on recommendations found in Indication and Usage guidance, which states that if the indication for a drug is to reduce the risk of the occurrence of a particular clinical outcome, phrases such as "reduce the risk of" or "reduce the incidence of" should be considered rather than using "prevent" in the indication.

Section	Applicant's Proposed Labeling	FDA Proposed Labeling
		(b) (4) revised age groups based on recommendations found in Indication and Usage guidance, which states that"…Age groups should be included in indications. As such, an indication should state that a drug is approved, for example, "in adults," "in pediatric patients X years of age and older," or "in adults and pediatric patients X years of age and older". (b) (4)
Dosage and Administration	Provided recommended dose and other information immediately following the section title with no subsections. (b) (4) PEDMARK is not substitutable with other sodium thiosulfate products.	Added subsections for recommended dosage, dosage modifications for adverse reactions, recommended premedications, and preparation and administration. Revised recommended dosage (b) (4)

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

Section	Applicant's Proposed Labeling	FDA Proposed Labeling
		nonclinical studies, mechanism of action and clinical studies. Revised the dosage because the strength of the product will be expressed as pentahydrate. Retained "not substitutable" statement for safety, given the risks that could be associated with medication errors or exposure to unacceptably high levels of boric acid if other approved STS products are substituted for PEDMARK.
Dosage Forms and Strengths	(b) (4)	Changed to single-dose vial based on Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use and USP Chapter <659>. Will revise the strength of the product based on the pentahydrate form of sodium thiosulfate based on USP monograph. Similar changes will be made to Description and How Supplied/Storage.
Contraindications	Included a contraindication for known hypersensitivity to sodium thiosulfate (b) (4)	Revised the contraindication to history of severe hypersensitivity. Removed (b) (4)

Section	Applicant's Proposed Labeling	FDA Proposed Labeling
Warnings and Precautions (W&P), Hypersensitivity	(b) (4)	Revised the W&P to describe the percentage of patients who developed a reaction in the entire safety population. Revised steps that should be taken if a reaction occurs based on clinical studies.
W&P, Electrolyte Imbalances	(b) (4)	Revised subsection title to describe the adverse reaction or risk based on best labeling practices. Stated the use of the drug product is not recommended in pediatric patients less than 1 month, because these pediatric patients have less well-developed sodium homeostasis and in patients with high baseline serum sodium level, because of the risk of hypernatremia. Added sodium load for each recommended dosage. (b) (4)
W&P, Sulfites	Included information regarding the risk of a hypersensitivity reaction in patients following sulfite exposure.	Incorporated the information into the W&P for hypersensitivity reactions.

Section	Applicant's Proposed Labeling	FDA Proposed Labeling
Adverse Reactions, Clinical Trials Experience	(b) (4) 6.2 Included other sources of safety information based on adverse events reported in the medical literature for sodium thiosulfate.	Based on current OOD labeling practices, independently summarized the dosing regimen, exposure, serious adverse reactions, permanent discontinuations, and most common adverse reactions for each trial. Included a tabular summary of the all grades and grades 3 to 4 adverse reactions for both treatment arms for each trial. Revised this heading to "Postmarketing Experience/Spontaneous Reports" to include adverse reactions from spontaneous reports with other sodium thiosulfate products.
Drug Interactions	(b) (4)	Omitted, because this section must contain a description of clinically significant interactions, either observed or predicted, with other prescription or over-the-counter drugs, classes of drugs, or foods (e.g., dietary supplements, grapefruit juice), and specific practical instructions for preventing or managing them. [21 CFR 201.57 (c)(8)(i).
Use in Specific Populations, Pregnancy	(b) (4) Included a summary of animal studies.	Included a risk statement based on human data and animal data and the percentage range of live births in US with a major birth defect and the percentage range of pregnancies in US that end in miscarriage as required by 21 CFR 201.57(c)(9)(i)(B)(1) and (2). Revised summary of animal data to include the number and type(s) of species

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

Section	Applicant's Proposed Labeling	FDA Proposed Labeling
		affected, timing of exposure, animal doses expressed in terms of human dose or exposure equivalents, and outcomes for pregnant animals and offspring based on regulations cited above.
Use in Specific Populations, Lactation	(b) (4)	Included presence of drug in human milk, effects of drug on breast-fed child and effects of drug on milk production as required by 21 CFR 201.57(c)(9)(ii).
Use in Specific Populations, Females and Males of Reproductive Potential	…	Omitted because recommendations were based on cisplatin, not sodium thiosulfate.
Use in Specific Populations, Pediatric Use	…	Added safety and effectiveness have not been established and is not recommended in pediatric patients younger than 1 month old due to the increased risk of hypernatremia based on recommendations in Pediatric Labeling guidance. Added safety and effectiveness have not been established in pediatric patients with metastatic cancer based on the trend for detriment in survival observed in the post-hoc analysis of patients with metastatic cancer in COG ACCL0431.
Use in Specific Populations, Geriatric Use	…	Added subsection and required geriatric use statement [21 CFR 201.57 (c)(9)(v)(B)(1)].
Use in Specific Populations, Renal Impairment	(b) (4)	Added steps to be taken to reduce risk of adverse reactions in patients with renal impairment.

Section	Applicant's Proposed Labeling	FDA Proposed Labeling
Overdosage	…	Omitted. The OVERDOSAGE section must be based on human overdosage data. If human data are unavailable, appropriate animal and in vitro data regarding overdosage may be included. Alternatively, if no specific overdosage data are available that would be useful to the health care practitioner, omit this section [21 CFR 201.57(c)(11)].
Clinical Pharmacology, Pharmacodynamics	(b) (4)	
		Revised summary of the effects on serum sodium level to include sodium load for each recommended dosage, the reported sodium levels in patients, and the time course of changes in serum sodium levels following administration of sodium thiosulfate.
Clinical Pharmacology, Pharmacokinetics	(b) (4)	Deleted, since animal information that should generally not be included in subsection 13.2 Animal Toxicology and/or Pharmacology unless it is necessary for the understanding of pharmacology data in humans, per guidance Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format.
Clinical Studies	(b) (4)	Separated information into a single subsection because both trials support a single indication and usage.

Section	Applicant's Proposed Labeling	FDA Proposed Labeling
		Added demographics and baseline characteristics to provide sufficient context for the study results. (b) (4) Revised study outcome measures for the COG trial to only include patients with localized disease based on the indication.
Patient Counselling Information		Inclusion of Hypernatremia and Hypokalemia as these are serious adverse reactions.

13 RISK EVALUATION AND MITIGATION STRATEGIES (REMS)

The FDA's Assessment:

The clinical review team does not recommend a REMS. Based on the risk/benefit profile of PEDMARK, safety issues can be adequately managed through appropriate labeling and routine post-marketing surveillance.

14 POSTMARKETING REQUIREMENTS AND COMMITMENT

The FDA's Assessment:

No new postmarketing requirements or commitments are recommended.

15 DIVISION DIRECTOR (DHOT) (NME ONLY)

X

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

16 DIVISION DIRECTOR (OCP)

X

17 DIVISION DIRECTOR (OB)

X

18 DIVISION DIRECTOR (CLINICAL)

X

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

19 OFFICE DIRECTOR (OR DESIGNATED SIGNATORY AUTHORITY)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

X _____

20 APPENDICES

20.1 REFERENCES

The Applicant's References:

American-Speech-Language-Hearing Association. Guidelines for the audiologic management of individuals receiving chochleotoxic drug therapy. ASHA. 1994;36(Suppl.12):11-19.

Arslan E, Orzan E, Santarelli R. Global problem of drug-induced hearing loss. Ann N Y Acad Sci. 1999;884:1-14.

Asplin, J.R., Donahue, S.E., Lindeman, C., et al. Thiosulfate reduces calcium phosphate nephrolithiasis. J. Am. Soc. Nephrol. 2009;20:1246-1253.

Berg AL, Spitzer JB, Garvin JH. Ototoxic impact of cisplatin in pediatric oncology patients. Laryngoscope 1999;109(11):1806-14.

Bijarnia RK, Bachtler M, Chandak PG, van Goor H, Pasch A. Sodium Thiosulfate Ameliorates Oxidative Stress and Preserves Renal Function in Hyperoxaluric Rats. PLoS ONE. 2015;10(4):e0124881.

Bertolini P, Lassalle M, Mercier G, Raquin MA, Izzi G, Corradini N, et al. Platinum compound related ototoxicity in children: long-term follow-up reveals continuous worsening of hearing loss. J Pediatr Hematol Oncol. 2004;26(10):649-55.

Bijarnia, R.K., Bachtler, M., Chandak, P.G. et al. Sodium Thiosulfate Ameliorates Oxidative Stress and Preserves Renal Function in Hyperoxaluric Rats. PLoS ONE. 2015;10(4):e0124881.

Bilska-Wilkosz, A., Iciek, M., Górny, M, Kowalczyk-Pachel D. The Role of Hemoproteins: Hemoglobin, Myoglobin and Neuroglobin in Endogenous Thiosulfate Production Processes. Int. J. Mol. Sci. 2017;18,1315-1325.

Blakley BW, Cohen JI, Doolittle ND, Muldoon LL, Campbell KC, Dickey DT, et al. Strategies for prevention of toxicity caused by platinum-based chemotherapy: review and summary of the annual meeting of the Blood brain barrier Disruption Program, Gleneden Beach, Oregon, March 10, 2001. Laryngoscope. 2002;112(11):1997 2001.

Braverman, B., Ivankovich, A.D., Shah, G. Thiosulfate pharmacokinetics in normal and anuretic dogs. Proceedings of the Society for Experimental Biology and Medicine. 1982;170:273-280.

Breglio AM, Rusheen AE, Shide ED, Fernandez KA, Spielbauer KK, McLachlin KM, et al. Cisplatin is retained in the cochlea indefinitely following chemotherapy. Nature Communications. 2017; 8:1654:1-9.

Brock PR, Bellman SC, Yeomans EC, Pinkerton CR, Pritchard J. Cisplatin ototoxicity in children: A practical grading system. Med Pediatr Oncol. 1991;19(4):295-300.

Brock PR, Knight KR, Freyer DR, Campbell KC, Steyger PS, Blakley BW, et al. Platinum-induced ototoxicity in children: a consensus review on mechanisms, predisposition, and protection, including a new International Society of Pediatric Oncology Boston ototoxicity scale. J Clin Oncol. 2012;30:2408-17.

Brock PR, Maiback R, Childs M, Rajput K, Roebuck D, Sullivan MJ, et al. Sodium thiosulfate for protection from cisplatin-induced hearing loss. New England J of Medicine 2018;378:2376-85.

Campbell, K.C.M., Meech, R.P., Rybak, L.P. et al. The Effect of D-Methionine on Cochlear Oxidative State with and without Cisplatin Administration: Mechanisms of Otoprotection. Journal of the American Academy of Audiology. 2003;14(3), 144-156.

Church, M.W., Kaltenbach, J.A., Blakley, B.W. et al. The comparative effects of sodium thiosulfate, diethyldithiocarbamate, fosfomycin and WR-2721 on ameliorating cisplatin-induced ototoxicity. Hearing Res. 1995;86(1-2):195-203.

Dedon, P.C. and Borch, R.F. Characterization of the reactions of platinum antitumor agents with biologic and nonbiologic sulfur-containing nucleophiles. Biochemical Pharmacology. 1987;36(12):1955-1964.

Dehne, N., Lautermann, J., Petrat, F. et al. Cisplatin Ototoxicity: Involvement of Iron and Enhanced Formation of Superoxide Anion Radicals. Toxicology and Applied Pharmacology. 2001;174:27-34.

Dennis, D.L. and Fletcher, W.S. Toxicity of sodium thiosulfate (NSC-45624), a nitrogen mustard antagonist, in the dog. Can. Chemo. Rep. 1966;50(5):255-257.

Dickey DT, Muldoon LL, Kraemer DF, Neuwelt EA. Protection against cisplatin-induced ototoxicity by N-acetylcysteine in a rat model. Hear Res. 2004;193:25-30.

Dickey DT, Wu JY, Muldoon LL, Neuwelt EA. Protection against cisplatin-induced toxicities by N-acetylcysteine and sodium thiosulfate as assessed at the molecular, cellular, and in vivo levels. J Pharmacol Exp Ther. 2005;314(3):1052-8.

Ding, D.L., Wang, J., Salvi, R., et al. Selective Loss of Inner Hair Cells and Type-I Ganglion Neurons in Carboplatin-Treated Chinchillas. Mechanisms of Damage and Protection. Annals New York Academy Of Sciences. 1999;884:152-170.

Doolittle ND, Muldoon LL, Brummett RE, Tyson RM, Lacy C, Bubalo JS, et al. Delayed sodium thiosulfate as an otoprotectant against carboplatin-inducted hearing loss in patients with malignant brain tumors. Clin Cancer Res. 2001;7(3):493-500.

Dorr, R.T. Chemoprotectants for cancer chemotherapy. Semin. Oncol. 1991;18(1suppl 2):48 58.

Elferink, F., van der Vijgh, W.J.F., Klein, I, et al. Interaction of Cisplatin and Carboplatin with Sodium Thiosulfate: Reaction Rates and Protein Binding. Clin. Chem. 1986;32(4):641-645.

Environmental Protection Agency (EPA). Sodium thiosulfate; Notice of Filing a Pesticide Petition to Amend a Tolerance for a Certain Pesticide Chemical in or on Food. Federal Register. 2003;68(228):66416-66421.

Evans, P., and Halliwell, B. Free radicals and Hearing. Cause, Consequence and Criteria. Annals New York Academy Of Sciences. 1999;884:19-40.

Farese S, Stauffer E, Kalicki R, Hildebrandt T, Frey BM, Frey FJ, et al. Sodium thiosulfate pharmacokinetics in hemodialysis patients and healthy volunteers. Clin J Am Soc Nephrol. 2011;6(6):1447-55.

Fausti SA, Henry JA, Schaffer HI, Olson DJ, Frey RH, Bagby GC. High-frequency monitoring for early detection of cisplatin ototoxicity. Arch Otolaryngol Head Neck Surgery. 1993;119(6):661-6.

Freyer DR, Chen L, Krailo MD, Knight K, Villaluna D, Bliss B, et al. Effects of sodium thiosulfate versus observation on development of cisplatin-induced hearing loss in children with cancer: results from the Children's Oncology Group ACCL0431 randomised clinical trial. Lancet Oncol. 2017;18(1):63-74.

Gilmer-Knight KR, Kraemer DF, Neuwelt EA. Ototoxicity in children receiving platinum chemotherapy: estimating a commonly occurring toxicity that may influence academic and social development. J Clin Oncol 2005;23(34):8588-96.

Hale GA, Marina NM, Jones-Wallace D, Greenwald CA, Jenkins JJ, Rao BN, et al. Late effects of treatment for germ cell tumors during childhood and adolescence. Journal of pediatric hematology/oncology. 1999;21:115-22.

Hazlitt, R.A., Min, J., Zuo, J. Progress in the Development of Preventative Drugs for Cisplatin-Induced Hearing Loss. J. Med. Chem. 2018;61:5512-5524.

Hildebrandt TM and Manfred KG. Three enzymatic activities catalyze the oxidation of sulfide to thiosulfate in mammalian and invertebrate mitochondria. FEBS J. 2008 Jul;275(13):3352-61.

Hindley P. Psychiatric aspects of hearing impairments. J Child Psychol Psychiatry. 1997;38(1):101-17.

Ishizawa, M., Taniguchi, S., and Baba, T. Protection by sodium thiosulfate and thiourea against lethal toxicity of cis-diamminedichloroplatinum(ii) in bacteria and mice. Japan J. Pharmacol. 1981;31:883-889.

Ivankovich AD, Braverman B, Stephens TS, Shulman M, Heyman HJ. Sodium thiosulfate disposition in humans: relation to sodium nitroprusside toxicity. Anesthesiology. 1983;58(1):11-7.

Iwamoto, Y., Kawano, T., Ishizawa, M. et al. Inactivation of cis-diamminedichloroplatinum (II) in blood and protection of its toxicity by sodium thiosulfate in rabbits. Cancer Chemother. Pharmacol. 1985;15:228-232.

Iwamoto, Y., Kawano, T., Uozumi, J., et al. "Two-route chemotherapy" using high-dose IP cisplatin and IV sodium thiosulfate, its antidote, for peritoneally disseminated cancer in mice. Can. Treat. Rep. 1984;68(11):1367-1373.

Kaltenbach, J.A., Church, M.W., Blakley, B.W., et al. Comparison of five agents in protecting the cochlea against the ototoxic effects of cisplatin in the hamster. Otolaryngol. Head Neck Surg. 1997;117(5):493-500.

Karasawa, T., Steyger, P.S. An integrated view of cisplatin-induced nephrotoxicity and ototoxicity. Toxicol. Lett. 2015;237(3): 219-227.

Katzenstein HM, Chang KW, Krailo M, Chen Z, Finegold MJ, Rowland J, et al. Amifostine does not prevent platinum-induced hearing loss associated with the treatment ofchildren with hepatoblastoma: a report of the Intergroup Hepatoblastoma Study P9645 as a part of the Children's Oncology Group. Cancer. 2009;115(24):5828-35.

Kelland, L. The resurgence of platinum-based cancer chemotherapy. Nat. Rev. Cancer. 2007;7(8):573-584.

Knight KR, Kraemer DF, Neuwelt EA. Ototoxicity in children receiving platinum chemotherapy: Underestimating a commonly occurring toxicity that may influence academic and social development. J Clin Oncol. 2005;23(34):8588-96.

Knight KR, Kraemer DF, Winter C, Neuwelt EA. Early changes in auditory function as a result of platinum chemotherapy: use of extended high-frequency audiometry and evoked distortion product otoacoustic emissions. J Clin Oncol. 2007;25(10):1190-5.

Kowalski HJ and Rutstein DD. The distribution of the thiosulfate ion with respect to normal serum and red blood cells and its application to extracellular fluid determination. J Clin Invest. 1952;31(4): 370-374.

Landier W, Knight K, Wong FL, Lee J, Thomas O, Kim H, et al. Ototoxicity in children with high-risk neuroblastoma: prevalence, risk factors, and concordance of grading scales--a report from the Children's Oncology Group. J Clin Oncol. 2014;32:527-534.

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

Li Y, Womer RB, Silber JH. Predicting cisplatin ototoxicity in children: the influence of age and the cumulative dose. Eur J Cancer. 2004;40(16):2445-51.

Liao, Y., Lu, X., Lu, C., et al. Selection of agents for prevention of cisplatin-induced hepatotoxicity. Pharmacological Research. 2008;57:125-131.

Lokich J. What is the best platinum: cisplatin, carboplatin, or oxaliplatin? Cancer Investigation. 2001;19:756-60.

Macdonald MR, Harrison RV, Wake M, Bliss B, Macdonald RE. Ototoxicity of carboplatin: Comparing animal and clinical models at The Hospital For Sick Children. J. Otolaryngol. 1994; 23(3):151-9.

Marutani E, Yamada M, Ida T. Thiosulfate Mediates Cytoprotective Effects of Hydrogen Sulfide Against Neuronal Ischemia. J. Am. Heart Assoc. 2015;4:e002125.

Mathews SJ, de las Fuentes L, Podaralla P, Cabellon A, Zheng S, Bierhals A, et al. Effects of sodium thiosulfate on vascular calcification in end-stage renal disease: a pilot study of feasibility, safety and efficacy. Am J Nephrol. 2011;33:131-8.

Meyers R, Maibach R, Hiyama E, Haberle B, Krailo M, et al. Risk-stratified staging in paediatric hepatoblastoma: a unified analysis from the Children's Hepatic tumors International Collaboration. Lancet Oncol 2017;18(1):122-131.

Mohan, D., Balasubramanian, E.D., Ravindran, S., et al. Renal mitochondria can withstand hypoxic/ischemic injury secondary to renal failure in uremic rats pretreated with sodium thiosulfate. Indian J. Pharmacol. 2017;49(4):317-321.

Muldoon, L.L., Pagel, M.A., Kroll, R.A., et al. Delayed administration of sodium thiosulfate in animal models reduces platinum ototoxicity without reduction of antitumor activity. Clin. Cancer Res. 2000;6(1):309-15.

Nagai, N., Hotta, K., Yamamura, H., et al. Effects of sodium thiosulfate on the pharmacokinetics of unchanged cisplatin and on the distribution of platinum species in rat kidney: protective mechanism against cisplatin nephrotoxicity. Cancer Chemother. Pharmacol. 1995;36:404-410.

Neuwelt EA, Brummett RE, Doolittle ND, Muldoon LL, Kroll RA, Pagel MA, et al. First evidence of otoprotection against carboplatin-induced hearing loss with a two-compartment

system in patients with central nervous system malignancy using sodium thiosulfate. J Pharmacol Exp Ther. 1998;286(1):77-84.

Neuwelt, E.A., Brummett, R.E., Remsen, L.G., et al. In vitro and animal studies of sodium thiosulfate as a potential chemoprotectant against carboplatin-induced ototoxicity. Canc. Res. 1996;56(40):706-709.

Neuwelt EA, Gilmer-Knight K, Lacy C, Nicholson HS, Kraemer DF, Doolittle ND, et al. Toxicity profile of delayed high dose sodium thiosulfate in children treated with carboplatin in conjunction with blood-brain-barrier disruption. Pediatr Blood Cancer. 2006;47(2):174-82.

Neuwelt, E.A., Pagel, M.A., Kraemer, D.F., et al. Bone marrow chemoprotection without compromise of chemotherapy efficacy in a rat brain tumor model. J. Pharmacol. Exp. Ther. 2004;309(2):594-599.

Newman, EV, Gilman A, Philips FS. The renal clearance of thiosulfate in man. Bulletin of the John Hopkins Hospital. 1946;79:229-242.

Ohe, T., Tsuda, S., Sakata, Y., et al. Cis-diamminedichloroplatinum(II)-induced sister-chromatid exchanges and chromosome aberration formation in cultured human lymphocytes and their inhibition by sodium thiosulfate. Mutat. Res. 1990;244(4):279-285.

Otto, W.C., Brown, R.D., Gage-White, L., et al. Effects of cisplatin and thiosulfate upon auditory brainstem responses of guinea pigs. Hearing Research. 1988;35:79-86.

Park KR. The utility of acoustic reflex thresholds and other conventional audiologic tests for monitoring cisplatin ototoxicity in the pediatric population. Ear and Hear. 1996;17(2):107-15.

Pasch, A., Schaffner, T., Huynh-Do, U. et al., Sodium thiosulfate prevents vascular calcifications in uremic rats. Kidney International. 2008:74, 1444–1453.

Peters AM, Snelling HL, Glass DM, Bird NJ. Estimation of lean body mass in children. Br J Anaesth. 2011 May;106(5):719-23.

Poore, G.A., Todd, G.C., and Grindey, G.B. Effect of sodium thiosulfate (S2O3) on intravenous cisplatin (cisplatin) toxicity and antitumor activity [abstract]. Proceedings of the Am. Assoc. Cancer Res. 1984;25:370.

Prival, M.J., Simmon, V.F. and Mortelmans, K.E. Bacterial mutagenicity testing of 49 food ingredients gives very few positive results. Mutat. Res. 1991;260(4):321-329.

Punnett A, Bliss B, Dupuis LL, Abdolell M, Doyle J, Sung L. Ototoxicity following pediatric hematopoietic stem cell transplantation: a prospective cohort study. Pediatr Blood Cancer. 2004;42(7):598-603.

Ravi, R., Somani, S.M., Rybak, L.P. Mechanism of cisplatin ototoxicity: antioxidant system. Pharmacol. Toxicol. 1995;76(6):386-394.

Registry of Toxic Effects of Chemical Substances (RTECS). Database on thiosulfuric acid, disodium salt. 2011;MDL Information Services.

Ross CJ, Katzov-Eckert H, Dube MP, Brooks B, Rassekh SR, Barhdadi A, et al. Genetic variants in TPMT and COMT are associated with hearing loss in children receiving cisplatin chemotherapy. Nat Genet. 2009;41(12):1345-9.

Rybak, L.P., Husain, K., Morris, C. et al. Effect of protective agents against cisplatin ototoxicity. Am. J. Otol. 2000;21(4):513-520.

Ryback LP and Somani S. Ototoxicity. Amelioration by protective agents. Ann NY Acad Sci. 1999;884:143-51.

Rybak, L.P., Whitworth, C.A., Mukherjea, D., et al. Mechanisms of cisplatin-induced ototoxicity and prevention. Hearing Research. 2007;226:157-167.

Ryback LP, Whitworth C, Somani S. Application of antioxidants and other agents to prevent cisplatin ototoxicity. Laryngoscope. 1999;109(11):1740-4.

Saito, T., Zhang, Z.J., Manabe, Y., et al. The effect of sodium thiosulfate on ototoxicity and pharmacokinetics after cisplatin treatment in guinea pigs. Eur. Arch. Otorhinolaryngol. 1997;254:281-286.

Sheth, S., Mukherjea, D., Rybak, L.P., et al. Mechanisms of Cisplatin-Induced Ototoxicity and Otoprotection. Front. Cell. Neurosci. 2017;11:338.

Skinner R, Pearson ADJ, Amineddine HA, Mathias DB, Craft AW. Ototoxicity of cisplatinum in children and adolescents. Br J Cancer. 1990;61:927-31.

Sooriyaarachchi, M., Gailer, J., Dolgova, N.V., et al. Chemical basis for the detoxification of cisplatin-derived hydrolysis products by sodium thiosulfate. J. Inorg. Biochem. 2016;162:96-101.

Stocks, R.M.S., Gould, H.J., Bush, A.J., et al. Ototoxic protection of sodium thiosulfate: daily vs constant infusion. Otolaryngology - Head and Neck Surgery. 2004;13(1):115-119.

Szczepkowski TW, Skarzynski B, Weber M. The metabolic state of thiosulphate. Nature. 1961;189:1007-8.

Taniguchi, S. and Baba, T. "Two route chemotherapy" using cis-diamminedichloroplatinum (II) and its antidote, sodium thiosulfate, for peritoneally disseminated cancer in rats. Gann. 1982;73(3):475-479.

Tod M, Lokiec F, Bidault R, De Bony F, Petitjean O, Aujard Y, et al. Pharmacokinetics of oral acyclovir in neonates and infants: a population analysis. Antimicrob Agents Chemother. 2001;45(1):150-7.

Uozumi, J., Ishizawa, M., Iwamoto, Y., et al. Sodium thiosulfate inhibits cis-diamminedichloroplatinum (II) activity. Cancer Chemother. Pharmacol. 1984;13:82-85.

Wang, J., Lloyd Faulconbridge, R.V., Fetoni, A., et al. Local application of sodium thiosulfate prevents cisplatin-induced hearing loss in the guinea pig. Neuropharmacology. 2003;45:380-393.

Whelan K, Stratton K, Kawashima T, Leisenring W, Hayashi S, Waterbor J, et al. Auditory complications in childhood cancer survivors: a report from the childhood cancer survivor study. Pediatr Blood Cancer. 2011;57(1):126-34.

Wile, A.G., Dileo, S.K., Gossett, D.A., et al. Intraperitoneal cisplatin with sodium thiosulfate protection in rats with intestinal anastomoses. Journal of Surgical Oncology. 1993;52:265-268.

Wimmer, C., Mees, K., Stumpf, P., et al. Round window application of D-methionine, sodium thiosulfate, brain-derived neurotrophic factor, and fibroblast growth factor 2 in cisplatin-induced ototoxicity. Otology & Neurotology. 2004;25(1):33-40.

Yancey A, Harris MS, Egbelakin A, Gilbert J, Pisoni DB, Renbarger. Risk factors for cisplatin-associated ototoxicity in pediatric oncology patients. Pediatr Blood Cancer. 2012;59(1):144-8.

The FDA's References:

10OECD Screening Information Data Set (SIDS) for 2,6-Di-tert-Butyl-p-Cresol (Processed by UNEP Chemicals). 2005. http://www.inchem.org/documents/sids/sids/128370.pdf

Lee, M., McGeer, EG., and McGeer, PL., Sodium thiosulfate attenuates glial-mediated neuroinflammation in degenerative neurological diseases. J Neuroinflammation 2016 13:32 DOI 10.1186/s12974-016-0488-8

Sen, U., Vacek, TP., Hughes, WM., et al. Cardioprotective Role of Sodium Thiosulfate on Chronic Heart Failure by Modulating Endogenous H2S Generation. Pharmacology 2008;82(3):201-213

Willhite, CC., Developmental Toxicology of Acetonitrile in the Syrian Golden Hamster. Teratology 1983; 27(3):313-325

Zdravkovic SA., Assessment of Patient Exposure to Leachables From Lyophilized Drug

Formulations Following Reconstitution, Storage, and Administration via Polymeric Packaging/Delivery Systems. *J Pharm Sci*. 2018;107(11):2837-2846.

20.2 FINANCIAL DISCLOSURE

The Applicant's Position:

Fennec provided financial disclosure for all clinical investigators involved in the studies included in this submission in Form 3455. No concerns were raised regarding the overall integrity of the data.

The FDA's Assessment:

Table completed by FDA. FDA did not identify and issues regarding financial disclosure.

Covered Clinical Study (Name and/or Number):SIOPEL 6 and ACCL0431

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 170		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____		

Significant equity interest held by investigator in study: _____ Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

*The table above should be filled by the Applicant, and confirmed/edited by the FDA.

20.3 NONCLINICAL PHARMACOLOGY/TOXICOLOGY

This is reserved for data that could not fit under PT section (Section 5), e.g. carci data. Limit to 2 pages

The Applicant's Position:
None.

The FDA's Assessment:
n/a

20.4 OCP APPENDICES (TECHNICAL DOCUMENTS SUPPORTING OCP RECOMMENDATIONS)

The FDA's Assessment:

20.4.1 Population Pharmacokinetic Analyses

The goal of population PK analysis (popPK) was to develop a population pharmacokinetic (PK) model to assess sources of variability (intrinsic and extrinsic covariates) of sodium thiosulfate in patients.

Two studies (International Childhood Liver Tumor Strategy Group [SIOPEL] 6 and Children's Oncology Group [COG] ACCL0431) were conducted to demonstrate the efficacy and safety of STS in pediatric patients treated with CIS. No PK analysis was performed for either study.

Sodium thiosulfate plasma data has been made available to the Applicant by authors from other academic studies investigating STS administration to prevent ototoxicity in brain cancer patients (Neuwelt et al, 1998; Doolittle et al, 2001; Neuwelt et al, 2006).

The data was obtained in 5 pediatric patients and 11 adult patients with malignant brain tumors (aged 2.5 to 69 years), who received IV administration by a 15-minute infusion, the same duration of infusion as used in SIOPEL 6 and COG ACCL0431. The population PK model for sodium thiosulfate was built based on PK data from these 16 patients. The baselines covariates for 16 patients were provided in Table 49.

Table 49: Covariate Distribution for 16 Patients Included in the PopPK Analysis

Covariate	Unit	N	Min	Perc5	Q1	Median	Mean	Q3	Perc95	Max	SD
AGE	years	16	2.50	8.43	15.2	32.5	34.8	52.5	67.5	69.0	21.7
BSA	m^2	16	0.560	1.04	1.53	1.71	1.64	1.84	2.08	2.19	0.390
HT	cm	16	93.0	128	162	170	161	170	170	170	20.0
LBM	kg	16	11.2	29.1	43.0	49.1	46.5	53.1	57.9	61.3	11.9
WT	kg	16	12.7	34.4	53.5	64.5	61.4	71.2	81.5	89.0	18.1

Source: Applicant's PopPK report, Table 2, Page 25

The popPK analysis was conducted by the sponsor and evaluated by the reviewer. The PK of sodium thiosulfate was characterized by a two-compartment model with endogenous

thiosulfate (TS) production rate. Drug clearance (CL) was modeled as the sum of the renal (CLR) and non-renal clearance (CLNR). The population CLR was fixed to the value found in literature, and the individual CLR was modeled as a function of body surface area and a maturation factor:

$$\text{MFCLR} = \frac{(12*(AGE+0.75))^{6.17}}{(12*(AGE+0.75))^{6.17}+13.4^{6.17}}$$

The CLNR was estimated independently of body size. The central (VC) and peripheral (VP) volume were modeled in function of the individual lean body mass. Residual variability was modeled proportionally and inter-individual variability (IIV) was not included on any of the model parameters.

FDA has made several modifications in its independent analysis:

> Applicant fixed the typical renal clearance at 1.36 mL/min/kg in the model according to the Farese et al. 2011. But this estimate was based on the data obtained in healthy volunteers instead of patients with malignant brain tumors. The typical renal clearance was estimated in FDA's independent analysis.
> The IIV for central volume of distribution was estimated.
> The residual error model was described by a proportional and additive error model.

Improvement in fit was observed with a decrease of -25.055 in objective function value (OFV). Parameter estimates of final model were provided in Table 50. No signs of model misspecification were identified in the goodness-of-fit plots (Figure 18). Prediction-corrected visual predictive check showed that the final model adequately described the observed PK profile of sodium thiosulfate (Figure 19).

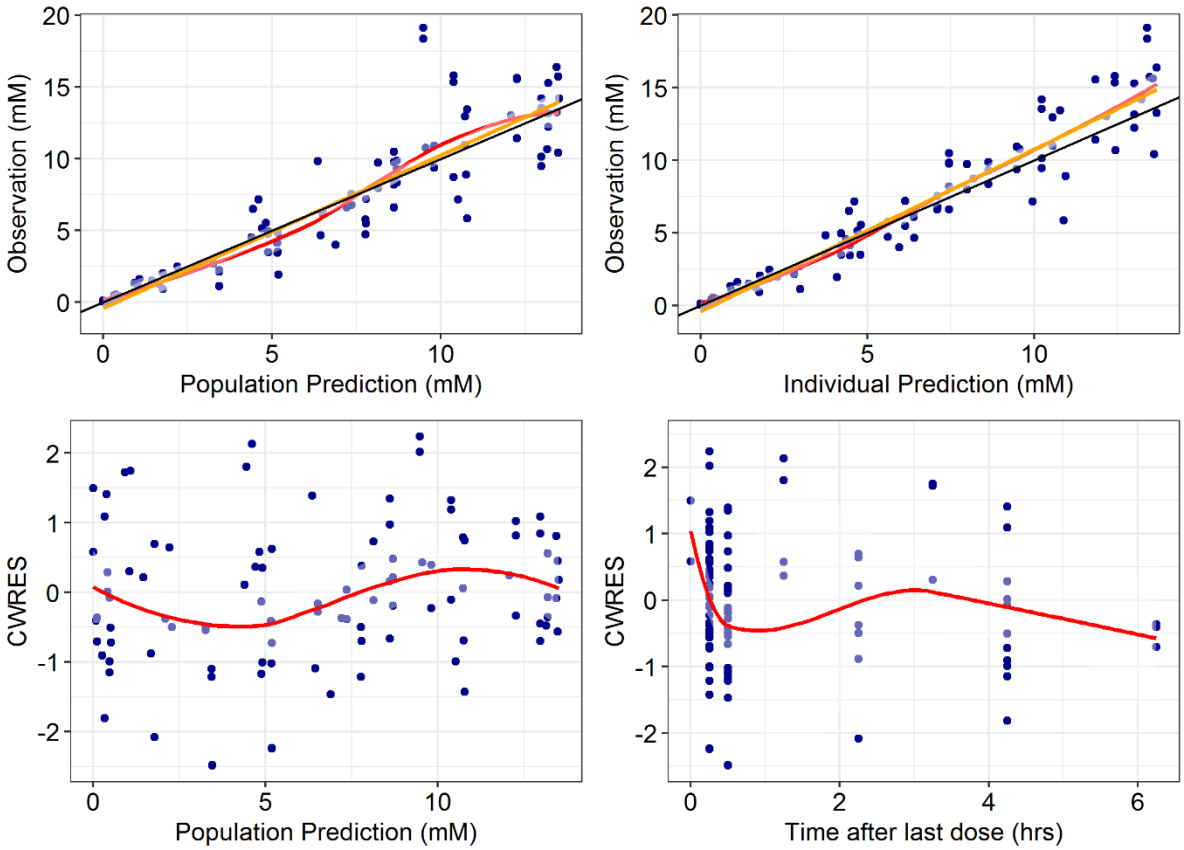
Table 50: Parameter Estimates of the Final PopPK Model for Sodium thiosulfate

Parameter	Estimate	SE	CV (%)
NRCL (L/h)	2.32	1.95	84.1

RCL (L/h)	6.98	1.84	26.4
VC (L/kg_LBM)	0.142	0.0205	14.4
Q (L/h)	31.9	14.7	46.1
VP (L/kg_LBM)	0.0882	0.026	29.5
KIN (mol/hr)	12.1	2.64	21.8
IIV-VC	29.8%		36.3
Prop Error	0.0664		33.3
Add Error	0.0074		48.4

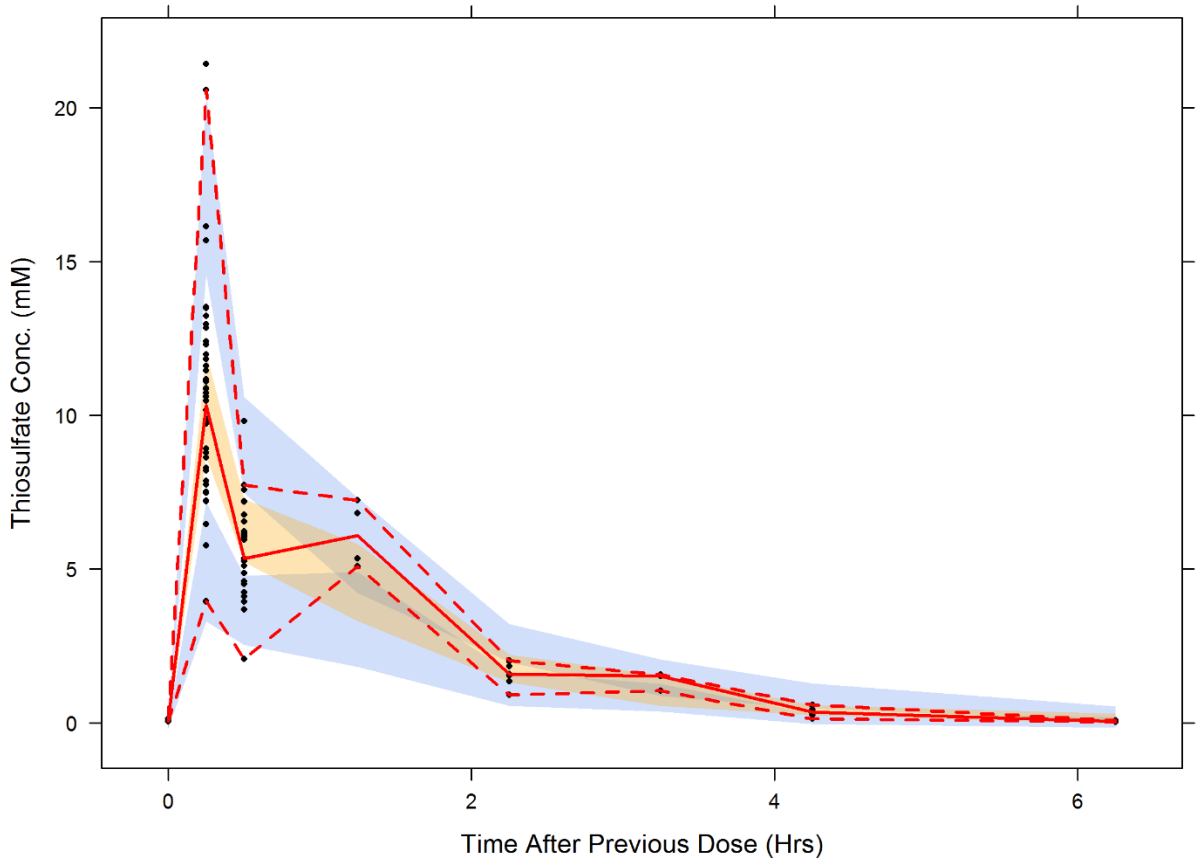
Source: Reviewer's analysis based on data "NM.STS.v2.csv"

Figure 18: Goodness of Fit Plots of the Final Model for Sodium thiosulfate



Source: Reviewer's analysis based on data "NM.STS.v2.csv"

Figure 19: Visual Predictive Checks of Sodium thiosulfate Concentration-Time Data.



Source: Reviewer's analysis based on data "NM.STS.v2.csv"

The developed thiosulfate PK model was used to perform simulations of the expected concentration following a 15 minute i.v. infusion of STS in the pediatric population with subjects ranging from 2 months to 18 years. The Applicant states that the Cmax correlates with efficacy as previous studies showed that a 15-minute infusion of STS was effective, while longer slow STS infusions did not reach sufficiently high concentrations to be effective.

FDA acknowledges that the current model has its limitation in predicting the exposure with proposed dosing regimen in young pediatric patients as the developed model is based on a limited dataset of five pediatric subjects and eleven adults. Although the model fits the observed data well, the model fails to demonstrate its ability to describe the PK data in pediatric patients at a younger age. Because of these uncertainties, sensitivity analysis was also conducted to test the robustness of the model simulation when the non-renal clearance is related to the body size or when it also follows the maturation function. The CL function for final model and 2 sensitivity analyses were described in the following equation:

$CL_{finalmodel}$ = CLNR + CLR = 2.32 + 6.98 * (BSA/1.73) * MFCLR

CL_{sen1} = CLNR + CLR = 5.35*(BSA/1.73) + 3.93* (BSA/1.73) * MFCLR

CL_{sen2} = CLNR + CLR = 9.27* (BSA/1.73) * MFCLR

The relationship between Cmax and weight based on the final model and 2 sensitivity analyses were illustrated in the Figure 20 and Table 51. Based on the simulation results, at the recommended dosage, the geometric mean (±SD) maximum concentration (Cmax) was 13 ± 1.2 mM in pediatric patients with cancer. The predicted Cmax in patients weighing 5 to 10kg is comparable to the predicted Cmax in patients weighing larger than 10kg (9.5% lower to 3% higher); the predicted Cmax in patients weighing less than 5kg is between 16% and 36% lower than the predicted Cmax in patients weighing larger than 10kg.

In addition, since sodium thiosulfate majorly distributes in the extracellular fluid, it is reasonable to predict its exposure in pediatric patients based on body size. The BSA-based dosing in patients lower than 5kg is half the dose of patients larger than 10 kg.

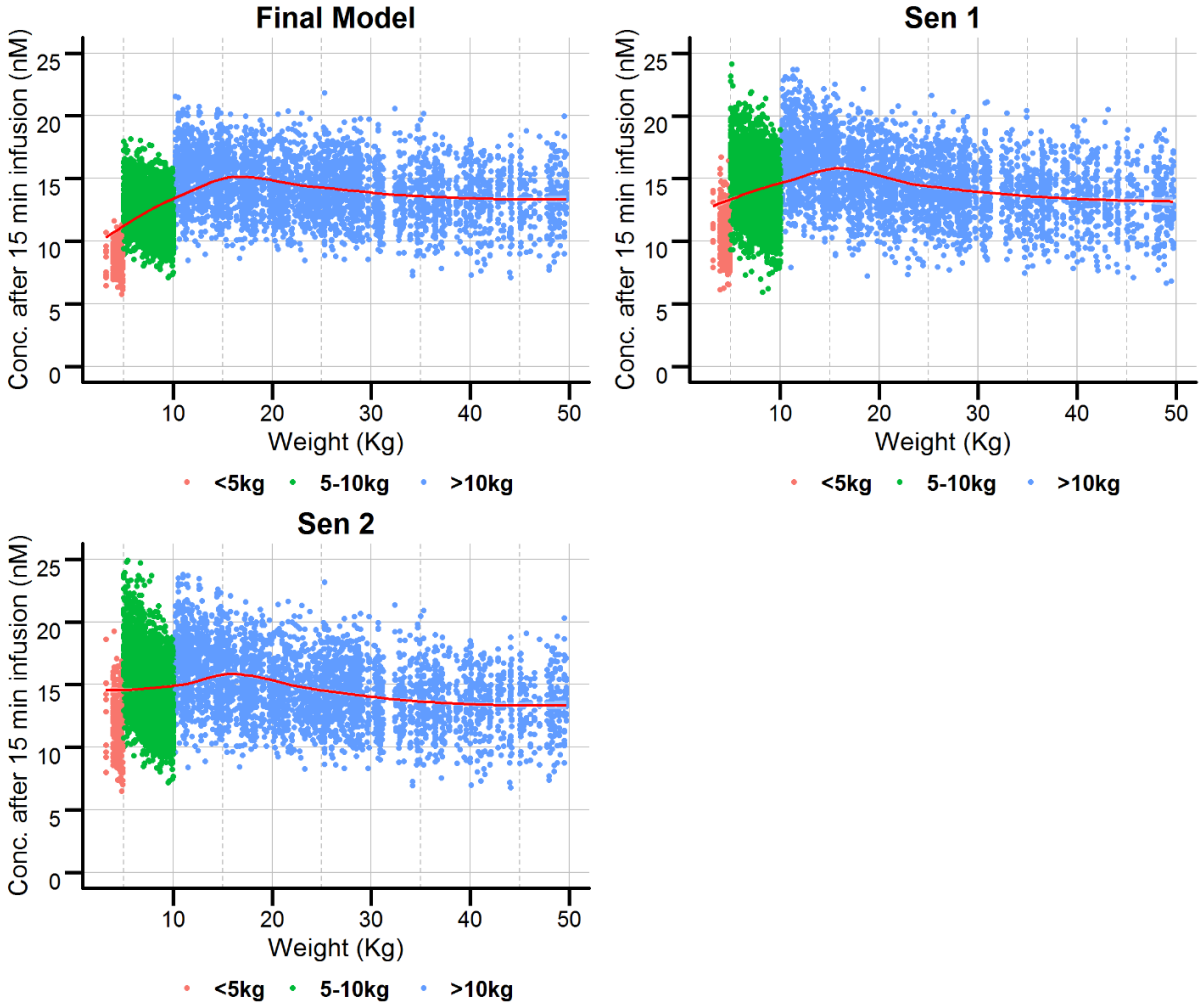
In summary, both the poppk model prediction and drug distribution characteristics support the proposed dosing regimen in the 3 weight categories.

Table 51: Cmax Prediction by Weight Categories in Pediatric Patients for the Proposed Dosing Regimen Based on the Final Model and 2 Sensitivity Analyses.

Weight Category	Exposure	Geo.Mean	2.5th Percentile	97.5th Percentile	Model
<5kg	Cmax	8.8	6.8	10.8	Final Model
5-10kg	Cmax	12.4	9.2	15.8	Final Model
>10kg	Cmax	13.7	9.2	18.6	Final Model
<5kg	Cmax	10.6	7.5	14.5	Sen 1
5-10kg	Cmax	13.8	9.5	19.2	Sen 1
>10kg	Cmax	13.9	9	19.8	Sen 1
<5kg	Cmax	11.8	8	16.3	Sen 2
5-10kg	Cmax	14.4	9.8	20.8	Sen 2
>10kg	Cmax	14	9	19.9	Sen 2

Source: Reviewer's analysis based on data "NM.STS.v2.csv"

Figure 20: Cmax Prediction versus Body Weight in Pediatric Patients for the Proposed Dosing Regimen based on the Final Model and 2 Sensitivity Analyses.



Source: Reviewer's analysis based on data "NM.STS.v2.csv"

20.4.2 Dose-Response Analyses

In Trial SIOPEL6, there were 31 pediatric patients with weight between 5 to 10 kg and 25 patients with weight higher than 10kg. Efficacy and safety results between these 2 weight groups were compared. For efficacy, the proportion of children with hearing loss was similar in the 5-10kg group compared to >10kg group, as shown in Table 52. Event free survival and

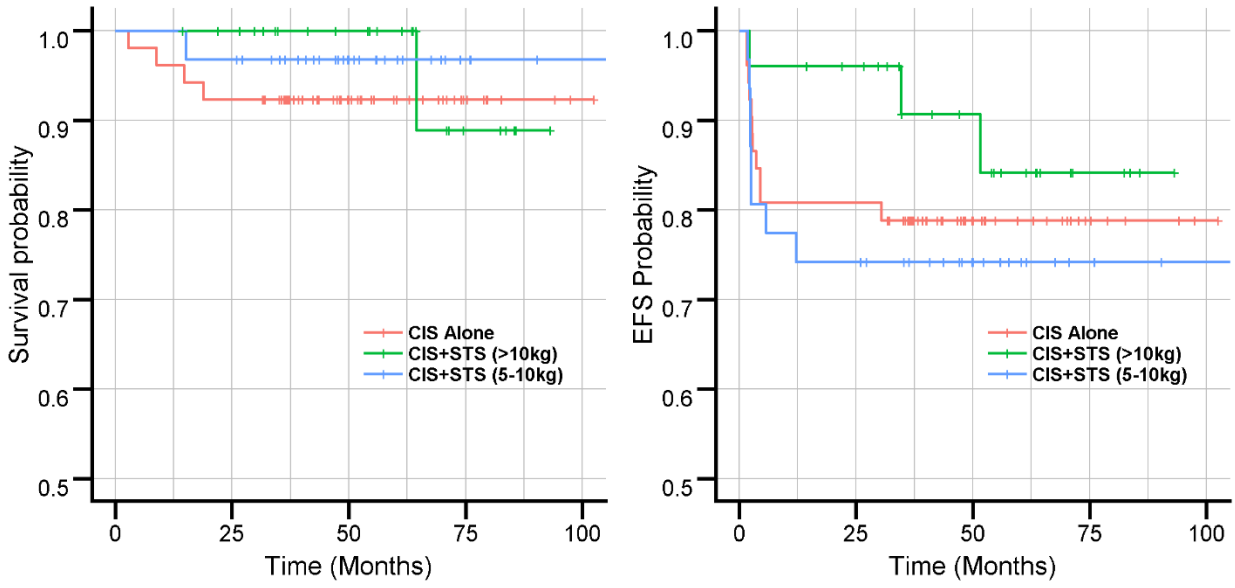
overall survival, presented in Figure 21, were also similar between these 2 weight groups and the control.

Table 52: Comparison of Hearing Loss by Weight Category in Trial SIOPEL6.

Results	CIS Alone	CIS+SIS (5-10kg)	CIS+SOS (>10kg)
Hearing Loss, n			
N (Total)	52	31	25
Yes, n (%)	35 (67.3%)	10 (32.3%)	10 (40%)
No, n (%)	17 (32.7%)	21 (67.7%)	15 (60%)

Source: Reviewer's analysis based on data "adeff.csv"

Figure 21: Comparison of Overall Survival and Even-free Survival between Weight Categories in Trial SIOPEL6.



Source: Reviewer's analysis based on data "adeff.csv"

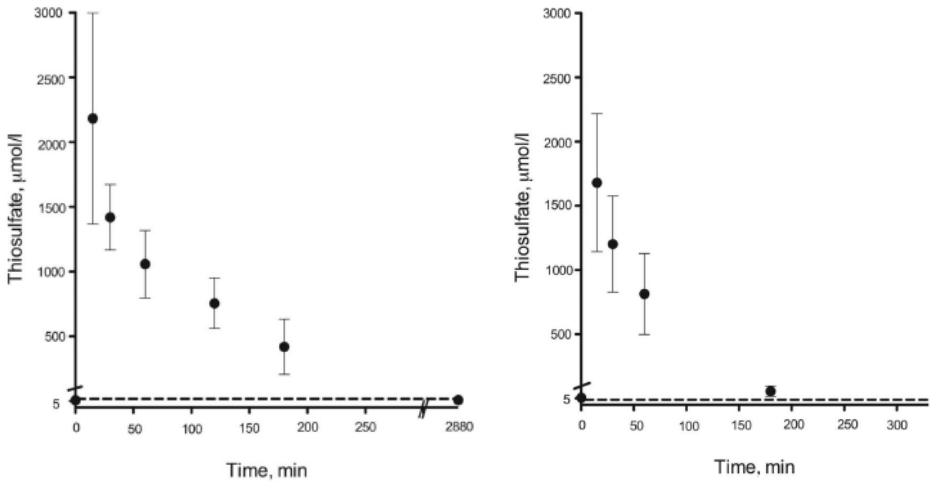
For safety, the overall incidence of AEs of all grades, SAEs, and deaths were similar between 5-10 kg and >10 kg weight groups. The efficacy and safety results from trial SIOPEL6 support the proposed dose in patients with weight between 5-10 kg and >10 kg. Only 1 patient with weight lower than 5kg received treatment in study SIOPEL 6, she did not experience hearing loss and was alive at the end of treatment. The limited number of subjects in category weight <5kg does not makes the comparison of efficacy and safety profile with other weight categories interpretable.

Exposure-response relationships for efficacy and safety were not reviewed in this submission since no PK analysis was performed for the confirmatory phase 3 trials SIOPEL6 or ACCL0431. Previous literature suggested STS dose response relation is fairly steep where dose levels of 5-8 g/m^2 STS anhydrous appeared not effective.

20.4.3 Clinical PK in hemodialysis patients

A literature study (Farese et al, 2011) provided clinical PK results of thiosulfate in 9 healthy volunteers with (GFR > 70 ml/min/1.72 m^2 according to the Modification of Diet in Renal Disease (MDRD))formula) and in 10 hemodialysis patients (GFR 0 to 6 ml/min/1.72 m^2, MDRD). The dose in the study was 8 g sodium thiosulfate IV infusion over 8 minutes.
Nonrenal clearance was similar in volunteers (2.25 ± 0.32 ml/min/kg) comparing to hemodialysis patients off-hemodialysis (2.04 ± 0.72 ml/min/kg). Hemodialysis patients in this study has very limited or no renal clearance. In healthy volunteers, renal clearance (1.86 ± 0.45 ml/min/kg) is comparable with the nonrenal clearance. Thiosulfate Cmax increased approximately 25% and AUC increased approximately 2-fold in hemodialysis patients off-hemodialysis (Figure 22 and Table 53). Thiosulfate Cmax in pediatric patients with renal impairments, including hemodialysis patients, is expected to lower than the Cmax of thiosulfate (IV injection equivalence of STS anhydrous 6.4 g/m2 in children) indicated for acute cyanide poisoning.

Figure 22. Thiosulfate plasma concentration (mean ± SD) versus time in (a) dialysis patients off-hemodialysis and (b) healthy volunteers
b)



Source: Figure 1a of Summary of Clinical Pharmacology Studies (Section 2.7.2) and Figure 2 of Farese et al, 2011

Table 53. PK parameter in hemodialysis patients and healthy volunteers

- Hemodialysis patients off-hemodialysis

Patient (ID)	Off-Hemodialysis $AUC_{0-\infty}$ (μmol·min/L)	Off-Hemodialysis Total Body Clearance (ml/min per kg body wt)
(b) (6)	261,753	1.34
	336,691	1.11
	197,000	2.39
	156,360	2.56
	253,618	2.28
	212,027	3.17
	154,521	2.47
	163,867	2.33
	338,150	0.92
	236,159	1.85
	231,015 ± 67,969	2.04 ± 0.72

- Healthy Volunteers

HV (ID)	Age (yr)	Gender (f/m)	Body Weight (kg)	$AUC_{0-\infty}$ (μmol·min/L)	24-Hour Urinary TS Excretion after iv STS (μmol/24 h)	Total Body Clearance (ml/min per kg body wt)	Renal Clearance (ml/min per kg body wt)	Nonrenal Clearance (ml/min per kg body wt)
(b) (6)	64	m	74	10,5573	12,620	4.13	2.08	2.05
	39	m	66	85,901	13,760	5.60	2.41	3.2
	57	f	65	133,773	15,670	3.71	1.82	1.9
	48	f	80	81,953	14,840	4.92	2.28	2.64
	63	f	78	98,145	14,910	4.21	1.99	2.22
	60	f	74	109,293	14,260	3.99	1.82	2.17
	45	f	56	144,313	15,310	3.99	1.99	2
	54	f	69	136,553	13,850	3.42	1.48	1.94
	59	f	53	202,486	9600	3.00	0.91	2.06
	57 (39 to 64)	7/2	68 ± 9.4	121,999 ± 37473	13,869 ± 1847	4.11 ± 0.77	1.86 ± 0.45	2.25 ± 0.42

Source: Table 2 and 3 of Farese et al, 2011

20.4.4 Serum Sodium Level

(b) (4)

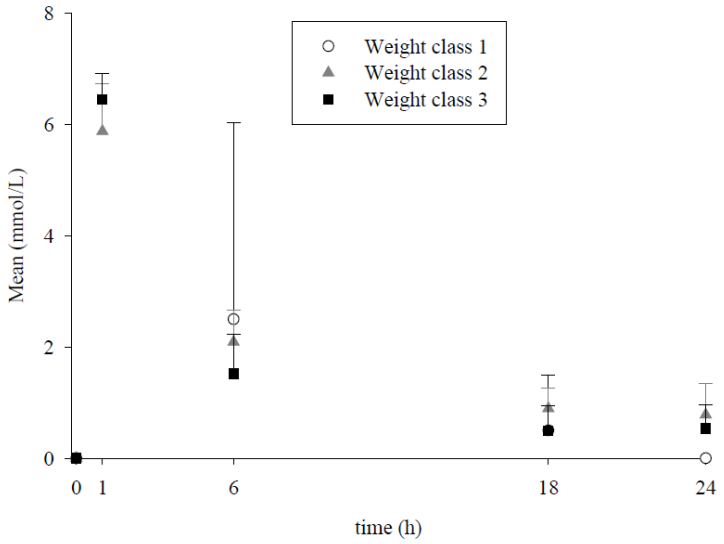
In SIOPEL 6, dose of sodium thiosulfate at the recommended dosage resulted in an average transient increase in serum sodium levels approximately 5 to 7.5 mmol/L (Table 39). Maximum increase was generally observed at 1 h after infusion and levels had returned to baseline by 18 h or 24 h after administration (Figure 17). Analysis of maximum increase in sodium (ΔCmax) versus weight did not reveal trends (Figure 18).

Table 54. Study SIOPEL 6 maximum increase in serum sodium levels (ΔCmax) from baseline after STS infusion

	ΔCmax (sodium) Cycle Mean ± SEM (n) (mM)		
Body weight	**BW ≥ 10.0 kg**	**10 kg > BW > 5 kg**	**BW < 5 kg**
STS dose (nominal)	**20 g/m²**	**15 g/m²**	**10 g/m²**
Cycle 1	6.50 ± 1.17 (16)	6.07 ± 0.67 (30)	5.0 (n=1)
Cycle 2	7.53 ± 0.73 (17)	6.29 ± 0.58 (31)	-
Cycle 3	6.61 ± 0.71 (18)	6.18 ± 0.49 (28)	2.0 (n=1)
Cycle 4	6.07 ± 0.64 (15)	5.52 ± 0.57 (27)	-
Cycle 5	6.64 ± 1.15 (14)	6.62 ± 0.70 (21)	-
Cycle 6	5.69 ± 0.97 (16)	5.07 ± 0.75 (15)	-

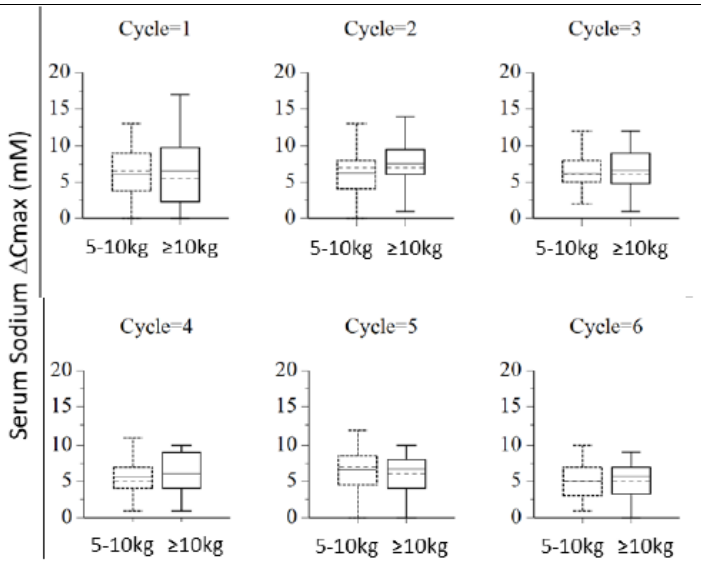
Source: Table 7 of Summary of Clinical Pharmacology Studies (Section 2.7.2)

Figure 23. Mean +SD serum sodium concentrations (mM) above baseline over cycles after STS infusion to children for weight classes 1 (BW<5 kg), 2 (BW 5 to 10 kg) and 3 (BW > 10 kg)



Source: Figure 9.4.4. of Sodium Pharmacokinetic Report Study: 2018-0146

Figure 24. Maximum increase in serum sodium levels (ΔCmax) above baseline throughout cycles after STS infusion to children for weight 2 (BW 5 to 10 kg) and 3 (BW > 10 kg)



The box represents the interquartile range. Within the box the mean is depicted by a solid line and the median by a striped line. The whiskers represent the minimum and maximum values within 1.5x the interquartile range of the box limits. Number of observations are given in Table 39

Source: Table 9 of Summary of Clinical Pharmacology Studies (Section 2.7.2)

20.5 ADDITIONAL SAFETY ANALYSES CONDUCTED BY FDA

The FDA's Assessment:

n/a

20.6 PHARMACOLOGY TOXICOLOGY ASSESSMENT OF BORIC ACID

On March 23, 2022, Fennec Pharmaceuticals Inc (Fennec) submitted a Class 2 Resubmission for NDA 212937 to address a Complete Response based on inspection and manufacturing deficiencies, and clinical concerns of hypophosphatemia and hyponatremia, issued on November 26, 2021. NDA 212937 is submitted under the 505(b)(2) pathway for sodium thiosulfate (STS; Pedmark) for intravenous use for the prevention of cisplatin-mediated ototoxicity in patients 1 month of age or older with localized, non-metastatic, solid tumors. STS

is an inorganic salt with reducing agent properties that is currently approved as an antidote used sequentially with sodium nitrite for acute cyanide poisoning under the name Nithiodote. The nonclinical review of NDA 212937 was completed and added to the Assessment Aid by Dr. G. Sachia Khasar and Dr. Whitney Helms and uploaded to DARRTS on August 20, 2020. There were no outstanding issues, from a nonclinical perspective, that would have prevented approval of NDA 212937 at that time. No new nonclinical studies were included with the current resubmission; however, Fennec proposed a statement of non-substitutability in the label so that Pedmark cannot be substituted with other sodium thiosulfate products, such as Nithiodote. In general, a difference in concentration or indication does not support adding a non-substitutability statement in absence of a specific safety concern. Thus, the Clinical Team consulted with the Nonclinical Team to discuss whether the Applicant could include a non-substitutability statement in their label based on a safety concern.

Nithiodote consists of a sodium nitrite injection, followed by a sodium thiosulfate injection. The Nonclinical Team determined that the Applicant's proposed non-substitutability statement is appropriate based on the safety concern that Nithiodote contains a box warning for sodium nitrite, which can cause hypotension and methemoglobin formation leading to serious adverse reactions and death. Additionally, Fennec's product, Pedmark, contains the excipient boric acid (0.25 mg/mL), while Nithiodote contains boric acid (2.8 mg/mL, undiluted product) and potassium chloride (4.4 mg/mL, undiluted product). The potential levels of administered boric acid and potassium chloride would be higher if using Nithiodote instead of Pedmark. See Tables 55 and 56, for levels of boric acid and potassium chloride (KCL) based on the proposed recommended dose by Fennec and the indicated assumptions (weight, body surface area [BSA]) using either Pedmark (Table 55) and Nithiodote undiluted or diluted 1:1 (Table 56). In particular, Table 56 shows levels of STS and excipients based on potential dosing errors with Nithiodote.

Table 55: Administered doses of Pedmark with associated boric acid levels

Proposed Recommended Dose		Assumptions			Pedmark (125 mg/mL)		Pedmark Excipients
Weight	Pedmark dose	Test weight	Test height	Test m^2	mg[a]	mL	Boric acid (0.25 mg/mL)
< 5 kg	10 g/m^2	2 kg	2.69 ft	0.25	2500 mg	20 mL	5 mg

5 – 10 kg	15 g/m^2	8 kg	5.4 ft	0.4	6000 mg	48 mL	12 mg
>10 kg	20 g/m^2	25 kg	4 ft 10 in	1	20,000 mg	160 mL	40 mg

a: Pedmark dose x Test m^2

Table 56: Potential medical errors: Administered doses of diluted or undiluted Nithiodote, STS with associated boric acid and KCL levels, plus estimated levels of Nithiodote product if using Pedmark dosing

Nithiodote (undiluted/*1:1 diluted*), STS (250 mg/mL/ *125 mg/mL*)[a]			Nithiodote, STS Excipients		Levels of Nithiodote (undiluted/*1:1 diluted*), STS (250 mg/mL/ *125 mg/mL*) and excipients using proposed Pedmark doses[b]		
Recommended Dose	Mg[c]	mL	Boric acid (2.5 mg/mL/ *1.4 mg/mL*)	KCL (4.4 mg/mL/ *2.2 mg/mL*)	STS in mL (250 mg/mL/ *125 mg/mL*)	Boric acid	KCL
10 g/m²	2500 mg	10 mL/ *20 mL*	25 mg/ *28 mg*	44 mg/ *44 mg*	10 mL/ *20 mL*	25 mg/ *28 mg*	44 mg/ *44 mg*
10 g/m²	4000 mg	16 mL/ *32 mL*	40 mg/ *44.8 mg*	70 mg/ *70 mg*	24 mL/ *48 mL*	60 mg/ *67 mg*	105 mg/ *105 mg*
10 g/m²	10000 mg	40 mL/ *80 mL*	100 mg/ *112 mg*	176 mg/ *176 mg*	80 mL/ *160 mL*	200 mg/ *224 mg*	352 mg/ *352 mg*

a: levels for diluted Nithiodote are shown in italics; b: Pedmark dose used, as indicated in Table 55; c: Nithiodote dose x Test m² from Table 55

The permitted daily exposure (PDE) for boron compounds, including boric acid, differs widely depending on non-US regulatory agencies (e.g., World Health Organization, European Medicines Agency) or US agencies (e.g., Environmental Protection Agency, Agency for Toxic Substances and Disease Registry [ATSDR]), ranging from 1 to 20 mg per day. Thus, levels of ≥ 100 mg/day based on potential dosing errors are not supported by the available data of acceptable intake levels. Additionally, Nithiodote treatment is expected to occur only if there is clinical suspicion of cyanide poisoning (consisting of one full dose and one-half the original dose if re-dosing is needed), in comparison the administration of Pedmark for the prevention of cisplatin-mediated ototoxicity will be in conjunction with cisplatin chemotherapy cycles, which can range from 6 and up to 30 administrations.

In summary, we agree with including a non-substitutability statement given the safety risks that could be associated with medication errors if other STS products are used, such as high levels of boric acid or inadvertently using sodium nitrite.

Based on calculations in Table 55, pediatric patients >10 kg administered Pedmark will receive 40 mg/day of boric acid, which is normally higher than acceptable intake levels. The Applicant was asked to provide a justification or toxicology risk assessment for this level of boric acid administered by the intravenous route. On August 24, 2022, the Applicant submitted their justification and safety assessment of boric acid. Briefly, as shown in Table 57, considering a PDE of 10 mg for adults, the Applicant determined that the exposures of boric acid as elemental boron equivalent for pediatric patients with a body weight of >10 kg and a recommended dose of 20 mg/m^2 is 1.2x or 20% higher than adjusted PDEs in children (2.9 to 9.8 mg of boron). The conversion of mg boric acid to mg boron was calculated by multiplying the ratio of the formula weight of boron to the molecular weight of boric acid, 10.81/61.84 = 0.1748.

Table 57: Exposure of boric acid in children administered Pedmark

Age	STS Dose (pentahydrate) (g/m^2)	Body Weight[a] (Kg)	Body surface area[a] (BSA in m^2)	Boric Acid Exposure (mg)	Boron (B) Exposure (mg)	PDE for children[b] (mg)	Relative boron exposure-to-PDE in children
< 2 years (1-23mo)	**10**	4.2 4.9	0.26 0.29	5.2 5.8	0.9 1.0	1.5 1.7	0.6 0.6
	15	5.0 10.0	0.30 0.49	9.0 15	1.6 2.6	1.7 2.8	0.9 0.9
	20	10.1 12.0	0.50 0.56	20 22	3.5 3.9	2.9 3.2	1.2 1.2
< 12 years (2-11yr)	**20**	12.0 36.5	0.56 1.2	22 48	3.9 8.4	3.2 6.9	1.2 1.2
< 18 years (12-17yr)	**20**	37.0 67.0	1.2 1.7	48 68	8.4 12	6.9 9.8	1.2 1.2

[a] age, body weight, body surface area relations taken from WHO simplified tables for birth to 5 years (boys and girls median) [ref 10]; Royal College of Paediatric and Child Health 2012 [ref 11a and 11b] and Children's British National Formulary [ref 12]

[b] The PDE of 10mg for adults is adjusted for children using BSA to capture changes volume of distribution and renal excretion) = 10 mg (PDE adult) * (BSA children) / 1.73 m^2. For example, the adult PDE of 10 mg/day boron is adjusted for a child of 1 m^2 by: 10 mg x 1/1.73 = 5.8 mg boron (B)/day.

(Excerpted from Applicant's submission)

To justify the 20% increase of boric acid, the Applicant cited ICH Q3D(R2) that may allow higher levels based on short term or intermittent dosing and indication (e.g., life-threatening, unmet medical needs, rare diseases). Cisplatin is the most common cause of hearing loss in children, which has serious implications on speech, language and social development. Pedmark is intended to prevent hearing loss induced by cisplatin in pediatric patients ≥ 1 month with localized, non-metastatic, solid tumors. Pediatric cancers will include germ cell tumors, hepatoblastomas, medulloblastomas, neuroblastomas and osteosarcomas. Pedmark will be administered as an intravenous infusion after completion of each cisplatin infusion. Depending on the type of cancer, cisplatin is administered once or on multiple consecutive days (up to five times) in monthly intervals. Based on cisplatin's schedule of administration, it is anticipated that Pedmark will be administered a total of 6 and up to 30 administrations over a 4- to 6-month period. Thus, treatment with Pedmark is expected to be short term and intermittent, to a population with an unmet medical need.

There have been extensive toxicology reviews of boron and related compounds conducted by various regulatory agencies discussing risks and effects in humans and animal studies. Intravenous administration of boron to rats resulted in 87.6% elimination in the urine within 2 hours post-dose, suggesting that excretion of boron is rapid and a low accumulation potential[1]. In animal toxicology studies, the most sensitive targets identified are reproductive organs and a developing fetus[2,3,4]. In general, boron limits have been established based on these toxicities. The adult PDE used in Table 57 by the Applicant was determined based on embryo-fetal toxicity in pregnant rats[5], which would not be relevant to a portion of the proposed population for Pedmark as they are not of reproductive age potential; furthermore, patients receiving cisplatin are already exposed to the risk of embryo-fetal toxicity and adverse effects on reproductive organs.

In summary, Pedmark will be given in a limited basis to a select population to address an unmet medical need (prevent cisplatin-mediated hearing loss); additionally, the potential toxicities with Pedmark are no different than those observed with cisplatin. Taken altogether, there were no further pharmacology/toxicology concerns on the levels of boric acid for intravenous administration in children.

There are no outstanding issues from a pharmacology/toxicology perspective that would prevent approval of the current resubmission for the proposed indication.

---

[1] Agency for Toxic Substances and Disease Registry (ATSDR), Public Health Service, U.S. Department of Health and Human Services. Toxicological profile for boron. (November 2010) (https://wwwn.cdc.gov/TSP/ToxProfiles/ToxProfiles.aspx?id=453&tid=80)

[2] National Toxicology Program (NTP), Public Health Service, U.S. Department of Health and Human Services. Technical report on the toxicology and carcinogenesis studies of boric acid (CAS No. 10043-35-3) in B6C3F1 mice. (October 1987)

[3] Heindel J, et al. Boric Acid. Environ Health Perspect., Vol 5 Suppl 1, February 1997, 275-276

[4] US Environmental Protection Agency (EPA). Toxicology Review of Boron and Compounds (CAS No. 7440-42-8). (June 2004) (https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/0410tr.pdf)

[5] European Medicines Agency. Boric acid and borate used as excipients (July 28, 2022) (https://www.ema.europa.eu/en/boric-acid-borates)

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	G. Sachia Khasar, PhD	CDER/OOD/DHOT	Sections: 5, 4.2	**Select one:** ___X Authored ___ Approved
	Signature: Gabriel S. Khasar -S Digitally signed by Gabriel S. Khasar -S Date: 2022.09.20 09:57:04 -04'00'			
Nonclinical Supervisor	Claudia P. Miller, PhD	CDER/OOD/DHOT	Sections: 5, 4.2, 19.6	**Select one:** ___X Authored ___X Approved
	Signature: Claudia Miller -S Digitally signed by Claudia Miller -S Date: 2022.09.20 10:00:46 -04'00'			
Nonclinical Team Division Director	John K. Leighton	CDER/OOD/DHOT	Sections: 5, 4.2, 19.6	**Select one:** ___ Authored ___X Approved
	Signature: John K. Leighton -S Digitally signed by John K. Leighton -S Date: 2022.09.20 09:26:39 -04'00'			
Clinical Pharmacology Reviewer	Wentao Fu, PhD	CDER/OTS/OCP/DCPII	Sections: 6, 19.4	**Select one:** ___x Authored _x_ Approved
	Signature: Wentao Fu -S Digitally signed by Wentao Fu -S Date: 2022.09.20 09:10:00 -04'00'			
Clinical Pharmacology and Division of Pharmacometrics Team Leader	Jeanne Fourie Zirkelbach, PhD	CDER/OTS/OCP/DCPII	Sections: 6, 19.4	**Select one:** ___x Authored ___X Approved
	Signature: Jeanne Fourie Zirkelbach -S Digitally signed by Jeanne Fourie Zirkelbach -S Date: 2022.09.20 08:54:14 -04'00'			
Division of Pharmacometrics (DPM) Reviewer	Youwei Bi, PhD	CDER/OTS/OCP/DPM	Sections: 6, 19.4	**Select one:** ___x Authored ___ Approved
	Signature: Youwei Bi -S Digitally signed by Youwei Bi -S Date: 2022.09.20 09:32:25 -04'00'			

Division of Pharmacometrics Team Leader	Jiang Liu, PhD	CDER/OTS/OCP/DPM	Sections: 6, 19.4	**Select one:** ___ Authored _____ Approved
	Signature: Jiang Liu -S Digitally signed by Jiang Liu -S Date: 2022.09.20 09:51:21 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED / APPROVED
Clinical Pharmacology Division Director	Atik Rahman, PhD	CDER/OTS/OCP/DCP II	Sections: 6, 19.4	**Select one:** ___ Authored ___ Approved x
	Signature: Nam A. Rahman -S Digitally signed by Nam A. Rahman -S Date: 2022.09.20 09:39:13 -04'00'			
Clinical Reviewer	Amy Barone, MD	CDER/OOD/DO2	Sections: 1, 2, 3, 4, 7-13	**Select one:** _x_ Authored ___ Approved
	Signature: Amy Barone -S Digitally signed by Amy Barone -S Date: 2022.09.20 10:17:49 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Team Leader	Amy Barone, MD	CDER/OOD/DO2	Sections: see CTDL	**Select one:** ___ Authored ___ Approved
	Signature: see CDTL signature			
Statistical Team Leader	Joyce Cheng, PhD	CDER/OTS/DBV	Sections: 1, 8.1, 8.3	**Select one:** x Authored x Approved
	Signature: Joyce Cheng -S Digitally signed by Joyce Cheng -S Date: 2022.09.20 09:44:30 -04'00'			
Deputy Division Director (OB/DBV)	Yuan-Li Shen, Dr. P.H.	CDER/OTS/DBV	Sections: 1, 8.1, 8.3	**Select one:** ___ Authored x Approved
	Signature: Yuan-li Shen -S Digitally signed by Yuan-li Shen -S Date: 2022.09.20 09:04:13 -04'00'			
Associate Director for Labeling (ADL)	Barbara Scepura, MS	CDER/OOD	Sections: 11	Select one: x Authored ___ Approved
	Barbara A. Scepura -S Digitally signed by Barbara A. Scepura -S Date: 2022.09.20 10:10:36 -04'00'			
Cross-Disciplinary Team Leader (CDTL)	Amy Barone, MD	CDER/OOD/DO2	Sections: All	**Select one:** x Authored x Approved
	Signature: see DARRTS electronic signature			
Deputy Division Director (Clinical)	Martha Donoghue, MD	CDER/OOD/DO2	Sections: All	**Select one:** ___ Authored ___ Approved
	Signature: see DARRTS electronic signature			

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

AMY K BARONE
09/20/2022 10:59:42 AM

MARTHA B DONOGHUE
09/20/2022 11:03:19 AM

Clinical and Labeling Review for NDA Resubmission after Complete Response
Division of Oncology 2

NDA (eCTD)	212937 (eCTD 0021)
Supporting document number	22
Drug	PEDMARK (sodium thiosulfate injection, STS)
Sponsor	Fennec Pharma (Fennec)
Clinical Reviewer	Amy Barone
Cross Disciplinary Team Leader	Amy Barone
Associate Director for Labeling	Barbara Scepura

Background:

On August 10, 2020, FDA issued a complete response (CR) for NDA 212937 which was received February 10, 2020 submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for PEDMARK (sodium thiosulfate injection), for intravenous use, 12.5 grams/100 mL. The CR was issued for deficiencies identified during the pre-license inspection of the manufacturing facility of STS. The clinical, nonclinical and clinical pharmacology data were supportive of regular approval of sodium thiosulfate (STS); see NDA Multidisciplinary Review and Evaluation (based on assessment aid submitted by Fennec as part of the original NDA submission, uploaded in DARRTS on August 10, 2020 as Division Director Review).

The clinical data supportive of regular approval as summarized in the NDA Multidisciplinary Review is based on the efficacy and safety data from two randomized, multicenter trials: SIOPEL 6 and COG ACCL0431.

- The primary efficacy outcome for both studies was the proportion of children with hearing loss confirmed by blinded independent review.
    - In SIOPEL 6, a total 114 patients with standard risk hepatoblastoma were randomized (1:1); the incidence of hearing loss was lower in the patients who received STS (n=24, 39%) compared to those who did not (n=36, 68%); unadjusted relative risk 0.58 (95% CI: 0.40, 0.83), adjusted relative risk based on stratification factors, 0.58 (95% CI: 0.41, 0.81).
    - In COG ACCL0431, a total of 125 patients with solid tumors who were receiving a chemotherapy regime that included a cumulative cisplatin dose of 200 mg/m2 or higher were randomized; the efficacy population used to support regulatory approval (patients with localized solid tumors) included 77 patients where 39 were randomized to the STS+cisplatin arm and 38 to the cisplatin alone arm. The incidence of hearing loss was lower in the patients who received STS (n=17, 44%) compared to those who did not (n=22, 58%); unadjusted relative risk 0.75 (95% CI: 0.48, 1.18), adjusted relative risk based on stratification factors, 0.84 (95% CI: 0.53, 1.35).
- Review of the original application also included an assessment of the theoretical risk that STS could impact the anti-tumor efficacy of cisplatin. Key endpoints used for this

assessment were event free survival (EFS) and overall survival (OS), which were evaluated in both studies, though neither study was powered for this comparison. SIOPEL 6 showed no apparent difference between arms for EFS and OS; however, COG ACCL0431 showed a potential detriment in both endpoints for the CIS+STS arm. Exploratory post-hoc analyses of EFS and OS in COG ACCL0431 suggested that the potential detriment in both may have been driven by patients with metastatic disease. After extensive review, the potential detriment in patients with metastatic disease was thought to be due to an imbalance in prognostic risk factors not due to an effect from STS treatment.

- The primary safety concerns attributable to STS in the indicated patient population identified were hypersensitivity reactions, nausea, vomiting, and AEs related to electrolyte changes (e.g. hypernatremia, hypokalemia, and hypophosphatemia). These concerns are consistent with the known safety profile of sodium thiosulfate.

On May 27, 2021, Fennec submitted an NDA Resubmission intended to provide a complete response to the deficiencies outlined in the CR Letter. Deficiencies were again identified as part of the re-inspection of manufacturing facility (b) (4) precluding approval of this NDA (see Office of Pharmaceutical Manufacturing Assessment for full detail). Based on these deficiencies, a CR letter will be issued.

At the time the original CR was issued, labeling negotiations were ongoing. Revised product labeling was included in the resubmission, and the outcome of labeling negotiations is the focus of this review.

The original CR letter also stated that when submitting a response to address the deficiencies, Fennec must include a safety update. On September 17, 2020, Fennec requested a Type A meeting to discuss steps needed to resolve the deficiencies identified in the CR letter and to reach agreement on the information need to be included in any resubmission. In that meeting package, Fennec asked if FDA required an updated literature search pertaining to the safety of STS included in the resubmission; FDA stated that inclusion of an updated literature search was not required as part of the submission. FDA issued preliminary meeting comments in response to Fennec's request for a Type A meeting on October 14, 2020. Based on FDA responses, Fennec requested to cancel the meeting.

Summary of Labeling Negotiations

At the time that the CR was issued, labeling negotiations were ongoing and the following recommendations had not yet been satisfactorily addressed:

- To be consistent with the USP drug product monograph, modifications to the container and carton labeling to change (b) (4) to "12.5 grams/100 mL (125 mg/mL)" where the strength is expressed as that of the pentahydrate.

- Addition of a Limitation of Use

  Limitations of Use

  [redacted] PEDMARK may not reduce the risk of ototoxicity when administered following longer cisplatin infusions, because irreversible ototoxicity may already have occurred.

- Clarification on the relationship between dose interruptions and hypernatremia
- Minor administrative changes and clarifications

In the revised label submitted as part of the NDA Resubmission, Fennec revised the label to address the issues described above.

During the review for the NDA Resubmission, FDA identified the additional issues outlined in the table below. Additional minor edits were made for clarity. For more detail, see Appendix for Labeling Review.

Table: High-Level Summary of Labeling Revisions as Part of the NDA Resubmission Review

Section	Summary of Change	Rationale
Section 1	Limitations of Use [redacted] PEDMARK may not reduce the risk of ototoxicity when administered following longer cisplatin infusions, because irreversible ototoxicity may have already occurred.	FDA recommendation at the time CR issued based on the rationale that reasonable concern or uncertainty about effectiveness in a patient [redacted] Fennec agreed and revised label to include the text.
Section 2.2	Revised administration instruction	Revised for clarity and brevity, no changes to content.
Section 4.2	Revised the Warning and Precaution for Hypernatremia	Revised for clarity and for consistency with Section 2. No changes to content.
Sections 6 and 14	Revised the description of the dose used in study COG ACCL043. Previous [redacted]	Modified to avoid confusion regarding why the dose administered in this trial is different from the recommended dose.

	Revised: …administered at a dose that is bioequivalent to the recommended dose as in intravenous infusion…	
Section 8.5	Deleted	To be consistent with standard labeling practice of excluding geriatric use in a pediatric population
Section 17	Added Hypernatremia and Hypokalemia	To be consistent with Warnings and Precautions

Safety Issue: Hyponatremia and Hypophosphatemia

Additional possible safety signals of severe hyponatremia and hypophosphatemia were identified during labeling negotiations. Notably, there was an increased incidence of Grade 3 - 4 hypophosphatemia (in SIOPEL6 and ACCL0431) and Grade 3 - 4 hyponatremia (in ACCL0431) in patients receiving STS with cisplatin compared to patients receiving cisplatin alone. The sponsor suggested that these findings were related to renal tubular damage and associated electrolyte disturbances related to administration of cisplatin. The sponsor also suggested that close monitoring for hypernatremia post administration of STS may have led to additional events of hyponatremia being identified in this group. Further analysis of this safety issue will be requested in the CR letter.

Overall Conclusions:

From a clinical perspective, there are no major outstanding deficiencies; a request for additional information regarding the incidence of hypophosphatemia and hyponatremia in patients receiving STS will be included in the CR letter. Fennec has agreed to the labeling changes described in this review; however, due to deficiencies identified in the inspection of the manufacturing facility of STS, a CR is recommended.

Appendix: Labeling Review

Summary of Significant Labeling Changes		
Section	**Applicant's Proposed Labeling**	**FDA's proposed Labeling**
INDICATIONS AND USAGE	PEDMARK is indicated to reduce the risk of ototoxicity associated with cisplatin in pediatric patients 1 month of age and older with localized, non metastatic solid tumors.	Added hyphen to non-metastatic. Added Limitations of Use (b) (4) PEDMARK may not reduce the risk of ototoxicity when administered following longer cisplatin infusions, because irreversible ototoxicity may have already occurred.
Recommended Dosage	(b) (4)	Edited to Recommended Dosage and Administration, Text edited for clarity. Administer PEDMARK as an intravenous infusion over 15 minutes, following cisplatin infusions that are 1 to 6 hours in duration [see Indications and Usage (1)]. Infuse PEDMARK as described

	(b) (4)	below to minimize the potential interference with the antitumor activity of cisplatin [see Clinical Pharmacology (12.1), Clinical Studies (14)] • Administer PEDMARK 6 hours after completion of a cisplatin infusion. • For multiday cisplatin regimens, administer PEDMARK 6 hours after completion of each cisplatin infusion and at least 10 hours before the next cisplatin infusion. Do not administer PEDMARK if the next cisplatin infusion is scheduled to begin in less than 10 hours [see Clinical Pharmacology (12.3), Clinical Studies (14)].
Warnings and Precautions Hypernatremia and Hypokalemia	(b) (4) Monitor serum sodium and potassium at baseline and as clinically indicated. Monitor for signs and symptoms of hypernatremia and hypokalemia. Provide supportive care and supplementation as	Text edited for clarity and safety. Withhold PEDMARK in patients with serum sodium greater than 145 mmol/liter [see Clinical Pharmacology (12.2)]. Monitor for signs and symptoms of hypernatremia and hypokalemia. Provide supportive care and supplementation as

	appropriate.	appropriate.
Clinical Trials Experience	(b) (4) [redacted]	Edited to remove (b) (4) [redacted] Patients received cisplatin-based chemotherapy with or without PEDMARK, administered at a dose that is bioequivalent to the recommended dose as an intravenous infusion over 15 minutes starting 6 hours after completion of each cisplatin infusion.
Use in Specific Populations 8.1 Pregnancy	PEDMARK is administered (b) (4) [redacted] (b) (4) which can cause embryo-fetal harm.	Text edited because PEDMARK is administered subsequent to cisplatin.
Use in Specific Populations 8.5 Geriatric Use		Removed because PEDMARK is indicated for pediatric patients.
Patient Counseling Information		Inclusion of Hypernatremia and Hypokalemia as these are serious adverse reactions of PEDMARK.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DIANA L BRADFORD on behalf of AMY K BARONE
11/24/2021 01:55:06 PM

NDA/BLA Multi-disciplinary Review and Evaluation

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant, which do not necessarily reflect the positions of the FDA.

Application Type	NDA
Application Number(s)	212937
Priority or Standard	Priority
Submit Date(s)	2-10-2020
Received Date(s)	2-10-2020
PDUFA Goal Date	8-10-2020
Division/Office	OOD/DO2
Review Completion Date	
Established Name	sodium thiosulfate injection
(Proposed) Trade Name	Pedmark
Pharmacologic Class	None
Code name	None
Applicant	Fennec Pharma
Formulation(s)	injection
Dosing Regimen	Administered as an intravenous infusion over 15 minutes starting 6 hours after the completion of each cisplatin (CIS) infusion. (b) (4) The recommended dose is weight-based: (b) (4)
Applicant Proposed Indication(s)/Population(s)	Prevention of ototoxicity induced by cisplatin (CIS) chemotherapy in patients 1 month to <18 years of age with localized, non-metastatic solid tumors
Recommendation on Regulatory Action	Complete response

Recommended Indication(s)/Population(s) (if applicable)	Reduce the risk of ototoxicity associated with cisplatin chemotherapy in pediatric patients 1 month of age and older with localized, non-metastatic solid tumors.

Table of Contents

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

Table of Tables

Table of Figures

Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Anuja Patel
Pharmocology/Toxicology Reviewer(s)	Sachia Khasar
Pharmocology/Toxicology Team Leader(s)	Whitney Helms
Clinical Pharmacology Reviewer(s)	Wentao Fu Youwei Bi
Clinical Pharmacology Team Leader(s)	Jeanne Fourie Zirkelbach Jiang Liu
Clinical Reviewer	Amy Barone
Clinical Team Leader	Amy Barone
Associate Director for Safety (if applicable)	Shaily Arora
Safety Team Analysts	Peter Schotland, Jizu Zhi
Statistical Reviewer	Abhishek Bhattacharjee
Statistical Team Leader	Joyce Cheng
Associate Director for Labeling (ADL)	Stacy Shord
Cross-Disciplinary Team Leader	Amy Barone
Division Director (DHOT)	John Leighton
Acting Deputy Division Director (OB)	Yuan-Li Shen
Division Director (OOD) (signatory authority)	Harpreet Singh

Glossary

Abbreviation or Specialist Term	Explanation
AdEERS	Adverse Event Expedited Reporting System
AE	Adverse event
AFP	Alpha-fetoprotein
ASHA	American Speech-Language-Hearing Association
AST	Aspartate aminotransferase
BBBD	Blood brain barrier disruption
BSA	Body surface area
CI	Confidence interval
CIS	Cisplatin
CMH	Cochran-Mantel-Haenszel
CNS	Central nervous system
COG	Children's Oncology Group
COMT	Catechol-O-methyltransferase
CR	Complete response
CRF	Case Report Form
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome
DSMC	Data Safety Monitoring Committee
EFS	Event-free survival
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GCT	Germ cell tumor
GFR	Glomerular filtration rate
HB	Hepatoblastoma
ICH	International Council for Harmonisation
IM	Intramuscular
IP	Intraperitoneal

Abbreviation or Specialist Term	Explanation
ITT	Intent-to-treat
IV	Intravenous(ly)
mITT	Modified Intent-to-treat
NCI	National Cancer Institute
NDA	New Drug Application
ODAC	Oncologic Drug Advisory Committee
OLT	Orthotopic liver transplantation
OS	Overall survival
pCO_2	Partial pressure of carbon dioxide
PD	Progressive disease
PI	Principal Investigator
PLADO	Cisplatin (=platinol) and doxorubicin
pO_2	Partial pressure of oxygen
PP	Per Protocol
PR	Partial response
PRETEXT	Pre-treatment Tumor Extension
PT	Preferred term
PTA	Pure-tone audiometry
SAE	Serious adverse event
SAP	Statistical analysis plan
SAR	Serious adverse reaction
SD	Standard deviation
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
TPMT	Thiopurine S-methyltransferase
US	United States
USP	United States Pharmacopoeia

1 Executive Summary

1.1. Product Introduction

Sodium thiosulfate (PEDMARK) is intended to inactive cisplatin to prevent cisplatin-induced irreversible damage to hair cells in the cochlea. The mechanism of sodium thiosulfate protection against ototoxicity is not fully understood but is thought to act directly with cisplatin to produce an inactive platinum species and act by affecting intracellular effects such as increasing antioxidant glutathione levels and inhibiting intracellular oxidative stress.

The proposed indication for NDA 212937 was:
PEDMARK is indicated for the prevention of ototoxicity induced by cisplatin (CIS) chemotherapy in patients 1 month to <18 years of age with localized, non-metastatic, solid tumors.

The recommended indication is:
PEDMARK is indicated to reduce the risk of ototoxicity associated with cisplatin in pediatric patients 1 month of age and older with localized, non-metastatic solid tumors.

The recommended dose of PEDMARK is based on body weight.

(b) (4)

(b) (4)

Note: For the purposes of this review, the words metastatic and disseminated are used interchangeable. The words non-metastatic and localized are also used interchangeably.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The clinical, nonclinical and clinical pharmacology data are supportive of regular approval of sodium thiosulfate (STS); however, due to deficiencies identified during the pre-license

inspection of the manufacturing facility of STS, a complete response (CR) is recommended. Please see the Integrated Quality Review and the CR letter for full detail. A summary of high level issues is included in Section 1.3 in the Benefit-Risk Assessment.

The clinical data that is supportive of regular approval is based on the efficacy and safety data from two randomized, multicenter trials: SIOPEL 6 and COG ACCL0431. The primary efficacy outcome for both studies was the proportion of children with hearing loss confirmed by blinded independent review; this was assessed by different criteria in each study. In SIOPEL 6, a total 114 patients with standard risk hepatoblastoma were randomized, 61 patients to the STS+cisplatin arm and 53 patients to the cisplatin alone arm. The incidence of hearing loss was lower in the patients who received STS (n=24, 39%) compared to those who did not (n=36, 68%); unadjusted relative risk 0.58 (95% CI: 0.40, 0.83), adjusted relative risk based on stratification factors, 0.58 (95% CI: 0.41, 0.81). In COG ACCL0431, a total of 125 patients with solid tumors who were receiving a chemotherapy regime that included a cumulative cisplatin dose of 200 mg/m2 or higher were randomized; the efficacy population used to support regulatory approval (patients with localized solid tumors) included 77 patients where 39 were randomized to the STS+cisplatin arm and 38 to the cisplatin alone arm. The incidence of hearing loss was lower in the patients who received STS (n=17, 44%) compared to those who did not (n=22, 58%); unadjusted relative risk 0.75 (95% CI: 0.48, 1.18), adjusted relative risk based on stratification factors, 0.84 (95% CI: 0.53, 1.35).

Review of this application also included an assessment of the theoretical risk that STS could impact the anti-tumor efficacy of cisplatin. Key endpoints used for this assessment were event-free survival (EFS) and overall survival (OS), which were evaluated in both studies, though neither study was powered for this comparison. SIOPEL 6 showed no apparent difference between arms for EFS and OS; however, COG ACCL0431 showed a potential detriment in both endpoints for the CIS+STS arm. Exploratory post-hoc analyses of EFS and OS in COG ACCL0431 suggested that the potential detriment in both may have been driven by patients with metastatic disease. After extensive review, this is potential detriment in patients with metastatic disease is thought to be due to an imbalance in prognostic risk factors not to an effect from STS treatment.

Although the patient populations and CIS and STS dosing differed between SIOPEL 6 and COG ACCL0431, the safety profile of STS administration was generally consistent. The primary safety concerns attributable to STS in the indicated patient population are hypersensitivity reactions, nausea, vomiting, and AEs related to electrolyte changes (e.g. hypernatremia, hypokalemia, and hypophosphatemia). These concerns are consistent with the known safety profile of sodium thiosulfate.

Based on these two randomized studies, the clinical data is supportive of regular approval of sodium thiosulfate to reduce the risk of ototoxicity associated with cisplatin in pediatric

patients 1 month of age and older with localized, non-metastatic solid tumors. However, the overall benefit-risk assessment of sodium thiosulfate is unfavorable, based upon the deficiencies identified during the pre-license inspection of the manufacturing facility of STS. FDA therefore recommends a complete response for the application.

At the time of action on this application, labeling negotiations had been initiated but final agreement had not been reached.

1.3. Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

The clinical data is supportive of regular approval of STS to reduce the risk of ototoxicity associated with cisplatin in pediatric patients 1 month of age and older with localized, non-metastatic solid tumors. However, the overall benefit-risk assessment of sodium thiosulfate is unfavorable based upon the deficiencies identified during the pre-license inspection of the manufacturing facility of STS. FDA therefore recommends a complete response for the application.

Cisplatin causes irreversible, high-frequency, bilaterally hearing loss in 50-60% of patients who receive it for treatment. In the US, approximately 5000 children are treated with cisplatin per year for various tumor types; cisplatin is the most common cause of hearing loss in children. Permanent hearing loss caused by cisplatin-induced ototoxicity may have serious communication, educational, and social consequences with detrimental effects on speech, language, and social development, in particular for young children who have an immature auditory system. Sodium thiosulfate is thought to act directly with cisplatin to produce an inactive platinum species and by affecting intracellular effects such as increasing antioxidant glutathione levels and inhibiting intracellular oxidative stress.

Support for this application is based on the efficacy and safety data from two multicenter trials (SIOPEL 6 and COG ACCL0431) where patients were randomized (1:1) to receive cisplatin-based chemotherapy with or without STS. The primary efficacy outcome for both studies was the was the proportion of children with hearing loss confirmed by blinded independent review; this was assessed by different criteria in each study. The patient populations differed between studies; children with a localized tumor type (standard-risk hepatoblastoma) were enrolled in SIOPEL 6 while children with various tumor types (both localized and metastatic) were enrolled in COG ACCL0431.

Efficacy

Treatment with sodium thiosulfate after cisplatin demonstrated clinically meaningful decrease in the incidence of hearing loss compared to those who were not treated with sodium thiosulfate.

- In SIOPEL 6, a total 114 patients with standard risk hepatoblastoma were randomized, 61 patients to the STS+cisplatin arm and 53 patients to the cisplatin alone arm. The incidence of hearing loss was lower in the patients who received STS (n=24, 39%) compared to those who did not (n=36, 68%); unadjusted relative risk 0.58 (95% CI: 0.40, 0.83), adjusted relative risk based on stratification factors, 0.58 (95% CI: 0.41, 0.81).

- In COG ACCL0431, a total of 125 patients with solid tumors who were receiving a chemotherapy regime that included a cumulative cisplatin dose of 200 mg/m2 or higher were randomized; the efficacy population used to support regulatory approval (patients with localized solid tumors) included 77 patients where 39 were randomized to the STS+cisplatin arm and 38 to the cisplatin alone arm. The incidence of hearing loss was lower in the patients who received STS (n=17, 44%) compared to those who did not (n=22, 58%); unadjusted relative risk 0.75 (95% CI: 0.48, 1.18), adjusted relative risk based on stratification factors, 0.84 (95% CI: 0.53, 1.35).

Review of this application also included an assessment of the theoretical risk that STS could impact the anti-tumor efficacy of cisplatin. Key endpoints used for this assessment were event-free survival (EFS) and overall survival (OS), which were evaluated in both studies, though neither study was powered for this comparison. SIOPEL 6 showed no apparent difference between arms for EFS and OS; however, COG ACCL0431 showed a potential detriment in both EFS and OS for the CIS+STS arm. A post-hoc exploratory evaluation of EFS and OS according to the extent of disease at the time of enrollment in COG ACCL0431 was conducted, categorizing patients with a binary assignment to groups of localized or disseminated disease. In children with localized, non-metastatic, solid tumors, treatment was STS was not associated with a reduction in EFS or OS. These results are supported by those from SIOPEL 6, where all patients had localized, non-metastatic disease. In COG ACCL0431 in patients characterized with disseminated disease, there was a disparity in the OS between the groups; however, after extensive review, this is thought to be due to an imbalance in prognostic risk factors not to an effect from STS treatment.

Safety
The safety assessment was based upon all patients who received least 1 dose of STS in SIOPEL 6 and COG ACCEL0431. The primary safety concerns attributable to STS in the indicated patient population are the potential for hypersensitivity reactions, nausea, vomiting, and AEs related to electrolyte changes (ie, hypernatremia, hypokalemia, and hypophosphatemia).

In SIOPEL 6, serious adverse reactions occurred in 40% of patients who received STS in combination with cisplatin-based chemotherapy. Serious adverse reactions in > 5% of patients who received STS included infection, decreased neutrophil count, and pyrexia. STS was permanently discontinued due to an adverse reaction in 1 patient (Grade 2 hypersensitivity). The most common adverse reactions (≥ 25% with difference between arms of >5% compared to cisplatin alone) were vomiting, infection, nausea, hemoglobin decreased, and hypernatremia.

In COG AACL0431, serious adverse reactions occurred in 36% of patients who received PEDMARK in combination with cisplatin-based chemotherapy. Serious adverse reactions in > 5% of patients who received PEDMARK included febrile neutropenia, decreased neutrophil count, decreased platelet count, decreased white blood cell count, anemia, stomatitis, infections, decreased lymphocyte count, and increased alanine

aminotransferase (ALT). Permanent discontinuation due to an adverse reaction occurred in 3.4% of patients who received PEDMARK. Adverse reactions which resulted in permanent discontinuation of patients included hypersensitivity. The most common adverse reaction (≥25% with difference between arms of >5% compared to cisplatin alone) was hypokalemia.

The major deficiencies identified in the manufacturing inspections included (b) (4) Additionally, the observations are identical or similar to pervious inspection observations; changes the site committed to fixing have not been implemented. The firm is now in a voluntary state of remediation and has ceased commercial production and release of batches from the firm's (b) (4) until remediation efforts and risk assessments are complete.

While the review team viewed the results of SIOPEL 6 and COG ACCL0431 favorably, the team concluded that the overall risk-benefit assessment of STS did not support approval based upon the deficiencies identified during the pre-license inspection. FDA therefore recommends a complete response for the applicant's request for marketing authorization.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Cisplatin is the most common cause of ototoxicity in children • Approximately 5,000 children in US receive cisplatin annually for solid tumors such as germ cell tumors, osteosarcoma, medulloblastoma, neuroblastoma, hepatoblastoma and others. • Cisplatin causes irreversible, high-frequency, bilaterally hearing loss in 50-60% of patients • Permanent hearing loss caused by cisplatin-induced ototoxicity may have serious communication, educational, and social consequences with detrimental effects on speech, language, and social development, in particular for young children who have an immature auditory system	Cisplatin-induced hearing loss is a serious condition that has significant morbidity for pediatric patients.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• There is no known drug approved for the prevention or treatment of cisplatin-inducted ototoxicity. • Therapeutic options are limited to reducing cisplatin dose, switching therapy, or managing hearing loss with assistive technology, speech-language therapy, etc.	Safe and effective treatments for this highly morbid condition are needed.
Benefit	• The efficacy and safety data are supported by two randomized, multicenter trials: SIOPEL 6 and COG ACCL0431 • The primary efficacy outcome for both studies was the was the proportion of children with hearing loss confirmed by blinded independent review; this was assessed by different criteria in each study. • In SIOPEL 6, a total 114 patients with standard risk hepatoblastoma were randomized. The incidence of hearing loss was lower in the patients who received STS (n=24, 39%) compared to those who did not (n=36, 68%); unadjusted relative risk 0.58 (95% CI: 0.40, 0.83), adjusted relative risk based on stratification factors, 0.58 (95% CI: 0.41, 0.81). • In COG ACCL0431, a total of 125 patients with solid tumors who were receiving a chemotherapy regime that included a cumulative cisplatin dose of 200 mg/m2 or higher were randomized; the efficacy population used to support regulatory approval (patients with localized solid tumors) included 77 patients. The incidence of hearing loss was lower in the patients who received STS (n=17, 44%) compared to those who did not (n=22, 58%); unadjusted relative risk 0.75 (95% CI: 0.48, 1.18), adjusted relative risk based on stratification factors, 0.84 (95% CI: 0.53, 1.35).	Substantial evidence of effectiveness was demonstrated for sodium thiosulfate in the patient population being indicated.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• Major deficiencies identified in the manufacturing inspections and potential risk was linked to actual data that may impact product quality. • There is a theoretical risk that STS could impact the anti-tumor efficacy of cisplatin • Neither study was powered to detect a difference in event-free survival (EFS) or overall survival (OS); however, given the risk, post-hoc analyses were done for both studies. SIOPEL6 showed no apparent difference between arms for EFS and OS; however, COG ACCL0431 showed a potential detriment in both endpoints on the CIS+STS arm. Exploratory post-hoc analyses of EFS and OS in COG ACCL0431 suggested that the potential detriment in both may have been driven by patients with metastatic disease. After extensive review, this potential detriment in patients with metastatic disease was thought to be due to an imbalance in prognostic factors, not due to effect from STS. • The primary safety concerns attributable to STS in the indicated patient population are hypersensitivity reactions, nausea, vomiting, and AEs related to electrolyte changes (e.g. hypernatremia, hypokalemia, and hypophosphatemia). These concerns are consistent with the known safety profile of sodium thiosulfate.	The safety profile of sodium thiosulfate based on the clinical data is acceptable in the intended population; however, the overall risk-benefit assessment of STS did not support approval based upon the deficiencies identified during the pre-license inspection. FDA therefore recommends a complete response for the applicant's request for marketing authorization.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

□	The patient experience data that was submitted as part of the application, include:				Section where discussed, if applicable
	□	Clinical outcome assessment (COA) data, such as			[e.g., Section 6.1 Study endpoints]
			□	Patient reported outcome (PRO)	
			□	Observer reported outcome (ObsRO)	
			□	Clinician reported outcome (ClinRO)	
			□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)			
	□	Patient-focused drug development or other stakeholder meeting summary reports			[e.g., Section 2.1 Analysis of Condition]
	□	Observational survey studies designed to capture patient experience data			
	□	Natural history studies			
	□	Patient preference studies (e.g., submitted studies or scientific publications)			
	□	Other: (Please specify)			
☐	Patient experience data that was not submitted in the application, but was considered in this review.				
X	**Patient experience data was not submitted as part of this application.**				

X _____

Cross-Disciplinary Team Leader

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

2 Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position:

Chemotherapeutic agents containing the heavy metal platinum have demonstrated efficacy in the treatment of a variety of malignant neoplasms in adults and children, and have been the standard of care in cancer therapy for 40 years (Macdonald et al, 1994; Kelland 2007). Cisplatin (CIS), the first-line platinum chemotherapeutic agent, treats many childhood cancers, such as nervous system cancers (medulloblastomas and neuroblastomas), liver tumors, bone and soft tissue sarcomas, and germ cell tumors (GCTs). Other platinum compounds are used less often because of suspected lower efficacy and other dose-related toxicities (Lokich, 2001). Cisplatin is the most ototoxic of all platinum-based drugs, including carboplatin and oxaliplatin, when used at standard doses (Park, 1996).

Cisplatin is the most common cause of ototoxicity in children (Langer et al, 2013; Arslan et al, 1999). Depending on data sources, the incidence of platinum-induced ototoxicity in children with diverse types of cancers varies from 4% to 95% (Li et al, 2004; Landier et al, 2014; Katzenstein et al, 2009; Skinner et al, 1990; Yancey et al, 2012; Knight et al, 2005; and Knight et al, 2007). Unfortunately, at commonly used doses and administration schedules, CIS frequently causes ototoxicity through progressive loss of outer and inner hair cells in the organ of Corti. The exact mechanism is still not understood, but the release of reactive oxygen species and depletion of antioxidants in the microenvironment contribute to this process (Blakley et al, 2002; Ryback and Somani, 1999; Ryback et al, 1999). Recent research suggests that CIS accumulates in the cochlea with long-term retention, making the inner ear uniquely susceptible to CIS-induced damage (Breglio et al 2017). Irreversible hearing loss, typically in the high frequency (4000 to 8000 Hz) and very high frequency (9000 to 20000 Hz) ranges, has been documented as early as following the first platinum chemotherapy dose, 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 CIS, and is likely to worsen after repeated doses (Berg et al, 1999; Hale et al, 1999; Li et al, 2004). This worsening hearing loss affects progressively lower frequencies in a cumulative, dose-dependent fashion (Berg et al, 1999; Punnett et al, 2004; Bertolini et al, 2004).

Factors that significantly increase a child's risk for moderate to severe hearing loss include age <5 years at treatment and a cumulative CIS dose of ≥400 mg/m^2 (Li et al, 2004). Cisplatin-induced hearing loss is often clinically significant, especially in young children who are critically dependent upon normal hearing for cognitive, psychosocial, and speech development (Gilmer-Knight et al, 2005; Fausti et al, 1993; Hindley 1997). In older children,

both educational and behavioral effects studies showed impaired functional status, cognitive status, depressive symptomatology, and disability (Brock et al, 2012).

The FDA's Assessment:
FDA agrees with the Applicant's overall assessment of hearing loss in children that is associated with cisplatin treatment.

2.2. Analysis of Current Treatment Options

The Applicant's Position:

Fennec Pharmaceuticals, Inc (Fennec) is unaware of any drug approved for the prevention or treatment of CIS-induced ototoxicity. Current therapeutic options are limited to reducing the CIS dose (or switching to a different platinum-based chemotherapy, both of which risk decreased tumor efficacy), or managing the hearing loss. This management includes hearing assistive technology, speech-language therapy, and other communication strategies (Whelan et al, 2011; Brock et al, 2012). While such interventions must be considered to help patients communicate, these management options cannot restore normal hearing.

As such, there is clearly a need for safe and effective treatments targeted at prevention of CIS-induced ototoxicity.

The FDA's Assessment:
FDA agrees with the Applicant's assessment of current treatment options to reduce the risk of hearing loss associated with cisplatin. There are no FDA approved drugs to reduce the risk of hearing loss associated with cisplatin or due to any cause.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:

PEDMARK is being developed for prevention of ototoxicity induced by CIS chemotherapy in patients 1 month to <18 years of age with localized, non-metastatic solid tumors. The New Drug Application (NDA) has been submitted to the Division of Oncology 1 in the Office of New Drugs; no other review division within the Office of New Drugs was involved prior to the submission, and, thus, all of the applicable United States (US) regulatory history is provided in Section 3.2 below. Fennec was recently notified that the review of the NDA is being moved to the Division of Oncology 2.

The FDA's Assessment:

FDA agrees with the Applicant's assessment. The review of the NDA was moved to DO2 based on the proposed indicated population of pediatric patients with solid tumors. DO2 is responsible for managing drug development for pediatric solid tumors.

PEDMARK is not approved in any country. Sodium thiosulfate is commercially available in the US and in Europe for the treatment of cyanide poisoning. In Belgium and Italy, sodium thiosulfate is also commercially available for the prevention of nephrotoxicity associated with cisplatin.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:

Clinical advice was sought from the Food and Drug Administration (FDA) during a Type C meeting in March 2011 and during a meeting of the Pediatric Subcommittee of Oncologic Drug Advisory Committee (ODAC) in November 2011. In response to a request for Breakthrough Therapy Designation, the FDA provided additional suggestions for PEDMARK clinical development in August 2014. Agency advice from FDA was also provided through a Type C clinical meeting request and written responses (January 2018), a pre-NDA meeting (December 2018) focused on clinical, nonclinical, and regulatory aspects of the NDA, and a pre-NDA chemistry, manufacturing, and controls meeting (September 2019). In the US, PEDMARK has received Orphan designation (March 2004), Breakthrough Therapy Designation (March 2018), and Fast-Track designation (March 2018).

Key discussions and agreements during these US agency interactions are summarized in Table 1.

Table 1: Summary of Key Agreements/Discussions with FDA

Correspondence	Key Agreements/Discussions with FDA	Implementation of Advice
FDA Clinical Type C Meeting Minutes (March 2011)	• Fennec is required to convincingly demonstrate that STS does not reduce the efficacy of CIS. • Pooling data from SIOPEL 6 and COG ACCL0431 was not recommended.	• Tumor response and survival evaluated (Module 2.5, Section 4.5). • No pooling was conducted.
Pediatric Subcommittee of ODAC Meeting (November 2011)	• Fennec discussed the COG ACCL0431 study design and efficacy evaluations. The subcommittee agreed that this study would support proof of concept with adequate follow up. • Possible tumor protection is a critical component of the safety profile of STS, and that it should be thoroughly investigated prior to drug approval.	• Tumor response and survival evaluated (Module 2.5,Section 4.5).
Breakthrough Therapy Designation Request Denial - Additional Responses from FDA Clinical Pharmacology Reviewer (August 2014)	• The PK of STS should be adequately characterized at the proposed dose. • Evaluation of the in vitro ability of STS and its major metabolite(s) to act as substrates, inhibitors, or inducers of CYP enzymes, transporters, and conjugating enzymes should be conducted. • Fennec should evaluate the impact of CIS doses, body size, and other demographic covariates on STS exposure and resulting efficacy and safety of STS in the proposed indication.	• PK and exposure response considering BSA, age, renal maturation, and weight were characterized through STS (thiosulfate) exposure modeling and sodium analysis (Module 2.5, Section 3; Section 3.1.2.1; Section 3.3). • Evaluation of DDIs, including induction/inhibition of CYP isoforms evaluated (Module 2.5, Section 3.1.2.2; Section 3.1.3.1).

Table 1: Summary of Key Agreements/Discussions with FDA

Correspondence	Key Agreements/Discussions with FDA	Implementation of Advice
FDA Clinical Type C Meeting Written Responses (January 2018)	• The available nonclinical data in the literature were sufficient to support the PEDMARK NDA for prevention of ototoxicity induced by CIS in pediatric patients with SR-HB. • Fennec's approach to evaluate STS dose and duration of treatment using PK modeling of serum STS and sodium concentration based on data from Neuwelt et al, 1998 was sufficient. Together with a summary of published data, the agency also agreed on the plans for in vitro evaluation of DDIs through CYP induction and inhibition studies. • SIOPEL 6 and COG ACCL0431 and further published STS clinical results provided sufficient efficacy and safety data to allow the filing of the PEDMARK NDA for the prevention of ototoxicity induced by CIS chemotherapy in pediatric patients with SR-HB. Further evaluation of OS would be conducted on the COG ACCL0431 study data to examine the observation of decreased survival in the disseminated subgroup of the CIS+STS arm.	• Nonclinical literature summarized (Module 2.4). • PK and exposure response considering BSA, age, renal maturation, and weight were characterized through STS (thiosulfate) exposure modeling and sodium analysis (Module 2.5, Section 3; Section 3.1.2.1; Section 3.3). • Evaluation of DDIs, including induction/inhibition of CYP isoforms evaluated (Module 2.5, Section 3.1.2.2; Section 3.1.3.1). • SIOPEL and COG data were summarized in addition to summary of available applicable literature. • Tumor response and survival evaluated (Module 2.5, Section 4.5).

Table 1: Summary of Key Agreements/Discussions with FDA

Correspondence	Key Agreements/Discussions with FDA	Implementation of Advice
FDA Pre-NDA Meeting Minutes (December 2018)	• The available nonclinical data in the literature were sufficient to support the PEDMARK NDA for prevention of ototoxicity induced by CIS in pediatric patients with SR-HB. Given that no novel excipients are used in the proposed STS formulation and any impurities will be qualified in accordance with ICH Q3 limits, no additional GLP toxicity studies of STS impurities were required. • The proposed approach for the literature review was generally acceptable. • Evaluation of serum sodium levels after STS administration was an adequate surrogate to evaluate safety at the recommended STS dose; however, it can be confounded by endogenous sodium and may not be reliable. Given that no STS PK samples were collected from SIOPEL 6 or COG ACCL0431, the use of STS PK literature to develop a popPK model and incorporation of growth and maturation models was acceptable to predict STS exposure. • The proposed approach of descriptive efficacy and safety data per weight category was acceptable. • The CYP inhibition and induction studies conducted were sufficient for the FDA to review the potential of drug-drug interaction with STS in the NDA. • The review of safety and efficacy can be based on the individual studies (SIOPEL 6 and COG ACCL0431) rather than pooled data.	• Nonclinical literature summarized (Module 2.4) • Clinical literature reviewed (Module 2.5, Section 1.2.2). • PK and exposure response considering BSA, age, renal maturation, and weight were characterized through STS (thiosulfate) exposure modeling and sodium analysis (Module 2.5, Section 3; Section 3.1.2.1; Section 3.3). • Efficacy and safety data were evaluated by weight category (Module 2.5, Section 4.6; Section 5.9.1). • Evaluation of DDIs, including induction/inhibition of CYP isoforms evaluated (Module 2.5, Section 3.1.2.2; Section 3.1.3.1). • No pooling was conducted.

Table 1: Summary of Key Agreements/Discussions with FDA

Correspondence	Key Agreements/Discussions with FDA	Implementation of Advice
FDA Pre-NDA Meeting Minutes (December 2018) *(continued)*	• Because SR-HB is obsolete in terms of classifying and reviewing patients for treatment, the Agency agreed with the proposed indication: STS for injection for the prevention of ototoxicity induced by CIS chemotherapy in patients 1 month to <18 years of age with localized, non-metastatic HB. [redacted] (b) (4) The effect of differing CIS regimens and prognosis on OS in each treatment group in the COG ACCL0431 study should be explored. • To satisfy the Integrated Summary of Effectiveness and Integrated Summary of Safety requirements (21CFR 314.50(d)(5)(v) and 21 CFR 314.50(d)(5)(vi)(a),respectively), data summarized within the Module 2 documents (Summary of Clinical Efficacy [2.7.3] and Summary of Clinical Safety [2.7.4], respectively) will be sufficient. • For SIOPEL 6 and COG ACCL0431, full narratives are provided for patients in the CIS+STS arm who (1) experienced an SAE or (2) discontinued STS due to an AE (depending on information available). In addition, full narratives are provided for patients who died during the study due to a cause other than progression of disease regardless of treatment group. • Data from the SIOPEL 6 and COG ACCL0431 studies are acceptable in SDTM and ADaM formats. The SAS programs used to create all analysis datasets are provided. The legacy datasets transferred from COG and SIOPEL were converted to CDISC format. Supporting documentation is provided (define.xml version 2.0, SDTM and ADaM reviewer guides and SAS programs in .txt format). • The Agency agreed to the plan for the NDA rolling submission. • No Pediatric Study Plan or Risk Evaluation and Mitigation Strategy are required for the submission of the NDA.	• An evaluation of prognostic factors that affect survival was conducted (Module 2.5, Section 4.5). • Module 2.7.3 and 2.7.4 include all data summaries. No Integrated Summary of Effectiveness or Integrated Summary of Safety were submitted. • Full narratives for these events are provided in the respective CSRs. • SDTM and ADaM datasets, SAS programs, and supporting documentation is provided. • The first part of the rolling submission for this NDA submitted in December 2018. • No Pediatric Study Plan or Risk Evaluation and Mitigation Strategy have been submitted.

Abbreviations: ADaM=Analysis Data Model; AE=adverse event; BSA=body surface area; CDISC=clinical data interchange standards consortium; CIS=cisplatin; COG=Children's Oncology Group; CSR=clinical study report; CYP=cytochrome P450; DDI=drug-drug interaction; FDA=Food and Drug

Administration; GLP=Good Laboratory Practice; ICH=International Council for Harmonisation; NDA=New Drug Application; ODAC= Oncological Drug Advisory Committee; OS=overall survival; PK=pharmacokinetics; popPK=population PK; SAE=serious adverse event; SAS=Statistical Analysis System; SIOPEL=International Childhood Liver Tumor Strategy Group; SDTM=Study Data Tabulation Model; SR-HB=standard risk hepatoblastoma; STS=sodium thiosulfate.

The FDA's Assessment:

FDA agrees with the pre-submission regulatory activity stated by the Applicant above.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

No clinical sites were inspected for this NDA. FDA determined that OSI inspections were not needed given that the safety profile is well known, it is a supportive care drug, and that that results of the two trials conducted independently and at different regions are similar.

4.2. Product Quality

The CMC team asked the nonclinical team whether there was toxicological justification for several extractables and for two impurities with specifications above the thresholds discussed in ICH Q3A and B: (b) (4) These data provide sufficient coverage for the safety of the (b) (4) at the proposed specifications without the need for additional toxicology studies.

The Applicant identified the following extractables at levels above a calculated analytical evaluation threshold (AET). The Applicant based the AET on the threshold of toxicological concern for genotoxic impurities discussed in ICH M7, of (b) (4) µg/day for drugs given for less than 1 month. The Applicant then established an AET with the expectations that most patients would receive no more than two vials of STS/day on cisplatin dosing days, with one stopper (device)/vial and each stopper weighing 2 g with the calculation as follows:

AET (µg/g) = (b) (4) µg/day x 1 day/2 vials x 1 vial/device x 1 device/2.0 g = (b) (4) µg/g.

Extractables that exceeded the (b) (4) µg/g threshold were limited to (b) (4) The Applicant based this threshold on a 2 vial maximum as most pediatric patients receive less than or equal to 2 vials maximum; however based on the maximum dose described in the label, up to 3 vials/dose may be needed.

Table 2: Extractable Levels

(b) (4)

While STS is not a genotoxic drug, for the proposed indication it is given only in combination with cisplatin, which is genotoxic. The Applicant did not provide any justification for the levels of these potential extractables. As these levels represent worse-case scenario extractions, it is unclear whether patients would receive (b) (4) at these levels.

(b) (4)

(b) (4) In addition, levels up to (b) (4) mg were detected in previously approved STS injectable projects. Given these high levels in previously approved products and the use of this product in combination with cisplatin, there is not a clear safety risk for the proposed level of (b) (4)

(b) (4) in another intravenous drug based on the methods for establishing exposure limits in ICH Q3C/D. In a repeat-dose oral toxicity study, after 28-day exposure in rats at 25, 250, and 500 mg/kg/day (b) (4) the liver was the main target organ of toxicity at doses of 250 and 500 mg/kg/day. The NOAEL was 25 mg/kg/day. Based on the NOAEL of 25 mg/kg from the repeat-dose toxicity study with (b) (4) in rats, the acceptable daily intake (ADI) for (b) (4) was calculated to be 250 µg/day with the following factors based on lifetime exposure:

(b) (4)

(b) (4)

The worse case scenario for (b) (4) presented by the Applicant would exceed the (b) (4) however, this dose is still over 800x lower than the NOAEL determined in the rat study and dosing with STS is limited in the currently proposed indication.

For the (b) (4) is likely an extractable in a wide array of parenteral products (solutions or lyophilized products), it was (b) (4) in the last few years. As a result, while there is some evidence that independent laboratories may be attempting to screen (b) (4) for their genotoxic potential, FDA was unable to find any toxicology data to support the safety of (b) (4) at any level. The actual genotoxic potential for patient exposure to (b) (4) following PEDMARK infusion is unclear.

4.3. Clinical Microbiology

Not applicable.

4.4. Devices and Companion Diagnostic Issues

Not applicable.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Fennec Pharmaceuticals has submitted NDA 212937 under the 505(b)(2) pathway for sodium thiosulfate (STS) for the prevention of ototoxicity induced by cisplatin chemotherapy in patients 1 month to <18 years of age with localized, non-metastatic, solid tumors. STS is an inorganic salt with reducing agent properties, currently approved as an antidote used sequentially with

sodium nitrite for acute cyanide poisoning. STS has been investigated clinically for over 100 years. Because Fennec submitted the application under the 505(b)(2) pathway, the Applicant submitted very limited nonclinical data and instead relies primarily on literature reports for the pharmacology/toxicology information needed to support approval in the current indication. Currently STS does not have an established pharmacological class; due to remaining uncertainties regarding the mechanism of its activity in several indications and its general characteristics as a reactive chemical compound/target no EPC is currently proposed.

While STS is an anion that does not diffuse across cell membranes, the Applicant cited data from Marutani et al., (2015) showing that it can enter cells by transport through the sodium sulfate cotransporter 2. Pharmacology studies suggest that STS neutralizes cisplatin by covalently binding to electrophilic platinum compounds, making an inactive easily excretable product; this neutralization may occur primarily extracellularly but can also occur intracellularly. STS also has an established role in decreasing oxidative stress in cells. The mechanism of cisplatin-induced hearing loss is not fully elucidated but appears to be due to uptake and accumulation of cisplatin into cochlear hair cells by various transporters where it may lead to cell death through DNA damage and excessive generation of reactive oxygen species (ROS) and inflammation.

The Applicant submitted multiple literature reports in several species, including hamsters, guinea pigs, and rats, showing that the addition of STS to cisplatin treatment resulted in protection from hearing loss. Investigators observed this protection in animals when STS was given systemically (intraperitoneally or intravenously) or by direct cochlear perfusion, but not when given locally by infusion in the round window membrane. When administered concurrently with cisplatin, STS reduces not only the general toxicity (including nephrotoxicity) but also the antitumor activity of cisplatin (Elferink, et al. (1986); Wimmer, et al. (2004), however, the cited studies showed that delayed administration of STS between 2 and 8 hours retained the otoprotective effect without significantly reducing antitumor activity; waiting longer than 12 hours post-cisplatin to administer STS resulted in a loss of the otoprotective activity.

A study of the pharmacokinetic interaction of STS co-administration with carboplatin or cisplatin showed no significant effects on the plasma pharmacokinetics of free platinum in the guinea pig ototoxicity model. STS has the potential to inhibit CYP2C8, CYP2C9, and CYP2C19, but very low potential to induce CYP enzymes.

Administration of single intravenous (IV) STS doses of up to 30 g/m^2 to anesthetized dogs showed no effect on heart rate or blood pressure, however, doses ≥ 60 g/m^2 led to muscular twitching and profound electrolyte and hemodynamic changes, cardiovascular, and respiratory changes (including hypoxemia and metabolic acidosis) that proved fatal to 3 of 5 dogs within 24

hours of dosing. The cardiovascular and respiratory effects appeared to be secondary to a rapid rise in sodium. In addition, the 60 g/m^2 dose in dogs resulted in urinary bladder filling to overflowing within minutes of the injection, with marked diuresis in the 4/5 dogs that survived to the 3-hour time point after injection. In rats given a single IV STS dose of 116. g/m^2 immediately after mannitol (to disrupt the blood-brain-barrier) there were seizures, consistent with the muscular twitching in dogs at the 60 g/m^2 dose level; no seizures occurred in the absence of mannitol. This data suggests that in patients with a compromised blood-brain-barrier, there may be a potential for STS-related seizures.

There are no chronic toxicology studies investigating the safety of IV-administered STS. Thiosulfate is an endogenous molecule and there is a long history of human use of STS both at high IV doses as a drug, at least acutely, and at low concentrations as a food additive. In addition, for the current indication STS is given on a limited basis on the same schedule as cisplatin (1-6 days/21-28-day cycle for up to 8 cycles) and only in combination with cisplatin. Given these considerations and the intended submission under the 505(b)(2) pathway, FDA did not request chronic toxicology by the IV route of administration. In addition to the single dose studies already discussed, the Applicant cited data from limited repeated dose studies of STS given by IP injection to guinea pigs or hamsters for up to 8 daily doses with no clear evidence of toxicity. In rats (4/group) given intramuscular (IM) sodium thiosulfate at a dose of 0.6 g/m^2 for 4 weeks there were pathological findings of changes in the capillary walls of the thyroid and adrenal cortex. Following 3 months of treatment with STS, the vessels of the kidneys displayed atrophy of the glomeruli and dilation of the glomerular capillaries, which were permeable to plasma. Increased permeability of liver capillary walls and an increase in Küppfer cells was also present in this study. Overall this study suggested some potential for damage to capillaries and renal toxicity with long term daily administration of high doses of STS, though the relevance of these findings to STS given by the intended route the intended dose intensity is limited.

STS showed no genotoxic potential in Ames and micronucleus assays. Carcinogenicity studies by the IV route of administration have not been conducted and are not necessary to support the safety of a drug intended for use in patients with advanced cancer in combination with cisplatin. Oral administration of STS was not embryotoxic or teratogenic in embryofetal development studies in mice, rats, hamsters, or rabbits. The highest dose in any of these studies was in the rabbit, 6 g/m^2 (~half the highest clinical dose of 12.6 g/m^2 based on BSA). In addition, STS has poor bioavailability, suggesting that the exposure in animals was significantly lower than in humans and making the relevance of this animal data for the current indication questionable. In one cited study hamsters did receive a single daily (multiple injections over 10 hours) STS dose of 9 g/m^2 during organogenesis and there were no reported developmental effects. A pharmacokinetic study in gravid ewes suggests that there is no significant transfer of STS across the placenta. While the available embryofetal development data are of questionable relevance given the intended clinical dose of 12.8 g/m2 and the IV route of

administration, STS is given only in combination with cisplatin in the intended patient population. As cisplatin is a genotoxic drug with embryotoxic and teratogenic effects in animals, no additional developmental studies with STS are warranted. The label includes references to the cisplatin label for relevant pregnancy considerations. Based on the available data, there was no clear need for the "Females and Males of Reproductive Potential" section of the label specifically for STS; this section was therefore removed and there are no recommendations for use of contraception for STS alone. There are no outstanding nonclinical issues for this 505(b)(2) application that would prevent the approval of PEDMARK for the prevention of cisplatin-mediated ototoxicity.

5.2. Referenced NDAs, BLAs, DMFs

The Applicant's Position:

There are no referenced NDAs, BLAs, or DMFs related to nonclinical pharmacology or toxicology for the PEDMARK NDA.

5.3. Pharmacology

The Applicant's Position:

Primary pharmacology

Effects of sodium thiosulfate on platinum-induced ototoxicity

Numerous studies in vitro and in animals have shown that sodium thiosulfate (STS) can protect against ototoxicity associated with platinum-based chemotherapy (Otto et al, 1988; Church et al, 1995; Kaltenbach et al, 1997; Saito et al, 1997; Muldoon et al, 2000; Wang et al, 2003; Stocks et al, 2004). Importantly, STS has been shown to inhibit ototoxicity even when administration is delayed for up to 8 hours after systemic platinum-based chemotherapy administration in rats (Dickey et al, 2005) and guinea pigs (Neuwelt et al, 1996).

Sodium thiosulfate was the most effective of several drugs tested as a protectant against CIS-induced ototoxicity in hamsters and provided a nearly complete protection (Church et al, 1995; Kaltenbach et al, 1997).

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). 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 loss in the basal and second turns of the cochlea. Damage to the outer hair cell s was mild when STS intra-peritoneal (IP) (8 g/m^2) was given concurrently, but was severe when STS dose was given 3 and 6 hours later (Saito et al, 1997). Otto et al (1988) confirmed the strong protective effect of STS IP against CIS-induced ototoxicity in guinea pigs: STS (12.8 g/m^2) 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.

In guinea pigs, STS blocked carboplatin-induced ototoxicity when administered IP 2 hours after carboplatin (Neuwelt et al, 1996). Protection against carboplatin-induced cochlear damage was observed when STS (14.64 g/m^2) was given at 2, 4, or 8 hours after carboplatin (192 mg/m^2); however, there was no protection if STS was given 24 hours after carboplatin.

In rats, STS intravenous (IV) protected against CIS-induced ototoxicity, even when STS 8 g/m^2 was given 8 hours after CIS (36 mg/m^2) (Dickey et al, 2005).

Mechanism(s) of Action

Several mechanisms of STS protection may be responsible for its effects, including conversion of the alkylating drug into a non-cytotoxic compound by thiol group binding of the electrophilic platinum to form a rapidly excreted complex, scavenging reactive oxygen species, and increasing levels of reducing agent. Furthermore, the cochlea may act similarly to the kidney to concentrate STS in perilymph or endolymph and enhance protection in the local environment (Dorr, 1991).

Within 4 hours after the end of CIS administration, free active platinum has largely disappeared from the circulation; however, it has recently been reported for mice and humans that platinum can accumulate and remain in the cochlea for many months after the last CIS treatment, making the cochlea uniquely susceptible to CIS-induced damage (Breglio et al, 2017). 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 defenses (Hazlitt et al, 2018; Sheth et al, 2017; Evans and Halliwell, 1999; Dehne et al, 2001; Rybak et al, 2007).

Cisplatin can react directly with STS to form the four-coordinate Pt (II) species [Pt(S2O3)4]6- with Pt-S bonds (Sooriyaarachchi et al, 2016). The Pt-thiosulfate complex is formed rapidly in extracellular fluid and this complex is cleared from plasma without cellular uptake and binding to intracellular macromolecules (Uozumi et al, 1984). At high molar excess, STS binds to and inactivates the electrophilic platinum compounds CIS and carboplatin in vitro (Dedon and Borch, 1987; Elferink et al, 1986). Upon simultaneous administration of STS with CIS in guinea pigs, it was noted that a Pt-thiosulfate complex formed in plasma can still distribute through the blood cochlear barrier and that prevention of ototoxicity is probably related to the inhibition of cellular uptake of free CIS or the binding of CIS to intracellular macromolecules (Saito et al, 1997). A study in rabbits, where plasma samples were analyzed by a bioassay specific for bioactive CIS,

showed that STS reduced bioactive CIS within 5 minutes in a dose dependent manner reaching complete inactivation of CIS at a 400-fold molar ratio for STS (Iwamoto, 1985). Results also indicated that CIS did not subsequently return to its active form.

However, the study also showed that bioactive CIS in plasma declined rapidly after IV administration also in the absence of STS. A 10 fold decline in free bioactive CIS was observed within 60 minutes after administration of CIS. In the clinical studies, STS was administered 6 hours after the end of infusion with CIS and hence the direct interaction between free CIS and STS appears marginal compared to the overall free CIS exposure up to that time point.

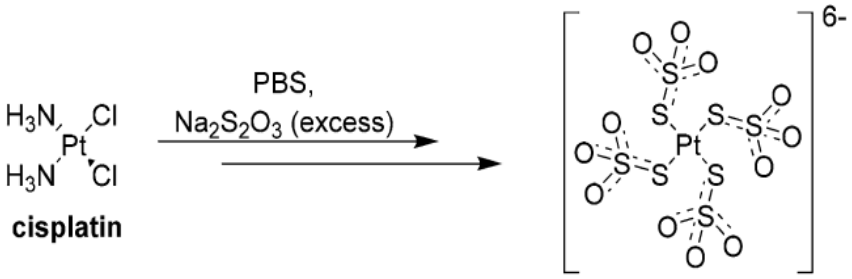
Cisplatin can also increase oxidative stress and reduce protective anti-oxidant enzymes and it has been widely suggested that such effects are more relevant for the toxicity of CIS (Karasawa and Steyger, 2015). Indeed, a depletion in glutathione, changes in anti-oxidant enzymes and increased oxidative 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 ototoxicity 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, while STS as an anion cannot diffuse through cell membranes and consequently distributes mainly in extracellular fluid, Marutani et al (2015) demonstrated that STS does 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 al (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 induced by 28-day adenine treatment, simultaneous oral treatment with STS resulted in improved renal glutathione levels, anti-oxidant enzymes and reduced oxidative stress (Mohan et al, 2017). While specific publications that measure oxidative stress and anti-oxidant factors in the cochlea after CIS with or without STS have not been found, it seems likely that a positive effect of STS on intracellular glutathione levels and other anti-oxidant enzymes can contribute to the prevention of CIS-induced ototoxicity.

The FDA's Assessment:

FDA reviewed the cited papers and generally agrees with the Applicant's summary. The thiosulfate portion of STS can form covalent bonds with cisplatin and the normally slow kinetics of the reaction are increased in the presence of high (relative to cisplatin) concentrations of STS (Elferink, et al. 1986). The formation of a Pt−STS complex has been characterized as a four-coordinate Pt(II) species, $[Pt(S_2O_3)_4]^{6-}$, that occurs through the external sulfur of STS (Figure 1). This complex is inactive and excreted renally.

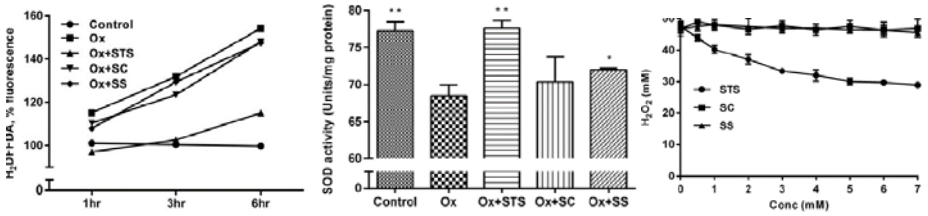
Figure 1: Depiction of a Cisplatin Complex with STS as Observed by X-ray Crystallography



(Excerpted from Hazlitt, et al. 2018)

While STS is an anion that does not diffuse across cell membranes, the Applicant cited data from Marutani et al. (2015) showing that it can transported across cells by the sodium sulfate cotransporter 2. In addition, Bijarnia et al. (2015) showed that incubation of LLC-PK1 (proximal tubule kidney cell line) with STS (but not sodium chloride (SC) or sodium sulfate (SS)) was able to reduce oxalate-induced intracellular oxidative stress and H_2O_2 release as well as stabilizing levels of superoxide dismutase (SOD) (Figure 2). Other authors showed similar anti-oxidant activity for STS including its ability to react with GSSG (oxidized glutathione) to produce reduced glutathione in the presence of hydroxyl radicals or peroxides ((Sen, et al. (2008), Lee, et al. (2016)) and a potential to produce hydrogen sulfide by reaction with trans-sulfuration enzymes.

Figure 2: STS Effects on Oxidative Stress Markers

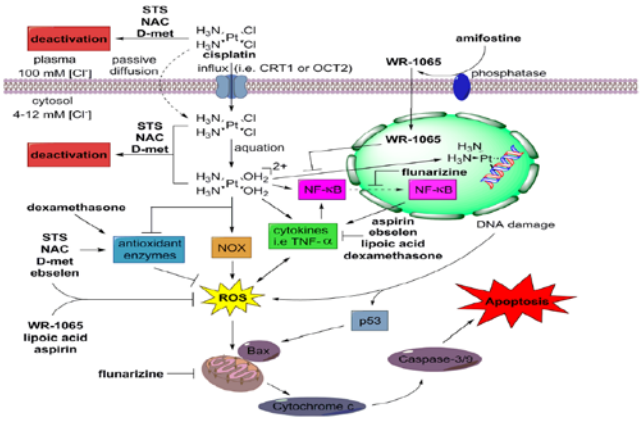


(Adapted from Bijarnia et al., 2015)

Although the cellular and molecular mechanisms by which cisplatin causes ototoxicity are not fully understood, scientists postulate that cisplatin-induced hearing loss is due to uptake of cisplatin into cochlear hair cells by various transporters such as copper transporter 1 (CTR1) or, in the case of inner-ear hair cells, organic cation transporters (OCT1−3). Cisplatin can accumulate in the perilymph and cochlear cells, where it may lead to cell death by cisplatin-mediated DNA damage and activation of apoptosis through DNA-damage induced pathways and to the excessive generation of reactive oxygen species (ROS); the ROS can also trigger cell

death and stimulation of cochlear inflammation including the release of proinflammatory cytokines such as TNF-α, IL-1β, and IL-6. STS can, therefore, also potentially reduce cisplatin-induced ototoxicity through its roles in quenching ROS (e.g., H_2O_2) and preserving the activity of antioxidant enzymes (e.g., SOD), as well as by forming biologically inactive complexes with cisplatin to effectively reduce exposure to active cisplatin (Hazlitt et al (2018) (Figure 3)).

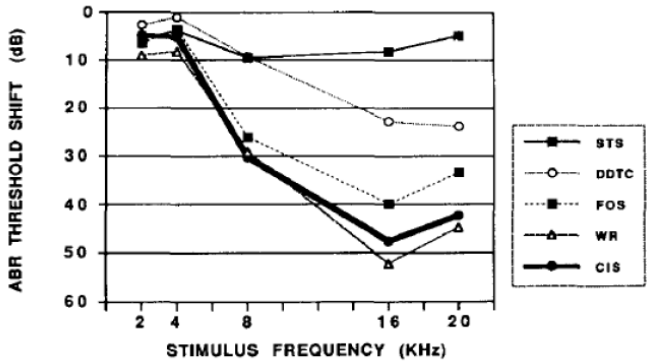
Figure 3: Schematic of Cisplatin-Induced Ototoxicity and the Mechanistic Pathways of Otoprotective Clinical Candidates



(Excerpted from Hazlitt et al. 2018)

The Applicant cited the study of Church et al (1995) investigating the effects of sodium thiosulfate (STS), diethyldithiocarbamate (DDTC), WR-2721 (WR), or Fosfomycin (FOS) against cisplatin-induced ototoxicity. Hamsters received a series of 5 cisplatin injections (3 mg/kg once every other day, intraperitoneally (i.p.)) either alone or in combination with 1600 mg/kg STS, 300 mg/kg DDTC, 18 mg/kg WR, or 300 mg/kg FOS (n = 10/group). Injections of both cisplatin and each of the other drugs were within of each other. Ototoxicity was assessed electrophysiologically by auditory brainstem responses (ABRs) and anatomically by cochlear histology. Five animals in the cisplatin + FOS and two each in the cisplatin + WR and cisplatin alone groups died during the study. All the animals in the cisplatin + STS and cisplatin + DDTC groups survived. As shown in Figure 4, STS provided the most auditory protection, followed by DDTC. Thus, it appears that the agents that were protective against ototoxicity were also protective against mortality.

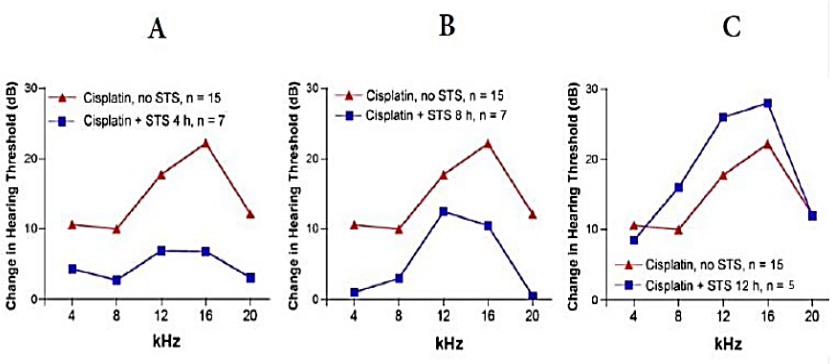
Figure 4: Effect of Treatment with STS, DDTC, WR, or FOS on ABR Threshold Shifts as Function of Treatment condition and tone burst frequency.



(Excerpted from Church, et al. 1995)

The Applicant also cited a study by Dickey, et al (2005) that evaluated the potential for STS to protect against cisplatin-induced ototoxicity in adult female Long-Evans rats given a single dose of cisplatin at 6 mg/kg (36 mg/m^2). At 4, 8, or 12 hours after cisplatin infusion, rats received a single IV dose of saline or STS at 8 g/m^2. Investigators tested auditory brainstem response thresholds at 4 to 20 kHz before and 7 days post-treatment. At the 7 -day post-dose timepoint, cisplatin significantly increased hearing thresholds at each frequency, however, STS given at 4 or 8 hours after cisplatin, decreased the cisplatin-induced increase in hearing threshold at all frequencies, suggesting that STS (8 g/m^2, IV) was otoprotective at the tested frequencies if given between 4 and 8 hours after cisplatin. STS given 12 hours post-cisplatin had a significantly diminished otoprotective effect.

Figure 5: Effect of STS on Cisplatin-Induced Ototoxicity in Rats

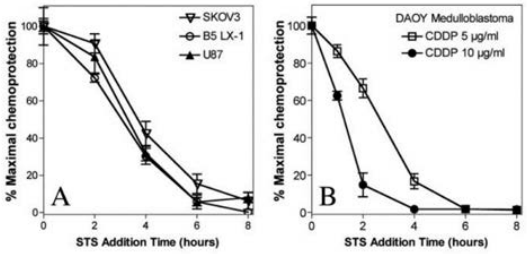


(Excerpted from Dickey, et al., 2005)

The authors went on to examine effects of STS on cisplatin-mediated cell death using multiple human tumor cell lines (LX-1 SCLC, SKOV3, B5 LX-1, U87, and DAOY). When investigators added

STS to cells within 1 hour of cisplatin treatment, STS prevented cell death. By 6 hours post cisplatin treatment, this protection was generally lost.

Figure 6: In Vitro Protection from Cisplatin Toxicity by STS in Tumor Cell Lines



(Excerpted from Dickey, et al., 2005)

Secondary Pharmacology

The Applicant's Position:

Sodium thiosulfate can protect against other types of toxicity associated with platinum-based chemotherapy; specifically, lethality in mice (Ishizawa et al, 1981), nephrotoxicity (Taniguchi and Baba, 1982; Iwamoto et al, 1984; Poore et al, 1984; Nagai et al, 1995), hematologic toxicity (Iwamoto et al, 1984; Neuwelt et al, 2004), hepatotoxicity (Liao et al, 2008) and CIS-impaired wound healing (Wile et al, 1993). In animal models, STS was shown to reduce kidney stone formation and prevent vascular calcifications (Asplin et al, 2009; Pasch et al, 2008).

The FDA's Assessment:

FDA did not review the additional studies on prevention of cisplatin-mediated impairment of wound healing, hepatotoxicity, and kidney stone formation in detail as they are not critical for the currently proposed indication. In general, the effects described by the Applicant do not appear to be secondary pharmacology, but rather related to the primary activity of STS described above.

Safety Pharmacology

The Applicant's Position:

Central Nervous System

An IV dose of STS at 60 mg/m^2 produced muscular twitching that was probably due to changes in serum electrolytes but no clinical signs suggesting an effect on central nervous system (CNS) function (Ref).

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). Sodium thiosulfate at a dose of 11.6 g/m^{2}produced no discernable neurotoxic effects when administered without BBBD or when administered 30 or 60 minutes after BBBD, ie, when the BBB was re-established. However, when given immediately after BBBD, STS produced neurotoxicity, including seizures. The results suggest that STS may produce CNS effects when large doses are given to patients with a compromised BBB, but that CNS effects are unlikely when the BBB is intact.

Cardiovascular System

Anesthetized and surgically instrumented 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 heart rate, blood pressure, or electrocardiogram 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 (Dennis and Fletcher, 1966). The QRS complex amplitude also decreased without a change in QT interval. These effects resolved within 3 hours post dose. The authors attributed the cardiovascular effects to sodium overload from STS. In addition, the increased blood pressure and tachycardia are also an appropriate adaptive response to hypoxia. Similarly, profound hypoxia can contribute to the flattened or inverted T waves as these typically reflect myocardial ischemia.

In another study, blood pressure and heart rate remained constant during and after administration of a single IV dose of STS at 3 g/m^{2}to anesthetized dogs (the STS dose would have taken perhaps two minutes to inject; therefore, the rate of STS administration was approximately 1.5 g/m^2/min) (Braverman et al, 1982).

In a third study, no changes in blood pressure or heart rate were reported during or immediately after 15-minute IV STS infusions at rates of 1.3, 2.0, and 2.7 g/m^2/min (Muldoon et al, 2000; personal communication).

Respiratory System

Dogs given an IV dose of STS at 30 g/m^2 at a rate of 1 g/m^2/min had no effects respiratory rate, partial pressure of oxygen [pO_2]; partial pressure of carbon dioxide [pCO_2], of blood pH (Dennis and Fletcher, 1966). However, dogs given STS at 60 g/m^2 at a rate of 3 g/m^2/min experienced rapid decreases in arterial pO_2 and pH, and increase in arterial pCO_2, and became tachypneic. One dog that died shortly after STS administration had pronounced pulmonary edema. Similar effects were produced in another dog by a single IV injection of sodium chloride at equimolar concentration. Respiratory effects observed with STS were considered secondary to a rapid rise in serum sodium concentration. In surviving dogs, these effects resolved within 3 hours post dose.

No significant changes were noted in blood gasses (pO_2; pCO_2) in dogs administered IV STS at either 20 g/m^2, 30 g/m^2, or 40 g/m^2 (Muldoon et al, 2000; personal communication).

Renal System

Sodium thiosulfate IV at 3 g/m^2 in anesthetized dogs produced a diuresis with a 50% increase in urine flow during the first ten minutes; 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.

Single IV doses of STS 60 g/m^2 caused the urinary bladder to fill to overflowing within minutes of injection. In the four of five dogs that survived the STS injection for > 3 hours, marked diuresis occurred (Ref).

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 hypokalemia (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).

The FDA's Assessment:

FDA generally agrees with the Applicant's position. Dr. Kimberly Benson previously reviewed the majority of the safety pharmacology data cited by the Applicant and her assessment is summarized here. In anesthetized dogs given single IV STS doses of up to 30 g/m^2, STS showed no effect on heart rate or blood pressure, however, at 60 g/m^2 STS led to muscular twitching and profound electrolyte and hemodynamic changes, cardiovascular, respiratory (including hypoxemia and metabolic acidosis), and electrolyte changes that proved fatal to 1/5 dogs shortly after dosing and to 2/5 more within 24 hours of dosing. The cardiovascular and respiratory effects appeared to be secondary to a rapid rise in sodium as they were also present in dogs that received equimolar doses of sodium and included increased blood pressure, tachycardia, flattening of T waves and frequent T-wave inversions as well as QRS voltage decrease but no change in the QT interval. In addition, dogs at the 60 g/m^2 dose had urinary bladder filling to overflowing within minutes of the injection, with marked diuresis in the 4/5 dogs that survived to the 3 hour time point after injection. A low dose of 3 g/m^2 caused up to 50% increase in urinary flow in anesthetized dogs. The effects resolved within 3 hours post-dose. In female Long-Evans rats, there were no neurotoxic effects following IV STS (11.6 g/m^2) without mannitol or 30 and 60 minutes after mannitol, but when STS was given immediately after mannitol (to disrupt the blood-brain-barrier), STS produced seizures, consistent with the muscular twitching in dogs at the 60 g/m^2 dose level. These data suggest that while STS is unlikely, under most circumstances, to be neurotoxic, in patients with a compromised blood-brain-barrier, there may a potential for STS-related seizures.

5.4. ADME/PK

The Applicant's Position:

Sodium thiosulfate is poorly absorbed after oral administration and has to be administered IV. Plasma levels of STS are maximal at the end of infusion and decline rapidly thereafter with a half-life of approximately 20 to 50 minutes. A return to pre-dose levels occurs within 3 to 6 hours after infusion. More than 95% of STS excretion in urine occurs within the first 4 hours after administration. Hence, there is no plasma accumulation when STS is administered on 2 consecutive days.

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. In animals, STS 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.

Metabolites of STS have not been determined. Thiosulfate is an endogenous intermediate product of sulfur-containing amino acid metabolism. Thiosulfate metabolism does not involve cytochrome P450 (CYP) enzymes; it is metabolized through thiosulfate sulfur transferase and thiosulfate reductase activity to sulfite, which is rapidly oxidized to sulfate.

No mass balance studies have been performed, but it is expected that non-renal clearance will mainly result in renal excretion of sulfates. A small part of the sulfane sulfur of STS may become part of endogenous cellular sulfur metabolism.

The FDA's Assessment:

FDA reviewed the cited data and generally agrees with the Applicant's assessment; however, the Applicant did include clinical data showing that sulfite and sulfate are metabolites of STS and that this metabolism (along with incorporation into endogenous sulphur compounds) is responsible for the clearance of up to 50% of the administered dose. (b) (4)

5.5. Toxicology

5.5.1. General Toxicology

The Applicant's Position:

Although no formal Good Laboratory Practices-compliant toxicology studies were discovered with STS, toxicity data for STS were reported in various literature studies. Single IV doses of STS are well tolerated at high dose levels in all species tested, with IV 50% lethal dose values

reported to be 3.6 g/m^2 in mice, > 15 g/m^2 in rats, and 60 g/m^2 in dogs (EPA, 2003; RTECS, 2011). The adverse effects of STS are due to hypernatremia and secondary diuresis and disturbances in electrolyte and acid-base balance, which affect the function of the cardiovascular, respiratory, and neuromuscular systems. For example, while rats tolerated single IV doses of STS at 11.6 g/m^2, single IV doses above 15 g/m^2 cause behavioral toxic effects in the rat (convulsions or effect on seizure threshold) (RTECS, 2011).

The toxicity of single IV doses of STS may be a function not only of total dose but also of administration rate. For example, dogs tolerated single IV doses of STS at 30 g/m^2 given by 30-minute infusion (ie, at a rate of 1 g/m^2/min) (Dennis and Fletcher, 1966) and at 20 g/m^2 (n = 2), 30 g/m^2 (n = 1), or 40 g/m^2 (n = 1) given by 15-minute infusion (ie, at rates of 1.3, 2.0, and 2.7 g/m^2/min) (Muldoon et al, 2000) However, dogs did not tolerate single IV doses of STS at 60 g/m^2 given by 20-minute infusion (ie, at a rate of 3 g/m^2/min); indeed, one of five dogs died shortly after infusion ended, and two more dogs died within 24 hours of dosing (Dennis and Fletcher, 1966). At the higher infusion rate and total dose, there were hemodynamic, cardiovascular, respiratory and electrolyte changes that were attributed to the sodium ion in STS, because essentially identical effects occurred with single IV doses of sodium chloride at equimolar concentrations and rates.

Repeated IP doses of STS at high dose levels also are well tolerated. For example, there were no adverse effects when STS was administered IP to hamsters at 8 g/m^2 every other day for 5 doses, to guinea pigs at 8 g/m^2 every 5 days for 3 doses, or to guinea pigs at 12.8 g/m^2 daily for 8 days.

Taken together, the publicly available nonclinical information indicates that STS has low toxicity when administered IV.

The FDA's Assessment:

FDA confirmed the cited data regarding the single dose IV studies as the IV route is the intended route of administration for STS in the current indication. The same studies are discussed in the safety pharmacology section of this review.

While FDA agrees that publicly available nonclinical data suggest low toxicity of acute treatment of animals with STS by IV route (the proposed route of administration of STS clinically), the Applicant also cited literature showing that chronic intramuscular treatment of 4 rats/group with 0.6 g/m^2 STS daily for 4 weeks or 3 months resulted in vascular wall lesions in the thyroid and adrenal glands and, only after 3-months, in renal atrophy of the glomeruli and dilation of the glomerular capillaries, which became permeable to plasma. This study suggests some potential vascular and renal toxicity with long-term repeated high dose administration by this route. Finally, in more limited repeat-dose cited studies by intraperitoneal injection of STS in guinea pigs (12.8 g/m^2 daily for 8 days) or hamsters (8 g/m^2 every other day for 5 injections) there was no evidence of STS-mediated target organ toxicity.

5.5.2. Genetic Toxicology

The Applicant's Position:

Sodium thiosulfate is considered not to pose a genotoxic hazard to patients. 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 in human lymphocytes in vitro (Ohe et al, 1990). These results are not surprising, as thiosulfate is regularly used in bacterial and cell culture media as a source of sulfur (EPA, 2003).

The FDA's Assessment:

FDA agrees that the available data do not suggest a genotoxic risk from treatment with STS. The study by Prival et al. (1991) was previously reviewed by Drs. Mellon and Delatte; these data were from a study published by the U.S. Food and Drug Administration which reports that sodium thiosulfate pentahydrate tested negative for mutagenic potential in the bacterial reverse mutation assay (Ames test) using *S. typhimurium* strains TA98, TA100, TA1535, TA1537, TA1538, and *E. coli* strain WP2 (with or without S9 metabolic activation).

5.5.3. Carcinogenicity

The Applicant's Position:

Long-term studies in animals have not been performed to evaluate the potential carcinogenicity of STS.

The FDA's Assessment:

FDA agrees. Consistent with the principles in ICH S9, animal carcinogenicity studies are not typically expected to support the approval of a drug intended for the treatment of patients with advanced cancer and as the intended use of STS in the current indication is only in combination with the cytotoxic and genotoxic drug, cisplatin, carcinogencity studies are not necessary.

5.5.4. Reproductive and Developmental Toxicology

The Applicant's Position:

Fertility

Nonclinical studies have not been conducted to evaluate the potential effects of STS on fertility or reproductive function in animals of either sex; however, STS is considered unlikely to add to the adverse effects associated with platinum-based chemotherapy itself.

Embryo-Fetal Development

In animal studies, STS was not embryotoxic or teratogenic in pregnant mice, rats, hamsters, or rabbits at maternal doses of up to 550, 400, 400, and 580 mg/kg/day (1.65, 2.4, 2.0, and 6.96 g/m^2/day), respectively, when STS was administered as an aqueous solution by oral intubation. Additionally, an IV pharmacokinetic (PK) study in gravid ewes indicated that STS does not cross the placenta.

Based on studies conducted in pregnant mice, rats, hamsters, and rabbits, STS is considered unlikely to affect embryofetal development in a female patient who is pregnant or to add to the risk of adverse effects on embryofetal development associated with platinum-based chemotherapy itself.

Pre- and Post-natal Development

There is no information about the potential effect of STS on postnatal development.

Sodium thiosulfate will be administered only in conjunction with platinum-based chemotherapy, which is generally cytotoxic and has the potential to affect development of multiple organ systems; therefore, any additional risk presented by STS is unlikely to be clinically meaningful.

The FDA's Assessment:

The Applicant did not conduct studies examining the potential for reproductive toxicity of STS, but relied instead on published literature. Fertility and pre-and postnatal development studies are not recommended to support a drug intended for the treatment of patients with advanced cancer. In addition, as the intended use of STS in the current indication is only in combination with the cytotoxic and genotoxic drug, cisplatin, FDA would not request additional embryo-fetal development studies.

The Applicant does cite previously conducted embryo-fetal development studies. FDA previously reviewed the cited literature regarding the potential for STS-mediated embryo-fetal developmental effects of STS. Relevant conclusions from the FDA review of these studies by Drs. Mellon and Delatte are consistent with the Applicant's conclusions and are included here.

> In animal studies, there are no teratogenic effects in offspring of hamsters treated during pregnancy with sodium thiosulfate in doses similar to those given intravenously to treat cyanide poisoning in humans (Willhite, 1983). In other studies, sodium

thiosulfate was not embryotoxic or teratogenic in mice, rats, hamsters, or rabbits at maternal doses of up to 550, 400, 400 and 580 mg/kg/day, respectively (Food and Drug Research Labs,1972;Food and Drug Research Labs, 1974).

FDA notes that the embryofetal development studies conducted by FDA were investigating the toxicity following oral administration of STS. While animals received doses up to approximately half of the highest clinical dose for STS for the treatment of ototoxicity, the Applicant states that STS has poor oral bioavailbility, suggesting that these studies may result in expsosures that are significantly lower than the clinical exposure by the IV route of administration.

In the cited Wilhite 1983 study, previously reviewed by Dr. Delatte, hamsters received IP STS as a divided dose of 1800 mg/kg (~9 g/m^2; given 300 mg/kg every 2 hours over a 10 hour period) as a single agent or in combination with acetonitrile (methyl cyanide); STS alone did not have an effect on development. Finally, the Applicant cites data from Graeme et al. (1999) in which five gravid ewes received IV STS (~1.8 g/m^2). Despite large increases in maternal thiosulfate levels following treatment, fetuses showed no clear increase plasma thiosulfate, suggesting that STS does not cross the placenta.

5.5.5. Other Toxicology Studies

The Applicant's Position:

Adverse effects at the STS injection site have not been reported in animals, and considerable clinical experience confirms that STS is well tolerated at the injection sites.

Studies have shown that excess STS beyond endogenous levels of thiosulfate is rapidly cleared from the body and there are no cumulative effects (EPA, 2003). In addition, no breakdown products which are anticipated to be toxic or likely to cause any unpredictable off target effects have been reported in the literature.

Impurities (b) (4) and solvents in the drug substance are fully controlled. Potential impurities and degradants of the drug product have been investigated and characterized (see Section 3.2.P.5).

The FDA's Assessment:

FDA agrees that injection site reactions are not predicted based on the available nonclinical data.

The Applicant is referring to impurity and degrandant information in Section 3.2.P.5 of the NDA submission rather than a discussion in this document. See section 4.2 of this document for FDA's assessment of the safety of impurities at levels above the ICH Q3A/B thresholds.

G. Sachia Khasar, PhD
Primary Reviewer

Whitney S. Helms, PhD
Supervisor

6 Clinical Pharmacology

6.1. Executive Summary

The FDA's Assessment:

The applicant seeks approval for sodium thiosulfate (STS) (b) (4) injection (PEDMARK) for the prevention of ototoxicity induced by cisplatin (CIS) chemotherapy in patients 1 month to <18 years of age with localized, non-metastatic, solid tumors. The clinical data to support the proposed indication are from two randomized, open-label Study SIOPEL 6 and Study COG ACCL0431. Patients were randomized 1:1 to receive either STS over 15 minutes intravenous infusion 6 hours after each CIS dose (CIS+STS) or chemotherapy that included CIS, without subsequent STS (CIS Alone). In the CIS+STS arm in Study SIOPEL 6, doses of STS were dependent on the child's weight (children > 10 kg received an equivalent of 12.8 g/m^2 PEDMARK, children ≥ 5 to ≤ 10 kg received an equivalent of 9.6 g/m^2 PEDMARK, and children < 5 kg received an equivalent of 6.4 g/m^2 PEDMARK). In the CIS+STS arm in Study COG ACCL0431, an equivalent of 10.2 g/m^2 PEDMARK was administered by intravenous infusion over 15 minutes. The proposed recommended dosing regimens are the same as these in Study SIOPEL 6. No pharmacokinetics (PK) data were collected in Study SIOPEL 6 or Study COG ACCL0431. In support of the proposed dosing regimens, population PK modeling and simulation approaches were applied to extrapolate PK across different weight and age groups. The Office of Clinical Pharmacology Division of Cancer Pharmacology II and Division of Pharmacometrics have reviewed the information contained in NDA 212937. This NDA is approvable from a clinical pharmacology perspective.
The key review questions focus on appropriateness of PEDMARK dose, recommendations PEDMARK dose in patients with renal impairment.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

The Applicant's Position:

Sodium thiosulfate plasma or serum level (thiosulfate) is maximal at the end of infusion and declines rapidly thereafter, with a half-life reported mostly in the range of 20 to 50 minutes (Module 2.7.2, Section 2.2). 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 (thiosulfate), levels return to pre-dose values within 3 to 6 hours after STS infusion. Hence, there was no accumulation of STS in plasma if STS was administered on 2 consecutive days (Neuwelt et al, 1998).

Maximum plasma levels increase in a dose proportional manner over a dose range of 8 to 20 g/m^2 administered by a 15-minute IV infusion (Module 2.7.2, Section 2.2.2; Neuwelt et al, 1998).

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 extracellular spaces (Ivankovich, 1983; Farese et al, 2011).

Nevertheless, STS has the ability to enter cells at least partly through the sodium sulfate co-transporter 2, and causes intracellular effects such as the increase in antioxidant 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 antioxidant status is considered to contribute to the mechanism of action of ototoxicity prevention by STS. Because CIS has shown to accumulate in the cochlea with long-term retention, the ability of STS to enter the cochlea to reduce oxidative stress allows prevention of CIS-induced damage (Breglio et al 2017).

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

Sodium thiosulfate (thiosulfate) is excreted through glomerular filtration. After administration, STS (thiosulfate) levels in urine are high, and approximately 50% of the STS dose is excreted unchanged in urine, nearly all within the first 4 hours after administration (Neuwelt et al, 1998; Ivankovich et al, 1983; Farese et al, 2011). Newman (1946) demonstrated that STS renal clearance correlated with inulin clearance as a measure for the glomerular filtration rate (GFR).

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

The FDA's Assessment:

FDA agrees with the applicant's characterization of sodium thiosulfate or thiosulfate clinical pharmacokinetics. Nine published studies were relied on as a bridge to support characterization of the clinical PK and ADME . The studies were reviewed by the review team and found scientifically relevant to the proposed product, because they use the same active moiety (sodium thiosulfate) as contained in the Sponsor's drug product, and the doses tested are scientifically relevant to the proposed recommended dosage. The list of the nine published studies are provided below.

- Population PK modeling and simulation: Farese et al, 2011; Neuwelt et al, 1998; Neuwelt et al, 2006; Doolittle et al, 2001
- Distribution: Kowalski et al, 1952 for Plasma Protein Binding
- Metabolism: Hildebrandt et al, 2008; Bilska-Wilkosz et al, 2017; Szczepkowski et al, 1961

- Excretion: Neuwelt et al, 1998; Ivankovich et al, 1983; Farese et al, 2011
- PK in hemodialysis patients: Farese et al, 2011

Please refer to the Section 5.3 for FDA's assessment of the mechanism of action of sodium thiosulfate in the prevention of otoxtoxicity induced by CIS.

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

The Applicant's Position:

Two studies (International Childhood Liver Tumor Strategy Group [SIOPEL] 6 and Children's Oncology Group [COG] ACCL0431) were conducted to demonstrate the efficacy and safety of STS in pediatric patients treated with CIS. SIOPEL 6 was designed to administer 20 g/m^2 STS (adjusted for body weights <10kg) 6 hours after completion of a 6-hour CIS infusion, which were to be administered every 2 weeks for up to 6 cycles in patients with standard risk hepatoblastoma (SR-HB). COG ACCL0431 was designed to administer 16 g/m^2 STS (or 533 mg/kg when CIS was dosed on a per-kg basis) 6 hours after the completion of a CIS infusion in patients with various tumor types. In the COG ACCL0431 study, the CIS dosing regimen was determined by each site's disease-specific cancer treatment protocols in use at the time, but the durations of CIS infusions were generally between 1 to 6 hours with up to 5 daily administrations per cycle. Together, these studies administered STS as single administrations in conjunction with CIS treatment cycles based on the disease-specific treatment regimen for the patient (eg, up to 5 daily administrations per cycle for up to 6 cycles) for approximately a 3- to 6-month period).

Because no PK analysis was performed for either study, the following approach was taken to support the PEDMARK dosing recommendations:

- As STS has been applied clinically for almost a century, available literature has been used to describe the PK characteristics of IV administered STS.
- Sodium thiosulfate plasma data of 45 administrations from 16 individual patients (aged 2.5 to 69 years) has been made available to Fennec by authors from other academic studies investigating STS administration to prevent ototoxicity in brain cancer patients (Neuwelt et al, 1998; Doolittle et al, 2001; Neuwelt et al, 2006). Data were obtained after IV administration by a 15-minute infusion, the same duration of infusion as used in SIOPEL 6 and COG ACCL0431. Various STS dose levels up to 20 g/m^2 were used. Using these data, Fennec performed a non-compartmental analysis and developed a population pharmacokinetic (popPK) model to evaluate potential maturation and growth effects on STS exposure when extrapolating to smaller children.
- Administration of STS is associated with a high sodium load and results in a transient increase in serum sodium levels. Because of the potential for adverse effects due to increases in serum sodium (eg, nausea and vomiting) and because renal maturation

effects during the first year after birth may influence sodium handling, serum sodium levels were monitored in SIOPEL 6. For these reasons, the STS dose in SIOPEL 6 was also adjusted for children <10kg of body weight. To confirm the consistency of STS dosing over different cycles and between body weight (based dose) groups in SIOPEL 6, a non-compartmental analysis was performed on the increase in sodium serum levels.

SIOPEL 6 and COG ACCL0431 confirmed that STS treatment at 16 to 20 g/m^2 resulted in statistically significant reductions in ototoxicity in patients with various types of solid tumors treated with CIS (Module 2.5, Section 4.4) while not affecting the anti-tumor efficacy of CIS in patients with localized, non-metastatic solid tumors (Module 2.5, Section 4.5). The studies also confirmed that the main and most frequently reported adverse events (AEs) attributable to STS were vomiting, nausea, and AEs related to electrolyte changes (ie, hypernatremia, hypokalemia, and hypophosphatemia) (Module 2.5, Section 5.8). None of these were considered dose limiting at a dose level of 16 or 20 g/m^2.

Depending on the tumor type, CIS administration may occur over multiple days per cycle followed each time by an STS infusion (as was done in the CIS+STS arm of COG ACCL0431). At the end of an IV infusion of STS, the plasma level of STS (thiosulfate) is maximal and declines rapidly thereafter with a half-life reported in the range of 20 to 50 minutes. Levels return to pre-dose levels within 3 to 6 hours after STS infusion (Module 2.7.2, Section 3.1). Therefore, the negligible amount of STS remaining at 6 hours after completion of an STS infusion would not be expected to interact with a subsequent CIS infusion.

Growth and maturation in pediatric patients need to be considered for the dose recommendation. The dose level of STS was normalized to body surface ara (BSA) in clinical studies, including SIOPEL 6 and COG ACCL0431, and literature (Neuwelt et al, 2006; Doolittle et al, 2001; Neuwelt et al, 1998). SIOPEL 6 included children of 1.2 months to 8.2 years and COG ACCL0431 between 1 and 18 years. Efficacy and safety outcomes were similar and independent of the ages or weights of the children, or the absolute doses of STS. Dose normalization to BSA is further supported by results from a non-compartmental analysis in patients >2.5 years where comparable maximum thiosulfate exposure levels and similar plasma half-lives were observed between adults and children (Module 2.5, Section 3.1.2.1). Similarly, popPK modelling and simulation of STS (thiosulfate) plasma levels after BSA-normalized STS dosing showed consistent exposure over wide age (1 to 18 years) and weight (>10 kg) ranges.

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 STS dosing scheme normalized to BSA and adjusted for body weight did not affect the efficacy of otoprotection or AEs in this study, both when analyzing different groups based on body weight (Module 2.5, Section 4.6 and Section 5.9.1). These clinical findings are supported by results from the popPK model for STS plasma levels incorporating renal glomerular maturation (Module 2.5, Section 3.1.2.1); simulation results showed consistent STS exposure over the

different body weight and STS dose groups. Further support is also observed in the results from the analysis of the transient increase in serum sodium levels following STS administration (Module 2.5, Section 3.1.2.1). Results similarly showed that the small transient increase in sodium after STS administration was consistent and independent of body weight and dose groups.

(b) (4) the STS doses administered in SIOPEL 6 where dosing was based on the higher molecular mass of STS pentahydrate: 20 g/m^2, 15 g/m^2, and 10 g/m^2, respectively. This dosing regimen is considered effective and tolerable in a pediatric population with localized, non-metastatic solid tumors, as supported by the 2 clinical studies (SIOPEL 6 and COG ACCL0341), literature, and available PK analyses. In addition, the results support delayed administration of PEDMARK with varying CIS treatment regimens (ie, number of cycles, days per cycle, and daily CIS doses) for a range of tumor types. Finally, (b) (4) there were no dose-limiting toxicities observed at these doses as well as to maximize the possibility for efficacy in the pediatric patient population that includes young children.

(b) (4)

The FDA's Assessment:

(b) (4) The efficacy and safety results from trial SIOPEL6 support the proposed dosage in patients with weight between 5-10 kg and >10 kg. The PopPK model predicted the proposed dosage would produce Cmax in patients weighing 5 to 10kg that is comparable to that in patients weighing more than 10kg. The predicted Cmax in patients weighing less than 5kg is 16% and 36% lower than the predicted Cmax in patients weighing more than 10kg based on

popPK simulation.
In Study SIOPEL 6, CIS and STS were administrated once every treatment cycle of two weeks (Q2W) for patients (age range 1 month to less than 18 years) with histologically confirmed newly diagnosed hepatoblastoma. In Study COG ACCL0341, CIS and STS were administered more frequently than once per treatment cycle in some patients . For example, patients with germ cell tumors (GCTs) received up to 5 doses of CIS (20 to 40 mg/m^2) and STS (equivalent of 10.2 g/m^2 STS anhydrous injection) per cycle. The average number of doses of STS was 2.5 per cycle. To understand the effect of multiple STS administrations per cycle on the safety and efficacy of CIS, the applicant conducted an exploratory analysis in patients by STS dose < 3 versus ≥ 3 per cycle as a response to FDA's information request. No meaningful differences were observed in the safety (Table 2) and efficacy (hearing loss, event-free survival, or overall survival) between the patients with the number of STS doses < 3 and ≥ 3 per cycle.

Table 3: Summary of the (b) (4) adverse drug reactions (b) (4) by number of STS doses per Cycle (COG ACCL0431, Safety Population)

SOC PT	CIS+STS Arm		
	<3 STS Doses per Cycle (n=34)	**≥3 STS Doses per Cycle (n=25)**	**Total (N=59)**
Gastrointestinal disorders			
Vomiting	1 (2.9)	3 (12.0)	4 (6.8)
Nausea	4 (11.8)	1 (4.0)	5 (8.5)
Metabolism and nutrition disorders			
Hypernatremia	6 (17.6)	1 (4.0)	7 (11.9)
Hypokalemia	11 (32.4)	5 (20.0)	16 (27.1)
Hypophosphatemia	8 (23.5)	4 (16.0)	12 (20.3)
Immune system disorders			
Hypersensitivity	3 (8.8)	2 (8.0)	5 (8.5)

Abbreviations: ADR=adverse drug reaction; CIS=cisplatin; COG=Children's Oncology Group; PT=preferred term; SOC=system organ class; STS=sodium thiosulfate.
Sources: Table 13 of Response to Clinical Pharmacology Information Request: NDA 212937 (17 April 2020)

6.2.2.2. Therapeutic Individualization

The Applicant's Position:

Pharmacokinetics Related to Intrinsic Factors

Age

Non-compartmental analysis of STS serum data obtained from 5 pediatric patients (mean age: 11 years; range: 2.5 to 16 years) and 11 adult patients (mean age: 46 years; range: 19 to 69 years) treated for brain tumors (Neuwelt et al, 1998; Neuwelt et al, 2006) indicated that the maximum STS plasma levels and the rate of decline thereafter were not influenced by age (Module 2.7.2, Section 2.2.2). These data support a nominal dose level based on BSA over a wide age range.

A 2-compartmental popPK model was developed based on data from these patients and from literature (Farese et al, 2011) to further investigate the influence of growth and renal maturation (Module 2.7.2, Section 2.2.3.1). Covariates were implemented in the model according to the following published relationships: lean body mass for the volume of distribution (of the central and peripheral compartments) (Peters et al, 2011) and BSA for renal clearance and an age-related adjustment for renal maturation (Tod et al, 2001). Two models were employed: one with constant non-renal clearance that best fit data in the available age range, and an additional one that scaled non-renal clearance to BSA to capture growth for very young children below 2.5 years.

The predicted maximum exposure at 20 g/m^2 STS for a virtual pediatric population was similar to levels at the end-of-infusion published for adults (Neuwelt et al, 1998). In the age range above 2 years and body weight above 20 kg, the results were independent of the PK model used for non-renal clearance (Module 2.7.2, Section 2.2.3.2). In the PK model with constant non-renal clearance, maximum predicted exposure remained constant until the dose level was decreased by 25% (to 15 g/m^2) for children between 5.0 and 10.0 kg. This predicted exposure was still in the effective range of a dose of 16 g/m^2 that showed otoprotective effects in COG ACCL0431 for children aged 1 to 18 years. If the PK model with a growth-dependent non-renal clearance was used, the predicted maximum exposure in thiosulfate gradually increased for children below 20 kg, which is then corrected by the dose level adjustments for children <10 kg (to 75%) and <5 kg (to 50%).

The above PK exposure analyses for STS regard the exposure to thiosulfate as it relates to efficacy for the prevention of ototoxicity. Thiosulfate exhibits a relatively low toxicity profile, and acute toxicity and dose-limiting effects in animals have been attributed to the sodium load if a high IV dose of STS is administered rapidly. In SIOPEL 6, sodium levels were monitored, and the transient increase in sodium was generally considered of limited clinical significance (Module 2.5, Section 5.6.1). Nevertheless, these sodium data can also be used to analyze the consistency of dosing and exposure of STS. The maximum increase in serum sodium levels after STS administration was similar for children with a body weight >10 kg receiving 20 g/m^2 compared with those with a body weight of 5 to10 kg receiving 15 g/m^2, across all cycles (Module 2.7.2, Section 2.2.4). In addition, the transient increase in sodium for individual children remained within the same range and was independent of age, weight, BSA, or total daily STS dose.

Cytochrome P450 Induction and Inhibition

Metabolism of STS is independent of CYP. Two standard in vitro studies were performed to evaluate the potential effect of STS on the inhibition and induction of CYP isoforms (Module 2.6.4, Section 7 and Module 2.6.5). In human liver microsomes, the half-maximal inhibitory concentration (IC_{50}) of STS corrected for osmolality effects for CYP2C8, CYP2C9, and CYP2C19 were 89.2 mM, 95.4 mM, and 104 mM, respectively, 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 from 1 of 3 donors after 72 hours incubation at 10 and 25 mM STS (approximately 2.2-fold and 27% of positive control; just above the respective thresholds of 2.0-fold and 20%).

Pharmacokinetics in Renal Impairment

Approximately 50% of STS (thiosulfate) is cleared through glomerular filtration; hence, renal clearance of STS decreases in patients with renal disease (Newman et al, 1946; Farese et al, 2001). In patients requiring hemodialysis, the total clearance declined approximately 50% and became similar to the non-renal (metabolic) clearance in healthy subjects. The maximum STS plasma levels increased approximately 25% (Module 2.7.2, Section 2.2.7). Sodium thiosulfate has also been administered safely to hemodialysis patients at a dose of 12.5 to 25 g, 3 times per week after each dialysis and for up to 5 months (Mathews et al, 2011).

PEDMARK is administered only after CIS treatment. Children receiving chemotherapy for cancer are routinely and carefully monitored for renal function. As a precaution to prevent CIS-induced nephrotoxicity, patients receive saline fluid hydration treatment with high chloride content before and after CIS administration to stimulate glomerular filtration and urinary flow. It is likely that under these conditions, glomerular filtration and excretion of STS is maintained, even when the tumor or chemotherapy has reduced renal function below normal values for the child's age.

Pharmacokinetics in Hepatic Impairment

Metabolism of STS occurs through thiosulfate sulfur transferase and thiosulfate reductase activity and is independent of CYP. Hence, STS metabolism is not confined to the liver; thus, the clinical impact on the STS PK in patients with hepatic impairment is likely limited.

Pharmacokinetics Related to Extrinsic Factors

Drug-drug Interactions

Sodium thiosulfate does not bind to human plasma proteins (Kowalski et al, 1952). The chemical properties of STS and observations that STS does not distribute readily across membranes (ie, 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. Results of in vitro studies did not reveal inhibition of CYP isoforms in microsomes close to the expected maximum plasma concentration for STS; only a borderline induction result for CYP2B6 was noted in cryopreserved hepatocytes from 1 donor (Module 2.5, Section 3.1.2.2).

For the overall risk assessment for PK drug-drug interactions, the STS PK profile and treatment schedule also need to be taken in to account. The duration of STS exposure during administration is limited and returns to pre-dose values within 3 to 6 hours after administration. High plasma levels are even more limited, given its half-life of 20 to 50 minutes. Furthermore, STS treatment is not chronically administered and is confined to a limited number of intermittent, single administrations generally over a 3- to 6-month period in conjunction with CIS treatment cycles. Even when given on consecutive days, plasma levels do not accumulate.

Therefore, given the in vitro results, STS chemical characteristics, PK profile, metabolism, and treatment schedule, clinically relevant PK drug-drug interactions would not be expected for STS. The potential for pharmacodynamic interaction of STS to interfere with CIS anti-tumor efficacy is considered elsewhere (Module 2.5, Section 3.2, Section 3.3, Section 3.4, and Section 4.5).

The FDA's Assessment:

Simulation results based on the final popPK model and sensitivity analyses suggest that the recommended dosage would produce comparable exposure across the proposed weight bands for approval. (b) (4)

In SIOPEL 6, the dose of sodium thiosulfate at the recommended dosage resulted in an average transient increase in serum sodium levels approximately 5 to 7 mmol/L. Maximum increase in serum sodium was generally observed at 1 hour after infusion and levels had returned to baseline by 18 h or 24 h after administration. The transient increase in sodium for individual pediatric patients remained within the same range and was independent of weight (See Section 19.4 for more details).

FDA agrees with the applicant that the thiosulfate clearance decreases by approximately 50% and Cmax increases approximately 25% in patients requiring hemodialysis compared with healthy subjects with normal renal function (See Section 19.4 for more details). See Section 6.3.2.3 for evaluation of the dosing regimen in patients with renal impairment. No dose adjustment is recommended for patients with renal impairment or end-stage renal disease.

FDA agrees with the applicant that hepatic impairment has limited impact on the thiosulfate PK as thiosulfate metabolism is modulated by thiosulfate sulfur transferase and thiosulfate reductase activity.

FDA agrees with the applicant that clinically relevant drug-drug interactions (DDI) are unlikely for sodium thiosulfate at the proposed dosing regimen (See Section 6.3.2.4 for more details).

6.2.2.3. Outstanding Issues

The Applicant's Position:

None.

The FDA's Assessment:

FDA agrees.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

The Applicant's Position:

PEDMARK is a clear and colorless sterile solution of STS anhydrous provided as a sterile solution in single use, United States Pharmacopoeia (USP) (b) (4) 100 mL, clear glass vials that contain STS at 80 mg/mL, water for injection (USP), boric acid (b) (4) and sodium hydroxide and hydrochloric acid for pH adjustment. The active ingredient, STS, is an inorganic salt that contains one thiosulfate anion and two sodium ions. Compared to commercially available STS drug products, PEDMARK has used drug substance STS anhydrous instead of STS pentahydrate and has lowered the boric acid concentration.

Given the high solubility of STS and the IV route of administration, no further specific formulation development was needed.

An overview of the absorption, distribution, metabolism, and elimination properties of PEDMARK is provided in Section 5.4 for nonclinical pharmacology/toxicology and Section 6.2.1 for clinical pharmacology and PK.

The FDA's Assessment: Refer to FDA's assessment in Section 6.2.1 for clinical PK and pharmacology.

6.3.2. Clinical Pharmacology Questions

6.3.2.1. Does the clinical pharmacology program provide supportive evidence of effectiveness?

The Applicant's Position:

Yes. In SIOPEL 6, the 20 g/m^2 STS dose was 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 STS dosing scheme normalized to BSA and adjusted for body weight did not affect the efficacy of otoprotection or AEs in this study, both when analyzing different groups based on body weight. Results from the popPK model and simulations incorporating maturation and growth effects support the use of a nominal STS dose level normalized to BSA as well as the proposed dose adjustments to 75% at a body weight of 5.0 to 10.0 kg and to 50% at a body weight below 5.0 kg. This dose regimen is expected to result in effective thiosulfate exposure levels as supported by simulation using popPK models irrespective of the functional relationship between growth (body size) and non-renal clearance. Only in the case of children with a body weight below 5.0 kg, the assumption of constant non-renal clearance would result in a potential underexposure. However, the same non-renal clearance in infants and adults seems highly

unlikely and when growth aspects are incorporated in the popPK model, simulated STS (thiosulfate) exposure at the end of infusion is within the same effective range for all children.

In SIOPEL 6 and COG ACCL0431, STS was administered 6 hours after the end of the CIS infusion. Cisplatin plasma levels were not determined in the clinical studies; however, a CIS population PK model from adults was used to extrapolate and predict exposures in children. Analyses showed that when STS is administered after a 6 hour delay, a direct interaction of STS with CIS causing interferance with tumoricidal effects is unlikely. This is because (i) CIS reactivity requires immediate pharmacodynamic initiation of tumoricidal effect following administration; (ii) only unbound CIS is active against tumor cells and protein binding is a major route of inactivation; (iii) unbound CIS levels rapidly decline by a factor of at least 10-fold after the end of the CIS infusion; (iv) persisting unbound platinum levels are likely to include platinum species without significant cytotoxic activity due to CIS metabolism. Hence, any remaining platinum levels 6 hours after CIS administration are considered insignificant compared to the total CIS exposure. Only in (newborn) children below 5 kg body weight, remaining platinum exposure may be above 10% because renal function is still developing in newborns during the first months. To what extent this fraction would still be active CIS or clinically significant is unknown.

Overall, the CIS data in the literature and the popPK model extrapolation support the delayed treatment of STS by 6 hours after the end of CIS as suggested by non-clinical studies and employed in clinical studies SIOPEL 6 and COG ACCL0431.

The FDA's Assessment:

FDA agrees with the proposed dosing regimen based on the clinical pharmacology information and the popPK simulations. FDA recommends not to administer PEDMARK if the time before starting the next cisplatin dose is less than 10 hours away, when cisplatin is to be administered on multiple consecutive days. FDA agrees that the predicted unbound plasma platinum levels 6 hours after CIS administration are low compared to the total CIS exposure (Table 3). The 6-hour delay of PEDMARK treatment after cisplatin chemotherapy can prevent interaction of sodium thiosulfate with the unbound cisplatin in plasma.

Table 4. Predicted Cisplatin Pharmacokinetics by Unbound Platinum in Children Mean (5th - 95th Percentile) prediction of 1000 virtual subjects per category

Weight	Dose	CL	V_{total}	Half-life	AUC0-∞ exposure	% AUC12-∞ remaining*
Kg		L/h/m²	L/m²	H	µg·min/mL to 100mg/m²	+12h to ∞ total AUC
2 – 5	1.8 mg/kg	16 12 - 20	58 46-75	Alpha: 0.05 h Beta: 3.5 h	394 297-510	13% 7.4 - 21%
5 – 10	2.7 mg/kg	16 13 - 21	37 31 – 44	Alpha: 0.10 h Beta: 2.4 h	376 289 – 477	5.6% 3.0 - 9.1%
10-15	78 mg/m²	20 15 - 25	30 27 – 33	Alpha: 0.13 h Beta: 1.9 h	314 240 – 394	2.5% 1.3 - 4.1%
15-25	80 mg/m²	22 17 - 28	25 22 – 28	Alpha: 0.17 h Beta: 1.6 h	283 219 – 358	1.2% 0.6 - 2.0%

** Residual unbound platinum exposure in plasma beyond 12 h after the start of CIS treatment (6 hour after the end of infusion; AUC12-∞) relative to the total exposure (AUC0-∞).*

Source: Table 10 of Section 2.7.2 Summary of Clinical Pharmacology Studies

Based on the 20 to 50 minute half-life of thiosulfate in plasma, a negligible amount of sodium thiosulfate remains in plasma 10 hours after completion of a sodium thiosulfate infusion. Therefore, subsequent cisplatin infusions administered no sooner than 10 hours after the completion of a PEDMARK infusion may avoid an interaction between thiosulfate and unbound cisplatin in plasma.

FDA identified that the proposed popPK model for STS has limitations in predicting the exposure with the proposed dosing regimen in young pediatric patients, as the developed model is based on a limited dataset of five pediatric subjects and eleven adults. Although the model fits the observed data well, the model is not able to describe the PK in pediatric patients at a younger ages (<6 months). Because of these uncertainties, sensitivity analysis was also conducted to test the robustness of the model simulations when the non-renal clearance is related to the body size, or when the non-renal clearance also follows the maturation function.

6.3.2.2. Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

The Applicant's Position:

Yes. The proposed PEDMARK dose normalized to BSA and adjusted for body weight when administered 6 hours after the end of each CIS infusion (up to 6 hours duration) is considered effective and tolerable in a pediatric population with localized, non-metastatic solid tumors, as supported by the 2 clinical studies (SIOPEL 6 and COG ACCL0341), literature, and available

PK analyses. In addition, the results support delayed administration of PEDMARK with varying CIS treatment regimens (ie, number of cycles, days per cycle, and daily CIS doses) for a range of tumor types.

The FDA's Assessment:

FDA agrees.

6.3.2.3. Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

The Applicant's Position:

No. Based on the assessment of intrinsic factors (ie, age, weight (SIOPEL 6 only), and gender), no dose adjustment or change in regimen is required.

No clinically meaningful differences in safety findings were observed between the age, gender, or weight subgroups within each study that would necessitate changes to the dosing recommendations in the proposed label.

SIOPEL 6 and COG ACCL0431 did not enroll patients <1 month of age, as patients in this age group have less well-developed sodium homeostasis; therefore, the safety of PEDMARK in this age group is unknown, 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. No new safety concerns were identified in these studies. 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.

The FDA's Assessment:

The proposed dosing regimen considered body weight and body surface area. Simulation results based on the final popPK model and sensitivity analyses suggest that at the recommended dosage, the geometric mean (±SD) maximum concentration (Cmax) was 13 ± 1.2 mM in pediatric patients with cancer. The predicted Cmax in patients weighing 5 to 10kg is comparable to the predicted Cmax in patients weighing more than 10kg (9.5% lower to 3% higher); the predicted Cmax in patients weighing less than 5kg is between 16% and 36% lower than the predicted Cmax in patients weighing more than 10kg.

FDA agrees with the applicant that no initial dose adjustment is needed for renal impairment. In the worst-case scenario, the Cmax of thiosulfate increased about 25% in patients requiring hemodialysis (off-hemodialysis). The Cmax of thiosulfate in patients with renal impairment is expected to lower than the Cmax of thiosulfate (IV injection equivalence of STS anhydrous 6.4 g/m^2 in children) indicated for acute cyanide poisoning. The labeling includes serum sodium and electrolytes monitoring for patients with glomerular filtration rate below 60 $mL/min/1.73m^2$. In

addition, the labeling recommend that PEDMARK is not administrated for patient with serum sodium > 145 mmol/liter.

6.3.2.4. Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

The Applicant's Position:

Dosing recommendations and the rationale for the recommendation is provided in Section 6.3.1, General Pharmacology and Pharmacokinetic Characteristics.

There have been no food effect studies with STS.

Sodium thiosulfate does not bind to human plasma proteins (Kowalski et al, 1952). The chemical properties of STS and observations that STS does not distribute readily across membranes (ie, 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. Results of in vitro studies did not reveal inhibition of CYP isoforms in microsomes close to the expected maximum plasma concentration for STS; only a borderline induction result for CYP2B6 was noted in cryopreserved hepatocytes from 1 donor (Module 2.5, Section 3.1.2.2).

For the overall risk assessment for PK drug-drug interactions, the STS PK profile and treatment schedule also need to be taken in to account. The duration of STS exposure during administration is limited and returns to pre-dose values within 3 to 6 hours after administration. High plasma levels are even more limited, given its half-life of 20 to 50 minutes. Furthermore, STS treatment is not chronically administered and is confined to a limited number of intermittent, single administrations generally over a 3- to 6-month period in conjunction with CIS treatment cycles. Even when given on consecutive days, plasma levels do not accumulate.

Therefore, given the in vitro results, STS chemical characteristics, PK profile, metabolism, and treatment schedule, clinically relevant PK drug-drug interactions would not be expected for STS. The potential for pharmacodynamic interaction of STS to interfere with CIS anti-tumor efficacy is considered elsewhere (Module 2.5, Section 3.2, Section 3.3, Section 3.4, and Section 4.5).

The FDA's Assessment:

Food does not affect the absorption of STS, as it isadministered by IV infusion.
FDA agrees with the applicant that clinically relevant drug-drug interactions (DDI) are unlikely for STS at the proposed dosing regimen based on following:

- The DDI potential of STS as an inhibitor of major CYP enzymes is unlikely based on AUCR calculations using static mechanistic models (FDA guidance for industry *In Vitro Drug Interaction Studies – Cytochrome P450 Enzyme and Transporter- Mediated Drug-Drug Interactions*). The predicted AUCR ratio for CYP2C19 is higher than the 1.25 cut-off value at Cmax. However, a clinically relevant DDI between STS and a CYP2C19 substrate is unlikely, as there is a very short time period for STS plasma concentration around Cmax

in a treatment cycle (thiosulfate half-life is 20 to 50 minutes and STS is administrated not more than 5 days daily in a given treatment cycle).

CYP Enzymes	IC_{50} (mM)	Probe Substrate	f_m	ACUR (Cmax = 13.3 mM; K_i = ½ IC_{50})
CYP1A2	180		1	1.15
CYP2C8	96.4	Repaglinide	0.71	1.18
CYP2C9	104	Celecoxib	0.89	1.22
CYP2C19	89.2	S-mephenytoin	0.91	1.26

- In vitro, sodium thiosulfate is an inducer of CYP2B6 but not of CYP1A2 or CYP3A4. Induction of CYP2B6 was noted in cryopreserved hepatocytes from 1 of 3 donors after a 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%). The clinical DDI potential of STS as an inducer of CYP2B6 is low as the thiosulfate half-life is 20 to 50 minutes and STS is administrated not more than 5 days daily in a given treatment cycle.
- The DDI potential of STS as a substrate of major CYP enzymes is unlikely as CYP isozymes are not involved in thiosulfate metabolism.

X X

Wentao Fu
Clinical Pharmacology Primary Reviewer

Jeanne Fourie Zirkelbach
Team Leader

X X

Youwei Bi
Pharmacometrics Primary Reviewer

Jiang Liu
Team Leader

7 Sources of Clinical Data

7.1. Table of Clinical Studies

The Applicant's Position:

Table 5: Efficacy and Safety 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

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

Abbreviations: ASAP=as soon as possible; BSA=body surface area; CIS=cisplatin; EFS=event-free survival; GCT=germ cell tumor; HB=hepatoblastoma; IV=intravenous(ly); OL=open-label; OS=overall survival; RD=Randomized; SR-HB=standard-risk hepatoblastoma; STS=sodium thiosulfate

[a] Five SIOPEL 6 randomized patients withdrew prior to treatment. Of the 109 patients remaining, 4 children randomized to the CIS+STS arm never received STS. These patients were assigned to the CIS Alone arm for the Safety Population (CIS Alone=56; CIS+STS=53) but remained in the CIS+STS arm for the ITT Population (CIS Alone=52; CIS+STS=57).

[b] Two COG ACCL0431 patients randomized to the CIS+STS arm did not receive STS and were excluded from both the Safety and Efficacy Populations (Observation=64; CIS+STS=59).

[c] "Newly diagnosed" meant previously untreated and not currently receiving cancer treatment for the diagnosis that made the child eligible for the study.

The FDA's Assessment:
FDA agrees with the Applicant's descriptions of the studies as outlined in Table 2.

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

The efficacy evaluation for this submission is based on SIOPEL 6 and COG ACCL0431.

SIOPEL 6 and COG ACCL0431 were designed and conducted by academic consortia for the purposes of establishing clinical practice guidelines for prevention of CIS-induced ototoxicity. In addition to being conducted in accordance with Good Clinical Practice (GCP), these studies were considered adequate and well-controlled studies as defined by 21CFR314.126 and form the primary evidence of efficacy of STS supporting this application. Both studies were open-label, multicenter, randomized, controlled studies evaluating the otoprotective effect of STS. The studies differed with regard to patient population, CIS and STS dosing, and assessment of the primary efficacy endpoint, as described below.

The patient populations differed between studies; children with a localized tumor type (SR-HB) were enrolled in SIOPEL 6 while children with various tumor types (both localized and disseminated) were enrolled in COG ACCL0431. As such, the demographics and Baseline disease characteristics differed between studies.

The dosing and administration of STS also differed between the studies (Table 4); though, importantly, in both studies, STS administration was within the desired 6- to 12-hour window relative to CIS administration. In both studies, STS was administered via a 15-minute IV infusion, beginning 6 hours after completion of each CIS infusion, as is the proposed STS dosing regimen for marketing. The dose of STS used in both studies was normalized to BSA, and, in both studies, adjusted based on the weight of the child for low-weight children.

The dosing regimen for CIS differed between disease types, with varying regimens of CIS being administered over 1 to 6 hours (Table 4). In SIOPEL 6, CIS dosing was weight based and administered as a 6-hour IV infusion. Four courses of CIS were given pre-surgery and 2 additional courses were given post-surgery. In COG ACCL0431, CIS 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, or associated hydration/mannitol diuresis; eligibility criteria required CIS infusion durations up to a maximum duration of 6 hours and an intended cumulative dose of $\geq$200 mg/m^2. When multiple daily doses of CIS were scheduled in COG ACCL0431, there must have been at least a 10-hour delay between any STS infusion and the beginning of the next day's CIS infusion.

The primary efficacy endpoint in SIOPEL 6 and COG ACCL0431 was the proportion of children with hearing loss; this was assessed by different criteria in each study, as described in Table 4, which is in keeping with the geographical regions of the consortia that conducted each study.

In both studies, all audiologic data were centrally reviewed by blinded reviewers. Hearing assessments in both studies included the following measurements:

- Measurement of bilateral pure tone air conduction thresholds at 8000, 6000, 4000, 2000, 1000, and 500 Hz (Brock Grade specifies to start with the high frequencies)
- Otoscopy
- Immittance evaluation (Brock allows for tympanometry as well)
- Where available, measurement of otoacoustic emissions including transient evoked otoacoustic emissions and distortion product otoacoustic emissions
- For children too young to cooperate with standard audiometric measurements, brainstem auditory evoked response should have been obtained instead

Additionally, American Speech Language Hearing Association (ASHA) specified that ultra-high frequency audiometry (bilateral pure tone air conduction thresholds at 9000 to 16000 Hz) was performed where available.

Regardless of the differences in study designs, populations, and efficacy evaluations between the studies, the efficacy of STS as an otoprotectant was consistent across studies, as described below.

Table 6: Key Design Elements of Phase 3 Studies in the STS Clinical Program

Study Name	SIOPEL 6	COG ACCL0431
Design	Multi-center, Open-label, Randomized, Controlled	Multi-center, Open-label, Randomized, Controlled
Regions	52 sites in 12 countries (United Kingdom, Ireland, Belgium, Denmark, France, Italy, Switzerland, Spain, Australia, New Zealand, United States, and Japan)	38 COG hospitals in the US and Canada
Tumor Type/Eligibility Criteria	• Histologically confirmed newly diagnosed HB • Standard-risk HB: PRETEXT I, II or III; Serum AFP >100 μg/L; No additional PRETEXT criteria • Children were not eligible if they had: o Previous chemotherapy o Hepatocellular carcinoma o Treatment starting more than 15 days from written biopsy report o Abnormal renal function o Recurrent disease o A previous hypersensitivity to STS	• Newly diagnosed[a] with any histologically confirmed GCT, HB, medulloblastoma, neuroblastoma, osteosarcoma, or other malignancy to be treated with CIS dose of ≥200 mg/m^2 (infused over ≤6 hours). This may have been the child's first or subsequent malignancy. • Receipt of prior CIS or carboplatin was not allowed, but other types of prior chemotherapy were permitted, including on a current treatment regimen to which CIS would be added • Normal audiometry results prior to enrollment • Performance status score ≥50 (Karnofsky criteria for >16 years; Lansky criteria for ≤16 years) • Serum sodium levels within a normal range, adequate hematological function, and adequate renal function
Treatment Groups (Randomization)	CIS (CIS Alone) vs CIS+STS (1:1)	CIS (Observation arm) vs CIS+STS (1:1)

Table 6: Key Design Elements of Phase 3 Studies in the STS Clinical Program

Study Name	SIOPEL 6	COG ACCL0431
Stratification Factors	• Country • Median age >15 months, <15 months • PRETEXT stage	• Prior cranial radiation • Without prior cranial radiation: o Age <5 years, ≥5 years o Duration of CIS infusion (<2 hours versus ≥2 hours)
Treatment	• CIS by infusion over a duration of 6 hours: 80 mg/m^2 (body weight >10 kg) 2.7 mg/kg (body weight ≥5 to ≤10 kg) 1.8 mg/kg (body weight <5 kg) • STS by a 15-minute infusion 6 hours after completion of CIS: 20 g/m^2 (body weight >10 kg) 15 g/m^2 (body weight ≥5 to ≤10 kg) 10 g/m^2 (body weight <5 kg)	• CIS: Eligibility required CIS treatment to be ≥200 mg/m^2 (variable) infused over a duration of ≤6 hours • STS: 16 g/m^2 by a 15-minute infusion 6 hours after completion of CIS (or 533 mg/kg for children whose therapeutic protocol administered CIS on a per-kg basis due to young age or small body size)
Treatment Regimen	• Pre-operative: 4 courses of CIS with or without STS on Days 1, 15, 29, and 43 • Post-operative: 2 courses of CIS with or without STS as soon as possible (but within 21 days of surgery completion) on Days 1 and 15. If surgery was delayed, 2 courses may also have been given prior to surgery, on Days 57 and 71 • Prior to surgery, patients with PD after 2 or more courses of CIS (with or without STS) were considered treatment failures and stopped STS treatment • Further chemotherapy treatment recommendations were provided, including treatment with PLADO	• 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 (except cumulative dose intended must be ≥200 mg/m^2), schedule, infusion rate (up to a maximum infusion of 6 hours) or associated hydration/mannitol diuresis • Treatment regimens in use included additional chemotherapeutic agents (other than CIS) depending on tumor type • 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

Table 6: Key Design Elements of Phase 3 Studies in the STS Clinical Program

Study Name	SIOPEL 6	COG ACCL0431
Duration of Follow-up	Per protocol, up to 5 years (or longer as clinically indicated and according to national guidelines); actual median 4.27 years	Per protocol, 10 years from the date that the patient started the study; actual median 5.33 years
Number of Patients Randomized	114 (CIS Alone=53; CIS+STS=61)[b]	125 (Observation [CIS]=64; CIS+STS=61)[c]
Age range[d]/ Gender (M/F)	1.2 months to 8.2 years (59 M/50 F)	1 to 18 years (76 M/47 F)
Primary Endpoint	Rate of Brock Grade (Brock et al, 1991) ≥1 hearing loss, measured by PTA, after[e] end of study treatment or at an age of at least 3.5 years, whichever was later	Proportional incidence of hearing loss between the CIS+STS arm and the Observation arm, as defined by comparison of ASHA criteria (ASHA, 1994) at Baseline and the 4-week follow-up evaluation
Secondary Endpoints	Response to preoperative chemotherapy, complete resection, complete remission, EFS, OS	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

Abbreviations: AFP=alpha fetoprotein ; CIS=cisplatin; ASHA= American Speech Language Hearing Association; COG=Children's Oncology Group; EFS=event-free survival; GCT=germ cell tumor; HB=hepatoblastoma; ITT=Intent-to-Treat; PRETEXT=pre-treatment tumor extension; OS=overall survival; PD=progressive disease; PLADO=CIS (=platinol) and doxorubicin; PTA=pure-tone audiometry; SIOPEL=International Childhood Liver Tumor Strategy Group; SR-HB=standard-risk hepatoblastoma; STS=sodium thiosulfate.

[a] "Newly diagnosed" meant previously untreated and not currently receiving cancer treatment for the diagnosis that made the child eligible for the study.

[b] Five SIOPEL 6 randomized patients withdrew prior to treatment. Of the 109 patients remaining, 4 children randomized to the CIS+STS arm never received STS. These patients were assigned to the CIS Alone arm for the Safety Population (CIS=56; CIS+STS=53) but remained in the CIS+STS arm for the ITT Population (CIS=52; CIS+STS=57).

[c] Two COG ACCL0431 patients randomized to the CIS+STS arm did not receive STS and were excluded from both the Safety and Efficacy Populations (Observation=64; CIS+STS=59).

[d] Age was recorded at the time of diagnosis. The age range presented is based on the Safety Population.

[e] All children had a definitive hearing evaluation when they completed treatment and were aged 3.5 years or older. If the child was old enough, the evaluation was done within 6 to 12 weeks after the last CIS dose.

8.1.1. SIOPEL 6

Trial Design

The Applicant's Description:

A comparison of the SIOPEL 6 and COG ACCL0431 trial designs was provided in Section 8.1, including a comparison of key design elements in Table 4 .

The FDA's Assessment:
FDA agrees with the Applicant's description of the studies as outlined in Table 3.

Study Endpoints

The Applicant's Description:

A comparison of the SIOPEL 6 and COG ACCL0431 study endpoints is provided in Section 8.1.

In SIOPEL 6, Brock grading (0 to 4, minimal to severe) was performed yearly until a reliable result (ie, a hearing test that could be centrally reviewed) was obtained through pure-tone audiometry (PTA) (age ≥3.5 years) (Module 2.7.3, Section 1.3.1.2.2). Though specified, children in SIOPEL 6 were often too young to have reliable Brock Grade assessments performed at Baseline. After the initial Baseline evaluation before the start of treatment, interim audiometry was recommended after every second cycle of CIS. In children younger than 3.5 years of age, interim audiometry was strongly recommended. All children had a definitive evaluation when they completed treatment and were aged 3.5 years or older. If the child was old enough, the evaluation was done within 6 to 12 weeks after the last CIS dose. If the children had hearing loss ≥Brock Grade 1 on the definitive audiologic evaluation, that was considered as positive for ototoxicity.

The FDA's Assessment:
FDA agrees with the applicant's description of the Brock grading as the endpoint to assess hearing for patients in SIOPEL 6. See Table 5 below for description of Brock grades. Because Brock grades use a cutoff of 40 dB HL, mild hearing loss may not be detected. All audiological data were centrally reviewed.

Statistical Analysis Plan and Amendments

The Applicant's Description:

Analysis Populations

In SIOPEL 6, the primary efficacy analysis was conducted on the Intent-to-Treat (ITT) Population, which comprised all randomized patients except those for whom informed consent

was withdrawn prior to start of study treatment, and those for whom study treatment would have been inappropriate because they had to be considered "high risk," regardless of whether or not study drug was administered. The Per-Protocol (PP) Population comprised all patients in the ITT Population who had received at least 1 dose of STS (if randomized to the CIS+STS arm); this population was used for evaluation of the secondary endpoints of response to preoperative chemotherapy, complete resection, complete remission, event-free survival (EFS), and overall survial (OS).

Analysis of Efficacy Endpoints

Primary Analysis

In SIOPEL 6, the primary endpoint was hearing impairment defined as Brock Grade ≥1 hearing loss determined by PTA at age ≥3.5 years. The Brock Grade of the better ear was used for the analysis (as shown in Table 5). Hearing impairment rates were calculated and compared between the 2 randomized treatment groups. 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 non-stratified Chi-square test with significance level of 5% and power of 80%. It was carried out in the ITT Population. Patients without a hearing loss assessment were counted as a failure (ie, had hearing loss) in this analysis. In response to FDA feedback, the primary efficacy analysis was changed from the Modified Intent-to-Treat (mITT) Population, which included patients in the ITT Population with a definitive hearing evaluation, to the ITT Population in the final statistical analysis plan (SAP). The ITT Population comprised all 109 patients in the study, and 101 patients 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 non-stratified Chi-square test was chosen to avoid any loss of power incurred by a stratified analysis. Patients without a hearing loss assessment were counted as a failure (ie, had hearing loss) in this analysis. A Cochran Mantel Haenszel (CMH) test stratified by factors used for the randomization was also performed.

In addition, the relative risk of hearing loss in the CIS+STS arm compared with the CIS Alone arm was also calculated, and shown with an exact 95% confidence interval (CI) (2.5% confidence limit to 97.5% confidence limit). Multiple sensitivity analyses were conducted to assess the robustness of the primary efficacy results.

Table 7: 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

PTA=pure-tone audiometry
Note: Results were obtained by PTA in both ears; the Brock Grade is derived from the "better" ear. Brock Grade 0 is not equivalent to normal hearing.
Source: Brock et al, 1991

Secondary Analyses

Multiple secondary endpoints were evaluated, as shown in Table 4. Event-free survival and OS was assessed and the methods of analysis are summarized below.

In SIOPEL 6, EFS was calculated from the time of randomization to the first of the following events: progression, relapse, second primary malignancy, or death. Event-free survival of patients without an event was censored at the time of last known follow-up visit. Overall survival was calculated from the time of randomization to death. Overall survival of alive patients was censored at the time of last known alive. Event-free survival and OS were graphically compared between the randomized groups by Kaplan-Meier plots. A log-rank test was calculated, stratified by the stratification factors used for randomization. The hazard ratio between the 2 groups was calculated by stratified Cox regression and was presented together with its asymmetrical 95% CI.

The statistical analyses for the remaining secondary endpoints conducted in SIOPEL 6 are summarized briefly below; full details can be found in SIOPEL 6 clinical study report (CSR) Section 4.6.3.2.3.

- **Response to preoperative chemotherapy:** The percentage of responders (complete response [CR] and partial response [PR]) was compared between the groups with a Chi-square test or Fisher's exact test (if the statistical assumptions for the Chi-square test were not fulfilled).
- **Complete resection**: Resection was reported as percentage of partial hepatectomy versus orthotopic liver transplantation (OLT) and was presented overall and by randomized group. The percentage of OLT was compared between the groups with a Chi-square test or Fisher's exact test (if the statistical assumptions for the Chi-square test were not fulfilled).

- **Remission status**: Complete remission was defined as lack of evidence of residual disease and normal (for age) alpha fetoprotein (AFP) at the end of study treatment. The percentages of complete remission, PR, progressive disease (PD), death, and not evaluable were presented overall and by randomized group. The percentage of complete remission was compared between the groups with a Chi-square test or Fisher's exact test (if the statistical assumptions for the Chi square test were not fulfilled).

The FDA's Assessment:

FDA generally agrees with the applicant's description of the efficacy endpoints. For the primary endpoint of hearing loss, the analysis was based on hearing loss assessments conducted within 6-12 weeks after the last dose for children 3.5 years or older. The applicant's CSR noted that the last patient reached 3.5 years of age in September 2017, so all patients should have had the opportunity to complete their definitive evaluation. However, there may have been cases when patients died or were lost to follow up prior to this final definitive hearing assessment, resulting in missing assessments. As mentioned by the applicant, patients with missing assessments were imputed as having hearing loss in the primary analysis.

FDA also has the following comments regarding the applicant's description of the analysis population and efficacy analysis methods:

1. The applicant's ITT population comprised all randomized patients except those for whom informed consent was withdrawn prior to start of study treatment, and those for whom study treatment would have been inappropriate because they had to be considered "high risk," regardless of whether or not study drug was administered. FDA does not agree with this definition and considers the ITT population to include all randomized patients. FDA will present the primary analysis results in this population with the excluded patients imputed as hearing loss.
2. The test for the primary analysis of hearing impairment was conducted at a nominal significance level of 5% (one-sided). There were two interim analyses for the primary endpoint and alpha was adjusted using a Lan-DeMets O'Brien Fleming alpha spending function: the first was after 34 patients were evaluable for the primary endpoint at a nominal alpha level of 0.00069 (one-sided) and the second was after 68 patients were evaluable at a nominal alpha level of 0.016 (one-sided), leaving a nominal alpha level of 0.045 (one-sided) for the final analysis. There was no multiplicity plan specified for the secondary endpoints, so they are considered exploratory only. Since the regulatory standard is to control type-1 error at a level of 5% (two-sided), all p-values reported for this study should be interpreted as nominal only.
3. The SAP pre-specified that the minimization method would be used for randomization. However, the applicant noted in the CSR that the database provider (CINECA) used a randomized permuted block design with block size 4 instead, contrary to what was pre-specified in the protocol/SAP. Thus, while the SAP pre-specified a re-randomization test,

this ultimately was not used due to the change in randomization scheme.

Protocol Amendments

The Applicant's Description:

Most amendments to the SIOPEL 6 protocol did not impact the study endpoints or assessments, safety meaurements, or analyses.

Those amendments impacting the safety assessments are described below.

Protocol Amendment 1

1. Added Bedside Nursing Worksheet and Figure 12.1 (Summary schema of treatment, hydration, sodium monitoring, blood pressure monitoring, and deoxyribonucleic acid blood sampling with 4 example start times);
2. Serum sodium monitoring time changed from 24 to 18 hours;
3. The text "Additionally, if the serum sodium is 146 to 150 mmol/L at 1 hour, the individual clinician looking after the patient may decide whether or not to give mannitol" was added;
4. Information was added regarding the use of anti-emetics.

Protocol Amendment 3

1. The cardioprotectant dexrazoxane was removed as a permitted concomitant medication in accordance with updated guidance from European Medicines Agency and clarification was added regarding the requirement for careful monitoring of cardiotoxicity;
2. The section on AE reporting was revised to add definitions; reference to events that were not to be regarded as serious adverse events (SAEs) were removed and replaced with "expected SARs (serious adverse reactions [SAR] which are expected can be reported on an 'expected SAR' form)";
3. The endpoints hypomagnesemia and renal toxicity were removed as events not collected as unexpected;
4. A section on monitoring pregnancies for potential SAEs was added;
5. The AE reporting period text changed from "occurring during therapy and until 30 days after the 'end of treatment visit"' to "from the date of commencement of protocol defined treatment until 30 days after the administration of the last treatment."

The FDA's Assessment:

The FDA agrees with the description of protocol amendments presented in this section. In addition, FDA acknowledges that clarification of the central audiology review procedures was added as part of Protocol amendment 1.
The SAP version 1.1 was amended to include the ITT population for primary efficacy analysis

instead of the modified ITT (mITT) population and added a re-randomization test to account for the minimization method used for randomization. However, as mentioned above, FDA does not agree with the Applicant's definition of ITT population; and the ITT population should include all randomized patients. Additionally, the re-randomization test was not used as the randomization scheme did not follow protocol.

8.1.2. SIOPEL 6 Study Results

Compliance with Good Clinical Practices

The Applicant's Position:

This study was conducted in accordance with the current version of the applicable regulatory and International Council for Harmonisation (ICH)- GCP requirements, the ethical principles that have their origin in the principles of the Declaration of Helsinki, and the local laws of the countries involved.

The FDA's Assessment:
The FDA acknowledges the Applicant's statement of compliance with GCP in the SIOPEL 6 Clinical Study Report.

Financial Disclosure

The Applicant's Position:

All financial interests/arrangements with clinical investigators have been adequately addressed as recommended in the FDA Guidance for Clinical Investigators, Industry, and FDA Staff, Financial Disclosure by Clinical Investigators (2013); please see Section 19.2.

The FDA's Assessment:
In accordance with 21 CFR 54, the Applicant submitted a financial disclosure certification document in module 1.3.4. The document includes a list of all investigators who participated in SIOPEL 6.

Patient Disposition

The Applicant's Position:

A total of 129 children were registered and 114 children were randomized in the study (61 patients in the CIS+STS arm and 53 patients in the CIS Alone arm) (SIOPEL 6 CSR Table 14.1.2.3). Of the 15 patients registered but not randomized, 13 patients were not randomized due to other (unspecified) reasons, 1 patient was due to withdrawal of parental consent, and 1 patient was due to ineligibility (SIOPEL 6 CSR Listing 16.2.1.1). Of the

114 patients randomized, 5 patients withdrew prior to treatment (2 patients due to withdrawal of parental consent, 2 patients due to reclassification as high risk, and 1 due to ineligibility) (SIOPEL 6 CSR Listing 16.2.2.1).

Study completion was defined as completion of the post-treatment hearing assessment. Therefore, patient disposition for study completion was based on the ITT Population. Of the 109 children in the ITT Population, 101 (92.7%) completed the study and 8 (7.3%) did not complete the study. The proportion of children who completed the study was higher in the CIS+STS arm than the CIS Alone arm (55 of 57 patients [96.5%] vs 46 of 52 patients [88.5%], respectively). In the CIS+STS arm, 1 child (1.8%) did not complete the post-treatment hearing assessment due to death and 1 child (1.8%) due to other reasons. In the CIS Alone arm, 4 children (7.7%) did not complete the post-treatment hearing assessment due to death and 2 children (3.8%) due to other reasons (SIOPEL 6 CSR Table 14.1.2.2).

The FDA's Assessment:

The FDA generally agrees with the Applicant's description of patient disposition. Of 109 patients in the applicant's ITT Population, 4 who were randomized to the CIS+STS arm did not receive STS and were analyzed in the CIS arm. As described above in Section 8.1.1, the applicant's ITT population excluded 5 randomized patients who withdrew prior to treatment. However, FDA considers the ITT population to include all 114 randomized patients. In FDA's analysis of the primary endpoint of hearing loss, the 5 patients excluded from the applicant's ITT population and the 8 patients who did not complete the study (missing hearing assessment) were counted as a failure (had hearing loss) for the primary analysis.

Protocol Violations/Deviations

The Applicant's Position:

A total of 23 children (21.1%) had protocol deviations during the study, all of whom had deviations in treatment compliance (for treatment compliance, see SIOPEL 6 CSR Section 5.4). 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) (Table 14.1.3). 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) (SIOPEL 6 CSR Listing 16.2.2.1).

The FDA's Assessment:

The FDA generally agrees with Applicant's description of protocol violations. Note that if the 5 patients randomized but not treated were considered protocol deviations in the 114 patient ITT population, then a total of 28 patients (24.6%) had protocol deviations. The reasons for protocol deviations/violations do not appear to be a significant cause of bias influencing the study results.

Table of Demographic Characteristics

The Applicant's Position:

Demographic characteristics were generally balanced between the CIS+STS and CIS Alone arms (Table 6).

Table 8: Summary of Patient Demographics (Safety Population; SIOPEL 6)

Variable	CIS Alone N=56	CIS+STS N=53	Total N=109
Age [a](months)			
N	56	53	109
Mean (SD)	18.1 (14.6)	18.9 (17.2)	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	25 (44.6)	25 (47.2)	50 (45.9)
Male	31 (55.4)	28 (52.8)	59 (54.1)
Race, n (%)			
White	36 (64.3)	28 (52.8)	64 (58.7)
Missing	6 (10.7)	11 (20.8)	17 (15.6)
Asian	7 (12.5)	6 (11.3)	13 (11.9)
Other	5 (8.9)	8 (15.1)	13 (11.9)
Black or African American	2 (3.6)	0	2 (1.8)
Height (cm)			
N	52	46	98
Mean (SD)	77 (11.9)	79.6 (15.1)	78.7 (13.5)
Median (Min, max)	76.0 (58, 113)	76.0 (45, 126)	76..0 (45, 126)
Weight [b] (kg)			
N	56	53	109
Mean (SD)	10.33 (3.19)	10.15 (3.85)	10.24 (3.51)
Median (Min, max)	9.55 (4.8, 20.7)	8.96 (2.6, 25.8)	9.30 (2.6, 25.8)

Variable	CIS Alone N=56	CIS+STS N=53	Total N=109

Abbreviations: CIS=cisplatin; CSR=clinical study report; max=maximum; min=minimum; SD=standard deviation; 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.
Source: SIOPEL 6 CSR Table 14.1.4.1.

The FDA's Assessment:

The FDA agrees with the demographic data as presented in Table 6 for the safety population. FDA also agrees with the demographic data for the ITT population efficacy population as presented in the SIOPEL 6 Clinical Study Report (see Table 9 below), note, race is missing for 6 patients in the CIS arm and 11 patients in the CIS+STS arm. This may be due to some EU countries not allowing the collection of race information. Demographic data were similar when considering all 114 randomized patients comprising the FDA's ITT population.

Table 9 Summary of Patient Demographics in the Efficacy Population, SIOPEL 6

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; 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.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The Applicant's Position:

Baseline disease characteristics were generally balanced between the CIS+STS and CIS Alone arms, with the exception of imbalances in the median AFP level and Pre-treatment Tumor Extension (PRETEXT) classification (see SIOPEL 6 CSR Table 14.1.4.1). The mean GFR for all patients in the Safety Set was 130.3 mL/min/1.73 m^2 and was similar in both treatment arms.

The majority of children had no caudate lobe involvement (89 patients [81.7%]), solitary tumor (98 patients [89.9%]), no evidence of tumor rupture (106 patients [97.2%]), no distant or lymph node metastases (107 patients [98.2%]) (though 2 patients [1.8%] had an uncertain status), and no portal vein involvement (91 patients [83.5%]). All patients with Baseline characteristics of multiple tumors, uncertain tumor rupture, uncertain distant metastases and uncertain lymph node metastases achieved complete remission at the end of treatment and none developed PD or had a relapse (see SIOPEL 6 CSR Listing 16.2.4.2, Listing 16.2.6.4, and Listing 16.2.6.6).

Diagnostic AFP levels >1000000 ng/mL have been shown to be a prognostic factor in hepatoblastoma (HB) outcome, and AFP levels between 1000 ng/ml and 1000000 ng/ml have been shown to have no prognostic value (Meyers et al, 2017). There was a slight imbalance in 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). Overall, 14 children (12.8%) had an AFP level of > 1000000 ng/mL, including 8 patients (14.0%) in the CIS+STS arm and 6 patients (11.5%) in the CIS Alone arm. Overall, 8 children (7.3%) had an AFP level of < 1000 ng/mL, including 4 patients (7.0%) in the CIS+STS arm and 4 patients (7.7%) in the CIS Alone arm.

There was a slight imbalance in 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), although this was consistent with the method of randomization (SIOPEL 6 CSR Section 3.5.3). There was no noticeable trend in children with PRETEXT III classification and death; of the 6 children who died during the study, 5 had a PRETEXT II classification at Baseline (SIOPEL 6 CSR Listing 16.2.4.2 and Listing 16.2.7.6).

The FDA's Assessment:

The FDA agrees with the description of baseline characteristics described above for the **safety population** with the exception of the AFP level at diagnosis. The FDA reviewers calculate the median AFP at diagnosis as 192,682.1 ng/mL (range 273-5,489,165) for the CIS+STS arm and 77,090 ng/mL (range 187-2,632,584.7). This discrepancy does not directly impact the interpretation of the results.

For the **efficacy population**, see Table 10 below. Baseline disease characteristics were generally balanced between treatment arms and similar to the Applicant's summary of the safety population. Baseline characteristic data in all 114 randomized patients comprising the FDA's ITT population were similar to what was seen in the applicant's ITT population .

Table 10 Baseline Disease Characteristics for the ITT Population, SIOPEL 6

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)

Variable	CIS Alone (N=52)	CIS+STS (N=57)	Total (N=109)
> 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)
Beckwith Wiedemann			
Yes	2 (3.8)	1 (1.8)	3 (2.8)
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)

Variable	CIS Alone (N=52)	CIS+STS (N=57)	Total (N=109)
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

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The Applicant's Position:

Cisplatin and STS were administered under the supervision of Investigators or attending staff, who monitored compliance. The mean CIS percent compliance (excluding PLADO) for the CIS+STS and CIS Alone arms were high and similar (97.55% and 97.28%, respectively) (Module 2.7.4, Section 1.2.3.1). The mean STS percent compliance in the CIS+STS arm was 94.79%. The mean CIS percent compliance (including PLADO) for the CIS+STS and CIS Alone arms was also high and similar (97.65% and 97.36%, respectively) (SIOPEL 6 CSR Table 14.3.1). The mean percent STS compliance in the CIS+STS arm (including PLADO) was 89.74%.

Concomitant medication use was not recorded comprehensively. The case report form (CRF) asked for "any other chemotherapy" and for "ototoxic medication," eg, aminoglycoside antibiotics, but not for other medication in general. In the CIS+STS and CIS Alone arms, the use of other chemotherapies was similar for carboplatin, doxorubicin, and irinotecan and the use of other ototoxic medications was similar as well (SIOPEL 6 CSR Table 14.3.1).

The FDA's Assessment:

The FDA reviewers calculate a discrepancy in treatment compliance, however, the difference is within a percent and does not impact the interpretation of the results.

Regarding concomitant medication, FDA agrees with the description above. Specifically, FDA acknowledges that ototoxic mediations were generally prohibited as defined by the protocol and if used, were well balanced between arms (see Table 11).

Table 11 Ototoxic Concomitant Medications by Treatment Arm (SIOPEL 6)

Ototoxic Drug	CIS Alone (n=56)	CIS+STS (n=53)	Total (n=109)
Gentamicin	1 (1.8)*	2 (3.8)	3 (2.8)
Vancomycin	1 (1.8)*	0	1 (0.9)
Teicoplanin	1 (1.8)*	1 (1.9)*	2 (1.8)

*Patients who had hearing loss as defined by the primary endpoint

Efficacy Results – Primary Endpoint (Including Sensitiity Analyses)

The Applicant's Position:

Hearing Loss

Primary Analysis

The primary objective of this study, to assess the efficacy of STS for reducing hearing impairment caused by CIS chemotherapy, was met. Hearing loss was defined by a Brock Grade ≥ 1 measured using audiologic evaluations (Module 2.7.3, Section 1.3.1.2.2). 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 8). The risk of having hearing loss was statistically significantly lower in the CIS+STS arm compared with the CIS Alone arm (relative risk: 0.521, 95% CI: 0.349, 0.778; p<0.001), corresponding to a clinically meaningful 48% lower risk after STS treatment. The results favoring CIS+STS over CIS Alone were similar using a CMH test stratified by country group, PRETEXT group, and age group (relative risk: 0.519, 95% CI: 0.356, 0.755; p<0.001).

Table 12: 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) (1)		0.521 (0.349, 0.778)
p-value (1)		<0.001
Relative Risk (95% CI) (2)		0.519 (0.356, 0.755)
p-value (2)		<0.001

Abbreviations: CI=confidence interval; CIS=cisplatin; CMH=Cochran-Mantel-Haenszel; ITT=Intent-to-treat; PRETEXT=Pretreatment Extent of Disease; PTA=pure-tone audiometry; SIOPEL=International Childhood Liver Tumors Strategy Group; STS=sodium thiosulfate.

(1) Relative risk and p-value from Chi-square test.

(2) Relative risk and p-value 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 subjects were randomized to and actually received during the study.
Source: SIOPEL 6 CSR Table 14.2.1.1

Sensitivity Analyses

Results of all sensitivity analyses supported the results of the primary analysis and demonstrated a statistically significantly lower risk of hearing loss in the CIS+STS arm compared with the CIS Alone arm; see SIOPEL 6 CSR Section 6.2.1.1.2 for details. These findings demonstrate that the results for the primary analysis are robust.

The FDA's Assessment:
FDA acknowledges the applicant's assessment of the primary endpoint of hearing loss in the 109 patient ITT population but notes that all reported p-values are nominal as the overall type-1 error was not controlled at 0.05 (two-sided) and no claims of statistical significance should be made. As previously discussed, FDA considers the ITT population to include all 114 randomized patients.

The primary efficacy results based on the 114 patient ITT population are provided below. Patients with missing hearing assessment were imputed as hearing loss. The relative risk along with Wald 95% confidence intervals are provided. The unadjusted relative risk (95% CI) is based on unstratified chi-squared test and the adjusted relative risk (95% CI) is based on CMH test based stratified by country group, age group and PRETEXT group.

Table 13: Hearing Loss in SIOPEL6 (ITT population)

Results (Patient experienced hearing loss, Y/N)	**CIS Alone (N=53)**	**CIS + STS (N=61)**
Yes, n (%)	36 (68%)	24 (39%)
No, n (%)	17 (32%)	37 (61%)
Unadjusted Relative Risk (95% CI)	0.58 (0.40, 0.83)	
Adjusted Relative Risk (95% CI)	0.58 (0.41, 0.81)	

Results were generally consistent across exploratory subgroup analyses as shown in the table below.

Table 14: Subgroup Analysis of Hearing Loss (ITT population)

Variable	**CIS**	**CIS + STS**	**Relative Risk (95% CI)**
Age Group			
< 15 months	22/30 (73%)	15/33 (45%)	0.62 (0.4, 0.95)
≥ 15 months	14/23 (61%)	9/28 (32%)	0.53 (0.28, 0.99)
Sex			
Male	21/30 (70%)	17/33 (52%)	0.74 (0.49, 1.1)
Female	15/23 (65%)	7/28 (25%)	0.38 (0.19, 0.78)

Race			
White	22/33 (67%)	17/36 (47%)	0.71 (0.46, 1.08)
Asian	6/7 (86%)	3/6 (50%)	0.58 (0.25, 1.37)
Black	2/2 (100%)	--	--
Other	3/5 (60%)	1/8 (13%)	0.21 (0.03, 1.49)
Country group			
Great Britain	14/21 (67%)	10/20 (50%)	0.75 (0.44, 1.28)
France	13/16 (81%)	8/23 (35%)	0.43 (0.23, 0.79)
Other	9/16 (56%)	6/18 (33%)	0.59 (0.27, 1.3)
PRETEXT			
I or II	21/31 (68%)	14/43 (33%)	0.48 (0.29, 0.79)
III	15/22 (68%)	10/18 (56%)	0.81 (0.49, 1.35)

There were a total of 13 patients in the 114 patient ITT population with missing hearing assessments: 7 patients on the CIS alone arm compared to 6 patients on the CIS+STS arm. In the primary analysis, these patients were included as failure/hearing impaired. The applicant conducted a sensitivity analysis in the modified ITT (mITT) population made up of the 101 patients in the ITT population with definite hearing assessment. Results in the mITT population were consistent with those in the ITT population as shown in the table below.

Table 15: Hearing Loss in SIOPEL6 (modified ITT population)

Results (Patient experienced hearing loss, Y/N)	**CIS Alone (N=46)**	**CIS + STS (N=55)**
Yes, n (%)	29 (63%)	18 (33%)
No, n (%)	17 (37%)	37 (67%)
Unadjusted Relative Risk (95% CI)	0.52 (0.33, 0.81)	
Adjusted Relative Risk (95% CI)	0.52 (0.34, 0.79)	

FDA conducted an additional sensitivity analysis based on the unlikely worst case scenario. Under the worst case scenario, instead of imputing a missing hearing assessment as a failure, missing assessments in the control arm of CIS alone were imputed as success/no hearing loss and missing assessments in the CIS+STS treatment arm were imputed as failure. The following table summarizes the results based on the worst case scenario.

Table 16: Sensitivity Analysis - Worst Case Scenario for SIOPEL6

Results (Patient experienced hearing loss, Y/N)	**CIS Alone (N=53)**	**CIS + STS (N=61)**
Yes, n (%)	29 (55%)	24 (39%)
No, n (%)	24 (45%)	37 (61%)
Unadjusted Relative Risk (95% CI)	0.72 (0.48, 1.07)	
Adjusted Relative Risk (95% CI)	0.74 (0.50, 1.08)	

FDA notes that the results of the primary endpoint of hearing loss in the 114 patient ITT population appear to be robust across the sensitivity analyses considered and agrees that the totality of the evidence supports a decreased incidence of hearing loss in the CIS+STS arm; however, FDA acknowledges several weaknesses to the study design and interpretation of the data.

- The Brock grading scale does not require baseline audiologic evaluation. Part of the applicant's explanation for the choice to use a grading system such as the Brock scale is that the majority of young children in this study would likely use different baseline tests as compared to the tests used at 3.5 years of age. Therefore, even if baseline testing was conducted, comparing change from baseline using two different tests is not feasible; however, the lack of a baseline assessment eliminates the ability to determine the degree of change that occurred after drug exposure. Since the presence of normal hearing was not an inclusion criteria in this trial, the lack of baseline data contributes to uncertainty about whether a patient with an abnormal grade on the Brock scale at the end of the study, developed this abnormality during the study or had this abnormality at baseline. The presence of baseline hearing loss in some patients could confound the study results.

- Additionally the Brock scale is focused on identifying functional difficulties, which is part of the applicant's rationale for using the better ear for assessment as well as lack of baseline testing. The Brock scale is less sensitive in identifying ototoxic hearing loss than the ASHA criteria (described below for COG ACCL0431 study) because of the use of absolute threshold criteria and reliance on the assessment of the better ear. The Brock scale would not identify all mild hearing loss since the threshold is ≥40 dB. The Brock scale allows for a patient to have ≥40 dB HL in one ear but would not be positive for ototoxicity if the better ear hearing threshold was <40 dB hearing loss.

Data Quality and Integrity

The Applicant's Position:

The data submitted are of sufficient quality and integrity.

The FDA's Assessment:
See FDA Assessment above of primary efficacy analysis.

Efficacy Results – Secondary and other relevant endpoints

The Applicant's Position:

Response to Preoperative Chemotherapy

Using SIOPEL 6 response criteria for the PP Population, the proportion of children with a PR at the last response evaluation after cycles 1 and 2 were 21 children (39.6%) in the CIS+STS arm and 28 children (53.8%) in the CIS Alone arm (Table 9). The proportion of children with stable disease after cycles 1 and 2 were 32 children (60.4%) in the CIS+STS arm and 24 children (46.2%) in the CIS Alone arm. Neither treatment arm had children with PD after cycles 1 and 2.

For the last response evaluation after cycles 3 and 4, the proportion of children with PR in the CIS+STS arm was 35 children (66.0%) and was 39 children (75.0%) in the CIS Alone arm. The CIS+STS arm had more children with stable disease (10 children [18.9%]) compared with the CIS Alone arm (5 children [9.6%]). A similar proportion of children had PD between the CIS+STS arm and the CIS Alone arm (5 children [9.4%] vs 5 children [9.6%], respectively).

After 4 cycles, the proportion of responders (defined as CR and PR, but no patients achieved CR after 4 cycles) were not significantly different between the CIS+STS arm (35 children [66.0%]) and the CIS Alone arm (39 children [75.0%]) (p=0.393). The proportion of children with PD was similar in the CIS+STS and CIS Alone arms (SIOPEL 6 CSR Listing 16.2.6.2). Compared with the PP Population, the responses in the CIS+STS and CIS Alone arms to preoperative chemotherapy using the SIOPEL 6 response criteria were similar in the ITT Population (SIOPEL 6 CSR Table 14.2.2.2).

Table 17: 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 (%)		

Statistic	CIS Alone (N=52)	CIS+STS (N=53)
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.
Source: SIOPEL 6 CSR Table 14.2.2.1.

Complete Tumor Resection

For the PP Population, there was no statistically significant difference in the percentage of partial hepatectomy vs OLT (p>0.999) (Table 10). Complete tumor resection results using the ITT Population were similar to the PP Population (SIOPEL 6 CSR Table 14.2.3.2).

Table 18: Summary of Complete Tumor Resection (SIOPEL 6, PP Population)

Statistic	CIS Alone (N=52)	CIS+STS (N=53)
Partial hepatectomy, n (%)	48 (92.3)	49 (92.5)
Liver transplantation, n (%)	4 (7.7)	4 (7.5)
P-value (1)		>0.999

Abbreviations: CIS=cisplatin; PP=Per Protocol; SIOPEL=International Childhood Liver Tumors Strategy Group; STS=sodium thiosulfate.

(1) P-value from Fisher's Exact Test.

Note: Treatment groups are treatments patients were randomized to receive and actually received.
Source: SIOPEL 6 CSR Table 14.2.3.1.

Remission Status

For the PP Population, there was no statistically significant difference in the proportion of children with complete remission 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) (Table 11).

The results of the complete remission assessment when performed by a Central Reviewer were generally similar for each category 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%]). Remission assessment results using the ITT Population were similar to the PP Population (SIOPEL 6 CSR Table 14.2.4.2).

Table 19: Summary of Remission Status at End of Treatment (SIOPEL 6, PP Population)

Statistic	CIS Alone (N=52)	CIS+STS (N=53)
Status as Reported by Investigator, n (%)		
Complete remission	45 (86.5)	49 (92.5)
Partial remission	1 (1.9)	2 (3.8)
Progressive disease	2 (3.8)	0
Died from disease	1 (1.9)	0
Died from other causes	1 (1.9)	0
Withdrawn from protocol	2 (3.8)	2 (3.8)
Complete remission	45 (86.5)	49 (92.5)
Not complete remission	7 (13.5)	4 (7.5)
P-value(1)		0.359
Status as Assessed by Central Reviewer, n (%)		
Complete remission	44 (84.6)	49 (92.5)
Partial remission	4 (7.7)	4 (7.5)
Progressive disease	2 (3.8)	0
Not Evaluable	1 (1.9)	0
Died from other causes	1 (1.9)	0
Complete remission	44 (84.6)	49 (92.5)
Not complete remission	8 (15.4)	4 (7.5)
P-value(1)		0.236

Abbreviations: CIS=cisplatin; PP=Per Protocol; SIOPEL=International Childhood Liver Tumors Strategy Group; STS=sodium thiosulfate.
(1) P-value from Fisher's Exact Test.
Note: Treatment groups are treatments patients were randomized to receive and actually received.
Note: Patients that were withdrawn from the protocol switched from protocol-defined treatment to other treatments.
Source: SIOPEL 6 CSR Table 14.2.4.1.

Duration of Follow-up

Overall, the median duration of follow-up for the PP Population was 4.27 years (interquartile range: 3.11 to 5.82 years), and was similar between the CIS+STS arm (4.55 years) and CIS Alone arm (4.17 years) (Table 12).

Table 20: Summary of Duration of Follow-up (Years) (SIOPEL 6, PP Population)

Statistic	CIS Alone (N=52)	CIS+STS (N=53)	Total (N=105)
Minimum	0.23	1.21	0.23
25%	3.10	3.27	3.11
Median	4.17	4.55	4.27
75%	5.81	5.82	5.82
Maximum	8.54	9.23	9.23

Abbreviations: CIS=cisplatin; PP=Per Protocol; SIOPEL=International Childhood Liver Tumors Strategy Group; STS=sodium thiosulfate.
Note: Duration of follow-up was derived based on the last survival follow-up date.
Source: SIOPEL 6 CSR Table 14.1.8.

Event-free Survival

For the PP Population, the proportion of children that had an event (defined as disease progression, relapse, secondary primary malignancy, or death) was similar between the CIS+STS arm (11 patients [20.8%]) and the CIS Alone arm (11 patients [21.2%]) (Table 13).

There was no statistically significant difference between the proportion of children that were censored at the time of their last known Follow-up Visit (ie, EFS) between the CIS+STS arm (42 patients [79.2%]) and the CIS Alone arm (41 patients [78.8%]) (hazard ratio: 0.96; 95% CI: 0.42, 2.23; p=0.932) (Table 13 and Figure 2).

Event-free survival results in the ITT Population were similar to those in the PP Population (SIOPEL 6 CSR Table 14.2.6.2 and Figure 1.2).

Table 21: 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 [Reference Group])		
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

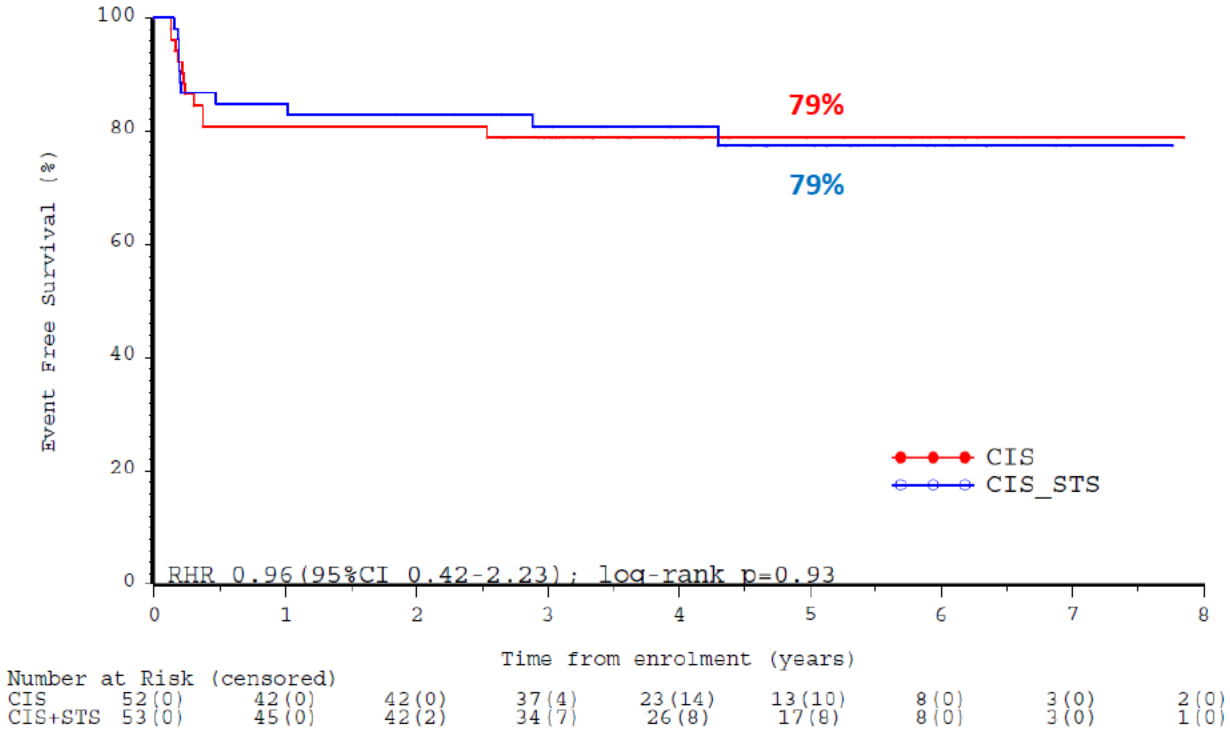
Abbreviations: CI=confidence interval; CIS=cisplatin; PP=Per Protocol; PRETEXT=Pre-treatment Tumor Extension; SIOPEL=International Childhood Liver Tumors Strategy Group; STS=sodium thiosulfate.

[a] Hazard ratio and 95% CI was 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.

Note: Time to event was calculated from the time of randomization to the first of the following events: progression, relapse, second primary malignancy or death. Patients without an event were censored at the time of last known Follow-up Visit.

Source: SIOPEL 6 CSR Table 14.2.6.1.

Figure 8: Event-free Survival (SIOPEL 6, PP Population)



Abbreviations: CI=confidence interval; CIS=cisplatin; EFS=event-free survival; PP=Per Protocol; RHR=relative hazard ratio; SIOPEL=International Childhood Liver Tumors Strategy Group; STS=sodium thiosulfate.
Note: The provided EFS percentages of censored patients are from 5 years after study entry.
Note: For the calculation of the EFS relative hazard ratio, the CIS Alone arm was the reference group.
Sources: SIOPEL 6 CSR Figure 1.1 and Table 13.

Overall Survival

For the PP Population, there was no statistically significant difference in the proportion of children who died during the study in the CIS+STS arm (2 patients [3.8%]) and in the CIS Alone arm (4 patients [7.7%]) (hazard ratio: 0.48; 95% CI: 0.09, 2.61; p=0.384) (Table 14 and Figure 3). For additional detail about deaths during the SIOPEL 6 study, see Module 2.7.4, Section 2.1.2.1.

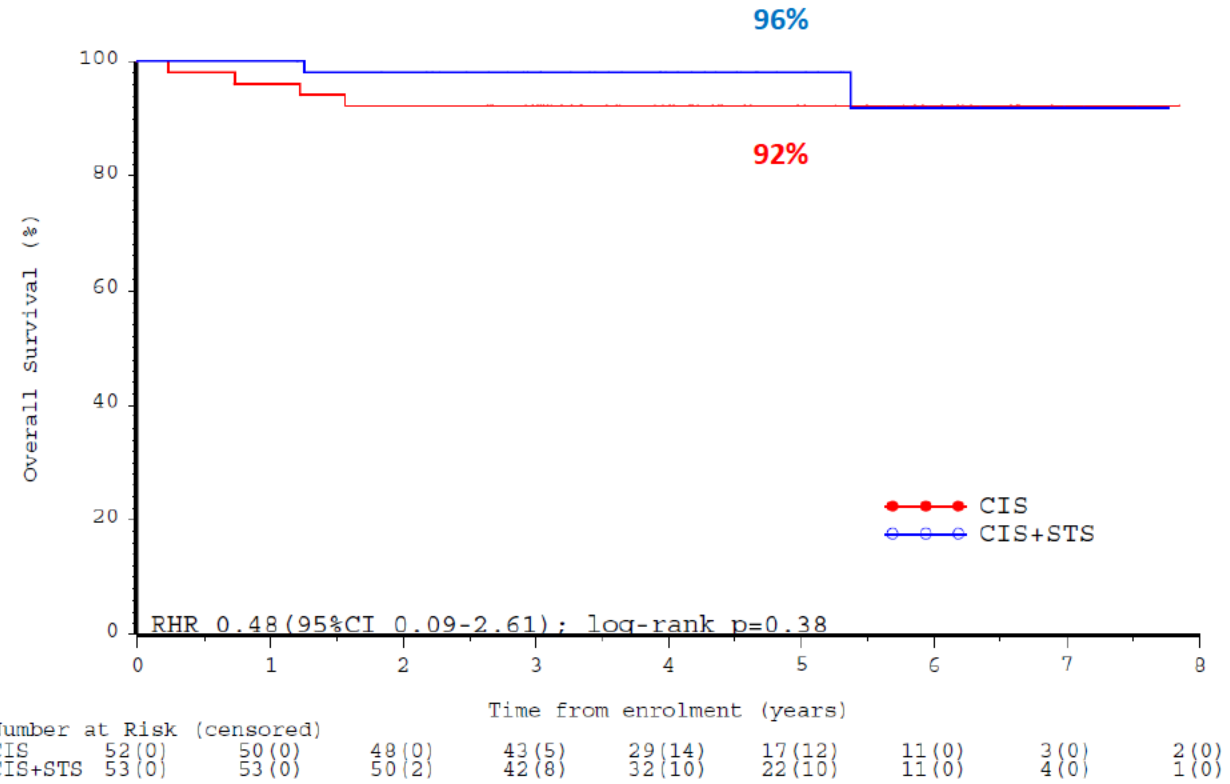
Overall survival results in the ITT Population were similar to those in the PP Population (SIOPEL 6 CSR Table 14.2.7.2 and Figure 2.2).

Table 22: Summary of Overall 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 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 [Reference Group])		
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; SIOPEL=International Childhood Liver Tumors Strategy Group; 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.
Source: SIOPEL 6 CSR Table 14.2.7.1.

Figure 9: Overall Survival (SIOPEL 6, PP Population)



Abbreviations: CI=confidence interval; CIS=cisplatin; OS=overall survival; PP-Per Protocol; RHR=relative hazard ratio; SIOPEL=International Childhood Liver Tumors Strategy Group; STS=sodium thiosulfate.
Note: The provided OS percentages of censored patients are from 5 years after study entry.
Note: For the calculation of the OS relative hazard ratio, the CIS Alone arm was the reference group.
Sources: SIOPEL 6 CSR Figure 2.1 and Table 14.

Alpha-fetoprotein Values

Alpha-fetoprotein values have been used as a tumor marker. In the PP Population, the mean AFP log-transformed values at baseline were similar between the CIS+STS and CIS Alone arms (5.031 ng/mL and 4.874 ng/mL, respectively) (Table 15).

Alpha-fetoprotein results in the ITT Population were similar to those in the PP Population (SIOPEL 6 CSR Table 14.3.5.1).

Table 23: Summary of Change in Log AFP from Baseline to End of Treatment and End of Follow-up (SIOPEL 6, PP Population)

Parameter Category/Statistic	CIS Alone (N=52)	CIS+STS (N=53)
Baseline AFP (log-transformed, ng/mL)		
N	52	53
Mean (SD)	4.897 (1.071)	5.031 (1.082)
Median (min, max)	5.029 (2.11, 6.42)	5.384 (2.20, 6.50)
After Course 2 Change from Baseline AFP		
N	52	53
Mean (SD)	-0.817 (0.496)	-0.635 (0.644)
Median (min, max)	-0.740 (-2.05, 0.00)	-0.650 (-2.48, 1.04)
95% CI (lower, upper)	-0.955, -0.679	-0.812, -0.457
P-value [a]	<0.001	<0.001
After Course 4 Change from Baseline AFP		
N	50	51
Mean (SD)	-1.956 (1.035)	-1.467 (0.769)
Median (min, max)	-1.890 (-4.28, 1.17)	-1.498 (-3.56, 0.08)
95% CI (lower, upper)	-2.250, -1.661	-1.683, -1.250
P-value [a]	<0.001	<0.001

Parameter Category/Statistic	CIS Alone (N=52)	CIS+STS (N=53)
End of Treatment Change from Baseline AFP		
N	49	53
Mean (SD)	-3.714 (1.149)	-3.792 (1.098)
Median (min, max)	-4.070 (-5.39, -0.66)	-4.013 (-5.66, -1.14)
95% CI (lower, upper)	-4.044, -3.384	-4.095, -3.490
P-value [a]	<0.001	<0.001

Abbreviations: AFP=alpha-fetoprotein; CI=confidence interval; CIS=cisplatin; max=maximum; min=minimum; PP=Per Protocol; SD=standard deviation; SIOPEL=International Childhood Liver Tumors Strategy Group; STS=sodium thiosulfate.

[a] P-value was from a paired t-test on mean change from baseline.

Source: SIOPEL 6 CSR Table 14.3.5.3.

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 (Table 16).

Disease relapse results in the ITT Population were similar to those in the PP Population (SIOPEL 6 CSR Table 14.2.8.2).

Table 24: Summary of Disease Relapse During Follow-up (SIOPEL 6, PP Population)

Parameter	CIS Alone (N=52) n (%)	CIS+STS (N=53) n (%)
Disease Status		
No Relapse	50 (96.2)	48 (90.6)
Relapse [a]	2 (3.8)	5 (9.4)
P-value [b]		0.437
Years from Surgery to Relapse		
Less than 1 Year	1 (1.9)	3 (5.7)
2 to 3 Years	1 (1.9)	1 (1.9)
3 to 4 Years	0	1 (1.9)

Abbreviations: CIS=cisplatin; PP=Per Protocol; SIOPEL=International Childhood Liver Tumors Strategy Group; STS=sodium thiosulfate.
[a] If the relapse date was missing, the patient contact date was used.
[b] P-value from Fischer's exact test.
Source: SIOPEL 6 CSR Table 14.2.8.1.

The FDA's Assessment:

The applicant's Per-Protocol (PP) Population comprised all patients in the ITT Population who had received at least 1 dose of STS (if randomized to the CIS+STS arm); this population was used for evaluation of the secondary endpoints of response to preoperative chemotherapy, complete resection, complete remission, event-free survival (EFS), and overall survival (OS).

With the exception of EFS and OS, FDA did not independently verify the secondary endpoint analysis since this trial was not designed to demonstrate anti-tumor activity. FDA notes that all secondary endpoint analyses are exploratory as no alpha was allocated to these endpoints. Thus, all p-values presented in relation to these endpoints should be considered nominal only and no claims of statistical significance should be made.

Though SIOPEL6 was not powered for EFS or OS, FDA considered the results of these analyses to help address the theoretical concern that STS could interact with CIS and decrease anti-tumor activity. In general, FDA agrees with the applicant's reported results for of EFS and OS in the PP population. FDA considers the 114 patient ITT population to be the more relevant population for analysis of EFS and OS but notes that no EFS or OS data was available for the 5 randomized patients the applicant excluded who withdrew prior to treatment. In the applicant's 109 patient ITT population, the EFS HR comparing CIS+STS arm with CIS alone was 0.89 (95% CI: 0.39, 2.05) and the OS HR comparing CIS+STS arm with CIS alone was 0.44 (95% CI: 0.08, 2.41). Though

there are limitations to these analyses due to small sample size, the results appear to show that there was no apparent difference between the two groups with respect to EFS or OS.

Dose/Dose Response

The Applicant's Position:

SIOPEL 6 confirmed that STS treatment at 16 to 20 g/m^2 resulted in statistically significant reductions in ototoxicity in patients with various types of solid tumors treated with CIS (Module 2.5, Section 4.4) while not affecting the anti-tumor efficacy of CIS in patients with localized, non-metastatic solid tumors (Module 2.5, Section 4.5).

The FDA's Assessment:
A consistent body-surface-area dose was used for this study; therefore FDA cannot determine if a there is dose-response related to the magnitude of prevention of hearing loss.

Durability of Response

The Applicant's Position:

All data related to the effect of STS over time in SIOPEL 6 is presented earlier in this section.

The FDA's Assessment:
This study was not designed to assess tumor response. Regarding persistence of effect of STS efficacy on hearing, see below (not relevant).

Persistence of Effect

The Applicant's Position:

Sodium thiosulfate was only given during chemotherapy treatment and audiometry was performed yearly until a reliable result (ie, a hearing test that could be centrally reviewed) was obtained through PTA (age ≥ 3.5 years). Thus, persistence of STS efficacy over time is not relevant.

The FDA's Assessment:
Not applicable.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

The Applicant's Position:

No patient-reporated outcome endpoints were included in the SIOPEL 6 study.

The FDA's Assessment:
Not applicable.

Additional Analyses Conducted on the Individual Trial

The Applicant's Position:

No additional analyses were conducted for the SIOPEL 6 study.

The FDA's Assessment:
Not applicable.

8.1.3. COG ACCL0431

Trial Design

The Applicant's Description:

A comparison of the SIOPEL 6 and COG ACCL0431 trial designs was provided in Section 8.1, including a comparison of key design elements in Table 4 .

The FDA's Assessment:
FDA agrees with the Applicant's description of the studies as outlined in Table 3.

Study Endpoints

The Applicant's Description:

A comparison of the SIOPEL 6 and COG ACCL0431 study endpoints is provided in Section 8.1.

In COG ACCL0431, ASHA (1994) criteria were used, which required audiological assessments at Baseline (prior to the first dose of CIS), at monitoring (within 8 days or, preferably, 72 hours prior to each CIS course), and at Follow up (at both 4 weeks and 1 year after final CIS course). Patients in follow up were to complete audiograms at 4 weeks and 1 year as per COG ACCL0431 Protocol, Section 7.1.

The FDA's Assessment:
FDA agrees with the applicant's description of the endpoints and has the following additional detail.

The primary endpoint was defined by ASHA criteria via comparison of the baseline and 4-week follow-up evaluations. Based on ASHA guidelines hearing loss is defined as the presence of any of these conditions:

(a) 20 dB decrease at any one test frequency,
(b) 10 dB decrease at any two adjacent test frequencies, or
(c) loss of response at three consecutive test frequencies where responses were previously obtained

*Results must be confirmed by repeat testing.

Audiological testing included: (a) measurement of bilateral pure tone air conduction thresholds at 0.5 to 8 kHz; (b) otoscopy by audiologist or other healthcare professional; (c) immittance evaluation; and (d) measurement of evoked OAEs, if available. For patients too young to cooperate with standard audiometric measurements, brainstem auditory evoked response (BAER) should have been obtained instead. Additionally, ultra-high frequency (UHF) audiometry was performed for patients 5 years of age or older at institutions where that modality was available. Measurements of UHF were of bilateral pure tone air conduction thresholds at 9 to 16 kHz.

Statistical Analysis Plan and Amendments

The Applicant's Description:

Analysis Populations

In COG ACCL0431, the primary efficacy analysis was conducted on the Efficacy Population, which comprised all children in the ITT Population who had both Baseline and 4-week follow-up hearing assessments. The ITT Population comprised all children who were randomized; this population was used for the anti-tumor efficacy data evaluation (ie, EFS and OS).

Analysis of Efficacy Endpoints

Primary Analysis

In COG ACCL0431, for the primary analysis comparing the proportional incidence of hearing loss between the CIS+STS arm and the Observation arm, hearing loss was treated as a dichotomous variable (as defined by ASHA criteria via comparison of the Baseline and 4-week follow-up evaluations). A logistic regression model was used to evaluate if there was any association between STS treatment and hearing loss when adjusting for the stratification variables. The odds ratio with associated 95% CI and p-value for the between-treatment comparison was estimated based on the model.

Similar analyses were performed for hearing loss by age group (<5 or ≥5 years) based on logistic regression including only the treatment as a fixed effect in the model. The odds ratio with associated 95% CI and p-value for the between-treatment comparison was estimated.

A sensitivity analysis was performed using the ITT Population. Children without hearing data were considered as hearing loss in the ITT analysis.

Secondary Analyses

Multiple secondary endpoints were evaluated, as shown in Table 4. Event-free survival and OS was assessed and the methods of analysis are summarized below.

In COG ACCL0431, for analyses on survival outcomes, with an estimated number of 65 eligible patients per arm, there was minimal power for a formal comparison of EFS between the 2 arms. The heterogeneous patient population further complicated the problem of estimating the power. Since the actual proportion for children with each tumor type could have been influenced by many factors such as competing COG disease-specific studies and different treatments by cancer type, the assumed 3-year EFS could only be approximate. Per COG ACCL0431 Protocol Amendment 1, the study also expanded enrollment to children with other rare tumors; the number of enrollments with each of the other diagnoses was even more difficult to speculate. These uncertainties and small number of patients per arm made calculations based on disease-stratified comparison impractical. Therefore, the observed ("pooled") EFS from the mixture of patients between the 2 arms was calculated. Since it was very difficult to predict the types and number of patients with other, rarer tumors who might have been enrolled, and since the power discussion was mostly for illustration, the sample size estimates for the "pooled" EFS were based on the 5 major tumor types only (see COG ACCL0431 SAP, Section 9.1). Per COG ACCL0431 Protocol Amendment 3, with approximately 130 eligible patients expected to be enrolled, there was only enough power (~84%) if the CIS+STS arm had much worse EFS; the power for detecting a smaller change in EFS would have been minimal. Therefore, a formal comparison of EFS/OS was not proposed between the 2 arms; instead, EFS and OS were monitored for the CIS+STS arm and the Observation Arm during the study.

For the secondary objective on monitoring EFS and OS, Kaplan-Meier curves (and corresponding 95% CI) of EFS/OS for the 2 arms were estimated. As exploratory analyses, EFS and OS between the 2 arms were compared using log rank tests. These analyses were performed at each scheduled interim monitoring period during accrual and in follow up after accrual was completed. Exploratory analyses of EFS/OS outcomes using Cox models with randomization stratification as covariates were performed.

The statistical analyses for the remaining secondary endpoints conducted in COG ACCL0431 are summarized briefly below; full details can be found in COG ACCL0431 CSR, Section 4.5.3.2.3.

- **Mean change in hearing thresholds for key frequencies:** hearing threshold was treated as a continuous variable and the mean change in hearing thresholds (from Baseline to the 4-week follow-up evaluation) was compared between the 2 arms for 5 key frequencies (500, 1000, 2000, 4000, and 8000 Hz). Linear regression analyses were used to assess whether STS treatment reduced the mean change in hearing thresholds when adjusting for stratification variables. Analyses were performed individually for each key frequency; no multiple comparison adjustment was made for these analyses. Hearing data were collected and reviewed by 2 different blinded central reviewers.

The FDA's Assessment: FDA notes that the sample size for COG ACCL0431 was planned to be 108 which would allow for 80% power to detect a treatment effect of 22.5% hearing loss in the CIS+STS arm compared to 45% hearing loss in the CIS only (observation) arm at a one-sided significance level of 0.05. Since the regulatory standard is to control type-1 error at a two-sided

level of 0.05, the p-value for the primary analysis for this study should be interpreted as nominal only. FDA also notes that no multiplicity plan was specified for the secondary endpoints, so they are considered exploratory and any p-values reported are nominal only.

Additionally, FDA does not agree with the applicant's definition of the efficacy population. For regulatory purposes, FDA defines the efficacy population as all patients enrolled and randomized in the trial who had non-metastatic disease. This population will be used to assess primary endpoint for this review and to support labeling.

Protocol Amendments

The Applicant's Description:

The significant amendments made to the COG ACCL0431 are described below.

Protocol Amendment 1

Protocol Amendment 1 was dated 31 Mar 2010. Based on the date of the amendment, 38 children were enrolled prior to this amendment (both first patient first visit and first patient first dose were 29 Oct 2008). This amendment was significant and included the changes summarized in the following subsections:

Expansion of Eligibility Criteria to Widen Patient Pool

Cranial Irradiation Prior to COG ACCL0431 Enrollment

COG ACCL0431 was originally written to exclude children with cranial irradiation prior to COG ACCL0431 enrollment, so that CIS would be the only treatment-related ototoxic exposure. One consequence of this was that most children with medulloblastoma were unable to enroll in COG ACCL0431 because those patients generally received their irradiation prior to administration of CIS. It was believed that accrual would be enhanced by including those children, provided they had normal hearing documented following irradiation (prior to study enrollment). It was anticipated that STS would provide its putative otoprotection from CIS, whether or not children had received prior irradiation. Thus, these children were expected to be equally evaluable for the primary study endpoint. With the addition of children with prior cranial irradiation, the randomization stratification was modified to include a separate stratum for them. As these enrollments were expected to be "older" medulloblastoma patients and only a minority of the future enrollments, randomization for them was not further stratified by age or CIS duration, unlike randomization for children without prior cranial irradiation. See Protocol Section 3.1.6, Section 3.2.4.2, Section 3.2.6.4, Section 3.3, Section 4.0, Section 4.4.2, Section 4.5.5, Section 7.1, and Section 9.1 for further information.

Any Newly Diagnosed Malignancy Treated with Cisplatin

COG ACCL0431 was originally written to include only children with GCTs, HB, medulloblastoma, neuroblastoma, or osteosarcoma. One consequence of this was that children

with other, less common malignancies also treated with CIS (eg, nasopharyngeal carcinoma and gastrointestinal cancers) were excluded. While individually rare, in aggregate, these patients would enhance accrual if allowed to be eligible. The original rationale for limiting eligible children to the 5 diagnostic categories previously mentioned was to estimate pooled EFS for purposes of monitoring the randomized children, as described in Protocol Section 9.0. However, monitoring of EFS involved comparison of 1 dosing arm with the other (CIS+STS versus Observation), not with historical or expected values. Randomization was expected to distribute children with other malignancies approximately evenly between the 2 dosing arms (note that the study was not designed to stratify by diagnosis). It was acknowledged that for each rare tumor type, it may not have been possible to achieve optimal balance between the 2 randomized arms. However, because of the small number of such patients, the imbalance was not expected to have significant impact on the observed survival outcomes for the 2 dosing arms. These added children were expected to experience similar otoprotective effect of STS as patients with the original 5 diagnoses, and therefore were to be equally evaluable for the primary endpoint. See Protocol Abstract, Experimental Design Schema, Section 1.1, Section 2.10, Section 3.2.2.1, Section 4.0, Section 9.1, and Section 9.2 for further information.

Addition of Optional Biology Study

As described in Protocol Section 2.9, an optional biology study was added to confirm the prior finding [Ross et al, 2009] that genetic variants in thiopurine S methyltransferase (TPMT) and catechol-O-methyltransferase (COMT) predispose to CIS-induced hearing loss, and to explore whether the effect of STS, if any, varied in children with and without genetic variants in TPMT and COMT. Due to an insufficient number of samples, however, this optional biology study was not included in the final analyses for COG ACCL0431.

Protocol Amendment 3

Protocol Amendment 3 was dated 10 Oct 2011. Based on the date of the amendment, 107 children were enrolled prior to this amendment. This amendment included a status change to "reactivation" and included changes to increase the maximum enrollment from 120 to 135 children over 3.5 years (rather than 3 years) (see Protocol Abstract and Sections 9.1, 9.2, 9.4, and Informed Consent).

The FDA's Assessment:

The FDA agrees with the description of protocol amendments presented in this section.

8.1.4. COG ACCL0431 Study Results

Compliance with Good Clinical Practices

The Applicant's Position:

This study was conducted in accordance with the current version of the applicable regulatory and ICH GCP requirements, the ethical principles that have their origin in the principles of the Declaration of Helsinki, and the local laws of the countries involved.

The FDA's Assessment:

The FDA acknowledges the Applicant's statement of compliance with GCP in the COG ACCL0431 Clinical Study Report.

Financial Disclosure

The Applicant's Position:

All financial interests/arrangements with clinical investigators have been adequately addressed as recommended in the FDA Guidance for Clinical Investigators, Industry, and FDA Staff, Financial Disclosure by Clinical Investigators (2013); see Section 19.2.

The FDA's Assessment:

In accordance with 21 CFR 54, the Applicant submitted a financial disclosure certification document in module 1.3.4. The document includes a list of all investigators who participated in COG ACCL04331.

Patient Disposition

The Applicant's Position:

A total of 131 children were enrolled in the study (Freyer et al, 2017). Six children were determined to be ineligible, and a total of 125 children were randomized to either the CIS+STS arm or the Observation arm (COG ACCL0431 CSR Table 14.1.4).

Two children in the CIS+STS arm did not receive any STS (COG ACCL0431 CSR Table 14.1.1). Of the remaining 123 children on the study, 102 of these children completed their chemotherapy regimen as planned; the number of children who completed chemotherapy was higher in the Observation arm (57 patients [89.1%]) than the CIS+STS arm (45 patients [76.3%]), and the 21 remaining children went off protocol therapy for other reasons including discontinuation of CIS therapy, refusal of protocol therapy by patient/parent/guardian, or because the physician determined it was in the patient's best interest. The patients continued to be followed-up after going off protocol therapy and remained in the study (COG ACCL0431 CSR Table 14.1.4).

The FDA's Assessment:
FDA agrees with the Applicant's description of patient disposition.

Protocol Violations/Deviations

The Applicant's Position:

Per COG policy, Protocol deviations were not defined in the protocol or recorded by the individual COG sites and therefore could not be summarized in this report. According to COG Policy 7.25 and in accordance with CTMB audit guidelines, deviations made in the best interest of the patient were not graded as deviations if they were well documented in the patient's medical record. Protocol deviations that were made in the interest of patient management were not subject to review and interpretation by a physician auditor (ie, COG Study Chair) or the COG quality coordinator. The physician responsible for the patient's management and care was stipulated to be the only individual authorized to decide if the patient should be removed from protocol therapy. Children's Oncology Group reviewed patient eligibility criteria and identified patients who were an eligibility deviation at the time of study entry (ineligible) or at the time of randomization (not evaluable).

The FDA's Assessment: The FDA agrees with Applicant's description of protocol violations.

Table of Demographic Characteristics

The Applicant's Position:

Demographics and baseline disease characteristics were balanced between the 2 arms overall (Table 17) and by age group (COG ACCL0431 CSR Table 14.1.3.2).

Table 25: Patient Demographics and Baseline Disease Characteristics (COG ACCL0431, ITT Population)

Variable	Observation (N=64)	CIS+STS (N=61)	Total (N=125)
Age (years), n (%)			
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)

Variable	Observation (N=64)	CIS+STS (N=61)	Total (N=125)
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 (%)			
GCT	16 (25.0)	16 (26.2)	32 (25.6)
Osteosarcoma	15 (23.4)	14 (23.0)	29 (23.2)
Medulloblastoma	14 (21.9)	12 (19.7)	26 (20.8)
Medulloblastoma	14 (21.9)	10 (16.4)	24 (19.2)
Supratentorial PNET	0	2 (3.3)	2 (1.6)
Neuroblastoma	12 (18.8)	14 (23.0)	26 (20.8)
Hepatoblastoma	5 (7.8)	2 (3.3)	7 (5.6)
Other	2 (3.1)	3 (4.9)	5 (4.0)
Atypical teratoid/rhabdoid 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)

Variable	Observation (N=64)	CIS+STS (N=61)	Total (N=125)
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; COG=Children's Oncology Group; ITT=Intent-to-treat; GCT=germ cell tumor; max=maximum; min=minimum; NOS=not otherwise specified; PNET=primitive neuroectodermal tumor; STS=sodium thiosulfate.
Source: COG ACCL0431 CSR Table 14.1.3.1.

The FDA's Assessment:
The FDA agrees with the applicant's description of the demographics for the ITT population; however, see Table 26 below for a comparison of demographics of those in the ITT population with non-metastatic disease (the relevant efficacy population). Note that the arms are not completely balanced with respect to certain demographics and baseline characteristics because randomization has been broken due to the fact that metastatic vs. non-metastatic disease was not a stratification factor.

Table 26 Patient Demographics and Baseline Disease Characteristics (COG ACCL0431, ITT Population, non-metastatic only)

Variable	Observation (N=38)	CIS+STS (N=39)	Total (N=77)
Age (years), n (%)			
N	38	39	77
Mean (SD)	8.6 (6.1)	8.6 (6.0)	8.6 (6.0)
Median (min, max)	7.1 (1.2, 17.7)	9.5 (1.1, 17.9)	8 (1.1, 17.9)
< 5, n (%)	15 (39.5)	16 (41)	31 (40.3)
≥ 5, n (%)	23 (60.5)	23 (59)	46 (59.7)
Sex, n (%)			
Male	25 (65.8)	22 (56.4)	47 (61)
Female	13 (34.2)	17 (43.6)	30 (39)
Race, n (%)			
White	24 (63.2)	24 (61.5)	48 (62.3)
Black	7 (18.4)	4 (10.3)	11 (14.3)
Asian	1 (2.6)	1 (2.6)	2 (2.6)

Variable	Observation (N=38)	CIS+STS (N=39)	Total (N=77)
American Indian or Alaska Native	0	1 (2.6)	1 (1.3)
Native Hawaiian or other Pacific Islander	1 (2.6)	1 (2.6)	2 (2.6)
Unknown	5 (13.2)	8 (20.5)	13 (16.9)
Ethnicity, n (%)			
Not Hispanic or Latino	30 (78.9)	28 (71.8)	58 (75.3)
Hispanic or Latino	5 (13.2)	10 (25.6)	15 (19.5)
Unknown	3 (7.9)	1 (2.6)	4 (5.2)
Diagnosis, n (%)			
GCT	9 (23.7)	9 (23.1)	18 (23.4)
Osteosarcoma	10 (26.3)	10 (25.6)	20 (26)
Medulloblastoma	12 (31.6)	9 (23.1)	21 (27.3)
Neuroblastoma	1 (2.6)	7 (17.9)	8 (10.4)
Hepatoblastoma	4 (10.5)	2 (5.1)	6 (7.8)
Other	2 (5.3)	2 (5.1)	4 (5.2)
Prior cranial irradiation	2 (5.3)	3 (7.7)	5 (6.5)

Abbreviations: CIS=cisplatin; COG=Children's Oncology Group; ITT=Intent-to-treat; GCT=germ cell tumor; max=maximum; min=minimum; NOS=not otherwise specified; PNET=primitive neuroectodermal tumor; STS=sodium thiosulfate.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The Applicant's Position:

Other baseline characteristics are discussed in the demographics section above.

The FDA's Assessment:
The FDA agrees.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The Applicant's Position:

Study medication was administered at the site, under the supervision of the Investigator or attending staff, and by trained personnel who recorded the dosing on the CRF.

The FDA's Assessment:

No consistent collection of data on specific concomitant medications was captured in the database. Antiemetics were indicated to prevent nausea and vomiting due to STS. Concurrent administration of loop diuretics (eg, ethacrynic acid, furosemide, and bumetanide) and/or aminoglycosides with CIS were to be avoided, if possible, because concurrent usage could have increased the risk of ototoxicity. If concurrent administration of these agents with CIS was indicated, administration information was recorded on standardized report forms but this was not included in the submission.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

The Applicant's Position:

Hearing Loss

Primary Analysis

The primary objective of this study, to assess the efficacy of STS for preventing hearing loss caused by CIS chemotherapy, was met.

Following the last dose of CIS, the proportion of children in the CIS+STS arm with hearing loss (14 patients [28.6%]) was approximately one-half of the proportion in the Observation arm (31 patients [56.4%]) (Table 18). The odds of having hearing loss as defined by the ASHA criteria were statistically significantly lower in the CIS+STS arm compared with the Observation arm (odds ratio: 0.274; 95% CI: 0.114, 0.660; p=0.0039), when adjusted for the stratification variables of prior cranial irradiation (yes versus no); age subgroup (< 5 years or ≥ 5 years), and duration of CIS infusion (< 2 versus ≥ 2 hours).

Table 27: Summary of Hearing Loss (COG ACCL0431, Efficacy Population)

Results	Observation (N=55)	CIS+STS (N=49)
N	55	49
Yes, n (%)	31 (56.4)	14 (28.6)
No, n (%)	24 (43.6)	35 (71.4)
Odds ratio (95% CI) (1)		0.274 (0.114, 0.660)
P-value (1)		0.0039

Abbreviations: ASHA=American Speech-Language-Hearing Association; CI=confidence interval; CIS=cisplatin; COG=Children's Oncology Group; STS=sodium thiosulfate.

(1) 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.
Source: COG ACCL0431 CSR Table 14.2.1.1.

Sensitivity Analysis

Results of the sensitivity analysis supported the results of the primary analysis and demonstrated a statistically significantly lower risk of hearing loss in the CIS+STS arm compared with the CIS Alone arm; see COG ACCL0431 CSR, Section 6.2.1.1.2 for details.

The FDA's Assessment: FDA acknowledges the applicant's assessment of the primary endpoint of hearing loss in their defined efficacy population but notes that all reported p-values are nominal as the overall type-1 error was not controlled at 0.05 (two-sided) and no claims of statistical significance should be made. Also, as noted above, for regulatory purposes, FDA does not agree with the efficacy population.

The FDA considers the population for efficacy to be patients in the ITT population with non-metastatic disease. The FDA evaluated the primary efficacy endpoint of hearing loss based on 77 patients in the ITT population with non-metastatic disease. Among these 77 patients with non-metastatic disease, 5 patients in the CIS alone arm and 8 patients in the CIS + STS arm had missing hearing assessments. Patient with missing hearing assessment were imputed as hearing impaired or failure for the primary efficacy analysis. The following table provides the primary efficacy results with relative risks and Wald 95% confidence intervals. The unadjusted relative risk (95% CI) is based on unstratified chi-squared test and the adjusted relative risk (95% CI) is based on CMH test based stratified by prior cranial irradiation, age group, and duration of CIS infusion.

Table 28: Hearing Loss in COG ACCL0431 for patients with non-metastatic disease (ITT population)

Results (Patient experienced hearing loss, Y/N)	**CIS Alone (N=38)**	**CIS + STS (N=39)**
Yes, n (%)	22 (58%)	17 (44%)
No, n (%)	16 (42%)	22 (56%)
Unadjusted Relative Risk (95% CI)	0.75 (0.48, 1.18)	
Adjusted Relative Risk (95% CI)	0.84 (0.53, 1.35)	

Additionally, the efficacy results from subgroup analysis involving patients in the ITT population with non-metastatic disease were generally consistent except for age group >=5 years. However, FDA notes that these results are based on post-hoc exploratory analyses with small subgroup sizes and the margin of error was high.

Table 29: Hearing Loss by Subgroup for patients with localized disease (ITT population)

Variables	CIS Alone	CIS + STS	Relative Risk (95% CI)
Age Group			
<5 years	13/15 (87%)	7/16 (44%)	0.5 (0.28, 0.91)
>=5 years	9/23 (39%)	10/23 (43%)	1.11 (0.56, 2.22)
Sex			
Female	7/13 (54%)	6/17 (35%)	0.66 (0.29, 1.48)
Male	15/25 (60%)	11/22 (50%)	0.83 (0.49, 1.41)
Race			
White	14/24 (58%)	10/24 (42%)	0.71 (0.4, 1.28)
Black	4/7 (57%)	1/4 (25%)	0.44 (0.07, 2.69)
Others	4/7 (57%)	6/11 (55%)	0.95 (0.41, 2.21)

The following table provides the efficacy results based on patients in the efficacy population, as defined by the Applicant, excluding any patient with missing hearing assessment, who have non-metastatic disease. There were a total of 13 patients with missing hearing assessment (5 patients on the CIS alone arm and 8 patients on the CIS+STS arm).

Table 30: Hearing Loss in COG ACCL0431 for patients with non-metastatic disease (efficacy population)

Results (Patient experienced hearing loss, Y/N)	**CIS Alone (N=33)**	**CIS + STS (N=31)**
Yes, n (%)	17 (52%)	9 (29%)
No, n (%)	16 (48%)	22 (71%)
Unadjusted Relative Risk (95% CI)	0.56 (0.30, 1.07)	
Adjusted Relative Risk (95% CI)	0.64 (0.32, 1.21)	

An additional sensitivity analysis was done considering the unlikely worst case scenario, where each missing hearing assessment in the CIS + STS arm is imputed as hearing impaired and each missing hearing assessment in the CIS alone arm is imputed as no hearing impairment. The adjusted and unadjusted relative risk are provided in the following table-

Table 31: Sensitivity Analysis - Worst Case Scenario for COG ACCL0431

Results (Patient experienced hearing loss, Y/N)	**CIS Alone (N=38)**	**CIS + STS (N=39)**

Yes, n (%)	17 (45%)	17 (44%)
No, n (%)	21 (55%)	22 (56%)
Unadjusted Relative Risk (95% CI)	0.97 (0.59, 1.61)	
Adjusted Relative Risk (95% CI)	1.07 (0.64, 1.79)	

FDA notes that these results should be considered exploratory and interpreted with caution since sample sizes are small and the study was not designed to study the non-metastatic patient population. Thus, while there may be a lower incidence of hearing loss in the CIS+STS arm compared to CIS alone, the true treatment effect is hard to quantify. Sensitivity analyses show that the unadjusted relative risk of hearing loss varies from 0.56 (95% CI: 0.30, 1.07) in the best case to 0.97 (95% CI: 0.59, 1.61) in the worst case. While adjusted relative risks estimated using a stratified CMH test were also provided, FDA notes that these stratified analyses may be limited by small sample sizes both overall and within strata, as well as heterogeneity of tumor types in the population.

Data Quality and Integrity

The Applicant's Position:

The data submitted are of high quality and integrity.

The FDA's Assessment:
FDA agrees that the data quality and integrity are acceptable.

Efficacy Results – Secondary and other relevant endpoints

The Applicant's Position:

Change in Hearing Thresholds

For both the left and right ears, there were no significant differences in the change in hearing threshold from baseline to 4 weeks after CIS treatment for the lower frequencies (≤ 2000 Hz) between the CIS+STS arm and the Observation arm, based on either independent reviewer's assessment (Table 19). Greater differences were observed for the CIS+STS arm compared with the Observation arm at the higher frequencies (≥ 4000 Hz) for both the left and right ears for both reviewers, with less hearing loss observed for the CIS+STS arm than the Observation arm at the higher frequencies. This finding is in keeping with high frequency hearing loss reported following platinum chemotherapy (Dickey et al, 2004; Dickey et al, 2005).

Table 32: Summary of Mean Change from Baseline Hearing Loss (COG 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

	Reviewer 1		Reviewer 2	
	Observation (N=55)	**CIS+STS (N=49)**	**Observation (N=55)**	**CIS+STS (N=49)**
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
4000 Hz – Right Ear, n	43	36	43	36
LS mean (SE)	11.2 (4.24)	4.1 (4.70)	11.2 (4.24)	4.0 (4.71)
LS mean treatment difference	--	-7.0	--	-7.3
P-value	--	0.0625	--	0.0553
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; COG=Children's Oncology Group; LS=least squares; SE=standard error; STS=sodium thiosulfate.
Note: Linear regression was used. Covariates included baseline values, stratum, and treatment. Observations with missing values were excluded from the model.
Sources: COG ACCL0431 CSR Table 14.2.4.1 and COG ACCL0431 CSR Table 14.2.4.2.

Duration of Follow-up

A summary of the duration of follow-up in years is presented for the ITT Population in Table 20.

Table 33: Summary of Duration of Follow-up (Years) (COG ACCL0431, ITT Population)

Statistic	Observation (N=64)	CIS+STS (N=61)	Total (N=125)
Minimum	0.57	0.23	0.23
25%	4.05	1.66	2.54
Median	5.60	4.95	5.33
75%	6.58	6.03	6.45
Maximum	8.27	8.28	8.28

Abbreviations: CIS=cisplatin; COG=Children's Oncology Group; ITT=Intent-to-treat; STS=sodium thiosulfate.
Note: Duration of follow-up was derived based on the last survival follow-up date.
Source: COG ACCL0431 CSR Table 14.1.3.3.

Event-free Survival

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 (Table 21).

Results of an exploratory analysis showed that there was no statistically significant difference in EFS between the CIS+STS arm and the Observation arm (hazard ratio: 1.27; 95% CI: 0.73, 2.18; p=0.3964) (Table 21 and Figure 4).

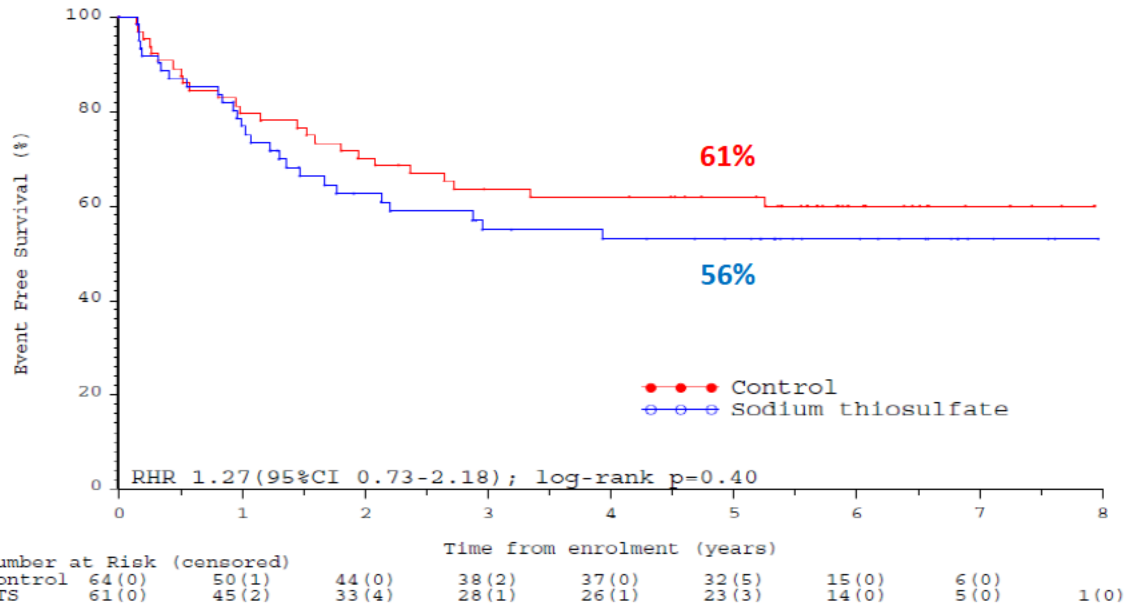
Results of a sensitivity analysis of EFS using stratification factors at randomization in a stratified log-rank test showed similar results (hazard ratio: 1.32; 95% CI: 0.76, 2.29; p=0.3263) (COG ACCL0431 CSR Table 14.2.2.2). Interpretation of these results is limited by the heterogeneity of the population.

Table 34: Summary of Event-free Survival (Median 5.33-year Follow-up) (COG ACCL0431, 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)
Treatment comparison (CIS+STS vs Observation [Reference Group])		
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; COG=Children's Oncology Group; ITT=Intent-to-treat; STS=sodium thiosulfate.
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.
Source: COG ACCL0431 CSR Table 14.2.2.1.

Figure 10: Event-free Survival (Median 5.33-year Follow-up) (COG ACCL0431, ITT Population)



Abbreviations: CI=confidence interval; COG=Children's Oncology Group; EFS=event-free survival; ITT=Intent-to-treat; RHR=relative hazard ratio; STS=sodium thiosulfate.
Note: "Control" is the Observation arm.

Note: The provided EFS percentages of censored patients are from 5 years after study entry.
Note: For the calculation of the EFS relative hazard ratio, the Observation arm was the reference group.
Sources: COG ACCL0431 CSR Figure 2.1 and Table 21.

Overall Survival

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 (Table 22).

Results of an exploratory analysis showed that there was no statistically significant difference in OS between the CIS+STS arm and the Observation arm (hazard ratio: 1.79; 95% CI: 0.86, 3.72; p=0.1132) (Table 22 and Figure 5). Interpretation of these results is limited by the heterogeneity of the population. Results of a sensitivity analysis of OS using stratification factors at randomization in a stratified log-rank test showed similar results (COG ACCL0431 CSR Table 14.2.3.2).

Of the 30 children who died during this study, 28 of these children died due to their underlying disease: 16 in the CIS+STS arm and 12 in the Observation arm (Module 2.7.4, Section 2.1.2.2). Of these, 13 of 16 deaths in the CIS+STS arm and 9 of 12 deaths in the Observation arm were related to progression of the disease, rather than to side effects of treatment.

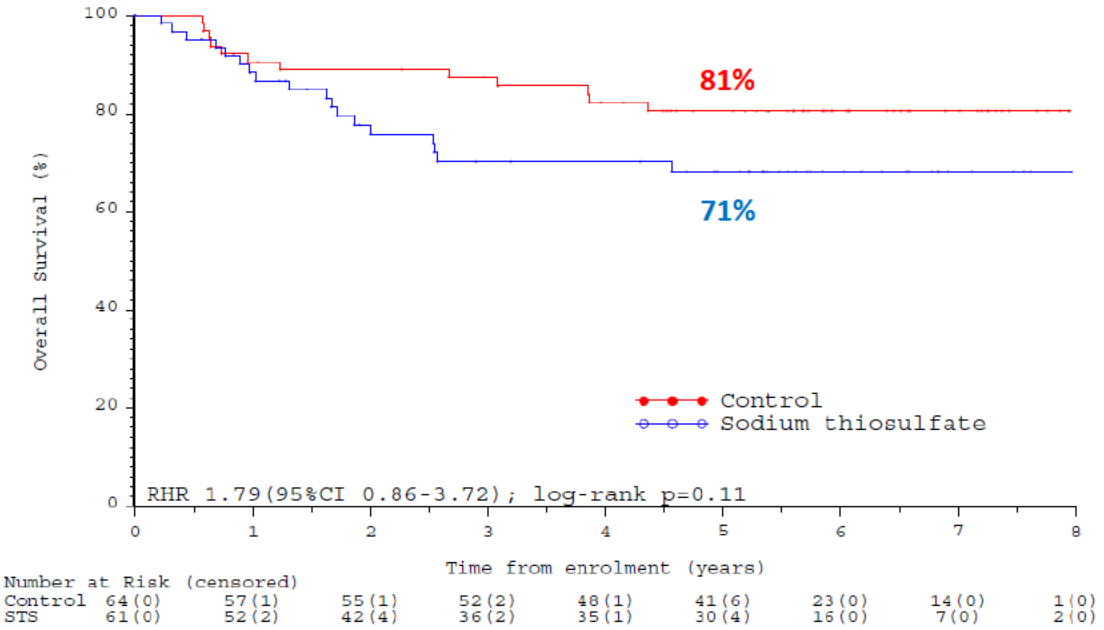
Two children, both in the CIS+STS arm, died due to causes other than their underlying disease. Neither of these deaths was considered by the Investigator to be related to study medication.

Table 35: Summary of Overall Survival (Median 5.33-year Follow-up) (COG ACCL0431, ITT Population)

Parameter Category (Statistic)	**Observation (N=64)**	**CIS+STS (N=61)**
Number of patients who died [(1)], n (%)	12 (18.8)	18 (29.5)
Number of patients censored, n (%)	52 (81.3)	43 (70.5)
Treatment comparison (CIS+STS vs Observation [Reference Group])		
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; COG=Children's Oncology Group; ITT=Intent-to-treat; STS=sodium thiosulfate.
(1) 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.
Source: COG ACCL0431 CSR Table 14.2.3.1.

Figure 11: Overall Survival (Median 5.33-year Follow-up) (COG ACCL0431, ITT Population)



Abbreviations: CI=confidence interval; COG=Children's Oncology Group; ITT=Intent-to-treat; OS=overall survival; RHR=relative hazard ratio; STS=sodium thiosulfate.
Note: "Control" is the Observation arm.
Note: The provided OS percentages of censored patients are from 5 years after study entry.
Note: For the calculation of the OS relative hazard ratio, the Observation arm was the reference group.
Sources: COG ACCL0431 CSR Figure 1.1 and Table 22.

The FDA's Assessment:

FDA notes that all secondary endpoint analyses are exploratory as no alpha was allocated to these endpoints. Thus, all p-values presented in relation to these endpoints should be considered nominal only and no claims of statistical significance should be made. FDA acknowledges the applicant's analyses of change in hearing thresholds as presented in the efficacy population. However these data were not verified by FDA and are considered exploratory. FDA also acknowledges that the study was not powered for EFS or OS and these analyses were exploratory. However, results for both endpoints suggested a potential detriment in the ITT population consisting of patients with metastatic and non-metastatic disease. FDA was particularly concerned about the potential detriment in OS. The study investigators shared this concern, and this is discussed further in the section on additional analyses conducted.

Dose/Dose Response

The Applicant's Position:

COG ACCL0431 confirmed that STS treatment at 16 to 20 g/m^2 resulted in statistically significant reductions in ototoxicity in patients with various types of solid tumors treated with CIS (Module 2.5, Section 4.4) while not affecting the anti-tumor efficacy of CIS in patients with localized, non-metastatic solid tumors (Module 2.5, Section 4.5).

The FDA's Assessment:
FDA agrees with the applicant's position.

Durability of Response

The Applicant's Position:

All data related to the effect of STS over time in COG ACCL0431 is presented earlier in this section.

The FDA's Assessment:

This study was not designed to assess tumor response. Regarding persistence of effect of STS efficacy on hearing, see below (not relevant).

Persistence of Effect

The Applicant's Position:

Because STS was only given during chemotherapy treatment and hearing was assessed up to 1 year later, persistence of STS efficacy over time is not relevant.

The FDA's Assessment:
Not applicable.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints
The Applicant's Position:

No patient-reported outcome endpoints were included in the COG ACCL0431 study.

The FDA's Assessment:
Not applicable.

Additional Analyses Conducted on the Individual Trial

The Applicant's Position:

A post-hoc analysis of EFS and OS in patients categorized with localized and disseminated disease (as determined post-hoc) was conducted by Fennec to address the findings published by COG in Freyer et al, 2017.

The protocol for COG ACCL0431 noted that, with the planned number of children at 65 per treatment arm, there would be minimal power for a formal comparison of EFS, with the heterogeneous patient population further complicating estimates of power. The statistical plan noted that the study had 84% power to detect a difference in EFS only if the Observation arm had a 3-year EFS of 59% with the STS arm being 34% and that such estimates would be highly dependent on the precise mix of tumor types of the patients who actually entered into the study. In the end, the difference between the groups was far less than this estimate, the OS was higher than expected, and there was no statistical difference in EFS or OS between the CIS+STS arm and the Observation arm (Module 2.7.3, Section 2.2.3.4 and Section 2.2.3.5).

Nevertheless, the study Investigators were concerned about a trend towards lower OS in the CIS+STS group and undertook a post-hoc evaluation of EFS and OS according to the extent of disease at the time of enrollment, classifying patients with a binary assignment to groups of localized or disseminated disease. The results of the post-hoc analysis (Freyer et al, 2017) suggested that, in patients categorized with disseminated disease, use of STS might be associated with reduced OS, although the publication noted that underlying diversity of patient tumor type, tumor biology, and staging were not taken into account during randomization and the study was only powered adequately for the primary hearing loss endpoint.

The following post-hoc analysis conducted by Fennec examines the results of the COG ACCL0431 study in patients categorized with localized and disseminated tumors to determine the possible explanations for the observed disparity in OS between the groups. Of note, 1 child (Patient (b) (6)) in the CIS+STS treatment arm had missing data for disease group and could not be categorized by localized or disseminated disease (Module 5.3.5.3 Table 12.1.1 and COG ACCL0431 CSR Listing 16.2.4.1). As such, 124 of the 125 randomized children in the COG ACCL0431 study were evaluated for this post-hoc analysis (77 children categorized with localized disease and 47 children categorized with disseminated disease).

Data are presented below for EFS and OS.

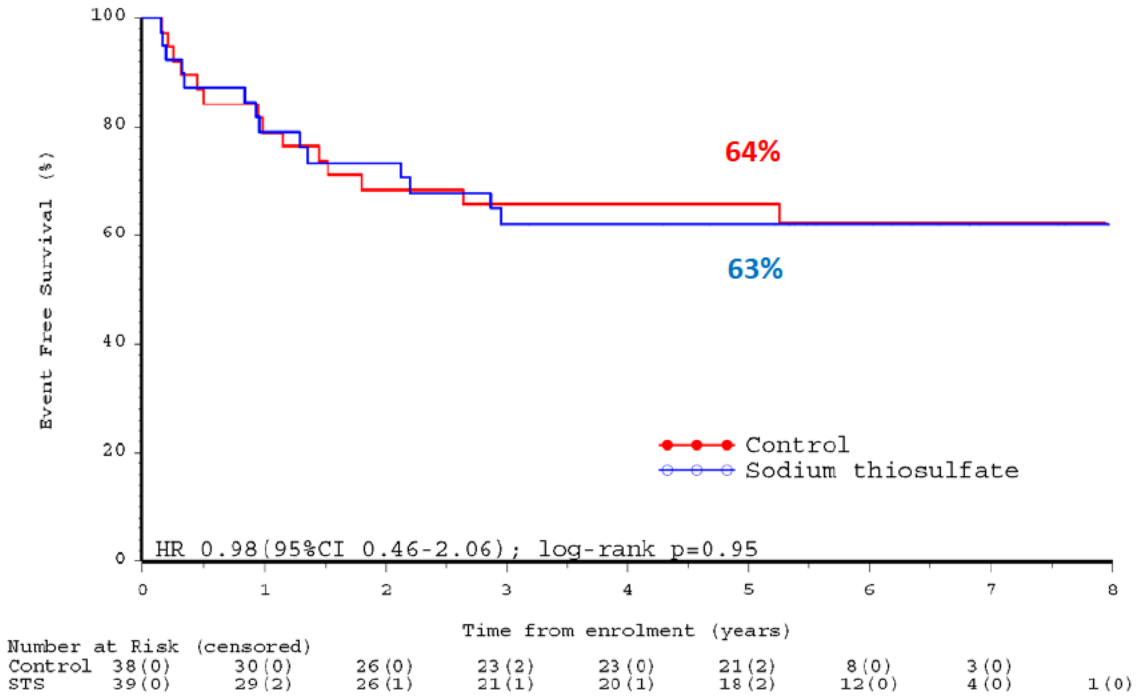
Post-hoc Analysis in Localized Disease

Fennec conducted a post-hoc analysis of EFS and OS by localized disease subgroup (determined post-hoc) with a median follow-up of 5.61 years (Module 5.3.5.3 Table 16.1). Results were similar to those with a median of 3.5 years follow-up, as published by Freyer et al 2017. Fennec further investigated efficacy and survival in the localized disease group to support the efficacy of STS and the effect of STS on anti-tumor efficacy of CIS.

Event-free Survival (Localized Disease)

Fourteen children categorized with localized disease in each arm experienced an event (Figure 6 and Module 5.3.5.3 Table 13.1). In children categorized with localized disease, a between group comparison showed no statistical difference in EFS between the arms (hazard ratio: 0.98; 95% CI: 0.46, 2.06 [p=0.9483]).

Figure 12: Event-free Survival (Median 5.61-year Follow-up) (COG ACCL0431, ITT Population, Localized Disease)

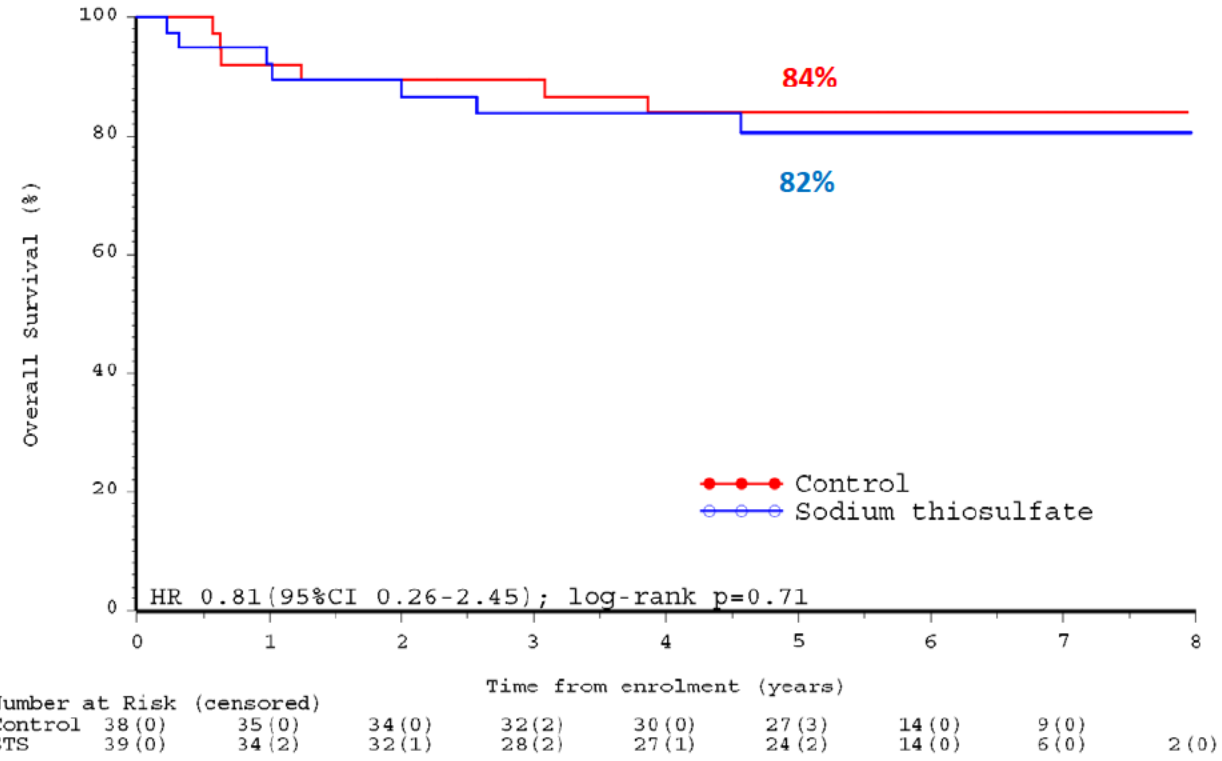


Abbreviations: CI=confidence interval; COG=Children's Oncology Group; EFS=event-free survival; HR=hazard ratio; ITT=Intent-to-treat; STS=sodium thiosulfate.
Note: The provided EFS percentages of censored patients are from 5 years after study entry.
Note: For the calculation of the EFS hazard ratio, the Observation arm was the reference group.
Sources: Module 5.3.5.3 Figure 2.1 and Module 5.3.5.3 Table 13.1.

Overall Survival (Localized Disease)

Thirteen children categorized with localized disease died during the study: 6 children (15.8%) in the Observation arm and 7 children (17.9%) in the CIS+STS arm (Module 5.3.5.3 Table 14.1). All deaths were considered due to disease progression with the exception of 1 death in the CIS+STS arm (Patient (b) (6)) (see COG ACCL0431 CSR Section 6.2.1.2.3 for additional detail), which was a cardiac arrest during the night, considered not related to STS. In children categorized with localized disease, a between-group comparison showed no statistical difference in OS between the arms (hazard ratio: 0.81; 95% CI: 0.26, 2.45 [p=0.7105]) (Figure 7).

Figure 13: Overall Survival (Median 5.61-year Follow-up) (COG ACCL0431, ITT Population, Localized Disease)



Abbreviations: CI=confidence interval; COG=Children's Oncology Group; HR=hazard ratio; ITT=Intent-to-treat; OS=overall survival; STS=sodium thiosulfate.
Note: The provided OS percentages of censored patients are from 5 years after study entry.
Note: For the calculation of the OS hazard ratio, the Observation arm was the reference group.
Sources: Module 5.3.5.3 Figure 3.1 and Module 5.3.5.3 Table 14.1.

Post-Hoc Analysis in Disseminated Disease

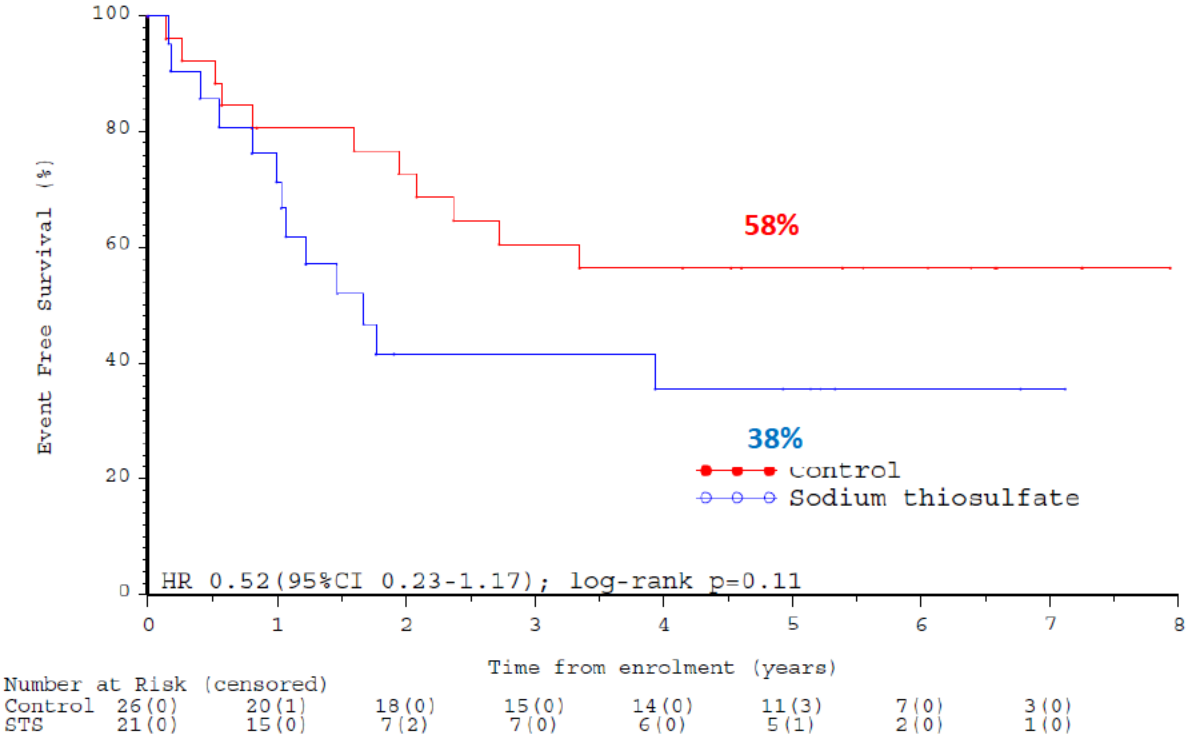
Fennec conducted a post-hoc analysis of EFS and OS by disseminated disease subgroup (determined post-hoc) with a median follow-up of 4.52 years (Module 5.3.5.3 Table 16.2). Results were similar to those with a median of 3.5 years follow-up, as published by Freyer et al 2017. Fennec further investigated efficacy and survival in the disseminated disease group to evaluate the efficacy of STS and the effect of STS on anti-tumor efficacy of CIS.

Event-free Survival (Disseminated Disease)

Thirteen children in the CIS+STS arm and 11 children categorized with disseminated disease in the Observation arm experienced an event (Module 5.3.5.3 Table 13.2 and Figure 8). Minimum and maximum EFS results were 1.5 to 7.1 years and 0.8 to 7.9 years in the CIS+STS and Observation arms, respectively. In children categorized with disseminated disease, a between group comparison of OS showed a hazard ratio of 0.52 in favor of the Observation arm (95% CI:

0.23, 1.17; p=0.1089) showing no statistically significant difference between the groups. However, Figure 8 below suggests a trend towards a reduced EFS in the CIS+STS arm.

Figure 14: Event-free Survival (Median 4.52-year Follow-up) (COG ACCL0431, ITT Population, Disseminated Disease)



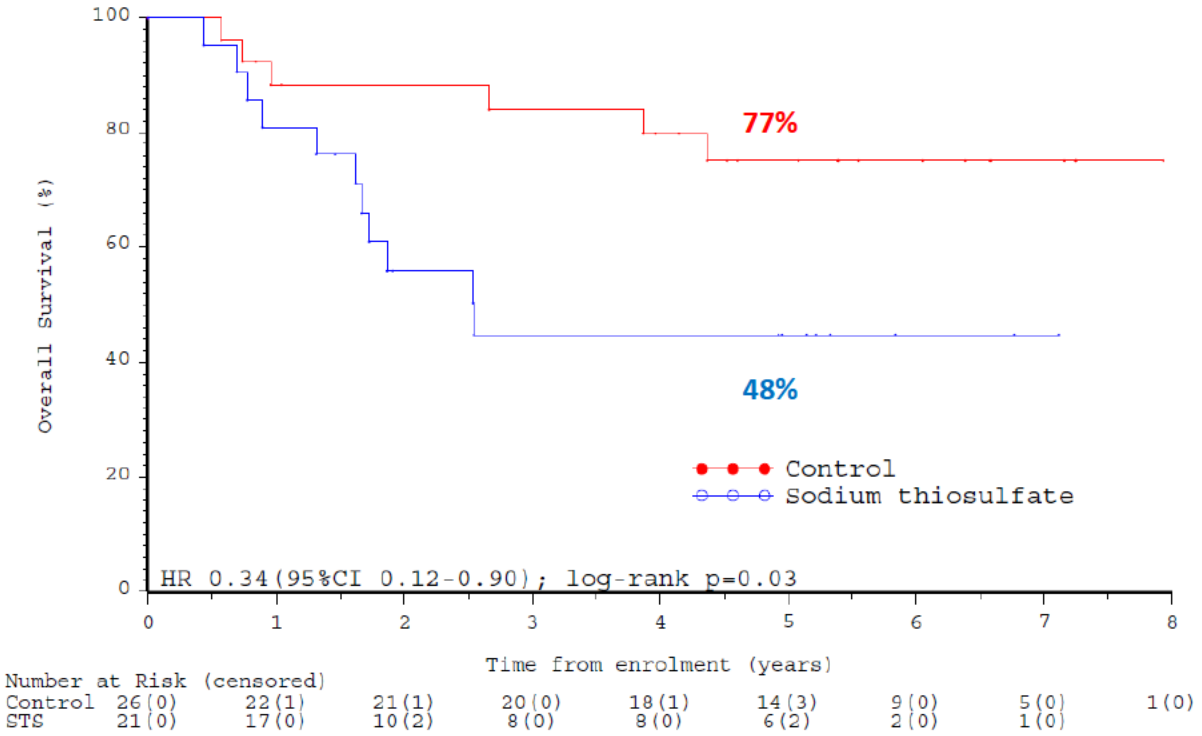
Abbreviations: CI=confidence interval; COG=Children's Oncology Group; EFS=event-free survival; HR=hazard ratio; ITT=Intent-to-treat; STS=sodium thiosulfate.
Note: The provided EFS percentages of censored patients are from 5 years after study entry.
Note: For the calculation of the EFS hazard ratio, the Observation arm was the reference group.
Sources: Module 5.3.5.3 Figure 2.2 and Module 5.3.5.3 Table 13.2.

Overall Survival (Disseminated Disease)

A total of 17 children categorized with disseminated disease died during the study; 6 children (23.1%) in the Observation arm and 11 children (52.4%) in the CIS+STS arm (Module 5.3.5.3 Table 14.2). In the Observation arm, all deaths were considered due to disease progression. In the CIS+STS arm, 10 deaths were due to disease progression and 1 was related to the child's participation in another trial at the time of disease relapse, during which he developed a consumptive coagulopathy as a result of experimental use of Vorinostat (Patient (b) (6).

In children categorized with disseminated disease, a between group comparison showed a difference in OS between the arms (hazard ratio: 0.34; 95% CI: 0.12, 0.90 [p=0.0265]) (Figure 9).

Figure 15: Overall Survival (Median 4.52-year Follow-up) (COG ACCL0431, ITT Population, Disseminated Disease)



Abbreviations: CI=confidence interval; COG=Children's Oncology Group; HR=hazard ratio; ITT=Intent-to-treat; OS=overall survival; STS=sodium thiosulfate.
Note: The provided OS percentages of censored patients are from 5 years after study entry.
Note: For the calculation of the OS hazard ratio, the Observation arm was the reference group.
Sources: Module 5.3.5.3 Figure 3.2 and Module 5.3.5.3 Table 14.2.

The FDA's Assessment:

FDA acknowledges the Applicant's rationale for conducting additional post-hoc analyses for survival given the theoretical concern for STS interference with anti-tumor activity of cisplatin. FDA again notes that this study was not designed to assess secondary endpoints of EFS and OS and the results should be interpreted with caution. However, FDA shares the study investigators' concern that results of the EFS and OS analyses suggest a potential detriment in these endpoints and agrees that additional analyses should be considered.

As noted by the applicant, the localized and disseminated disease (non-metastatic and

metastatic) subgroups were determined post-hoc. Thus, FDA notes that randomization was not stratified by these groups which may lead to some imbalances between arms within the subgroups. Additionally, sample size in these subgroups is small. Given these limitations, results from the post-hoc exploratory analyses of EFS and OS by localized and disseminated disease subgroups appear to suggest that the potential detriment seen for both endpoints may be driven by the disseminated disease subgroup. For this reason and others, the applicant proposed to limit the indication to patients with non-metastatic/localized disease and FDA agreed.

For discussion regarding possible explanation for decreased OS in patients with metastatic disease, see Section 8.1.5 (Assessment of Efficacy Across Trial, secondary endpoints).

8.1.5. Assessment of Efficacy Across Trials

Primary Endpoints

The Applicant's Position:

SIOPEL 6 and COG ACCL0431 were each designed with adequate statistical power to evaluate the primary endpoint of their respective studies, ie, to assess the effectiveness of STS as an otoprotectant. Though both studies were open-label, all audiologic data were centrally reviewed by blinded reviewers in each study. Due to the different study populations, control arms, and hearing assessment scales (Brock grading or ASHA) utilized in the Phase 3 studies, it is not possible to directly compare results of the 2 studies. That said, the extent of reduction in ototoxicity with STS was remarkably similar in the 2 studies.

Within each study, treatment with STS 6 hours after the end of CIS infusion resulted in statistically significant and clinically relevant reductions (approximately 50%) in the proportion of children with CIS-induced hearing loss whether evaluated using the Brock Grading scale (as in SIOPEL 6) or the ASHA criteria (as in COG ACCL0431) (Table 23). Replication of this finding across both studies demonstrates the efficacy of STS in the prevention of CIS-induced ototoxicity in patients with SR-HB as well as other solid tumor types.

In SIOPEL 6, the risk of having hearing loss at ages ≥3.5 years was statistically significantly lower in the CIS+STS arm compared with the CIS Alone arm (relative risk: 0.521, 95% CI: 0.349, 0.778; p<0.001), corresponding to a clinically meaningful 48% lower risk after STS treatment.

In COG ACCL0431, the odds of having hearing loss 4 weeks after the last course of CIS, as defined by the ASHA criteria, were statistically significantly lower in the CIS+STS arm compared with the Observation arm (odds ratio: 0.274; 95% CI: 0.114, 0.660; p=0.0039). The greatest difference between groups was observed for children <5 years of age. Results of a post-hoc analysis categorizing patients by localized and disseminated disease showed similar reductions in hearing loss regardless of the extent of disease (Module 2.7.3, Section 2.2.3.7.1.2 [localized] and Section 2.2.3.7.2.2 [disseminated]).

Multiple sensitivity analyses within each study support the robustness of these primary efficacy results (Module 2.7.3, Section 2.1.3.1.2 [SIOPEL 6] and Module 2.7.3, Section 2.2.3.1.2 [COG ACCL0431]).

Table 36: Summary of Hearing Loss in Phase 3 Studies of STS

Results	SIOPEL 6 ITT Population		COG ACCL0431 Efficacy Population	
	CIS Alone (N=52)	CIS+STS (N=57)	Observation (N=55)	CIS+STS (N=49)
Yes, n (%)	35 (67.3)	20 (35.1)	31 (56.4)	14 (28.6)
No, n (%)	17 (32.7)	37 (64.9)	24 (43.6)	35 (71.4)
Relative Risk (95% CI)		0.521 (0.349, 0.778)		0.516 (0.318, 0.839)
P-value [a]		<0.001		0.0040
Odds Ratio [b] (95% CI)		0.254 (0.111, 0.579)		0.274 (0.114, 0.660)
P-value [b]		0.001		0.0039

Abbreviations: ASHA=American Speech-Language-Hearing Association; CI=confidence interval; CIS=cisplatin; CMH=Cochran-Mantel-Haenszel; COG=Children's Oncology Group; ITT=Intent-to-treat; OR=odds ratio; PRETEXT=Pre-treatment Tumor Extension; PTA=pure tone audiometry; RR=relative risk; SIOPEL=International Childhood Liver Tumor Strategy Group; STS=sodium thiosulfate.

[a] In SIOPEL 6, relative risk was calculated non-stratified. In COG ACCL0431, relative risk was calculated using a CMH test including stratification variable.

[b] In SIOPEL 6 and COG ACCL0431, the odds ratio was based on logistic regression including treatment and stratification variable as a covariate in the model.

Note: In SIOPEL 6, patients without hearing loss assessment were included as a 'Yes' for hearing loss. Hearing impairment was defined as Brock Grade ≥1 hearing loss determined by PTA at age ≥3.5 years.

Note: In COG ACCL0431, 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.

Sources: Module 5.3.5.3 Table 8.1 and Module 5.3.5.3 Table 8.10.

In addition to the evaluation of the primary efficacy endpoint, a secondary endpoint in COG ACCL0431 provides further support for the effectiveness of STS as an otoprotectant. This secondary endpoint was the mean change in hearing thresholds for key frequencies (500, 1000, 2000, 4000, and 8000 Hz) between the CIS+STS arm and the Observation arm. The effect of STS at various hearing thresholds was not evaluated in SIOPEL 6.

For both the left and right ears in COG ACCL0431, there were no significant differences in the change in hearing threshold from Baseline to 4 weeks after CIS treatment for the lower frequencies (≤2000 Hz) between the CIS+STS arm and the Observation arm, based on either independent reviewer's assessment (Module 2.7.3, In-text Table 21). Greater differences were observed for the CIS+STS arm compared with the Observation arm at the higher frequencies (≥4000 Hz) for both the left and right ears for both reviewers, with less hearing loss observed for the CIS+STS arm than the Observation arm at the higher frequencies. This finding is in keeping

with high frequency hearing loss reported following platinum chemotherapy (Dickey et al, 2004; Dickey et al, 2005).

The FDA's Assessment:

FDA reiterates that, though both SIOPEL 6 and COG ACCL0431 were designed with adequate power for their respective primary endpoints, the type-1 error was controlled at a level of 0.05 (one-sided). Since the regulatory standard is to control type-1 error at a level of 0.05 (two-sided), the p-values associated with the primary endpoint in these studies were interpreted as nominal only and no claims of statistical significance should be made. Furthermore, FDA did not agree with the analysis populations in these studies, and the regulatory decision was based on FDA's analysis of the primary endpoint of each study in their respective re-defined populations.

FDA's analysis of the primary endpoint of hearing loss in SIOPEL 6 was based on the 114 patient ITT population which includes 5 randomized patients the applicant originally excluded who withdrew prior to treatment. In this population, the unadjusted relative risk was 0.58 (95% CI: 0.40, 0.83) and the adjusted relative risk was 0.58 (95% CI: 0.41, 0.81), both in the direction of a lower incidence of hearing loss in the CIS+STS arm. Results were robust across various sensitivity analyses. However, as noted in Section 8.1.2, limits to the interpretation of the data include the inability of the Brock scale to identify mild hearing loss and a slight imbalance in missing data. These factors could potentially bias the study results in favor of the STS arm, however, given the totality of the evidence, FDA agrees that the results are clinically meaningful.

FDA's analysis of the primary endpoint of hearing loss in COG ACCL0431 was based on the 77 patients in the ITT population with non-metastatic disease. In this population, the unadjusted relative risk was 0.75 (95% CI: 0.48, 1.18) and the adjusted relative risk was 0.84 (95% CI: 0.53, 1.35), both in the direction of a lower incidence of hearing loss in the CIS+STS arm. Since the study was not designed to assess hearing loss in the non-metastatic subgroup, the sample size is small and these results should be interpreted with caution. Sensitivity analyses suggested that the unadjusted relative risk of hearing loss could vary from 0.56 (95% CI: 0.30, 1.07) in the best case to 0.97 (95% CI: 0.59, 1.61) in the worst case.

FDA did not independently confirm the secondary endpoint of mean change in hearing thresholds for key frequencies in COG ACCL0431 and considers these results to be exploratory.

Secondary and Other Endpoints

The Applicant's Position:

When evaluating the effectiveness of STS as an otoprotectant, it was equally important to ensure that STS did not negatively impact the anti-tumor efficacy of CIS. The timing of administration of STS relative to CIS dosing was optimized in each study to minimize any potential of STS to affect the anti-tumor efficacy of CIS.

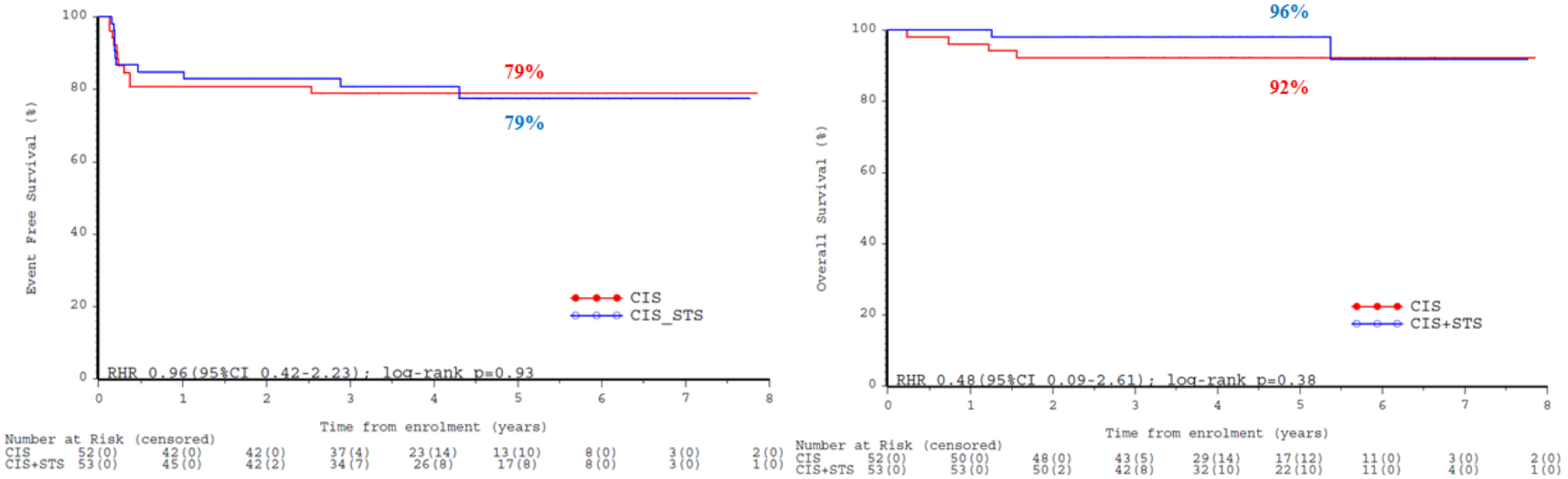
In addition to optimizing the timing of administration of CIS and STS relative to one another, multiple endpoints were evaluated in each study to assess the potential effect of STS on CIS anti-tumor efficacy. Event-free and OS were evaluated in both studies, though neither study was powered for this comparison. Specifically, it should be noted that in COG ACCL0431 (which enrolled children with various tumor types), the protocol proactively stated that there would be minimal power for a formal comparison of EFS, with the heterogeneous patient population further complicating estimates of power.

Both studies showed that there was no statistically significant difference in EFS or OS for the CIS+STS arm compared with the CIS Alone arm (SIOPEL 6) or with the Observation arm (COG ACCL0431) (Figure 10). This finding supports that treatment with STS does not negatively affect the anti-tumor efficacy of CIS.

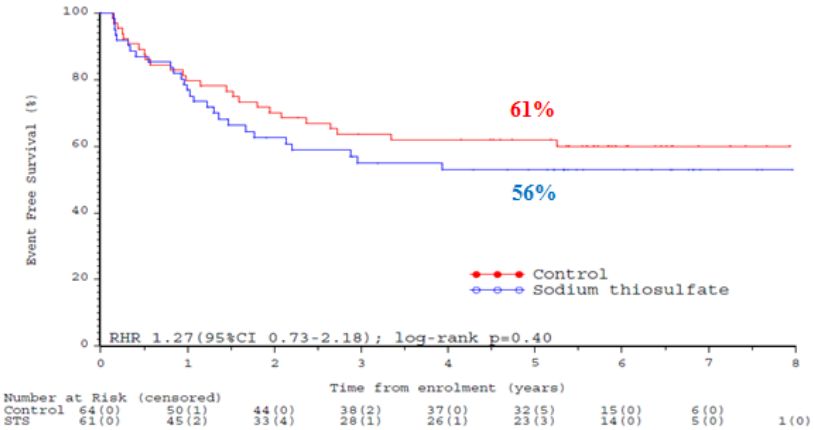
Figure 16: Event-free and Overall Survival in SIOPEL 6 and COG ACCL0431

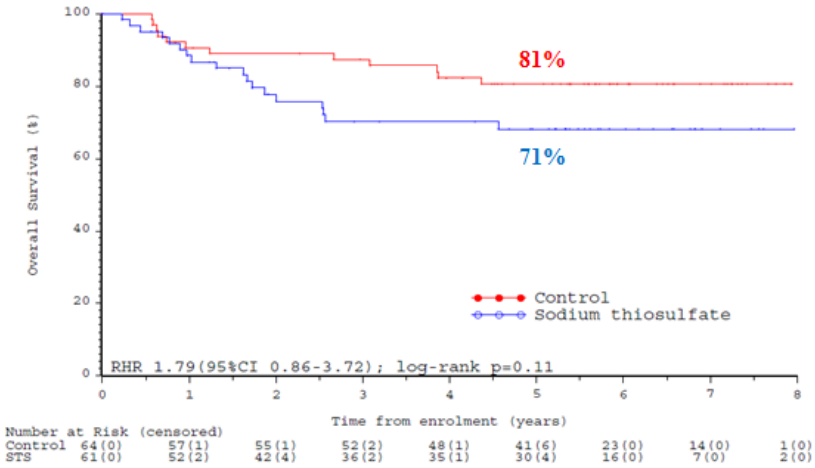
Event-free Survival **Overall Survival**

SIOPEL 6 (Median 4.27-year Follow-up)



COG ACCL0431 (Median 5.33-year Follow-up)





Abbreviations: CI=confidence interval; COG=Children's Oncology Group; EFS=event-free survival; ITT=Intent-to-treat; OS=overall survival; RHR=relative hazard ratio; SIOPEL=International Childhood Liver Tumor Strategy Group; STS=sodium thiosulfate.
Note: "Control" is the Observation arm.
Note: The provided EFS and OS percentages of censored patients are from 5 years after study entry.
Note: For the calculation of the EFS and OS relative hazard ratio, the CIS arm (in SIOPEL 6) and Control/Observation arm (in COG ACCL0431) was the reference group.
Sources: SIOPEL 6 CSR Figure 1.1, SIOPEL 6 CSR Figure 2.1, COG ACCL0431 CSR Figure 1.1, COG ACCL0431 CSR Figure 2.1.

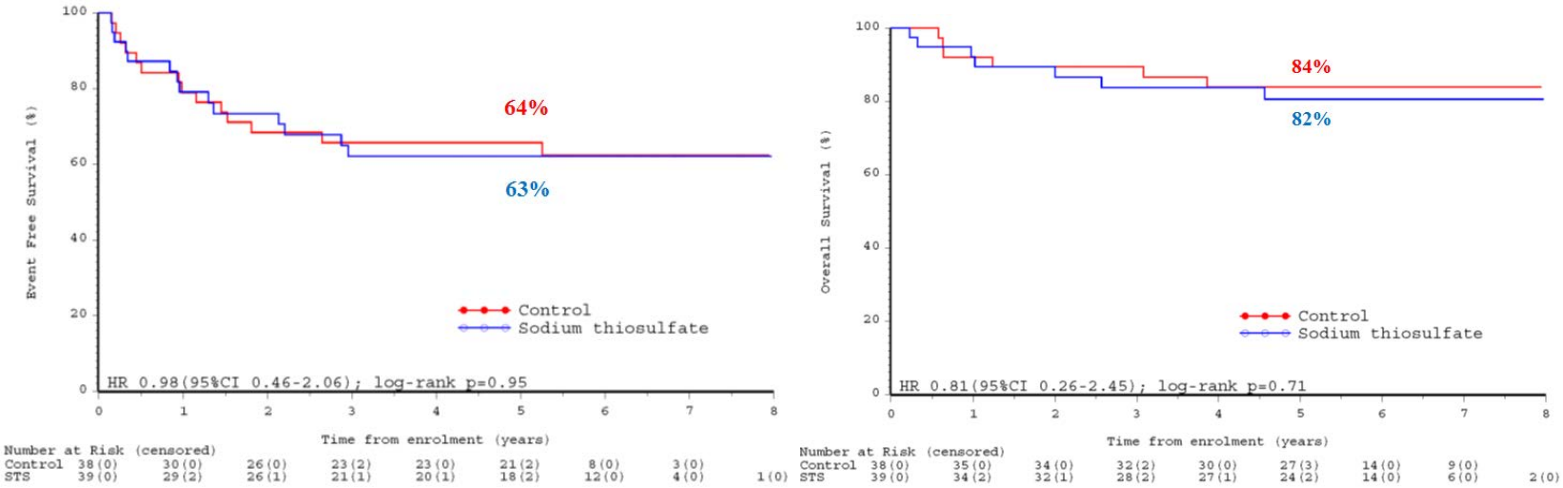
Nevertheless, the COG ACCL0431 study Investigators were concerned about a trend towards lower OS in the CIS+STS group and undertook a post-hoc evaluation of EFS and OS according to the extent of disease at the time of enrollment, classifying patients with a binary assignment to groups of localized or disseminated disease. The results of the post-hoc analysis (Freyer et al, 2017) suggested that, in patients categorized with disseminated disease, use of STS might be associated with reduced EFS and OS, although the publication noted that underlying diversity of patient tumor type, tumor biology, and staging were not taken into account during randomization and the study was only powered adequately for the primary hearing loss endpoint.

To address these published results, Fennec conducted its own post-hoc analysis of EFS and OS for patients categorized by localized and disseminated disease subgroup (determined post-hoc) with a median follow up of 5.61 years and 4.52 years, respectively (see Figure 11). Results were similar to those with a median of 3.5 years follow up, as published by Freyer et al, 2017. No difference was observed in EFS or OS in patients with localized disease, as assessed for SR-HB in SIOPEL 6 (upper panel; Figure 10) and for various tumor types by post-hoc designation in COG ACCL0431 (upper panel; Figure 11). This evaluation reiterates the overall conclusion that treatment with STS does not negatively affect the anti-tumor efficacy of CIS in patients with localized, non-metastatic, solid tumors, the population for which STS is proposed in this application.

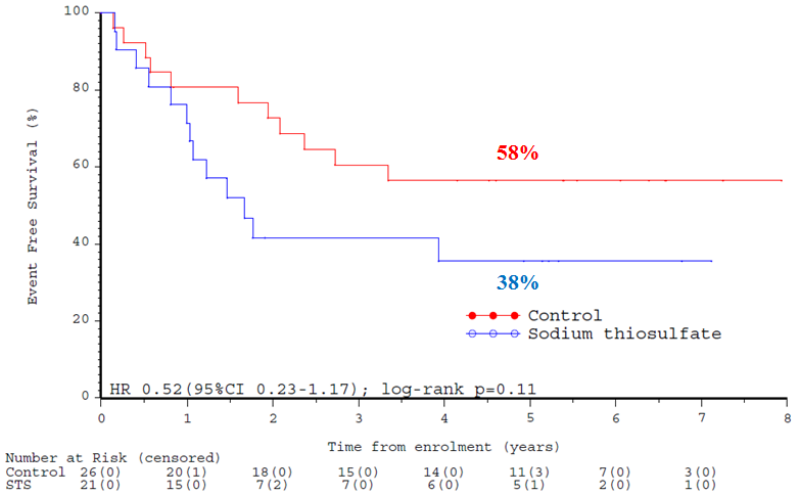
Figure 17: Event-free and Overall Survival in COG ACCL0431 (By Post-hoc Categorization of Localized or Disseminated Disease)

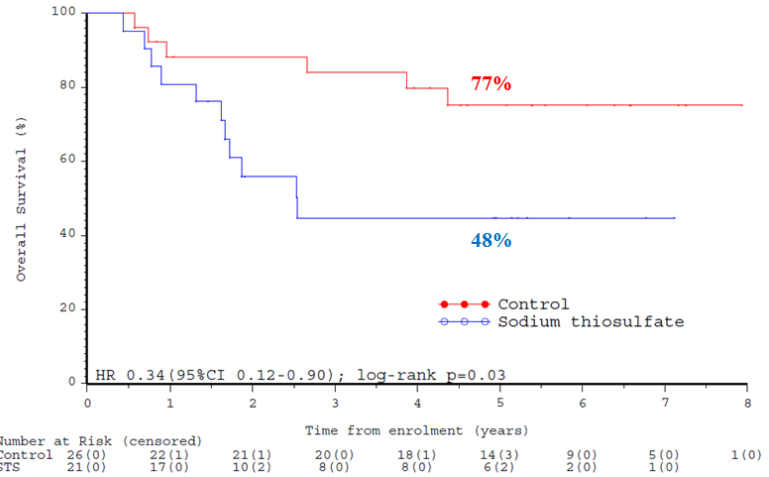
Event-free Survival **Overall Survival**

COG ACCL0431 (Localized; Median 5.61-year Follow-up)



COG ACCL0431 (Disseminated; Median 4.52-year Follow-up)





Abbreviations: CI=confidence interval; COG=Children's Oncology Group; HR=hazard ratio; ITT=Intent-to-treat; OS=overall survival; STS=sodium thiosulfate.
Note: The provided EFS and OS percentages of censored patients are from 5 years after study entry.
Note: For the calculation of the EFS and OS hazard ratio, the CIS arm (in SIOPEL 6) and Control/Observation arm (in COG ACCL0431) was the reference group.
Sources: Module 5.3.5.3 Figure 2.1, Figure 2.2, Figure 3.1, and Figure 3.2.

To further investigate the disparity in OS in patients categorized with disseminated disease in COG ACCL0431 (lower panel; Figure 11), Fennec undertook a patient-by-patient analysis of results in children with disseminated tumors to determine the possible explanations for this finding. This effort focused on the predicted OS for each specific tumor type, EFS/OS published for the chemotherapy regimens the children received in COG ACCL0431, and the individual prognostic indicators derived from the data set provided by COG to Fennec.

Table 24 Column 3 shows the predicted 3-year EFS rates from the COG statistical plan (which did not discriminate between localized and disseminated disease), which predicted EFS of 59% and long-term EFS (OS) of 48%. In reality, the EFS was similar to what was predicted at 58.4% (73/125 censored).

In the literature, OS rates for the common tumor types in COG ACCL0431 vary according to various prognostic indicators present at the time of diagnosis and the common ranges are summarized in Column 4, Table 24. The OS for all children categorized with mixed disseminated disease in COG ACCL0431 was within that expected in the literature at 64% (Column 5, Table 24) as was that observed in the CIS+STS arm of 48% (Column 7, Table 24). However, OS in the Observation arm was higher than would be predicted for a group of children categorized with mixed, disseminated disease at 77% (Column 6, Table 24) and very close to what was observed for children categorized with localized disease (84.2%).

Table 37: Predicted vs Observed Survival Rates in COG ACCL0431, ITT Population (Median 4.52-year Follow-up)

Disease type	Age Range in COG ACCL0431 (years)	Expected 3-year EFS from COG ACCL0431[a] (All Patients)	Expected 5-year OS Disseminated Disease (literature)	Observed OS in Disseminated Disease in COG ACCL0431		
				All Patients % (n/N)	Observation Arm % (n/N)	CIS+STS Arm % (n/N)
GCTs	10.7 to 17.8	75%	40% to 83%[b]	93% (13/14)	100% (7/7)	86% (6/7)
Medulloblastomas	2.3 to 12.4	55%	20% to 89%[c]	60% (3/5)	100% (2/2)	33% (1/3)
Neuroblastomas	1.4 to 15.4	45%	46% to 68%[d]	59% (10/17)	64% (7/11)	50% (3/6)
Osteosarcomas	3.3 to 15.4	70%	29% to 31%[e]	33% (3/9)	60% (3/5)	0% (0/4)
Overall	1.1 to 17.8	59%	~34% to 68%[f]	64% (30/47)	77% (20/26)	48% (11/21) [g]

Abbreviations: CIS=cisplatin; COG=Children's Oncology Group; CSR=clinical study report; EFS=event-free survival; GCT=Germ cell tumor; NOS=not otherwise specified; OS=overall survival; STS=sodium thiosulfate.

[a] Statistical considerations in the COG ACCL0431 protocol: Observation arm all patients (localized and disseminated) 3-year EFS: 59%, 3-year long term EFS: 48%.

[b] MaGIC study results for children ≥ 11 years with Stage IV (metastatic disease) (Frazier et al, 2015).

[c] Von Bueren et al, 2016.

[d] National Cancer Institute, OS children age 1 to 14 years and 10 to 21 years

[e] Kager et al, 2003 and Boye et al, 2014.

[f] Assuming an even preponderance of tumor types

[g] One additional death occurred in the CIS+STS arm, the child had disseminated carcinoma (NOS), and a poor prognosis.

Source: COG ACCL0431 CSR Listing 16.2.8.1.

When comparing the observed survival rates in COG ACCL0431 to the predicted survival rates in the literature, the clear outlier was the OS in the Observation arm, which was higher than would be predicted for a group of children with mixed, disseminated tumors at 77% and very close to what was observed for children with localized disease (84.2%) (right-hand panels in Figure 11). As a result of this finding, Fennec conducted a by-patient review of prognostic factors for children with disseminated disease to determine if there was an imbalance between the groups prior to randomization.

Table 25 below summarizes the number of children identified with poor prognostic risk indicators at diagnosis and the response to chemotherapy recorded for patients with disseminated disease. These results clearly suggest that the most likely explanation for the difference is an imbalance in prognostic indicators relating to the underlying tumor types in the 2 arms with 67% (14 of 21) children in the CIS+STS arm having identified poor prognostic indicators compared to 38% (10 of 26) in the Observation arm. These prognostic indicators were not controlled for during randomization and were not stratification variables and the study was not sufficiently large such that the variability in prognostic indicators would be taken care of during randomization without stratification since the study was powered for the hearing loss endpoint only.

Table 38: Children with Factors Indicating a Poor Prognosis (COG 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)
Stable disease	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; STS=sodium thiosulfate.

Sources: COG ACCL0431 CSR Listing 16.2.4.1, Module 2.7.3, In-text Table 33, Table 35, Table 38, Table 40, and Table 42.

To examine whether the STS treatment regimens used in COG ACCL0431 somehow interfered with the anti-tumor efficacy of CIS (and thereby would affect the safety profile of the proposed use of STS), the patterns of CIS and STS dosing were evaluated with respect to children categorized with localized vs disseminated disease and survival status. If STS was the reason for the differences observed in survival, this would be most likely to be seen in children who were given cycles of 5 days of 20 mg/m^2 CIS with 5 days of 16 g/m^2 of STS since this scenario represents the greatest risk of an interaction between the 2 agents, and yet it was the group who

received less than 3 days of CIS and STS per cycle that contained the preponderance of children who died (7 of 9) compared with 4 of 12 deaths in those receiving >3 doses of CIS and STS per cycle. Furthermore, receiving fewer doses of STS (<8 doses) was also associated with a lower likelihood of survival during the study compared to those who received >8 doses of STS. The likelihood of dying was not associated with the cumulative dose of STS received. The recorded response to chemotherapy is similar between the arms, although analysis is hampered by a larger number of unrecorded responses in the CIS+STS arm. The slightly lower proportion of PR/CR in the CIS+STS arm compared with the Observation arm is not unexpected given the poor prognostic risk factors identified in the CIS+STS arm.

In conclusion, the reason for the observed disparity in OS between the groups categorized with disseminated disease in COG ACCL0431 is most likely due to an imbalance in tumor types and prognostic indicators at randomization rather than to the use of STS. The characteristics of the tumors in COG ACCL0431 have a far greater potential to affect survival than the use of STS. Thus the Observation arm, containing by chance some children with a better prognosis from the outset, did better than expected from the published literature with an overall 5-year survival rate of 77% despite disseminated disease at diagnosis, whereas more children in the CIS+STS arm, by chance, had poor prognostic indicators from the outset and had survival rates (48%) in keeping with the literature for disseminated disease at diagnosis across a mixed group of solid tumors.

In addition to the EFS and OS assessed in both SIOPEL 6 and COG ACCL0431, additional endpoints were evaluated in SIOPEL 6 to address the potential effect of STS treatment on the anti-tumor efficacy of CIS, including response to preoperative chemotherapy, complete tumor resection, remission status, and AFP values (used as a tumor marker). These endpoints were not evaluated in COG ACCL0431. Although not powered for these analyses, results for each of these endpoints showed that there were no statistically significant differences between the CIS+STS arm and the CIS Alone arm, as detailed below, supporting that treatment with STS 6 hours after the end of each CIS infusion did not affect the anti-tumor efficacy of CIS.

With regard to the response to preoperative chemotherapy, after 4 cycles, the proportion of responders (defined as CR and PR, but no patients achieved CR after 4 cycles) were not significantly different between the CIS+STS arm (35 children [66.0%]) and the CIS Alone arm (39 children [75.0%]) (p=0.393) (Module 2.7.3, In-text Table 8). The proportion of children with PD was similar in the CIS+STS and CIS Alone arms (SIOPEL 6 CSR, Listing 16.2.6.2).

There was no statistically significant difference in the percentage of children with partial hepatectomy vs OLT (p>0.999) (Module 2.7.3, In-text Table 10).

There was no statistically significant difference in the proportion of children with complete remission 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) (Module 2.7.3, In-text Table 11). 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).

In both the CIS+STS and the CIS Alone arms, the mean change from Baseline in log-transformed AFP values were similar and statistically significant reductions were observed after course 2 (-0.635 ng/mL [p<0.001] and -0.817 ng/mL [p<0.001], respectively) and after course 4 (-1.467 ng/mL [p<0.001] and -1.956 ng/mL [p<0.001], respectively) (Module 2.7.3, In-text Table 15). In both the CIS+STS and the CIS Alone arms, the mean changes from Baseline to end of treatment in log-transformed 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).

Taken together, the results of the evaluation of EFS and OS in both studies and the additional evaluations of response to preoperative chemotherapy, complete tumor resection, remission status, and AFP values (used as a tumor marker) in SIOPEL 6, support that treatment with STS did not negatively impact the anti-tumor effectiveness of CIS chemotherapy (with infusion times of 1 to 6 hours) in children with localized, non-metastatic, solid tumors.

The FDA's Assessment:

FDA acknowledges that neither study was designed to assess EFS or OS, so the results should be interpreted with caution. Given the theoretical risk of STS interference with anti-tumor activity, FDA agrees with the due diligence conducted by the study sponsors of COG ACCL0431 and the Applicant's independent analysis to attempt to analyze the potential risk of decreased OS.

Results for EFS and OS in the SIOPEL6 study showed no apparent difference between arms for either endpoint. However, as noted previously, FDA shared the study investigators' concern that there could be a potential detriment in EFS and OS in the ITT population (consisting of metastatic and non-metastatic patients) for the COG ACCL0431 study. The post-hoc exploratory analysis of OS in COG ACCL0431 by subgroups defined by extent of disease suggested that this difference was potentially driven by patients with metastatic disease. Note that extent of disease (metastatic or non-metastatic) was determined post-hoc and was not a stratification factor and sample size in each subgroup was small, so these results should be considered with these limitations in mind.

The applicant provides further evidence that the potential detriment in OS seen in patients with metastatic/disseminated disease in COG ACCL0431 could be due to heterogeneity in the patient population due to the enrollment of diverse tumor types without controlling for certain prognostic factors at randomization. FDA acknowledges that enrollment on COG ACCL0431 did not account for important prognostic variables (e.g. age, histology, stage, biologic features, prior therapy, tumor location, ability resect, tumor size, etc.) and that an imbalance in prognostic factors could be driving the potential detriment in OS observed in patients with metastatic disease. However, FDA considers the analyses conducted to support this explanation to be exploratory and also notes that the selection of factors indicating a poor prognosis could

be subjective.

The applicant also examined STS treatment regimens and notes that, in general, patients receiving more STS did not appear to account for more deaths than those who received less STS. FDA also considers these analyses to be exploratory and does not believe any conclusions should be made due to the very limited data available.

Analyses of additional secondary endpoints in SIOPEL6 and COG ACCL0431 (other than EFS and OS) were not verified by FDA, results are considered exploratory, and any p-values reported are nominal only.

As a whole, FDA does not believe there is enough evidence to determine whether or not STS impacts the anti-tumor effectiveness of CIS. However, FDA agrees that limiting the indication to patients with non-metastatic disease will help alleviate these concerns.

Subpopulations

The Applicant's Position:

The SIOPEL 6 and COG ACCL0431 studies had small sample sizes (Module 2.7.3, In-text Table 51) which limits the interpretation of data by subgroups. Overall, the results of the subgroup analyses in each study showed that there was no clinically meaningful association of gender, age group, or weight with the otoprotective effect of STS that would necessitate changes to the dosing recommendations in the proposed label.

Nevertheless, in the pre-specified analysis of COG ACCL0431 by age group, the greatest difference between the CIS+STS arm and the Observation arm was observed for children <5 years of age (3 patients [21.4%] vs 11 patients [73.3%], respectively) compared with children ≥5 years of age (11 patients [31.4%] vs 20 patients [50.0%], respectively) (Module 2.7.3, Section 3.3.2.2). Children <5 years old are known to be at increased risk for moderate to severe hearing loss (Li et al, 2004).

The FDA's Assessment:

The FDA generally agrees with the applicant's position on subpopulations. Refer to the respective efficacy sections above for results from FDA's exploratory subgroup analyses for SIOPEL6 and COG ACCL0431 in the relevant re-defined analysis populations. No conclusions should be drawn regarding hearing loss by age group in COG ACCL0431.

Additional Efficacy Considerations

The FDA's Assessment:

n/a

8.1.6. Integrated Assessment of Effectiveness

The Applicant's Position:

The totality of evidence from the STS clinical development program and available literature demonstrates that PEDMARK is effective when administered for the prevention of ototoxicity induced by CIS chemotherapy in patients 1 month to <18 years of age with localized, non-metastatic, solid tumors.

Effective Otoprotectant

Both SIOPEL 6 and COG ACCL0431 showed that treatment with STS administered via a 15-minute IV infusion 6 hours after the end of CIS infusion resulted in statistically significant and clinically relevant reductions (approximately 50%) in the proportion of children with CIS-induced hearing loss compared with patients not receiving STS, whether evaluated using the Brock Grading scale (35.1% vs 67.3%; as in SIOPEL 6) or the ASHA criteria (28.6% vs 56.4%; as in COG ACCL0431). Replication of this finding across both studies demonstrates the efficacy of STS in the prevention of CIS-induced ototoxicity in patients with a range of tumor types. Prevention of ototoxicity after STS treatment was particularly seen in children <5 years of age (21.4% vs 73.3%; as in COG ACCL0431), who are most vulnerable to the effects of hearing loss on their language development and future communication.

Although these results are straightforward, their impact should not be minimized given the very good chances for long-term survival in these children. In the context of the impact of hearing loss in children, the clinical relevance of the results obtained from SIOPEL 6 and COG ACCL0431 are obvious. Use of PEDMARK in children undergoing CIS treatment for various types of localized, non-metastatic solid tumors can reduce the risk of hearing loss by 50%. Such a reduction is especially meaningful in this patient population as it can improve the chances that these children will not have to suffer the challenges of profound and irreversible hearing loss on top of those challenges already associated with their disease.

No Impact on Anti-tumor Efficacy of Cisplatin

When evaluating the effectiveness of STS as an otoprotectant, it was equally important to ensure that STS did not negatively impact the anti-tumor efficacy of CIS. Multiple endpoints were evaluated in SIOPEL 6 and COG ACCL0431 to assess the potential effect of STS on anti-tumor efficacy of CIS. The key endpoints used for this assessment were EFS and OS, which were evaluated in both studies, though neither study was powered for this comparison. Both studies showed that there was no statistically significant difference in EFS or OS for the CIS+STS arm compared with the CIS Alone arm (SIOPEL 6) or with the Observation arm (COG ACCL0431); though in COG ACCL0431, a trend for disparity in OS was observed between the arms.

A post-hoc evaluation of EFS and OS according to the extent of disease at the time of enrollment in COG ACCL0431 was conducted, categorizing patients with a binary assignment to groups of localized or disseminated disease. In children with localized, non-metastatic, solid tumors,

PEDMARK administered 6 hours after completion of a 1- to 6-hour CIS infusion no association with a reduction in EFS or OS, indicating that treatment does not negatively impact the anti-tumor efficacy of CIS chemotherapy. These results are confirmed by those from SIOPEL 6, where all patients had localized, non-metastatic disease (SR-HB). In COG ACCL0431 in patients characterized with disseminated disease, there was a disparity in the OS between the groups due to an imbalance in prognostic risk factors.

Furthermore, based on the known PK profile of CIS, unbound active platinum levels are no longer detected at 6 hours after the end of CIS infusion, or only low residual platinum exposure remains likely consisting of inactive platinum species. Therefore, the 6-hour delay in STS administration prevents a pharmacodynamic drug-interaction interference with the anti-tumor efficacy of CIS. Based on the half-life of STS in plasma, a negligible amount of STS would remain 6 hours after completion of an STS infusion and would not be expected to interact with a subsequent CIS infusion.

Taken together, the results of the evaluation of EFS and OS in both studies, the additional evaluations of response to preoperative chemotherapy, complete tumor resection, remission status, and AFP values (used as a tumor marker) in SIOPEL 6, and the known PK profile of CIS and STS, support that treatment with STS did not affect the anti-tumor efficacy of CIS in patients with localized, non-metastatic solid tumors.

In context with the efficacy of PEDMARK, these results are meaningful as they enable parents and physicians to be confident about the use of PEDMARK as part of the child's CIS treatment regimen without concern for an impact on survival.

The FDA's Assessment:

Regarding the applicant's claims with respect to STS as an effective otoprotectant, FDA reiterates that neither SIOPEL 6 nor COG ACCL0431 controlled type-1 error at a level of 0.05 (two-sided). Thus, p-values associated with the primary endpoint of hearing loss in these studies were interpreted as nominal only and no claims of statistical significance should be made. Furthermore, as noted in Sections 8.1.3 and 8.1.4, FDA does not agree with the definition of the patient population to support regulatory decision making in either study (SIOPEL6: Applicant excluded 5 randomized patients who withdrew prior to treatment, FDA uses all randomized patients; COG ACCL0431: Applicant uses all patients who had a baseline and 4-week post-CIS follow-up assessment, FDA uses all patients with localized disease despite missing assessment). FDA analyses of the primary endpoints in each respective study showed evidence of a decreased incidence of hearing loss in favor of the CIS+STS arm. However, for COG ACCL0431 in particular, small sample size makes it hard to quantify the true treatment effect. No conclusions should be drawn regarding hearing loss by age group in COG ACCL0431 as this was an exploratory subgroup analysis with limited sample size.

(b) (4)

FDA again reiterates that no secondary endpoint analyses were verified outside of those for EFS and OS. In COG ACCL0431, results of the EFS and

OS analyses showed a potential detriment in both endpoints. The applicant provided several possible explanations for this observed detriment. However, as noted previously in section 8.1.5, these explanations have caveats, cannot be verified, and are considered exploratory. Overall, FDA agrees that limiting the indication to patients with non-metastatic disease will help alleviate these concerns and generally agrees that the totality of the evidence supports the use of STS after CIS to prevent ototoxicity in pediatric patients with localized solid tumors.

8.2. Review of Safety

The Applicant's Position:

Sodium thiosulfate has been safely used for over 100 years as a therapeutic agent, and medical uses of STS have been well documented since 1895 (EPA, 2003). However, the majority of support for the safety of PEDMARK in the proposed indication was derived from the 2 confirmative Phase 3 studies, SIOPEL 6 and COG ACCL0431, with additional support from the published literature. SIOPEL 6 and COG ACCL0431 enrolled patients who comprise the intended target population for PEDMARK. Data are presented from a total of 232 patients with a variety of solid tumor types of whom 112 received at least 1 dose of STS in addition to CIS and 120 received CIS without STS.

Although the patient populations and CIS and STS dosing differed between SIOPEL 6 and COG ACCL0431 (Table 4), the safety profile of STS administration was generally consistent. The primary safety concerns attributable to STS in the indicated patient population are the potential for hypersensitivity reactions, nausea, vomiting, and AEs related to electrolyte changes (ie, hypernatremia, hypokalemia, and hypophosphatemia). These events are included as ADRs for the proposed label. All of these events are transitory and manageable considering the support that is typically already standard for a pediatric patient population receiving CIS chemotherapy.

Due to the open-label study designs for SIOPEL 6 and COG ACCL0431 and the nature of the data provided by these academic consortium-led studies, there are expected limitations of the safety analyses conducted. Both studies were designed and conducted for the purposes of establishing clinical practice guidelines for prevention of CIS-induced ototoxicity. As such, these studies were conducted in a "real-world" setting; thus, the safety results can be easily generalized to clinical practice.

The FDA's Assessment:
FDA agrees with the applicant's statement.

8.2.1. Safety Review Approach

The Applicant's Position:

Safety findings are based primarily on the key safety results from 2 confirmative Phase 3 studies (SIOPEL 6 and COG ACCL0431) that enrolled patients who comprise the intended target population for PEDMARK.

In SIOPEL 6, AEs were recorded during and up to 30 days after chemotherapy during the Treatment Phase; SAEs were recorded during the Treatment Phase and Follow-up. Serious AEs were reported in accordance with the local reporting requirements and to the main Research Ethics Committee. Fatal or life-threatening suspected unexpected serious adverse reactions (SUSARs) were also reported to the MHRA. An independent Data Monitoring Committee (DMC) reviewed all SAEs. The following AEs were termed Targeted Acute Toxicity AEs and were specifically analyzed: allergic reaction/hypersensitivity, febrile neutropenia, infection, hypomagnesemia, hypernatremia, vomiting, nausea, left ventricular systolic dysfunction, and hypertension.

In COG ACCL0431, AEs were recorded for all patients during the Reporting Period (defined as the treatment cycle where children received the first through final doses of CIS and/or STS excluding the 4-week Follow-up Period) and through last Follow-up. Serious AEs were to be reported only for patients in the CIS+STS arm during the Reporting Period, unless a death or secondary malignancy occurred. Serious AEs of death or secondary malignancy were to be reported through last Follow-up for patients in the Observation and CIS+STS arms. Serious AEs, deaths, and secondary malignancies for patients in the CIS+STS arm were to be reported using Adverse Event Expedited Reporting System (AdEERs). Serious AEs were only captured in the clinical database for those patients with SAEs who also had AdEERs forms. However, there were a few exceptions. The COG Data Safety Monitoring Committee (DSMC) monitored the safety of the study including intermittent assessments of tumor response. The following hematological toxicity AEs were specifically evaluated: neutrophil count decreased, platelet count decreased, and anemia. The following nephrotoxicity AEs were also specifically evaluated: acidosis, creatinine increased, GFR decreased, hypokalemia, hypomagnesemia, and hypophosphatemia.

For this submission, the following AEs of special interest were analyzed for both studies: Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or higher events of hypomagnesemia, hypernatremia, vomiting, and nausea.

In both studies, clinical laboratory assessments (sodium, magnesium [SIOPEL 6 only], and GFR [SIOPEL 6 only]), vital sign measurements, echocardiograms (SIOPEL 6 only), and physical examination results were measured at protocol-specified time points. However, for COG ACCL0431, vital signs, physical findings, and other observations related to safety were assessed but these data were not captured in the clinical database or analyzed; AEs related to abnormal vital signs or physical examinations were summarized.

Analyses of EFS, OS, and other measures of tumor response were evaluated; these data were analyzed as efficacy endpoints (Module 2.5, Section 4.2.3).

Based on the safety findings in SIOPEL 6 and COG ACCL0431, adverse drug reactions (ADRs) were identified (AEs with an incidence that was ≥10% higher in the CIS+STS arm compared

with the CIS Alone arm in either SIOPEL 6 or COG ACCL0431 or those identified by medical review) and included in the proposed PEDMARK labeling.

The FDA's Assessment:

FDA aggress with the applicant's description of the collection of safety data from the two trials (SIOPEL-6 and ACCL0431) that support the safety profile for this application. FDA emphasizes that there are key limitations to the interpretation of the safety data; these limitations are listed below:

- AEs start and stop dates were not collected for either study
- For SIOPEL
  - Information on dose alteration and discontinuation was only collected in conjunction with SAEs; the corresponding information on AEs was not collected.
- For ACCL0431,
  - AEs leading to discontinuation were not systematically collected
  - SAEs were only captured for the CIS+STS arm
  - Serum sodium was the only lab captured
  - Vital signs and physical findings but were not captured in the clinical database or analyzed; they were summarized where available.

8.2.2. Review of the Safety Database

Overall Exposure

The Applicant's Position:

SIOPEL 6

Of the 129 children registered, a total of 114 children from 12 countries were randomized in SIOPEL 6. Five randomized patients withdrew prior to treatment. Therefore, 109 children were included in the Safety Population, including 53 children in the CIS+STS arm and 56 children in the CIS Alone arm. Four children randomized to the CIS+STS arm never received STS and were thus assigned to the CIS Alone arm in the Safety Population (ie, as treated).

The median total duration of therapy (including CIS [=platinol] and doxorubicin [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]) (Module 2.7.4, Section 1.2.2.1). Cisplatin exposure was similar between the CIS+STS and CIS Alone arms, as measured by mean number of cycles (5.9 and 5.8 cycles, respectively) and mean cumulative actual dose (363.860 mg/m^2 vs 362.851 mg/m^2, respectively). When analyzed by weight group (<5kg, 5 to 10kg, >10kg), the number of cycles was similar between the arms, while mean cumulative actual CIS doses were more variable.

In the CIS+STS arm, the overall mean cumulative actual STS dose was 85.149 g/m^2, which differed by weight group (28.446 g/m^2 [1 child <5kg], 75.555 g/m^2 [5 to 10kg], and 100.537 g/m^2 [>10kg]).

COG ACCL0431

Of the 131 patients enrolled in the study from sites in the US and Canada, Fennec was provided data from the 125 children who were randomized to either the CIS+STS arm or the Observation arm. Two children randomized to the CIS+STS arm did not receive STS and were not included in the Safety Population. Of the 123 total patients, 59 children were in the CIS+STS arm and 64 children were in the Observation arm.

Children in the CIS+STS and Observation arms received mean cumulative CIS doses of 337.57 and 391.47 mg/m^2, respectively (Module 2.7.4, Section 1.2.2.2). Differences were observed between arms in the mean number of CIS cycles (3.1 and 3.8 in the CIS+STS and Observation arms, respectively) as well as the mean number of administration days (7.6 and 9.0, respectively). Variability in the CIS dosing regimens was observed across the diagnosed tumor types. This variability reflected the differences in each child's cancer treatment plan, which was dependent on the tumor type and staging, as well as the patient's age.

Children in the CIS+STS arm received a mean cumulative STS dose of 108.23 g/m^2. Although the STS dosing regimen per protocol was fixed at 16 g/m^2, the number of STS doses was variable and dependent on the number of CIS cycles and the number of CIS administrations per cycle.

The FDA's Assessment:

FDA agrees with the applicant's assessment of exposure. See Section 5 for more detail.

Table 39 SIOPEL 6 Analysis Population

Population	Randomized Treatment		Actual Treatment		Total n (%)
	CIS Alone (N=53) n (%)	CIS+STS (N=61) n (%)	CIS Alone (N=56) n (%)	CIS+STS (N=53) 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.

[a] The following patients were ineligible for randomization: (b) (6) (ineligible), (b) (6) (due to parental refusal), (b) (6) and (b) (6) (reclassified as high risk). These patients were excluded from the ITT Population.

[b] Patients (b) (6) were randomized to the CIS+STS arm but did not receive any STS. They were assigned to CIS Alone arm.

[c] Patients (b) (6) were randomized to the CIS+STS arm, but never received STS, and were excluded from the PP Population.

[d] Patients (b) (6) did not have hearing loss data, and were excluded from mITT Population.

Table 40 ACCL0431 Analysis Population

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.

Relevant characteristics of the safety population:

The Applicant's Position:

Demographics and Baseline disease characteristics differed between SIOPEL 6 and COG ACCL0431, as was expected based on the different patient populations enrolled in each study (children with SR-HB in SIOPEL 6 and children with various tumor types in COG ACCL0431). As described below, the children evaluated in these studies are considered representative of the target population for marketed STS (ie, patients 1 month to <18 years of age receiving CIS chemotherapy).

In SIOPEL 6, children between 1 month and 18 years old with standard-risk HB were eligible, as defined by PRETEXT I, II, or III (indicating the number of sections involved by tumor), serum AFP >100 μg/L, and no vascular invasion/no extra-hepatic or metastatic disease (Table 4). A total of 114 patients (61 patients in the CIS+STS arm and 53 patients in the CIS Alone arm) from 12 countries were randomized into the study (Module 2.7.3, Section 2.1.2.1). Overall, the median age was 13.0 months (range: 1.2 to 98.6 months [8.2 years]) and the majority of children were male (59 patients [54.1%]) and White (64 patients [58.7%]) (Module 2.7.3, Section 2.1.2.2.1). Baseline disease characteristics were generally balanced between the 2 arms (Module 2.7.3, Section 2.1.2.2.2), with the exception of a slight imbalance in the PRETEXT classification. Only the CIS+STS arm included 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), though this was consistent with the method of randomization (SIOPEL 6 CSR, Section 3.5.3).

In contrast, in COG ACCL0431, a heterogeneous population of children between 1 year and 18 years old receiving CIS chemotherapy for the treatment of various tumor types were eligible (Table 4). A total of 125 patients (61 patients in the CIS+STS arm and 64 patients in the Observation arm) were randomized into the study (Module 2.7.3, Section 2.2.1). Overall, the median age was 9.5 years (range: 1 to 18 years) (Module 2.7.3, Section 2.2.2). The majority of children in the study were ≥5 years of age (81 patients [64.8%]); male (76 patients [60.8%]); White (81 patients [64.8%]); and Not Hispanic or Latino (87 patients [69.6%]). The most common disease diagnoses were: GCT (32 patients [25.6%]), osteosarcoma (29 patients [23.2%]), medulloblastoma (26 patients [20.8%]), and neuroblastoma (26 patients [20.8%]); a total of 7 patients (5.6%) had HB. Unlike in SIOPEL 6, children in COG ACCL0431 could have had metastases (ie, disseminated disease) at study entry, though the majority (77 patients [61.6%]) did not. Importantly, COG ACCL0431 did not take the differing prognostic factors by tumor type into consideration when randomizing children to treatment, since the study was designed to evaluate hearing loss rather than tumor efficacy. The effect of these prognostic factors on the anti-tumor efficacy of CIS was evaluated and results are presented in Module 2.5, Section 4.5.

The FDA's Assessment:

The Applicant's description of the baseline characteristics for both studies is based on the ITT population, not the safety populations.

For SIOPEL 6, four patients randomized to the CIS+STS arm in the ITT population did not receive STS and are included in the CIS alone arm for the safety population. The demographics and characteristics pertinent to the interpretation of the primary endpoint of hearing loss (e.g. weight, age) are balanced between arms.

For COG ACCL0431, 2 children randomized to the CIS+STS arm did not receive STS due to parent refusal or physician determined it was in the patient's best interest. The demographics and characteristics pertinent to interpretation of the primary endpoint of hearing loss (e.g. weight,

age, prior radiation, tumor type, presence of metastatic disease) were generally balance between arms. Prognostic factors (e.g. tumor stage, histology, biologic features, prior therapy, tumor location, ability to resect, etc.) were not stratified for or included in the eligibility criteria.

Adequacy of the safety database:

The Applicant's Position:

Due to the nature of the open-label study designs for SIOPEL 6 and COG ACCL0431 and the data provided by these academic consortium-led studies, there are expected limitations of the safety analyses conducted. Both studies were designed and conducted for the purposes of establishing clinical practice guidelines for prevention of CIS-induced ototoxicity. As such, these studies were conducted in a "real-world" setting; thus, the safety results can be easily generalized to clinical practice.

There are similarities and differences between the SIOPEL 6 and COG ACCL0431 study designs. Key limitations of the study designs (eg, open-label) and differences between the studies (eg, patient population, CIS and STS exposure [Table 4]) could affect interpretation of the safety profile across the indicated patient population.

The STS (pentahydrate) formulation used in SIOPEL 6 and COG ACCL0431 differs from the formulation of STS (anhydrous) (b) (4) intended for marketing. However, the STS solutions prepared and administered in the clinical studies and publications are considered representative for PEDMARK since all formulations were based on a solution of STS dissolved in water with a boric acid (b) (4) and no further specific requirements. Both the clinical study formulations and PEDMARK use the same infusion volume, molar amount of dissolved STS, and rate of infusion. Therefore, there is no reason to expect an impact on the safety profile of PEDMARK in the intended patient population.

Data collection practices for these academic consortium-led studies could also limit the interpretation of safety data. For example, AE start and stop dates and times were not collected in the clinical database for either study, which restricted the understanding of AE duration as well as what AEs were concurrent. Furthermore, collection of AE relatedness to STS or other concomitant medications was also limited. In SIOPEL 6, relatedness to STS was only captured for SAEs. In COG ACCL0431, relatedness to STS was captured for all AEs. Additional information about the timing of AEs and relatedness to STS or other medications was included on some SAE reporting forms for those patients with SAEs. Where those details were provided, additional insights could be drawn. Finally, in COG ACCL0431, AEs leading to discontinuation were not systematically collected in the CRF and therefore were not reliably identified in the clinical database. However, AE data were manually reviewed for any patient who discontinued STS due to reasons related to an AE, per entry on the disposition CRF or because the

discontinuation occurred in close proximity to the occurrence of an AE (but was not specifically attributed to an AE).

Although additional support on the safety of STS comes from the published literature, the amount of safety information on use of STS in the indicated patient population (ie, use of STS in combination with platinum-based chemotherapy) was very limited and most events were attributable to the chemotherapy or underlying disease (Module 2.7.4, Section 7.2.2). The majority of the available published information on the safety of STS comes from its use in different patient populations (eg, cyanide poisoning, calcific uremic arteriolopathy [calciphylaxis], tumoral calcinosis, vascular calcifications, and nephrogenic systemic fibrosis). Relevant safety findings in these indications were considered based on their relevance to the proposed indication.

The FDA's Assessment:

See FDA Assessment in Section 8.2.1, Safety Review Approach for comment on key limitations of the safety data collection. The focus of this review from the FDA perspective is on the review of the datasets from the two trials supporting the application.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The Applicant's Position:

The limitations of the safety database are presented under "Adequacy of the safety database." Fennec is not aware of any issues or concerns regarding the data quality or quality of the overall submission that would have an effect on the safety review.

The global clinical development program supporting the efficacy and safety of PEDMARK in the proposed indication included 2 confirmatory Phase 3 clinical studies (SIOPEL 6 and COG ACCL0431).

SIOPEL 6 and COG ACCL0431 were designed and conducted by academic consortia for the purposes of establishing clinical practice guidelines for prevention of CIS-induced ototoxicity. These studies were conducted in accordance with GCP; the results of COG ACCL0431 were published by Freyer et al, 2017 and results of SIOPEL 6 were published by Brock et al, 2018. Although they did not sponsor these studies, Fennec provided study medication (STS) and obtained rights to the data. Study results summarized in this marketing application represent the analyses conducted by Fennec, which are provided in ICH-compliant CSRs.

As agreed with the Agency at the pre- NDA meeting (see Module 2.5, Table 2), Fennec did not conduct any integrated analyses based on pooled study data given the different patient populations (ie, SR-HB in SIOPEL 6 and various cancer types in COG ACCL0431), study designs, and dosing evaluated.

The FDA's Assessment:

FDA agrees with the applicant's statement.

Categorization of Adverse Event

The Applicant's Position:

In both SIOPEL 6 and COG ACCL0431, AEs were collected and assessed using the National Cancer Institute (NCI) CTCAE (V3.0 [SIOPEL 6]; V4.0 [COG ACCL0431]). For analysis, AEs were mapped to MedDRA Version 21.0 system organ classification (SOC) and preferred term (PT). Adverse events were evaluated by CTCAE grade, Investigator assigned relationship to STS (evaluated only for SAEs in SIOPEL 6), seriousness, and those leading to discontinuation. Deaths were also analyzed regardless of whether they were the result of an AE.

In SIOPEL 6, AEs were recorded during and up to 30 days after chemotherapy during the Treatment Phase; SAEs were recorded during the Treatment Phase and Follow-up. Serious AEs were reported in accordance with the local reporting requirements and to the main Research Ethics Committee. Fatal or life-threatening SUSARs were also reported to the MHRA. An independent Data Monitoring Committee (DMC) reviewed all SAEs. The following AEs were termed Targeted Acute Toxicity AEs and were specifically analyzed: allergic reaction/hypersensitivity, febrile neutropenia, infection, hypomagnesemia, hypernatremia, vomiting, nausea, left ventricular systolic dysfunction, and hypertension.

In COG ACCL0431, AEs were recorded for all patients during the Reporting Period (defined as the treatment cycle where children received the first through final doses of CIS and/or STS excluding the 4-week Follow-up Period) and through last Follow-up. Serious AEs were to be reported only for patients in the CIS+STS arm during the Reporting Period, unless a death or secondary malignancy occurred. Serious AEs of death or secondary malignancy were to be reported through last Follow-up for patients in the Observation and CIS+STS arms. Serious AEs, deaths, and secondary malignancies for patients in the CIS+STS arm were to be reported using AdEERs. Serious AEs were only captured in the clinical database for those patients with SAEs who also had AdEERs forms. However, there were a few exceptions. The COG DSMC monitored the safety of the study including intermittent assessments of tumor response. The following hematological toxicity AEs were specifically evaluated: neutrophil count decreased, platelet count decreased, and anemia. The following nephrotoxicity AEs were also specifically evaluated: acidosis, creatinine increased, GFR decreased, hypokalemia, hypomagnesemia, and hypophosphatemia.

The FDA's Assessment:

FDA agrees with the applicant's statement.

Routine Clinical Tests

The Applicant's Position:

In both studies, clinical laboratory assessments (sodium, magnesium [SIOPEL 6 only], and GFR [SIOPEL 6 only]), vital sign measurements, echocardiograms (SIOPEL 6 only), and physical examination results were measured at protocol-specified time points. However, for COG ACCL0431, vital signs, physical findings, and other observations related to safety were assessed but these data were not captured in the clinical database or analyzed; AEs related to abnormal vital signs or physical examinations were summarized.

Analyses of EFS, OS, and other measures of tumor response were evaluated; these data were analyzed as efficacy endpoints (Module 2.5, Section 4.2.3).

Although vital signs, physical findings, and other observations related to safety were assessed per the Protocol (see COG ACCL0431 CSR Table 2), these data were not captured in the clinical database or analyzed. However, AEs related to abnormal vital signs or physical examinations were summarized.

The FDA's Assessment:

FDA agrees with the applicant's statement.

8.2.4. Safety Results

Deaths

The Applicant's Position:

SIOPEL 6

Overall, a total of 6 children (5.5%) died during the study, including 5 who had PRETEXT II disease (Module 2.7.4, Section 2.1.2.1). Of these, 2 children in the CIS Alone arm died by the end of treatment and 4 children died during Follow-up (2 children in each arm). Both children in the CIS+STS arm died due to tumor progression. Of the 4 children in the CIS Alone arm who died, 2 children died due to tumor progression, 1 child died due to surgical complications, and 1 child due to cardiac arrest (after receiving additional alternative chemotherapy for progression).

COG ACCL0431

Overall in both arms of the study, 30 children died, including 18 children (30.5%) in the CIS+STS arm and 12 children (18.8%) in the Observation arm (Module 2.7.4, Section 2.1.2.2). The majority of deaths were due to the child's underlying disease. No deaths in the CIS+STS arm were considered related to STS.

The FDA's Assessment:

The FDA generally agrees with the Applicant's description of deaths in the SIOPEL 6 trial. Of the 6 deaths, 4 patients were in the CIS alone arm (7.1%) and 2 were in the CIS + STS arm (3.8%). Narratives were provided for the two children (both in the CIS alone arm) who did not die due to disease progression (cardiac arrest and surgery). The patient who died due to cardiac arrest was an 11 month old male (originally diagnosed with hepatoblastoma (b) (6)) who went on to receive carboplatin and doxorubicin ((b) (6) followed by paclitaxel (b) (6) after progressing on upfront cisplatin/resection therapy; the investigator considered the cardiac arrest and death (b) (6) possibly related to paclitaxel. The patient who died due to a surgical complication was a 9 month old female (b) (6) who died during partial hepatectomy (b) (6) after two courses of pre-operative CIS; no further information is available. These two deaths occurred in patients who did not receive STS and the deaths overall are generally well-balanced between arms.

The FDA generally agrees with the Applicant's description of deaths in the COG trial. A broader discussion of the higher death rate for patients in the CIS+STS arm is included in the efficacy section. One patient death not due to progressive disease was associated with an AE while on treatment (CIS+STS arm). A full narrative is provided for this patient. The patient was an 8 year old male with osteosarcoma who experienced cardiac arrest and died 6 days after a cycle of chemotherapy (cisplatin and doxorubicin). The death was confounded by several factors including recent history of febrile neutropenia, pancytopenia, and *C.difficile* pseudomembranous colitis.

Serious Adverse Events

The Applicant's Position:

SIOPEL 6

Twenty-one children (39.6%) in the CIS+STS arm and 18 children (32.1%) in the CIS Alone arm had non-fatal SAEs during the Treatment Phase (Module 2.7.4, Section 2.1.3.1). In both CIS+STS and CIS Alone arms, the PTs of infection (13.2% and 8.9%, respectively) and pyrexia (9.4% and 5.4%, respectively) were among the most frequently reported SAEs. In addition, 2 other SAEs were reported by more than 1 patient in the CIS+STS arm (neutrophil count decreased and procedural complications). The incidence of SAEs of neutrophil count decreased was numerically higher in the CIS+STS arm (6 children [11.3%]) compared with the CIS Alone arm (1 child [1.8%]), but there is no plausible mechanism by which this could be caused by STS.

No patients required a dose alteration due to an SAE. Relatedness to STS as determined by the Investigator was only captured for SAEs. In the CIS+STS arm, 4 children (7.5%) overall experienced an SAE determined by the Investigator as being related to STS, which included neutrophil count decreased, infection, and hypersensitivity. This drug-related CTCAE Grade 2 SAE of hypersensitivity also led to discontinuation of study medication and was considered as a SUSAR (Patient (b) (6)). The event was noted 15 minutes after the end of STS infusion and the

child had a tachycardia of 180 bpm and a systolic blood pressure of 130 mmHg. The child 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.

COG ACCL0431

Serious AEs (fatal and non-fatal) were recorded only for patients in the CIS+STS arm (21 children [35.6%]) (Module 2.7.4, Section 2.1.3.2). 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.

The FDA's Assessment:

Regarding SIOPEL 6, FDA agrees with the characterization of SAEs. FDA additionally notes that 5 patients (9%) had an SAE of pyrexia in the CIS+STS arm compared to 3 in the CIS alone arm (5%).

Regarding COG ACCL0431, FDA agrees with the total number of patients who had a SAE and that the most commonly reported SAE was febrile neutropenia in 12 patients (20%). Other SAEs reported in more than one patient included neutrophil count decreased in 11 patients (19%), white blood cell and platelet count decreased in 8 patients each (14%), anemia in 7 patients (12%), stomatitis in 5 patients (8%), lymphocyte count decrease in 4 patients (7%), ALT increased in 3 patients (5%), and diarrhea, colitis, nausea, UTI, decreased appetite, dehydration, and syncope in 2 patients each (3.4%).

One patient in COG ACCL0431 was reported to have a secondary malignancy of AML that was reported to AdEERS but not captured as an SAE. The patient was a 2 year old male with localized neuroblastoma who received one dose of STS. Confounded by treatment with etoposide which is known to be associated with secondary AML. The patient is alive and cancer-free 7 years after study entry.

Dropouts and/or Discontinuations Due to Adverse Effects

The Applicant's Position:

SIOPEL 6

During the Treatment Phase, 1 child (1.9%), in the CIS+STS arm, experienced a Grade 2 SAE of hypersensitivity that led to discontinuation of study medication (SIOPEL 6 CSR Table 14.3.9.4). This event is discussed in the SAE section above.

No additional AEs led to study medication discontinuation (SIOPEL 6 CSR Listing 16.2.7.5).

COG ACCL0431

Discontinuations due to AEs were not systematically collected in the CRF and therefore were not reliably identified in the clinical database. However, 1 child in the CIS+STS arm discontinued STS due to reasons related to an AE of hypersensitivity (considered definitely related to STS by the Investigator), and 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 [1 AE considered probably and 1 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]) (Module 2.7.4, Section 2.1.4.1.2).

The FDA's Assessment:
FDA agrees with the assessment of treatment discontinues due to treatment-emergent adverse events.

Dose Interruption/Reduction Due to Adverse Effects

The Applicant's Position:

Dose reductions are described only for the SIOPEL 6 and COG ACCL0431 studies.

SIOPEL 6

No patients required a dose alteration due to an SAE.

COG ACCL0431

The overall incidence of AEs, total number of AEs, and total number of STS administrations were summarized by cumulative and mean daily STS dosing quartiles (Module 2.7.4, Section 2.1.1.2.5). As expected, the total number of STS administrations and the average number of STS administrations per patient increased across STS dose quartiles. However, there was no correlation between the average number of AEs per patient and the cumulative STS dosing quartile. No STS dose-related trends in the PTs of nausea, vomiting, hypernatremia, hypokalemia, hypophosphatemia, and hypersensitivity were observed.

The FDA's Assessment:
Regarding SIOPEL 6, FDA notes that dose alterations and discontinuations were only collected in conjunction with SAEs. Based on the dataset, it appears that there were two event of STS interruption and CIS delay (due to infection and neutrophil count decreased). According to the narrative for the patient with neutrophil count decreased (191), surgery was delayed due to low neutrophil count but patient received all planned doses of CIS and STS. According to the narrative for the patient with infection (135), the patient did not receive the final dose of STS (received 5 of 6) due to Grade 3 infection; CIS still given.

Dose reductions and interruptions were not captured for ACCL0431.

Significant Adverse Events

The Applicant's Position:

Adverse events of special interest were identified as Grade 3 severity or higher events in the PTs of nausea, vomiting, hypomagnesemia, and hypernatremia for both SIOPEL 6 and COG ACCL0431.

SIOPEL 6

Adverse events of special interest during the Treatment Phase are summarized for the Safety Population in Table 28. The overall number of patients experiencing AESIs was low and the incidence was similar between the arms.

Table 41: Summary of AESI Reported During the Treatment Phase (Safety Population; SIOPEL 6)

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.
Source: SIOPEL 6 CSR Table 14.3.9.12.2.

COG ACCL0431

Adverse events of special interest during the Reporting Period are summarized for the Safety Population in Table 29. The incidences of AESIs were similar between the treatment arms. No Grade 3 severity or higher events of hypernatremia were reported.

Table 42: Summary of AESI Reported During the Reporting Period (Safety Population; COG ACCL0431)

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)

SOC PT	Observation (N=64) n (%)	CIS+STS (N=59) n (%)	Total (N=123) n (%)
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.
Source: COG ACCL0431 CSR Table 14.3.1.2.

The FDA's Assessment:

FDA agrees with the Applicant's assessment of the predefined adverse events of special interest. The overall numbers were low and balanced between arms.

Treatment Emergent Adverse Events and Adverse Reactions

The Applicant's Position:

SIOPEL 6

Overview of Adverse Events

An overview of AEs during both the Treatment and Follow-up Phases is provided in Table 30. Overall during both the Treatment and Follow-up Phases, the incidences of AEs, SAEs, SAEs requiring dose alteration, discontinuations due to SAEs, and SAEs resulting in death were similar between the 2 treatment arms. The majority of these events occurred during the Treatment Phase and are summarized further below. During the Follow-up Phase, only SAEs and deaths were captured, which included 2 non-fatal SAEs and 1 fatal SAE in the CIS Alone arm and no events in the CIS+STS arm.

Table 43: Overview of Adverse Events during both the Treatment and Follow-up Phases (Safety Population; SIOPEL 6)

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)	19[(1)] (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; SIOPEL=International Childhood Liver Tumor Strategy Group; STS=sodium thiosulfate.
Note: Information on dose alteration and discontinuation was only collected in conjunction with SAEs; the corresponding information on AEs was not collected.
(1) One SAE in the CIS Alone arm occurred during Follow-up.
Source: SIOPEL 6 CSR Table 14.3.3.1.

Most Common Adverse Events during the Treatment Phase

The most common AEs by PT (frequency of ≥10% in either arm) during the Treatment Phase are summarized in Table 31. The 3 most frequently reported AEs by PT were the same in both arms (nausea, vomiting, and infection). In the CIS+STS arm compared with the CIS Alone arm, vomiting (84.9% vs 53.6%, respectively) and nausea (39.6% vs 30.4%, respectively) occurred at higher incidences. In the CIS+STS arm compared with the CIS Alone arm, infection (41.5% vs 35.7%, respectively) occurred at a similar incidence. Generally, the incidences of other most common AEs by PT were similar between the CIS+STS and the CIS Alone arms.

Table 44: Summary of the Most Common AEs (PT Frequency of ≥10% in Either Arm) During the Treatment Phase (Safety Population; SIOPEL 6)

SOC PT	CIS Alone (N=56) n (%)	CIS+STS (N=53) n (%)	Total (N=109) n (%)
Patients with at least 1 AE	49 (87.5)	51 (96.2)	100 (91.7)
Gastrointestinal disorders	**33 (58.9)**	**47 (88.7)**	**80 (73.4)**
Vomiting	30 (53.6)	45 (84.9)	75 (68.8)
Nausea	17 (30.4)	21 (39.6)	38 (34.9)
Diarrhea	6 (10.7)	5 (9.4)	11 (10.1)
Investigations	**29 (51.8)**	**33 (62.3)**	**62 (56.9)**
Hemoglobin decreased	16 (28.6)	18 (34.0)	34 (31.2)
Neutrophil count decreased	12 (21.4)	12 (22.6)	24 (22.0)
Acoustic stimulation tests	12 (21.4)	11 (20.8)	23 (21.1)
AST increased	10 (17.9)	9 (17.0)	19 (17.4)
ALT increased	12 (21.4)	6 (11.3)	18 (16.5)
GGT increased	7 (12.5)	4 (7.5)	11 (10.1)
Metabolism and nutrition disorders	**21 (37.5)**	**30 (56.6)**	**51 (46.8)**
Hypomagnesemia	16 (28.6)	17 (32.1)	33 (30.3)
Hypernatremia	2 (3.6)	14 (26.4)	16 (14.7)
Hypermagnesemia	3 (5.4)	6 (11.3)	9 (8.3)
Hypokalemia	1 (1.8)	8 (15.1)	9 (8.3)
Hypophosphatemia	1 (1.8)	8 (15.1)	9 (8.3)
Infections and infestations	**21 (37.5)**	**23 (43.4)**	**44 (40.4)**
Infection	20 (35.7)	22 (41.5)	42 (38.5)
Blood and lymphatic system disorders	**12 (21.4)**	**10 (18.9)**	**22 (20.2)**
Febrile neutropenia	11 (19.6)	8 (15.1)	19 (17.4)

SOC PT	CIS Alone (N=56) n (%)	CIS+STS (N=53) n (%)	Total (N=109) n (%)
General disorders and administrative site conditions	**8 (14.3)**	**11 (20.8)**	**19 (17.4)**
Pyrexia	5 (8.9)	8 (15.1)	13 (11.9)
Immune system disorders	**6 (10.7)**	**7 (13.2)**	**13 (11.9)**
Hypersensitivity	6 (10.7)	7 (13.2)	13 (11.9)

Abbreviations: AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CIS=cisplatin; CSR=clinical study report; GGT=gamma-glutamyl transferase; PT=preferred term; SAE=serious adverse event; SIOPEL=International Childhood Liver Tumor Strategy Group; SOC=system organ class; STS=sodium thiosulfate.
Note: In the Follow-up Period, only SAEs were collected.
Note: AEs were only recorded in the Treatment Phase up 30 days after the end of treatment.
Source: SIOPEL 6 CSR Table 14.3.9.9.2

Adverse Events by CTCAE Grade During the Treatment Phase

The majority of AEs experienced by patients during the Treatment Phase were CTCAE Grade 3 or higher and occurred at similar incidences in the CIS+STS and CIS Alone arms (66.0% vs 60.7%, respectively) (Module 2.7.4, Section 2.1.1.1.3). The incidences of AESIs (Grade 3 severity or higher AEs of nausea, vomiting, hypomagnesemia, and hypernatremia) were generally similar between the treatment arms (Module 2.7.4, Section 2.1.4.2.1).

COG ACCL0431

Overview of Adverse Events

An overview of AEs is presented in Table 32. Details of these events are described further below.

Table 45: Overview of AEs (Safety Population; COG ACCL0431)

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)
SAEs(1)	ND	21 (35.6)	NA
Drug-related AEs(2)	NA	23 (39.0)	23 (39.0)
AEs graded CTCAE category 3 or higher	57 (89.1)	55 (93.2)	112 (91.1)
Deaths(3)	12 (18.8)	18 (30.5)	30 (24.4)

Abbreviations: AE=adverse event; CIS=cisplatin; COG=Children's Oncology Group; CRF=Case Report Form; CSR=clinical study report; CTCAE=Common Terminology Criteria for Adverse Events; NA=not applicable; ND=not defined; SAE=serious AE; SAP=statistical analysis plan; STS=sodium thiosulfate.

(1) As described in the SAP, SAEs were reported only for the CIS+STS arm.

(2) Relationship was to the STS treatment; "drug-related" included AEs that were considered Possible, Probable, or Definite in the CRF.

(3) Eight patients were off Study ACCL0431 and subsequently died while enrolled into different COG studies.

Sources: COG ACCL0431 CSR Table 14.3.1.1, Table 14.3.1.2, Table 14.3.1.3, Table 14.3.1.4, and Table 14.1.5.

Most Common Adverse Events During the Reporting Period

The most common AEs by PT (frequency of ≥10% in either arm) during the Treatment Phase are summarized in Table 31. The 3 most frequently reported AEs by PT occurred at similar incidences in the CIS+STS and Observation arms: neutrophil count decreased (83.1% vs. 79.7%, respectively), white blood cell count decreased (64.4% vs. 65.6%, respectively), and platelet count decreased (64.4% vs. 60.9%, respectively). These events are commonly known to be associated with chemotherapy.

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.

Table 46: Summary of the Most Common AEs (Frequency of ≥10% in Either Arm, by PT) During the Reporting Period (Safety Population; COG ACCL0431)

SOC PT	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)
Investigations	**57 (89.1)**	**54 (91.5)**	**111 (90.2)**
Neutrophil count decreased	51 (79.7)	49 (83.1)	100 (81.3)
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)**
Anemia	36 (56.3)	30 (50.8)	66 (53.7)
Febrile neutropenia	19 (29.7)	14 (23.7)	33 (26.8)
Metabolism and nutrition disorders	**23 (35.9)**	**32 (54.2)**	**55 (44.7)**
Hypokalemia	13 (20.3)	16 (27.1)	29 (23.6)
Hypophosphatemia	7 (10.9)	12 (20.3)	19 (15.4)
Hyponatremia	4 (6.3)	8 (13.6)	12 (9.8)
Hypernatremia	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; COG=Children's Oncology Group; CSR=clinical study report; CTCAE= Common Terminology Criteria for Adverse Events; PT=preferred term; SOC=system organ class; STS=sodium thiosulfate.
Source: COG ACCL0431 CSR Table 14.3.1.1.

Adverse Events by CTCAE Grade During the Reporting Period

The majority of AEs experienced by patients during the reporting period were CTCAE Grade 3 or higher and occurred at similar incidences in the CIS+STS and Observation arms (93.2% vs 89.1%, respectively) (Module 2.7.4, Section 2.1.1.2.3). The incidences of AESIs (Grade 3 severity or higher AEs of nausea, vomiting, hypomagnesemia, and hypernatremia) were also similar between the treatment arms (Module 2.7.4, Section 2.1.4.2.2).

The FDA's Assessment:

Regarding SIOPEL 6, FDA agrees with the incidence of common AEs as described by the Applicant. In addition, FDA emphasizes that the incidence of electrolyte imbalances was higher

in the CIS+STS arm compared to CIS alone (>5%): hypernatremia 14 patients (26.4%) compared to 2 patients (3.6%), hypokalemia and hypophosphatemia with 8 patients (15%) each compared to 1 (1.8%), and hypermagnesemia in 6 patients (11%) vs 3 patients (5%).

Regarding COG ACCL0431, FDA agrees with the incidence of common AEs as described by the Applicant with the exception of neutrophil count decreased in the observation arm (FDA calculated 53 events (83%) compared to Applicant's 51 events (80%); this does not impact the risk profile of the study. Similar to the SIOPEL-6 trial, the incidence of electrolyte imbalances was higher in the CIS+STS arm compared to the observation arm of CIS alone (>5%): hypernatremia in 7 patients (12%) vs. 4 patients (6%); hypokalemia in 16 patients (27%) vs. 13 patients (20%); and hypophosphatemia in 12 patients (20%) vs. 7 patients (11%). Stomatitis was also reported at a higher incidence in patients who received STS [8 patients (14%) vs. 4 patients (6%)].

Laboratory Findings

The Applicant's Position:

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 (Module 2.7.4, Section 3.1).

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.

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 the CIS Alone arms 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%]).

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 >151 mmol/L in the CIS+STS arm

or >146 mmol/L in the Observation arm (Module 2.7.4, Section 3.2). The remaining laboratory evaluations were not captured in the clinical database.

The FDA's Assessment:
In both the COG ACCL0431 and the SIOPEL 6 studies, laboratory results that were captured in the datasets were not graded by CTCAE criteria unless they were reported as AEs; the standard variable ATOXGR was not available for laboratory analysis and review. FDA acknowledges the Applicant's statements but cannot draw conclusions based on the laboratory data provided. See sections above for review of laboratory findings that were reported as AEs.

Vital Signs

The Applicant's Position:

SIOPEL 6

Overall, there were no clinically relevant mean changes in vital signs over the course of the study (see SIOPEL 6 CSR, Section 7.5.1).

In the CIS+STS arm, the mean systolic BP was similar at pre-course 1 (101.8 mmHg) and pre-course 6 (104.3 mmHg). In the CIS Alone arm, the mean systolic BP was similar at pre-course 1 (100.7 mmHg) and pre-course 6 (98.0 mmHg) (SIOPEL 6 CSR, Table 14.3.4.1).

Across all courses, in the CIS+STS arm, the mean pre-course systolic BP was 102.1 mmHg, rose 5.8 mmHg at 30 minutes post-course ($p<0.001$), and returned to a pre-course level at 60 minutes post-course (-0.3 mmHg change from pre-course [$p=0.771$]) (SIOPEL 6 CSR, Table 14.3.4.2).

COG ACCL0431

Although vital signs were assessed per the Protocol (see COG ACCL0431 CSR Table 2), these data were not systematically collected in the CRF and therefore were not reliably identified in the clinical database. However, AEs related to abnormal vital signs were summarized (see COG ACCL0431 CSR Section 7.5).

Adverse events in the PT of hypotension were reported in 2 patients (3.4%) in the CIS+STS arm, and 1 patient (1.6%) in the Observation arm (COG ACCL0431 CSR Table 14.3.1.1). An AE in the PT of hypertension was reported in 1 patient (1.7%) in the CIS+STS arm (COG ACCL0431 CSR Table 14.3.1.1).

The FDA's Assessment:
FDA agrees with the Applicant's assessment.

Electrocardiograms

The Applicant's Position:

***SIOPEL* 6**

Echocardiograms were not a mandatory assessment, but were only performed if clinically indicated (ie, after doxorubicin treatment) (SIOPEL 6 CSR, Section 7.5.2 and Table 2).

The CIS+STS and the CIS Alone arms had no notable differences in mean percent shortening fractions at the end of treatment (35.871% and 37.334%, respectively) and at Follow-up (34.138% and 34.744%, respectively) (SIOPEL 6 CSR Table 14.3.4.1). The CIS+STS and the CIS Alone arms also had no notable differences in mean percent ejection fractions at the end of treatment (67.426% and 68.942%, respectively) and at Follow-up (69.786% and 63.744%, respectively).

Overall, 3 patients experienced AEs in the SOC Cardiac disorders during the Treatment Phase. In the CIS+STS arm, 1 patient each (1.9%) experienced arrhythmia and ventricular arrhythmia; both AEs were Grade 1 in severity (SIOPEL 6 CSR Table 14.3.9.6.1). In the CIS Alone arm, 1 patient (1.8%) experienced a Grade 1 AE of left ventricular dysfunction.

COG ACCL0431

Cardiac function was not reported in the clinician database for this study.

Adverse events in the PT of hypotension were reported in 2 patients (3.4%) in the CIS+STS arm, and 1 patient (1.6%) in the Observation arm (COG ACCL0431 CSR Table 14.3.1.1). An AE in the PT of hypertension was reported in 1 patient (1.7%) in the CIS+STS arm (COG ACCL0431 CSR Table 14.3.1.1).

The FDA's Assessment:
FDA agrees with the Applicant's assessment.

QT

The Applicant's Position:

Pursuant to 21 CFR 314.90, Fennec Pharmaceuticals, Inc.has requested a waiver of the Thorough QTc data requirements for approval of PEDMARK (sodium thiosulfate injection), for IV use. Available data adequately establish the cardiac conduction safety of sodium thiosulfate for the intended use, in the intended patient population; therefore, no further data are required to support approval of PEDMARK.

Sodium thiosulfate has been used clinically for nearly a century. Moreover PEDMARK treatment is confined to a limited number of distinct administrations and will not be indicated for chronic use. Furthermore, PEDMARK is only administered to cancer patients receiving CIS treatment. Therefore, STS at the studied and proposed dose regimen is not considered to increase the risk for cardiotoxicity in these conditions.

The FDA's Assessment:
FDA agrees with the Applicant's assessment and request for waiver.

Immunogenicity

The Applicant's Position:

Not applicable.

The FDA's Assessment:
FDA agrees.

8.2.5. Analysis of Submission-Specific Safety Issues

The Applicant's Position:

Adverse events of special interest were identified as Grade 3 severity or higher events in the PTs of nausea, vomiting, hypomagnesemia, and hypernatremia for both SIOPEL 6 and COG ACCL0431. These AEs are discussed in Section 8.2.4.

The FDA's Assessment:
FDA agrees with the Applicant's assessment. See Section 82.4.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

The Applicant's Position:

There were no clinical outcome assessments or patient-reported outcomes in the studies.

The FDA's Assessment:
FDA agrees.

8.2.7. Safety Analyses by Demographic Subgroups

The Applicant's Position:

Overall, SIOPEL 6 and COG ACCL0431 were smaller studies (N=109 and N=104 patients, respectively), which can limit the interpretation of data by subgroups with small sample sizes. Demographics, exposure, incidence of AEs, and serum sodium levels were evaluated by the subgroups of gender and age for each study. Due to differences in median age between the SIOPEL 6 and COG ACCL0431 patient populations, the age cutoffs evaluated were different for each study. Evaluations of magnesium and GFR levels (by subgroups) were conducted for SIOPEL 6 only.

In addition to gender and age subgroup analyses, data were evaluated by weight subgroup (≤10 kg and >10 kg) in SIOPEL 6 only. The weight subgroup analysis was not conducted for COG ACCL0431 because only 1 child treated with STS was ≤10 kg.

Overall in SIOPEL 6, demographics and incidence of AEs were balanced across the age, gender, and weight subgroups. As expected, the total cumulative CIS doses over all cycles were higher in the ≥24 months subgroup compared with the <24 months subgroup, regardless of whether treatment included or excluded PLADO, due to weight/BSA-based dose calculations. Total

cumulative STS doses over all cycles were also higher in the ≥24 months subgroup compared with the <24 months subgroup, for the same reason. Adverse events were more common in children in the <24 months age group, regardless of treatment arm, and SAEs were more common in children weighing >10 kg in the CIS Alone arm, compared with the other weight subgroup and treatment arm. The incidences of AESIs were similar across subgroups and treatment arms. There were no notable differences across subgroups and treatment arms for GFR, magnesium, and sodium.

Overall in COG ACCL0431, demographics were mostly balanced across the age subgroups and treatment arms; however, the percentage of females was lower in both age subgroups. Baseline disease characteristics reflected the specific tumor type expected to be associated with the age of the child. The total cumulative CIS administered doses over all cycles was higher in the ≥5 years subgroup compared with the <5 years subgroup, which was expected based on the size of the child and prescribed chemotherapy regimen. Mean STS doses and dosing days in the ≥5 years subgroup were higher because more doses of CIS were required for tumor types that occur in older children and because older/larger children received larger doses of STS (calculated as g/m^2). The incidence of AEs (of all grades) and SAEs were similar across age subgroups, with slightly higher incidences of AEs, SAEs, and drug-related AEs in females compared with males. The incidence of death was generally similar across the age subgroups regardless of treatment; however, among patients in the <5 years subgroup, a higher number of patients in the CIS+STS arm died (9 patients) than in the CIS Alone arm (3 patients), which is most likely related to the underlying prognostic factors of tumors which occur in younger children. Among children in the ≥5 years subgroup, the incidences of AESIs of nausea and vomiting were higher in the CIS+STS arm compared with the Observation arm. There were no noticeable differences in sodium level across subgroups and treatment arms.

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 would necessitate changes to the dosing recommendations in the proposed label. SIOPEL 6 and COG ACCL0431 did not enroll patients <1 month of age, as patients in this age group have less well-developed sodium homeostasis (Module 2.7.2, Section 2.2.7); therefore, the safety of PEDMARK in this age group is unknown, and the proposed indication is limited to the ages of 1 month to <18 years.

No new safety concerns were identified in clinical studies evaluating the PK of STS in patients with renal impairment in the literature. 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.

The FDA's Assessment:

FDA did not conduct separate safety analyses by demographic subgroups.

8.2.8. Specific Safety Studies/Clinical Trials

The Applicant's Position:

No separate studies were conducted to evaluate a specific safety concern.

The FDA's Assessment:
Not applicable.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development
The Applicant's Position:

No carcinogenicity studies have been conducted with STS. As the ICH S1A guidance noted 23 years ago, "since carcinogenicity studies are time consuming and resource intensive, they should only be performed when human exposure warrants the need for information from life-time studies in animals in order to assess carcinogenic potential."

Fennec does not plan to conduct a carcinogenicity study with STS because:

- Patients will not be exposed to STS on a chronic basis or "frequently in an intermittent manner in the treatment of a chronic or recurrent condition," as described in the ICH S1A guidance. While STS will be administered in an intermittent manner (ie, typically for 5 days/month and for up to six months in conjunction with platinum chemotherapy), cancer is not a chronic or recurrent condition of the sort given as examples in the ICH S1A guidance (allergic rhinitis, depression, or anxiety).
- There is no cause for concern that STS might pose a carcinogenic hazard to patients because it does not pose a genotoxic hazard and is generally recognized as safe by the FDA when used in food.
- Sodium thiosulfate will be administered only in conjunction with platinum-based chemotherapy, which already presents a carcinogenic hazard to patients. Therefore, the additional carcinogenic hazard presented by STS (if any) would be negligible in comparison.

The FDA's Assessment:
FDA aggress with the Applicant's assessment.

Human Reproduction and Pregnancy
The Applicant's Position:

There are no adequate and well-controlled studies in pregnant women. No pregnancies were reported in either SIOPEL 6 or COG ACCL0431.

There are no reported epidemiological studies of congenital anomalies in infants born to women treated with sodium thiosulfate during pregnancy.

Sodium thiosulfate was not embryotoxic or teratogenic in pregnant mice, rats, hamsters, or rabbits at maternal doses of up to 550, 400, 400, and 580 mg/kg/day (1.65, 2.4, 2.0, and 6.96 g/m^2/day), respectively, when STS was administered as an aqueous solution by oral

intubation (Module 2.6.6 Section 6.3). Additionally, a PK study in gravid ewes indicated that IV STS does not cross the placenta (Module 2.6.4 Section 4.4).

Based on all available information, PEDMARK is considered unlikely to affect embryofetal development in a female patient who is pregnant. Importantly, PEDMARK is only intended to be administered in conjunction with CIS chemotherapy, which already presents a risk of adversely affecting embryofetal development in a pregnant female patient.

There are no studies regarding the excretion of STS into breast milk in humans or animals; however, breast milk is produced within alveolar cells and, since thiosulfate remains extracellularly, it is extremely unlikely that thiosulfate would be found in breast milk (Module 2.6.6 Section 6.3.3). In addition, PEDMARK is only intended to be administered in conjunction with CIS chemotherapy, during which female patients are advised not to breastfeed an infant.

The FDA's Assessment:
See Section 5 for FDA comments.

Pediatrics and Assessment of Effects on Growth
The Applicant's Position:

As the proposed indication for PEDMARK™ (b) (4) is in patients 1 month to <18 years of age, all of the data included in Section 8.2, Review of Safety, addresses safety in pediatric patients.

The FDA's Assessment:
FDA agrees with the Applicant's assessment and refers to Section 8.2. FDA is not aware of any in vitro, in vivo or clinical data that suggest sodium thiosulfate may interfere with pediatric growth or development.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound
The Applicant's Position:

There is limited information about the effects of large doses of STS administered IV in humans.

Drug abuse potential, withdrawal, and rebound are not applicable for STS.

The FDA's Assessment:
FDA agrees with the Applicant's assessment.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience
The Applicant's Position:

PEDMARK is not approved for human use; therefore, no postmarketing information is available for this product.

The following adverse events (AEs), potentially relevant to the use of PEDMARK, have been reported in the medical literature in association with STS administration used for other indications. These AEs were not reported in the context of controlled trials; therefore, frequency of occurrence cannot be assessed.

Cardiovascular System: hypertension, hypotension

Laboratory Investigations: hypocalcemia

Metabolic and Nutritional Disorders: metabolic acidosis

The FDA's Assessment:
FDA does not object to including the proposed terms as safety concerns identified through the post-marketing experience. Terms reported on other labels for sodium thiosulfate were not based on controlled trials and are confounded by different indications and comorbidities.

Expectations on Safety in the Postmarket Setting
The Applicant's Position:

Potential safety concerns beyond the risks conveyed in the proposed labeling are not expected. Routine pharmacovigilance will be conducted to monitor for unexpected adverse events.

The FDA's Assessment:
FDA agrees with the Applicant's assessment.

8.2.11. Integrated Assessment of Safety

The Applicant's Position:

The totality of evidence from the STS clinical development program and available literature demonstrates that PEDMARK has a favorable safety profile for the proposed indication. Fennec's conclusions from the review of safety is provided in Section 8.2.

To provide context for the safety of PEDMARK in the proposed indication, the following subsections provide critical evaluations of these safety concerns as well as overviews of other key elements in the safety profile of STS.

Adverse Drug Reactions

As an inorganic salt in solution, a (b) (4) dose of PEDMARK delivers a sodium load of 162 mmol/m^2. In animal toxicity studies, sodium-related effects have been the dose-limiting factor for STS. Adverse events of hypernatremia were frequently reported in STS-treated patients in SIOPEL 6 (26.4% and 3.6% of patients in the CIS+STS and CIS Alone arms, respectively). No seizures and no ocular problems from sudden high sodium levels translating into sudden high blood pressure levels were observed. In COG ACCL0431, the overall incidence of hypernatremia was lower than observed in SIOPEL 6, but AEs of hypernatremia were still more frequently reported in patients who received STS (11.9% and 6.3% of patients in the CIS+STS and Observation arms, respectively). No events of hypernatremia were serious in

either study, and the majority had a maximum severity of CTCAE Grade 1. In SIOPEL 6, sodium levels were recorded over time, and results showed that increases in sodium levels at 1 hour after STS infusion were transitory and well tolerated. Analysis of modeling and simulation using the proposed PEDMARK dosing showed that the increase in sodium was independent of body weight-dependent dose class, age, or total daily STS dose. Results did not indicate that under- or overdosing occurred in relation to (renal) sodium handling by subjects across the proposed pediatric age range. However, due to the potential for hypernatremia, electrolyte balance should be monitored carefully and PEDMARK should not be given if serum sodium is >145 mmol/L.

Patients receiving CIS are treated with large volumes of fluid and electrolytes (to reduce renal toxicity), sometimes resulting in transient electrolyte imbalances. Other AEs related to electrolyte changes (ie, hypokalemia and hypophosphatemia) were also frequently reported in SIOPEL 6 and COG ACCL0431. In SIOPEL 6, hypokalemia and hypophosphatemia were reported more often in patients treated with STS (15.1% and 1.8% of patients in the CIS+STS and CIS Alone arms, respectively, for both PTs). In COG ACCL0431, hypophosphatemia was also reported more often in patients treated with STS (20.3% and 10.9% of patients the CIS+STS and Observation arms, respectively), while the incidence of hypokalemia was generally similar between arms (27.1% and 20.3% of patients in the CIS+STS and Observation arms, respectively). Nearly all events in both studies were non-serious and considered unlikely related or unrelated to STS. As these patients are already monitored closely for sodium, potassium, and magnesium levels, no additional monitoring of these electrolytes should be required with the use of PEDMARK.

In SIOPEL 6, nausea and vomiting were among the most frequently reported AEs and were more likely to be observed in STS-treated patients. In the CIS+STS arm, 39.6% of patients reported nausea and 84.9% of patients reported vomiting compared with 30.4% and 53.6%, respectively, in the CIS Alone arm. Based on observations from the Investigators, transient increases in incidence and severity of nausea and vomiting during the infusion of STS were probably due to the high sodium levels administered over a short time period; nausea and vomiting tended to stop soon after the STS infusion had finished. In SIOPEL 6, no AEs of nausea or vomiting were serious and the majority had a maximum severity of CTCAE Grade 2 or lower. In COG ACCL0431, the incidences of nausea (8.5% and 4.7% of patients in the CIS+STS and Observation arms, respectively) and vomiting (6.8% and 4.7%, respectively) were much lower than those observed in SIOPEL 6; however, most events were Grade 3 or higher and 2 SAEs of nausea and 1 SAE of vomiting were reported in the CIS+STS arm. The higher incidences of nausea and vomiting AEs in SIOPEL 6 compared with COG ACCL0431 in both treatment arms are explained by the proactive collection of data on nausea and vomiting in the SIOPEL 6 CRF. Events of nausea and vomiting are manageable with appropriate pre-medication. Children receiving chemotherapy known to cause nausea and vomiting, such as CIS, receive prophylactic anti-emetics. Additional multi-agent anti-emetics should be given in the 30 minutes prior to the administration of PEDMARK.

Although not frequently reported, hypersensitivity reactions were observed in SIOPEL 6 and COG ACCL0431 and were more likely to be reported in STS-treated patients. In SIOPEL 6, the

hypersensitivity AEs were reported in 13.2% of patients in the CIS+STS arm and 10.7% of patients in the CIS Alone arm. In COG ACCL0431, the incidence was 8.5% in the CIS+STS arm and 4.7% in the Observation arm. With the exception of 1 SAE of hypersensitivity leading to discontinuation (also considered a SUSAR) that was reported in the CIS+STS arm of SIOPEL 6, no other AEs of hypersensitivity were considered serious. Other non-serious AEs of hypersensitivity were reported in both studies; although incidences were generally similar across arms. Nonetheless, the potential for hypersensitivity reactions is included as an ADR. In addition, because PEDMARK may contain trace amounts of sodium sulfite, hypersensitivity reactions due to sulfite are possible. Such events are manageable with appropriate observation and treatment.

Other Serious Adverse Events and Death

In SIOPEL 6, the overall incidence of non-fatal SAEs during the Treatment Phase was similar between the CIS+STS arm (39.6%) and the CIS Alone arm (32.1%). In COG ACCL0431, SAEs were only collected for patients in the CIS+STS arm, but the overall incidence of SAEs (fatal and non-fatal) in the CIS+STS arm was similar to that observed in SIOPEL 6 (35.6%). The most frequently reported SAEs observed in both studies (eg, febrile neutropenia, anemia, neutrophil count decreased, infection, pyrexia) are commonly known to be associated with chemotherapy and are not plausibly associated with the known mechanism of action of STS.

As expected for a pediatric oncology study, deaths were reported in both studies (6 deaths in SIOPEL 6 [2 deaths in the CIS+STS arm and 4 deaths in the CIS Alone arm]; 30 deaths in COG ACCL0431 [18 deaths in the CIS+STS arm and 12 deaths in the Observation arm]). The majority were due to tumor progression occurring during long-term follow up. No deaths were considered related to STS by the Investigators.

Although not powered for the analysis, both studies evaluated survival during treatment and long-term follow up (SIOPEL 6 median 4.27 years; COG ACCL0431 median 5.33 years). No differences in EFS or OS for the CIS+STS arm compared with the CIS Alone/Observation arm were observed for patients with a localized tumor type (SR-HB; SIOPEL 6) or for patients in COG ACCL0431 categorized post-hoc as having localized disease (various tumor types). For patients in COG ACCL0431 categorized post-hoc with disseminated disease, OS favored the Observation arm; however, the OS for patients in the Observation arm was higher than that predicted for children with mixed disseminated disease based on the literature and very similar to the OS observed in children categorized as having localized disease. A detailed review concluded that the most likely explanation for the difference between the 2 arms in patients with disseminated disease was an imbalance in tumor types and prognostic indicators at randomization rather than the use of STS. The characteristics of the tumors in COG ACCL0431 have a far greater potential to affect survival than the use of STS.

For all of these reasons, deaths due to disease may be expected given the patient population in pediatric oncology, but STS treatment administered 6 hours after completion of CIS infusions does not negatively affect the anti-tumor efficacy of CIS.

Potential for AEs in Patients with Impaired Renal Function or Insufficiency

Evaluation of long-term GFR/creatinine clearance in SIOPEL 6 showed that there was no deterioration in renal function and results were similar between treatment arms. Children receiving chemotherapy for cancer are routinely and carefully monitored for renal function. As a precaution to prevent CIS accumulation in the kidney and CIS-induced nephrotoxicity, patients receive saline fluid hydration treatment with high chloride content before and after CIS administration to stimulate glomerular filtration and urinary flow. It is likely that, under these conditions, glomerular filtration and excretion of STS is maintained, even when the tumor or chemotherapy has affected renal function. However, because STS is known to be substantially excreted by the kidney, the risk of AEs may be greater in patients with impaired renal function. In children with moderate to severe renal insufficiency, PEDMARK should be used with caution and careful monitoring.

Renal function and its maturation in infants are important to the control of sodium hemostasis. PEDMARK is contraindicated in neonates under the age of 1 month due to the potential risk of hypernatremia considering the immaturity of a neonate's renal system. In the PIP, a waiver was granted for preterm and term newborn infants from birth to <1 month of age.

Other Safety Information for Sodium Thiosulfate from Published Literature

In addition to the ADRs, adverse effects associated with STS administration that were reported in the medical literature or in labels from other marketed STS products used for other indications were reviewed. The following events were judged to be relevant to the indicated patient population for PEDMARK based on medical plausibility and occurrence in SIOPEL 6 or COG ACCL0431. These AEs were not reported in the context of controlled studies or with consistent monitoring and reporting methodologies. Therefore, frequency of occurrence of these AEs cannot be assessed.

Cardiovascular System: hypertension, hypotension

Laboratory Investigations: hypocalcemia

Metabolic and Nutritional Disorders: metabolic acidosis

The FDA's Assessment:

FDA agrees with the applicant's integrated assessment of safety. Overall, the safety profile of STS is consistent with the known safety profile of other STS products. No new safety issues were identified.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

The FDA's Assessment:

FDA reiterates that the primary analyses of hearing loss for both SIOPEL6 and COG ACCL0431 were not controlled for type-1 error at a level of 0.05 (two-sided), so no claims of statistical

significance should be made. Additionally, FDA did not agree with the analysis populations in either study, and the regulatory decision was based on FDA's analysis of the primary endpoint of each study in their respective re-defined populations.

Though neither study was powered for EFS or OS, SIOPEL6 showed no apparent difference between arms for either endpoint while COG ACCL0431 showed a potential detriment in both endpoints. Exploratory post-hoc analyses of EFS and OS in COG ACCL0431 suggested that the potential detriment in both may have been driven by patients with metastatic disease. FDA noted that extent of disease (metastatic or non-metastatic), determined post-hoc, was not a stratification factor and sample size in each subgroup was small, so these results should be considered with these limitations in mind. The indication was limited to patients with non-metastatic disease which helps alleviate concerns of a potential survival detriment.

8.4. Conclusions and Recommendations

The FDA's Assessment:

The clinical and statistical reviewers agree that the data from SIOPEL 6 and COG ACCL0431 support regular approval for this NDA, however, due to deficiencies identified during manufacturing sections, the reviewers agree with a complete response.

X	X
Primary Statistical Reviewer	Statistical Team Leader
X	X
Primary Clinical Reviewer	Clinical Team Leader

9 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:

This application was not presented to external consultants because it did not raise significant efficacy or safety issues for the proposed indication.

10 Pediatrics

The Applicant's Position:

The proposed indication for PEDMARK™ (b) (4) is prevention of ototoxicity induced by CIS chemotherapy in patients 1 month to <18 years of age with localized, non-metastatic solid tumors. Thus, all clinical study data included in this document is for pediatric patients.

PEDMARK was granted orphan status and thus there is no requirement for a PSP.

The FDA's Assessment:

FDA agrees with the Applicant's assessment.

11 Labeling Recommendations

The Applicant's Position:

Fennec provided a draft labeling with the NDA.

The FDA's Assessment:

The table below summarizes changes to the proposed prescribing information made by FDA. See the final approved prescribing information for PEDMARK (sodium thiosulfate injection) accompanying the approval letter for more information. At the time of the CR, labeling negotiations were ongoing.

Section	Applicant's Proposed Labeling	FDA Proposed Labeling
General	Proposed a product title of PEDMARK (b) (4)	(b) (4)
Highlights	…	Modified based on changes made to the full prescribing information.
Full Prescribing Information		
Indications and Usage	(b) (4)	Revised indication statement based on recommendations found in Indication and Usage guidance, which states that if the indication for a drug is to reduce the risk of the occurrence of a particular clinical outcome, phrases such as "reduce the risk of" or "reduce the incidence of" should be considered rather than using "prevent" in the indication. (b) (4) revised age groups based on recommendations found in Indication and Usage guidance, which states that"…Age groups should be included in indications. As such, an indication should state that a drug is approved, for example, "in adults," "in pediatric patients X years of age and older," or "in adults and pediatric patients X years of age and older". (b) (4)

Disclaimer: In this document, the sections labeled as "The Applicant's Position" are completed by the Applicant and do not necessarily reflect the positions of the FDA.

		(b) (4)
Dosage and Administration	Provided recommended dose and other information immediately following the section title with no subsections. (b) (4)	Added subsections for recommended dosage, dosage modifications for adverse reactions, recommended premedications, and preparation and administration. Revised recommended dosage (b) (4)
Dosage Forms and Strengths	(b) (4)	Changed to single-dose vial based on Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use and USP Chapter <659>. Will revise the strength of the product based on the pentahydrate form of sodium thiosulfate based on USP monograph. Similar changes will be made to Description and How Supplied/Storage.
Contraindications	Included a contraindication for known hypersensitivity to sodium thiosulfate (b) (4)	Revised the contraindication to history of severe hypersensitivity. Removed (b) (4)
Warnings and Precautions (W&P), Hypersensitivity	(b) (4)	Revised the W&P to describe the percentage of patients who developed a reaction in the entire safety population.

	(b) (4)	Revised steps that should be taken if a reaction occurs based on clinical studies.
W&P, Electrolyte Imbalances	(b) (4)	Revised subsection title to describe the adverse reaction or risk based on best labeling practices. Stated the use of the drug product is not recommended in pediatric patients less than 1 month, because these pediatric patients have less well-developed sodium homeostasis and in patients with high baseline serum sodium level, because of the risk of hypernatremia. Added sodium load for each recommended dosage.
W&P, Sulfites	Included information regarding the risk of a hypersensitivity reaction in patients following sulfite exposure.	Incorporated the information into the W&P for hypersensitivity reactions.
Adverse Reactions, Clinical Trials Experience	(b) (4) Included other sources of safety information based on adverse events reported in the medical literature for sodium thiosulfate.	Based on current OOD labeling practices, independently summarized the dosing regimen, exposure, serious adverse reactions, permanent discontinuations, and most common adverse reactions for each trial. Included a tabular summary of the all grades and grades 3 to 4 adverse reactions for both treatment arms for each trial. Moved this information into a new subsection "Postmarketing Experience" to include adverse reactions from spontaneous reports with other sodium thiosulfate products.
Drug Interactions	(b) (4)	Omitted, because this section must contain a description of clinically significant interactions, either observed or predicted, with other prescription or over-the-counter drugs, classes of drugs, or foods (e.g., dietary supplements, grapefruit juice), and specific practical instructions for preventing or managing them. [21 CFR 201.57 (c)(8)(i).
Use in Specific Populations, Pregnancy	(b) (4)	Included a risk statement based on human data and animal data and the percentage range of live births in US with a major birth defect and the percentage range of pregnancies in US that end in

	Included a summary of animal studies.	miscarriage as required by 21 CFR 201.57(c)(9)(i)(B)(1) and (2). Revised summary of animal data to include the number and type(s) of species affected, timing of exposure, animal doses expressed in terms of human dose or exposure equivalents, and outcomes for pregnant animals and offspring based on regulations cited above.
Use in Specific Populations, Lactation	(b) (4)	Included presence of drug in human milk, effects of drug on breast-fed child and effects of drug on milk production as required by 21 CFR 201.57(c)(9)(ii).
Use in Specific Populations, Females and Males of Reproductive Potential	…	Omitted because recommendations were based on cisplatin, not sodium thiosulfate.
Use in Specific Populations, Pediatric Use	…	Added safety and effectiveness have not been established and is not recommended in pediatric patients younger than 1 month old due to the increased risk of hypernatremia based on recommendations in Pediatric Labeling guidance.
Use in Specific Populations, Geriatric Use	…	Added subsection and required geriatric use statement [21 CFR 201.57 (c)(9)(v)(B)(1)].
Use in Specific Populations, Renal Impairment	(b) (4)	Added steps to be taken to reduce risk of adverse reactions in patients with renal impairment.
Overdosage	…	Omitted. The OVERDOSAGE section must be based on human overdosage data. If human data are unavailable, appropriate animal and in vitro data regarding overdosage may be included. Alternatively, if no specific overdosage data are available that would be useful to the health care practitioner, omit this section [21 CFR 201.57(c)(11)].
Clinical Pharmacology, Pharmacodynamics	(b) (4)	

		Revised summary of the effects on serum sodium level to include sodium load for each recommended dosage, the reported sodium levels in patients, and the time course of changes in serum sodium levels following administration of sodium thiosulfate.
Clinical Pharmacology, Pharmacokinetics	(b) (4)	Deleted, since animal information that should generally not be included in subsection 13.2 Animal Toxicology and/or Pharmacology unless it is necessary for the understanding of pharmacology data in humans, per guidance Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format.
Clinical Studies	(b) (4)	Separated information into a single subsection because both trials support a single indication and usage. Added demographics and baseline characteristics to provide sufficient context for the study results. (b) (4) Revised study outcome measures for the COG trial to only include patients with localized disease based on the indication.

12 Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:

Not applicable as this recommendation for this application is CR; however, the clinical review team does not recommend a REMS. Based on the risk/benefit profile of PEDMARK, safety issues can be adequately managed through appropriate labeling and routine post-marketing surveillance.

13 Postmarketing Requirements and Commitment

The FDA's Assessment:
Not applicable as this recommendation for this application is CR.

14 Division Director (DHOT) (NME ONLY)

X _____

15 Division Director (OCP)

X _____

16 Division Director (OB)

X _____

17 Division Director (Clinical)

X

18 Office Director (or designated signatory authority)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

X _____

19 Appendices

19.1. References

The Applicant's References:

American-Speech-Language-Hearing Association. Guidelines for the audiologic management of individuals receiving chochleotoxic drug therapy. ASHA. 1994;36(Suppl.12):11-19.

Arslan E, Orzan E, Santarelli R. Global problem of drug-induced hearing loss. Ann N Y Acad Sci. 1999;884:1-14.

Asplin, J.R., Donahue, S.E., Lindeman, C., et al. Thiosulfate reduces calcium phosphate nephrolithiasis. J. Am. Soc. Nephrol. 2009;20:1246-1253.

Berg AL, Spitzer JB, Garvin JH. Ototoxic impact of cisplatin in pediatric oncology patients. Laryngoscope 1999;109(11):1806-14.

Bijarnia RK, Bachtler M, Chandak PG, van Goor H, Pasch A. Sodium Thiosulfate Ameliorates Oxidative Stress and Preserves Renal Function in Hyperoxaluric Rats. PLoS ONE. 2015;10(4):e0124881.

Bertolini P, Lassalle M, Mercier G, Raquin MA, Izzi G, Corradini N, et al. Platinum compound related ototoxicity in children: long-term follow-up reveals continuous worsening of hearing loss. J Pediatr Hematol Oncol. 2004;26(10):649-55.

Bijarnia, R.K., Bachtler, M., Chandak, P.G. et al. Sodium Thiosulfate Ameliorates Oxidative Stress and Preserves Renal Function in Hyperoxaluric Rats. PLoS ONE. 2015;10(4):e0124881.

Bilska-Wilkosz, A., Iciek, M., Górny, M, Kowalczyk-Pachel D. The Role of Hemoproteins: Hemoglobin, Myoglobin and Neuroglobin in Endogenous Thiosulfate Production Processes. Int. J. Mol. Sci. 2017;18,1315-1325.

Blakley BW, Cohen JI, Doolittle ND, Muldoon LL, Campbell KC, Dickey DT, et al. Strategies for prevention of toxicity caused by platinum-based chemotherapy: review and summary of the annual meeting of the Blood brain barrier Disruption Program, Gleneden Beach, Oregon, March 10, 2001. Laryngoscope. 2002;112(11):1997 2001.

Braverman, B., Ivankovich, A.D., Shah, G. Thiosulfate pharmacokinetics in normal and anuretic dogs. Proceedings of the Society for Experimental Biology and Medicine. 1982;170:273-280.

Breglio AM, Rusheen AE, Shide ED, Fernandez KA, Spielbauer KK, McLachlin KM, et al. Cisplatin is retained in the cochlea indefinitely following chemotherapy. Nature Communications. 2017; 8:1654:1-9.

Brock PR, Bellman SC, Yeomans EC, Pinkerton CR, Pritchard J. Cisplatin ototoxicity in children: A practical grading system. Med Pediatr Oncol. 1991;19(4):295-300.

Brock PR, Knight KR, Freyer DR, Campbell KC, Steyger PS, Blakley BW, et al. Platinum-induced ototoxicity in children: a consensus review on mechanisms, predisposition,

and protection, including a new International Society of Pediatric Oncology Boston ototoxicity scale. J Clin Oncol. 2012;30:2408-17.

Brock PR, Maiback R, Childs M, Rajput K, Roebuck D, Sullivan MJ, et al. Sodium thiosulfate for protection from cisplatin-induced hearing loss. New England J of Medicine 2018;378:2376-85.

Campbell, K.C.M., Meech, R.P., Rybak, L.P. et al. The Effect of D-Methionine on Cochlear Oxidative State with and without Cisplatin Administration: Mechanisms of Otoprotection. Journal of the American Academy of Audiology. 2003;14(3), 144-156.

Church, M.W., Kaltenbach, J.A., Blakley, B.W. et al. The comparative effects of sodium thiosulfate, diethyldithiocarbamate, fosfomycin and WR-2721 on ameliorating cisplatin-induced ototoxicity. Hearing Res. 1995;86(1-2):195-203.

Dedon, P.C. and Borch, R.F. Characterization of the reactions of platinum antitumor agents with biologic and nonbiologic sulfur-containing nucleophiles. Biochemical Pharmacology. 1987;36(12):1955-1964.

Dehne, N., Lautermann, J., Petrat, F. et al. Cisplatin Ototoxicity: Involvement of Iron and Enhanced Formation of Superoxide Anion Radicals. Toxicology and Applied Pharmacology. 2001;174:27-34.

Dennis, D.L. and Fletcher, W.S. Toxicity of sodium thiosulfate (NSC-45624), a nitrogen mustard antagonist, in the dog. Can. Chemo. Rep. 1966;50(5):255-257.

Dickey DT, Muldoon LL, Kraemer DF, Neuwelt EA. Protection against cisplatin-induced ototoxicity by N-acetylcysteine in a rat model. Hear Res. 2004;193:25-30.

Dickey DT, Wu JY, Muldoon LL, Neuwelt EA. Protection against cisplatin-induced toxicities by N-acetylcysteine and sodium thiosulfate as assessed at the molecular, cellular, and in vivo levels. J Pharmacol Exp Ther. 2005;314(3):1052-8.

Ding, D.L., Wang, J., Salvi, R., et al. Selective Loss of Inner Hair Cells and Type-I Ganglion Neurons in Carboplatin-Treated Chinchillas. Mechanisms of Damage and Protection. Annals New York Academy Of Sciences. 1999;884:152-170.

Doolittle ND, Muldoon LL, Brummett RE, Tyson RM, Lacy C, Bubalo JS, et al. Delayed sodium thiosulfate as an otoprotectant against carboplatin-inducted hearing loss in patients with malignant brain tumors. Clin Cancer Res. 2001;7(3):493-500.

Dorr, R.T. Chemoprotectants for cancer chemotherapy. Semin. Oncol. 1991;18(1suppl 2):48 58.

Elferink, F., van der Vijgh, W.J.F., Klein, I, et al. Interaction of Cisplatin and Carboplatin with Sodium Thiosulfate: Reaction Rates and Protein Binding. Clin. Chem. 1986;32(4):641-645.

Environmental Protection Agency (EPA). Sodium thiosulfate; Notice of Filing a Pesticide Petition to Amend a Tolerance for a Certain Pesticide Chemical in or on Food. Federal Register. 2003;68(228):66416-66421.

Evans, P., and Halliwell, B. Free radicals and Hearing. Cause, Consequence and Criteria. Annals New York Academy Of Sciences. 1999;884:19-40.

Farese S, Stauffer E, Kalicki R, Hildebrandt T, Frey BM, Frey FJ, et al. Sodium thiosulfate pharmacokinetics in hemodialysis patients and healthy volunteers. Clin J Am Soc Nephrol. 2011;6(6):1447-55.

Fausti SA, Henry JA, Schaffer HI, Olson DJ, Frey RH, Bagby GC. High-frequency monitoring for early detection of cisplatin ototoxicity. Arch Otolaryngol Head Neck Surgery. 1993;119(6):661-6.

Freyer DR, Chen L, Krailo MD, Knight K, Villaluna D, Bliss B, et al. Effects of sodium thiosulfate versus observation on development of cisplatin-induced hearing loss in children with cancer: results from the Children's Oncology Group ACCL0431 randomised clinical trial. Lancet Oncol. 2017;18(1):63-74.

Gilmer-Knight KR, Kraemer DF, Neuwelt EA. Ototoxicity in children receiving platinum chemotherapy: estimating a commonly occurring toxicity that may influence academic and social development. J Clin Oncol 2005;23(34):8588-96.

Hale GA, Marina NM, Jones-Wallace D, Greenwald CA, Jenkins JJ, Rao BN, et al. Late effects of treatment for germ cell tumors during childhood and adolescence. Journal of pediatric hematology/oncology. 1999;21:115-22.

Hazlitt, R.A., Min, J., Zuo, J. Progress in the Development of Preventative Drugs for Cisplatin-Induced Hearing Loss. J. Med. Chem. 2018;61:5512-5524.

Hildebrandt TM and Manfred KG. Three enzymatic activities catalyze the oxidation of sulfide to thiosulfate in mammalian and invertebrate mitochondria. FEBS J. 2008 Jul;275(13):3352-61.

Hindley P. Psychiatric aspects of hearing impairments. J Child Psychol Psychiatry. 1997;38(1):101-17.

Ishizawa, M., Taniguchi, S., and Baba, T. Protection by sodium thiosulfate and thiourea against lethal toxicity of cis-diamminedichloroplatinum(ii) in bacteria and mice. Japan J. Pharmacol. 1981;31:883-889.

Ivankovich AD, Braverman B, Stephens TS, Shulman M, Heyman HJ. Sodium thiosulfate disposition in humans: relation to sodium nitroprusside toxicity. Anesthesiology. 1983;58(1):11-7.

Iwamoto, Y., Kawano, T., Ishizawa, M. et al. Inactivation of cis-diamminedichloroplatinum (II) in blood and protection of its toxicity by sodium thiosulfate in rabbits. Cancer Chemother. Pharmacol. 1985;15:228-232.

Iwamoto, Y., Kawano, T., Uozumi, J., et al. "Two-route chemotherapy" using high-dose IP cisplatin and IV sodium thiosulfate, its antidote, for peritoneally disseminated cancer in mice. Can. Treat. Rep. 1984;68(11):1367-1373.

Kaltenbach, J.A., Church, M.W., Blakley, B.W., et al. Comparison of five agents in protecting the cochlea against the ototoxic effects of cisplatin in the hamster. Otolaryngol. Head Neck Surg. 1997;117(5):493-500.

Karasawa, T., Steyger, P.S. An integrated view of cisplatin-induced nephrotoxicity and ototoxicity. Toxicol. Lett. 2015;237(3): 219-227.

Katzenstein HM, Chang KW, Krailo M, Chen Z, Finegold MJ, Rowland J, et al. Amifostine does not prevent platinum-induced hearing loss associated with the treatment ofchildren with hepatoblastoma: a report of the Intergroup Hepatoblastoma Study P9645 as a part of the Children's Oncology Group. Cancer. 2009;115(24):5828-35.

Kelland, L. The resurgence of platinum-based cancer chemotherapy. Nat. Rev. Cancer. 2007;7(8):573-584.

Knight KR, Kraemer DF, Neuwelt EA. Ototoxicity in children receiving platinum chemotherapy: Underestimating a commonly occurring toxicity that may influence academic and social development. J Clin Oncol. 2005;23(34):8588-96.

Knight KR, Kraemer DF, Winter C, Neuwelt EA. Early changes in auditory function as a result of platinum chemotherapy: use of extended high-frequency audiometry and evoked distortion product otoacoustic emissions. J Clin Oncol. 2007;25(10):1190-5.

Kowalski HJ and Rutstein DD. The distribution of the thiosulfate ion with respect to normal serum and red blood cells and its application to extracellular fluid determination. J Clin Invest. 1952;31(4): 370-374.

Landier W, Knight K, Wong FL, Lee J, Thomas O, Kim H, et al. Ototoxicity in children with high-risk neuroblastoma: prevalence, risk factors, and concordance of grading scales--a report from the Children's Oncology Group. J Clin Oncol. 2014;32:527-534.

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

Li Y, Womer RB, Silber JH. Predicting cisplatin ototoxicity in children: the influence of age and the cumulative dose. Eur J Cancer. 2004;40(16):2445-51.

Liao, Y., Lu, X., Lu, C., et al. Selection of agents for prevention of cisplatin-induced hepatotoxicity. Pharmacological Research. 2008;57:125-131.

Lokich J. What is the best platinum: cisplatin, carboplatin, or oxaliplatin? Cancer Investigation. 2001;19:756-60.

Macdonald MR, Harrison RV, Wake M, Bliss B, Macdonald RE. Ototoxicity of carboplatin: Comparing animal and clinical models at The Hospital For Sick Children. J. Otolaryngol. 1994; 23(3):151-9.

Marutani E, Yamada M, Ida T. Thiosulfate Mediates Cytoprotective Effects of Hydrogen Sulfide Against Neuronal Ischemia. J. Am. Heart Assoc. 2015;4:e002125.

Mathews SJ, de las Fuentes L, Podaralla P, Cabellon A, Zheng S, Bierhals A, et al. Effects of sodium thiosulfate on vascular calcification in end-stage renal disease: a pilot study of feasibility, safety and efficacy. Am J Nephrol. 2011;33:131-8.

Meyers R, Maibach R, Hiyama E, Haberle B, Krailo M, et al. Risk-stratified staging in paediatric hepatoblastoma: a unified analysis from the Children's Hepatic tumors International Collaboration. Lancet Oncol 2017;18(1):122-131.

Mohan, D., Balasubramanian, E.D., Ravindran, S., et al. Renal mitochondria can withstand hypoxic/ischemic injury secondary to renal failure in uremic rats pretreated with sodium thiosulfate. Indian J. Pharmacol. 2017;49(4):317-321.

Muldoon, L.L., Pagel, M.A., Kroll, R.A., et al. Delayed administration of sodium thiosulfate in animal models reduces platinum ototoxicity without reduction of antitumor activity. Clin. Cancer Res. 2000;6(1):309-15.

Nagai, N., Hotta, K., Yamamura, H., et al. Effects of sodium thiosulfate on the pharmacokinetics of unchanged cisplatin and on the distribution of platinum species in rat kidney: protective mechanism against cisplatin nephrotoxicity. Cancer Chemother. Pharmacol. 1995;36:404-410.

Neuwelt EA, Brummett RE, Doolittle ND, Muldoon LL, Kroll RA, Pagel MA, et al. First evidence of otoprotection against carboplatin-induced hearing loss with a two-compartment system in patients with central nervous system malignancy using sodium thiosulfate. J Pharmacol Exp Ther. 1998;286(1):77-84.

Neuwelt, E.A., Brummett, R.E., Remsen, L.G., et al. In vitro and animal studies of sodium thiosulfate as a potential chemoprotectant against carboplatin-induced ototoxicity. Canc. Res. 1996;56(40):706-709.

Neuwelt EA, Gilmer-Knight K, Lacy C, Nicholson HS, Kraemer DF, Doolittle ND, et al. Toxicity profile of delayed high dose sodium thiosulfate in children treated with carboplatin in conjunction with blood-brain-barrier disruption. Pediatr Blood Cancer. 2006;47(2):174-82.

Neuwelt, E.A., Pagel, M.A., Kraemer, D.F., et al. Bone marrow chemoprotection without compromise of chemotherapy efficacy in a rat brain tumor model. J. Pharmacol. Exp. Ther. 2004;309(2):594-599.

Newman, EV, Gilman A, Philips FS. The renal clearance of thiosulfate in man. Bulletin of the John Hopkins Hospital. 1946;79:229-242.

Ohe, T., Tsuda, S., Sakata, Y., et al. Cis-diamminedichloroplatinum(II)-induced sister-chromatid exchanges and chromosome aberration formation in cultured human lymphocytes and their inhibition by sodium thiosulfate. Mutat. Res. 1990;244(4):279-285.

Otto, W.C., Brown, R.D., Gage-White, L., et al. Effects of cisplatin and thiosulfate upon auditory brainstem responses of guinea pigs. Hearing Research. 1988;35:79-86.

Park KR. The utility of acoustic reflex thresholds and other conventional audiologic tests for monitoring cisplatin ototoxicity in the pediatric population. Ear and Hear. 1996;17(2):107-15.

Pasch, A., Schaffner, T., Huynh-Do, U. et al., Sodium thiosulfate prevents vascular calcifications in uremic rats. Kidney International. 2008:74, 1444–1453.

Peters AM, Snelling HL, Glass DM, Bird NJ. Estimation of lean body mass in children. Br J Anaesth. 2011 May;106(5):719-23.

Poore, G.A., Todd, G.C., and Grindey, G.B. Effect of sodium thiosulfate (S2O3) on intravenous cisplatin (cisplatin) toxicity and antitumor activity [abstract]. Proceedings of the Am. Assoc. Cancer Res. 1984;25:370.

Prival, M.J., Simmon, V.F. and Mortelmans, K.E. Bacterial mutagenicity testing of 49 food ingredients gives very few positive results. Mutat. Res. 1991;260(4):321-329.

Punnett A, Bliss B, Dupuis LL, Abdolell M, Doyle J, Sung L. Ototoxicity following pediatric hematopoietic stem cell transplantation: a prospective cohort study. Pediatr Blood Cancer. 2004;42(7):598-603.

Ravi, R., Somani, S.M., Rybak, L.P. Mechanism of cisplatin ototoxicity: antioxidant system. Pharmacol. Toxicol. 1995;76(6):386-394.

Registry of Toxic Effects of Chemical Substances (RTECS). Database on thiosulfuric acid, disodium salt. 2011;MDL Information Services.

Ross CJ, Katzov-Eckert H, Dube MP, Brooks B, Rassekh SR, Barhdadi A, et al. Genetic variants in TPMT and COMT are associated with hearing loss in children receiving cisplatin chemotherapy. Nat Genet. 2009;41(12):1345-9.

Rybak, L.P., Husain, K., Morris, C. et al. Effect of protective agents against cisplatin ototoxicity. Am. J. Otol. 2000;21(4):513-520.

Ryback LP and Somani S. Ototoxicity. Amelioration by protective agents. Ann NY Acad Sci. 1999;884:143-51.

Rybak, L.P., Whitworth, C.A., Mukherjea, D., et al. Mechanisms of cisplatin-induced ototoxicity and prevention. Hearing Research. 2007;226:157-167.

Ryback LP, Whitworth C, Somani S. Application of antioxidants and other agents to prevent cisplatin ototoxicity. Laryngoscope. 1999;109(11):1740-4.

Saito, T., Zhang, Z.J., Manabe, Y., et al. The effect of sodium thiosulfate on ototoxicity and pharmacokinetics after cisplatin treatment in guinea pigs. Eur. Arch. Otorhinolaryngol. 1997;254:281-286.

Sheth, S., Mukherjea, D., Rybak, L.P., et al. Mechanisms of Cisplatin-Induced Ototoxicity and Otoprotection. Front. Cell. Neurosci. 2017;11:338.

Skinner R, Pearson ADJ, Amineddine HA, Mathias DB, Craft AW. Ototoxicity of cisplatinum in children and adolescents. Br J Cancer. 1990;61:927-31.

Sooriyaarachchi, M., Gailer, J., Dolgova, N.V., et al. Chemical basis for the detoxification of cisplatin-derived hydrolysis products by sodium thiosulfate. J. Inorg. Biochem. 2016;162:96-101.

Stocks, R.M.S., Gould, H.J., Bush, A.J., et al. Ototoxic protection of sodium thiosulfate: daily vs constant infusion. Otolaryngology - Head and Neck Surgery. 2004;13(1):115-119.

Szczepkowski TW, Skarzynski B, Weber M. The metabolic state of thiosulphate. Nature. 1961;189:1007-8.

Taniguchi, S. and Baba, T. "Two route chemotherapy" using cis-diamminedichloroplatinum (II) and its antidote, sodium thiosulfate, for peritoneally disseminated cancer in rats. Gann. 1982;73(3):475-479.

Tod M, Lokiec F, Bidault R, De Bony F, Petitjean O, Aujard Y, et al. Pharmacokinetics of oral acyclovir in neonates and infants: a population analysis. Antimicrob Agents Chemother. 2001;45(1):150-7.

Uozumi, J., Ishizawa, M., Iwamoto, Y., et al. Sodium thiosulfate inhibits cis-diamminedichloroplatinum (II) activity. Cancer Chemother. Pharmacol. 1984;13:82-85.

Wang, J., Lloyd Faulconbridge, R.V., Fetoni, A., et al. Local application of sodium thiosulfate prevents cisplatin-induced hearing loss in the guinea pig. Neuropharmacology. 2003;45:380-393.

Whelan K, Stratton K, Kawashima T, Leisenring W, Hayashi S, Waterbor J, et al. Auditory complications in childhood cancer survivors: a report from the childhood cancer survivor study. Pediatr Blood Cancer. 2011;57(1):126-34.

Wile, A.G., Dileo, S.K., Gossett, D.A., et al. Intraperitoneal cisplatin with sodium thiosulfate protection in rats with intestinal anastomoses. Journal of Surgical Oncology. 1993;52:265-268.

Wimmer, C., Mees, K., Stumpf, P., et al. Round window application of D-methionine, sodium thiosulfate, brain-derived neurotrophic factor, and fibroblast growth factor 2 in cisplatin-induced ototoxicity. Otology & Neurotology. 2004;25(1):33-40.

Yancey A, Harris MS, Egbelakin A, Gilbert J, Pisoni DB, Renbarger. Risk factors for cisplatin-associated ototoxicity in pediatric oncology patients. Pediatr Blood Cancer. 2012;59(1):144-8.

The FDA's References:

10OECD Screening Information Data Set (SIDS) for 2,6-Di-tert-Butyl-p-Cresol (Processed by UNEP Chemicals). 2005. http://www.inchem.org/documents/sids/sids/128370.pdf

Lee, M., McGeer, EG., and McGeer, PL., Sodium thiosulfate attenuates glial-mediated neuroinflammation in degenerative neurological diseases. J Neuroinflammation 2016 13:32 DOI 10.1186/s12974-016-0488-8

Sen, U., Vacek, TP., Hughes, WM., et al. Cardioprotective Role of Sodium Thiosulfate on Chronic Heart Failure by Modulating Endogenous H2S Generation. Pharmacology 2008;82(3):201-213

Willhite, CC., Developmental Toxicology of Acetonitrile in the Syrian Golden Hamster.

Teratology 1983; 27(3):313-325

Zdravkovic SA., Assessment of Patient Exposure to Leachables From Lyophilized Drug Formulations Following Reconstitution, Storage, and Administration via Polymeric Packaging/Delivery Systems. *J Pharm Sci*. 2018;107(11):2837-2846.

19.2. Financial Disclosure

The Applicant's Position:

Fennec provided financial disclosure for all clinical investigators involved in the studies included in this submission in Form 3455. No concerns were raised regarding the overall integrity of the data.

The FDA's Assessment:
Table completed by FDA. FDA did not identify and issues regarding financial disclosure.

Covered Clinical Study (Name and/or Number):SIOPEL 6 and ACCL0431

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 170		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in study: _____ Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial	Yes ☐	No ☐ (Request details from Applicant)

interests/arrangements:		
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

*The table above should be filled by the applicant, and confirmed/edited by the FDA.

19.3. Nonclinical Pharmacology/Toxicology

This is reserved for data that could not fit under PT section (Section 5), e.g. carci data. Limit to 2 pages

The Applicant's Position:
None.

The FDA's Assessment:
n/a

19.4. OCP Appendices (Technical documents supporting OCP recommendations)

The FDA's Assessment:

19.4.1. Population Pharmacokinetic Analyses

The goal of population PK analysis (popPK) was to develop a population pharmacokinetic (PK) model to assess sources of variability (intrinsic and extrinsic covariates) of sodium thiosulfate in patients.

Two studies (International Childhood Liver Tumor Strategy Group [SIOPEL] 6 and Children's Oncology Group [COG] ACCL0431) were conducted to demonstrate the efficacy and safety of STS in pediatric patients treated with CIS. No PK analysis was performed for either study. Sodium thiosulfate plasma data has been made available to the applicant Fennec by authors from other academic studies investigating STS administration to prevent ototoxicity in brain cancer patients (Neuwelt et al, 1998; Doolittle et al, 2001; Neuwelt et al, 2006).

The data was obtained in 5 pediatric patients and 11 adult patients with malignant brain tumors (aged 2.5 to 69 years), who received IV administration by a 15-minute infusion, the same duration of infusion as used in SIOPEL 6 and COG ACCL0431. The population PK model for sodium thiosulfate was built based on PK data from these 16 patients. The baselines covariates for 16 patients were provided in Table 34.

Table 47: Covariate Distribution for 16 Patients Included in the PopPK Analysis

Covariate	Unit	N	Min	Perc5	Q1	Median	Mean	Q3	Perc95	Max	SD
AGE	years	16	2.50	8.43	15.2	32.5	34.8	52.5	67.5	69.0	21.7
BSA	m^2	16	0.560	1.04	1.53	1.71	1.64	1.84	2.08	2.19	0.390
HT	cm	16	93.0	128	162	170	161	170	170	170	20.0
LBM	kg	16	11.2	29.1	43.0	49.1	46.5	53.1	57.9	61.3	11.9
WT	kg	16	12.7	34.4	53.5	64.5	61.4	71.2	81.5	89.0	18.1

Source: Applicant's PopPK report, Table 2, Page 25

The popPK analysis was conducted by the sponsor and evaluated by the reviewer. The PK of sodium thiosulfate was characterized by a two-compartment model with endogenous thiosulfate (TS) production rate. Drug clearance (CL) was modeled as the sum of the renal (CLR) and non-renal clearance (CLNR). The population CLR was fixed to the value found in literature, and the individual CLR was modeled as a function of body surface area and a maturation factor:

$$\text{MFCLR} = \frac{(12*(AGE+0.75))^{6.17}}{(12*(AGE+0.75))^{6.17}+13.4^{6.17}}$$

The CLNR was estimated independently of body size. The central (VC) and peripheral (VP) volume were modeled in function of the individual lean body mass. Residual variability was modeled proportionally and inter-individual variability (IIV) was not included on any of the model parameters.

FDA has made several modifications in its independent analysis:

1. Applicant fixed the typical renal clearance at 1.36 mL/min/kg in the model according to the Farese et al. 2011. But this estimate was based on the data obtained in healthy volunteers instead of patients with malignant brain tumors. The typical renal clearance was estimated in FDA's independent analysis.
2. The IIV for central volume of distribution was estimated.
3. The residual error model was described by a proportional and additive error model.

Improvement in fit was observed with a decrease of -25.055 in objective function value (OFV). Parameter estimates of final model were provided in Table 35. No signs of model

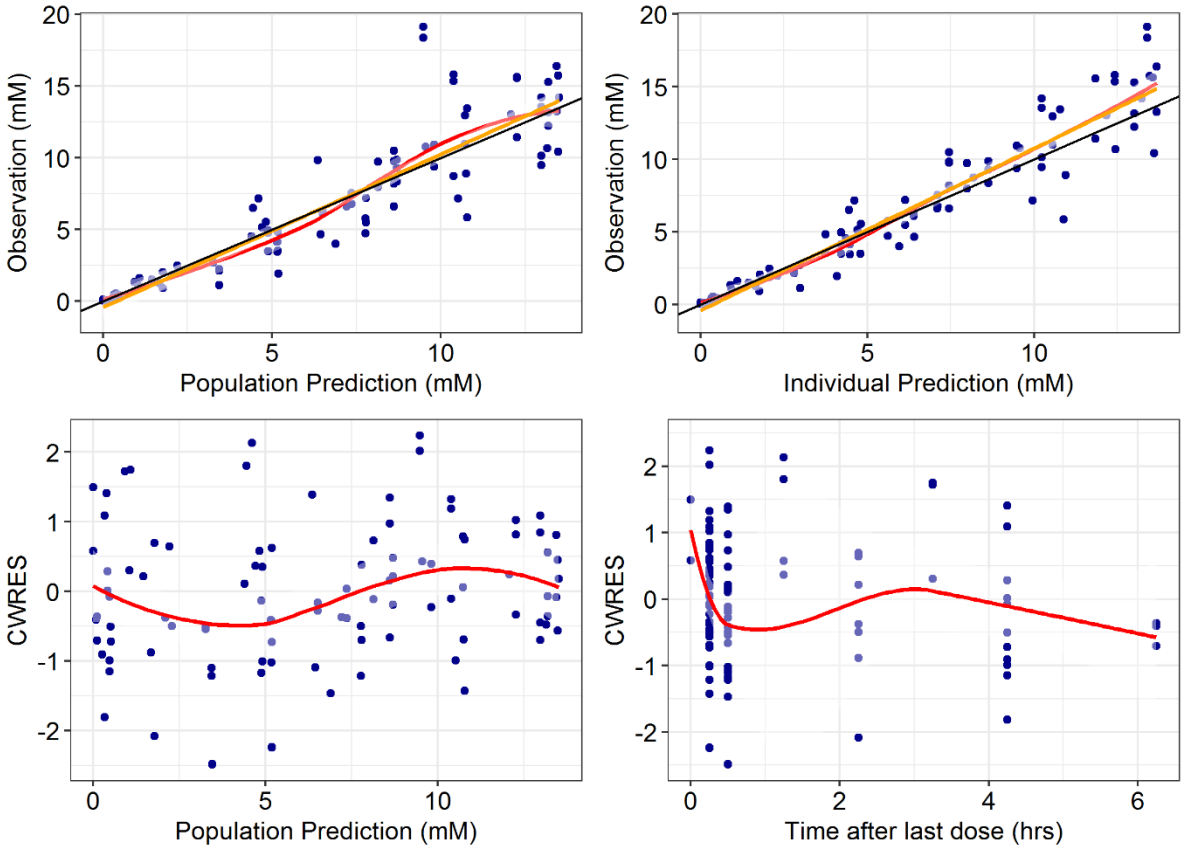
misspecification were identified in the goodness-of-fit plots (Figure 12). Prediction-corrected visual predictive check showed that the final model adequately described the observed PK profile of sodium thiosulfate (Figure 13).

Table 48: Parameter Estimates of the Final PopPK Model for Sodium thiosulfate

Parameter	Estimate	SE	CV (%)
NRCL (L/h)	2.32	1.95	84.1
RCL (L/h)	6.98	1.84	26.4
VC (L/kg_LBM)	0.142	0.0205	14.4
Q (L/h)	31.9	14.7	46.1
VP (L/kg_LBM)	0.0882	0.026	29.5
KIN (mol/hr)	12.1	2.64	21.8
IIV-VC	29.8%		36.3
Prop Error	0.0664		33.3
Add Error	0.0074		48.4

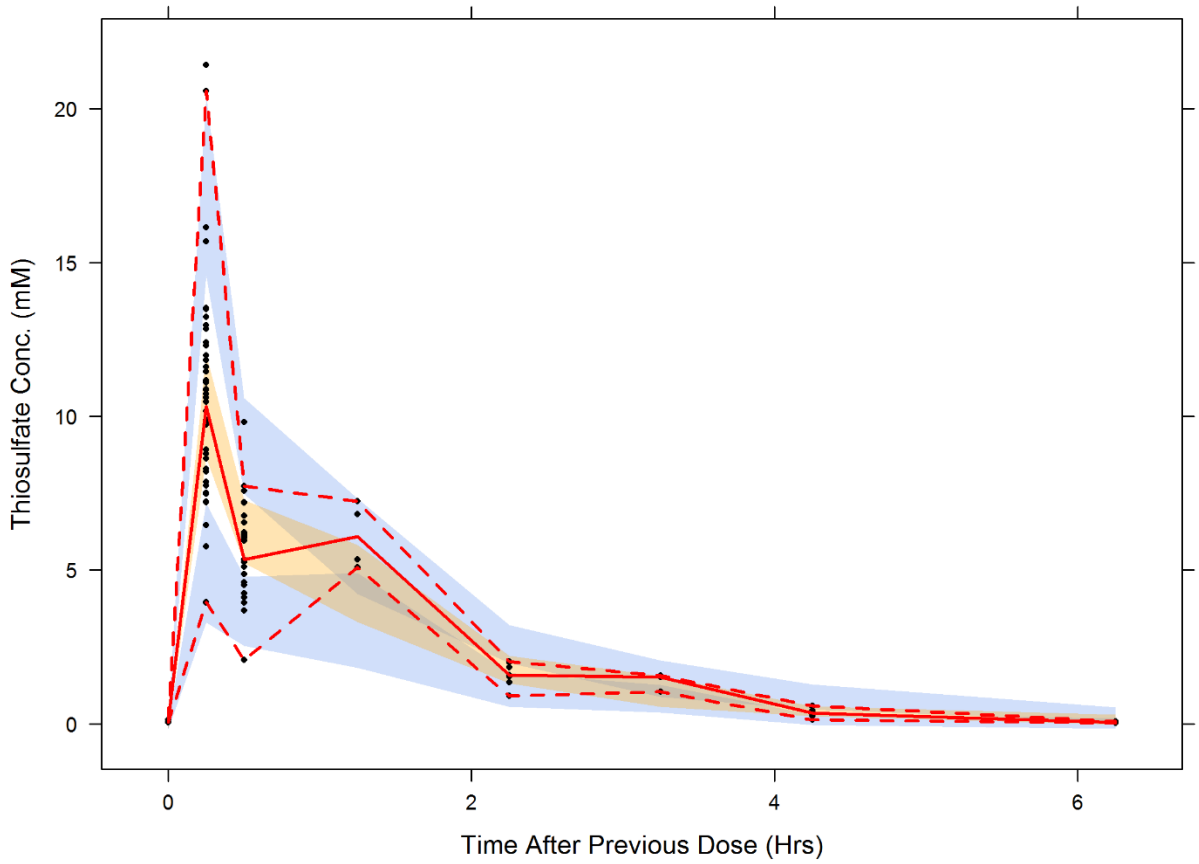
Source: Reviewer's analysis based on data "NM.STS.v2.csv"

Figure 18: Goodness of Fit Plots of the Final Model for Sodium thiosulfate



Source: Reviewer's analysis based on data "NM.STS.v2.csv"

Figure 19: Visual Predictive Checks of Sodium thiosulfate Concentration-Time Data.



Source: Reviewer's analysis based on data "NM.STS.v2.csv"

The developed thiosulfate PK model was used to perform simulations of the expected concentration following a 15 minute i.v. infusion of STS in the pediatric population with subjects ranging from 2 months to 18 years. The applicant states that the Cmax correlates with efficacy as previous studies showed that a 15-minute infusion of STS was effective, while longer slow STS infusions did not reach sufficiently high concentrations to be effective.

FDA acknowledges that the current model has its limitation in predicting the exposure with proposed dosing regimen in young pediatric patients as the developed model is based on a limited dataset of five pediatric subjects and eleven adults. Although the model fits the observed data well, the model fails to demonstrate its ability to describe the PK data in pediatric patients at a younger age. Because of these uncertainties, sensitivity analysis was also conducted to test the robustness of the model simulation when the non-renal clearance is related to the body size or when it also follows the maturation function. The CL function for final model and 2 sensitivity analyses were described in the following equation:

$CL_{finalmodel}$ = CLNR + CLR = 2.32 + 6.98 * (BSA/1.73) * MFCLR

CL_{sen1} = CLNR + CLR = 5.35*(BSA/1.73) + 3.93* (BSA/1.73) * MFCLR
CL_{sen2} = CLNR + CLR = 9.27* (BSA/1.73) * MFCLR

The relationship between Cmax and weight based on the final model and 2 sensitivity analyses were illustrated in the Figure 14 and Table 36. Based on the simulation results, at the recommended dosage, the geometric mean (±SD) maximum concentration (Cmax) was 13 ± 1.2 mM in pediatric patients with cancer. The predicted Cmax in patients weighing 5 to 10kg is comparable to the predicted Cmax in patients weighing larger than 10kg (9.5% lower to 3% higher); the predicted Cmax in patients weighing less than 5kg is between 16% and 36% lower than the predicted Cmax in patients weighing larger than 10kg.

In addition, since sodium thiosulfate majorly distributes in the extracellular fluid, it is reasonable to predict its exposure in pediatric patients based on body size. The BSA-based dosing in patients lower than 5kg is half the dose of patients larger than 10 kg.

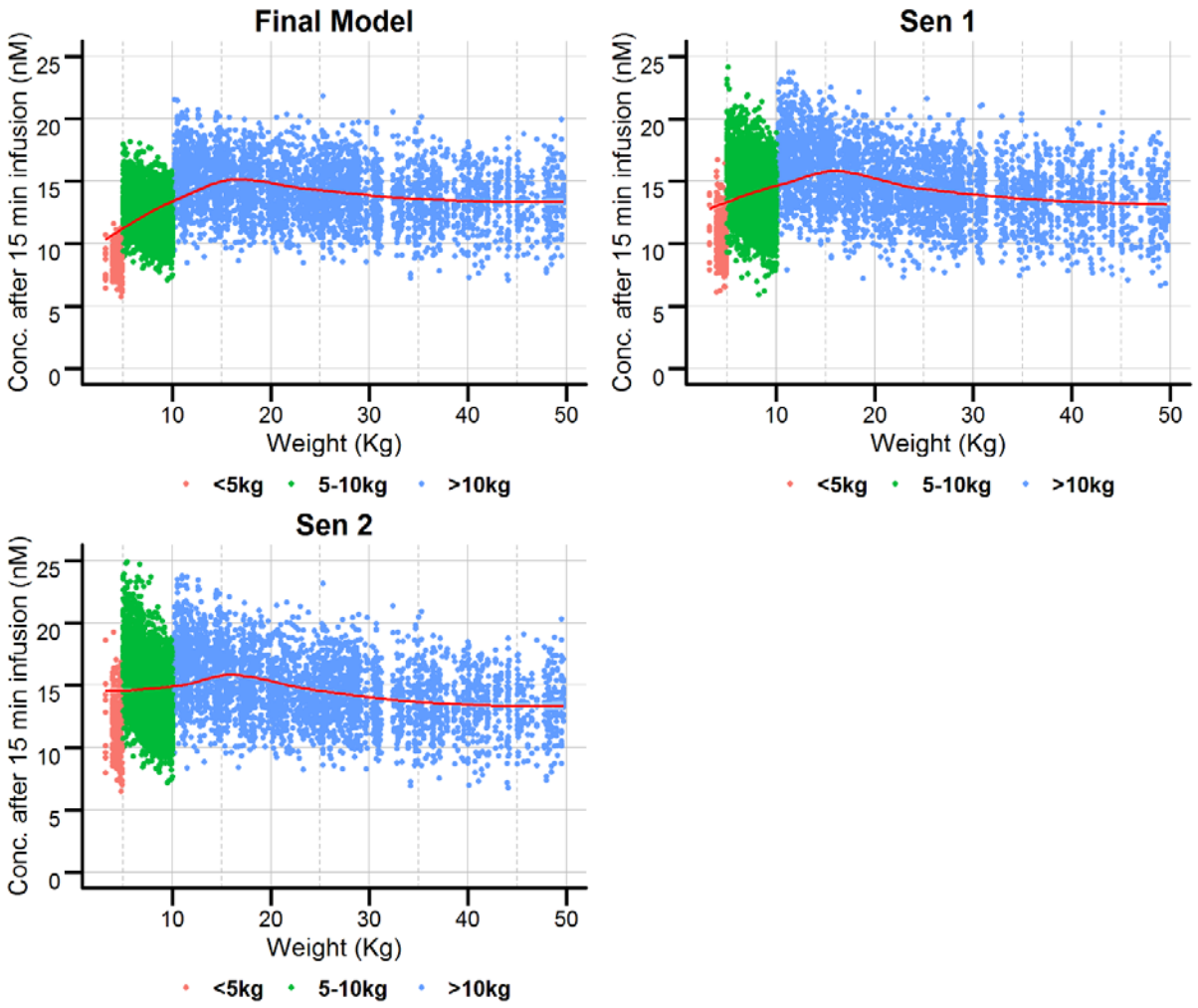
In summary, both the poppk model prediction and drug distribution characteristics support the proposed dosing regimen in the 3 weight categories.

Table 49: Cmax Prediction by Weight Categories in Pediatric Patients for the Proposed Dosing Regimen Based on the Final Model and 2 Sensitivity Analyses.

Weight Category	Exposure	Geo.Mean	2.5th Percentile	97.5th Percentile	Model
<5kg	Cmax	8.8	6.8	10.8	Final Model
5-10kg	Cmax	12.4	9.2	15.8	Final Model
>10kg	Cmax	13.7	9.2	18.6	Final Model
<5kg	Cmax	10.6	7.5	14.5	Sen 1
5-10kg	Cmax	13.8	9.5	19.2	Sen 1
>10kg	Cmax	13.9	9	19.8	Sen 1
<5kg	Cmax	11.8	8	16.3	Sen 2
5-10kg	Cmax	14.4	9.8	20.8	Sen 2
>10kg	Cmax	14	9	19.9	Sen 2

Source: Reviewer's analysis based on data "NM.STS.v2.csv"

Figure 20: Cmax Prediction versus Body Weight in Pediatric Patients for the Proposed Dosing Regimen based on the Final Model and 2 Sensitivity Analyses.



Source: Reviewer's analysis based on data "NM.STS.v2.csv"

19.4.2. Dose-Response Analyses

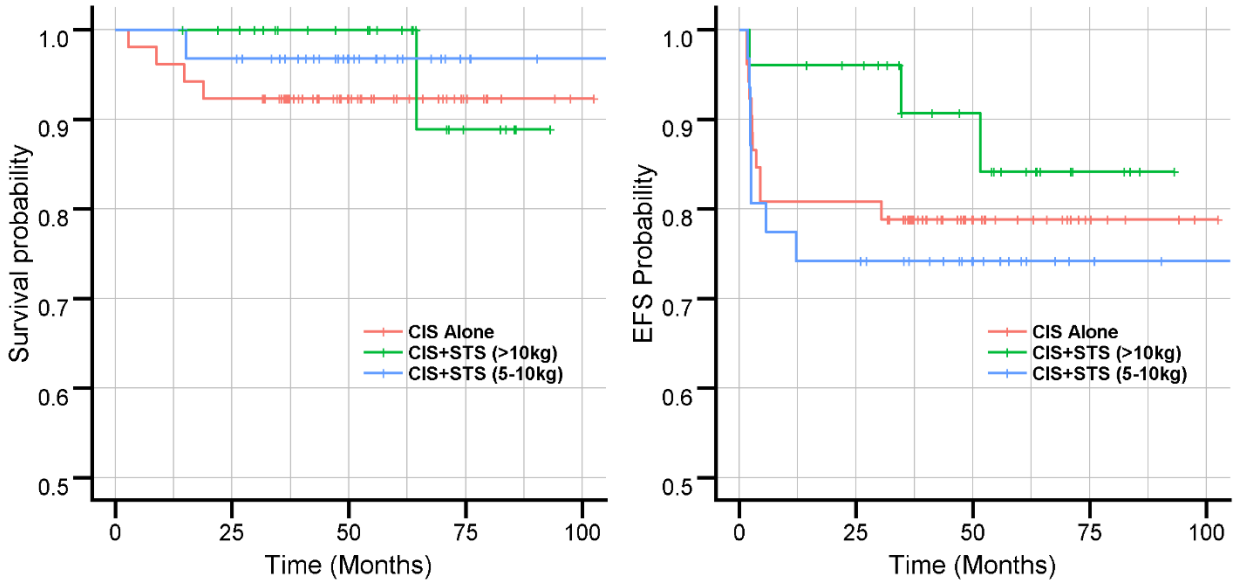
In Trial SIOPEL6, there were 31 pediatric patients with weight between 5 to 10 kg and 25 patients with weight higher than 10kg. Efficacy and safety results between these 2 weight groups were compared. For efficacy, the proportion of children with hearing loss was similar in the 5-10kg group compared to >10kg group, as shown in Table 37. Event free survival and overall survival, presented in Figure 15, were also similar between these 2 weight groups and the control.

Table 50: Comparison of Hearing Loss by Weight Category in Trial SIOPEL6.

Results	CIS Alone	CIS+SIS (5-10kg)	CIS+SOS (>10kg)
Hearing Loss, n			
N (Total)	52	31	25
Yes, n (%)	35 (67.3%)	10 (32.3%)	10 (40%)
No, n (%)	17 (32.7%)	21 (67.7%)	15 (60%)

Source: Reviewer's analysis based on data "adeff.csv"

Figure 21: Comparison of Overall Survival and Even-free Survival between Weight Categories in Trial SIOPEL6.



Source: Reviewer's analysis based on data "adeff.csv"

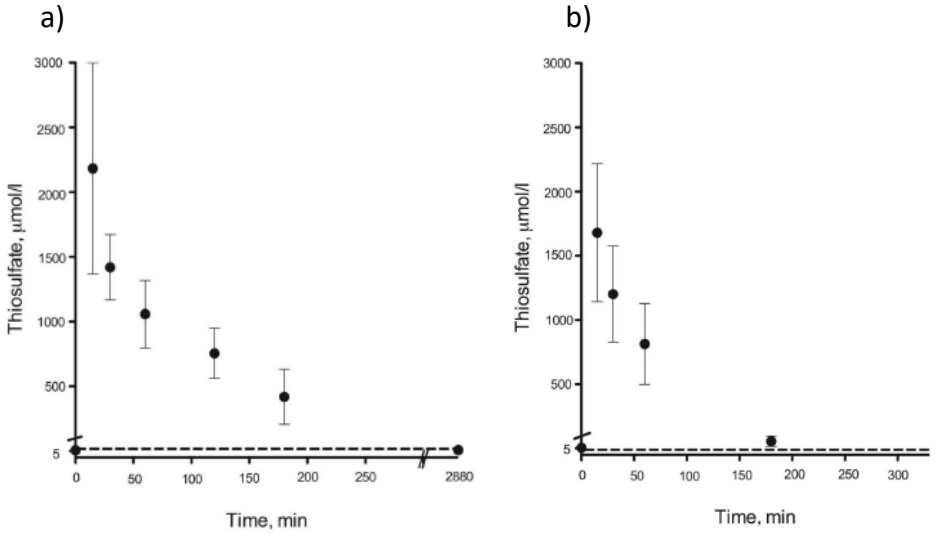
For safety, the overall incidence of AEs of all grades, SAEs, and deaths were similar between 5-10 kg and >10 kg weight groups. The efficacy and safety results from trial SIOPEL6 support the proposed dose in patients with weight between 5-10 kg and >10 kg. Only 1 patient with weight lower than 5kg received treatment in study SIOPEL 6, she did not experience hearing loss and was alive at the end of treatment. The limited number of subjects in category weight <5kg does not makes the comparison of efficacy and safety profile with other weight categories interpretable.

Exposure-response relationships for efficacy and safety were not reviewed in this submission since no PK analysis was performed for the confirmatory phase 3 trials SIOPEL6 or ACCL0431. Previous literature suggested STS dose response relation is fairly steep where dose levels of 5-8 g/m^2 STS anhydrous appeared not effective.

19.4.3. Clinical PK in hemodialysis patients

A literature study (Farese et al, 2011) provided clinical PK results of thiosulfate in 9 healthy volunteers with (GFR > 70 ml/min/1.72 m^2 according to the Modification of Diet in Renal Disease (MDRD))formula) and in 10 hemodialysis patients (GFR 0 to 6 ml/min/1.72 m^2, MDRD). The dose in the study was 8 g sodium thiosulfate IV infusion over 8 minutes.
Nonrenal clearance was similar in volunteers (2.25 ± 0.32 ml/min/kg) comparing to hemodialysis patients off-hemodialysis (2.04 ± 0.72 ml/min/kg). Hemodialysis patients in this study has very limited or no renal clearance. In healthy volunteers, renal clearance (1.86 ± 0.45 ml/min/kg) is comparable with the nonrenal clearance. Thiosulfate Cmax increased approximately 25% and AUC increased approximately 2-fold in hemodialysis patients off-hemodialysis (Figure 16 and Table 38). Thiosulfate Cmax in pediatric patients with renal impairments, including hemodialysis patients, is expected to lower than the Cmax of thiosulfate (IV injection equivalence of STS anhydrous 6.4 g/m2 in children) indicated for acute cyanide poisoning.

Figure 22. Thiosulfate plasma concentration (mean ± SD) versus time in (a) dialysis patients off-hemodialysis and (b) healthy volunteers



Source: Figure 1a of Summary of Clinical Pharmacology Studies (Section 2.7.2) and Figure 2 of Farese et al, 2011

Table 51. PK parameter in hemodialysis patients and healthy volunteers

a) Hemodialysis patients off-hemodialysis

Patient (ID)	Off-Hemodialysis $AUC_{0\rightarrow\infty}$ (μmol·min/L)	Off-Hemodialysis Total Body Clearance (ml/min per kg body wt)
(b) (6)	261,753	1.34
	336,691	1.11
	197,000	2.39
	156,360	2.56
	253,618	2.28
	212,027	3.17
	154,521	2.47
	163,867	2.33
	338,150	0.92
	236,159	1.85
	231,015 ± 67,969	2.04 ± 0.72

b) Healthy Volunteers

HV (ID)	Age (yr)	Gender (f/m)	Body Weight (kg)	$AUC_{0\rightarrow\infty}$ (μmol·min/L)	24-Hour Urinary TS Excretion after iv STS (μmol/24 h)	Total Body Clearance (ml/min per kg body wt)	Renal Clearance (ml/min per kg body wt)	Nonrenal Clearance (ml/min per kg body wt)
(b) (6)	64	m	74	10,5573	12,620	4.13	2.08	2.05
	39	m	66	85,901	13,760	5.60	2.41	3.2
	57	f	65	133,773	15,670	3.71	1.82	1.9
	48	f	80	81,953	14,840	4.92	2.28	2.64
	63	f	78	98,145	14,910	4.21	1.99	2.22
	60	f	74	109,293	14,260	3.99	1.82	2.17
	45	f	56	144,313	15,310	3.99	1.99	2
	54	f	69	136,553	13,850	3.42	1.48	1.94
	59	f	53	202,486	9600	3.00	0.91	2.06
	57 (39 to 64)	7/2	68 ± 9.4	121,999 ± 37473	13,869 ± 1847	4.11 ± 0.77	1.86 ± 0.45	2.25 ± 0.42

Source: Table 2 and 3 of Farese et al, 2011

19.4.4. **Serum Sodium Level**

(b) (4)

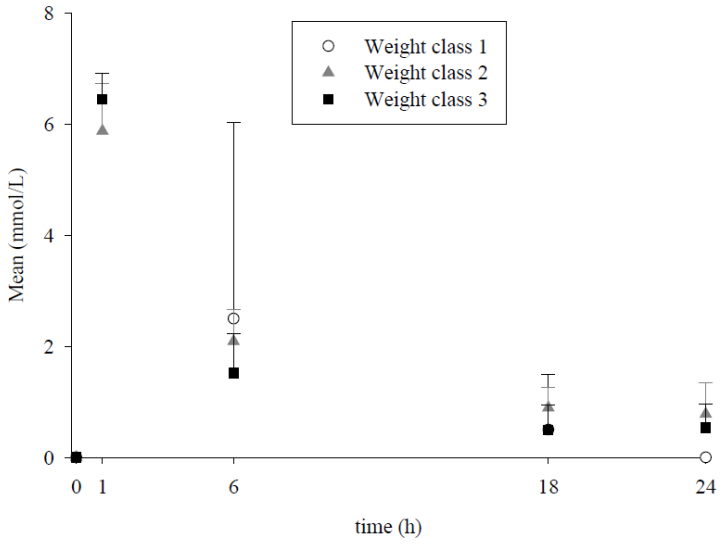
In SIOPEL 6, dose of sodium thiosulfate at the recommended dosage resulted in an average transient increase in serum sodium levels approximately 5 to 7.5 mmol/L (Table 39). Maximum increase was generally observed at 1 h after infusion and levels had returned to baseline by 18 h or 24 h after administration (Figure 17). Analysis of maximum increase in sodium (ΔCmax) versus weight did not reveal trends (Figure 18).

Table 52. Study SIOPEL 6 maximum increase in serum sodium levels (ΔCmax) from baseline after STS infusion

	ΔCmax (sodium) Cycle Mean ± SEM (n) (mM)		
Body weight	**BW ≥ 10.0 kg**	**10 kg > BW > 5 kg**	**BW < 5 kg**
STS dose (nominal)	**20 g/m²**	**15 g/m²**	**10 g/m²**
Cycle 1	6.50 ± 1.17 (16)	6.07 ± 0.67 (30)	5.0 (n=1)
Cycle 2	7.53 ± 0.73 (17)	6.29 ± 0.58 (31)	-
Cycle 3	6.61 ± 0.71 (18)	6.18 ± 0.49 (28)	2.0 (n=1)
Cycle 4	6.07 ± 0.64 (15)	5.52 ± 0.57 (27)	-
Cycle 5	6.64 ± 1.15 (14)	6.62 ± 0.70 (21)	-
Cycle 6	5.69 ± 0.97 (16)	5.07 ± 0.75 (15)	-

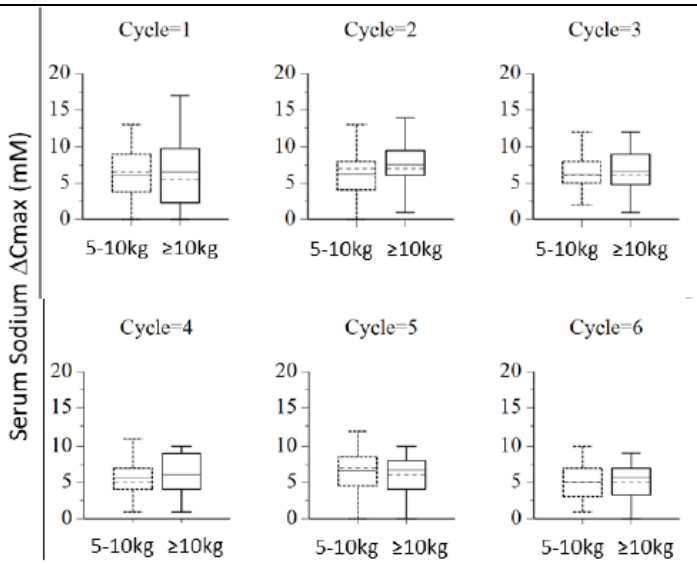
Source: Table 7 of Summary of Clinical Pharmacology Studies (Section 2.7.2)

Figure 23. Mean +SD serum sodium concentrations (mM) above baseline over cycles after STS infusion to children for weight classes 1 (BW<5 kg), 2 (BW 5 to 10 kg) and 3 (BW > 10 kg)



Source: Figure 9.4.4. of Sodium Pharmacokinetic Report Study: 2018-0146

Figure 24. Maximum increase in serum sodium levels (ΔCmax) above baseline throughout cycles after STS infusion to children for weight 2 (BW 5 to 10 kg) and 3 (BW > 10 kg)



The box represents the interquartile range. Within the box the mean is depicted by a solid line and the median by a striped line. The whiskers represent the minimum and maximum values within 1.5x the interquartile range of the box limits. Number of observations are given in Table 39

Source: Table 9 of Summary of Clinical Pharmacology Studies (Section 2.7.2)

19.5. Additional Safety Analyses Conducted by FDA

The FDA's Assessment:
n/a

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	G. Sachia Khasar, PhD	CDER/DHOT	Sections: 5, 4.2	**Select one:** x Authored ___ Approved
	Signature: Whitney Helms proxy signing for G. Sachia Khasar, PhD Whitney S. Helms -S Digitally signed by Whitney S. Helms -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000585776, cn=Whitney S. Helms -S Date: 2020.08.10 10:40:36 -04'00'			
Nonclinical Supervisor	Whitney S. Helms, PhD	CDER/DHOT	Sections: 5, 4.2	**Select one:** x Authored x Approved
	Signature: Whitney S. Helms -S Digitally signed by Whitney S. Helms -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000585776, cn=Whitney S. Helms -S Date: 2020.08.10 10:42:33 -04'00'			
Nonclinical Team Division Director (NME only)	John K. Leighton, PhD	CDER/DHOT	Sections: 5, 4.2	**Select one:** ___ Authored x Approved
	Signature: John K. Leighton -S Digitally signed by John K. Leighton -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300085260, cn=John K. Leighton -S Date: 2020.08.10 09:58:34 -04'00'			
Clinical Pharmacology Reviewer	Wentao Fu, PhD Youwei Bi, Ph.D.	CDER/OTS/OCP/DCP I CDER/OTS/OCP/DPM	Sections: 6, 19.4	**Select one:** x Authored ___ Approved
	Signature: Wentao Fu -S Digitally signed by Wentao Fu -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Wentao Fu -S, 0.9.2342.19200300.100.1.1=2001855706 Date: 2020.08.10 11:53:16 -04'00' Youwei Bi -S Digitally signed by Youwei Bi -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Youwei Bi -S, 0.9.2342.19200300.100.1.1=2001767281 Date: 2020.08.10 11:08:11 -04'00'			
Clinical Pharmacology Team Leader	Jeanne Fourie Zirkelbach, Ph.D. Jiang Liu, Ph.D.	CDER/OTS/OCP/DCP II CDER/OTS/OCP/DPM	Sections: 6, 19.4	**Select one:** x Authored x Approved
	Signature: Jeanne Fourie Zirkelbach -S Digitally signed by Jeanne Fourie Zirkelbach -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300434575, cn=Jeanne Fourie Zirkelbach -S Date: 2020.08.10 10:11:45 -04'00' Jiang Liu -S Digitally signed by Jiang Liu -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jiang Liu -S, 0.9.2342.19200300.100.1.1=2000348510 Date: 2020.08.10 11:40:21 -04'00'			

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED / APPROVED
Clinical Pharmacology Division Director	Nam Atiqur Rahman, Ph.D	CDER/OTS/OCP/DCP II	Sections: 6, 19.4	**Select one:** ___ Authored X Approved
	Signature: Nam A. Rahman -S Digitally signed by Nam A. Rahman -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Nam A. Rahman -S, 0.9.2342.19200300.100.1.1=1300072597 Date: 2020.08.10 10:07:19 -04'00'			
Clinical Reviewer	Amy Barone, MD	CDER/OOD/DO2	Sections: 1-4, 7-13, 19	**Select one:** x Authored ___ Approved
	Signature: Amy Barone -S Digitally signed by Amy Barone -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Amy Barone -S, 0.9.2342.19200300.100.1.1=2001366575 Date: 2020.08.10 11:20:58 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Team Leader	Amy Barone, MD	CDER/OOD/DO2	Sections: 1-4, 7-13, 19	Select one: x Authored x Approved
	Signature: Amy Barone -S Digitally signed by Amy Barone -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Amy Barone -S, 0.9.2342.19200300.100.1.1=2001366575 Date: 2020.08.10 11:23:58 -04'00'			
Statistical Reviewer	Abhishek Bhattacharjee, PhD	CDER/OTS/DBV	Sections: 8.1, 8.3	Select one: x Authored ___ Approved
	Signature: Abhishek Bhattacharjee -S Digitally signed by Abhishek Bhattacharjee -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002979095, cn=Abhishek Bhattacharjee -S Date: 2020.08.10 10:02:55 -04'00'			
Statistical Team Leader	Joyce Cheng, PhD	CDER/OTS/DBV	Sections: 1, 8.1, 8.3	Select one: x Authored x Approved
	Signature: Joyce Cheng -S Digitally signed by Joyce Cheng -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Joyce Cheng -S, 0.9.2342.19200300.100.1.1=2001702039 Date: 2020.08.10 10:22:40 -04'00'			
Division Director (OB)	Yuan-Li Shen, PhD (Acting)	CDER/OTS/DBV	Sections: 1, 8.1, 8.3	Select one: x Authored x Approved
	Signature: Yuan-li Shen -S Digitally signed by Yuan-li Shen -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Yuan-li Shen -S, 0.9.2342.19200300.100.1.1=1300142755 Date: 2020.08.10 15:07:42 -04'00'			
Associate Director for Labeling (ADL)	Stacy Shord, PharmD		Sections: 11	Select one: x Authored ___ Approved
	Signature: Stacy Shord -S Digitally signed by Stacy Shord -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Stacy Shord -S, 0.9.2342.19200300.100.1.1=2000356537 Date: 2020.08.10 10:27:28 -04'00'			
Cross-Disciplinary Team Leader (CDTL)	Amy Barone, MD	CDER/OOD/DO2	Sections: All sections	Select one: ___ Authored x Approved
	Signature: Refer to Multidisciplinary Review signed in DARRTS Amy Barone -S Digitally signed by Amy Barone -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Amy Barone -S, 0.9.2342.19200300.100.1.1=2001366575 Date: 2020.08.10 11:24:49 -04'00'			

Division Director (OOD) (signatory authority)	Harpreet Singh, MD	CDER/OOD/DO2	Sections:	**Select one:** ___ Authored ___ Approved
	Signature: Refer to Multidisciplinary Review signed in DARRTS			

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ANUJA PATEL
08/10/2020 04:14:14 PM

AMY K BARONE
08/10/2020 04:17:07 PM

B HARPREET SINGH
08/10/2020 04:19:37 PM