CLINICAL REVIEW

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Established/Proper Name	paclitaxel protein-bound particles (*nab*-paclitaxel)
(Proposed) Trade Name	ABRAXANE®
Applicant	Celgene Corporation
Dosage Form(s)	n/a
Applicant Proposed Dosing Regimen(s)	n/a
Applicant Proposed Indication(s)/Population(s)	n/a
Recommendation on Regulatory Action	Approve label changes (Section 8.5)
Recommended Indication(s)/Population(s) (if applicable)	n/a

Table of Contents

Table of Tables

Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application

NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

nab-Paclitaxel (also called paclitaxel protein-bound particles, terms used interchangeably throughout this review) is a formulation of a noncrystalline, amorphous form of paclitaxel in an insoluble particle state. Paclitaxel is an anti-microtubule agent that has a broad spectrum of activity against human cancers. *nab*-Paclitaxel was designed to improve the chemotherapeutic effects of paclitaxel by exploiting endogenous transport pathways to deliver higher doses of paclitaxel to tumor tissue and to eliminate the (b) (4) hypersensitivity and other toxicities associated with paclitaxel injections (b) (4)

nab-Paclitaxel is approved in the US and European Union (EU) for the treatment of metastatic breast cancer, pancreatic adenocarcinoma, and non-small cell lung cancer. The approved dosage regimens for the treatment of the approved indications are as follows:

- Metastatic breast cancer: 260 mg/m^2 administered intravenously (IV) over 30 minutes once every 3 weeks;
- Locally advanced or metastatic non-small cell lung cancer: 100 mg/m^2 on Days 1, 8, and 15 in combination with carboplatin (AUC = 6) on Day 1, every 21 days;
- First-line metastatic pancreatic adenocarcinoma: 125 mg/m^2 (followed immediately bine 1000 mg/m) on Days 1, 8, and 15 of each 28-day cycle.

1.2. Conclusions on the Substantial Evidence of Effectiveness

(b) (4)

The Division and Medical Policy Council recommend that Pediatric Exclusivity be granted for paclitaxel protein-bound particles and that relevant information obtained from pediatric studies of *nab*-paclitaxel be incorporated into the Abraxane® package insert. This recommendation is based on the review finding that the Application Holder fairly responded to all of the elements in the Pediatric Written Request (PWR).

1.3. Benefit-Risk Assessment

Not applicable. (b) (4)

1.4. Patient Experience Data

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

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

2. Therapeutic Context

2.1. Analysis of Condition and Current Treatment Options

Neuroblastoma is a malignant embryonal tumor of the neural crest cells and is the most common tumor in children younger than 1 year old worldwide. The 5-year survival rate for children aged 0 to 14 years is 80% in the US. The treatment options for neuroblastoma include surgery, particularly for low-risk tumors, multi-agent chemotherapy, and radiation therapy. For high-risk patients, standard treatment generally consists of induction chemotherapy to achieve remission, surgery, and radiotherapy for local control, high-dose chemotherapy with autologous hematopoietic stem-cell rescue, and oral 13-cis-retinoic acid for consolidation and immunotherapy. The risk of local relapse has decreased with modern surgery and radiotherapy practices along with induction chemotherapy; however, in high-risk neuroblastoma, refractory or recurrent disease in bone and bone marrow occurs in most patients. For patient with recurrent disease, the overall survival is less than 20%. Various combinations of cyclophosphamide, doxorubicin, cisplatin, carboplatin, etoposide, topotecan, vincristine, temozolomide, and irinotecan have been used with response rates of 50% to 60%.

Rhabdomyosarcoma is a malignant childhood soft-tissue sarcoma of mesenchymal origin with a 5-year survival rate of 70%. The prognosis depends on the location and disease stage. Treatment is also driven by the primary tumor location and disease stage, which defines the clinical group, and generally includes some combination of pre-operative chemotherapy, surgery, irradiation, and systemic chemotherapy. Standard chemotherapeutic agents include vincristine, dactinomycin, and cyclophosphamide. In the most high-risk disease, more intensive use of multi-agent chemotherapy with other agents is being evaluated in clinical trials. Although rhabdomyosarcoma is sensitive to first-line therapy with a complete response (CR) achieved in the majority of patients, local recurrences still occur in a substantial number of patients. Patients who have gross residual disease following initial surgery in unfavorable sites and those who initially present with metastatic disease more commonly experience relapse. The prognosis has not improved significantly in the last 15 years for the more than 15% of children who present with metastatic rhabdomyosarcoma, and the overall cure rate remains below 30%, despite the development of more intensive therapies.

The second most common bone tumor in the pediatric population is Ewing's sarcoma. Patients who develop recurrent disease within the initial 2 years of life have 5-year survival rates of 7% compared with 30% if recurrent disease occurs after 2 years. The 5-year survival rate in patients with bone metastases (< 20%) is lower than those with lung/pleura metastases (20% to 40%). Treatment of Ewing's sarcoma combines both neoadjuvant and

adjuvant chemotherapy along with local control measures, such as surgery and/or radiation. In patients with localized disease, this approach has improved 5-year survival to $\geq$ 60%. Commonly used therapeutic agents, either as single-agent or primarily in combination, include vincristine, dactinomycin, cyclophosphamide, doxorubicin, etoposide, topotecan, irinotecan, and ifosfamide, while clinical activity has also been observed with paclitaxel and docetaxel.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

nab-Paclitaxel was first approved in the United States (US) on January 07, 2005 for the treatment of breast cancer in adult patients after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated. *nab*-Paclitaxel was also approved in the US on October 11, 2012 for the first line treatment of locally advanced or metastatic non–small cell lung cancer (NSCLC), in combination with carboplatin, in patients who are not candidates for curative surgery or radiation therapy. On September 06, 2013, *nab*-paclitaxel was approved in the US for the first-line treatment of metastatic adenocarcinoma of the pancreas, in combination with gemcitabine.

3.2. Summary of Pre-submission/Submission Regulatory Activity

A Written Request (WR) for nab-paclitaxel was issued by FDA on October 29, 2014. Amendments 1 and 2 to the WR were issued on April 17, 2015 and July 27, 2017, respectively. The recently completed Study ABI-007-PST-001 is part of the WR. On February 21, 2019, Amendment 3 was issued, modifying the WR (b) (4)

3.3. Foreign Regulatory Actions and Marketing History

nab-Paclitaxel is marketed worldwide under the trade name Abraxane® for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) (albumin bound). *nab*-Paclitaxel received centralized marketing authorization in the European Union (EU) on January 11, 2008. As of January 06, 2019, *nab*-paclitaxel is approved in 74 countries worldwide. *nab*-Paclitaxel is approved in 74 countries for the treatment of patients with metastatic breast cancer (MBC), in 65 countries for the first-line treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC), in 70 countries for the first-line treatment of metastatic adenocarcinoma of the pancreas, and in Japan for the treatment of gastric cancer where Taiho Pharmaceutical is the marketing authorization holder (MAH). The MAH has also received approval for *nab*-paclitaxel to be used for the indications of MBC, NSCLC, and pancreatic cancer in the Dominican Republic; the MAH received approval for nab-paclitaxel to be used for the additional indications of NSCLC and pancreatic cancer in Kuwait and the United Arab Emirates.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

An OSI audit was not requested for this supplemental application.

4.2. Product Quality

No new product quality issues were identified during the review of this supplemental application.

4.3. Clinical Microbiology

No new microbiology issues were identified during the review of this supplement application.

4.4. Nonclinical Pharmacology/Toxicology

No new nonclinical pharmacology or toxicology issues were identified during the review of this supplement application

4.5. Clinical Pharmacology

No new clinical pharmacology issues were identified during the review of this supplement application. See Clinical Pharmacology review for more detail.

4.6. Devices and Companion Diagnostic Issues

No companion diagnostic issues were identified during the review of this supplement application

4.7. Consumer Study Reviews

No consumer study review issues were identified during the review of this supplement application

5. Sources of Clinical Data and Review Strategy

This supplement is supported by the results of one dose-finding and dose expansion study, ABI-007-PST-001.

5.1. Table of Clinical Studies

Table 1 Clinical Studies Conducted in Pediatric Patients

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
	Controlled Studies to Support Efficacy and Safety							
ABI-007-PST-001	NCT01962103	Rolling-6 dose escalation design to determine the MTD/RP2D ("Phase 1") followed by dose-expansion cohorts ("Phase 2"	Starting Dose: 120 mg/m2 *nab*-paclitaxel (80% of the weekly investigated adult dosage) *nab*-Paclitaxel was administered IV over approximately 30 minutes, without corticosteroid or antihistamine premedication, weekly on Days 1, 8, and 15 of a 28-day cycle. Following administration, the IV line was flushed with sodium chloride 9 mg/mL (0.9%) solution for injection to ensure administration of the complete dose, according to local practice.	"Phase 1": maximum tolerated dose (MTD) and the Recommended Phase 2 Dose (RP2D) "Phase 2" overall response rate (ORR)	Until disease progression, the patient began a new anticancer treatment, withdrawal of parent/guardian /patient consent/assent, parent/guardian /patient refusal, physician decision, toxicity that could not be managed by dose delay or dose reduction alone	Total: 106 "Phase 1": 64 "Phase 2": 42	"Phase 1": patients was ≥ 6 months to < 18 years of age with recurrent or refractory solid tumors (excluding primary or metastatic brain tumors) that had progressed or did not respond to standard therapy, or for which no standard anticancer therapy existed. "Phase 2": patients ≥ 6 months to ≤ 24 years of age with radiologically documented measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 in several discrete recurrent or refractory solid tumor types (rhabdomyosarcoma, neuroblastoma, and Ewing's sarcoma) who failed up to three lines of treatment.	20 sites in Canada, France, Italy, Spain, Switzerland, United Kingdom, and the United States.

5.2. Review Strategy

The objectives of this review were two-fold: 1) to determine if the Applicant fairly responded to the elements outlined in the Written Request (WR) and 2) (b) (4) To accomplish these objectives, data from the clinical trials submitted with this supplement were comprehensively reviewed. Documentation from previous interactions with FDA regarding (b) (4) the WR, and relevant published literature were also reviewed.

6. Review of Relevant Individual Trials Used to Support Efficacy

(b) (4) In this section, the trial design and results will be briefly summarized.

Compliance with Good Clinical Practices
Study ABI-007-PST-001 was conducted in accordance with International Conference on Harmonization Good Clinical Practice (GCP) guidelines.

Financial Disclosure
This submission contained the required financial disclosure information for the clinical investigators who participated in Study ABI-007-PST-001. In accordance with 21 CFR 54, the Applicant submitted FDA form 3454 and a list of clinical investigators/subinvestigators certified to have no financial interests or arrangements that could affect the outcome of the trial.

Data Quality and Integrity
This submission contained sufficient datasets and relevant case report forms. The quality and integrity of the submission were adequate to permit a comprehensive review to describe the trials where the sponsor does not seek a new indication claim.

6.1. ABT-007-PST-001

Title: ""A Phase 1/2, Multicenter, Open-label, Dose-finding Study to Assess the Safety, Tolerability, and Preliminary Efficacy of Weekly *nab*®-Paclitaxel in Pediatric Patients With Recurrent or Refractory Solid Tumors"

6.1.1. Study Design

Overview and Objective

Primary objectives:

- "Phase 1": To determine the pediatric maximum tolerated dose (MTD) and the Recommended Phase 2 Dose (RP2D) and characterize the safety and tolerability of *nab*-paclitaxel administered intravenously (IV) over approximately 30 minutes on Days 1, 8, and 15 of a 28-day cycle in patients ≥ 6 months and < 18 years old with recurrent or refractory solid tumors.

- "Phase 2": To determine the antitumor activity assessed by the overall response rate (ORR) of *nab*-paclitaxel given at the RP2D in patients ≥ 6 months and ≤ 24 years old with several discrete recurrent or refractory solid tumor types including Ewing's sarcoma, neuroblastoma, and rhabdomyosarcoma.

Trial Design

The Phase 1 portion was a rolling-6 dose escalation design to determine the MTD/RP2D. A safety monitoring committee (SMC) made all dose escalation decisions. Approximately 64 patients were planned to be enrolled in this portion of the study; approximately 44 patients into the dose-determining set (DDS) and approximately 20 additional patients at dose levels evaluated as safe by the SMC.

The Phase 2 portion enrolled additional patients at the RP2D (240 mg/m2 in patients weighing > 10 kg and 11.5 mg/kg in patients weighing ≤ 10 kg) into one of three solid tumor groups using a Simon two-stage minimax design for each group of up to 23 patients for the Ewing's sarcoma, neuroblastoma, and rhabdomyosarcoma groups.

Study Endpoints

Efficacy was not the primary objective of this study; however, response data were to be documented in patients who were evaluable for response. Evaluation Criteria in Solid Tumors

(RECIST Version 1.0) was to be used to classify response for patients with measurable disease at study entry and at the end of each cycle.

Statistical Analysis Plan

Descriptive statistics were used to summarize the response data.

Protocol Amendments

The original protocol was amended five times. Most changes were administrative, clarifications or minor edits. Substantial changes are summarized below.

- In the Phase 2 portion, a change to the sample size for the Phase 2 neuroblastoma arm, and modifications of the Simon two-stage minimax design to implement acceptance rates of approximately 20% response rates for the neuroblastoma and rhabdomyosarcoma arms
- The addition of ≥ Grade 2 peripheral neuropathy to the exclusion criteria
- Add specific language to discontinue and not rechallenge treatment for hypersensitivity
- Clarify with specific language to discontinue treatment at the third recurrence for neutropenia events
- Change of the third solid tumors group in Phase 2 from mixed tumors to Ewing's sarcoma
- Harmonization of sample size and Simon two-stage minimax design for the three groups in Phase 2
- Updated assessment of the primary endpoint (ORR) in the Phase 2 neuroblastoma group to use both the RECIST version 1.1 criteria and the Curie score
- Confirmation of CR in Phase 2 neuroblastoma

6.1.2. Study Results

Demographic Characteristics

Phase 1
The demographic characteristics of different dosing cohorts were comparable at baseline; minor differences were considered unlikely to influence overall outcomes. Overall, there were 33 female patients (52%) and 31 male patients (48%). The median (range) age was 12.0 (2 to 17) years and most patients (37 patients [58%]) were aged ≥ 12 years to < 18 years. The majority of patients were white (50 patients [78%]). The median weight of the patients was 41.40 kg. Three patients (5%) reported a race category of "other" because they were not categorized under the designations for race agreed to in the FDA Written Request dated July 27, 2017.

No patients were enrolled who weighed ≤ 10 kg or were under 2 years of age.

Karnofsky performance status score was collected for the 37 patients who were ≥ 12 years of age, with baseline scores of 100 (13 patients [20%]), 90 (10 patients [16%]), 80 (6 patients [9%]), and 70 (8 patients [13%]). Lansky performance status was collected for the 27 patients who were < 12 years of age, with baseline scores of 100 (15 patients [23%]), 90 (6 patients [9%]), 80 (4 patients [6%]), and 70 (2 patients [3%])

Phase 2

For the Ewing's sarcoma group, 8 patients (57%) were male and 6 patients (43%) were female. The median (range) age was 8.5 (4 to 18) years and most patients (10 patients [71%]) were aged ≥ 2 years to < 12 years. The majority of patients were white (11 patients [79%]). The median weight of the patients was 25.05 kg. No patients were enrolled who weighed ≤ 10 kg or were under 2 years of age. Karnofsky performance status (for patients ≥ 12 years old) baseline scores were 100 (1 patient [7%]), 90 (1 patient [7%]), and 80 (2 patients [14%]). Lansky performance status (for patients < 12 years old) baseline scores were 100 (5 patients [36%]) and 90 (5 patients [36%]).

For the neuroblastoma group, 9 patients (64%) were male and 5 patients (36%) were female. The median (range) age was 7.0 (1 to 15) years and most patients (11 patients [79%]) were aged ≥ 2 years to < 12 years. The majority of patients were white (11 patients [79%]). The median weight of the patients was 21.45 kg. No patients were enrolled who weighed ≤ 10 kg and only 1 patient (7%) under 2 years of age was enrolled. Karnofsky performance status (for patients ≥ 12 years old) baseline score was 100 (2 patients [14%]). Lansky performance status (for patients < 12 years old) baseline scores were 100 (8 patients [57%]), 90 (1 patient [7%]), 80 (2 patients [14%]), and 70 (1 patient [7%]).

For the rhabdomyosarcoma group, 9 patients (64%) were female and 5 patients (36%) were male. The median (range) age was 14.0 (3 to 24) years and most patients (7 patients [50%]) were aged ≥ 12 years to < 18 years. The majority of patients were white (12 patients [86%]). The median weight of the patients was 49.35 kg. No patients were enrolled who weighed ≤ 10 kg or were under 2 years of age. Karnofsky performance status (for patients ≥ 12 years old) baseline scores were 100 (4 patients [29%]), 90 (3 patients [21%]), 80 (1 patient [7%]), and 70 (1 patient [7%]). Lansky performance status (for patients < 12 years old) baseline scores were 100 (3 patients [21%]) and 90 (2 patients [14%])

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

Phase 1

The most frequently reported tumor types were rhabdomyosarcoma (14 patients [22%]), Ewing's sarcoma (13 patients [20%]), neuroblastoma (10 patients [16%]), and osteosarcoma (8 patients [13%]) (Table 14.1.9.1). The median time from initial diagnosis to the first dose of study drug was 21.5 months (range: 4 to 170 months). Disease stage reported at enrollment was Stage II (2 patients [3%]); Stage III (6 patients [9%]); and Stage IV (56 patients [88%]). The majority of patients (54 patients [84%]) had at least one ongoing medical history condition

at study entry. The most frequently reported (in > 15.0% of patients) medical history PTs were anemia (25 patients [39%]) and alopecia (10 patients [16%]). In Phase 1, 62 patients (97%) overall received at least one concomitant medication during the study. The most frequently used (≥ 30.0% of patients) concomitant medications were ondansetron (49 patients [77%]), paracetamol (47 patients [73%]), and Bactrim (42 patients [66%]).

Phase 2

For the Ewing's sarcoma group, the median time from initial diagnosis to the first dose of study drug was 20.4 months (range: 9 to 85 months). Disease stages reported at enrollment were Stage II (1 patient [7%]), Stage III (1 patient [7%]), and Stage IV (12 patients [86%]). The only medical history PT reported in > 2 patients was pain in extremity (3 patients [21%]).

For the neuroblastoma group, the median time from initial diagnosis to the first dose of study drug was 29.4 months (range: 8 to 122 months). Disease stages reported at enrollment were Stage II (1 patient [7%]), Stage III (1 patient [7%]), and Stage IV (12 patients [86%]). The only medical history PTs reported in > 2 patients were anemia (4 patients [29%]) and neutropenia (3 patients [21%]).

For the rhabdomyosarcoma group, the median time from initial diagnosis to the first dose of study drug was 16.9 months (range: 5 to 58 months). Disease stages reported at enrollment were Stage III (3 patient [21%]) and Stage IV (11 patients [79%]). The only medical history PTs reported in > 2 patients were anemia (4 patients [29%]) and alopecia (3 patients [21%]).

Efficacy Results – Primary Endpoint

Phase 1: Efficacy was not the primary endpoint of this part of the study. See below for secondary efficacy endpoints.

Phase 2: (b) (4)

Efficacy Results – Secondary and other relevant endpoints

Phase 1: The secondary endpoint of ORR based on RECIST version 1.1 was (b) (4)

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

Not applicable, only one trial was conducted in pediatric patients.

8. Review of Safety

8.1. Safety Review Approach

The data evaluating the safety of nab-paclitaxel for the treatment of pediatric patients are available from Study ABI-007-PST-001 as described in Sections 5 and 6. All patients in the safety population were included in the safety analyses. Adverse events, vital sign measurements, physical examination findings, clinical laboratory information, ECG, LVS assessment, Lansky/Karnofsky performance status, and concomitant medications and procedures were tabulated and summarized by the sponsor by study phase, dose level, and tumor group, as appropriate.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

In general, exposure to *nab*-paclitaxel increased with increasing dose in pediatric patients and the weekly drug exposures were higher than those seen in adult patients. At the RP2D of 240 mg/m2, the mean CL of *nab*-paclitaxel was 19.1 L/h and the mean t½ was 13.5 hours. The exposure-safety analysis showed a dose-dependent increase in the probability of safety endpoints (any drug-related AE > Grade 2 in Cycle 1 and neutropenia > Grade 2 in Cycle 1). However, higher exposure parameters were not associated with higher probabilities of safety endpoints (saturable elimination at higher doses). Please see the Clinical Pharmacology Review for more detail.

8.2.2. Relevant characteristics of the safety population

The demographics for the safety and efficacy populations are the same (see Section 6.1.2).

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

None.

8.3.2. Categorization of Adverse Events

Adverse events observed during both Phase 1 and Phase 2 were coded using the Medical Dictionary for Regulatory Activities (MedDRA) classification system. The severity of the AEs was graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 whenever possible. Adverse events were analyzed in terms of treatment-emergent AEs (TEAEs). Treatment emergent AEs were defined as any AEs that began or worsened in grade after the start of IP through 28 days after the last dose. The frequency of AEs was tabulated by MedDRA system organ class and preferred term.

Adverse events were also summarized by NCI CTCAE grade. If a patient reported the same AE more than once, the event with the maximum grade was tabulated in "by grade" tables. The incidence of serious AEs (SAEs) and AEs that lead to dose reduction, drug interruption, or discontinuation of study drug was summarized. Adverse events of special interest based on the Risk Management Plan were also summarized. Listings of patients who discontinued study drug due to an AE, patients with SAEs, and deaths were presented.

8.4. Safety Results

8.4.1. Deaths

There were no treatment emergent adverse events leading to death. All deaths were due to progressive disease.

8.4.2. Serious Adverse Events

Treatment-emergent serious adverse events (SAEs) reported were similar to the SAEs reported in adults.

- In the Phase 1 portion, serious TEAEs were reported in 35 patients (55%), with the majority of events being reported in $\leq$ 2 patients. Serious TEAEs reported in > 2 patients were pyrexia (11 patients [17%]), back pain (3 patients [5%]), edema peripheral (3 patients [5%]), and vomiting (3 patients [5%]).

- In patients with Ewing's sarcoma in the Phase 2 portion, serious TEAEs were reported in 6 patients (43%), with the majority of events being reported in 1 patient each. Serious TEAEs reported in > 1 patient were pneumothorax (2 patients [14%]) and pyrexia (2 patients [14%]).
- In patients with neuroblastoma in the Phase 2 portion, serious TEAEs were reported in 6 patients (43%) with most events being reported in 1 patient. Serious TEAEs reported in > 1 patient were general physical health deterioration (2 patients [14%]), pyrexia (2 patients [14%]), and thrombocytopenia (2 patients [14%]).
- In patients with rhabdomyosarcoma in the Phase 2 portion, serious TEAEs were reported in 11 patients (79%), with most events being reported in 1 patient each., Serious TEAEs reported in > 1 patient were febrile neutropenia (3 patients [21%]), general physical health deterioration (2 patients [14%]), headache (2 patients [14%]), and pyrexia (2 patients [14%]).

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Treatment emergent AEs leading to treatment discontinuation, dose reduction and dose discontinuation in the pediatric population are consistent with the TEAEs leading to treatment discontinuation in adults.

- The only TEAE leading to dose reduction was reported in more than one patient was neutropenia.
- The only TEAEs leading to study drug interruption in more than one patient was neutropenia and pyrexia.
- The only TEAE leading to study drug discontinuation in reported in > 1 patients with pneumothorax (Ewing's sarcoma) and peripheral neuropathy (rhabdomyosarcoma)

8.4.4. Significant Adverse Events

The safety monitoring committee (SMC) unanimously declared the 270 mg/m2 dose level as the non-tolerable dose and the 240 mg/m2 dose level was selected as the RP2D. Seven patients were enrolled in the 270 mg/m2 dose level; 1 DLT of Grade 4 neutropenia lasting > 7 days was observed in this cohort and 5 patients developed Grade 4 neutropenia in Cycle 1. In addition, Grade 3 peripheral neuropathies were seen at this dose level and more skin toxicities were reported than in patients who received 240 mg/m2 and lower dose levels. It was also noted that at the time of the SMC meeting, only 1 of 4 patients who were enrolled in the 270 mg/m2 cohort and had continued to Cycle 2 remained at that dose; the other 3 patients had dose reductions to 240 mg/m2 or even 210 mg/m2. These safety data led the SMC to declare that the 270 mg/m2 dose was too toxic and to select the 240 mg/m2 dose of *nab*-paclitaxel for use in the Phase 2 portion of the study.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

All patients experienced at least one treatment emergent adverse events (TEAE). The most frequently reported TEAEs in the Phase 1 portion were neutropenia (38 patients [59%]), anemia (37 patients [58%]), pyrexia (32 patients [50%])and leukopenia (23 patients [36%]). Similar results were seen across cohorts in the Phase 2 portion.

The most frequently reports adverse events of special interest in the Phase 1 portion were general myelosuppression (51 patients [80%]), neutropenia (39 patients [61%]), anemia (37 patients [58%]), gastrointestinal events (36 patients [56%]), hypersensitivity reactions (35 patients [55%]), and skin toxicity (29 patients [45%]). Similar results were seen across cohorts in the Phase 2 portion.

8.4.6. Laboratory Findings

Abnormalities in hematology and chemistry parameters were infrequent with no related SAEs reported. There were no clinically meaningful changes in vital signs, ECGs, LVSF, or performance status during the study.

8.4.7. Vital Signs

There were no clinically relevant changes in physical examination abnormalities reported.

8.4.8. Electrocardiograms (ECGs)

There were no clinically meaningful changes in ECGs or left ventricular shortening fraction during the study.

8.4.9. Immunogenicity

Immunogenicity studies were not included in this application.

8.5. Analysis of Submission-Specific Safety Issues

No submission-specific safety issues were identified in this review.

8.6. Safety Analyses by Demographic Subgroups

The incidence rates of TEAEs were similar between the ≥ 2 years to < 12 years and ≥ 12 years to < 18 years groups.

8.7. Specific Safety Studies/Clinical Trials

No additional specific safety studies were included in this application.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

Human carcinogenicity studies were not included in this application.

8.8.2. Human Reproduction and Pregnancy

No pregnancies were reported in female patients of childbearing potential during the study.

8.8.3. Pediatrics and Assessment of Effects on Growth

See pertinent sections of this review; all data reviewed as part of this application is based on pediatric patients.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Overdose has not been reported in pediatric patients.

9. Advisory Committee Meeting and Other External Consultations

The Division did not obtain the advice of the Oncologic Drug Advisory Committee (ODAC) for this application as no new indication is being reviewed.

10. Labeling Recommendations

Labeling review was ongoing at the time this clinical/statistical review was completed. Please see the package insert for nab-paclitaxel.

At the time of this review, the following language is proposed for Section 8.4:

> Safety and effectiveness in pediatric patients have not been established. Pharmacokinetics, safety, and antitumor activity of ABRAXANE were assessed in an open-label, dose escalation, dose expansion study (NCT01962103) in 96 pediatric patients aged 1.4 to < 17 years with recurrent or refractory pediatric solid tumors. The maximum tolerated dose (MTD) normalized for body surface area (BSA) was lower in pediatric patients compared to adults. No new safety signals were observed in pediatric patients across these studies.
>
> Paclitaxel protein-bound exposures normalized by dose were higher in 96 pediatric patients (aged 1.4 to < 17 years) as compared to those in adults.

11. Risk Evaluation and Mitigation Strategies (REMS)

A Risk Evaluation and Mitigation Strategy (REMS) was deemed not necessary as no new indication is being reviewed.

12. Postmarketing Requirements and Commitments

None.

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/s/

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12/05/2019 02:18:23 PM

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