CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212937Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 072877

MEETING MINUTES

Fennec Pharmaceuticals, Inc.
Attention: Anne McKay
PO Box 13628
68 TW Alexander Drive
Research Triangle Park, NC 27709

Dear Ms. McKay:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for PEDMARK™ (sodium thiosulfate).

We also refer to the meeting between representatives of your firm and the FDA on December 13, 2018. The purpose of the meeting was to discuss the proposed plan for submitting a New Drug Application.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, contact Clara Lee, Regulatory Project Manager, at (240) 402-4809 or Clara.Lee@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Clara Lee, PharmD
Regulatory Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

{See appended electronic signature page}

Sanjeeve Balasubramaniam, MD, MPH
Clinical Team Leader
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes
Sponsor presentation slides

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-NDA
Meeting Date and Time:	December 13, 2018/3:00 PM – 4:00 PM
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1315 Silver Spring, Maryland 20903
Application Number:	IND 072877
Product Name:	PEDMARK™ (sodium thiosulfate)
Indication:	Prevention for cisplatin-induced ototoxicity
Sponsor/Applicant Name:	Fennec Pharmaceuticals, Inc.
Meeting Chair:	Sanjeeve Balasubramaniam, MD
Meeting Recorder:	Clara Lee, PharmD

FDA ATTENDEES
Julia Beaver, MD, Director, DOP1
Sanjeeve Balasubramaniam, MD, MPH, Clinical Team Leader, DOP1
Gregory Reaman, MD, Associate Director for Oncology Sciences, OCE
Ihid Carneiro Leao, MD, PhD, Commissioner's Fellow, OC
Tara Berman, MD, Clinical Reviewer, DOP1
Elaine Chang, MD, Clinical Reviewer, DOP1
Candace Mainor, MD, Clinical Reviewer, DOP1
Suzanne Demko, PA-C, Clinical Team Leader, DOP2
Amy Barone, MD, Clinical Reviewer, DOP2
Tiffany Ricks, PhD, Acting Supervisory Pharmacologist/Toxicologist Reviewer, DHOT
Shenghui Tang, PhD, Biometrics Team Leader, DBV
Hui Zhang, PhD, Biostatistics Reviewer, DBV
Clara Lee, PharmD, Regulatory Project Manager, DOP1

SPONSOR ATTENDEES
Penelope "Peppy" Brock, MD, PhD, MA, International Chair, SIOPEL 6
[redacted] (b) (4)
David Freyer, DO, MS, Chair, COG ACCL0431
Khalid Islam, PhD, Chairman, Fennec Board of Directors

(b) (4)
Rudolf Maibach, PhD, SIOPEL 6 Statistician
(b) (4)
Rosty Raykov, CEO, Fennec
Robert Andrade, CFO, Fennec

1.0 BACKGROUND

Post-meeting note: Sponsor noted some discrepancies in the background section in the preliminary comments sent on November 26, 2018. This is a revised version with the sponsor's suggested edits that were provided to the RPM via email dated December 16, 2018.

The objective of this meeting is to discuss the nonclinical and clinical data required for submission and the regulatory submission pathway of an NDA for PEDMARK ™ (sodium thiosulfate [STS], anhydrous) injection for the prevention of ototoxicity induced by cisplatin (CIS) chemotherapy in patients 1 month to <18 years of age with localized, non-metastatic (b) (4)

STS (Na_2S2O_3) is an inorganic salt with reducing agent properties. PEDMARK ™ is an aqueous solution formulated from anhydrous STS (b) (4) for intravenous (IV) administration supplied in glass vials containing 100 mL (b) (4) STS is a food additive recognized as safe, and other STS products were approved since 1992 as an infusion after sodium nitrate infusion for the management of cyanide poisoning. It also has been used in oncology to prevent CIS-induced nephrotoxicity and as an antidote for extravasation of various chemotherapy agents. Side effects in adults include transient hypernatremia, hypertension, and nausea. Other toxicities include hypotension, headache, and disorientation. Hypersensitivity reactions have been reported. PEDMARK ™ is not FDA approved.

Sponsor proposes that STS can inactivate platinum complexes by covalently binding electrophilic platinum with thiol to form a complex that is not cytotoxic and is readily excretable by the kidneys (Howell and Taetle, 1980). Studies in vitro and in animals have shown that STS can protect against ototoxicity associated with platinum-based chemotherapy. Other mechanisms of action: 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).

Sodium thiosulfate administration prior to 4 hours after chemotherapy has been shown to reduce chemotherapy-related antitumor activity. For prevention of ototoxicity in children, STS is administered intravenously at six hours after cisplatin infusion. Treatment with platinum

compounds, particularly cisplatin as compared to carboplatin or oxaliplatin, is known to produce high frequency sensorineural hearing loss due mainly to damage to cochlear hair cells in the inner ear in up to 80% of pediatric patients. This irreversible hearing loss may result in impairment or failure of speech development particularly in younger patients. STS is intended for use in the pediatric population in whom the inner ear is not fully developed and therefore susceptible to damage from cisplatin. Available therapeutic options are currently limited to reducing the CIS dose (or switching to a different platinum-based chemotherapy) which risks decreased tumor efficacy or the management of resulting hearing loss. There is no approved drug to prevent or treat CIS-induced ototoxicity.

The sponsor filed a breakthrough therapy designation (BTD) request based on published literature in 2013 which purported to demonstrate a reduction in hearing loss in children who received STS while on cisplatin therapy. The sponsor withdrew the request when advised that the submitted literature did not support the designation. In a second BTD request, data from ACCL0431, a COG clinical trial, was presented which showed a statistically significant ($p=0.00022$) decrease in the proportion of evaluable patients with hearing loss for the STS group (28.6%) as compared to the control group (56.4%). This BTD request was denied on August 1, 2014 because of a nominally statistically significant ($p=0.011$) decreased survival in patients with extensive disease reported for the STS + cisplatin arm). However, this was a non-specified, post-hoc analysis. On October 31, 2018, the sponsor requested a Type C meeting to discuss the clinical development program for PEDMARK ™ and written responses were provided on January 16th, 2018. Data from two main Phase 3 clinical trials were proposed to support an NDA:

	SIOPEL-6	ACCL0431
Phase	Phase III	Phase III
Trial Design	Multi-center, Open-label, Randomized (1:1)	Multi-center, Open-label, Randomized (1:1)
Primary Endpoint	Proportion of patients in each group with any hearing loss, defined by Brock grade ≥1, determined after end of trial treatment or at an age of at least 3.5 years, whichever was later.	Rate of ASHA hearing loss determined 4 weeks and 12 months after the last course of CIS.
Stratification Factors:	• Country • Age > 15 mos, < 15 mos • PRETEXT stage	• Age • Duration of CIS infusion • Prior cranial radiation
Tumor Type/Eligibility	Hepatoblastoma (SR-HB) • PRETEXT I, II, or III • No vascular invasion, no extra-hepatic or metastatic disease	Newly diagnosed HB, germ cell tumor, osteosarcoma, neuroblastoma, medulloblastoma, or other malignancy treated with CIS

	• Serum alpha-fetoprotein >100 ng/mL	
Treatment Groups	Cisplatin vs Cisplatin +STS	Cisplatin vs Cisplatin +STS
Cummulative Cisplatin dose		>200 mg/m^2
Treatment	Cisplatin 80 mg/m^2 over 6 hrs STS 20 g/m^2 6 hrs after Cisplatin	Cisplatin: variable STS: 16 g/m^2 6 hrs after Cisplatin (or 533mg/kg for young age, low body weight)
No of Patients Enrolled	109 (CIS=52;CIS+STS=57)	125 (CIS=64; CIS+STS=61)
No. Evaluable	101**(CIS=46, CIS+STS=55)	104 (CIS=55; CIS+STS=49)
Age	3-70 months	1-18 years
Statistical Plan	25% absolute reduction in Brock grade ≥1 hearing loss at age ≥ 3.5 years	50% relative reduction in the proportion of subjects with hearing loss in the STS treated group versus the control group
Results		
Primary:		
Percent with hearing loss	CIS alone: 35/52 (67.3%) CIS+ STS: 20/57 (35.1%) P<0.001	CIS alone: 56.4% CIS+ STS: 28.6% P=0.0036
Relative Risk of Hearing Loss	RR=0.52 (95% CI:0.33-0.81) P=0.002	OR=0.31 (95% CI:0.13-0.73) P=0.0036

For SIOPEL-6, the 3 years Event-Free Survival/Overall Survival was the same for both groups. For COG ACCL0431, there was some concern that in disseminated disease, use of STS might be associated with reduced OS (based on a post-hoc analysis with a 3.5 year follow up), although the underlying diversity of patient tumor type, tumor biology, and staging were not taken into account during randomization. In addition, the study was only powered adequately for the primary hearing loss endpoint. For the current type C meeting request, an additional post-hoc reanalysis at 5.3 years of follow up using the data provided by COG was conducted.

Safety information: Safety information is available for a total of 234 patients. A total of 33 deaths occurred with 27 deaths reported on ACCL0421 and 6 on SIOPEL-6 all reported as unrelated. All deaths were related to tumor progression except for 1 on ACCL0421 due to sepsis. On SIOPEL-6, 11 patients discontinued STS, one due to metabolic acidosis coupled with lethargy and ten because of the addition of doxorubicin to cisplatin. The patient who developed metabolic acidosis had Brock Grade 4 hearing loss. Regarding serious adverse events (SAEs), 35 were reported for the CIS+STS arm while 23 were reported for the CIS alone arm. One patient on the STS+CIS arm had a Grade 2 hypersensitivity reaction with rash, flushing, urticaria, and drug fever >38^0 C. On SIOPEL-6, Grade 3/4 adverse events were increased on the CIS+STS arm (63 AEs) as compared to the CIS alone arm (32 AEs). On the combination arm more patients had a decrease in hemoglobin (12 vs 7); neutropenia (13 vs 7); hypermagnesemia

(11 vs. 2); hypophosphatemia (7 vs 0); and hypokalemia (9 vs 0). Little difference was observed between arms in the incidence of Grade 3/ 4 febrile neutropenia, infection, or nausea. For the two Phase 3 studies (ACCL0431 and SIOPEL 6) safety findings included ≥Grade 1 hypernatremia, ≥Grade 3 nonhematologic AEs (any attribution), and all grades of allergic reaction. Adverse events of particular interest included ≥Grade 3 nephrotoxicity including creatinine, GFR, hypomagnesemia, hypokalemia, hypophosphatemia, urinary electrolyte wasting syndrome (Fanconi syndrome), as well the hematologic toxicities including ≥Grade 3 cytopenia (leukopenia, neutropenia, anemia or thrombocytopenia) and were higher on the treatment arm.

In the Type C Written Response (dated 16 Jan 2018), the Agency confirmed that the pivotal SIOPEL 6 data, supported by results of the COG ACCL0431 study and further published clinical results of STS prevention of ototoxicity, provided sufficient efficacy and safety data to support NDA filing of PEDMARK™ injection for the prevention of ototoxicity induced by CIS chemotherapy in pediatric patients with standard-risk HB (SR-HB). Fast Track designation was granted on March 19, 2018 and Breakthrough Therapy Designation granted on March 20, 2018.

FDA sent Preliminary Comments to Fennec Pharmaceuticals, Inc. on November 26, 2018.

2.0 QUESTIONS AND RESPONSES

Question 1: Fennec plans to satisfy the nonclinical data requirements for PEDMARK™ via references to STS use in published literature. A high-level summary of the results, the planned literature search parameters, and how the data will be presented in the NDA are provided within the company position.

Does the Agency agree that the nonclinical literature search and data presentation plan, coupled with clinical safety data, in vitro studies to investigate the potential for inhibition or induction of Cytochrome P450 (CYP) isozymes and evaluation of clinical pharmacokinetics (PK), are sufficient to support NDA filing and review?

FDA Response to Question 1: The nonclinical studies described in your meeting package appear acceptable to support your NDA for the proposed indication, pending review of the studies submitted.

- **Summarize and submit copies of all the study reports/publications of the nonclinical studies used to support the safety of any novel excipient.**
- **Any impurities in STS that are present at levels that exceed ICH Q3 limits and are above those in the listed drug (in a side-by-side comparative assessment) will need to be qualified in GLP toxicology studies or their levels adequately justified at the time of an NDA submission.**
- **In the NDA, identify each nonclinical element that is supported by reliance on published literature or FDA's previous finding of safety or effectiveness for a listed drug (i.e., the listed drug's approved labeling). Submit copies of any cited publications.**

Sponsor Response to Question 1 dated November 30, 2018: Please note that no novel excipients are used in the proposed PEDMARK™ formulation. The stability studies for the

registration batches of drug substance and drug product are underway; any impurities will be qualified in accord with ICH Q3 limits as required. These data will be provided in the Chemistry, Manufacturing and Controls Module 3 when filed.

The initial submission for the nonclinical modules 2.4, 2.6, and 4 will also include a draft label identifying what published literature supports each nonclinical element. These articles will be submitted in Module 4.3.

If the Agency is in agreement with this response, no further discussion is suggested at the meeting.

Meeting Discussion: The sponsor's proposal is acceptable.

Question 2a: Dose selection in SIOPEL 6 was based on published clinical, PK, and nonclinical information on the dose-response relationship for STS and considered dose level, duration of infusion, and timing of administration. Does the Agency agree that review of available literature will be sufficient to evaluate the dose–response relationship and dose-selection to support the recommended dosing for PEDMARK ™ for the NDA?

FDA Response to Question 2a: The proposed approach of literature review appears to be generally acceptable; however, the final determination will be an NDA review issue.

Sponsor Response to Question 2a dated November 30, 2018: For Questions 2, 3, 4, 5, 8, 10, 11, 12, 13, 14, 16, 17, and 18, Fennec acknowledges the Division's written responses with thanks. No further discussion at the meeting is requested.

Meeting Discussion: No discussion took place

Question 2b: The potential influence of renal maturation on serum sodium load with STS administration was addressed in SIOPEL 6 by lowering the STS dose by 25% for children below 10.0 kg body weight and by 50% for children below 5.0 kg body weight. The majority of children treated with STS were in the 5 to 10 kg weight group. Serum sodium was monitored after the infusion of STS, but PK samples for thiosulfate analysis were not taken in SIOPEL 6 to evaluate STS exposure. Does the Agency agree that the weight-based dose adjustment and STS exposure can be supported sufficiently for review of an NDA by (i) analysis of serum sodium concentrations; (ii) review of STS PK literature and its use (including individual STS data) to develop a population PK (popPK) model (Question 3 separately addresses the popPK model assumptions); and (iii) providing descriptive efficacy and safety data per weight category.

FDA Response to Question 2b: It is acceptable to use the increase in serum sodium levels after STS administration as a safety measurement to support the recommended dose adjustment. However, the use of serum sodium concentration as a surrogate for STS exposure may not be reliable, as it can be confounded by the individual endogenous sodium level. Your proposed approach of descriptive efficacy and safety data per weight category is acceptable. The adequacy of your data and interpretation will be an NDA review issue.

Sponsor Response to Question 2b dated November 30, 2018: For Questions 2, 3, 4, 5, 8, 10, 11, 12, 13, 14, 16, 17, and 18, Fennec acknowledges the Division's written responses with thanks. No further discussion at the meeting is requested.

Meeting Discussion: No discussion took place

See FDA Response to Question 3 regarding the approach of reviewing of STS PK literature and its use (including individual STS data) to develop a population PK model.

Question 3: In support of the proposed dose levels of STS in children, Fennec applied popPK modeling and simulation to extrapolate across different weight and age groups. Does the Agency agree that the incorporated growth and maturation relationships in the popPK model and the predicted STS exposures as presented in Section 7.2.3 of this Information Package are relevant to the indicated population and will be sufficient to support NDA filing and review?

FDA Response to Question 3: The approach of using STS PK literature to develop a population PK model and incorporation of growth and maturation models is acceptable to predict STS exposure, given there were no STS PK samples collected from Studies SIOPEL 6 or COG ACCL0431. The adequacy of your population PK model and the simulated PK data to support the approval of STS will be an NDA review issue.

Sponsor Response to Question 3 dated November 30, 2018: For Questions 2, 3, 4, 5, 8, 10, 11, 12, 13, 14, 16, 17, and 18, Fennec acknowledges the Division's written responses with thanks. No further discussion at the meeting is requested.

Meeting Discussion: No discussion took place

Question 4: The FDA and Fennec previously agreed to investigate the potential for STS to inhibit or induce CYP activity in vitro as part of the assessment for drug-drug interactions (DDI). Does the Agency agree that the results summarized in the company position will provide sufficient information in the NDA submission to allow FDA review of the potential for PK DDI?

FDA Response to Question 4: Your proposal appears acceptable. The final decision will be made at the NDA review.

Sponsor Response to Question 4 dated November 30, 2018: For Questions 2, 3, 4, 5, 8, 10, 11, 12, 13, 14, 16, 17, and 18, Fennec acknowledges the Division's written responses with thanks. No further discussion at the meeting is requested.

Meeting Discussion: No discussion took place.

Question 5: In the Type C Written Response (dated 16 Jan 2018), the Agency confirmed that the pivotal SIOPEL 6 data, supported by results of the COG ACCL0431 study and further published clinical results of STS prevention of ototoxicity, provided sufficient efficacy and safety data to support NDA filing of PEDMARK™ injection for the prevention of ototoxicity induced by CIS chemotherapy in pediatric patients with standard-risk HB (SR-HB). Based on

the new and ongoing SIOPEL, COG, German Pediatric Oncology and Hematology (GPOH) Group, and Japanese Pediatric Liver Tumors Group (JPLT) cooperative study, "Pediatric Hepatic International Tumor Trial (PHITT)", SR-HB and high-risk (HR)-HB have been reclassified into 4 separate groups in the protocol: Groups A (very low risk HB), B (low risk HB), C (intermediate risk HB), and D (high-risk HB). Groups A, B, and C include all children with localized disease and Group D includes all children with metastatic disease. Because SR-HB is obsolete in terms of classifying and reviewing patients for treatment, the indication is proposed as follows, "PEDMARK™ (sodium thiosulfate, anhydrous) injection for the prevention of ototoxicity induced by cisplatin chemotherapy in patients 1 month to < 18 years of age with localized, non-metastatic HB". Does the Agency agree with this newly proposed indication wording?

FDA Response to Question 5: Your proposal to change the wording of the indication appears reasonable. The final determination of the indication will depend on the benefit risk analysis based on the totality of the evidence in your NDA submission and will be a review issue.

Sponsor Response to Question 3 dated November 30, 2018: For Questions 2, 3, 4, 5, 8, 10, 11, 12, 13, 14, 16, 17, and 18, Fennec acknowledges the Division's written responses with thanks. No further discussion at the meeting is requested.

Meeting Discussion: No discussion took place.

Question 6: In the Type C Written Response (dated 16 Jan 2018), the Agency expressed concern regarding the decreased overall survival observed in the CIS+STS arm of the COG ACCL0431 study. Fennec has analyzed these survival data by localized/disseminated disease, as determined post-hoc and similar to that conducted by COG in Freyer et al, 2017, but with a median of 5.33 years of follow up. Results of this post-hoc analysis will be submitted in the NDA. Does the Agency agree that the results of the post-hoc analysis, as presented in Section 8.2.3 of this Information Package, are sufficient to address the Agency's question about overall survival in COG ACCL0431?

FDA Response to Question 6: This approach appears reasonable, but the interpretation of your data in support of a more general indication will be a review issue. You should provide any supportive evidence/data regarding the safety of your agent given our concern regarding the tumor protective potential of your agent and the small sample size of the studies.

Sponsor Response to Question 6 dated November 30, 2018: We wish to focus the meeting on discussion of responses to Question 6 and Question 7. We would appreciate the Agency's advice and guidance on data that would support this issue.

Meeting Discussion: The FDA acknowledged the sponsor's presentation. Ultimately, FDA reiterated that the indication would be a review issue and the sponsor should provide justification for a broader indication in the submission.

Question 7: Results of the post-hoc analysis conducted in the COG ACCL0431 study and mentioned in Question 6 showed that, in patients with localized disease, there were no significant differences in EFS or OS between the CIS+STS arm and the Observation arm. Results of this analysis are provided in Section 8.2.4. A similar finding was observed in patients with SR-HB in the SIOPEL 6 study (see Section 8.1.2). Does the Agency agree that the results of SIOPEL 6 and COG ACCL0431, in combination with results from the literature review, support expanding the proposed PEDMARK™ indication of localized, non-metastatic HB (b) (4) solid tumors?

FDA Response to Question 7: Since other pediatric solid tumors are treated with different cisplatin-containing regimens, and because (b) (4) solid tumors have the same prognosis, you may require clinical data to support any additional indication.

Expansion of the indication for STS to (b) (4) solid tumors in your proposed submission will be a review issue.

Sponsor Response to Question 7 dated November 30, 2018: We wish to focus the meeting on discussion of responses to Question 6 and Question 7. We would appreciate the Agency's advice and guidance on data that would support this issue.

Meeting Discussion: The sponsor will provide to the extent possible information regarding prognostic factors and histology between the treatment groups. Also see Meeting Discussion under Question 6.

Question 8: Fennec plans to support data from the SIOPEL 6 and COG ACCL0431 studies with a clinical literature review on the use of STS in cancer patients treated with platinum-based compounds. The literature search parameters and how the data will be presented in the NDA are provided within the company position. Does the Agency agree that the literature search and data presentation plan is sufficient to support NDA filing?

FDA Response to Question 8: Your literature search parameters and data presentation appear reasonable.

Sponsor Response to Question 8 dated November 30, 2018: For Questions 2, 3, 4, 5, 8, 10, 11, 12, 13, 14, 16, 17, and 18, Fennec acknowledges the Division's written responses with thanks. No further discussion at the meeting is requested.

Meeting Discussion: No discussion took place.

Question 9: Prompted by interactions with the European Medicines Agency's (EMA) Pediatric Committee (PDCO), Fennec would like to understand the Agency's position on expanding the PEDMARK™ indication from CIS-induced chemotherapy (b) (4). As indicated in Question 8, Fennec plans to conduct a review of the literature supporting this request. Does the Agency agree that the planned literature search supports expanding the indication to include use of STS for the prevention of ototoxicity (b) (4) ?

FDA Response to Question 9: We have insufficient evidence to support an expanded indication to include STS for the prevention of ototoxicity (b) (4) ; this will be a review issue upon submission of your NDA.

Sponsor Response to Question 9 dated November 30, 2018: We propose to limit the indication to cisplatin-based chemotherapy until further evidence is available.

If the Agency are in agreement with this response, no further discussion is suggested at the meeting.

Meeting Discussion: The Agency agrees with this approach.

Question 10: Given the different patient populations (ie, SR-HB in SIOPEL 6 and various cancer types in COG ACCL0431), study designs, and dosing evaluated in the SIOPEL 6 and COG ACCL0431 studies, Fennec does not intend to conduct any integrated analyses based on pooled study data. Does the Agency agree that the review of safety and efficacy can be based on the individual studies rather than pooled data?

FDA Response to Question 10: This approach appears reasonable.

Sponsor Response to Question 10 dated November 30, 2018: For Questions 2, 3, 4, 5, 8, 10, 11, 12, 13, 14, 16, 17, and 18, Fennec acknowledges the Division's written responses with thanks. No further discussion at the meeting is requested.

Meeting Discussion: No discussion took place.

Question 11: Fennec plans to satisfy the Integrated Summary of Efficacy and Integrated Summary of Safety requirements (21CFR 314.50(d)(5)(v) and 21 CFR 314.50(d)(5)(vi)(a), respectively) within the Module 2 documents, Summary of Clinical Efficacy (2.7.3) and Summary of Clinical Safety (2.7.4), respectively. These documents will not be duplicated in Module 5.3.5.3. Tables supporting analyses not conducted as part of the clinical study reports (CSRs) (eg, subgroups) will be included in Module 5.3.5.3 as required per the guidance. Does the Agency agree with this approach?

FDA Response to Question 11: This approach appears reasonable.

Sponsor Response to Question 11 dated November 30, 2018: For Questions 2, 3, 4, 5, 8, 10, 11, 12, 13, 14, 16, 17, and 18, Fennec acknowledges the Division's written responses with thanks. No further discussion at the meeting is requested.

Meeting Discussion: No discussion took place.

Question 12: In SIOPEL 6, it was pre-specified in the Statistical Analysis Plan (SAP) that the minimization method would be used for randomization; however, the database provider (CINECA) used block randomization. This difference will be mentioned in the CSR, as a

change to the conduct of the study. In the June 20, 2017 Request for Information, the Agency had requested, and Fennec had subsequently agreed, to use a permutation (re-randomization) test to account for the use of the minimization (dynamic randomization) method; however, this is no longer applicable since the block randomization method was used. Does the Agency agree that the re-randomization test for SIOPEL 6 is no longer necessary?

FDA Response to Question 12: The re-randomization test is no longer necessary. An assessment of the impact of not conducting randomization according to the protocol will be a review issue.

Sponsor Response to Question 12 dated November 30, 2018: For Questions 2, 3, 4, 5, 8, 10, 11, 12, 13, 14, 16, 17, and 18, Fennec acknowledges the Division's written responses with thanks. No further discussion at the meeting is requested.

Meeting Discussion: No discussion took place.

Question 13: Fennec plans to provide individual patient narratives in the SIOPEL 6 and COG ACCL0431 CSRs for patients in the CIS+STS arm who experienced a serious adverse event (SAE) or who discontinued STS due to an AE, and for any patient who died during the study due to a cause other than progression of disease regardless of treatment group. Full or brief (ie, tabular) narratives will be provided for each patient with these types of events, as outlined in the company position. Does the Agency agree with the planned approach for these narratives?

FDA Response to Question 13: No, full narratives should be provided for every patient with any incident from the list you provide. The Agency may request additional patient narratives via information requests during the review, and these data should be provided in a timely fashion.

Sponsor Response to Question 13 dated November 30, 2018: For Questions 2, 3, 4, 5, 8, 10, 11, 12, 13, 14, 16, 17, and 18, Fennec acknowledges the Division's written responses with thanks. No further discussion at the meeting is requested.

Meeting Discussion: No discussion took place.

Question 14: Fennec believes that the proposed labeling for PEDMARK™ injection for the prevention of ototoxicity induced by CIS chemotherapy in pediatric patients with localized, non-metastatic HB will be sufficient to ensure safe use of the product, and that a Risk Evaluation and Mitigation Strategy (REMS) will not be necessary. Although Fennec understands that this will be a review issue, does the Agency agree that a proposed REMS is not required for the NDA submission?

FDA Response to Question 14: A proposed REMS is not necessary for an NDA submission. However, the need for a REMS will be a review issue.

Sponsor Response to Question 14 dated November 30, 2018: For Questions 2, 3, 4, 5, 8, 10, 11, 12, 13, 14, 16, 17, and 18, Fennec acknowledges the Division's written responses with thanks. No further discussion at the meeting is requested.

Meeting Discussion: No discussion took place.

Question 15: Fennec will submit data from the SIOPEL 6 COG and ACCL0431 studies in SDTM and ADaM formats. We will also provide SAS programs used to create all analysis datasets. The legacy datasets transferred from COG and SIOPEL will be converted to clinical data interchange standards consortium (CDISC) format. Fennec will include supporting documentation (define.xml version 2.0, SDTM and ADaM reviewer guides and SAS programs in .txt format). Does the Agency agree with the e-Data submission plan?

FDA Response to Question 15: Yes, this approach is reasonable. Comment if you are interested in participating in the Assessment Aid pilot program. For more information on this pilot program, refer to: https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OCE/ucm612923.htm.

Sponsor Response to Question 15 dated November 30, 2018: We are investigating the Assessment Aid pilot program and will advise should we wish to participate. No further discussion requested.

Question 16: Fennec proposes to submit the PEDMARK™ application via the 505(b)(2) regulatory pathway, with reliance on published literature to support parts of the application. Adequate data are available in the public domain to support specific aspects of labeling, and reference to FDA findings of safety and/or effectiveness for any approved STS product will not be necessary. Does the Agency agree with the planned 505(b)(2) regulatory pathway?

FDA Response to Question 16: This approach appears acceptable.

Sponsor Response to Question 16 dated November 30, 2018: For Questions 2, 3, 4, 5, 8, 10, 11, 12, 13, 14, 16, 17, and 18, Fennec acknowledges the Division's written responses with thanks. No further discussion at the meeting is requested.

Meeting Discussion: No discussion took place.

Question 17: Based on the Fast Track designation of PEDMARK™ granted 19 March 2018, Fennec proposes to submit the NDA for a Rolling Review, with nonclinical data (and corresponding portions of the Module 2 documents) submitted in Q4 2018, clinical data (and corresponding portions of the Module 2 documents) submitted in Q1 2019, and CMC data submitted in Q2 2019. Does the Agency agree with this rolling submission proposal?

FDA Response to Question 17: This approach appears acceptable.

Sponsor Response to Question 17 dated November 30, 2018: For Questions 2, 3, 4, 5, 8, 10, 11, 12, 13, 14, 16, 17, and 18, Fennec acknowledges the Division's written responses with thanks. No further discussion at the meeting is requested.

Meeting Discussion: No discussion took place.

Question 18: Given the Orphan Drug Designation of PEDMARK™ granted on March 17, 2004, and the pediatric target population for the medication, does the Agency agree that a Pediatric Study Plan is not required for this application?

FDA Response to Question 18: This approach is reasonable.

Sponsor Response to Question 18 dated November 30, 2018: For Questions 2, 3, 4, 5, 8, 10, 11, 12, 13, 14, 16, 17, and 18, Fennec acknowledges the Division's written responses with thanks. No further discussion at the meeting is requested.

Meeting Discussion: No discussion took place.

Additional comments from sponsor dated November 30, 2018:

1. Recognizing the indication will be a review issue, Fennec plans to file the NDA with the proposed indication, "PEDMARK™ (sodium thiosulfate, anhydrous) injection is for the prevention of ototoxicity induced by cisplatin chemotherapy in patients 1 month to <18 years of age with localized, non-metastatic, solid tumors."
2. Fennec would very much like to participate in the Real-Time Oncology Review pilot program. Please provide guidance for our participation.
3. As advised in response to Question 15, Fennec is investigating the Assessment Aid pilot program and will advise should we wish to participate. No further discussion requested.

3.0 ADDITIONAL INFORMATION

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that any original marketing application for certain adult oncology

drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA has determined to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020 contain reports of molecularly targeted pediatric cancer investigations. See link to list of relevant molecular targets below. These molecularly targeted pediatric cancer investigations must be "designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling" (section 505B(a)(3)). Applications for drugs or biological products for which orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2)) and will be required to include plans to conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

Under section 505B(e)(2)(A)(i) of the FD&C Act, you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase 2 (EOP2) meeting, or such other time as agreed upon with FDA. (In the absence of an EOP2 meeting, refer to the draft guidance below.) The iPSP must contain an outline of the pediatric assessment(s) or molecularly targeted pediatric cancer investigation(s) that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation; and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For the latest version of the molecular target list, please refer to https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OCE/ucm544641.htm.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf.
In addition, you may contact the OCE Subcommittee of PeRC Regulatory Project Manager by email at OCEPERC@fda.hhs.gov. For further guidance on pediatric product development, please refer to:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review

resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.
- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).
- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).
- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission "**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**" in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: http://www.fda.gov/ectd.

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway.

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please

note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry, *Applications Covered by Section 505(b)(2)* (October 1999), available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at http://www.regulations.gov).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. by trade name(s)).

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If FDA has approved one or more pharmaceutically equivalent products in one or more NDA(s) before the date of submission of the original 505(b)(2) application, you must identify one such pharmaceutically equivalent product as a listed drug (or an additional listed drug) relied upon (see 21 CFR 314.50(i)(1)(i)(C), 314.54, and 314.125(b)(19); see also 21 CFR 314.101(d)(9)). If you identify a listed drug solely to comply with this regulatory requirement, you must provide an appropriate patent certification or statement for any patents that are listed in the Orange Book for the pharmaceutically equivalent product, but you are not required to establish a "bridge" to justify the scientific appropriateness of reliance on the pharmaceutically equivalent product if it is scientifically unnecessary to support approval.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that is supported by reliance on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature (see table below). In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information

for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying the source of supporting information in your annotated labeling, we encourage you to include in your marketing application a summary of the information that supports the application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and effectiveness for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	**Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)**
1. Example: Published literature	*Nonclinical toxicology*
2. Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication A*
3. Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section B*
4.	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This

information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications:

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332466.pdf

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf.

OCE REAL-TIME ONCOLOGY REVIEW AND ASSESSMENT AID

The FDA Oncology Center of Excellence (OCE) is conducting two pilot projects, the Real-Time Oncology Review (RTOR) and the Assessment Aid. RTOR is a pilot review process allowing interactive engagement with the applicant for earlier review and analysis of data prior to full supplemental NDA/BLA submission. Assessment Aid is a voluntary submission from the applicant to facilitate FDA's assessment of the NDA/BLA application (original or supplemental). An applicant can communicate interest in participating in these pilot programs to the FDA review division by sending a notification to the Regulatory Project Manager when the top-line results of a pivotal trial are available or at the pre-sNDA/sBLA meeting. RTOR discussions are predicated on understanding the top-line results. Those applicants who do not wish to participate in the pilot programs will follow the usual submission process with no impact on review timelines or benefit-risk decisions. More information on these pilot programs, including eligibility criteria and timelines, can be found at the following FDA websites:

- RTOR: https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OCE/ucm612927.htm. In general, the data submission should be fully CDISC-compliant to facilitate efficient review.

- Assessment Aid: https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OCE/ucm612923.htm

4.0 ATTACHMENTS AND HANDOUTS

See Attachment 1.

18 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

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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/

CLARA J LEE
12/18/2018

SANJEEVE BALASUBRAMANIAM
12/18/2018

CDER Breakthrough Therapy Designation Determination Review Template

IND	072877 (SND078)
Request Receipt Date	01/29/2018
Product	PEDMARK™ (sodium thiosulfate)
Indication	Prevention of ototoxicity induced by cisplatin chemotherapy in pediatric patients with standard risk hepatoblastoma (SR-HB)
Drug Class/ Mechanism of Action	Inorganic salt (thiol-containing reducing agent) Prevention of cis-platin damage to the cochlear hair cells and nerve
Sponsor	Fennec Pharmaceuticals
ODE/Division	OHOP/DOP1
Breakthrough Therapy Request Goal Date	03/30/2018

<u>Section I:</u> Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.*Section I to be completed within 14 days of receipt for all BTDRs*

1. **Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):**

   Prevention of ototoxicity induced by cisplatin chemotherapy in pediatric patients with standard risk hepatoblastoma (SR-HB)

2. **Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?** NO

3. **Consideration of Breakthrough Therapy Criteria:**

   a. Is the condition serious/life-threatening[1])? **YES**

If 3a is checked "No," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:

   b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequeate and sufficiently complete to permit a substantive review?

   YES, the BTDR is adequate and sufficiently complete to permit a substantive review.

4. **Provide below a brief description of the deficiencies for each box checked above in Section 3b:**

   None

5. **Clearance and Sign-Off (no MPC review)**

   N/A

[1] For a definition of serious and life threatening see Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

Reference ID: 4237028

Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.

6. A brief description of the drug, the drug's mechanism of action (if known), the drug's relation to existing therapy(ies), and any relevant regulatory history. Consider the following in your response.

Product: Sodium thiosulfate (STS) is an inorganic nitrate and is a thiol-reducing agent. Sodium thiosulfate is a food additive recognized as safe. Sodium thiosulfate has been approved since 1992 as an infusion after sodium nitrate infusion for the management of cyanide poisoning. The sodium thiosulfate label warns that in the children with cyanide poisoning requiring a dose of 30-40 ml/m^2, the administration volume should not to exceed 50 ml due to the potential for extreme hypernatremia. Side effects in adults include transient hypernatremia, hypertension, and nausea. Other toxicities include hypotension, headache, and disorientation. Hypersensitivity reactions have been reported.

STS inactivates platinum complexes by covalently binding electrophilic platinum with thiol to form a complex that is not cytotoxic and is readily excretable renally. Sodium thiosulfate administration prior to 4 hours after chemotherapy has been shown to reduce chemotherapy-related antitumor activity. For prevention of ototoxicity in children sodium thiosulfate is administered intravenously at six hours after cisplatin infusion. Treatment with platinum compounds, particularly cisplatin as compared to carboplatin or oxaliplatin, is known to produce high frequency hearing loss in up to 40% of pediatric patients. This hearing loss may result in impairment or failure of speech development particularly in younger patients. Sodium thiosulfate is intended for use in the pediatric population in whom the inner ear is not fully developed and therefore susceptible to damage from cisplatin. Sodium thiosulfate has not demonstrated the prevention of ototoxicity caused by platinum compounds in the adult population in controlled clinical trials since the hearing mechanism (cochlea) is fully developed.

Grading of Hearing Loss: Multiple grading scales exist for evaluation of hearing loss due to cisplatin ototoxicity.Two main types of ototoxicity assessment criteria are recognized: (1) those that rely on change of hearing from baseline, including WHO Common Toxicity Criteria, National Cancer Institute Common Toxicity Criteria for Adverse Events (CTCAE), protocol criteria from Children's Cancer Group A9961 (CCG-A9961; phase III intergroup average-risk medulloblastoma protocol, and the Children's Hospital Boston (CHB) scale, ,and (2) those specifically written for children that measure absolute hearing levels, including Brock et al and Chang and Chinosornvatana (hereafter Brock and Chang), and the new SIOP Boston scale. At the 42nd Congress of the International Society of Pediatric Oncology (SIOP) in Boston, October 21-24, 2010, based on input from multiple experts a new set pf recommendations were developed to advance research and for use in clinical trials for otoprotection.The SIOP Boston Scale is thought to combine the best elements from all the scales and is intended for use at the end of the clinical trial. The scale is shown in the following table:

Table 2. SIOP Boston Ototoxicity Scale

Grade	Parameters
0	≤ 20 dB HL at all frequencies
1	> 20 dB HL (ie, 25 dB HL or greater) SNHL above 4,000 Hz (ie, 6 or 8 kHz)
2	> 20 dB HL SNHL at 4,000 Hz and above
3	> 20 dB HL SNHL at 2,000 Hz or 3,000 Hz and above
4	> 40 dB HL (ie, 45 dB HL or more) SNHL at 2,000 Hz and above

NOTE. Scale is based on sensorineural hearing thresholds in dB hearing level (HL; bone conduction or air conduction with a normal tympanogram). Bone conduction thresholds are used to determine the grade in the case of abnormal tympanometry and/or suspected conductive or mixed hearing loss. Even when the tympanogram is normal, bone conduction is strongly recommended at the single frequency that is determining the ototoxicity grade to fully confirm that the hearing loss at that frequency is sensorineural. Temporary, fluctuating conductive hearing loss due to middle ear dysfunction or cerumen impaction is common in the pediatric population, and decreases in hearing thresholds that include conductive hearing losses do not reflect ototoxicity to the cochlea.

Abbreviations: SIOP, International Society of Pediatric Oncology; SNHL, sensorineural hearing loss.

An article by Landier et al in JCO the Children's Oncology Group (COG) reported on the assessment of hearing loss in children with high-risk neuroblastomas treated with cisplatin to determine the prevalence, risk factors, and the concordance of the grading scales. The article states that the prevalence of cisplatin ototoxicity ranges from 13- 95% . The following factors influence risk: platinum type, dose, infusion duration, host factors (e.g. age, renal function, genetic susceptibility) and receipt of additional ototoxic therapy (cranial irradiation, aminoglycosides, loop diuretics). To compare concordance and discordance among the various ototoxicity grading scales (ASHA, Brock, Chang, CTCAE vc.3) a review of the audiology data obtained from 330 evaluable patients from COG Study A3972 was performed. The audiology reports obtained for toxicity monitoring (conducted before first platinum exposure, after cumulative cisplatin exposure of 200 and 400 mg/m^2, and after myeloablative doses of carboplatin for transplantation) were submitted by the treating institutions to the COG Statistics and Data Center. Air and bone-conduction thresholds (tone-burst thresholds for auditory brainstem response) for each tested frequency and details of testing (e.g., type of testing performed, masking, tympanometry, use of hearing aids or assistive devices) contained in the audiology reports was evaluated using a standardized process. Audiology reports were graded independently by two investigators using each of the four grading scales. A grade was assigned to each ear with evaluable thresholds or to the sound field; in cases where disagreement in grading between investigators was observed, a consensus grading determination was made.

The authors concluded that no significant differences existed in discriminating normal from impaired hearing (range, 99.3% to 100% concordant pairs) across grading scales. However, significant discordance was identified among the scales in identifying severe hearing loss with > 50% discordance in assignment of severe ratings between the two most commonly used scales: CTCAEv3 and Brock. For children who received cisplatin and myeloablative carboplatin, hearing loss was rated as severe in only 30% by the Brock scale, but it was rated as severe in 59% by Chang and 71% by CTCAEv3. A similar pattern was observed for patients who received cisplatin only with 8% receiving a rating of severe by Brock, 32% by Chang, and 47% by CTCAEv3. The Brock scale was the first ototoxicity scale specifically developed to assess platinum-related hearing loss, and its design was based on audiograms from 41 children with high-frequency hearing loss that sloped an average of 45 dB per octave over the impaired frequencies. Given these large decrements per octave and assuming that hearing would be normal or only minimally impaired at the octave below, 40 dB was selected as the cutoff for significant loss at each frequency. The Chang scale was built on the design employed by Brock to assess the typical pattern of hearing loss seen in platinum-based regimens, but it includes modifications that address functional deficits caused by losses < 40 dB and at interval frequencies not assessed by Brock, with the goal of

aligning objective severity grading with audiologists' clinical recommendations for amplification. The importance of the inclusion of modest (<40 dB) decrements and key interval frequencies in assessing the functional implications of hearing loss (particularly with regard to need for amplification) is underscored by our finding that only 49% of children requiring a hearing aid were rated as having severe hearing loss according to the Brock scale, whereas 91% and 100% of these children received a severe rating according to the Chang and CTCAEv3 scales, respectively. Thus, the commonly used Brock scale significantly underestimated functionally severe hearing loss in this cohort.

Cisplatin Ototoxicity: Cisplatin-induced ototoxicity results from damage from the oxidative potential of cis-platin (CIS) which affects the cochlear hair cells residing in the inner ear. Cisplatin ototoxicity targets at least three tissues in the cochlea: the organ of Corti, spiral ganglion cells, and the lateral wall (stria vascularis and spiral ligament). Auditory sequelae include tinnitus and sensorineural hearing loss mainly at the high-frequency range. Tinnitus may subside, but hearing loss is almost always permanent in adults and children. Hearing loss may progress after discontinuation of cisplatin therapy. A review by Paken et al in 2016 noted that in adults the incidence of hearing loss is reported as 15-100% depending on the dose of cisplatin. 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). A number of studies have documented that children treated with CIS are at high risk for incurring significant hearing loss. Li et al (2004) evaluated post treatment audiograms from 153 children, aged 6 months to 18 years. Children were treated with CIS for germ cell tumors, hepatoblastoma, neuroblastoma, or osteosarcoma. Cisplatin doses ranged from 40mg/m^2/cycle to 200mg/m^2/cycle with cumulative doses of 120mg/m^2 to 1213mg/m^2 (median dose 397mg/m^2). Twenty-six patients (17%), developed mild hearing loss, and 54 patients (35%) developed moderate to severe hearing loss. Patients <5 years old were 21 times more likely to develop moderately severe, high-frequency hearing loss compared with patients between 15 years and 20 years old. The children who were <5 years old during treatment had a cumulative CIS dose of > 400mg/m^2. After adjusting for cumulative dose, larger individual doses of CIS were not found to be significantly associated with the development of hearing loss. Susceptibility to CIS ototoxicity was highly variable among individuals. Ilveskoski et al (1996) obtained repeated audiograms from 30 children treated with CIS and concluded that young patients treated with high cumulative doses of CIS had a >50% risk of sustaining severe hearing loss. However, the study showed that the true incidence of CIS ototoxicity in pediatric patients was highly variable, ranging from 26% to >90% due to several treatment- and patient-related factors.

Kushner et al (2006) specifically focused on ototoxicity when evaluating platinum chemotherapy in 173 patients with neuroblastoma. The median age at diagnosis was between 3 years and 4 years, and patients were divided into 3 groups depending on dosing schedules. Overall, 42% of patients experienced Grade 3 to 4 ototoxicity. A French study followed 120 children with various cancers (75% of patients had neuroblastoma) treated with platinum regimens (Bertolini et al, 2004). The median cumulative CIS dose was 400mg/m^2 (range: 80mg/m^2 to 800mg/m^2). Hearing loss at Grade 2 or greater occurred in 37% of patients treated with CIS and 43% of patients treated with a combination of CIS and carboplatin. Among the 10 patients who received a cumulative CIS dose <400mg/m^2, only 1 patient experienced ototoxicity (Grade 2). For 38 patients with a cumulative dose ≥ 400mg/m^2, 42% of patients had Grade 2 or greater ototoxicity, and 22 patients (46%) with a cumulative dose of exactly 400mg/m^2 experienced Grade 2 or greater ototoxicity. At 2 years post-treatment, 15% of patients had Grade 3-4 ototoxicity, and 29% of patients had Grade 2 ototoxicity (Bertolini et al, 2004). In 148 patients with high-risk germ cell tumors studied by the Pediatric Oncology Group and COG, Grade 3-4 hearing loss occurred in 18% of patients, and nephrotoxicity occurred in 22% of patients (Cushing et al, 2004). An international trial compared treatments with CIS Alone and with CIS + doxorubicin in 126 patients with HB. Grade 2-4 ototoxicity occurred in 20% of patients (7% had Grade 3-4) and a GFR <60ml/min/1.73m2 in 4% of patients (Perilongo et al, 2009). In a study of 363 patients with medulloblastoma treated with radiation and various doses of CIS, 25% of patients experienced Grade 3-4 objective hearing loss. Younger age was significantly associated with hearing loss (Nageswara et al, 2014)

Table 1: Prevalence of cisplatin-induced ototoxicity in pediatric patients with hepatoblastoma

Study	N	Age (years)	Prevalence, % (n) Brock grade	Chemotherapy Cumulative dose
Knight 2007	2 (2 F)	1.1 and 8.5	100% (2) Grade 1	CIS 400mg/m^2 and 600 mg/m^2
Katzenstein 2009	82 evaluable (44 M, 38 F)	0 to 11	38% (31)	CIS, 5-FU, C5V for Stage I or II patients and C5V or carboplatin/CIS for Stage III or IV patients Total intended platinum dose for stage I (nonpure fetal) and II: 400mg/m^2 of CIS. For stage III and IV patients: 600mg/m^2 CIS and 3640mg/m^2 carboplatin
Yancey 2012	7 (6 M, 1 F)	2 to 10	100 % (7) Grade ≥2, 71% (n=5) Grade ≥3, 28% (n=2)	CIS 478mg/m^2

CIS=cisplatin; C5V=vincristine; F=female; 5-FU=5-fluorouracil; M=male; n=number of patients

Regulatory History: A request for breakthrough therapy (BK) request based on published literature which purported to demonstrate a reduction in hearing loss in children who received STS while on cisplatin therapy was submitted in 2013. All the published literature was from uncontrolled studies with small sample sizes. The sponsor (Adherex) withdrew the request when advised that the submitted literature would not support a breakthrough designation. In a second breakthrough request submitted by Adherex in 2014 data from ACCL0431, an exploratory COG randomized clinical trial in which multiple tumor types with localized and extensive disease were included, was presented. The efficacy results showed a statistically significant (p=0.00022) decrease in the proportion of evaluable patients with hearing loss for the STS group (28.6%) as compared to the control group (56.4%). No difference in event-free survival (log-rank p=0.36) and in overall survival (log rank p=0.07) was observed on ACCL0431. On a post-hoc exploaratory subgroup analysis for the localized disease subgroup, no difference in overall survival (OS) was observed between the two treatment groups (CIS alone-72.5%, STS+CIS-68.3%; unadjusted log rank p=0.94). However in the extensive disease subgroup OS on the CIS +STS arm (55.9%) was significantly decreased as compared to the CIS alone arm (88.1%) with unadjusted log-rank p=0.009. Since sodium thiosulfate has tumor promotion potential the Breakthrough Therapy Request, which was reviewed by the MPC, was denied on August 1, 2014. At the time the request was denied, a second non-IND controlled clinical trial, SIOPEL-6, was ongoing having been initiated in 2007 with enrollment completed on December 31, 2014. Fennec submitted a request for a pre-NDA meeting in December, 2017 which included the results of SIOPEL-6. Analysis of the study results showed a statically significant reduction in hearing loss for the patients treated with STS and cisplatin with an acceptable toxicity profile (see Table in #10 below). With regard to tumor related endpoints, the event-free survvial on the SIOPEL-6 trial for the CIS arm was 79%, and for the CIS+STS was 82.1% with the HR=0.89 (95% CI: 0.39, 2.06; p=0.79). At three years the overall survival (OS) on the CIS arm was 92.3% and on the CIS+STS arm was 98.2% with a HR=0.44 (95% CI; 0.08-2.42, p=0.33. The OS results from SIOPEL-6 suggest that concerns about tumor growth potentiation may be unfounded. After review of the meeting package FDA agree that an NDA should be submitted and that it would be appropriate to submit Fast Track and Breakthrough Therapy requests.

7. Information related to endpoints used in the available clinical data:

a. Describe the endpoints considered by the sponsor as supporting the BTDR and any other endpoints the sponsor plans to use in later trials. Specify if the endpoints are primary or secondary, and if they are surrogates.

For SIOPEL-6:
Primary endpoint: Assess the efficacy of delayed STS in reducing the hearing impairment caused by CIS chemotherapy. [Blinded audiology review]
Secondary endpoints:

- To monitor potential impact of STS on response to CIS and survival;
- To assess the tolerability of CIS+STS;
- To prospectively evaluate and validate various biological, radiological, and pathological features of SR-HB for future risk-adapted management;
- To investigate the effect of STS on the formation of CIS-DNA adducts; and,
- To collect patient DNA for the analysis of predisposing genetic factors.

For ACCL0431 (Supporting Trial):
Primary endpoint: Rate of ASHA hearing loss determined 4 weeks and 12 months after the last course of CIS [Blinded audiology review]
Secondary Endpoints:

- Mean change in hearing thresholds for key frequencies
- EFS
- OS
- Incidence of CIS-related Grade 3 and 4 nephrotoxicity and cytopenia

Endpoints in any future trials conducted by this or other sponsors would be similar.

b. Describe the endpoint(s) that are accepted by the Division as clinically significant (outcome measures) for patients with the disease. Consider the following in your response:

The division accepts the endpoints listed in Section 8.a as a direct measure of clinical benefit.

c. Describe any other biomarkers that the Division would consider likely to predict a clinical benefit for the proposed indication even if not yet a basis for accelerated approval.

N/A

8. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population. Consider the following in your response:

No therapies are available for prevention of cisplatin-induced hearing loss

9. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation[2].

No other drugs have requested Breakthrough Therapy designation for this indication.

10. Information related to the preliminary clinical evidence:

a. Table of clinical trials supporting the BTDR (only include trials which were relevant to the designation determination decision), including study ID, phase, trial design[3], trial endpoints, treatment group(s), number of subjects enrolled in support of specific breakthrough indication, hazard ratio (if applicable), and trial results.

[2] Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.

	SIOPEL-6	ACCL0431
Phase	Phase III	Phase III
Trial Design	Multi-center, Open-label, Randomized (1:1)	Multi-center, Open-label, Randomized (1:1)
Primary Endpoint	Proportion of patients in each group with any hearing loss, defined by Brock* grade ≥1, determined after end of trial treatment or at an age of at least 3.5 years, whichever was later.	Rate of ASHA hearing loss determined 4 weeks and 12 months after the last course of CIS
Stratification Factors:	• Country • Age: > 15 mos., < 15 mos., • PRETEXT stage	• Age • Duration of CIS infusion • Prior cranial radiation
Tumor Type / Eligibility	Hepatoblastoma (SR-HB) • PRETEXT I, II or III* • No vascular invasion, no extra-hepatic or metastatic disease • Serum alpha-fetoprotein >100μg/L	Newly diagnosed HB, germ cell tumor, osteosarcoma, neuroblastoma, medulloblastoma, or other malignancy treated with CIS
Treatment Groups	Cis-Platin vs. Cis-Platin + STS	Cis-Platin vs. Cis-Platin + STS
Cumulative Cis-platin dose		➢ 200 mg/m^2
Treatment	CIS-Platin 80 mg/m^2 over 6 hrs. STS 20 g/m^2 6 hrs after Cis-platin	CIS-platin: variable STS: 16 mg/m^2 6 hr. after CIS (or 533 mg/kg for young age, low body weight)
No. of Patient Enrolled	109 (CIS-52; CIS+STS-57)	125 (CIS-64; CIS+STS-61)
No. Evaluable	96*** (CIS-46; CIS+STS-55)	104 (CIS-55; CIS+STS-49)
Age	3-70 months	1-18 yrs.
Statistical Plan	25% absolute reduction in Brock Gr. ≥ 1 hearing loss at age ≥ 3.5 years	50% relative reduction in the proportion of subjects with hearing loss in the STS treated group versus the control group.
Results:		
Primary:		
Percent with Hearing Loss	CIS alone: 31/46 (67%) CIS+STS: 20/55 (36%) P=0.002	CIS alone: 28.6% CIS+STS: 56.4% P=0.0036 (adjusted)
Relative Risk of Hearing Loss	RR=0.54 (95% CI: 0.36-0.81) P=0.0019	OR=0.31 (95% CI: 0.13-0.73) P=0.0036
Tolerability		
Nephrotoxicity	---	CIS: 13% (all < Gr. 3) CIS+ STS:25% (all < Gr. 3)
Neutropenia	CIS: 7 (15%) Gr. 3/4 CIS+STS: 13 (24%) Gr. 3/4	CIS: 60- 70% All Grades CIS+STS: 60-70%
Febrile Neutropenia	CIS: 7 (14%) CIS+STS: 5 (9%)	Not provided
Thrombocytopenia	---	CIS: 40-60% CIS+STS: 41-60%

*Brock Grade: Normal hearing sensitivity for children is defined as hearing thresholds ≥15dB HL across the entire speech spectrum, from 0.25kHz to 8kHz.

- Grade 0: thresholds are >40dB HL, from 0.25kHz to 8kHz
- Grade 1: thresholds are ≥40dB HL at 8kHz
- Grade 2: thresholds ≥40 dB HL at ≥4kHz
- Grade 3: thresholds ≥40dB HL, from 2kHz to 8kHz
- Grade 4: thresholds ≥40dB HL at ≥1kHz

[3] Trial design information should include whether the trial is single arm or multi-arm, single dose or multi-dose, randomized or non-randomized, crossover, blinded or unblinded, active comparator or placebo, and single center or multicenter.

**PRETEXT Stage:
Standard risk patients

- PRETEXT I: one section of liver involved
- PRETEXT II: one or two sections are involved; adjoining sections are free
- PRETEXT III: Two or three sections are involved; no two adjoining sections free

High risk patients:

- •PRETEXT IV: All four section of liver involved; extrahepatic disease, venous involvement

***Reliable hearing test results were available for 101 of the 109 patients. Five patients died from their disease before the hearing test could be performed. Two patients could not be tested due to their condition (one autistic, one syndromic). For 1 patient, the hearing test was not obtained due to logistical problems at the treating site.

b. Include any additional relevant information. Consider the following in your response:

See above table for all relevant information.

11. Division's recommendation and rationale (pre-MPC review):

☒ GRANT :

Two adequate and well-controlled randomized clinical trials in pediatric patients with solid tumor malignancies have shown a statistical significant decrease in hearing loss with an acceptable toxicity profile with the use of sodium thiosulfate after cis-platin infusion. FDA's concerns about STS' potentiation of tumor growth and worsening survival were not confirmed when no difference in event-free and overall survival were observed on the SIOPEl-6 clinical trial. Fennec's request for breakthrough therapy for prevention of hearing loss in pediatric patients with standard-risk neuroblastoma should be granted at this time.

12. Division's next steps and sponsor's plan for future development:

If recommendation is to grant the request, explain next steps and how the Division would advise the sponsor (for example, plans for phase 3, considerations for manufacturing and companion diagnostics, considerations for accelerated approval, recommending expanded access program):

The Sponsor's request for fast tract will also be approved. The division will provide support / guidance regarding the submission of the proposed NDA for the indication of prevention of cis-platin related ototoxicity in pediatric patients with standard-risk neuroblastoma for consideration for approval. At this point the sponsor (a small pharmaceutical company) has not requested implementation of an expanded access program.

13. List references, if any:

Paken, J et al. "Cisplatin-Associated Ototoxicity: A Review for the Health Professional". Journal of Reference Volume 2016, Article ID 1809394, 13 pages http://dx.doi.org/10.1155/2016/1809394

Brock, P.R. 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." JCO 2012 30(19):2408-2417.

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

Arslan E, Orzan E, Santarellli R. Global problem of drug-induced hearing loss. Ann NY Acad Sci. 1999;884:1-14.

Landier W, Knight K, Wong FL, 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(6):527-34

Li Y, Womer RB, Silber JH. Predicting ototoxicity in children: influence of age and the cumulative dose. Eur J Canc. 2004;40(16):2445-51.

Landier W, Knight K, Wong FL, 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(6):527-34

Katzenstein HM, Chang KW, Krailo M, et al.; Children's Oncology Group. Amifostine does not prevent platinum-induced hearing loss associated with the treatment of children with hepatoblastoma: a report of the Intergroup Hepatoblastoma Study P9645 as a part of the Children's Oncology Group. Cancer. 2009;115(24):5828-35.

Skinner R, Pearson AD, Amineddine HA, Mathias D, Craft A. Ototoxicity of cisplatinum in children and adolescents. Br J Cancer. 1990;61(6):927-31.

Yancey A, Harris MS, Egbelakin A, Gilbert J, Pisoni DB, Renbarger J. Risk factors for cisplatin-associated ototoxicity in pediatric oncology patients. Pediatr Blood Cancer. 2012;59(1):144-8.

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Ilveskoski, I, Saarinen, UM, Wildund, T, Perkkio, M, Salmi, TT, Lanning, M, Makipernaa, A, Pihko, H. Ototoxicity in children with malignant brain tumors treted with the “8 in 1” chemotherapy protocol. Med Pediatri Oncol. 1996;27(1):26-31.

Kushner BH, Budnick A, Kramer K, Modak S, Cheung NK. Ototoxicity from high-dose use of platinum compounds in patients with neuroblastoma. Cancer. 2006;107(2):417-22.

Bertolini P, Lassalle M, Mercier G, 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.

Cushing B, Giller R, Cullen JW, et al. Randomized comparison of combination chemotherapy with etoposide, bleomycin, and either high-dose or standard-dose cisplatin in children and adolescents with high-risk malignant germ cell tumors: a pediatric intergroup study—Pediatric Oncology Group 9049 and Children’s Cancer Group 8882. J Clin Oncol. 2004;22(13):2691-2700.

Perilongo G, Maibach R, Shafford E, et al. Cisplatin versus cisplatin plus doxorubicin for standard-risk hepatoblastoma. N Engl J Med. 2009;361(17):1662-70.

Nageswara Rao AA, Wallace DJ, Billups C, Boyett JM, Gajjar A, Packer RJ. Cumulative cisplatin dose is not associated with event-free or overall survival in children with newly diagnosed average-risk medulloblastoma treated with cisplatin based adjuvant chemotherapy: report from the Children’s Oncology Group. Pediatr Blood Cancer. 2014;61(1):102-6.

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.

Katzenstein HM, Chang KW, Krailo M, et al.; Children's Oncology Group. Amifostine does not prevent platinum-induced hearing loss associated with the treatment of children with hepatoblastoma: a report of the Intergroup Hepatoblastoma Study P9645 as a part of the Children's Oncology Group. Cancer. 2009;115(24):5828-35.

Yancey A, Harris MS, Egbelakin A, Gilbert J, Pisoni DB, Renbarger J. Risk factors for cisplatin-associated ototoxicity in pediatric oncology patients. Pediatr Blood Cancer. 2012;59(1):144-8.

14. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting? Yes X☐

15. Clearance and Sign-Off (after MPC review):

Grant Breakthrough Therapy Designation ☐
Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

5-7-15/M. Raggio

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

GENEVIEVE A SCHECHTER
03/20/2018

SANJEEVE BALASUBRAMANIAM
03/20/2018

JULIA A BEAVER
03/20/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 72877

**MEETING REQUEST-
WRITTEN RESPONSES**

Fennec Pharmaceuticals, Inc.
Attention: Anne McKay
Regulatory Affairs Agent
P.O. Box 13628
69 TW Alexander Drive
Research Triangle Park, NC 27709

Dear Ms. McKay:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for PEDMARK™ (sodium thiosulfate) (b) (4)

We also refer to your submission dated October 31, 2017, containing a meeting request. The purpose of the requested meeting was to discuss the clinical development program for PEDMARK™ (sodium thiosulfate) (b) (4) for the prevention of ototoxicity induced by cisplatin in pediatric patients with standard-risk hepatoblastoma.

Further reference is made to our Meeting Granted letter dated November 6, 2017, wherein we stated that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your December 7, 2017, background package.

If you have any questions, call Leyish Minie, Regulatory Project Manager, at (301) 796-5522.

Sincerely,

{See appended electronic signature page}

Leyish Minie, RN, MSN
Regulatory Project Manager
Division of Oncology Products 1
Office of Hematology & Oncology Products
Center for Drug Evaluation & Research

{See appended electronic signature page}

Sanjeeve Balasubramaniam, MD, MPH
Acting Clinical Team Leader
Division of Oncology Products 1
Office of Hematology & Oncology Products
Center for Drug Evaluation & Research

Enclosure: Written Responses

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

WRITTEN RESPONSES

Meeting Type: Type C
Meeting Category: Guidance

Application Number: IND 72877

Product Name: PEDMARK™ (sodium thiosulfate) (b) (4)
Indication: Prevention of ototoxicity induced by cisplatin chemotherapy in pediatric patients with standard risk hepatoblastoma (SR-HB).

Sponsor/Applicant Name: Fennec Pharmaceuticals, Inc.
Regulatory Pathway: 505(b)(1)

BACKGROUND

Thiosulfate is an endogenous substance produced by sulfur metabolism in humans and other mammals. STS inactivates platinum complexes by covalently binding electrophilic platinum with thiol to form a complex that is not cytotoxic and is readily excretable. Sodium thiosulfate, a reducing agent, is a food additive recognized as safe. Sodium thiosulfate is approved as an infusion after sodium nitrate infusion for the indication of cyanide poisoning. The label warns that in the children with cyanide poisoning at a dose of 30-40 ml/m^2, the volume should not to exceed 50 ml. Side effects in adults include transient hypernatremia, hypertension, and nausea. Other toxicities include hypotension, headache, and disorientation. Hypersensitivity reactions may occur. Excretion is primarily renal. Sodium thiosulfate administration prior to 4 hours after chemotherapy has been shown to reduce antitumor activity of chemotherapy. Treatment with platinum compounds, particularly cisplatin as compared to carboplatin or oxaliplatin, is known to produce high frequency, sensorineural hearing loss due mainly to damage to cochlear hair cells in the inner ear.

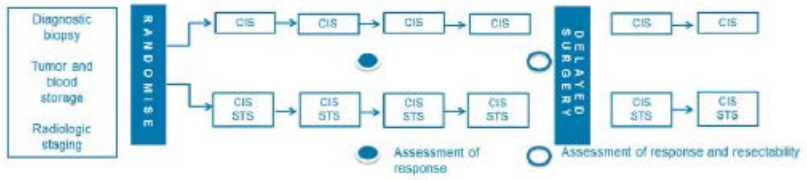
The sponsor filed a breakthrough therapy (BK) request based on published literature in 2013 which purported to demonstrate a reduction in hearing loss in children who received STS while on cisplatin therapy. The sponsor withdrew the request when advised that the submitted literature did not support the designation. In a second BK request, data from ACCL0431, a COG clinical trial, was presented which showed a statistically significant (p=0.00022) decrease in the proportion of evaluable patients with hearing loss for the STS group (28.6%) as compared to the control group (56.4%). This BK request was denied on August 1, 2014 because of a statistically significant (p=0.011) decreased survival in patients with extensive disease reported for the STS + cisplatin arm.

The proposed NDA submission is based on the data from the non-IND clinical trial, SIOPEL-6, entitled "A Multicentre Open Label Randomised Phase 3 Trial of the Efficacy of Sodium Thiosulfate in Reducing Ototoxicity in Patients Receiving Cisplatin Chemotherapy for Standard

Risk Hepatoblastoma" conducted solely in Europe by the International Liver Tumor Strategy Group (SIOPEL). Supporting data comes from a Children's Oncology Group (COG) proof of concept study, ACCL0431, entitled "A Randomized Phase 3 Study of Sodium Thiosulfate for the Prevention of CIS-Induced Ototoxicity in Children". SIOPEL-6 was initiated in 2007 and enrollment completed on December 31, 2014.

Study design is shown in the following scheme:

Figure 13: SIOPEL 6 Study Design



CIS=cisplatin; STS=sodium thiosulfate

The primary objective of SIOPEL-6 was to reduce hearing impairment caused by cisplatin (CIS) chemotherapy. The primary endpoint was centrally-reviewed absolute hearing threshold, at the age of ≥3.5 years by pure tone audiometry (PTA). Audiological results were analyzed and assigned a numeric grade that described the severity of hearing loss based on the grading system developed by Brock et al which does not use change from baseline hearing levels, but rather measures the absolute hearing level. The Brock numerical grades are shown here:

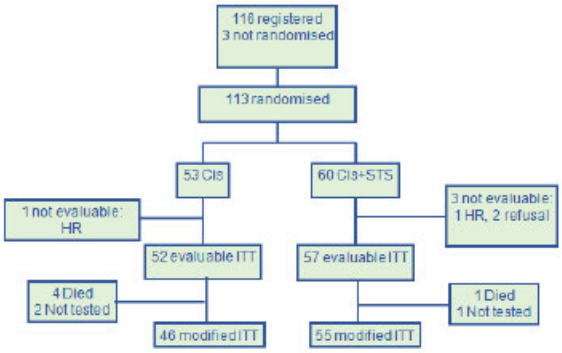
- Grade 0: thresholds are >40dB HL, from 0.25kHz to 8kHz
- Grade 1: thresholds are ≥40dB HL at 8kHz
- Grade 2: thresholds are ≥40 dB HL at ≥4kHz
- Grade 3: thresholds ≥ 40dB HL, from 2kHz to 8kHz
- Grade 4: thresholds ≥ 40dB HL at ≥1kHz

A sample size of 102 evaluable patients would be able to detect a 25% reduction in the rate of Brock grade ≥1 hearing loss from a 35% hearing loss in the CIS+STS group as compared to a 60% hearing loss in the CIS alone group using a chi-square test with a significance level of 5% and a power of 80%. Eligible patients included patients >1 month to ≤18 years with histologically confirmed standard risk hepatoblastoma (SR-HB) of PRETEXT I, II, or III[1] who had no evidence of vascular invasion, extra-hepatic, metastatic disease or serum alpha-fetoprotein (AFP) >100 ug/l. Randomization was stratified by country, age (>15 months,

[1] PRETEXT Scoring
- PRETEXT I: one section of liver involved
- PRETEXT II: one or two sections are involved; adjoining sections are free
- PRETEXT III: Two or three sections are involved; no two adjoining sections free
  High risk patients:
- PRETEXT IV: All four section of liver involved; extrahepatic disease, venous involvement

<15 months, and PRETEXT Stage (I or II vs III).

One-hundred thirteen patients were randomized and one hundred nine patients were evaluable. Four patients randomized to the CIS+STS arm did not receive STS due to unavailability of the study medication. Study Disposition is shown in the following diagraph.



CIS=cisplatin, ITT=intent-to-treat population, STS=sodium thiosulfate, HR=high risk
Note: patients with HR disease were excluded from evaluation.

Baseline characteristics are included in the following table. Imbalances in the AFP level and in the PRETEXT class are noted.

Characteristic	CIS Alone [a] N=52	CIS+STS [b] N=57
Age, months	13.4 Range: 3.0-70.2	12.8 Range: 1.2-98.6
Sex, n (%) male	29 (56)	30 (53)
AFP, median, ng/mL	73,760 Range: 187-2,175,690	154,638 Range: 273-4,536,500
PRETEXT, n (%) I/II III	 31 (60) 21 (40)	 41(72) 16 (28)

AFP=alpha-fetoprotein, CIS=cisplatin, N=number of patients; PRETEXT=pretreatment extent of disease, STS=sodium thiosulfate
[a] CIS Alone dose: 80mg/m^2 via 6-hr IV infusion
[b] CIS+STS doses: CIS 80mg/m^2 via 6-hr IV infusion; 6 hr after stopping CIS, STS 20g/m^2 administered via 15 min IV infusion

Pure Tone Audiometry was conducted once the child was old enough to cooperate (~3.5 years of age). The audiograms were read by an audiologist specialist who was blinded to the study therapy. Two patients were not able to complete the audiology testing due to unrelated issues (autism, syndromic problems). Efficacy and tumor-related safety endpoints are shown in the following table.

Efficacy and Tumor-Related Safety Results

	CIS-PLATIN Alone (N=52)	**CIS-PLATIN + STS (N=57)**
Proportion with Hearing Loss (mITT)	31/46 (67.4%)	20/55 (36.4%)
	RR= 0.54 (95% Ci: 0.36, 0.81) p=0.0019	
3 yr. Event-Free Survival	80.4% (95% CI: 66.6, 88.9%)	81.9% (95% CI:81.9%
	HR=0.89 (95%CI: 0.39, 2.06) p=0.79	
3 yr. Overall Survival	92.3% (95% CI: 8.0.8%, 97%)	98.2% (95% CI: 87.8%, 99.7%)
	HR=0.44 (95% CI: 0.08-1.42) p=0.33	

Assigning worst-case outcomes to the 8 patients not currently evaluable for hearing loss in the ITT population (i.e., hearing loss to patients randomized to CIS+STS and no hearing loss to patients randomized to CIS Alone) still yields a statistically significant result (hearing loss in 22 of 57 patients in the CIS+STS group, and hearing loss in 31 of 52 patients in the CIS Alone group; p=0.028).

Hearing test results by treatment arm using the Brock Grading system are included in the following table:

Table 15: Hearing test results by treatment arm in SIOPEL 6

Brock grade	**CIS Alone (n=46) N (%)**	**CIS+STS (n=55) N (%)**
0	15 (33%)	35 (64%)
1	13 (28%)	12 (22%)
2	12 (26%)	6 (11%)
3	5 (11%)	1 (2%)
4	1 (2%)	1 (2%)
Any Hearing Loss (Grade 1-4)	31 (67%)	20 (36%)

The rates of any hearing loss for the 2 randomized groups are shown in Figure 15

Safety information: Safety information is available for a total of 234 patients. A total of 33 deaths occurred with 27 deaths reported on ACCL0421 and 6 on SIOPEL-6 all reported as unrelated. All deaths were related to tumor progression except for 1 on ACCL0421 due to sepsis.

On SIOPEL-6, 11 patients discontinued STS, one due to metabolic acidosis coupled with lethargy and ten because of the addition of doxorubicin to cisplatin. The patient who developed metabolic acidosis had Brock Grade 4 hearing loss. Regarding serious adverse events (SAEs) 35 were reported for the CIS+STS arm while 23 were reported for the CIS alone arm. One patient on the STS+CIS arm had a Grade 2 hypersensitivity reaction with rash, flushing, urticaria, and drug fever $\geq 38^0$ C. On SOIPEL-6, Grade 3/4 adverse events were increased on the CIS+STS

arm (63 AEs) as compared to the CIS alone arm (32 AEs). On the combination arm more patients had a decrease in hemoglobin (12 vs 7); neutropenia (13 vs 7); hypermagnesia (11 vs. 2); hypophosphatemia (7 vs 0); hypokalemia (9 vs 0). Little difference was observed between arms in the incidence of Grade 3/ 4 febrile neutropenia, infection, or nausea.

For the two Phase 3 studies (ACCL0431 and SIOPEL 6) safety findings included ≥Grade 1 hypernatremia, ≥Grade 3 nonhematologic AEs (any attribution), and all grades of allergic reaction. Adverse events of particular interest included ≥Grade 3 nephrotoxicity including creatinine, GFR, hypomagnesemia, hypokalemia, hypophosphatemia, urinary electrolyte wasting syndrome (Fanconi syndrome), as well the hematologic toxicities including ≥Grade 3 cytopenia (leukopenia, neutropenia, anemia or thrombocytopenia) and were higher on the treatment arm.

QUESTIONS AND RESPONSES

1. Given the nonclinical data available in the literature, together with extensive clinical experience, does the Agency agree that no additional nonclinical studies are required to support the NDA for the proposed indication?

   FDA Response: Your proposed approach appears to be acceptable for the proposed indication of prevention of ototoxicity induced by cisplatin in pediatric patients with SR-HB. For any potential future labeled indications that you pursue that do not include administration of STS with cisplatin, additional nonclinical studies may be needed. A final determination of what nonclinical studies constitute a complete NDA submission will be made at a future pre-NDA meeting. If you intend to rely on existing data to support the nonclinical safety assessment of STS that are necessary for approval of an NDA, and for which you do not have right of reference, such as published literature or FDA's finding of safety and/or effectiveness of a listed drug, your application would be considered a 505(b)(2) NDA.

   Please also refer to the information under the heading "505(b)(2) Regulatory Pathway" below.

2. Does the Agency agree with the approach to support dose and duration of STS administration?

   FDA Response: The proposed approach appears to be generally acceptable; however, the final determination will be an NDA review issue. Please clarify the reason for not using STS exposure to evaluate the exposure-response relationship of efficacy and safety.

   In addition, refer to our response to Question 5.

3. Does the Agency agree with the planned PK modelling (which is based on scientific advice received to date from MHRA and the Pediatric Committee [European Union])?

   FDA Response: We appreciate your proposal to use the modeling approach to facilitate drug development and your general strategy seems reasonable. However, the appropriateness of the model will be an NDA review issue, and will depend on the purpose of the modeling.

4. Does the Agency agree that considering the limited treatment duration and indication, a literature review on TS metabolism and in vitro CYP studies will provide sufficient information in the NDA submission to review the potential for pharmacokinetic drug-drug interaction (DDI)?

   FDA Response: We agree that you should conduct *in vitro* assessment of STS as CYP inhibitor or inducer. In addition, please calculate the R values or ratios of the mean steady-state concentrations to the 50% maximal inhibitory concentration (IC_{50}) or the enzyme inhibition constant Ki to determine the need for pharmacokinetic interaction studies. Refer to the Guidance for Industry, "*Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations*" for greater detail.

5. Does the Agency agree that the pivotal SIOPEL 6 data, supported by results of the proof of concept study COG ACCL0431 and further published STS clinical results, provide sufficient efficacy data to allow the filing of an NDA for PEDMARK™ (sodium thiosulfate) for Injection for the prevention of ototoxicity induced by cisplatin chemotherapy in pediatric patients with SR-HB?

   FDA Response: Yes; however, in your application you should discuss and provide justification for the decreased overall survival seen in the STS+cisplatin arm of the COG ACCL0431 trial.

6. Does the Agency agree that the pivotal SIOPEL 6 data, supported by results of COG ACCL0431 and further published STS clinical results, provide sufficient safety data to allow the filing of an NDA for PEDMARK™ (sodium thiosulfate) for Injection for the prevention of ototoxicity induced by cisplatin chemotherapy in pediatric patients with SR-HB?

   FDA Response: Yes.

7. The Sponsor believes that STS for the proposed indication qualifies for the following expedited programs based primarily upon the results of the pivotal SIOPEL 6 study:

   a. Fast Track Designation
   b. Breakthrough Therapy Designation

   Does the Agency agree?

FDA Response: Based on your summary clinical information and the lack of agents for this indication, you would likely qualify for both Fast Track Designation and Breakthrough Therapy Designation. Final decisions regarding Fast Track Designation and Breakthrough Therapy Designation are made after the applications for the designations are received.

Additional Comments:

In the SAP for the study SIOPEL 6, it is stated that "Interim analyses will be conducted at 1/3 and 2/3 of process time, i.e., after 34 and 68 patients are evaluable for the primary endpoint". However, we noticed the following in the meeting package (page 79): "Interim evaluations of chemotherapy efficacy were completed after every 20 patients, and an Independent Data Monitoring Committee (IDMC) reviewed the results. Early termination was considered if concerns of chemotherapy efficacy arose in either treatment group. At all of its meetings, the IDMC recommended to continue the trial as planned". In your NDA submission, clarify whether the interim analyses were conducted according to the SAP.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that marketing applications for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA determines to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020 contain reports of molecularly targeted pediatric cancer investigations. These molecularly targeted pediatric cancer investigations must be "designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling" (section 505B(a)(3)). Applications for drugs or biological products for which orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2)) and will be required to conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

Under section 505B(e)(2)(A)(i) of the FD&C Act, you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase 2 (EOP2) meeting, or such other time as agreed

upon with FDA. (In the absence of an EOP2 meeting, refer to the draft guidance below.) The iPSP must contain an outline of the pediatric assessment(s) or molecularly targeted pediatric cancer investigation(s) that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation; and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry, *Applications Covered by Section 505(b)(2)* (October 1999), available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at http://www.regulations.gov).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. by trade name(s)).

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s)

in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If FDA has approved one or more pharmaceutically equivalent products in one or more NDA(s) before the date of submission of the original 505(b)(2) application, you must identify one such pharmaceutically equivalent product as a listed drug (or an additional listed drug) relied upon (see 21 CFR 314.50(i)(1)(i)(C), 314.54, and 314.125(b)(19); see also 21 CFR 314.101(d)(9)). If you identify a listed drug solely to comply with this regulatory requirement, you must provide an appropriate patent certification or statement for any patents that are listed in the Orange Book for the pharmaceutically equivalent product, but you are not required to establish a "bridge" to justify the scientific appropriateness of reliance on the pharmaceutically equivalent product if it is scientifically unnecessary to support approval.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that is supported by reliance on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature (see table below). In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying the source of supporting information in your annotated labeling, we encourage you to include in your marketing application a summary of the information that supports the application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and effectiveness for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	**Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)**
1. Example: Published literature	*Nonclinical toxicology*

2. Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication A*
3. Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section B*
4.	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a *Study Data Standards Resources* web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER

strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm.

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm.

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, Study Data Standards Resources and the CDER/CBER Position on Use of SI Units for Lab Tests website found at http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. As of **May 5, 2017,** the following submission types: **NDA, ANDA,** and **BLA** must be submitted in eCTD format. **Commercial IND** and **Master File** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: http://www.fda.gov/ectd.

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

PATIENT-FOCUSED ENDPOINTS

An important component of patient-focused drug development is describing the patient's perspective of treatment benefit in labeling based on data from patient-focused outcome measures [e.g., patient-reported outcome (PRO) measures]. Therefore, early in product development, we encourage sponsors to consider incorporating well-defined and reliable patient-focused outcome measures as key efficacy endpoints in clinical trials, when appropriate, and to discuss those measures with the Agency in advance of confirmatory trials. For additional information, refer to FDA's guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Claims*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf.

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/s/

LEYISH MINIE
01/16/2018

SANJEEVE BALASUBRAMANIAM
01/16/2018

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type C
Meeting Category: Phase 3

Meeting Date and Time: March 8, 2011; 11:00AM-12:00PM
Meeting Location: W.O. Bldg. #22 Conf. Room 1421

Application Number: 072877
Product Name: Sodium Thiosulfate
Indication: (b) (4)

Sponsor/Applicant Name: Adherex Technologies, Inc.
Meeting Request Date: November 18, 2010
Meeting BGP date: February 8 and March 1, 2011

Meeting Chair: Patricia Cortazar, M.D.
Meeting Recorder: Kim J. Robertson

FDA ATTENDEES
Robert Justice, M.D., M.S., Director DDOP
Patricia Cortazar, M.D., Lead Medical Officer
Kristen Snyder, M.D., Medical Officer
Kimberly Ringgold, Ph.D., Pharmacology Reviewer
Shenghui Tang, Ph.D, Team Leader, DB 5
Lijun Zhang, Ph.D., Mathematical Statistician, DB 5
Soumya Patel, Pharm.D., Pharmacology Reviewer, OOPD
Kim J. Robertson, Regulatory Project Manager, DDOP

ADHEREX TECHNOCOLOGIES, INC.
(b) (4)

David R. Freyer, DO, MS, Chair of the ACCL0431 Study, Director, LIFE Cancer Survivorship and Transition Program, Children's Center for Cancer & Blood Diseases, Children's Hospital Los Angeles, California
Anne McKay
Joe Quinn
Rosty Raykov
Franck Rousseau, M.D.

1.0 BACKGROUND

The purpose of this meeting is to discuss the regulatory development plan for the submission of a NDA for Sodium Thiosulfate Injection (b) (4) The specific objectives of the meeting are to reach agreement regarding 1) the data required for submission of a NDA for Sodium Thiosulfate (STS) f (b) (4) 2) proposed primary safety and efficacy endpoints of the pivotal and supporting trials and 3) the acceptance of the NDA submission under Section 505(b)(2).

Proposed studies:
The sponsor is proposing to submit data from two Phase 3 clinical studies currently being conducted by pediatric oncology cooperative groups.

Proposed Pivotal Trial:
ACCL0431 is a randomized phase 3 study of STS for the prevention of cisplatin-induced ototoxicity in children conducted by the Children's Oncology Group (COG). The planned enrollment is 120 patients with newly diagnosed hepatoblastoma, germ cell tumor, osteosarcoma, neuroblastoma, medulloblastoma, or other malignancy treated with cisplatin. Patients will be stratified by prior cranial radiation, for those patients without cranial radiation randomization will be further stratified by age (< 5 or ≥ 5 years) and duration of cisplatin infusion (< 2 or ≥ 2 hours). The primary endpoint is the rate of American Speech-Language-Hearing-Association (ASHA) hearing loss determined 4 weeks and 12 months after last course of cisplatin. As of December 2010, 72 children were enrolled.

The table below describes the histological diagnoses of enrolled patients as of September 30, 2010 data cut-off:

HISTOLOGICAL DIAGNOSIS OF MALIGNANCY	Observation Arm	STS arm
Extragonadal germ cell tumors, NOS	1	0
Germ cell cancer, NOS	5	3
Hepatoblastoma	1	2
Medulloblastoma	4	3
Neuroblastoma	7	8
Testicular nonseminomatous germ cell tumor, NOS	2	2
Ovarian nondysgerminomatous germ cell tumor, NOS	0	1
Ovarian dysgerminoma	0	2
Osteosarcoma	5	2
Germinoma of CNS	0	0
Nongerminomatous germ cell tumor of the CNS	0	0
Not yet reported	1	1
TOTAL	26	24

Proposed Supportive Trial:
SIOPEL 6 is a multi-center open label randomized phase 3 trial of the efficacy of STS in reducing ototoxicity in patients receiving cisplatin chemotherapy for standard risk hepatoblastoma conducted by the International Childhood Liver Tumor Strategy Group, SIOPEL under the umbrella of the International Society of Paediatric Oncology (SIOP). The planned enrollment is 100 patients. The primary endpoint is the rate of Brock ≥ grade 1 hearing loss determined after end of trial treatment or at an age of at least 3.5 years whichever is later. As of December 2010, 32 children were enrolled.

The protocol and statistical analysis plan of neither study is included in the submission. According to the submission, both trials are powered to demonstrate otoprotection but not powered to demonstrate potential loss of efficacy. The statistical design will allow monitoring for an excess relapse or treatment failure rate comparing pooled event free survival/overall survival from the two studies.

2.0 DISCUSSION/QUESTIONS

Based on its mechanism of action, sodium thiosulfate may reduce the anticancer activity of platinum-containing compounds. Provide all available data, both non-clinical and clinical, regarding the potential tumor-protective effects of sodium thiosulfate. You will need to convincingly demonstrate that sodium thiosulfate does not reduce the efficacy of cisplatin. If the data are not convincing, non-inferiority trials would be required and neither trial described below would be adequate. Our comments below assume that you are able to demonstrate that sodium thiosulfate does not have tumor-protective effects.

1. Should the ongoing Phase III study being conducted by the Children's' Oncology Group (COG Study ACCL0431) show positive outcomes, will this study, supported by the study conducted by the International Society of Pediatric Oncology (Study SIOPEL 6) be sufficient

for submission of a NDA for STS for the prevention of platinum-induced ototoxicity in pediatric patients?

FDA Preliminary Response:

We are unable to answer this question, since you did not submit the clinical protocols and statistical analysis plans.

Meeting Discussion: No discussions were necessary.

2. Adherex proposes that event free survival (EFS) and overall survival (OS) at the end of treatment be the primary safety endpoint. The NDA would be submitted when the COG Study ACCL0431 is completed. The NDA would include separate analyses of both studies and a pooled analysis of the completed COG Study ACCL0431 and the available data for all children enrolled and evaluable from the SIOPEL 6 study (anticipating SIOPEL 6 will not have completed recruitment at the time of NDA submission).
   Does the Agency agree?

   FDA Preliminary Response:

   The pooled analysis would not be adequate to rule out a tumor-protective effect because of the different diseases, treatment regimens (including cisplatin dose and schedule), and small sample size.

   Meeting Discussion: The Agency reiterated the problems with the pooled analysis. The Agency suggested doing one or more non-inferiority studies in adults to provide some assurance that tumor protection may not be an issue. The sponsor pointed out a number of problems with conducting studies in the adult population.

3. Adherex proposes that the cumulative incidence of hearing loss determined by the percentage of children with a Brock rating of greater than or equal to (≥) Grade 1 hearing loss after the end of treatment is acceptable as the primary efficacy endpoint.
   Does the Agency agree?

   FDA Preliminary Response:

   With the limited information you have submitted we can not make a determination on the acceptability of the study endpoint.

   We have the following concerns:
   - **You have referred in your questions to the Brock grading system to evaluate your primary endpoint. However, your primary study (ACCL0431) plan on page 22 of your submission refers to ASHE grading. The study protocol itself (ACCL0431) (which is not included in your submission) refers to ASHA grading. Please clarify which grading scale you intend to use to measure your primary endpoint.**

- **According to a publication by Bertolini et al evaluating the severity of hearing loss in 120 pediatric oncology patients treated with cisplatin and/or carboplatin only 5% of pediatric patients' audiograms showed toxicity of ≥ Grade 2 (Brock's grading system) before the end of therapy, 11% at early post-therapy evaluations and 44% at more than 2 years of follow-up.[1] If it is true that only 11% of patients demonstrate ≥ Grade 2 toxicity using Brock's grading system at early post-therapy evaluations please explain your rationale for using only the end of treatment is an acceptable primary efficacy endpoint?**
- **Submit the most updated version of both protocols and statistical analysis plans.**

Meeting Discussion: The sponsor explained the difference between the ASHA and Brock grading systems. They proposed to assess the hearing loss in the COG study by both grading systems. The main concern with the European study is that there are no baseline audiograms; therefore, there is no comparison prior to chemotherapy. The Agency stated that pooling data from both studies is not recommended. Both studies would need to be complete at the time of NDA submission and each study will need to be analyzed according to its pre-specified statistical analysis plan. Other analyses would be considered exploratory. The sponsor was referred to the evidence guidance for criteria for when a single study will suffice: (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071590.pdf)**.**

4. Does the Agency agree that the NDA for Sodium Thiosulfate is covered by Section 505(b)(2) and that no preclinical data will be required in the submission?

   FDA Preliminary Response:

   Your plan to submit an NDA via the 505(b)(2) mechanism is acceptable. All nonclinical sections of the label should be adequately addressed in your NDA. You may conduct the nonclinical studies or rely on published literatures and/or the label of a US-approved listed drug for nonclinical information. Please note that in addition to the above, impurities above the threshold defined in ICH Q3(R2) should be qualified or their levels should be adequately justified.

   Meeting Discussion: No discussions were necessary.

ADDITIONAL COMMENT

Trials are only using cisplatin, not carboplatin therefore, the indication would be for reduction in cisplatin-induced ototoxicity.

Meeting Discussion: No discussions were necessary.

Minutes Preparer:

{See appended electronic signature page}

Kim J. Robertson
Project Manager

Meeting Chair:

{See appended electronic signature page}

Patricia Cortazar, M.D.
Clinical Team Leader

Meeting Adjourned:
12:01PM

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KIM J ROBERTSON
03/11/2011
08March11 IND 072877 Sponsor Meeting Minutes Sodium Thiosulfate; Adherex Technologies, Inc.

PATRICIA CORTAZAR
03/11/2011