EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Amsterdam, 30 January 2020
EMA/116095/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Abraxane

International non-proprietary name: paclitaxel

Procedure No. EMEA/H/C/000778/II/0097

Note

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

Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure:	16 Sep 2019		☐
☐	CHMP Rapporteur Assessment Report	21 Oct 2019	29 Aug 2019	☐
☐	CHMP members comments	04 Nov 2019	04 Nov 2019	☐
☐	Updated CHMP Rapporteur Assessment Report	07 Nov 2019	06 Nov 2019	☐
☐	Request for supplementary information (RSI)	14 Nov 2019	14 Nov 2019	☐
☐	CHMP Rapporteur Assessment Report	15 Jan 2020	15 Jan 2020	☐
☐	CHMP members comments	20 Jan 2020	n/a	
☐	Updated CHMP Rapporteur Assessment Report	23 Jan 2020	n/a	
☒	Opinion	30 Jan 2020	30 Jan 2020	

[1] Tick the box corresponding to the applicable step – do not delete any of the steps. If not applicable, add n/a instead of the date.

[2] Criteria for PRAC plenary discussion: proposal for update of SmPC/PL, introduction of or changes to imposed conditions or additional risk minimisation measures (except for generics aligning with the originator medicinal product), substantial changes to the pharmacovigilance plan (relating to additional pharmacovigilance activities, except for generics adapting aligning with the originator medicinal product), substantial disagreement between the Rapporteur and other PRAC members, at the request of the Rapporteur, any other PRAC member, the Chair or EMA.

Criteria for CHMP plenary discussion: substantial disagreement between the Rapporteur and other CHMP members and/or at the request of the Rapporteur or the Chair.

Declarations

☒ The assessor confirms that reference to ongoing assessments or development plans for other products is not included in this assessment report, including in the Product Information, if any.

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List of abbreviations

AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
AUC	area under the blood concentration-time curve
AUC_t	area under the plasma concentration-time curve from time zero to the last quantifiable time point
AUC_{24}	area under the plasma concentration-time curve from time zero to 24 hours
AUC_∞	area under the plasma concentration-time curve from time zero extrapolated to infinity
BLQ	below the limit of quantitation
CI	confidence interval
CL	clearance
C_{max}	peak (maximum) whole blood concentration
CNS	central nervous system
CR	complete response
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DCR	disease control rate
DDS	dose-determining set
DLT	dose-limiting toxicity
DOR	duration of response
ECG	electrocardiogram
Ecrf	electronic case report form
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HSCT	hematopoietic stem cell transplantation
HUS	haemolytic-uremic syndrome
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IP	investigational product
IV	intravenous
IRB	Institutional Review Board
IRT	integrated response technology
LVSF	left ventricular shortening fraction
MedDRA	Medical Dictionary for Regulatory Activities
MIBG	^{123}I-metaiodobenzylguanidine
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MUGA	multi-gated acquisition
NCI	National Cancer Institute
ORR	overall response rate
PD	progressive disease
PFS	progression-free survival
PK	pharmacokinetic
PR	partial response
PT	preferred term
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase 2 Dose
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SMC	Safety Monitoring Committee
SMQ	standardised MedDRA query
SOC	system organ class
λ_z	terminal phase rate constant

TEAE	treatment-emergent adverse event
$t_{1/2}$	terminal elimination half-life
t_{max}	time to maximum concentration
ULN	upper limit of normal
US	United States
V_{ss}	volume of distribution at the steady state
V_z	volume of distribution based on area
WBC	white blood cell
WHO	World Health Organization
WHODD	World Health Organization drug dictionary

1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Celgene Europe BV submitted to the European Medicines Agency on 28 June 2019 an application for a variation.

The following changes were proposed:

Variation requested		Type	Annexes affected
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I, II, IIIA and IIIB

Update of sections 4.2, 4.5, 4.8, 5.1 and 5.2 of the SmPC based on the results of study ABI-007-PST-001. This was a phase 1/2, multicenter, open-label, dose-finding study to assess the safety, tolerability and efficacy of weekly Abraxane in paediatric patients with recurrent or refractory solid tumours, listed in the PIP, submitted in order to fulfil Article 46. The Package Leaflet is updated accordingly. The MAH took the opportunity to make minor editorial changes to the Annex II and to the Labelling.

The requested variation proposed amendments to the Summary of Product Characteristics.

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0257/2018 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0257/2018 was completed.

The PDCO issued an opinion on compliance for the PIP P/0257/2018.

2. Overall conclusion and impact on the benefit/risk balance

The variation to update the Summary of Product Characteristics with new information on pharmacokinetics, efficacy, and safety in the paediatric population is recommended for approval.

The benefit-risk balance of Abraxane remains positive.

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation accepted		Type	Annexes affected
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I, II, IIIA and IIIB

Update of sections 4.2, 4.5, 4.8, 5.1 and 5.2 of the SmPC based on the results of study ABI-007-PST-001. This was a phase 1/2, multicenter, open-label, dose-finding study to assess the safety, tolerability and efficacy of weekly abraxane in paediatric patients with recurrent or refractory solid tumours, listed in the PIP, submitted in order to fulfil Article 46. The Package Leaflet is updated accordingly. The MAH took the opportunity to make minor editorial changes to the Annex II and to the Labelling.

☒ is recommended for approval.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I, II, IIIA and IIIB are recommended.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0257/2018 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

Annex: Rapporteur's assessment comments on the type II variation

4. Scientific discussion

4.1. Introduction

About the product

nab-Paclitaxel (also called Abraxane® or ABI-007) is a protein 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 the tumour and to eliminate the solvent (Cremophor® EL)-related hypersensitivity and other toxicities associated with paclitaxel injections amongst others due to the ethanol vehicle.

In adults, *nab*-paclitaxel is approved in the following indications:

- As monotherapy for the treatment of metastatic breast cancer in adult patients who have failed first-line treatment for metastatic disease and for whom standard, anthracycline containing therapy is not indicated.
  - o Posology: 260 mg/m2 IV over 30 minutes once every 3 weeks
- In combination with gemcitabine is indicated for the first-line treatment of adult patients with metastatic adenocarcinoma of the pancreas.
  - o Posology: 125 mg/m2 (followed immediately by gemcitabine 1000 mg/m2) on Days 1, 8, and 15 of each 28-day cycle
- In combination with carboplatin is indicated for the first-line treatment of non-small cell lung cancer in adult patients who are not candidates for potentially curative surgery and/or radiation therapy.
  - o Posology: 100 mg/m2 on Days 1, 8, and 15 in combination with carboplatin (AUC = 6) on Day 1, every 21 days

Safety experiences in Phase 1 studies in adults with advanced solid tumours showed the following dose-limiting toxicities (DLTs): keratitis, blurred vision, sensory neuropathy, stomatitis, and Grade 4 neutropaenia. In general, haematologic toxicities were not important dose-limiting events; no life-threatening neutropaenic infections and no Grade 4 anaemia or thrombocytopaenia were reported. The most frequently (>50%) reported toxicities were all expected for this therapeutic drug class, namely, fatigue, myalgia, nausea, alopecia, and stomatitis. The most common clinically significant adverse reactions associated with the use of *nab*-paclitaxel are neutropaenia, peripheral neuropathy, arthralgia/myalgia, and gastrointestinal disorders.

Regulatory background

The Paediatric Investigational Plan (PIP) of *nab*-paclitaxel which included three clinical studies in the treatment of paediatric solid malignant tumour and chemotherapy-naïve metastatic melanoma (EMEA-011308-PIP01-12) was approved by EMA on 26 Apr 2013 (P/0116/2013). The PIP was twice modified with key changes noted below:

- Modification 01 (EMEA-001308-PIP01-12-M01) – removed melanoma from PIP indication following results of the Phase 3 CA033 melanoma study in adults and deferred the PIP completion date to December 2024;
- Modification 02 (EMEA-001308-PIP01-12-M02) – results of ABI-007-PST-001 (PST-001) demonstrated a lack of efficacy of *nab*-paclitaxel monotherapy in paediatric population. Based on these results, PDCO agreed to stop further paediatric development due to lack of efficacy. As a

consequence, the development of paediatric-dose vials and two subsequent paediatric clinical studies were removed from the PIP.

Following the approval of the PIP modification 02, a request for a full compliance check on the PIP was submitted to EMA on 16 Jul 2018. The PDCO confirmed that the available evidence can be considered conclusive enough to stop the paediatric development and that all paediatric commitments for *nab*-paclitaxel have been fulfilled.

The current Type II variation application is an update of the EU SmPC to reflect the results of the ABI-007-PST-001 study conducted in compliance with the agreed PIP.

4.2. Clinical pharmacology aspects

4.2.1. Introduction

The ABI-007-PST-001 study was a Phase 1/2 study that was designed to establish the recommended dose of nab-paclitaxel in the paediatric population and to determine its clinical activity in three distinct paediatric solid tumor types (Ewing's sarcoma, neuroblastoma, and rhabdomyosarcoma). Patients in the study were 1 to 24 years old, with most patients in the age categories of 2 to 11 years (50%) and 12 to 17 years (46%).

4.2.2. Methods – analysis of data submitted

Pharmacokinetics

The ABI-007-PST-001 study consisted of two phases. Phase 1 portion of the study was a rolling, 6 dose levels, escalation part designed to determine the maximum tolerated dose (MTD) /recommended phase II dose (RP2D), safety, tolerability, and pharmacokinetics (PK) parameters of nab-paclitaxel in paediatric patients with recurrent or refractory solid tumors who progressed on standard therapy or for whom no standard anticancer therapy exists.

Six dose levels of nab-paclitaxel were tested in Phase 1: 120, 150, 180, 210, 240, and 270 mg/m^2, with a total of 64 patients enrolled in these 6 cohorts. Of these, 37 patients constituted the dose-determining set (DDS) (including 6 patients in each dose level except for 270 mg/m^2, which included 7 patients). Dense PK sampling was performed.

The Phase 2 portion enrolled additional patients at the RP2D (240 mg/m^2 in patients weighing > 10 kg and 11.5 mg/kg in patients weighing $\leq$ 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. During phase II sparse sampling for PK was performed.

The PK of nab-paclitaxel in paediatric patients with solid tumors was examined using non-compartmental analysis based on dense samples collection during phase I. Pharmacokinetic parameters included the maximum observed concentration in blood (Cmax), area under the blood concentration-time curve (AUC), clearance (CL), and volume of distribution (Vss). If the data allowed, main PK parameters (CL and Vss) were summarized by age group as appropriate (eg, < 2 years, 2 to < 6 years, 6 to < 12 years, and 12 to $\leq$ 24 years). Data from the Phase 1 and 2 portions were analyzed together for this endpoint.

Population PK analysis was performed using nonlinear mixed effect modeling. Concentration data obtained from both dense and sparse PK sampling were combined to develop the population pharmacokinetic model (popPK). Effects of age and body size on nab-paclitaxel PK were assessed. Other relevant covariates for the main PK parameters were also identified. The between-patient

variability for PK parameters was estimated, as appropriate. The relationship between systemic drug exposure and selected efficacy and toxicity endpoints could be explored.

The popPK model was developed with NONMEM software using standard methodology in three stages, including structural model selection, covariate analysis, and model evaluation with goodness-of-fit criteria, visual predictive checks, and the bootstrap resampling approach.

CHMP comment:

The planned non-compartmental and POP-PK methods to establish PK are in general acceptable. However, no validation, bioanalytical, statistical or POP-PK reports were submitted. The applicant should submit these reports, before definite conclusions can be drawn **(LoQ, OC)**

4.2.3. Results

<u>Phase I (non-compartmental analysis):</u>

Individual concentration values of paclitaxel were reported and summarized with descriptive statistics. Mean whole blood concentration-time profiles of paclitaxel for Phase 1, following a single IV infusion of nab-paclitaxel over approximately 30 minutes, are presented on semi-logarithmic and linear scales (top and bottom, respectively) in the figure below.

Figure 1 **Mean (+SD) Whole Blood Concentration-time Profiles of Paclitaxel Following a Single 30-minute IV Infusion of nab-Paclitaxel in Pediatric Patients With Recurrent or Refractory Solid Tumors (Semi-logarithmic and Linear Plots)** — **Cycle 1, Day 1 (Phase 1)**
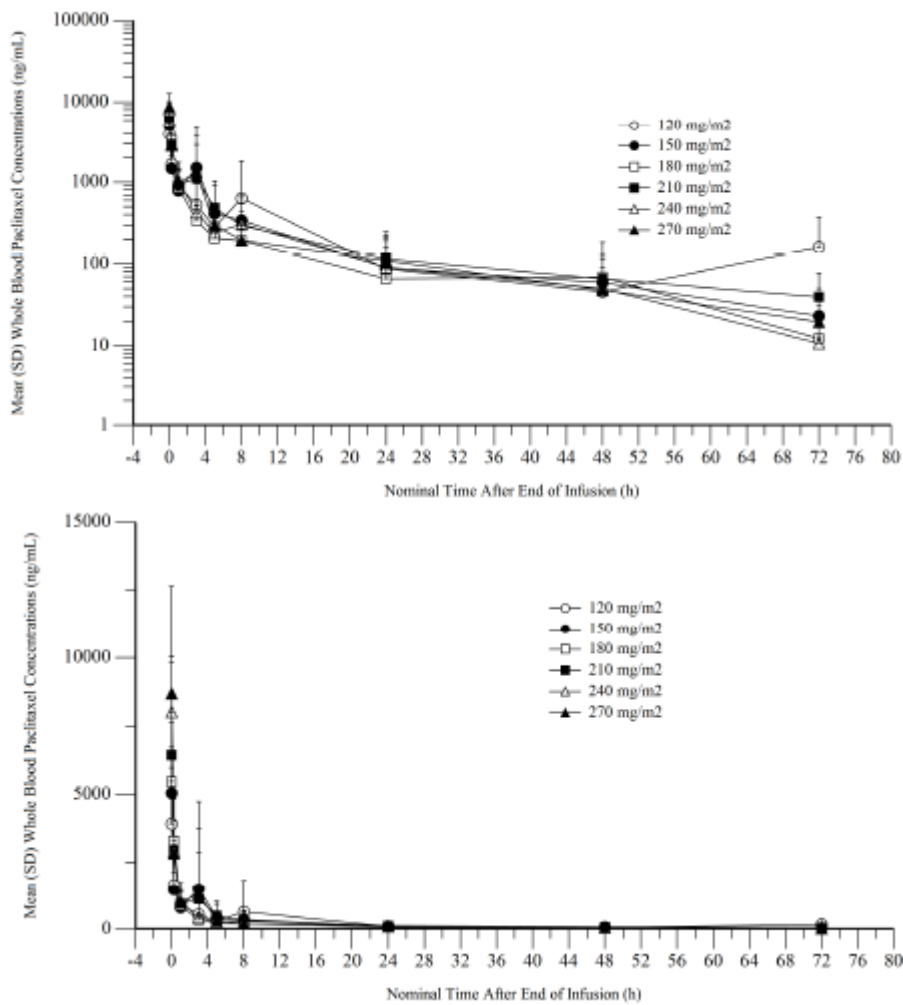
After a single 30-minute IV infusion of nab-paclitaxel in pediatric patients, mean whole blood concentration-time profiles of paclitaxel were characterized by an initial rapid decline followed by slower multi-exponential declines and remained above the LLOQ (5 ng/mL) of the assay up to the last sample collected (ie, the planned last was 24 hours for patients 2 to < 6 years and 72 hours for patients >= 6 years). All pediatric patients had solid recurrent or refractory tumors. Descriptive statistics of non-compartmental PK parameters of paclitaxel in whole blood are presented in the table below.

Table 1 Summary Pharmacokinetic Parameters of Whole Blood Paclitaxel Following a Single 30-minute IV Infusion of nab-Paclitaxel in Pediatric Patients With Recurrent or Refractory Solid Tumors — Cycle 1, Day 1 (Phase 1)

Geometric Mean (GeoCV%); N	Age Group	nab-Paclitaxel Dose 120 mg/m²	150 mg/m²	180 mg/m²	210 mg/m²	240 mg/m²	270 mg/m²
N		16	8	14	11	8	7
Dose (mg)[a]	Overall	156 (24.8); 13	224 (25.5); 7	213 (27.6); 12	265 (44.2); 9	295 (33.0);7	389 (14.4); 6
	2 - <6	60 (NC); 1	102 (NC); 1	153 (NC); 1	160 (16.4); 3	125 (NC); 1	N/A (N/A)
	6 - <12	140 (19.3); 4	NA (NA)	163 (13.1); 5	180 (0.0); 2	220 (NC); 1	319 (6.0); 2
	12 - ≤18	176 (10.6); 8	244 (8.6); 6	264 (11.3); 6	387 (6.5); 4	344 (14.6); 5	424 (3.2); 4
AUCt (ng.h/mL)		7844 (73.4); 13	10374 (91.8); 7	9690 (37.1); 12	11817 (64.0); 9	12706 (29.2); 7	11245 (22.6); 6
AUC24 (ng.h/mL)		6392 (79.0); 13	8944 (85.9); 7	8365 (37.7); 12	10932 (66.3); 8	11167 (27.4); 7	9768 (20.7); 6
AUC∞ (ng.h/mL)		8867 (85.4); 9	11992 (99.8); 6	10087 (38.4); 10	14361 (72.1); 6	14242 (29.2); 6	12424 (28.5); 5
Cmax (ng/mL)		3488 (73.7); 13	5468 (38.0); 7	5597 (33.4); 12	5616 (63.9); 9	7831 (23.1); 7	8078 (41.5); 6
tmax[b] (h)		0.48 (0.47, 1.52); 13	0.47 (0.47, 3.58); 7	0.48 (0.47, 0.78); 12	0.47 (0.47, 0.75); 9	0.47 (0.47, 0.52); 7	0.47 (0.47, 0.52); 6
tlast[b] (h)		48.50 (5.62, 72.90); 16	59.48 (21.68, 74.88); 8	47.45 (22.42, 72.42); 14	47.92 (21.63, 73.58); 11	47.75 (24.50, 72.67); 8	48.50 (46.58, 72.50); 7
t½ (h)		11.0 (101); 11	17.9 (13.4); 6	11.8 (38.6); 11	11.3 (52.3); 7	13.5 (41.9); 7	20.5 (43.6); 6
CL (L/h)		16.1 (75.6); 9	20.3 (101); 6	20.9 (39.9); 10	15.4 (25.4); 6	19.1 (67.4); 6	31.9 (35.0); 5
Vss (L)		127 (145); 9	266 (78.3); 6	146 (106); 10	89.8 (45.1); 6	175 (117); 6	446 (17.6); 5
Vz (L)		253 (154); 9	526 (90.9); 6	345 (73.0); 10	236 (45.0); 6	393 (125); 6	992 (33.9); 5
DOSE-NORMALIZED							
AUC24 (ng*h/mL/[mg])		42.7 (77.4); 13	41.6 (87.0); 7	40.8 (39.7); 12	43.3 (63.6); 8	40.2 (65.4); 7	25.4 (26.1); 6
AUC∞ (ng*h/mL/[mg])		62.0 (75.7); 9	49.2 (101); 6	47.8 (39.8); 10	64.8 (25.4); 6	52.3 (67.4); 6	31.3 (34.9); 5
Cmax (ng/mL/[mg])		23.3 (87.5); 13	25.4 (46.6); 7	27.3 (47.3); 12	23.2 (80.3); 9	28.2 (48.7); 7	21.0 (46.6); 6
BSA-NORMALIZED							
CL (L/h/m²)		13.5 (85.1); 9	12.5 (99.3); 6	17.8 (38.3); 10	14.6 (72.3); 6	16.7 (29.2); 6	21.8 (28.4); 5
Vss (L/m²)		106 (95.3); 9	164 (78.4); 6	124 (82.8); 10	84.9 (49.7); 6	154 (56.5); 6	304 (29.0); 5
Vz (L/m²)		213 (101); 9	323 (90.1); 6	294 (64.7); 10	223 (76.1); 6	344 (61.2); 6	676 (46.7); 5

AUC24 = area under the plasma concentration-time curve from time zero to 24 hours; AUC∞ = area under the plasma concentration-time curve from time zero to infinity; AUCt = area under the plasma concentration-time curve from time zero to the last measurable concentration; BSA = body surface area; CL = clearance; Cmax = peak (maximum) whole blood concentration; GeoCV% = geometric coefficient of variation; IV = intravenous; t½ = terminal phase half-life; tlast = time of last sample collected; Tmax = time to maximum concentration; Vss = volume of distribution at the steady state; Vz = volume of distribution based on area.

[a] Mean (CV%); n.
[b] Median (min, max); N.
Source: PK Report, Appendix A, Section 1.3.1.

The PK of paclitaxel following a single 30-minute infusion of nab-paclitaxel at dose levels of 120 to 270 mg/m² were determined. Mean AUC24 of whole blood paclitaxel ranged from 6392 to 11167 ng.h/mL when dose levels were increased from 120 to 270 mg/m². Mean AUC∞ of whole blood paclitaxel ranged from 8867 to 14361 ng.h/mL when dose levels were increased from 120 to 270 mg/m². The mean peak whole blood concentration of paclitaxel ranged from 3488 to 8078 ng/mL when dose levels were increased from 120 to 270 mg/m². Dose-normalized peak drug exposure values were comparable across the dose range studied; however, dose-normalized total drug exposure values were only comparable across 120 to 240 mg/m² with lower dose-normalized AUC24 and AUC∞ at the 270 ng/m² dose level. These results suggest a less than dose-proportional increase extent of exposure at the highest dose level tested. Median times of peak whole blood paclitaxel concentrations were observed at the end of the 30-minute IV infusion. Whole blood paclitaxel volume of distribution, CL, and half-life remained constant over the 120 to 240 mg/m² dose range, but they increased at the 270 mg/m² dose level. The BSA-normalized whole blood paclitaxel volume of distribution increased at the 270 mg/m² dose level (304 L/m² and 676 L/m² for Vss and Vz, respectively) relative to the 120 to 240 mg/m² dose levels, where paclitaxel mean volume of distribution ranged from 84.9 to 164 L/m² (Vss) and 213 to 344 L/m² (Vz), respectively. Clearance normalized to BSA remained constant over the dose range

studied, with the exception of the highest dose level tested where a slightly higher BSA-normalized CL was observed (ie, 12.5 to 17.8 L/h/m^2 from 120 to 240 mg/m^2 compared to 21.8 L/h/m^2 for 270 mg/m^2). Mean paclitaxel half-life ranged from 11.0 to 17.9 hours over the 120 to 240 mg/m^2 dose levels. At the highest dose level of 270 mg/m^2, paclitaxel half-life was slightly longer (20.5 hours). Taken together, these results are consistent with saturable elimination at higher doses, as well as the deep distribution of paclitaxel that was previously observed in adult patients with advanced or metastatic solid tumors.

CHMP comment:

Pharmacokinetic parameters using a non-compartmental approach have been established in children between 2-18 years. Presented data are in line with the wording proposed in the SPC, section 5.2 However, as validation, bioanalytical, statistical or POP-PK reports are not available at this moment, no definite conclusions on the acceptability of the text proposal can be made.

Phase I and II (POP-PK):

A three-compartment model with saturable elimination resulted in the best quality of fit of whole blood concentration-time profiles of nab-paclitaxel. The population PK model was first customized by including an allometric function on PK parameters to take into account the BSA of patients. A thorough covariate analysis within NONMEM (stepwise forward additive approach) was performed to identify sources of variability in the population. None of the tested covariates were retained in the final population PK model of nab-paclitaxel. Final population PK parameters of nab-paclitaxel for maximum elimination rate from the central compartment (VMEL), concentration in the central compartment at 50% of VMEL (KMEL), volume of distribution of the central compartment (V1), intercompartmental CL between the central compartment and the first peripheral compartment (Q2), volume of distribution of the first peripheral compartment (V2), intercompartmental CL between the central compartment and the second peripheral compartment (Q3), and volume of distribution of the second peripheral compartment (V3) were 31983 (µg/h), 951 (µg/L), 11.8 (L), 22.4 (L/h), 545 (L), 34.8 (L/h), and 45.3 (L), respectively. The estimated allometric exponent for VMEL, Q2, and Q3 was 1.12. The estimated allometric exponent for V1, V2, and V3 was 0.888. As previously described in adults (Chen, 2014), the distribution of paclitaxel to tissues was not only rapid, but also extensive, with deep tissue penetration as demonstrated by the finding that the volume of the two peripheral compartments (545 and 45.3 L) far exceeded the total body water volume (approximately 40 L). The between-subject variability was determined for VMEL, V1 and Q2. Shrinkage associated with VMEL, V1, and Q2 was less than 5%. The final population PK model robustly described nab-paclitaxel concentrations (according to goodness of fit, VPC, and individual observed versus model-predicted concentration-time profiles).

CHMP comment:

The POP-PK results seem to be in agreement with previously submitted population pharmacokinetic (popPK) meta-analysis (ABI-007-CP-001). However, a complete assessment is not possible as the POP-PK report was not submitted. **(LoQ, OC)**

4.2.4. Discussion

The new data on pharmacokinetics from the ABI-007-PST-001 study in the paediatric population is used to update the SmPC, section 5.2. The proposed wording is in general in line with the results. However, as validation, bioanalytical, statistical or POP-PK reports are not available at this moment no definite conclusions can be made and some additional minor changes to the text should be made (see SmPC assessment below).

4.3. Clinical efficacy and safety aspects

4.3.1. Introduction

Paediatric malignancies

Solid tumours account for 60% of all paediatric malignant neoplasms and the spectrum of tumour types observed in children differs substantially from that in adults regarding origin and histologic subtype, etiologic characteristics, responses to treatment, and clinical outcomes. Paediatric malignancies are most commonly of primary central nervous system (CNS) or haematopoietic origin. Specifically, these comprise CNS tumours; neuroblastoma; soft-tissue sarcoma, including rhabdomyosarcoma and non-rhabdomyosarcoma soft tissue tumours; Wilm's tumour; bone tumours such as osteosarcoma and Ewing's sarcoma; retinoblastoma; and miscellaneous tumours such as hepatoblastoma, germ cell tumours, and melanoma.

Although childhood cancer is rare and the 5-year survival rate is relatively high, it is the second leading cause of childhood death in developed countries. Therefore, effective treatment options are needed.

Paediatric taxane use

Among adults, taxanes are one of the most powerful and most commonly used anticancer drugs. They show a wide range of activity in malignancies such as breast, ovarian, and lung cancer. In paediatric oncology, data are quite limited. Clinical trials with paclitaxel or docetaxel show limited efficacy and significant toxicity (neurological, mucous, haematological and dermatologic). In the study protocol the Applicant describes the studies with taxanes in children (Appendix 16.1.1: Table 2 and Table 3). At the time of study initiation, taxanes have been studied in children in nine Phase 1 and five Phase 2 studies. Off label use of docetaxel for Ewing's sarcoma, osteosarcoma, and other recurrent/refractory solid tumours is described.

Rationale for use of nab-*paclitaxel in paediatric tumours*

Although the efficacy and safety of *nab*-paclitaxel have been evaluated in adult patients with various cancers, there had been no human studies on the effects of *nab*-paclitaxel in the paediatric age group prior to the initiation of Study PST-001. The Applicant describes that single agent *nab*-paclitaxel has displayed dose-dependent cytotoxicity in several paediatric solid-tumour cell lines and anti-tumour activity in rhabdomyosarcoma, neuroblastoma, and Ewing's sarcoma mouse xenograft models. According to the Applicant, these preclinical results suggest that *nab*-paclitaxel, delivered at a higher dose than conventional paclitaxel, may achieve clinical benefits in paediatric diseases where conventional paclitaxel is not effective. The Applicant choose to investigate recurrent or refractory solid tumour in the phase 1 portion of the trial and 3 tumour types in the phase 2 portion, i.e. Ewing's sarcoma, neuroblastoma and rhabdomyosarcoma. These tumour types will be described in more detail below.

Although brain tumours such as gliomas and medulloblastomas frequently occur in the paediatric population, patients with brain tumours were not enrolled in Study PST-001 because *nab*-paclitaxel was not shown to cross the blood-brain-barrier and there are no data to indicate that *nab*-paclitaxel has efficacy in primary or metastatic brain tumours. At the time of Study PST-001 initiation, *nab*-paclitaxel was still under consideration for the treatment of melanoma in both the adult and paediatric populations, hence, the inclusion of melanoma in the Phase 1 portion of the study. Since that time, the development of *nab*-paclitaxel for the melanoma indication has been discontinued due to lack of an overall survival benefit with *nab*-paclitaxel compared with the standard of care chemotherapy regimen (dacarbazine). No patients with melanoma were enrolled in study PST-001.

Ewing's sarcoma

Ewing's sarcoma is a rare malignancy that most often presents as an undifferentiated primary bone tumour, but can also present in soft tissue. The peak incidence is between the age of 10 and 20 years (70% of patients are <20 years). Ewing's sarcoma most often arises in the long bones of the extremities and the bones of the pelvis. Primary bone tumours are responsible for 6 percent of all childhood cancers. Although rare, the Ewing's sarcoma represent the second most common primary bone malignancy affecting children and adolescents, after osteosarcoma. Ewing's sarcoma have a tendency towards early dissemination to the lungs, bone, and bone marrow, and are responsive to chemotherapy and radiation therapy. In data derived from the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute (NCI), five-year survival rates rose between 1975 and 2000 in all age groups, although the improvements were mostly observed in younger individuals. Five-year survival rates in those treated between 1993 and 2000 were >65%, whereas for those over the age of 15, they were <50%.

Treatment of Ewing's sarcoma combines both neoadjuvant and adjuvant chemotherapy along with local control measures, such as surgery and/or radiation. Commonly used chemotherapeutic agents, either as single agent or primarily in combination, include vincristine, dactinomycin, cyclophosphamide, doxorubicin, etoposide, topotecan, irinotecan, and ifosfamide. Clinical activity has also been observed with paclitaxel and docetaxel. Ewing's sarcoma was selected for Phase 2 of this study in Protocol Amendment 4, based on consideration of the available preclinical data for Ewing's sarcoma and following review of the patients enrolled at the time in the Phase 1 portion.

Neuroblastoma

Neuroblastomas are malignant embryonal tumours of the neural crest cells and can arise anywhere throughout the sympathetic nervous system. The adrenal gland is the most common primary site (40%), followed by abdominal (25%), thoracic (15%), cervical (5%), and pelvic sympathetic ganglia (5%). Neuroblastoma metastasises to lymph nodes, bone marrow, cortical bone, dura, orbits, liver, and skin, and less frequently to pulmonary and intracranial sites. Neuroblastoma is almost exclusively a disease of children. It is the third most common childhood cancer, after leukaemia and brain tumours, and is the most common solid extracranial tumour in children. The 5-year survival rate for children aged 0 to 14 years is around 80%.

Treatment strategies are based on risk groups, i.e. low-, intermediate-, or high-risk groups. For children with low-risk disease, surgery is the primary treatment modality when complete resection is feasible. For patients with low-risk tumours that cannot be completely resected or which have life-threatening complications, chemotherapy and/or radiation therapy may be required. For children with intermediate-risk disease, a combined-modality approach that includes chemotherapy and surgical resection is standard. In high-risk neuroblastoma, substantial improvements have been seen with aggressive combined modality approaches. These generally include chemotherapy, surgical resection, high dose chemotherapy with stem cell rescue, radiation therapy and biologic/immunologic therapy. These approaches have improved event free survival, but the majority of patients eventually relapse and die of their disease. Whenever possible, children with high-risk neuroblastoma should be enrolled in randomised controlled trials. Regarding chemotherapy, various combinations of cyclophosphamide, doxorubicin, cisplatin, carboplatin, etoposide, topotecan, vincristine, temozolomide, and irinotecan have been used with response rates of 50% to 60%. Preclinical and clinical paediatric studies showed potential utility of chemotherapy with paclitaxel and docetaxel in neuroblastomas.

Rhabdomyosarcoma

Paediatric soft tissue sarcomas are a heterogeneous group of tumours that are presumed to arise from a primitive mesenchymal cell. These tumours can arise in many anatomic locations and can resemble fat, fibrous tissue, and muscle. Rhabdomyosarcoma is the most common soft tissue tumour of childhood and is responsible for approximately one-half of all soft tissue sarcomas in this age group.

However, they are rare, representing only 3-4% of paediatric cancers overall. Two-thirds of cases are diagnosed in children younger than 6 years of age.

The treatment has evolved considerably over the past several decades. Using modern combined modality therapy, over 70% of children with localised disease can now be cured. Modern treatment includes chemotherapy for primary tumour cytoreduction and eradication of both macroscopic and microscopic metastatic disease; surgery, if feasible; and radiation therapy to control microscopic local residual disease. 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 achieved in the majority of patients, local recurrences still occur in a substantial number of patients. The prognosis for patients who recur or progress after first-line therapy is poor. However, patients who remain disease-free after 5 years have a good prognosis and relapses are uncommon; at 10 years, only 9% of these patients have late events. However, patients who have gross residual disease following initial surgery in unfavourable sites and those who initially present with metastatic disease more commonly experience relapse. Both docetaxel and paclitaxel have anti-tumour activity in paediatric rhabdomyosarcoma solid tumour models, as well as in Phase 1 and 2 clinical studies; however, hypersensitivity and neurological reactions, among others, were dose-limiting with paclitaxel, and clinical activity with taxanes was short-lived.

4.3.2. Methods – analysis of data submitted

GCP

According to the Applicant the procedures set out in the study protocol pertaining to the conduct, evaluation, and documentation of this study were designed to ensure that Celgene, its authorised representative, and investigator abided by Good Clinical Practice (GCP), as described in the International Council for Harmonisation (ICH) E6 guideline and in accordance with the general ethical principles outlined in the Declaration of Helsinki. The study received approval from an IRB/IEC prior to commencement. The investigator conducted all aspects of this study in accordance with applicable national, state, and local laws of the pertinent regulatory authorities.

Study design

ABI-007-PST-001 (PST-001) is a phase 1/2 multi-center, open-label, dose-finding study to assess the safety, tolerability, pharmacokinetics (PK), and efficacy of *nab*-paclitaxel administered intravenously (IV) in paediatric patients and consists of 2 phases.

Phase 1 design

The primary objective of the Phase 1 (Figure 1) of the study was to determine the paediatric maximum tolerated dose (MTD) and the Recommended Phase 2 Dose (RP2D) and characterise the safety and tolerability of *nab*-paclitaxel administered IV in patients ≥ 6 months and < 18 years old with recurrent or refractory solid tumours. Phase 1 started with a dose of 120 mg/m^2 weekly, 80% of the maximum weekly dose investigated in adult patients (120 mg/m^2).

Figure 1. Phase 1 study design

Screening
Patients ≥ 6 months and < 18 years old with recurrent/refractory solid tumors
excluding patients with brain tumors/metastasis
N = Approximately 12 - 44 patients in DDS

⇩ Eligibility check

Treatment
Rolling-6 design
nab-Paclitaxel weekly on days 1, 8 and 15 of 28 day cycle starting with 120 mg/m^2
Cohorts of up to 6 patients per dose level, until MTD/RP2D
Treatment until disease progression, death, withdrawal of consent, unacceptable toxicity

⇩ End of treatment

Post treatment follow-up
28 days post-treatment visit
Tumor evaluation according to protocol until progression or new cancer therapy
Survival follow-up for 1 year or until death

DDS = dose-determining set; MTD = maximum tolerated dose; RP2D = Recommended Phase 2 Dose.
Source: Appendix 16.1.1, Figure 1.

Of note, patients younger than 6 months old were excluded from this study. The Applicant described that spontaneous regressions of cancers have been reported, especially in neuroblastoma and renal cell carcinoma, and may occur in the excluded patient population. The current practice is to adopt a conservative observation (wait-and-see) strategy for patients identified at 6 months of age with limited-stage disease. Furthermore, for more advanced paediatric tumours, surgical treatment (in the case of resectable tumours), radiotherapy, or combination of chemotherapy provide good results as first-line treatment. Therefore, it would have been highly unlikely that patients 0 to 6 months old would have been enrolled in the study while a wait-and-see strategy was recommended for limited-stage diseases, and as effective treatment options were available for more advanced tumours; consequently, enrollment in a clinical study would not have been the preferred treatment option according to the Applicant.

The Phase 1 portion was a rolling-6 dose escalation design to determine the MTD/RP2D, safety, tolerability, and PK parameters of *nab*-paclitaxel in paediatric patients with recurrent and refractory solid tumours that progressed on standard therapy or for which no standard anticancer therapy exists. The decision to dose-escalate or to declare an MTD/RP2D was determined by the safety monitoring committee (SMC) when clinical and laboratory safety data for the Dose-determining Set (DDS) of a given cohort was available for review. The SMC also determined the dose appropriate for the RP2D. The members of the SMC included the coordinating principal investigator, each country's coordinating investigator, all investigators who recruited patients into the current cohort, the Celgene Clinical Research Physician, the Celgene Clinical Research Scientist, and the Product Safety Physician, or their corresponding designees.

The DLT assessment period was defined as the first cycle including Cycle 2 Day 1 predose evaluations for patients > 10 kg and the first two cycles including Cycle 3 Day 1 predose evaluations for patients ≤ 10 kg. A DLT was defined as investigational product (IP)-related AE(s) occurring during the DLT assessment period that led to treatment discontinuation or met one of the following criteria:

- Grade 3 or 4 non-haematologic toxicity (excluding transient transaminitis)
- Grade 3 or 4 nausea or vomiting that persisted > 5 days despite maximal anti-emetic treatment
- Grade 4 thrombocytopaenia or anaemia that persisted > 7 days or required transfusion > 7 days

- Grade 3 thrombocytopaenia with bleeding
- Grade 4 uncomplicated neutropaenia lasting > 7 days
- Febrile neutropaenia with confirmed bacterial infection
- Grade 3 hematologic toxicity requiring treatment delay > 21 days

Events that were considered DLTs based on their duration were considered a DLT if they started during the DLT assessment period. Events due to disease progression or to current underlying disease could not be considered DLTs. Events that were not considered related to IP could not be considered DLTs. If a patient experienced a DLT, the dose should have been delayed until resolution of the AE to Common Terminology Criteria for Adverse Events (CTCAE) Grade 1.

Up to 6 patients eligible for the dose-determining set (DDS) were treated at the first dose level, and subsequent dose escalation proceeded using the rolling-6 design. In each cohort, a minimum of 2 patients treated and eligible for the DDS were required to make a dose decision. If no DLT was observed in the first 3 patients eligible for the DDS, the SMC may have decided to escalate the dose for the next cohort. An additional 3 patients (up to a total of 6 per cohort) may have been enrolled at the same dose while awaiting the DDS eligibility of 3 patients and SMC decision. If 1 DLT occurred prior to an SMC dose escalation decision, the cohort was required to enrol 6 patients. If one or fewer patients experienced a DLT in these 6 patients, the dose would be escalated in the next cohort, unless there were other safety considerations by the SMC. If more than 1 DLT occurred within the first dose level, a 1-dose level (100 mg/m2) would be evaluated. If two or more patients in a given cohort experienced a DLT at any time during enrollment, the MTD would have been exceeded and the previous lower dose would be declared the MTD.

Phase 2 design

The primary objective of the Phase 2 (Figure 2) of the study was to determine the antitumour 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 tumour types including Ewing's sarcoma, neuroblastoma, and rhabdomyosarcoma. The Phase 2 portion using a Simon two-stage minimax design was conducted at the RP2D, 240 mg/m2, in patients weighing > 10 kg and 11.5 mg/kg in patients weighing ≤ 10 kg. A Simon two-stage minimax design was used to limit *nab*-paclitaxel exposure to 14 patients in each group without confirmation of some activity (≥ 2 patients) before moving forward with 9 additional patients in each group. The Simon two-stage minimax design was chosen to minimise the number of patients exposed to *nab*-paclitaxel if the true ORR was < 10% and allowed the trial to establish that an ORR > 10% was efficacious.

Figure 2. Phase 2 study design
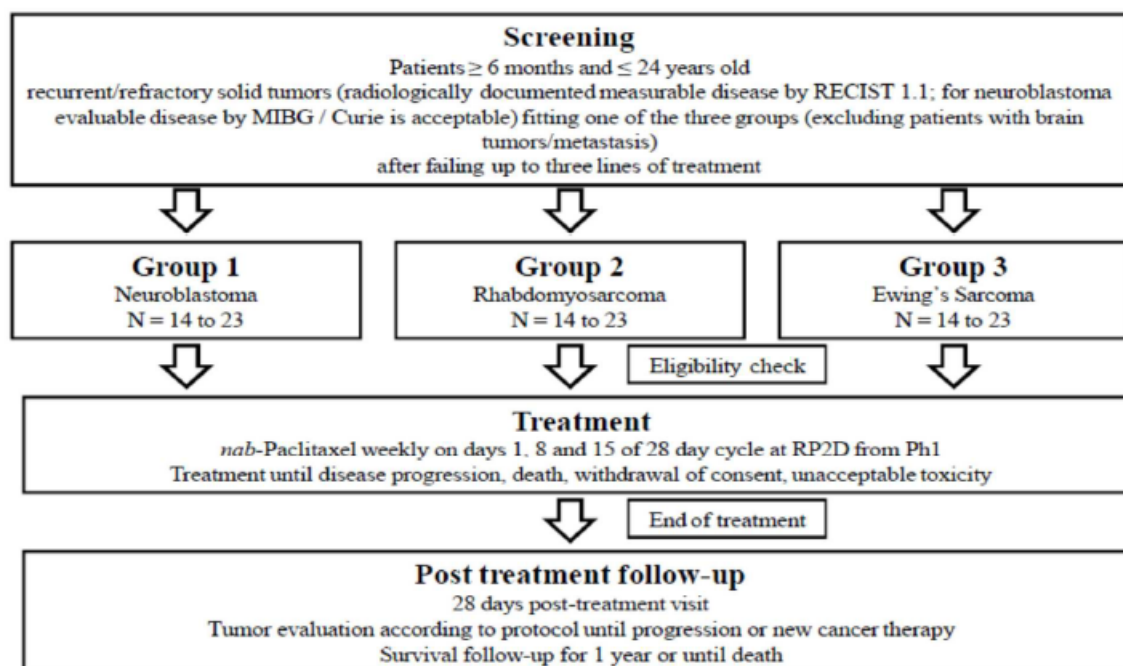
MIBG = ^{123}I-metaiodobenzylguanidine; Ph1 = Phase 1; RECIST = Response Evaluation Criteria in Solid Tumors; RP2D = Recommended Phase 2 Dose.
Source: Appendix 16.1.1, Figure 2.

Study endpoints

The primary endpoint of the Phase 1 portion was the incidence of DLTs and the incidence of treatment-emergent adverse events (TEAEs). Adverse events were analysed in terms of TEAEs, which were defined as any AEs that began or worsened in severity on or after the start of study drug through 28 days after the last dose of study drug. Adverse events were documented according to the NCI CTCAE version 4.0. For the categorisation of the AEs, the MedDRA version 20.0 was used and TEAEs were summarised by SOC and PT.

The primary endpoint of the Phase 2 portion was the investigator-determined Overall Response Rate (ORR), which was the combined incidence of complete response (CR) and partial response (PR), confirmed no less than 4 weeks after the criteria for response was first met, based on Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. In the neuroblastoma group, the ORR was determined by RECIST and/or the Curie scale (MIBG response). If both assessment types had been performed on a given patient across the assessment time points, to be considered as a partial response for the ORR analysis, both methodologies should have shown no worse than stable disease and at least one method should have indicated CR or PR. A response was only considered complete if both methodologies indicated CR.

The secondary endpoints for the Phase 1 portion were:

− PK parameters including the peak (maximum) whole blood concentration (C_{max}), area under the blood concentration-time curve (AUC), clearance (CL), and volume of distribution (V_{ss})
− ORR

The secondary endpoints for the Phase 2 portion were:

− Duration of Response (DOR) in patients with a confirmed objective CR or PR
− Disease Control Rate (DCR) was the percentage of patients with a confirmed objective CR or PR, or stable disease for at least 16 weeks

– Progression-free Survival (PFS) based on investigator assessment of response using RECIST version 1.1 guidelines. PFS was defined as the time from the date of first *nab*-paclitaxel dose until the data a PD was first observed or date of death (any cause), whichever occurred first. In the neuroblastoma group, the PFS was determined by RECIST and/or the Curie scale (MIBG response).
– Survival at 1 year
– The incidence of TEAEs
– Population PK parameters (e.g., CL and volume of distribution); data from the Phase 1 and 2 portions were analysed together for this endpoint

The exploratory endpoints for the entire study were:

– In the Phase 1 portion only, MIBG response using the Curie score in patients with neuroblastoma
– Biomarker analysis prioritised after study completion, as informed by emerging data
– In the Phase 2 portion only, bone marrow biopsy verification of confirmed CR in patients with neuroblastoma

In- and exclusion criteria

Key inclusion criteria

1. The patient was male or female; meeting the following age requirements at the time the informed consent document (and assent form, if applicable) was signed.
   a. Phase 1: patient was ≥ 6 months to < 18 years of age.
   b. Phase 2: patient was ≥ 6 months to ≤ 24 years of age.
2. The patient had a confirmed solid tumour diagnosis according to the following:
   a. Phase 1: patient had a recurrent or refractory solid tumour that has progressed or did not respond to standard therapy, or for which no standard anticancer therapy exists.
   b. Phase 2: patient had radiologically documented measurable disease by RECIST version 1.1 (for neuroblastoma, evaluable disease by MIBG/Curie score was also acceptable) in one of the following tumour types and had failed up to three lines of treatment.
      a. Group 1: neuroblastoma (patients with bone marrow disease only were not permitted).
      b. Group 2: rhabdomyosarcoma.
      c. Group 3: Ewing's sarcoma.
3. The patient had a Lansky/Karnofsky performance status score of ≥ 70%.
4. The patient had adequate serum chemistry levels, evidenced by the following laboratory values:
   a. Aspartate aminotransferase (AST; SGOT), alanine aminotransferase (ALT; SGPT) ≤ 2.5 × upper limit of normal range (ULN).
   b. Total bilirubin ≤ 1.5 × ULN.
   c. Creatinine ≤ 1.5 × ULN.
5. The patient had adequate bone marrow function, evidenced by the following:
   a. Absolute neutrophil count ≥ 1.0 × 109 cells/L.
   b. Platelets ≥ 80 × 109 cells/L (transfusion independent, defined as not having received platelet transfusions within 7 days prior to laboratory sample). In the Phase 2 portion, for patients with known bone marrow involvement, platelets ≥ 50 × 109 cells/L.
   c. Haemoglobin ≥ 8 g/dL (transfusion was permitted to fulfill this criterion).

Key exclusion criteria

1. The patient had a primary brain tumour(s) or brain metastasis (unless metastasis was treated and stable for > 28 days). In patients who were symptomatic, a brain scan was required to exclude metastasis.
2. The patient had ≥ Grade 2 peripheral neuropathy by NCI CTCAE at screening.

3. The patient had received therapeutic dose chemotherapy or radiotherapy ≤ 21 days prior to start of IP.
4. The patient had received maintenance dose chemotherapy (e.g., low dose cyclophosphamide) ≤ 7 days from the first dose of IP.
5. The patient had received any investigational therapy ≤ 28 days prior to start of IP. Investigational therapy was defined as any medicinal product that was not approved in the country of treatment for any indication, adult or paediatric.
6. The patient had received any biological therapy ≤ 7 days prior to the start of IP, or monoclonal antibody ≤ 3 half-lives or 28 days, whichever was shorter, prior to the first dose of IP.
7. The patient had received allogeneic hematopoietic stem cell transplantation (HSCT) ≤ 3 months or autologous HSCT ≤ 21 days prior to start of IP.
8. The patient had major surgery or significant trauma ≤ 14 days prior to start of IP.
9. The patient had not recovered from the acute toxic effects of prior chemotherapy, radiation, or major surgery/significant trauma.
10. The patient had minor surgery ≤ 7 days from the start of study treatment (excluding the placement of central/peripheral lines, skin biopsy).
11. The patient had a known history of stroke, myocardial infarction, peripheral vascular disease, or recent (within 3 months) uncontrolled deep venous thrombosis.
12. The patient had a known history or current diagnosis of human immunodeficiency virus infection, regardless of treatment status.

Treatments

In both the Phase 1 and 2 portions, the treatment was given 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 (reductions were prohibited in Cycle 1 [and Cycle 2 for patients ≤ 10 kg] for the Phase 1 portion only), or the study ended for any reason. *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: Dose escalation

In the Phase 1 portion, up to 6 DDS-eligible patients were assessed at a starting dose of 120 mg/m2 *nab*-paclitaxel (80% of the weekly investigated adult dosage). Preliminary evaluation of the relationship between paclitaxel CL and body surface area (BSA) or weight suggested that BSA or weight had minimal impact on paclitaxel CL in adult patients treated with *nab*-paclitaxel. However, it was unknown if this observation could have been extrapolated from adults to children. Since the BSA-based dosing was more conservative and was the approved dosing approach for adult patients, the *nab*-paclitaxel dose was based on BSA in the paediatric study.

Dose escalation occurred according to example dose levels described in Table 1, using the rolling-6 design. Doses not listed, including intermediate doses or doses higher than 210 mg/m2, may have been tested based on study data and recommendations from the SMC.

For patients who weighed ≤ 10 kg, the dosage was calculated per kg, and *nab*-paclitaxel was administered according to the schedule in Table 1. As it was impractical to accurately calculate BSA in children weighing ≤ 10 kg, the BSA-based dose was converted to mg per kg of weight in these children. The weight-based dose in each cohort was calculated by dividing the total dose at the median BSA (0.41 m2) with the median weight (8.7 kg) for children weighing ≤ 10 kg and aged ≥ 6 months.

In order to ensure their safety, patients weighing ≤ 10 kg received a reduced dose (by one level) in Cycle 1, and if well tolerated (no DLTs) received the full dose starting in Cycle 2.

Table 1. Phase 1 example dose levels

Dose Level[a]	Dose All Cycles	Dose (Patients ≤ 10 kg) Cycle 1	Dose (Patients ≤ 10 kg) Subsequent Cycles
-1	100 mg/m^2	4.0 mg/kg[b]	4.5 mg/kg
1 (Starting dose)	120 mg/m^2	4.5 mg/kg	5.5 mg/kg
2	150 mg/m^2	5.5 mg/kg	7.0 mg/kg
3	180 mg/m^2	7.0 mg/kg	8.5 mg/kg
4	210 mg/m^2	8.5 mg/kg	10.0 mg/kg

[a] Dose levels are also used for dose reductions in both the Phase 1 and 2 portions. Dose level -1 may have been reduced to 80 mg/m^2 and 60 mg/m^2, or 3.0/4.0 mg/kg and 2.0/3.0 mg/kg (Cycle 1/Subsequent Cycles).
[b] 4.0 mg/kg is the calculated equivalent of 80 mg/m^2.
Source: Appendix 16.1.1, Table 7.

Phase 2: Dose expansion

The Phase 2 portion was conducted at the established RP2D at the same schedule as in the Phase 1 portion. On 14 Jan 2016, the SMC determined that the RP2D was 240 mg/m2 in patients weighing > 10 kg and 11.5 mg/kg in patients weighing ≤ 10 kg.

Concomitant medication

Erythropoietin may have been administered at the discretion of the investigator, consistent with institutional guidelines. Granulocyte colony-stimulating factor was not given during the DLT assessment period, but subsequently may have been given according to institutional guidelines for the treatment of neutropaenic fever or infections associated with neutropaenia and for the prevention of febrile neutropaenia in patients with an absolute neutrophil count (ANC) < 500 cells/μL.

Other prohibited concomitant medications and procedures were:

– Radiotherapy, except for palliative purposes for non-target lesions.
– Surgical intervention as anticancer therapy during Cycle 1 required the patient to discontinue from study treatment.
– Administration of 131I-MIBG therapy (e.g., for neuroblastoma treatment).
– Administration of other chemotherapy, immunotherapy, anti-tumour hormonal therapy, investigational therapy, or other anticancer therapy.
– Administration of coumadin or coumarin derivatives was not allowed during this study; low-molecular weight heparin should have been used instead.

In addition, the potential drug-drug interaction precautions contained in the *nab*-paclitaxel prescribing information were applied to this study. Specifically, the metabolism of paclitaxel was catalysed by cytochrome P450 (CYP) isozymes CYP2C8 and CYP3A4. Strong inducers of CYP3A4 and CYP2C8 were prohibited for use from the first dose of IP until permanent discontinuation. Strong inhibitors of CYP3A4 and CYP2C8 should have been avoided whenever possible from the first dose of IP until permanent discontinuation. If possible, patients should have been switched to other medications for the comorbidity prior to starting IP. Caution was recommended when administering *nab*-paclitaxel concomitantly with any substrates or inhibitors of CYP2C8 and CYP3A4. Similarly, drugs, herbal preparations, and/or dietary supplements known to influence the expression of CYP3A (eg, garlic supplements) and/or CYP2C8 should have been used with caution.

Study assessments

Efficacy assessments

Response assessments (tumour evaluations) were performed at screening (up to 28 days before the start of IP) and every 8 weeks (± 5 days) from Cycle 1 Day 1 until disease progression, start of a new anticancer therapy, or withdrawal of consent from the entire study. Evaluation of response was performed using RECIST version 1.1 guidelines. All patients with evidence of objective tumour response (CR or PR) should have had the response confirmed with repeat assessments at the next scheduled scan, but after no less than 4 weeks. Response assessments must have occurred ≥ 6 weeks from Cycle 1 Day 1 to be considered as stable disease for a best response.

In the Phase 2 portion, patients with neuroblastoma were also assessed at screening for response using MIBG evaluation and the Curie score, and then (if evaluable by MIBG scan at screening) every 8 weeks (± 5 days) from Cycle 1 Day 1 until disease progression, start of a new anticancer therapy, or withdrawal of consent from the entire study. Patients without MIBG evaluable lesions at screening should have had a subsequent MIBG scan at suspected progression only. Patients with confirmed objective CR were assessed for bone marrow disease through bone marrow biopsy. If the patient was assessed by both RECIST and MIBG/Curie score, both methodologies must have shown confirmed objective CR.

New anticancer therapies were also collected at the same schedule. New anticancer therapy included (but was not limited to) any systemic or local-regional medication, surgery, radiation, or any other therapy intended to treat the patient's cancer.

Biomarkers

The most recently available tumour tissue sample was optionally collected at the time of study entry. The specific use of these samples was not pre-specified and will be determined in the future based on emerging data and methodological advances. A potential use of these samples was to assess in the paediatric patients in this study the value of markers of response to *nab*-paclitaxel that may be identified in studies of adult patients.

Safety assessments

Safety was to be assessed through clinical evaluations, vital sign measurements, review of laboratory test results, and monitoring of AEs.

Statistical methods

Analysis populations

- **Informed consent/assent population**: all patients who signed informed consent and/or assent, ie, all patients who entered the screening period regardless of later being a screen failure.
- **Enrolled population**: all patients enrolled, ie, all patients who were marked as enrolled in the clinical database regardless of whether they received *nab*-paclitaxel.
- **Safety population**: all patients who received at least one dose of *nab*-paclitaxel.
- **Efficacy evaluable populations**
  - Phase 1 regardless of disease condition: all treated patients who met eligibility criteria, completed at least one dose of *nab*-paclitaxel, and had baseline and either at least one post baseline efficacy assessment or discontinued *nab*-paclitaxel due to disease progression or symptomatic deterioration before a post baseline efficacy assessment could have been conducted. In this instance, efficacy assessment was defined as a radiological assessment of the tumour or tumour assessment by other appropriate means.

- Phase 2 rhabdomyosarcoma and Ewing's sarcoma indications: all treated patients who met eligibility criteria relevant to efficacy, completed at least one dose of *nab*-paclitaxel, had baseline and either at least one post baseline efficacy assessment assessed per RECIST version 1.1 or discontinued *nab*-paclitaxel due to disease progression or symptomatic deterioration before a post baseline efficacy assessment could have been conducted. In this instance, efficacy assessment was defined as a radiological assessment of the tumour or tumour assessment by any means appropriate.

- Phase 2 neuroblastoma indication: one dose of *nab*-paclitaxel, and had either baseline and at least one post baseline efficacy assessment assessed per the RECIST version 1.1 and/or the Curie score (MIBG response) or discontinued *nab*-paclitaxel due to disease progression or symptomatic deterioration before a post baseline efficacy assessment could have been conducted. In this instance, efficacy assessment was defined as a radiological assessment of the tumour or tumour assessment by any appropriate means. The neuroblastoma response criteria using RECIST version 1.1 and/or the Curie score are consistent with the updated International Neuroblastoma Response Criteria guidelines (Park 2017).

- **Dose-determining set**: the primary endpoint for Phase 1, determination of the MTD/RP2D, was performed on the DDS for each dose level tested. In patients weighing > 10 kg, the DDS included all patients who experienced a DLT, or received all 3 weekly doses of *nab*-paclitaxel at the cohort planned dose during Cycle 1 and had adequate safety assessments during the DLT assessment period (Cycle 1, including predose assessments on Cycle 2 Day 1). In patients weighing ≤ 10 kg, the DDS included all patients who experienced a DLT, or received all 6 weekly doses of *nab*-paclitaxel at the cohort planned doses during Cycles 1 and 2 and had adequate safety assessments during the DLT assessment period (Cycles 1 and 2, including predose assessments on Cycle 3 Day 1).

Sample size calculation

During Phase 1, a rolling-6 patient dose escalation design was used to establish the MTD/RP2D, with approximately 64 patients enrolled depending on the number of dose levels required (approximately 44 considered evaluable for determination of the MTD/RP2D and approximately 20 additional patients at dose levels previously evaluated as safe by the SMC). Patients who were ineligible for determination of the MTD/RP2D may have been replaced at the discretion of the sponsor. Additional patients may have been enrolled at dose levels evaluated as safe by the SMC.

In Phase 2, a Simon two-stage minimax design was employed per disease indication with each incorporating the following parameters: 5% significance level, 80% power and an upper and lower boundary of interest of 10% and 28%, respectively, for the ORR. Each of the three disease indications would therefore enroll up to 23 patients across Phase 2 (14 patients in Stage 1 and an additional 9 patients in Stage 2) meaning a maximum total of 69 patients evaluable for the primary endpoint. For purposes of the primary endpoint analysis, the ORR was defined using the maximum likelihood estimator. For each of the three groups in Stage 1, if < 2 of the 14 evaluable patients had a response, then enrollment into that disease indication group would be stopped; otherwise, enrollment would continue as planned in Stage 2. At the final analysis, the study treatment would be concluded with more than a 5% true response rate if ≥ 5 of 23 patients had a response. The Phase 2 target response rate was therefore 21.74% with 80% power and a 10% significance level.

Study conduct

Protocol amendments

The original protocol (dated 13 May 2013) was amended five times. Below the key changes per amendments will be summarised:

– Protocol Amendment 1 (dated 10 Sep 2013)
   • Addition of echocardiogram/MUGA scans for increased cardiotoxicity monitoring
   • Modification of the schedule of events to increase the frequency of 12-lead ECG testing
   • Addition of a 3-month washout period for HSCT to the exclusion criteria
   • Decrease in the volume of blood drawn for PK sampling
– Protocol Amendment 2 (dated 12 Mar 2014)
   • 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
   • The addition of information concerning the use of syringe-based devices for administration of small volumes of *nab*-paclitaxel suspension
   • A change from cautionary use to prohibition of concomitant medications classified as strong inducers of CYP2C8 and CYP3A4, and additional guidance on the use of strong inhibitors of the same isozymes
– Protocol Amendment 3 (dated 11 Jun 2014)
   • Add specific language to discontinue and not rechallenge treatment for hypersensitivity
   • Clarify with specific language to discontinue treatment
– Protocol Amendment 4 (dated 25 Mar 2015)
   • Increased scope of dense PK sample collection
   • Change of the third solid tumours group in Phase 2 from mixed tumours to Ewing's sarcoma
   • Harmonisation of sample size and Simon two-stage minimax design for the three groups in Phase 2
   • Updated inclusion criterion 2 for Phase 2 to require radiologically documented measurable disease by RECIST version 1.1 (for neuroblastoma evaluable disease by MIBG/Curie Score is also acceptable)
   • 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
   • Decreased minimum platelet level in inclusion criterion 5 for Phase 2 patients with known bone marrow involvement
– Protocol Amendment 5 (dated 13 Jul 2016)
   • Updated inclusion criterion 1b for Phase 2 to allow enrollment of patients ≥ 6 months to ≤ 24 years of age
   • Updated inclusion criterion 2b for Phase 2 to allow enrollment of patients who have failed up to three lines of treatment
   • Modification of exclusion criterion 7 to differentiate between autologous and allogeneic HSCT
   • Updated assessment of the primary endpoint (ORR) in the Phase 2 neuroblastoma group using both RECIST version 1.1 criteria and the Curie score
   • Identification of the RP2D

Protocol deviations and violations

Protocol deviations were defined as any unplanned diversion from the approved protocol that did not result in harm to the study patients or significantly affect the scientific value of study data. Protocol violations were defined as any departures from the approved protocol that impacted the safety, rights, and/or welfare of the patient; may have negatively impacted the quality of the study data; or made the informed consent document/process inaccurate.

In Phase 1, 56 patients overall had at least 1 protocol deviation. Most protocol deviations were related to study procedures/assessments. In Phase 1, 9 patients (14%) had protocol violations. The most common protocol violation categories were "study procedures/assessments" (3 patients [5%]) along with "inclusion criteria" and "other protocol deviation", each noted in 2 patients (3%). Most patients (8 patients [12%]) only had one protocol violation.

For the Ewing's sarcoma, neuroblastoma, and rhabdomyosarcoma groups in Phase 2, 13 patients per group had at least one protocol deviation. Most protocol deviations were related to study procedures/assessments. For the Ewing's sarcoma group, 4 patients (29%) had 1 protocol violation each. The protocol violations categories were "concomitant medication", "exclusion criteria", "study procedures/assessments" and "inclusion criteria", each noted in 1 patient (7%). For the neuroblastoma group, 2 patients (14%) had 1 protocol violation each. The protocol violations categories were "other protocol deviation" and "study procedures/assessments", each noted in 1 patient (7%). For the rhabdomyosarcoma group, 4 patients (29%) had protocol violations. The protocol violations categories were "inclusion criteria", noted in 3 patients (21%), and "exclusion criteria", noted in 1 patient (7%). The majority of the patients with protocol violations only had 1 protocol violation (3 patients [21%]) and 1 patient (7%) had 2 protocol violations.

4.3.3. Results

Clinical efficacy

Phase 1

Patient disposition and data sets

Sixty-five patients were included in the Enrolled Population, and 64 enrolled patients received at least one dose of study drug and were included in the Safety and PK Populations (Table 2). Fifty-nine patients were included in the Efficacy Evaluable Population. 7 patients were screened and excluded from enrollment because they did not meet eligibility criteria.

Table 2. Phase 1 - Analysis Populations

	Dose Level						
	120 mg/m² n (%)	150 mg/m² n (%)	180 mg/m² n (%)	210 mg/m² n (%)	240 mg/m² n (%)	270 mg/m² n (%)	Total n (%)
Informed Consent Population[a]	16	8	14	11	8	7	72
Enrolled Population[b]	16	8	14	11	8	7	65
Safety Population[c]	16 (100)	8 (100)	14 (100)	11 (100)	8 (100)	7 (100)	64 (100)
Efficacy Evaluable Population[d]	14 (88)	8 (100)	12 (86)	10 (91)	8 (100)	7 (100)	59 (92)
Dose-determining Set[e]	6 (38)	6 (75)	6 (43)	6 (55)	6 (75)	7 (100)	37 (58)
Pharmacokinetic Population[f]	16 (100)	8 (100)	14 (100)	11 (100)	8 (100)	7 (100)	64 (100)

[a] All patients with signed informed consent/assent.
[b] Included all patients enrolled.
[c] Included all patients who took at least 1 dose of study drug.
[d] Included all who met eligibility criteria (relevant to efficacy in Phase 2), completed at least 1 dose of study drug, and had baseline and at least 1 postbaseline efficacy assessment (per Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1) if having not discontinued the investigational product prior to postbaseline efficacy assessment due to disease progression or symptomatic deterioration.
[e] Included all Phase 1 patients who received all 3 weekly doses of *nab*-paclitaxel at the cohort planned dose during Cycle 1 and had adequate safety assessments during the dose-limiting toxicity (DLT) assessment period (Cycle 1, including predose assessments on Cycle 2 Day 1) or experienced a DLT. The dose-determining set did not include patients who were enrolled at each dose once the dose had been determined to be safe. Patients xxxxxxx and xxxxxxx were identified as being Efficacy Evaluable Population eligible based on their baseline disease assessment information reported on the concomitant procedures surgeries page in the case report form.
[f] Included all patients who received at least 1 dose of *nab*-paclitaxel and had evaluable concentration data.
Source: Table 14.1.2.

Patient disposition for the Safety Population in Phase 1 is presented in Table 3. A total of 65 patients were enrolled in Phase 1 with 1 patient enrolled but not assigned to a cohort or given a dose due to patient withdrawal by parent/guardian, 16 patients enrolled in the 120 mg/m2 cohort, 8 patients enrolled in the 150 mg/m2 cohort, 14 patients enrolled in the 180 mg/m2 cohort, 11 patients enrolled in the 210 mg/m2 cohort, 8 patients enrolled in the 240 mg/m2 cohort, and 7 patients enrolled in the 270 mg/m2 cohort.

The DDS was a subgroup of 37 patients (6 patients in each dose cohort except for the 270 mg/m2 cohort, which included 7 patients) enrolled in Phase 1 whose data were used to determine the dose escalation decisions. The additional 27 patients were treated but did not meet the qualifications for eligibility in the DDS and were enrolled in a cohort previously considered safe by the SMC once there was no availability in a given cohort, but the investigator considered that the patients were eligible and would benefit from treatment.

Overall in Phase 1, all 64 patients (100%) discontinued from the study. The most frequently reported reasons for study treatment discontinuation were progressive disease (35 patients [55%]), AE (11 patients [17%]), and symptomatic deterioration (11 patients [17%]) (Table 3). A total of 13 patients completed the 1-year survival follow-up portion of the study, 50 patients died prior to 1 year, and 1 patient was lost to follow-up.

Table 3. Patient Disposition – Phase 1 (Safety Population)

	Dose Level						
	120 mg/m² N = 16 n (%)	150 mg/m² N = 8 n (%)	180 mg/m² N = 14 n (%)	210 mg/m² N = 11 n (%)	240 mg/m² N = 8 n (%)	270 mg/m² N = 7 n (%)	Total N = 64 n (%)
Number of Patients Who Discontinued Treatment	16 (100)	8 (100)	14 (100)	11 (100)	8 (100)	7 (100)	64 (100)
Primary Reason for Treatment Discontinuation							
Adverse Event	4 (25)	0	2 (14)	1 (9)	2 (25)	2 (29)	11 (17)
Progressive Disease	8 (50)	6 (75)	8 (57)	4 (36)	5 (63)	4 (57)	35 (55)
Withdrawal by Patient	0	0	0	2 (18)	0	0	2 (3)
Withdrawal by Parent/Guardian	0	0	2 (14)	1 (9)	0	0	3 (5)
Physician Decision	0	0	0	1 (9)	0	0	1 (2)
Symptomatic Deterioration	3 (19)	2 (25)	2 (14)	2 (18)	1 (13)	1 (14)	11 (17)
Other	1 (6)	0	0	0	0	0	1 (2)

Source: Table 14.1.3.1.

Baseline and disease characteristics

Demographic characteristics of Phase 1 patients are summarised in Table 4. 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 categorised under the designations for race agreed to in the FDA Written Request dated 27 Jul 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%]). Demographic characteristics based on the Efficacy Evaluable Population are summarised in Table 14.1.5.2 of the Appendices of the CSR.

Table 4. Phase 1 (Safety Population) - Demographic and Baseline Characteristics

	Dose Level						
	120 mg/m² N = 16	150 mg/m² N = 8	180 mg/m² N = 14	210 mg/m² N = 11	240 mg/m² N = 8	270 mg/m² N = 7	Total N = 64
Age (years)[a]							
Mean (Standard Deviation)	11.7 (3.32)	12.1 (5.84)	10.2 (4.64)	10.2 (5.36)	11.6 (4.63)	12.1 (2.97)	11.2 (4.40)
Median	12.5	14.0	11.0	9.0	12.0	13.0	12.0
Minimum, Maximum	2, 16	2, 17	2, 17	3, 17	2, 16	8, 16	2, 17
Age (years)[a], n (%)							
≥ 2 to < 12	6 (38)	2 (25)	7 (50)	6 (55)	3 (38)	3 (43)	27 (42)
≥ 12 to < 18	10 (63)	6 (75)	7 (50)	5 (45)	5 (63)	4 (57)	37 (58)
Sex, n (%)							
Male	7 (44)	4 (50)	5 (36)	4 (36)	7 (88)	4 (57)	31 (48)
Female	9 (56)	4 (50)	9 (64)	7 (64)	1 (13)	3 (43)	33 (52)
Race, n (%)							
White	11 (69)	8 (100)	9 (64)	9 (82)	8 (100)	5 (71)	50 (78)
Not Collected or Reported	5 (31)	0	5 (36)	0	0	1 (14)	11 (17)
Other[b]	0	0	0	2 (18)	0	1 (14)	3 (5)
Ethnicity, n (%)							
Hispanic or Latino	2 (13)	3 (38)	1 (7)	1 (9)	3 (38)	0	10 (16)
Not Hispanic or Latino	6 (38)	5 (63)	7 (50)	10 (91)	5 (63)	5 (71)	38 (59)
Not Reported	8 (50)	0	6 (43)	0	0	2 (29)	16 (25)
Subjects With Any Prior Cancer Treatment, n (%)	16 (100)	8 (100)	14 (100)	11 (100)	8 (100)	7 (100)	64 (100)
Prior Radiation Therapy	9 (56)	4 (50)	11 (79)	7 (64)	6 (75)	6 (86)	43 (67)
Prior Cancer Surgeries	14 (88)	7 (88)	9 (64)	9 (82)	5 (63)	7 (100)	51 (80)
Prior Systemic Anticancer Therapy	16 (100)	8 (100)	14 (100)	11 (100)	8 (100)	7 (100)	64 (100)
Prior Systemic Anticancer Regimens	16 (100)	8 (100)	14 (100)	11 (100)	8 (100)	7 (100)	64 (100)
Prior Stem Cell Transplants	2 (13)	2 (25)	3 (21)	2 (18)	3 (38)	2 (29)	14 (22)
Other Prior Anticancer Therapies	2 (13)	0	1 (7)	3 (27)	2 (25)	0	8 (13)

[a] Age was calculated as age = integer ≤ [(date of informed consent − date of birth + 1)/365.25].
[b] Patients did not fall under the designations for race
Source: Table 14.1.5.1 and Table 14.1.10.1.

Phase 1 allowed enrollment of patients with recurrent and refractory solid tumours. The most frequently reported **tumour types** were rhabdomyosarcoma (14 patients [22%]), Ewing's sarcoma (13 patients [20%]), neuroblastoma (10 patients [16%]), and osteosarcoma (8 patients [13%]). Other included tumour types were adrenalcortical carcinoma (n=2), clear cell sarcoma (n=2), desmoplastic small round cell tumour (n=1), hepatoblastoma (n=3), hepatocarcinoma (n=1), immature ovarian teratoma (n=1), left adrenalcortical carcinoma (n=1), left renal tumour with pulmonary metastases (high grade malignant tumour NOS; n=1), nasopharyngeal carcinoma (n=1), sarcoma NAS (n=1), Wilm's tumour (n=4), and yolk sac tumour (n=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%]). Baseline lesion status using RECIST version 1.1 is summarised in Table 14.1.12 of the Appendices of the CSR.

The majority of patients (54 patients [84%]) had at least one **ongoing medical history** condition at study entry. The most frequently reported (in ≥ 25% of patients) SOCs were blood and lymphatic system disorders (34 patients [53%]), gastrointestinal disorders (19 patients [30%]), musculoskeletal and connective tissue disorders (17 patients [27%]), and skin and subcutaneous tissue disorders (16 patients [25%]). The most frequently reported (in > 15.0% of patients) medical history PTs were anaemia (25 patients [39%]) and alopecia (10 patients [16%]).

In Phase 1, 53 patients (83%) overall received at least one **prior medication** (besides prior cancer treatment which is shown in Table 4). The most frequently used prior medications (in ≥ 15.0% of patients) were Bactrim (29 patients [45%]), paracetamol (18 patients [28%]), and ondansetron (11 patients [17%]).

Concomitant medication was received by 62 patients (97%) The most frequently used (≥ 30.0% of patients) concomitant medications were ondansetron (49 patients [77%]), paracetamol (47 patients [73%]), and Bactrim (42 patients [66%]). 32 patients (50%) overall had at least one **concomitant procedure/surgery** performed during the study. Most concomitant procedures were reported in ≤ 2 patients except packed red blood cell transfusions (17 patients [27%]) and transfusion (4 patients [6%]).

A majority of patients in Phase 1 received **subsequent anticancer therapies**, primarily cyclophosphamide, etoposide, ifosfamide, irinotecan, temozolomide, and topotecan.

Secondary efficacy endpoint- Overall Response Rate

A summary of the ORRs and best overall responses based on RECIST Version 1.1 in the Efficacy Evaluable Population is provided in Table 5. Overall, 2 patients had confirmed PRs (ORR of 3.4% [95% CI: 0.4, 11.7]): 1 patient each in the 240 mg/m2 (patient with rhabdomyosarcoma) and 270 mg/m2 (patient with Ewing's sarcoma) cohorts, which lasted 23.36 weeks. There were 5 unconfirmed responses (1 CR and 4 PRs). The CR was observed in the 210 mg/m2 cohort (1 patient). The PRs were observed in the 240 mg/m2 (3 patients) and 270 mg/m2 (1 patient) cohorts.

Table 5. Summary of ORR by RECIST Version 1.1 – Phase 1 (Efficacy Evaluable Population)

	Dose Level						
	120 mg/m^2 N = 14	150 mg/m^2 N = 8	180 mg/m^2 N = 12	210 mg/m^2 N = 10	240 mg/m^2 N = 8	270 mg/m^2 N = 7	Total N = 59
ORR[a], n (%)	0	0	0	0	1 (12.5)	1 (14.3)	2 (3.4)
95% CI of ORR[b]	0.0, 23.2	0.0, 36.9	0.0, 26.5	0.0, 30.8	0.3, 52.7	0.4, 57.9	0.4, 11.7
Best Overall Response[c], n (%)							
Complete Response (unconfirmed)	0	0	0	1 (10.0)	0	0	1 (1.7)
Partial Response (unconfirmed)	0	0	0	0	3 (37.5)	1 (14.3)	4 (6.8)
Stable Disease	2 (14.3)	2 (25.0)	4 (33.3)	2 (20.0)	1 (12.5)	2 (28.6)	13 (22.0)
Stable Disease ≥ 16 weeks	0	2 (25.0)	1 (8.3)	1 (10.0)	0	1 (14.3)	5 (8.5)
Stable Disease < 16 weeks	2 (14.3)	0	3 (25.0)	1 (10.0)	1 (12.5)	1 (14.3)	8 (13.6)
Progressive Disease	8 (57.1)	5 (62.5)	7 (58.3)	5 (50.0)	3 (37.5)	4 (57.1)	32 (54.2)
Symptomatic Deterioration[d]	3 (21.4)	1 (12.5)	1 (8.3)	2 (20.0)	1 (12.5)	0	8 (13.6)
Not Evaluable	1 (7.1)[e]	0	0	0	0	0	1 (1.7)

CI = confidence interval; ORR = overall response rate; RECIST = Response Evaluation Criteria in Solid Tumors.
[a] Overall response rate was defined as the percentage of patients who achieved a complete or partial response (confirmed no less than 4 weeks after the criteria for response were first met) using RECIST version 1.1 guidelines over the total number of patients available for the analysis.
[b] Confidence interval was obtained using the Clopper-Pearson method.
[c] The best overall response was based on unconfirmed responses.
[d] Patients discontinuing treatment due to symptomatic deterioration before a tumor assessment was conducted.
[e] Patient was started on another therapy but still had the tumor assessment performed (Listing 16.2.5.4 and Listing 16.2.5.9.1).
Source: Table 14.2.1.1.1.

Exploratory efficacy endpoints

123I-metaiodobenzylguanidine response (MIBG)

Overall, 2 patients out of 8 patients had a confirmed PR and ORR of 25.0% (95% CI: 3.2, 65.1) based on MIBG response in the neuroblastoma group in the Efficacy Evaluable Population (Table 6). The PRs were observed in the 180 mg/m2 and 210 mg/m2 cohorts.

Table 6. Summary of ORR by MIBG Scan for Neuroblastoma Patients – Phase 1 (Efficacy Evaluable Population)

	Dose Level						
	120 mg/m^2 N = 2	150 mg/m^2 N = 0	180 mg/m^2 N = 1	210 mg/m^2 N = 3	240 mg/m^2 N = 2	270 mg/m^2 N = 0	Total N = 8
ORR[a], n (%)	0	NA	1 (100.0)	1 (33.3)	0	NA	2 (25.0)
95% CI of ORR[b]	0.0, 84.2	NA	2.5, 100.0	0.8, 90.6	0.0, 84.2	NA	3.2, 65.1
Best Overall Response[c], n (%)							
Complete Response	0	NA	0	0	0	NA	0
Partial Response	0	NA	1 (100.0)	1 (33.3)	0	NA	2 (25.0)
Stable Disease	0	NA	0	1 (33.3)	0	NA	1 (12.5)
Stable Disease ≥ 16 Weeks	0	NA	0	0	0	NA	0
Stable Disease < 16 Weeks	0	NA	0	1 (33.3)	0	NA	1 (12.5)
Progressive Disease	0	NA	0	0	1 (50.0)	NA	1 (12.5)
Symptomatic Deterioration[d]	1 (50.0)	NA	0	1 (33.3)	1 (50.0)	NA	3 (37.5)
Not Evaluable	1 (50.0)	NA	0	0	0	NA	1 (12.5)

CI = confidence interval; MIBG = ^{123}I-metaiodobenzylguanidine; NA = not applicable; ORR = overall response rate.
[a] Overall response rate was defined as the percentage of patients who achieved a complete or partial response (confirmed no less than 4 weeks after the criteria for response were first met) using the Curie score guidelines over the total number of patients available for the analysis.
[b] Confidence interval was obtained using the Clopper-Pearson method.
[c] The best overall response was based on unconfirmed responses.
[d] Patients discontinuing treatment due to symptomatic deterioration before a tumor assessment was conducted.
Source: Table 14.2.1.2.1.

Biomarker analysis

Biomarker analysis was planned as an exploratory objective of this study to investigate the potential utility of markers of response to *nab*-paclitaxel. Per protocol, Stage 2 of the Phase 2 portion of the study did not proceed because the results demonstrated lack of clinical activity by *nab*-paclitaxel in the paediatric tumours studied. Due to the low response rate in recurrent or refractory Ewing's sarcoma, neuroblastoma, and rhabdomyosarcoma, it was determined that further development in these indications is not warranted and biomarker analysis was not conducted, as such data would not have provided any additional data that could have informed further development.

Phase 2

Patient disposition and data sets

The Enrolled, Safety, and PK populations all contained 14 patients each in the Ewing's sarcoma, neuroblastoma, and rhabdomyosarcoma groups. The Efficacy Evaluable Population also contained 14 patients in the neuroblastoma and rhabdomyosarcoma groups, but the Ewing's sarcoma contained only 13 patients. One Ewing's sarcoma patient failed to meet eligibility criteria relevant to efficacy. 8 patients were screened and excluded from enrollment because they did not meet eligibility criteria.

Table 7. Phase 2 - Analysis Populations

	Phase 2 Group			Overall[a] n (%)
	Ewing's Sarcoma n (%)	Neuroblastoma n (%)	Rhabdomyosarcoma n (%)	
Informed Consent Population[b]	14	14	14	122
Enrolled Population[c]	14	14	14	107
Safety Population[d]	14 (100)	14 (100)	14 (100)	106 (100)
Efficacy Evaluable Population[e]	13 (93)	14 (100)	14 (100)	100 (94)
Pharmacokinetic Population[f]	14 (100)	14 (100)	14 (100)	106 (100)

[a] The Overall column includes all patients in Phase 1 and Phase 2 in this table.
[b] All patients with signed informed consent/assent.
[c] Included all patients enrolled.
[d] Included all patients who took at least 1 dose of study drug.
[e] Included all who met eligibility criteria (relevant to efficacy in Phase 2), completed at least 1 dose of study drug, and had baseline and at least 1 postbaseline efficacy assessment (per Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1 in Phase 2 for Ewing's sarcoma and rhabdomyosarcoma, or either RECIST version 1.1 and Curie score in Phase 2 for neuroblastoma) if having not discontinued the investigational product prior to postbaseline efficacy assessment due to disease progression or systematic deterioration.
[f] Included all patients who received at least 1 dose of *nab*-paclitaxel and had evaluable concentration data.
Source: Table 14.1.2.

Patient disposition for the Safety Population in Phase 2 is presented in Table 8. In each group, all patients were discontinued from treatment.

Table 8. Patient Disposition – Phase 2 (Safety Population)

	Phase 2 Group			Overall[a] N = 106 n (%)
	Ewing's Sarcoma N = 14 n (%)	Neuroblastoma N = 14 n (%)	Rhabdomyosarcoma N = 14 n (%)	
Number of Patients Who Discontinued Treatment	14 (100)	14 (100)	14 (100)	106 (100)
Primary Reason for Treatment Discontinuation				
Adverse Event	1 (7)	0	3 (21)	15 (14)
Progressive Disease	11 (79)	12 (86)	11 (79)	69 (65)
Withdrawal by Patient	0	0	0	2 (2)
Withdrawal by Parent/Guardian	0	0	0	3 (3)
Physician Decision	0	0	0	1 (1)
Symptomatic Deterioration	2 (14)	2 (14)	0	15 (14)
Other	0	0	0	1 (1)

[a] The Overall column includes all patients in Phase 1 and Phase 2 in this table.
Source: Table 14.1.3.1.

As of the cut-off date for this CSR (05 Dec 2017), the 1-year survival follow-up status of the patients was as follows:

– One Ewing's sarcoma patient completed the 1-year survival follow-up portion of the study, 6 patients died prior to 1 year, 1 patient was lost to follow-up, and 6 patients are ongoing in survival follow-up.
– Two neuroblastoma patients completed the 1-year survival follow-up portion of the study, 8 patients died prior to 1 year, and 3 patients are ongoing in survival follow-up.
– One rhabdomyosarcoma patient completed the 1-year survival follow-up portion of the study, 11 patients died prior to 1 year, and 1 patient are ongoing in survival follow-up.

Results for the currently ongoing patients will be provided in a separate report once all subjects have completed the 1-year survival follow-up period or died.

Baseline and disease characteristics

Demographic characteristics of Phase 2 patients are summarised in Table 9. 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%]).

Demographic characteristics based on the Efficacy Evaluable Population are summarised in Table 14.1.5.2.

Table 9. Phase 2 (Safety Population) - Demographic and Baseline Characteristics

	Phase 2 Group			Overall[a] N = 106
	Ewing's Sarcoma N = 14	Neuroblastoma N = 14	Rhabdomyosarcoma N = 14	
Age (years)[b]				
Mean (Standard Deviation)	10.1 (4.63)	7.1 (3.42)	12.4 (6.42)	10.7 (4.81)
Median	8.5	7.0	14.0	11.0
Minimum, Maximum	4, 18	1, 15	3, 24	1, 24
Age (years)[b], n (%)				
< 2	0	1 (7)	0	1 (1)
≥ 2 to < 12	10 (71)	11 (79)	5 (36)	53 (50)
≥ 12 to < 18	3 (21)	2 (14)	7 (50)	49 (46)
≥ 18 to ≤ 24	1 (7)	0	2 (14)	3 (3)
Sex, n (%)				
Male	8 (57)	9 (64)	5 (36)	53 (50)
Female	6 (43)	5 (36)	9 (64)	53 (50)
Race, n (%)				
Black or African American	0	0	1 (7)	1 (1)
White	11 (79)	11 (79)	12 (86)	84 (79)
Not Collected or Reported	3 (21)	3 (21)	1 (7)	18 (17)
Other	0	0	0	3 (3)
Ethnicity, n (%)				
Hispanic or Latino	0	2 (14)	5 (36)	17 (16)
Not Hispanic or Latino	11 (79)	8 (57)	8 (57)	65 (61)
Not Reported[c]	3 (21)	4 (29)	1 (7)	24 (23)
Subjects With Any Prior Cancer Treatment, n (%)	14 (100)	14 (100)	14 (100)	106 (100)
Prior Radiation Therapy	12 (86)	10 (71)	10 (71)	75 (71)
Prior Cancer Surgeries	10 (71)	11 (79)	6 (43)	78 (74)
Prior Systemic Anticancer Therapy	14 (100)	14 (100)	14 (100)	106 (100)
Prior Systemic Anticancer Regimens	14 (100)	14 (100)	14 (100)	106 (100)
Prior Stem Cell Transplants	3 (21)	10 (71)	0	27 (25)
Other Prior Anticancer Therapies	1 (7)	6 (43)	0	15 (14)

[a] The Overall column includes all patients in Phase 1 and Phase 2 in this table.
[b] Age was calculated as age = integer ≤ [(date of informed consent – date of birth + 1)/365.25].
[c] Patients did not fall under the designations for race
Source: Table 14.1.5.1 and Table 14.1.10.1.

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%]). 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%]). 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%]). Baseline lesion status using RECIST version 1.1 is summarised in Table 14.1.12.

For the Ewing's sarcoma group, the majority of patients (10 patients [71%]) had at least one **ongoing medical history** condition at study entry. The most frequently reported (in ≥ 25% of patients) SOC was musculoskeletal and connective tissue disorders (4 patients [29%]). The only medical history PT reported in > 2 patients was pain in extremity (3 patients [21%]). For the neuroblastoma group, the majority of patients (11 patients [79%]) had at least one ongoing medical history condition at study entry. The most frequently reported (in ≥ 25% of patients) SOCs were blood and lymphatic system disorders (7 patients [50%]), gastrointestinal disorders (4 patients [29%]), and general disorders and administration site conditions (4 patients [29%]). The only medical history PTs reported in > 2 patients were anaemia (4 patients [29%]) and neutropaenia (3 patients [21%]). For the rhabdomyosarcoma group, the majority of patients (11 patients [79%]) had at least one ongoing medical history condition at study entry. The most frequently reported (in ≥ 25% of patients) SOCs were blood and lymphatic system disorders (5 patients [36%]), gastrointestinal disorders (4 patients [29%]), and musculoskeletal and connective tissue disorders (4 patients [29%]). The only medical history PTs reported in > 2 patients were anaemia (4 patients [29%]) and alopecia (3 patients [21%]).

Prior cancer treatment is shown in Table 9. Regarding other **prior medication** in the Ewing's sarcoma group, 13 patients (93%) received at least one prior medication. The most frequently used prior medications (in ≥ 15.0% of patients) were Bactrim (11 patients [79%]), paracetamol (6 patients [43%]), gabapentin (4 patients [29%]), enoxaparin sodium (3 patients [21%]), and ondansetron (3 patients [21%]). For the neuroblastoma group, 10 patients (71%) received at least one prior medication. The most frequently used prior medications (in ≥ 15.0% of patients) were Bactrim (7 patients [50%]), paracetamol (5 patients [36%]), and morphine sulfate (3 patients [21%]). For the rhabdomyosarcoma group, 12 patients (86%) received at least one prior medication. The most frequently used prior medications (in ≥ 15.0% of patients) were Bactrim (5 patients [36%]), paracetamol (4 patients [29%]), and fentanyl (3 patients [21%]).

For the Ewing's sarcoma group, 13 patients (93%) received at least one **concomitant medication** during Phase 2. The most frequently used (≥ 30.0% of patients) concomitant medications were Bactrim (11 patients [79%]), ondansetron (11 patients [79%]), paracetamol (11 patients [79%]), gabapentin (8 patients [57%]), ketorolac tromethamine (6 patients [43%]), and ranitidine hydrochloride (5 patients [36%]). For the neuroblastoma group, all 14 patients (100%) received at least one concomitant medication during Phase 2. The most frequently used (≥ 30.0% of patients) concomitant medications were Bactrim (11 patients [79%]), ondansetron (10 patients [71%]), and paracetamol (9 patients [64%]). For the rhabdomyosarcoma group, all 14 patients (100%) received at least one concomitant medication during Phase 2. The most frequently used (≥ 30.0% of patients) concomitant medications were paracetamol (11 patients [79%]), ondansetron (10 patients [71%]), Bactrim (7 patients [50%]), morphine (7 patients [50%]), dexamethasone (5 patients [36%]), metamizole (5 patients [36%]), morphine sulfate (5 patients [36%]), and omeprazole (5 patients [36%]). For the Ewing's sarcoma group, 9 patients (64%) had at least one **concomitant procedure/surgery** performed during Phase 2. Most concomitant procedures were reported in ≤ 2 patients. The concomitant procedures reported in > 2 patients were packed red blood cell transfusion (5 patients [36%]) and computerised tomogram thorax (4 patients [29%]). For the neuroblastoma group, 7 patients (50%) had at least one concomitant procedure/surgery performed during Phase 2. Most concomitant procedures were reported in ≤ 2 patients. The concomitant procedures reported in > 2 patients were packed red blood cell transfusion (3 patients [21%]) and platelet transfusion (3 patients [21%]). For the rhabdomyosarcoma group, 11 patients (79%) had at least one concomitant procedure/surgery performed during Phase 2. Most concomitant procedures were reported in ≤ 2 patients. The concomitant procedures reported in > 2 patients were packed red blood cell transfusion (7 patients [50%]) and platelet transfusion (3 patients [21%]).

A majority of patients in Phase 2 received subsequent/posttreatment anticancer therapies, primarily cyclophosphamide, etoposide, ifosfamide, irinotecan, temozolomide, and topotecan. Since 10 patients were still in the survival follow-up period at the time of the data cut-off for this study report, a full listing of posttreatment anticancer therapies will be presented at the time of the final overall survival study report.

Primary efficacy endpoint- Overall response rate

A summary of the ORRs and best overall responses based on RECIST version 1.1 and/or MIBG response (neuroblastoma group only) and MIBG response alone in the Efficacy Evaluable Population is provided in Table 10 and Table 11, respectively.

One patient in the rhabdomyosarcoma group had a confirmed PR resulting in an ORR of 7.1% (95% CI: 0.2, 33.9). No confirmed CR or PR was observed in either the Ewing's sarcoma group or the neuroblastoma group based on RECIST version 1.1 and/or MIBG response (neuroblastoma group only). There were 5 unconfirmed PRs reported: 3 patients (21.4%) and 2 patients (15.4%) in the rhabdomyosarcoma and Ewing's sarcoma groups, respectively. No unconfirmed best response of CR or PR was seen in the neuroblastoma group based on RECIST version 1.1 and/or MIBG response. Based on Listing 16.2.5.4 some of the unconfirmed responses were in patients that had PD after an initial response (1 Ewing's sarcoma, 1 rhabdomyosarcoma) and some responses could not be confirmed because no subsequent tumour evaluation was performed (1 in Ewing's sarcoma, 2 rhadomyosarcoma).

Table 10. Summary of ORR by RECIST Version 1.1 and/or MIBG Response (Neuroblastoma Group Only) – Phase 2 (Efficacy Evaluable Population)

	Phase 2 Group		
	Ewing's Sarcoma N = 13	Neuroblastoma N = 14	Rhabdomyosarcoma N = 14
ORR[a], n (%)	0	0	1 (7.1)
95% CI of ORR[b]	0.0, 24.7	0.0, 23.2	0.2, 33.9
Best Overall Response[c], n (%)			
Complete Response	0	0	0
Partial Response (unconfirmed)	2 (15.4)	0	3 (21.4)
Stable Disease	5 (38.5)	1 (7.1)	0
Stable Disease ≥ 16 Weeks	3 (23.1)	1 (7.1)	0
Stable Disease < 16 Weeks	2 (15.4)	0	0
Progressive Disease	5 (38.5)	10 (71.4)	11 (78.6)
Symptomatic Deterioration[d]	1 (7.7)	2 (14.3)	0
Not Evaluable	0	1 (7.1)[e]	0

CI = confidence interval; MIBG = ^{123}I-metaiodobenzylguanidine; ORR = overall response rate; RECIST = Response Evaluation Criteria in Solid Tumors.

[a] Overall response rate was defined as the percentage of patients who achieved a complete or partial response (confirmed no less than 4 weeks after the criteria for response were first met) using RECIST version 1.1 guidelines over the total number of patients available for the analysis. For Phase 2 neuroblastoma patients who had both RECIST version 1.1 and Curie Score tumor evaluations, both tumor response results were considered and an overall response was derived based on Appendix 16.1.9, SAP Table 2.

[b] Confidence interval was obtained using the Clopper-Pearson method.

[c] The best overall response was based on unconfirmed responses.

[d] Patients discontinuing treatment due to symptomatic deterioration before a tumor assessment was conducted.

[e] Patient was started on another therapy but still had the tumor assessment performed (Listing 16.2.5.4 and Listing 16.2.5.9.1).

Source: Table 14.2.1.1.1.

Table 11. Summary of ORR by MIBG Scan for Neuroblastoma Patients – Phase 2 (Efficacy Evaluable Population)

	Neuroblastoma N = 14
ORR[a], n (%)	0
95% CI of ORR[b]	0.0, 23.2
Best Overall Response[c], n (%)	
Complete Response	0
Partial Response	0
Stable Disease	3 (21.4)
Stable Disease ≥ 16 Weeks	1 (7.1)
Stable Disease < 16 Weeks	2 (14.3)
Progressive Disease	5 (35.7)
Symptomatic Deterioration[d]	2 (14.3)
Not Evaluable	4 (28.6)[e]

CI = confidence interval; MIBG = ^{123}I-metaiodobenzylguanidine; ORR = overall response rate.

[a] Overall response rate was defined as the percentage of patients who achieved a complete or partial response (confirmed no less than 4 weeks after the criteria for response were first met) using Curie Score guidelines over the total number of patients available for the analysis.

[b] Confidence interval was obtained using the Clopper-Pearson method.

[c] The best overall response was based on unconfirmed responses.

[d] Patients discontinuing treatment due to symptomatic deterioration before a tumor assessment was conducted.

[e] Patient was started on another therapy but still had the tumor assessment performed. Three patients did not have tumor assessments performed by MIBG scan (Listing 16.2.5.6 and Listing 16.2.5.9.1).

Source: Table 14.2.1.2.1.

Secondary efficacy endpoint – Duration of response

One patient showed a confirmed PR in the rhabdomyosarcoma group, which lasted 6.14 weeks. No confirmed responses were observed in the Ewing's sarcoma and neuroblastoma groups.

Secondary efficacy endpoint – Disease control rate

The DCR was 30.8% (4 patients; 95% CI: 9.1, 61.4) for the Ewing's sarcoma group; 7.1% (1 patient; 95% CI: 0.2, 33.9) for the neuroblastoma group; and 7.1% (1 patient; 95% CI: 0.2, 33.9) for the rhabdomyosarcoma group.

Of note, in the Ewing's sarcoma group, 2 patients had a Best Overall Response of unconfirmed PR. As reported in Listing 16.2.5.5 (see ABI-007-PST-001 Listing of Individual Laboratory Measurements by Patients), one of these 2 patients with a Best Overall Response of (unconfirmed) PR also met the requirements for a Best Confirmed Overall Response of SD ≥ 16 weeks (in accordance with the ABI-007-PST-001 Statistical Analysis Plan, SD duration was calculated as the time from first study drug administration until first observed disease progression). This brings the total number of patients with SD ≥ 16 weeks in the Ewing's sarcoma group to 4 for the calculation of DCR.

Secondary efficacy endpoint – Progression-free survival

The PFS results for the Efficacy Evaluable Population are demonstrated in Table 12. For the Ewing's sarcoma group, the median PFS was 13 weeks (95% CI: 7.4, 16.1). The estimated Kaplan-Meier PFS rate at 2 months was 54% (95% CI: 25, 76), at 6 months was 15% (95% CI: 2, 39), and at 12-months could not be estimated because zero patients were at risk. For the neuroblastoma group, the

median PFS was 7.4 weeks (95% CI: 4.6, 8.1). The estimated Kaplan-Meier PFS rate at 2 months was 16% (95% CI: 3, 40) and could not be estimated at 6 and 12 months because zero patients were at risk. For the rhabdomyosarcoma group, the median PFS was 5.1 weeks (95% CI: 2.1, 7.9). The estimated Kaplan-Meier PFS rate at 2 months was 21% (95% CI: 5, 45) and could not be estimated at 6 and 12 months because zero patients were at risk.

Table 12. Progression-free Survival – Phase 2 (Efficacy Evaluable Population)

	Phase 2 Group		
	Ewing's Sarcoma N = 13	Neuroblastoma N = 14	Rhabdomyosarcoma N = 14
Number (%) of Patients Who Died or Had Progression	12 (92)	13 (93)	12 (86)
Progression	12 (92)	12 (86)	12 (86)
Death	0	1 (7)	0
Number (%) of Patients Censored	1 (8)	1 (7)	2 (14)
Completed 12 Months Follow-up[a]	0	0	1 (7)
PFS Follow-up Ongoing	1 (8)	1 (7)	1 (7)
Number (%) of Patients With New Anticancer Therapy or Lesion Sites Surgery	12 (92)	11 (79)	10 (71)
Progression-free Survival[b] (weeks)			
Median[c]	13	7.4	5.1
95% CI[d]	7.4, 16.1	4.6, 8.1	2.1, 7.9
Timepoint, Month 2			
Number of Patients at Risk	7	2	3
KM Estimate of PFS Rate (95% CI)[d]	54 (25, 76)	16 (3, 40)	21 (5, 45)
Timepoint, Month 6			
Number of Patients at Risk	2	0	0
KM Estimate of PFS Rate (95% CI)[d]	15 (2, 39)	NE	NE
Timepoint, Month 12			
Number of Patients at Risk	0	0	0
KM Estimate of PFS Rate (95% CI)[d]	NE	NE	NE

CI = confidence interval; KM = Kaplan-Meier; NE = not evaluable; PFS = progression-free survival.
[a] The 12-month follow-up period was still ongoing as of the report data cutoff (05 Dec 2017).
[b] Progression-free survival was defined as the time from the first dose date to the start of disease progression or patient death (any cause), whichever occurred first. Disease progression was classed as either a disease progression observed as a response assessment, or a disease progression or symptomatic deterioration on the treatment/study discontinuation. Patients who did not have disease progression or had not died were censored at the last known time that the patient was progression free. Disease progression was considered according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 for Phase 2 Ewing's sarcoma and rhabdomyosarcoma patients or Curie score for Phase 2 neuroblastoma patients. For Phase 2 neuroblastoma patients who had both RECIST 1.1 and Curie score tumor evaluations, both tumor responses results were considered and an overall response was derived based on Appendix 16.1.9, SAP Table 2.
[c] Median PFS time was estimated through Kaplan-Meier methods.
[d] 95% confidence interval about the median time to PFS event using Greenwood's method.
Source: Table 14.2.3.1.1

Secondary efficacy endpoint - Overall survival

The estimated Kaplan-Meier overall survival for the Efficacy Evaluable Population at 1 year was 48% (95% CI: 14, 76), 25% (95% CI: 4, 54), and 15% (95% CI: 2, 39) for the Ewing's sarcoma, neuroblastoma, and rhabdomyosarcoma groups, respectively. Overall survival follow-up was still ongoing for 6 patients (46%), 3 patients (21%), and 1 patient (7%) in the Ewing's sarcoma, neuroblastoma, and rhabdomyosarcoma groups, respectively. The median overall survival was 32.1 weeks, 26.7 weeks, and 19.6 weeks for the Ewing's sarcoma, neuroblastoma, and rhabdomyosarcoma groups, respectively.

Exploratory efficacy endpoints

– **Bone marrow biopsy**- No exploratory analysis of bone marrow biopsy was performed because complete response was not observed in a neuroblastoma patient.
– **Biomarker analysis**- Biomarker analysis was not performed.

Clinical safety

Phase 1

Extent of exposure

Exposure to study treatment in Phase 1 is summarised in Table 13. No patients weighing ≤ 10 kg were enrolled, so no patients were dosed by mg/kg.

Median treatment duration was 7.0 weeks, with minimum and maximum duration of 1 and 49 weeks, respectively. The minimum duration occurred in 1 patient in the 120 mg/m2 cohort and the maximum duration in 1 patient in the 270 mg/m2 cohort. The median (range) total number of treatment cycles per patient was 2 cycles (range: 1 to 12). The maximum total number of treatment cycles was in the 150 mg/m2 cohort (12 cycles).

Overall, 11 patients (17%) had at least one dose reduction. The mean time to first dose reduction was 5.8 weeks. No dose reductions were observed in the 120 mg/m2 cohort. The number of reductions increased with the dose, with 3 patients (38%) and 4 patients (57%) having reductions in the 240 mg/m2 and 270 mg/m2 cohorts, respectively.

5 patients (8%) had at least one dose escalation. The mean time to first dose escalation was 11.7 weeks. No dose escalations were observed in the 270 mg/m2 cohort. Per the protocol, if a patient was doing well at a given dose, the dose could have been increased to a dose that was determined by the SMC to be safe.

Overall, 7 patients (11%) experienced at least one dose interruption. The mean time to first dose interruption was 3.2 weeks. No dose interruptions were observed in the 120 mg/m2 cohort and the most dose interruptions were observed in the 240 mg/m2 cohort.

Table 13. Treatment Exposure and Dose Modification – Phase 1 (Safety Population)

	Dose Level						
	120 mg/m^2 N = 16	150 mg/m^2 N = 8	180 mg/m^2 N = 14	210 mg/m^2 N = 11	240 mg/m^2 N = 8	270 mg/m^2 N = 7	Total N = 64
Total Number of Treatment Cycles							
Mean (Standard Deviation)	2.0 (1.10)	3.5 (3.63)	2.6 (1.91)	2.4 (1.21)	3.0 (1.69)	3.1 (3.13)	2.6 (2.06)
Median	2.0	2.0	2.0	2.0	3.0	2.0	2.0
Minimum, Maximum	1, 5	1, 12	1, 8	1, 5	1, 5	1, 10	1, 12
Patients Dosed per Cycle, n (%)							
Cycle 1	16 (100)	8 (100)	14 (100)	11 (100)	8 (100)	7 (100)	64 (100)
Cycle 2	11 (69)	7 (88)	10 (71)	9 (82)	6 (75)	5 (71)	48 (75)
Cycle 3	2 (13)	2 (25)	5 (36)	3 (27)	4 (50)	3 (43)	19 (30)
Cycle 4	2 (13)	2 (25)	4 (29)	2 (18)	4 (50)	1 (14)	15 (23)
Cycle 5	1 (6)	2 (25)	1 (7)	1 (9)	2 (25)	1 (14)	8 (13)
Cycle 6	0	1 (13)	1 (7)	0	0	1 (14)	3 (5)
Cycle 7	0	1 (13)	1 (7)	0	0	1 (14)	3 (5)
Cycle 8	0	1 (13)	1 (7)	0	0	1 (14)	3 (5)
Cycle 9	0	1 (13)	0	0	0	1 (14)	2 (3)
Cycle 10	0	1 (13)	0	0	0	1 (14)	2 (3)
Cycle 11	0	1 (13)	0	0	0	0	1 (2)
Cycle 12	0	1 (13)	0	0	0	0	1 (2)
Maximum Number of Cycles Received per Patient, n (%)							
1	5 (31)	1 (13)	4 (29)	2 (18)	2 (25)	2 (29)	16 (25)
2	9 (56)	5 (63)	5 (36)	6 (55)	2 (25)	2 (29)	29 (45)
3	0	0	1 (7)	1 (9)	0	2 (29)	4 (6)
4	1 (6)	0	3 (21)	1 (9)	2 (25)	0	7 (11)
5	1 (6)	1 (13)	0	1 (9)	2 (25)	0	5 (8)
6	0	0	0	0	0	0	0
7	0	0	0	0	0	0	0
8	0	0	1 (7)	0	0	0	1 (2)
9	0	0	0	0	0	0	0
10	0	0	0	0	0	1 (14)	1 (2)
11	0	0	0	0	0	0	0
12	0	1 (13)	0	0	0	0	1 (2)
Total Number of Doses Taken[a]							
Mean (Standard Deviation)	5.7 (3.53)	9.8 (11.15)	7.6 (5.76)	6.7 (3.44)	8.4 (4.44)	7.9 (6.59)	7.4 (5.79)
Median	6.0	5.5	6.0	6.0	8.0	6.0	6.0
Minimum, Maximum	1, 15	3, 36	2, 24	3, 14	3, 14	3, 22	1, 36

Treatment Duration[b] (weeks)							
Mean (Standard Deviation)	6.8 (4.59)	12.9 (14.96)	9.4 (7.73)	8.6 (5.14)	11.1 (6.72)	12.8 (16.29)	9.6 (9.04)
Median	7.0	7.1	7.0	7.1	10.5	7.9	7.0
Minimum, Maximum	1, 19	3, 48	2, 31	3, 20	3, 20	3, 49	1, 49
Patients With at Least One Dose Reduction, n (%)	0	1 (13)	2 (14)	1 (9)	3 (38)	4 (57)	11 (17)
Frequency of Reductions, n (%)							
1	0	1 (13)	2 (14)	1 (9)	2 (25)	2 (29)	8 (13)
2	0	0	0	0	0	2 (29)	2 (3)
3	0	0	0	0	1 (13)	0	1 (2)
Reason for Dose Reduction[c], n (%)							
Adverse Event	0	1 (13)	2 (14)	1 (9)	3 (38)	3 (43)	10 (16)
Other	0	0	0	0	0	2 (29)	2 (3)
Time to First Reduction (weeks)							
n	0	1	2	1	3	4	11
Mean (Standard Deviation)	-	12.6 (NA)	3.6 (1.82)	13.1 (NA)	4.4 (1.17)	4.5 (0.43)	5.8 (3.59)
Median	-	12.6	3.6	13.1	4.1	4.4	4.7
Minimum, Maximum	-	13, 13	2, 5	13, 13	3, 6	4, 5	2, 13
Patients With at Least One Dose Escalation, n (%)	1 (6)	1 (13)	1 (7)	1 (9)	1 (13)	0	5 (8)
Frequency of Escalations, n (%)							
1	1 (6)	0	1 (7)	1 (9)	1 (13)	0	4 (6)
2	0	1 (13)	0	0	0	0	1 (2)
Time to First Escalation (weeks)							
n	1	1	1	1	1	0	5
Mean (Standard Deviation)	4.1 (NA)	20.4 (NA)	16.4 (NA)	4.3 (NA)	13.0 (NA)	0	11.7 (7.29)
Median	4.1	20.4	16.4	4.3	13.0	0	13.0
Minimum, Maximum	4, 4	20, 20	16, 16	4, 4	13, 13	0	4, 20
Patients With at Least One Dose Interruption, n (%)	0	1 (13)	1 (7)	1 (9)	3 (38)	1 (14)	7 (11)
Frequency of Interruptions, n (%)							
1	0	1 (13)	1 (7)	1 (9)	3 (38)	0	6 (9)
6	0	0	0	0	0	1 (14)	1 (2)
Reason for Dose Interruption[c], n (%)							
Adverse Event	0	1 (13)	1 (7)	1 (9)	3 (38)	1 (14)	7 (11)
Other	0	0	0	0	0	1 (14)	1 (2)
Time to First Interruption (weeks)							
n	0	1	1	1	3	1	7
Mean (Standard Deviation)	-	1.3 (NA)	1.1 (NA)	2.1 (NA)	3.7 (2.36)	6.7 (NA)	3.2 (2.36)
Median	-	1.3	1.1	2.1	2.6	6.7	2.1
Minimum, Maximum	-	1, 1	1, 1	2, 2	2, 6	7, 7	1, 7

NA = not available.
[a] The sum of doses completed over all cycles.
[b] Treatment duration = ([date of last study drug administration] — [date of first study drug administration] + 7) / 7.
[c] A subject could have been in multiple categories.
Source: Table 14.3.1.1.1.

Adverse events

A **summary of TEAEs** reported during Phase 1 is provided in Table 14. Overall, all 64 patients (100%) experienced at least 1 TEAE during the study. Serious TEAEs, Grade 3 or 4 TEAEs, and TEAEs leading to death were reported in 35 patients (55%), 56 patients (88%), and 5 patients (8%), respectively. Treatment-emergent AEs related to the study drug were reported in 59 patients (92%). Ten patients (16%) experienced a TEAE leading to dose reduction, 16 patients (25%) experienced a TEAE leading to drug interruption, and 11 patients (17%) experienced a TEAE leading to drug discontinuation.

Table 14. Summary of Treatment-emergent Adverse Events – Phase 1 (Safety Population)

Patients With at Least 1	Dose Level						
	120 mg/m^2 N = 16 n (%)	150 mg/m^2 N = 8 n (%)	180 mg/m^2 N = 14 n (%)	210 mg/m^2 N = 11 n (%)	240 mg/m^2 N = 8 n (%)	270 mg/m^2 N = 7 n (%)	Total N = 64 n (%)
TEAE	16 (100)	8 (100)	14 (100)	11 (100)	8 (100)	7 (100)	64 (100)
Treatment-related TEAE	14 (88)	8 (100)	12 (86)	11 (100)	7 (88)	7 (100)	59 (92)
Grade 3 or 4 TEAE	13 (81)	8 (100)	10 (71)	10 (91)	8 (100)	7 (100)	56 (88)
Treatment-related Grade 3 or 4 TEAE	9 (56)	7 (88)	7 (50)	9 (82)	7 (88)	7 (100)	46 (72)
Serious TEAE	10 (63)	7 (88)	6 (43)	5 (45)	3 (38)	4 (57)	35 (55)
Treatment-related Serious TEAE	1 (6)	4 (50)	4 (29)	2 (18)	1 (13)	3 (43)	15 (23)
TEAE Leading to Drug Discontinuation	4 (25)	0	2 (14)	1 (9)	2 (25)	2 (29)	11 (17)
Treatment-related TEAE Leading to Drug Discontinuation	1 (6)	0	0	1 (9)	2 (25)	2 (29)	6 (9)
TEAE Leading to Dose Reduction	0	1 (13)	2 (14)	1 (9)	3 (38)	3 (43)	10 (16)
Treatment-related TEAE Leading to Dose Reduction	0	1 (13)	2 (14)	1 (9)	3 (38)	3 (43)	10 (16)
TEAE Leading to Drug Interruption	2 (13)	2 (25)	3 (21)	4 (36)	3 (38)	2 (29)	16 (25)
Treatment-related TEAE Leading to Drug Interruption	0	2 (25)	1 (7)	3 (27)	3 (38)	2 (29)	11 (17)
TEAE Leading to Death	2 (13)	1 (13)	0	0	1 (13)	1 (14)	5 (8)
Treatment-related TEAE Leading to Death	0	0	0	0	0	0	0

TEAE = treatment-emergent adverse event.
Treatment-emergent adverse events were defined as adverse events (AEs) that began or worsened in severity on or after the date of the first dose of study drug and within 28 days of the date of the last dose of study drug. The severity of the AEs was graded according to the Common Terminology Criteria for Adverse Events, Version 4.0. Adverse events were coded using Medical Dictionary for Regulatory Activities, Version 20.0.
Source: Table 14.3.1.3.

A summary of the **most frequently reported TEAEs** (≥ 10% of patients in the Total group) during Phase 1 is provided in Table 15. Overall, the SOCs with the highest proportion of patients reporting TEAEs during Phase 1 were blood and lymphatic system disorders (53 patients [83%]), general disorders and administration site conditions (51 patients [80%]), gastrointestinal disorders (47 patients [73%]), skin and subcutaneous tissues disorders (40 patients [63%]), and musculoskeletal and connective tissue disorders (34 patients [53%]). Overall, the most frequently reported TEAEs (in > 35% of patients) were neutropaenia (38 patients [59%]), anaemia (37 patients [58%]), pyrexia (32 patients [50%]), and leukopaenia (23 patients [36%]).

The incidence of neutropaenia and thrombocytopaenia increased as the dose escalated. The percentage of patients with neutropaenia doubled between the 120 mg/m2 cohort (7 patients [44%]) and the 240 mg/m2 cohort (7 patients [88%]). Thrombocytopaenia was reported in ≤ 2 patients in all cohorts except the 270 mg/m2 cohort (4 patients [57%]).

Table 15. TEAEs by SOC and PT (in at Least 10% of Patients in the Total Group) – Phase 1 (Safety Population)

System Organ Class Preferred Term[a]	120 mg/m² N = 16 n (%)	150 mg/m² N = 8 n (%)	180 mg/m² N = 14 n (%)	210 mg/m² N = 11 n (%)	240 mg/m² N = 8 n (%)	270 mg/m² N = 7 n (%)	Total N = 64 n (%)
Patients With at Least 1 TEAE	16 (100)	8 (100)	14 (100)	11 (100)	8 (100)	7 (100)	64 (100)
Blood and Lymphatic System Disorders	13 (81)	7 (88)	8 (57)	10 (91)	8 (100)	7 (100)	53 (83)
Anaemia	8 (50)	6 (75)	6 (43)	5 (45)	6 (75)	6 (86)	37 (58)
Neutropenia	7 (44)	4 (50)	6 (43)	8 (73)	7 (88)	6 (86)	38 (59)
Leukopenia	7 (44)	1 (13)	2 (14)	5 (45)	5 (63)	3 (43)	23 (36)
Lymphopenia	6 (38)	2 (25)	1 (7)	2 (18)	2 (25)	3 (43)	16 (25)
Thrombocytopenia	1 (6)	2 (25)	2 (14)	1 (9)	2 (25)	4 (57)	12 (19)
General Disorders and Administration Site Conditions	11 (69)	8 (100)	11 (79)	10 (91)	8 (100)	3 (43)	51 (80)
Pyrexia	6 (38)	5 (63)	6 (43)	7 (64)	5 (63)	3 (43)	32 (50)
Oedema Peripheral	3 (19)	4 (50)	3 (21)	1 (9)	1 (13)	0	12 (19)
Fatigue	3 (19)	3 (38)	4 (29)	4 (36)	2 (25)	0	16 (25)
Asthenia	1 (6)	1 (13)	1 (7)	1 (9)	3 (38)	1 (14)	8 (13)
Gastrointestinal Disorders	13 (81)	6 (75)	10 (71)	7 (64)	7 (88)	4 (57)	47 (73)
Vomiting	8 (50)	3 (38)	2 (14)	3 (27)	3 (38)	2 (29)	21 (33)
Nausea	6 (38)	3 (38)	2 (14)	4 (36)	2 (25)	3 (43)	20 (31)
Constipation	4 (25)	3 (38)	3 (21)	6 (55)	2 (25)	1 (14)	19 (30)
Diarrhoea	3 (19)	4 (50)	4 (29)	3 (27)	4 (50)	2 (29)	20 (31)
Abdominal Pain	2 (13)	3 (38)	3 (21)	2 (18)	3 (38)	2 (29)	15 (23)
Stomatitis	1 (6)	1 (3)	0	2 (18)	1 (13)	2 (29)	7 (11)
Skin and Subcutaneous Tissue Disorders	7 (44)	4 (50)	6 (43)	10 (91)	8 (100)	5 (71)	40 (63)
Alopecia	2 (13)	4 (50)	4 (29)	5 (45)	3 (38)	2 (29)	20 (31)
Pruritus Generalised	3 (19)	0	1 (7)	1 (9)	0	2 (29)	7 (11)
Dry Skin	0	0	1 (7)	2 (18)	2 (25)	2 (29)	7 (11)
Musculoskeletal and Connective Tissue Disorders	8 (50)	7 (88)	5 (36)	5 (45)	6 (75)	3 (43)	34 (53)
Pain in Extremity	2 (13)	4 (50)	2 (14)	0	3 (38)	1 (14)	12 (19)
Arthralgia	1 (6)	2 (25)	0	4 (36)	2 (25)	2 (29)	11 (17)
Back Pain	3 (19)	3 (38)	3 (21)	0	2 (25)	0	11 (17)
Nervous System Disorders	7 (44)	5 (63)	6 (43)	3 (27)	6 (75)	4 (57)	31 (48)
Headache	3 (19)	2 (25)	3 (21)	2 (18)	1 (13)	1 (14)	12 (19)
Peripheral Sensory Neuropathy	1 (6)	0	2 (14)	0	3 (38)	2 (29)	8 (13)
Respiratory, Thoracic, and Mediastinal Disorders	5 (31)	5 (63)	6 (43)	6 (55)	3 (38)	3 (43)	28 (44)
Cough	2 (13)	3 (38)	2 (14)	4 (36)	3 (38)	0	14 (22)
Metabolism and Nutrition Disorders	6 (38)	6 (75)	7 (50)	2 (18)	2 (25)	2 (29)	25 (39)
Decreased Appetite	3 (19)	3 (38)	5 (36)	1 (9)	1 (13)	1 (14)	14 (22)
Hypokalaemia	1 (6)	3 (38)	2 (14)	1 (9)	1 (13)	2 (29)	10 (16)
Hyponatraemia	1 (6)	4 (50)	1 (7)	0	0	1 (14)	7 (11)
Investigations	3 (19)	6 (75)	3 (21)	4 (36)	5 (63)	2 (29)	23 (36)
Alanine Aminotransferase Increased	0	3 (38)	1 (7)	3 (27)	1 (13)	1 (14)	9 (14)
Weight Decreased	2 (13)	0	0	1 (9)	2 (25)	2 (29)	7 (11)

TEAE = treatment-emergent adverse event.
Treatment-emergent adverse events were defined as adverse events (AEs) that began or worsened in severity on or after the date of the first dose of study drug and within 28 days of the date of the last dose of study drug.
[a] Adverse events were coded using Medical Dictionary for Regulatory Activities, Version 20.0. Patients with multiple AEs were counted once for each system organ class and/or preferred term using worst reported grade.
Source: Table 14.3.1.4.

The majority of the TEAEs were Grade 1 (63 patients [98%]) and Grade 2 (63 patients [98%]) in severity. **Grade 3 or 4 TEAEs** reported in ≥ 2 patients overall during Phase 1 are summarised in Table 16. The majority of the Grade 3 or 4 TEAEs were reported in ≤ 3 patients overall. Grade 3 or 4 TEAEs reported in more than 3 patients were neutropaenia (34 patients [53%]), anaemia (17 patients [27%]), leukopaenia (17 patients [27%]), lymphopaenia (11 patients [17%]), back pain (5 patients [8%]), and hyponatraemia (4 patients [6%]). Grade 4 TEAEs were reported in 27 patients (42%). The majority of the Grade 4 TEAEs were reported in ≤ 3 patients overall. Grade 4 TEAEs reported in more than 3 patients were neutropaenia (21 patients [33%]) and leukopaenia (9 patients [14%]).

Table 16. Grade 3 or 4 TEAEs by SOC and PT (in 2 or More Patients in the Total Group) – Phase 1 (Safety Population)

System Organ Class Preferred Term[a]	120 mg/m² N = 16 n (%)	150 mg/m² N = 8 n (%)	180 mg/m² N = 14 n (%)	210 mg/m² N = 11 n (%)	240 mg/m² N = 8 n (%)	270 mg/m² N = 7 n (%)	Total N = 64 n (%)
Patients With at Least 1 Grade 3 or 4 TEAE	13 (81)	8 (100)	10 (71)	10 (91)	8 (100)	7 (100)	56 (88)
Blood and Lymphatic System Disorders	10 (63)	7 (88)	6 (43)	9 (82)	8 (100)	7 (100)	47 (73)
Anaemia	4 (25)	4 (50)	3 (21)	2 (18)	2 (25)	2 (29)	17 (27)
Neutropenia	5 (31)	3 (38)	5 (36)	8 (73)	7 (88)	6 (86)	34 (53)
Leukopenia	5 (31)	0	2 (14)	3 (27)	4 (50)	3 (43)	17 (27)
Lymphopenia	3 (19)	2 (25)	1 (7)	1 (9)	1 (13)	3 (43)	11 (17)
Thrombocytopenia	1 (6)	1 (13)	0	0	1 (13)	0	3 (5)
Febrile Neutropenia	0	0	1 (7)	0	1 (13)	1 (14)	3 (5)
General Disorders and Administration Site Conditions	0	2 (25)	3 (21)	1 (9)	1 (13)	0	7 (11)
Oedema Peripheral	0	1 (13)	1 (7)	0	1 (13)	0	3 (5)
Fatigue	0	1 (13)	1 (7)	1 (9)	0	0	3 (5)
Gastrointestinal Disorders	0	2 (25)	1 (7)	0	0	1 (14)	4 (6)
Vomiting	0	1 (13)	1 (7)	0	0	1 (14)	3 (5)
Nausea	0	1 (13)	0	0	0	1 (14)	2 (3)
Skin and Subcutaneous Tissue Disorders	0	0	0	2 (18)	1 (13)	2 (29)	5 (8)
Pruritus	0	0	0	1 (9)	1 (13)	0	2 (3)
Pain of Skin	0	0	0	0	0	2 (29)	2 (3)
Musculoskeletal and Connective Tissue Disorders	3 (19)	2 (25)	1 (7)	2 (18)	0	0	8 (13)
Arthralgia	0	1 (13)	0	2 (18)	0	0	3 (5)
Back Pain	3 (19)	1 (13)	1 (7)	0	0	0	5 (8)
Nervous System Disorders	3 (19)	1 (13)	0	1 (9)	2 (25)	1 (14)	8 (13)
Peripheral Sensory Neuropathy	0	0	0	0	1 (13)	1 (14)	2 (3)
Respiratory, Thoracic, and Mediastinal Disorders	2 (13)	1 (13)	3 (21)	1 (9)	0	0	7 (11)
Dyspnoea	1 (6)	0	2 (14)	0	0	0	3 (5)
Pleural Effusion	2 (13)	0	0	0	0	0	2 (3)
Hypoxia	1 (6)	0	0	1 (9)	0	0	2 (3)
Infections and Infestations	1 (6)	2 (25)	1 (7)	1 (9)	0	1 (14)	6 (9)
Cellulitis	1 (6)	1 (13)	0	0	0	0	2 (3)
Metabolism and Nutrition Disorders	3 (19)	3 (38)	1 (7)	0	0	0	7 (11)
Decreased Appetite	1 (6)	1 (13)	0	0	0	0	2 (3)
Hypokalaemia	0	1 (13)	1 (7)	0	0	0	2 (3)
Hyponatraemia	1 (6)	3 (38)	0	0	0	0	4 (6)
Investigations	1 (6)	3 (38)	1 (7)	0	2 (25)	1 (14)	8 (13)
Alanine Aminotransferase Increased	0	1 (13)	0	0	1 (13)	0	2 (3)
Neutrophil Count Decreased	0	0	0	0	1 (13)	1 (14)	2 (3)
Renal and Urinary Disorders	2 (13)	1 (13)	0	0	0	0	3 (5)
Urinary Tract Obstruction	2 (13)	0	0	0	0	0	2 (3)
Vascular Disorders	0	2 (25)	1 (7)	0	0	0	3 (5)
Hypotension	0	2 (25)	1 (7)	0	0	0	3 (5)

TEAE = treatment-emergent adverse event.

Treatment-emergent adverse events were defined as adverse events (AEs) that began or worsened in severity on or after the date of the first dose of study drug and within 28 days of the date of the last dose of study drug.

[a] Adverse events were coded using Medical Dictionary for Regulatory Activities, Version 20.0. Patients with multiple AEs were counted once for each system organ class and/or preferred term using worst reported grade.

Source: Table 14.3.1.14.

Treatment-related TEAEs during Phase 1 were reported in 59 patients (92%). Treatment-related TEAEs reported in ≥ 10% of patients during Phase 1 are summarised in Table 17. The most frequently reported treatment-related TEAEs (in > 30% of patients overall) were neutropaenia (36 patients [56%]), anaemia (28 patients [44%]), leukopaenia (21 patients [33%]), and alopecia (20 patients [31%]). The majority of the treatment-related Grade 3 or 4 TEAEs were reported in ≤ 3 patients overall. Treatment-related Grade 3 or 4 TEAEs reported in more than 3 patients were neutropaenia (32 patients [50%]), anaemia (13 patients [20%]), leukopaenia (15 patients [23%]), and lymphopaenia (8 patients [13%]).

Table 17. TEAEs Related to Study Drug by SOC and PT (in at Least 10% of Patients in the Total Group) – Phase 1 (Safety Population)

System Organ Class Preferred Term[a]	Dose Level						
	120 mg/m^2 N = 16 n (%)	150 mg/m^2 N = 8 n (%)	180 mg/m^2 N = 14 n (%)	210 mg/m^2 N = 11 n (%)	240 mg/m^2 N = 8 n (%)	270 mg/m^2 N = 7 n (%)	Total N = 64 n (%)
Patients With at Least 1 Treatment-related TEAE	14 (88)	8 (100)	12 (86)	11 (100)	7 (88)	7 (100)	59 (92)
Blood and Lymphatic System Disorders	10 (63)	7 (88)	6 (43)	9 (82)	6 (75)	7 (100)	45 (70)
Neutropenia	6 (38)	4 (50)	6 (43)	8 (73)	6 (75)	6 (86)	36 (56)
Anaemia	6 (38)	4 (50)	4 (29)	5 (45)	3 (38)	6 (86)	28 (44)
Leukopenia	6 (38)	1 (13)	2 (14)	5 (45)	4 (50)	3 (43)	21 (33)
Lymphopenia	4 (25)	2 (25)	1 (7)	2 (18)	2 (25)	2 (29)	13 (20)
Thrombocytopenia	1 (6)	2 (25)	2 (14)	1 (9)	1 (13)	4 (57)	11 (17)
Skin and Subcutaneous Tissue Disorders	5 (31)	4 (50)	6 (43)	10 (91)	6 (75)	4 (57)	35 (55)
Alopecia	2 (13)	4 (50)	4 (29)	5 (45)	3 (38)	2 (29)	20 (31)
General Disorders and Administration Site Conditions	5 (31)	5 (63)	6 (43)	7 (64)	4 (50)	2 (29)	29 (45)
Pyrexia	1 (6)	2 (25)	4 (29)	3 (27)	2 (25)	2 (29)	14 (22)
Fatigue	2 (13)	1 (13)	1 (7)	4 (36)	2 (25)	0	10 (16)
Gastrointestinal Disorders	6 (38)	3 (38)	4 (29)	4 (36)	6 (75)	4 (57)	27 (42)
Diarrhoea	2 (13)	1 (13)	3 (21)	2 (18)	3 (38)	2 (29)	13 (20)
Vomiting	2 (13)	1 (13)	2 (14)	0	2 (25)	2 (29)	9 (14)
Nausea	2 (13)	1 (13)	1 (7)	2 (18)	2 (25)	2 (29)	10 (16)
Nervous System Disorders	2 (13)	1 (13)	3 (21)	2 (18)	5 (63)	4 (57)	17 (27)
Peripheral Sensory Neuropathy	1 (6)	0	2 (14)	0	3 (38)	2 (29)	8 (13)
Metabolism and Nutrition Disorders	2 (13)	2 (25)	5 (36)	1 (9)	2 (25)	2 (29)	14 (22)
Decreased Appetite	0	0	5 (36)	1 (9)	1 (13)	1 (14)	8 (13)

TEAE = treatment-emergent adverse event.
Treatment-emergent adverse events were defined as adverse events (AEs) that began or worsened in severity on or after the date of the first dose of study drug and within 28 days of the date of the last dose of study drug.
[a] Adverse events were coded using Medical Dictionary for Regulatory Activities, Version 20.0. Patients with multiple AEs were counted once for each system organ class and/or preferred term using worst reported grade.
Source: Table 14.3.1.6.

A summary of **TEAEs by age group** (< 2 years, ≥ 2 years to < 12 years, ≥ 12 years to < 18 years) is provided in Table 14.3.1.5 in the Appendices of the CSR. There were no patients in the < 2 years age group and the others groups also contain limited number of patients. Interpretation of results in the different age groups are therefore difficult to interpret. This is also the case for TEAEs related to the study drug by age group (Table 14.3.1.7), Grade 3 or 4 TEAEs by age group (14.3.1.15) and Grade 3 or 4 TEAEs related to the study drug by age group (Table 14.3.1.17).

A summary of protocol-defined **DLT** is provided in Table 18. Overall, 2 patients (5%) experienced a protocol-defined DLT during Phase 1. One patient in the 120 mg/m2 cohort experienced Grade 3 dizziness that lasted 19 days, which met the DLT definition of Grade 3 or 4 nonhematologic toxicity. One patient in the 270 mg/m2 cohort experienced Grade 4 neutropaenia that lasted 13 days, which met the DLT definition of Grade 4 uncomplicated neutropaenia lasting > 7 days. The DMC established

the RP2D, 240 mg/m2, after reviewing the safety data from the 270 mg/m2 cohort where one DLT was reported (as described above) as well as an increase in skin toxicity events. The skin toxicity events were pain of skin (2 patients), palmar-plantar erythrodysesthesia syndrome (1 patient), and toxic erythema of chemotherapy (1 patient). Skin toxicities of pruritus (1 patient) and dermatitis bullous (1 patient) were reported in the 240 mg/m2 cohort. Based on the overall safety evaluation, the DMC recommended the dose of 240 mg/m2 for Phase 2.

Table 18. Summary of Dose-limiting Toxicity – Phase 1 (Safety Population)

	Dose Level						
	120 mg/m^2 N = 6 n (%)	150 mg/m^2 N = 6 n (%)	180 mg/m^2 N = 6 n (%)	210 mg/m^2 N = 6 n (%)	240 mg/m^2 N = 6 n (%)	270 mg/m^2 N = 7 n (%)	Total N = 37 n (%)
Patients With at Least 1 DLT	1 (17)	0	0	0	0	1 (14)	2 (5)
Grade 3 or 4 Nonhematologic Toxicity (Excluding Transient Transaminitis)	1 (17)	0	0	0	0	0	1 (3)
Grade 3 or 4 Nausea or Vomiting Persisting > 5 Days Despite Maximal Anti-emetic Treatment	0	0	0	0	0	0	0
Grade 4 Thrombocytopenia or Anemia Persisting > 7 Days or Requiring Transfusion > 7 Days	0	0	0	0	0	0	0
Grade 3 Thrombocytopenia with Bleeding	0	0	0	0	0	0	0
Grade 4 Uncomplicated Neutropenia Lasting > 7 Days	0	0	0	0	0	1 (14)	1 (3)
Febrile Neutropenia with Confirmed Bacterial Infection	0	0	0	0	0	0	0
Grade 3 Hematologic Toxicity Requiring Treatment Delay > 21 Days	0	0	0	0	0	0	0

DLT = dose-limiting toxicity.
Source: Table 14.3.1.2.

Serious adverse events

SAEs

Serious TEAEs reported during Phase 1 are summarised in Table 19. Overall, 35 patients (55%) experienced at least 1 serious TEAE. The majority of serious TEAEs were reported in ≤ 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%]). Overall, 15 patients (23%) experienced at least 1 treatment-related serious TEAE. The majority of treatment-related serious TEAEs were reported in ≤ 2 patients. The only treatment-related serious TEAE reported in > 2 patients was pyrexia (7 patients [11%]).

Table 19. Treatment-emergent Serious Adverse Events by System Organ Class and Preferred Term – Phase 1 (Safety Population)

System Organ Class Preferred Term[a]	Dose Level						
	120 mg/m² N = 16 n (%)	150 mg/m² N = 8 n (%)	180 mg/m² N = 14 n (%)	210 mg/m² N = 11 n (%)	240 mg/m² N = 8 n (%)	270 mg/m² N = 7 n (%)	Total N = 64 n (%)
Patients With at Least 1 Serious TEAE	10 (63)	7 (88)	6 (43)	5 (45)	3 (38)	4 (57)	35 (55)
General Disorders and Administration Site Conditions	1 (6)	3 (38)	4 (29)	3 (27)	2 (25)	2 (29)	15 (23)
Pyrexia	0	3 (38)	2 (14)	3 (27)	1 (13)	2 (29)	11 (17)
General Physical Health Deterioration	0	1 (13)	0	0	1 (13)	0	2 (3)
Oedema Peripheral	1 (6)	1 (13)	1 (7)	0	0	0	3 (5)
Chills	0	0	0	1 (9)	0	0	1 (2)
Generalised Oedema	0	0	1 (7)	0	0	0	1 (2)
Blood and Lymphatic System Disorders	2 (13)	1 (13)	2 (14)	0	0	1 (14)	6 (9)
Febrile Neutropenia	0	0	1 (7)	0	0	1 (14)	2 (3)
Neutropenia	1 (6)	0	1 (7)	0	0	0	2 (3)
Thrombocytopenia	0	1 (13)	0	0	0	0	1 (2)
Leukopenia	1 (6)	0	0	0	0	0	1 (2)
Respiratory, Thoracic, and Mediastinal Disorders	2 (13)	0	1 (7)	1 (9)	0	0	4 (6)
Pleural Effusion	2 (13)	0	0	0	0	0	2 (3)
Dyspnoea	1 (6)	0	0	0	0	0	1 (2)
Hypoxia	1 (6)	0	0	0	0	0	1 (2)
Pneumonitis	0	0	0	1 (9)	0	0	1 (2)
Pulmonary Embolism	0	0	1 (7)	0	0	0	1 (2)
Gastrointestinal Disorders	1 (6)	2 (25)	1 (7)	0	0	1 (14)	5 (8)
Vomiting	0	1 (13)	1 (7)	0	0	1 (14)	3 (5)
Abdominal Pain	0	1 (13)	0	0	0	0	1 (2)
Diarrhoea	1 (6)	0	1 (7)	0	0	0	2 (3)
Nausea	0	0	0	0	0	1 (14)	1 (2)
Infections and Infestations	0	1 (13)	0	1 (9)	0	1 (14)	3 (5)
Cellulitis	0	1 (13)	0	0	0	0	1 (2)
Pneumonia	0	0	0	0	0	1 (14)	1 (2)
Soft Tissue Infection	0	0	0	1 (9)	0	0	1 (2)
Nervous System Disorders	2 (13)	1 (13)	0	0	1 (13)	0	4 (6)
Dizziness	1 (6)	0	0	0	0	0	1 (2)
Intracranial Pressure Increased	1 (6)	0	0	0	0	0	1 (2)
Seizure	0	0	0	0	1 (13)	0	1 (2)
Somnolence	0	1 (13)	0	0	0	0	1 (2)

Musculoskeletal and Connective Tissue Disorders	2 (13)	2 (25)	0	0	0	0	4 (6)
Back Pain	2 (13)	1 (13)	0	0	0	0	3 (5)
Pain in Extremity	0	1 (13)	0	0	0	0	1 (2)
Neoplasms Benign, Malignant, and Unspecified (Including Cysts and Polyps)	2 (13)	0	2 (14)	0	0	1 (14)	5 (8)
Cancer Pain	0	0	1 (7)	0	0	0	1 (2)
Osteosarcoma	1 (6)	0	0	0	0	0	1 (2)
Osteosarcoma Metastatic	0	0	0	0	0	1 (14)	1 (2)
Refractory Anaemia With an Excess of Blasts	0	0	1 (7)	0	0	0	1 (2)
Tumour Pain	1 (6)	0	0	0	0	0	1 (2)
Renal and Urinary Disorders	2 (13)	1 (13)	0	0	0	0	3 (5)
Acute Kidney Injury	0	1 (13)	0	0	0	0	1 (2)
Anuria	1 (6)	0	0	0	0	0	1 (2)
Urinary Retention	1 (6)	0	0	0	0	0	1 (2)
Urinary Tract Obstruction	1 (6)	0	0	0	0	0	1 (2)
Skin and Subcutaneous Tissue Disorders	0	0	0	1 (9)	1 (13)	0	2 (3)
Dermatitis Acneiform	0	0	0	1 (9)	0	0	1 (2)
Dermatitis Bullous	0	0	0	0	1 (13)	0	1 (2)
Vascular Disorders	0	2 (25)	1 (7)	0	0	0	3 (5)
Hypotension	0	1 (13)	1 (7)	0	0	0	2 (3)
Hypertension	0	1 (13)	0	0	0	0	1 (2)
Metabolism and Nutrition Disorders	0	2 (25)	0	0	0	0	2 (3)
Hyponatraemia	0	2 (25)	0	0	0	0	2 (3)
Dehydration	0	1 (13)	0	0	0	0	1 (2)
Hypercreatininaemia	0	1 (13)	0	0	0	0	1 (2)
Cardiac Disorders	0	1 (13)	0	0	0	0	1 (2)
Tachycardia	0	1 (13)	0	0	0	0	1 (2)
Psychiatric Disorders	0	1 (13)	0	0	0	0	1 (2)
Restlessness	0	1 (13)	0	0	0	0	1 (2)

TEAE = treatment-emergent adverse event.
Treatment-emergent adverse events were defined as adverse events (AEs) that began or worsened in severity on or after the date of the first dose of study drug and within 28 days of the date of the last dose of study drug.
[a] Adverse events were coded using Medical Dictionary for Regulatory Activities, Version 20.0. Patients with multiple AEs were counted once for each system organ class and/or preferred term using worst reported grade.
Source: Table 14.3.2.1.

Deaths

As shown in Table 20, 50 patients (78%) died during Phase 1 and all deaths were attributed to "death from malignant disease under study, or complication due to malignant disease under study." None of these deaths were related to treatment. Five patients (8%) experienced disease progression-related TEAEs with the outcome of death during Phase 1. In the 120 mg/m2 cohort, 1 patient each experienced the events of anuria and osteosarcoma. One patient each in the 150 mg/m2 and 240 mg/m2 cohorts experienced an event of general physical health deterioration. In the 270 mg/m2 cohort, 1 patient experienced an event of osteosarcoma metastatic.

Table 20. Summary of Deaths and Causes of Death Category – Phase 1 (Safety Population)

Primary Cause	Dose Level						
	120 mg/m^2 N = 16 n (%)	150 mg/m^2 N = 8 n (%)	180 mg/m^2 N = 14 n (%)	210 mg/m^2 N = 11 n (%)	240 mg/m^2 N = 8 n (%)	270 mg/m^2 N = 7 n (%)	Total N = 64 n (%)
Number of Deaths	14 (88)	7 (88)	11 (79)	5 (45)	8 (100)	5 (71)	50 (78)
Cause of Death							
Death From Malignant Disease Under Study, or Complication Due to Malignant Disease Under Study	14 (88)	7 (88)	11 (79)	5 (45)	8 (100)	5 (71)	50 (78)

Source: Table 14.3.2.5.

Discontinuations

Study drug discontinuations

Overall, 11 patients (17%) had a TEAE leading to study drug discontinuation. All TEAEs leading to study drug discontinuation were reported in 1 patient each. Treatment-emergent AEs related to the study drug leading to study drug discontinuation were reported in 6 patients (9%). All TEAEs related to the study drug leading to study drug discontinuation were reported in 1 patient each.

Dose reductions

Overall, 10 patients (16%) had a TEAE leading to dose reduction. The majority of TEAEs leading to dose reduction were reported in 1 patient each. The only TEAE leading to dose reduction reported in > 1 patient was neutropaenia (6 patients [9%]). 10 patients (16%) had a TEAE related to the study drug leading to dose reduction. The majority of TEAEs related to the study drug leading to dose reduction were reported in 1 patient each. The only TEAE related to the study drug leading to dose reduction reported in > 1 patient was neutropaenia (6 patients [9%]).

Study drug interruption

Overall, 16 patients (25%) had a TEAE leading to study drug interruption. The majority of TEAEs leading to study drug interruption were reported in 1 patient each. The TEAEs leading to study drug interruption reported in > 1 patient were neutropaenia (9 patients [14%]) and pyrexia (2 patients [3%]). In 11 patients (17%) the TEAE leading to study drug interruption was related to the study drug. The majority of TEAEs related to the study drug leading to study drug interruption were reported in 1 patient each. The only TEAE related to the study drug leading to study drug interruption reported in > 1 patient was neutropaenia (8 patients [13%]).

AEs of special interest

The criteria used to define the Adverse Events of Special Interest (AESI) are described in Appendix 16.1.9 of the CSR. AESIs for the Phase 1 part are summarised in Table 21. In both Part 1 and Part 2 there were no reports of cystoid macular oedema, cranial nerve palsies, Steven-Johnson syndrome or toxic epidermal necrolysis, infusion site reaction/extravasation, and drug-induced lupus erythematosus and these AESIs will therefore not be further discussed in this report.

Table 21. Treatment-emergent Adverse Events of Special Interest – Phase 1 (Safety Population)

Event of Interest	Dose Level						
	120 mg/m^2 N = 16 n (%)	150 mg/m^2 N = 8 n (%)	180 mg/m^2 N = 14 n (%)	210 mg/m^2 N = 11 n (%)	240 mg/m^2 N = 8 n (%)	270 mg/m^2 N = 7 n (%)	Total N = 64 n (%)
Patients With at Least 1 TEAE of Special Interest	16 (100)	8 (100)	12 (86)	11 (100)	8 (100)	7 (100)	62 (97)
General Myelosuppression	12 (75)	7 (88)	8 (57)	9 (82)	8 (100)	7 (100)	51 (80)
Neutropenia	8 (50)	4 (50)	6 (43)	8 (73)	7 (88)	6 (86)	39 (61)
Anaemia	8 (50)	6 (75)	6 (43)	5 (45)	6 (75)	6 (86)	37 (58)
Gastrointestinal Events	12 (75)	5 (63)	5 (36)	6 (55)	5 (63)	3 (43)	36 (56)
Hypersensitivity Reactions	6 (38)	5 (63)	7 (50)	9 (82)	4 (50)	4 (57)	35 (55)
Skin Toxicity	5 (31)	2 (25)	3 (21)	8 (73)	6 (75)	5 (71)	29 (45)
Peripheral Neuropathy	2 (13)	0	3 (21)	2 (18)	5 (63)	3 (43)	15 (23)
Hepatic Toxicity (Drug-induced Liver Injury)	2 (13)	6 (75)	2 (14)	3 (27)	1 (13)	2 (29)	16 (25)
Thrombocytopenia	1 (6)	2 (25)	2 (14)	1 (9)	2 (25)	4 (57)	12 (19)
Myalgia and Arthralgia	1 (6)	5 (63)	0	4 (36)	2 (25)	2 (29)	14 (22)
Acute Renal Failure Including HUS	1 (6)	3 (38)	0	1 (9)	0	0	5 (8)
Cardiotoxicity	1 (6)	3 (38)	0	0	0	0	4 (6)
Clinically Severe Infection-sepsis	1 (6)	0	0	0	0	0	1 (2)
Pneumonitis	0	0	0	1 (9)	0	0	1 (2)

HUS = hemolytic-uremic syndrome; TEAE = treatment-emergent adverse event.
Treatment-emergent adverse events were defined as adverse events that began or worsened in severity on or after the date of the first dose of study drug and within 28 days of the date of the last dose of study drug.
Source: Table 14.3.2.6.1.

Myelosuppression

Grade 3 or 4 myelosuppression AESIs were reported for 45 patients (70%) in Phase 1 and serious myelosuppression in 6 patients (9%). Myelosuppression AESIs leading to study drug discontinuation were reported for 1 patient (2%), leading to dose reduction for 7 patients (11%), and leading to study drug interruption for 9 patients (14%).

Neutropaenia

Neutropaenia AESIs were reported for 39 patients (61%), AESI of febrile neutropaenia for 3 patients (5%), Grade 3 or 4 neutropaenia AESIs for 36 patients (56%), and serious neutropaenia AESIs for 5 patients (8%). Neutropaenia AESI led to study drug discontinuation in 1 patient (2%), dose reduction in 7 patients (11%), and study drug interruption in 9 patients (14%). No neutropaenia AESIs with an outcome of death were reported. The time to first occurrence of Grade 3 or higher neutropaenia is presented in Table 22.

Table 22. Time to First Occurrence of Grade 3 or Higher Treatment-emergent Neutropaenia – Phase 1 (Safety Population)

	Dose Level						
	120 mg/m^2 N = 16 n (%)	150 mg/m^2 N = 8 n (%)	180 mg/m^2 N = 14 n (%)	210 mg/m^2 N = 11 n (%)	240 mg/m^2 N = 8 n (%)	270 mg/m^2 N = 7 n (%)	Total N = 64 n (%)
Number of Subjects With Grade 3 or Higher Treatment-emergent Neutropenia	5 (31)	3 (38)	5 (36)	8 (73)	7 (88)	6 (86)	34 (53)
Time to Onset (days), n	5	3	5	8	7	6	34
Mean (Standard Deviation)	21.4 (14.24)	27.0 (19.97)	15.0 (4.95)	18.4 (10.39)	16.7 (12.87)	11.8 (6.68)	17.6 (11.36)
Median	21.0	17.0	15.0	15.0	15.0	13.5	15.0
Minimum, Maximum	3, 43	14, 50	8, 22	8, 37	8, 45	4, 21	3, 50

Analysis was only on subjects with Grade 3 or higher treatment-emergent neutropenia. Time to onset was defined as the time from the first dose of study drug to the first occurrence of Grade 3 or higher treatment-emergent neutropenia. Adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA), Version 20.0. Classification for neutropenia was based on MedDRA, Version 20.0 preferred terms 'Neutropenia' and 'Neutrophil count decreased'.
Source: Table 14.3.3.2.

Anaemia

Anaemia AESIs were reported for 37 patients (58%) and Grade 3 or 4 anaemia AESIs for 17 patients (27%). There were no reports of anaemia AESI in the serious category, with fatal outcome, leading to study drug discontinuation or dose reduction. Anaemia AESIs leading to study drug interruption was reported for 1 patient (2%).

Thrombocytopaenia

Thrombocytopaenia AESIs were reported for 12 patients (19%), Grade 3 or 4 thrombocytoapaenia AESIs for 3 patients (5%), and serious thrombocytopaenia AESIs for 1 patient (2%). None of the thrombocytopaenia AESIs led to study drug discontinuation or dose adjustments. No fatal outcomes were observed. The time to first occurrence of Grade 3 or higher thrombocytopaenia are shown in Table 23.

Table 23. Time to First Occurrence of Grade 3 or Higher Treatment-emergent Thrombocytopaenia – Phase 1 (Safety Population)

	Dose Level						
	120 mg/m^2 N = 16 n (%)	150 mg/m^2 N = 8 n (%)	180 mg/m^2 N = 14 n (%)	210 mg/m^2 N = 11 n (%)	240 mg/m^2 N = 8 n (%)	270 mg/m^2 N = 7 n (%)	Total N = 64 n (%)
Number of Subjects With Grade 3 or Higher Treatment-emergent Thrombocytopenia	1 (6)	1 (13)	0	0	1 (13)	0	3 (5)
Time to Onset (days), n	1	1	0	0	1	0	3
Mean (Standard Deviation)	71.0 (NE)	47.0 (NE)	-	-	76.0 (NE)	-	64.7 (15.50)
Median	71.0	47.0	-	-	76.0	-	71.0
Minimum, Maximum	71, 71	47, 47	-	-	76, 76	-	47, 76

NE = not estimated.
Analysis was only on subjects with Grade 3 or higher treatment-emergent thrombocytopenia. Time to onset was defined as the time from the first dose of study drug to the first occurrence of Grade 3 or higher treatment-emergent thrombocytopenia. Adverse Events were coded using Medical Dictionary for Regulatory Activities (MedDRA), Version 20.0. Classification for thrombocytopenia was based on MedDRA, Version 20.0 preferred terms 'Thrombocytopenia' and 'Platelet count decreased'.
Source: Table 14.3.3.4.

Peripheral neuropathy

Peripheral neuropathy AESIs were reported for 15 patients (23%) and Grade 3 or 4 peripheral neuropathy AESIs for 2 patients (3%). Grade 3 or 4 peripheral neuropathies were only seen in the 240 mg/m2 and 270 mg/m2 cohorts. No serious peripheral neuropathy AESIs or with fatal outcome were reported. Peripheral neuropathy AESIs leading to study drug discontinuation were reported for 1 patient (2%), no dose reductions, and dose interruptions for 1 patient (2%). The overall incidence of

Grade 2 or higher peripheral neuropathy and the time to improvement to Grade 1 or better are presented in Table 24.

Table 24. Time to First Occurrence of Grade 2 or Higher Treatment-emergent Peripheral Neuropathy and Time to Improvement of CTCAE Grade 2 or Higher Treatment-emergent Peripheral Neuropathy to Grade 1 or Better – Phase 1 (Safety Population)

Number of Subjects With	Dose Level						
	120 mg/m^2 N = 16 n (%)	150 mg/m^2 N = 8 n (%)	180 mg/m^2 N = 14 n (%)	210 mg/m^2 N = 11 n (%)	240 mg/m^2 N = 8 n (%)	270 mg/m^2 N = 7 n (%)	Total N = 64 n (%)
Grade 2 or Higher Treatment-emergent Peripheral Neuropathy	1 (6)	0	1 (7)	0	4 (50)	2 (29)	8 (13)
Time to Onset (days), n	1	0	1	0	4	2	8
Mean (Standard Deviation)	30.0 (NE)	-	23 (NE)	-	94.5 (27.18)	30.5 (30.41)	61.5 (41.22)
Median	30.0	-	23.0	-	103.0	30.5	54.0
Minimum, Maximum	30, 30	-	23, 23	-	56, 116	9, 52	9, 116
Improvement to Grade 1 or Better	0	0	0	0	2 (25)	0	2 (3)
Time to Improvement (days), n	0	0	0	0	2	0	2
Mean (Standard Deviation)	-	-	-	-	32.5 (26.16)	-	32.5 (26.16)
Median	-	-	-	-	32.5	-	32.5
Minimum, Maximum	-	-	-	-	14, 51	-	14, 51

CTCAE = Common Terminology Criteria for Adverse Events; NE = not estimated.
Analysis was only on subjects with Grade 2 or higher treatment-emergent peripheral neuropathy. Time to onset was defined as the time from the first dose of study drug to the first occurrence of Grade 2 or higher treatment-emergent peripheral neuropathy. Adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA), Version 20.0. Classification for peripheral neuropathy was based on MedDRA, Version 20.0 broad scope standardized MedDRA query (SMQ) (SMQ term = "Peripheral Neuropathy", SMQ number = "20000034").
Analysis was only on subjects with Grade 2 or higher treatment-emergent peripheral neuropathy. Time to Improvement was defined as the time from the first occurrence of Grade 2 or higher treatment-emergent peripheral neuropathy to improvement to Grade 1 or better. Adverse events were coded using MedDRA, Version 20.0. Classification for peripheral neuropathy was based on MedDRA, Version 20.0 broad scope SMQ (SMQ term = "Peripheral Neuropathy", SMQ number = "20000034").
Source: Table 14.3.3.1 and Table 14.3.3.5.

Gastrointestinal events

Gastrointestinal AESIs were reported for 36 patients (56%), Grade 3 or 4 gastrointestinal AESIs for 4 patients (6%), serious gastrointestinal AESIs for 4 patients (6%), and none with fatal outcome. Study drug discontinuation and dose reduction were not reported, study drug interruption in 1 patient (2%).

Myalgia and arthralgia

Myalgia and arthralgia AESIs were reported for 14 patients (22%), Grade 3 or 4 for 3 patients (5%), and no serious or fatal cases. No dose adjustments were needed.

Hypersensitivity reactions

In Phase 1 no anaphylactic transfusion reactions were observed. Oedema-related PTs were reported in 4 patients (6%) periorbital and 2 patients (3%) face. Rash was reported for 1 patient (2%) (Grade 1, non-serious, and did not lead to study drug discontinuation, dose reduction, or dose interruption). Rash erythematous was reported for 3 patients (5%), which were all Grade 1/2, non-serious and no dose adjustments were needed.

Pneumonitis

In 1 patient (2%) pneumonitis AESI was reported, which was serious. No Grade 3 or 4 pneumonitis or pneumonitis with fatal outcome was reported. In 1 patient drug interruption was needed, no study drug discontinuation or dose reduction was reported.

Hepatic toxicity

Hepatic toxicity AESIs were reported for 16 patients (25%) and Grade 3 or 4 hepatic toxicity AESIs for 4 patients (6%). None were serious or had a fatal outcome. No PTs related to more severe hepatic toxicity (hepatic failure, fibrosis, cirrhosis, and other liver damage-related conditions) were reported. In 1 patient the drug was interrupted, no discontinuations or dose reductions were needed.

Acute renal failure and haemolytic uremic syndrome

Acute renal failure AESIs including HUS were reported for 5 patients (8%). No PTs of renal failure acute or haemolytic-uremic syndrome were observed. Acute kidney injury was reported for 2 patients (3%) and blood creatinine increased for 1 patient (2%; Grade 1, non-serious, no dose modification needed). Grade 3 or 4 acute renal failure AESIs including HUS were reported for 2 patients (3%) and serious acute renal failure AESIs including HUS for 3 patients (5%). An acute renal failure AESI including HUS with an outcome of death was reported for 1 patient (2%) in the Phase 1 group (anuria, dose level 1).No dose modifications were needed.

Clinically severe infections-sepsis

Clinically severe infections-sepsis AESIs were reported for 1 patient (2%), but no Grade 3 or 4, serious or fatal infections-sepsis. No dose modifications were needed.

Cardiotoxicity

Cardiotoxicity AESIs were reported for 4 patients (6%), Grade 3 or 4 cardiotoxicity AESIs for 3 patients (5%), and serious cardiotoxicity AESI for 1 patient (2%). The PTs reported were primarily related to abnormal rhythms. None of the cases were fatal and no dose modifications were observed.

Congestive heart failure and left ventricular dysfunction

No case of congestive heart failure and left ventricular dysfunctions was reported in the Phase 1 part.

Skin toxicity

Skin toxicity AESIs were reported for 29 patients (45%), Grade 3 or 4 skin toxicity AESIs for 5 patients (8%), serious skin toxicity AESIs for 2 patients (3%), and no skin toxicity with fatal outcome. Skin toxicity AESIs leading to study drug discontinuation were reported for 2 patients (3%), dose reduction for 3 patients (5%), and drug interruption for 1 patient (2%). The time to first occurrence of Grade 2 and Grade 3 or higher skin toxicity is shown in Table 25.

Table 25. Time to First Occurrence of Grade 2 and Grade 3 or Higher Treatment-emergent Skin Toxicity – Phase 1 (Safety Population)

Number of Subjects With	Dose Level						
	120 mg/m² N = 16 n (%)	150 mg/m² N = 8 n (%)	180 mg/m² N = 14 n (%)	210 mg/m² N = 11 n (%)	240 mg/m² N = 8 n (%)	270 mg/m² N = 7 n (%)	Total N = 64 n (%)
Grade 2 or Higher Treatment-emergent Skin Toxicity	3 (19)	2 (25)	1 (7)	7 (64)	3 (38)	2 (29)	18 (28)
Time to Onset (days), n	3	2	1	7	3	2	18
Mean (Standard Deviation)	17.7 (17.56)	193.5 (207.18)	2.0 (NE)	34.4 (26.23)	39.0 (17.44)	38.5 (3.54)	48.7 (75.62)
Median	16.0	193.5	2.0	37.0	47.0	38.5	36.5
Minimum, Maximum	1, 36	47, 340	2, 2	2, 76	19, 51	36, 41	1, 340
Grade 3 or Higher Treatment-emergent Skin Toxicity	0	0	0	2 (18)	1 (13)	2 (29)	5 (8)
Time to Onset (days), n	0	0	0	2	1	2	5
Mean (Standard Deviation)	-	-	-	38.5 (2.12)	56.0 (NE)	43.0 (2.83)	43.8 (7.40)
Median	-	-	-	38.5	56.0	43.0	41.0
Minimum, Maximum	-	-	-	37, 40	56, 56	41, 45	37, 56

NE = not estimated.
Analysis was only on subjects with Grade 2 or higher treatment-emergent skin toxicity. Time to onset was defined as the time from the first dose of study drug to the first occurrence of Grade 2 or higher treatment-emergent skin toxicity. Adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA), Version 20.0. Classification for skin toxicity was based on a search of 430 MedDRA, Version 20.0 preferred terms within the skin system organ class.
Source: Table 14.3.3.3.

Laboratory evaluations

For each of the haematology parameters, the majority of the patients experienced worst CTCAE values of Grade 1 or 2, with the exception of lymphocytes with 22 patients (34%) having worst CTCAE values of Grade 3 and neutrophils with 21 patients (33%) having worst CTCAE values of Grade 4. For each of the chemistry parameters, the majority of the patients experienced worst CTCAE values of Grade 1 or 2.

The majority of patients did not experience shifts from baseline or maintained or experienced improvements from baseline during treatment for haematology and chemistry laboratory parameters.

There were no SAEs related to laboratory parameters. The majority of clinical laboratory-related TEAEs were reported in ≤ 3 patients. Clinical laboratory-related TEAEs reported in > 3 patients were alanine aminotransferase increased (9 patients [14%]), aspartate aminotransferase increased (5 patients [8%]), and blood alkaline phosphatase increased (5 patients [8%]).

Vital signs, physical finding and other observations related to safety

- **Vital signs**- The majority of patients had no changes from baseline to the worst classification during treatment. No notable changes from baseline in vital sign measurements were observed.
- **Electocardiogram**- The majority of patients had no clinically meaningful changes in ECG overall interpretation or ECG values from baseline to the final evaluation. No patients had "abnormal, clinically significant" ECG findings at either baseline or worst postbaseline evaluation. No notable trends in abnormal postbaseline QTc values were observed.
- **Left ventricular shortening fraction assessment**- Overall, there were few shifts from baseline LVSF values and no worst postbaseline visit value was abnormal and clinically significant. The majority of patients had no clinically meaningful changes in the LVSF values from baseline to the final evaluation.
- **Lansky and Karnofsky performance status**- No notable changes from baseline in Lansky and Karnofsky performance status measurements were observed.

– **Pregnancy status**- No pregnancies were reported in female patients of childbearing potential during the study.

Phase 2

Extent of exposure

Exposure to study treatment in Phase 2 is summarised in Table 26. No patients weighing ≤ 10 kg were enrolled, so no patients were dosed by mg/kg.

For the Ewing's sarcoma group, median treatment duration was 14.0 weeks, with minimum and maximum duration 3 and 31 weeks, respectively. The median (range) total number of treatment cycles per patient was 4.0 cycles (range: 1 to 6). Four patients (29%) had at least one dose reduction related to AEs. The mean time to first dose reduction was 10.4 weeks. Two patients (14%) had at least one dose interruption. The mean time to first dose interruption was 8.2 weeks. No dose escalations occurred in this group.

For the neuroblastoma group, median treatment duration was 7.0 weeks, with minimum and maximum duration 3 and 23 weeks, respectively. The median (range) total number of treatment cycles per patient was 2.0 cycles (range: 1 to 6). Six patients (43%) had at least one dose reduction related to AEs. The mean time to first dose reduction was 4.5 weeks. Two patients (14%) had at least one dose interruption. The mean time to first dose interruption was 4.3 weeks. No dose escalations occurred in this group.

For the rhabdomyosarcoma group, median treatment duration was 5.0 weeks, with minimum and maximum duration 1 and 13 weeks, respectively. The median (range) total number of treatment cycles per patient was 2.0 cycles (range: 1 to 4). Four patients (29%) had at least one dose reduction related to AEs. The mean time to first dose reduction was 5.1 weeks. One patient (7%) had at least one dose interruption. The mean time to first dose interruption was 2.6 weeks. No dose escalations occurred in this group.

The RP2D group includes all patients in Phase 1 and Phase 2 treated at 240 mg/m2. The median treatment duration was 7.0 weeks, with minimum and maximum duration 1 and 31 weeks, respectively. The median (range) total number of treatment cycles per patient was 2.0 cycles (range: 1 to 6). Seventeen patients (34%) had at least one dose reduction related to AEs. The mean time to first dose reduction was 6.0 weeks. Eight patients (16%) had at least one dose interruption. The mean time to first dose interruption was 4.8 weeks. One patient (2%) had at least one dose escalation. The mean time to first dose escalation was 13 weeks.

Table 26. Treatment Exposure and Dose Modification – Phase 2 (Safety Population)

	Phase 2 Group			RP2D[a] N = 50	Overall[b] N = 106
	Ewing's Sarcoma N = 14	Neuroblastoma N = 14	Rhabdomyosarcoma N = 14		
Total Number of Treatment Cycles					
Mean (Standard Deviation)	3.5 (1.65)	2.1 (1.17)	1.9 (0.86)	2.6 (1.47)	2.6 (1.83)
Median	4.0	2.0	2.0	2.0	2.0
Minimum, Maximum	1, 6	1, 6	1, 4	1, 6	1, 12
Patients Dosed per Cycle, n (%)					
Cycle 1	14 (100)	14 (100)	14 (100)	50 (100)	106 (100)
Cycle 2	13 (93)	12 (86)	9 (64)	40 (80)	82 (77)
Cycle 3	8 (57)	1 (7)	2 (14)	15 (30)	30 (28)
Cycle 4	8 (57)	1 (7)	1 (7)	14 (28)	25 (24)
Cycle 5	4 (29)	1 (7)	0	7 (14)	13 (12)
Cycle 6	2 (14)	1 (7)	0	3 (6)	6 (6)
Cycle 7	0	0	0	0	3 (3)
Cycle 8	0	0	0	0	3 (3)
Cycle 9	0	0	0	0	2 (2)
Cycle 10	0	0	0	0	2 (2)
Cycle 11	0	0	0	0	1 (1)
Cycle 12	0	0	0	0	1 (1)
Maximum Number of Cycles Received per Patient, n (%)					
1	1 (7)	2 (14)	5 (36)	10 (20)	24 (23)
2	5 (36)	11 (79)	7 (50)	25 (50)	52 (49)
3	0	0	1 (7)	1 (2)	5 (5)
4	4 (29)	0	1 (7)	7 (14)	12 (11)
5	2 (14)	0	0	4 (8)	7 (7)
6	2 (14)	1 (7)	0	3 (6)	3 (3)
7	0	0	0	0	0
8	0	0	0	0	1 (1)
9	0	0	0	0	0
10	0	0	0	0	1 (1)
11	0	0	0	0	0
12	0	0	0	0	1 (1)
Total Number of Doses Taken[c]					
Mean (Standard Deviation)	9.9 (4.73)	5.8 (2.86)	4.4 (2.37)	7.0 (4.19)	7.1 (5.19)
Median	11.0	5.5	4.0	6.0	6.0
Minimum, Maximum	3, 18	3, 15	1, 9	1, 18	1, 36

Treatment Duration (weeks)[d]					
Mean (Standard Deviation)	13.6 (8.21)	7.4 (4.72)	5.4 (3.52)	9.2 (6.68)	9.3 (8.17)
Median	14.0	7.0	5.0	7.0	7.0
Minimum, Maximum	3, 31	3, 23	1, 13	1, 31	1, 49
Patients With at Least One Dose Reduction, n (%)	4 (29)	6 (43)	4 (29)	17 (34)	25 (24)
Frequency of Reductions, n (%)					
1	3 (21)	6 (43)	3 (21)	14 (28)	20 (19)
2	1 (7)	0	1 (7)	2 (4)	4 (4)
3	0	0	0	1 (2)	1 (1)
Reason for Dose Reduction[e], n (%)					
Adverse Event	4 (29)	6 (43)	4 (29)	17 (34)	24 (23)
Other	0	0	0	0	2 (2)
Time to First Reduction (weeks)					
n	4	6	4	17	25
Mean (SD)	10.4 (7.36)	4.5 (2.48)	5.1 (2.94)	6.0 (4.51)	6.1 (4.30)
Median	8.4	4.4	4.6	4.7	4.7
Minimum, Maximum	5, 20	2, 8	2, 9	2, 20	2, 20
Patients With at Least One Dose Escalation, n (%)	0	0	0	1 (2)	5 (5)
Frequency of Escalations, n (%)					
1	0	0	0	1 (2)	4 (4)
2	0	0	0	0	1 (1)
Time to First Escalation (weeks)					
n	0	0	0	1	5
Mean (Standard Deviation)	0	0	0	13.0 (NA)	11.7 (7.29)
Median	0	0	0	13.0	13.0
Minimum, Maximum	0	0	0	13, 13	4, 20
Patients With at Least One Dose Interruption, n (%)	2 (14)	2 (14)	1 (7)	8 (16)	12 (11)
Frequency of Interruptions, n (%)					
1	2 (14)	1 (7)	0	6 (12)	9 (8)
3	0	1 (7)	1 (7)	2 (4)	2 (2)
6	0	0	0	0	1 (1)
Reason for Dose Interruption[e], n (%)					
Adverse Event	1 (7)	2 (14)	1 (7)	7 (14)	11 (10)
Other	1 (7)	1 (7)	0	2 (4)	3 (3)
Time to First Interruption (weeks)					
N	2	2	1	8	12
Mean (Standard Deviation)	8.2 (2.73)	4.3 (3.03)	2.6 (NA)	4.8 (2.93)	4.2 (2.89)
Median	8.2	4.3	2.6	4.4	2.6
Minimum, Maximum	6, 10	2, 6	3, 3	2, 10	1, 10

RP2D = Recommended Phase 2 Dose.
[a] The RP2D column includes all patients in Phase 1 and Phase 2 treated at 240 mg/m^2.
[b] The Overall column includes all patients in Phase 1 and Phase 2 in this table.
[c] The sum of doses completed over all cycles.
[d] Treatment duration = ([date of last study drug administration] — [date of first study drug administration] + 7) / 7.
[e] A subject could have been in multiple categories.
Source: Table 14.3.1.1.1.

Adverse events

A **summary of TEAEs** reported during Phase 2 is provided in Table 27. All patients in Phase 2 experienced at least 1 TEAE during the study.

For the Ewing's sarcoma group, 14 patients (100%) experienced at least 1 TEAE during the study. Serious TEAEs, Grade 3 or 4 TEAEs, and TEAEs leading to death were reported in 6 patients (43%), 12

patients (86%), and 0 patients (0%), respectively. Treatment-emergent AEs related to the study drug were reported in 13 patients (93%). Four patients (29%) experienced a TEAE leading to dose reduction, 5 patients (36%) experienced a TEAE leading to drug interruption, and 3 patients (21%) experienced a TEAE leading to drug discontinuation.

For the neuroblastoma group, 14 patients (100%) experienced at least 1 TEAE during the study. Serious TEAEs, Grade 3 or 4 TEAEs, and TEAEs leading to death were reported in 6 patients (43%), 13 patients (93%), and 2 patients (14%), respectively. Treatment-emergent AEs related to the study drug were reported in 12 patients (86%). Five patients (36%) experienced a TEAE leading to dose reduction, 3 patients (21%) experienced a TEAE leading to drug interruption, and 1 patients (7%) experienced a TEAE leading to drug discontinuation.

For the rhabdomyosarcoma group, 14 patients (100%) experienced at least 1 TEAE during the study. Serious TEAEs, Grade 3 or 4 TEAEs, and TEAEs leading to death were reported in 11 patients (79%), 12 patients (86%), and 3 patients (21%), respectively. Treatment-emergent AEs related to the study drug were reported in 12 patients (86%). Four patients (29%) experienced a TEAE leading to dose reduction, 4 patients (29%) experienced a TEAE leading to drug interruption, and 3 patients (21%) experienced a TEAE leading to drug discontinuation.

For the RP2D group, 50 patients (100%) experienced at least 1 TEAE during the study. Serious TEAEs, Grade 3 or 4 TEAEs, and TEAEs leading to death were reported in 26 patients (52%), 45 patients (90%), and 6 patients (12%), respectively. Treatment-emergent AEs related to the study drug were reported in 44 patients (88%). Sixteen patients (32%) experienced a TEAE leading to dose reduction, 15 patients (30%) experienced a TEAE leading to drug interruption, and 9 patients (18%) experienced a TEAE leading to drug discontinuation.

Table 27. Summary of Treatment-emergent Adverse Events – Phase 2 (Safety Population)

	Phase 2 Group			RP2D[a] N = 50 n (%)	Overall[b] N = 106 n (%)
Patients With at Least 1	Ewing's Sarcoma N = 14 n (%)	Neuroblastoma N = 14 n (%)	Rhabdomyosarcoma N = 14 n (%)		
TEAE	14 (100)	14 (100)	14 (100)	50 (100)	106 (100)
Treatment-related TEAE	13 (93)	12 (86)	12 (86)	44 (88)	96 (91)
Grade 3 or 4 TEAE	12 (86)	13 (93)	12 (86)	45 (90)	93 (88)
Treatment-related Grade 3 or 4 TEAE	9 (64)	9 (64)	10 (71)	35 (70)	74 (70)
Serious TEAE	6 (43)	6 (43)	11 (79)	26 (52)	58 (55)
Treatment-related Serious TEAE	2 (14)	2 (14)	6 (43)	11 (22)	25 (24)
TEAE Leading to Drug Discontinuation	3 (21)	1 (7)	3 (21)	9 (18)	18 (17)
Treatment-related TEAE Leading to Drug Discontinuation	1 (7)	0	3 (21)	6 (12)	10 (9)
TEAE Leading to Dose Reduction	4 (29)	5 (36)	4 (29)	16 (32)	23 (22)
Treatment-related TEAE Leading to Dose Reduction	4 (29)	4 (29)	4 (29)	15 (30)	22 (21)
TEAE Leading to Drug Interruption	5 (36)	3 (21)	4 (29)	15 (30)	28 (26)
Treatment-related TEAE Leading to Drug Interruption	3 (21)	3 (21)	2 (14)	11 (22)	19 (18)
TEAE Leading to Death	0	2 (14)	3 (21)	6 (12)	10 (9)
Treatment-related TEAE Leading to Death	0	0	0	0	0

RP2D = Recommended Phase 2 Dose; TEAE = treatment-emergent adverse event.
Treatment-emergent adverse events were defined as adverse events (AEs) that began or worsened in severity on or after the date of the first dose of study drug and within 28 days of the date of the last dose of study drug. The severity of the AEs was graded according to the Common Terminology Criteria for Adverse Events, Version 4.0. Adverse events were coded using Medical Dictionary for Regulatory Activities, Version 20.0.
[a] The RP2D column includes all patients in Phase 1 and Phase 2 treated at 240 mg/m^2.
[b] The Overall column includes all patients in Phase 1 and Phase 2 in this table.
Source: Table 14.3.1.3.

A summary of the **most frequently reported TEAEs** (≥ 20% of patients in any group) during Phase 2 is provided in Table 28.

For the Ewing's sarcoma group, the SOCs with the highest proportion of patients reporting TEAEs during Phase 2 were general disorders and administration site conditions (12 patients [86%]), gastrointestinal disorders (12 patients [86%]), blood and lymphatic system disorders (11 patients [79%]), musculoskeletal and connective tissue disorders (10 patients [71%]), and nervous system disorders (8 patients [57%]). The most frequently reported TEAEs (in > 35% of patients) were anaemia (9 patients [64%]), pyrexia (9 patients [64%]), pain in extremity (8 patients [57%]), neutropaenia (7 patients [50%]), leukopaenia (6 patients [43%]), and diarrhoea (5 patients [36%]).

For the neuroblastoma group, the SOCs with the highest proportion of patients reporting TEAEs during Phase 2 were blood and lymphatic system disorders (12 patients [86%]), general disorders and administration site conditions (8 patients [57%]), and gastrointestinal disorders (8 patients [57%]). The most frequently reported TEAEs (in > 35% of patients) were anaemia (9 patients [64%]), neutropaenia (8 patients [57%]), leukopaenia (6 patients [43%]), thrombocytopaenia (6 patients [43%]), pain in extremity (5 patients [36%]), and headache (5 patients [36%]).

For the rhabdomyosarcoma group, the SOCs with the highest proportion of patients reporting TEAEs during Phase 2 were blood and lymphatic system disorders (12 patients [86%]), gastrointestinal disorders (11 patients [79%]), general disorders and administration site conditions (10 patients [71%]), and skin and subcutaneous tissues disorders (8 patients [57%]). The most frequently reported TEAEs (in > 35% of patients) were anaemia (9 patients [64%]), neutropaenia (8 patients [57%]), leukopaenia (6 patients [43%]), vomiting (6 patients [43%]), constipation (5 patients [36%]), nausea (5 patients [36%]), and pyrexia (5 patients [36%]).

The RP2D group included all patients in Phase 1 and Phase 2 treated at 240 mg/m2. The SOCs with the highest proportion of patients reporting TEAEs were blood and lymphatic system disorders (43 patients [86%]), general disorders and administration site conditions (38 patients [76%]), gastrointestinal disorders (38 patients [76%]), skin and subcutaneous tissues disorders (30 patients [60%]), nervous system disorders (27 patients [54%]), and musculoskeletal and connective tissue disorders (26 patients [52%]). The most frequently reported TEAEs (in > 35% of patients) were anaemia (33 patients [66%]), neutropaenia (30 patients [60%]), leukopaenia (23 patients [46%]), pyrexia (23 patients [46%]), and pain in extremity (20 patients [40%]).

Table 28. TEAEs by SOC and PT (in at Least 20% of Patients in Any Phase 2 Group) – Phase 2 (Safety Population)

| System Organ Class[a] Preferred Term | Phase 2 Group | | | RP2D[b] N = 50 n (%) | Overall[c] N = 106 n (%) |
	Ewing's Sarcoma N = 14 n (%)	Neuroblastoma N = 14 n (%)	Rhabdomyosarcoma N = 14 n (%)		
Patients With at Least 1 TEAE	14 (100)	14 (100)	14 (100)	50 (100)	106 (100)
Blood and Lymphatic System Disorders	11 (79)	12 (86)	12 (86)	43 (86)	88 (83)
Anaemia	9 (64)	9 (64)	9 (64)	33 (66)	64 (60)
Neutropenia	7 (50)	8 (57)	8 (57)	30 (60)	61 (58)
Leukopenia	6 (43)	6 (43)	6 (43)	23 (46)	41 (39)
Thrombocytopenia	0	6 (43)	3 (21)	11 (22)	21 (20)
Febrile Neutropenia	1 (7)	0	3 (21)	5 (10)	7 (7)
General Disorders and Administration Site Conditions	12 (86)	8 (57)	10 (71)	38 (76)	81 (76)
Pyrexia	9 (64)	4 (29)	5 (36)	23 (46)	50 (47)
Oedema Peripheral	4 (29)	2 (14)	2 (14)	9 (18)	20 (19)
Asthenia	4 (29)	1 (7)	4 (29)	12 (24)	17 (16)
Gastrointestinal Disorders	12 (86)	8 (57)	11 (79)	38 (76)	78 (74)
Vomiting	4 (29)	4 (29)	6 (43)	17 (34)	35 (33)
Nausea	4 (29)	1 (7)	5 (36)	12 (24)	30 (28)
Constipation	4 (29)	1 (7)	5 (36)	12 (24)	29 (27)
Diarrhoea	5 (36)	2 (14)	1 (7)	12 (24)	28 (26)
Abdominal Pain	4 (29)	1 (7)	2 (14)	10 (20)	22 (21)
Stomatitis	3 (21)	2 (14)	3 (21)	9 (18)	15 (14)
Skin and Subcutaneous Tissue Disorders	7 (50)	7 (50)	8 (57)	30 (60)	62 (58)
Alopecia	3 (21)	2 (14)	1 (7)	9 (18)	26 (25)
Erythema	3 (21)	1 (7)	3 (21)	9 (18)	13 (12)
Pruritus Generalized	1 (7)	1 (7)	3 (21)	5 (10)	12 (11)
Rash Maculo-papular	4 (29)	2 (14)	1 (7)	9 (18)	11 (10)
Musculoskeletal and Connective Tissue Disorders	10 (71)	6 (43)	4 (29)	26 (52)	54 (51)
Pain in Extremity	8 (57)	5 (36)	4 (29)	20 (40)	29 (27)
Arthralgia	3 (21)	0	0	5 (10)	14 (13)
Nervous System Disorders	8 (57)	6 (43)	7 (50)	27 (54)	52 (49)
Headache	3 (21)	5 (36)	4 (29)	13 (26)	24 (23)
Metabolism and Nutrition Disorders	6 (43)	3 (21)	4 (29)	15 (30)	38 (36)
Hypokalaemia	3 (21)	0	2 (14)	6 (12)	15 (14)
Eye Disorders	1 (7)	3 (21)	5 (36)	10 (20)	21 (20)
Vision Blurred	0	1 (7)	4 (29)	6 (12)	7 (7)

RP2D = Recommended Phase 2 Dose; TEAE = treatment-emergent adverse event.
Treatment-emergent adverse events were defined as adverse events (AEs) that began or worsened in severity on or after the date of the first dose of study drug and within 28 days of the date of the last dose of study drug.
[a] Adverse events were coded using Medical Dictionary for Regulatory Activities, Version 20.0. Patients with multiple AEs were counted once for each system organ class and/or preferred term using worst reported grade.
[b] The RP2D column includes all patients in Phase 1 and Phase 2 treated at 240 mg/m^2.
[c] The Overall column includes all patients in Phase 1 and Phase 2 in this table.

The majority of the TEAEs were Grade 1 (40 patients [95%]) and Grade 2 (36 patients [86%]) in severity. **Grade 3 or 4 TEAEs** reported in ≥ 2 patients in any Phase 2 group are summarised in Table 29.

For the Ewing's sarcoma group, the majority of the Grade 3 or 4 TEAEs were reported in ≤ 2 patients overall. Grade 3 or 4 TEAEs reported in more than 2 patients were neutropaenia (6 patients [43%]), anaemia (5 patients [36%]), and leukopaenia (5 patients [36%]). Of these, Grade 4 TEAEs were reported in 3 patients (21%), none of which were reported in > 2 patients.

For the neuroblastoma group, the majority of the Grade 3 or 4 TEAEs were reported in ≤ 2 patients overall. Grade 3 or 4 TEAEs reported in more than 2 patients were anaemia (8 patients [57%]), neutropaenia (8 patients [57%]), leukopaenia (6 patients [43%]), and thrombocytopaenia (5 patients [36%]). Of these, Grade 4 TEAEs were reported in 8 patients (57%), with the only Grade 4 TEAEs reported in > 2 patients being neutropaenia (5 patients [36%]) and thrombocytopaenia (3 patients [21%]).

For the rhabdomyosarcoma group, the majority of the Grade 3 or 4 TEAEs were reported in ≤ 2 patients overall. Grade 3 or 4 TEAEs reported in more than 2 patients were anaemia (7 patients [50%]), neutropaenia (7 patients [50%]), leukopaenia (5 patients [36%]), and febrile neutropaenia (3 patients [21%]). Of these, Grade 4 TEAEs were reported in 5 patients (36%), with the only Grade 4 TEAE reported in > 2 patients being neutropaenia (3 patients [21%]).

In the RP2D group the majority of the Grade 3 or 4 TEAEs were reported in ≤ 3 patients overall. Grade 3 or 4 TEAEs reported in more than 3 patients were neutropaenia (28 patients [56%]), anaemia (22 patients [44%]), leukopaenia (20 patients [40%]), thrombocytopaenia (8 patients [16%]), and febrile neutropaenia (5 patients [10%]). Of these, Grade 4 TEAEs were reported in 21 patients (42%). The majority of the Grade 4 TEAEs were reported in ≤ 3 patients overall. Grade 4 TEAEs reported in more than 3 patients were neutropaenia (15 patients [30%]), leukopaenia (6 patients [12%]), and thrombocytopaenia (6 patients [12%]).

Table 29. Grade 3 and 4 TEAEs by SOC and PT (in 2 or More Patients in Any Phase 2 Group) – Phase 2 (Safety Population)

System Organ Class Preferred Term[a]	Phase 2 Group			RP2D[b] N = 50 n (%)	Overall[c] N = 106 n (%)
	Ewing's Sarcoma N = 14 n (%)	Neuroblastoma N = 14 n (%)	Rhabdomyosarcoma N = 14 n (%)		
Patients With at Least 1 TEAE	12 (86)	13 (93)	12 (86)	45 (90)	93 (88)
Blood and Lymphatic System Disorders	10 (71)	12 (86)	11 (79)	41 (82)	80 (75)
Anaemia	5 (36)	8 (57)	7 (50)	22 (44)	37 (55)
Neutropenia	6 (43)	8 (57)	7 (50)	28 (56)	55 (52)
Leukopenia	5 (36)	6 (43)	5 (36)	20 (40)	33 (31)
Lymphopenia	2 (14)	0	0	3 (6)	13 (12)
Thrombocytopenia	0	5 (36)	2 (14)	8 (16)	10 (9)
Febrile Neutropenia	1 (7)	0	3 (21)	5 (10)	7 (7)
General Disorders and Administration Site Conditions	1 (7)	2 (14)	2 (14)	6 (12)	12 (11)
General Physical Health Deterioration	0	2 (14)	1 (7)	3 (6)	4 (4)
Nervous System Disorders	0	1 (7)	4 (29)	7 (14)	13 (12)
Headache	0	1 (7)	2 (14)	3 (6)	4 (4)
Metabolism and Nutrition Disorders	3 (21)	0	1 (7)	4 (8)	11 (10)
Hypokalaemia	2 (14)	0	0	2 (4)	4 (4)

RP2D = Recommended Phase 2 Dose; TEAE = treatment-emergent adverse event.
Treatment-emergent adverse events were defined as adverse events (AEs) that began or worsened in severity on or after the date of the first dose of study drug and within 28 days of the date of the last dose of study drug.
[a] Adverse events were coded using Medical Dictionary for Regulatory Activities, Version 20.0. Patients with multiple AEs were counted once for each system organ class and/or preferred term using worst reported grade.
[b] The RP2D column includes all patients in Phase 1 and Phase 2 treated at 240 mg/m^2.
[c] The Overall column includes all patients in Phase 1 and Phase 2 in this table.
Source: Table 14.3.1.14.

Treatment-related TEAEs reported in ≥ 10% of patients in any Phase 2 group are summarised in Table 30.

For the Ewing's sarcoma group, treatment-related TEAEs were reported in 13 patients (93%). The most frequently reported treatment-related TEAEs (in > 35% of patients overall) were neutropaenia (7 patients [50%]), anaemia (6 patients [43%]), and leukopaenia (6 patients [43%]). Treatment-related

Grade 3 or 4 TEAEs reported in more than 3 patients were neutropaenia (6 patients [43%]) and leukopaenia (5 patients [36%]).

For the neuroblastoma group, treatment-related TEAEs were reported in 12 patients (86%). The most frequently reported treatment-related TEAEs (in > 35% of patients overall) were neutropaenia (6 patients [43%]) and anaemia (6 patients [43%]). Treatment-related Grade 3 or 4 TEAEs reported in more than 2 patients were neutropaenia (6 patients [43%]), anaemia (5 patients [36%]), and leukopaenia (4 patients [29%]).

For the rhabdomyosarcoma group, treatment-related TEAEs were reported in 12 patients (86%). The most frequently reported treatment-related TEAEs (in > 35% of patients overall) were neutropaenia (8 patients [57%]), anaemia (6 patients [43%]), and leukopaenia (5 patients [36%]). Treatment-related Grade 3 or 4 TEAEs reported in more than 2 patients were neutropaenia (7 patients [50%]), anaemia (4 patients [29%]), leukopaenia (4 patients [29%]), and febrile neutropaenia (3 patients [21%]).

The RP2D group included all patients in Phase 1 and Phase 2 treated at 240 mg/m2. Treatment-related TEAEs were reported in 44 patients (88%). The most frequently reported treatment-related TEAEs (in > 35% of patients overall) were neutropaenia (27 patients [54%]), anaemia (21 patients [42%]), and leukopaenia (19 patients [38%]). Treatment-related Grade 3 or 4 TEAEs reported in more than 3 patients were neutropaenia (25 patients [50%]), leukopaenia (16 patients [32%]), anaemia (13 patients [26%]), febrile neutropaenia (5 patients [10%]), and thrombocytopaenia (4 patients [8%]).

Table 30. TEAEs Related to Study Drug by SOC and PT (in at Least 10% of Patients in Any Phase 2 Group) – Phase 2 (Safety Population)

System Organ Class Preferred Term[a]	Phase 2 Group			RP2D[b] N = 50 n (%)	Overall[c] N = 106 n (%)
	Ewing's Sarcoma N = 14 n (%)	Neuroblastoma N = 14 n (%)	Rhabdomyosarcoma N = 14 n (%)		
Patients With at Least 1 Treatment-related TEAE	13 (93)	12 (86)	12 (86)	44 (88)	96 (91)
Blood and Lymphatic System Disorders	9 (64)	9 (64)	10 (71)	34 (68)	73 (69)
Neutropenia	7 (50)	6 (43)	8 (57)	27 (54)	57 (54)
Anaemia	6 (43)	6 (43)	6 (43)	21 (42)	46 (43)
Leukopenia	6 (43)	4 (29)	5 (36)	19 (38)	36 (34)
Lymphopenia	2 (14)	1 (7)	1 (7)	6 (12)	17 (16)
Thrombocytopenia	0	3 (21)	3 (21)	7 (14)	17 (16)
Febrile neutropenia	1 (7)	0	3 (21)	5 (10)	7 (7)
Skin and Subcutaneous Tissue Disorders	6 (43)	7 (50)	4 (29)	23 (46)	52 (49)
Alopecia	3 (21)	2 (14)	1 (7)	9 (18)	26 (25)
Rash Maculo-papular	4 (29)	2 (14)	1 (7)	9 (18)	10 (9)
Erythema	3 (21)	1 (7)	1 (7)	6 (12)	9 (8)
Skin Exfoliation	1 (7)	2 (14)	0	3 (6)	5 (5)
Photosensitivity Reaction	0	2 (14)	1 (7)	3 (6)	4 (4)
General Disorders and Administration Site Conditions	7 (50)	5 (36)	5 (36)	21 (42)	46 (43)
Pyrexia	4 (29)	2 (14)	3 (21)	11 (22)	23 (22)
Oedema Peripheral	2 (14)	2 (14)	1 (7)	5 (10)	10 (9)
Asthenia	2 (14)	0	1 (7)	5 (10)	9 (8)
Gastrointestinal Disorders	5 (36)	3 (21)	5 (36)	19 (38)	40 (38)
Diarrhoea	2 (14)	0	0	5 (10)	15 (14)
Vomiting	1 (7)	2 (14)	1 (7)	6 (12)	13 (12)
Stomatitis	1 (7)	2 (14)	3 (21)	7 (14)	12 (11)
Nervous System Disorders	3 (21)	1 (7)	4 (29)	13 (26)	25 (24)
Peripheral Sensory Neuropathy	1 (7)	0	2 (14)	6 (12)	11 (10)
Metabolism and Nutrition Disorders	2 (14)	1 (7)	1 (7)	6 (12)	18 (17)
Decreased Appetite	2 (14)	1 (7)	0	4 (8)	11 (10)
Musculoskeletal and Connective Tissue Disorders	4 (29)	1 (7)	0	6 (12)	14 (13)
Pain in Extremity	3 (21)	1 (7)	0	4 (8)	6 (6)
Eye Disorders	1 (7)	1 (7)	2 (14)	4 (8)	7 (7)
Vision Blurred	0	1 (7)	2 (14)	3 (6)	3 (3)

RP2D = Recommended Phase 2 Dose; TEAE = treatment-emergent adverse event.
Treatment-emergent adverse events were defined as adverse events (AEs) that began or worsened in severity on or after the date of the first dose of study drug and within 28 days of the date of the last dose of study drug.
[a] Adverse events were coded using Medical Dictionary for Regulatory Activities, Version 20.0. Patients with multiple AEs were counted once for each system organ class and/or preferred term using worst reported grade.
[b] The RP2D column includes all patients in Phase 1 and Phase 2 treated at 240 mg/m².
[c] The Overall column includes all patients in Phase 1 and Phase 2 in this table.
Source: Table 14.3.1.6.

A summary of **TEAEs by age group** (< 2 years, ≥ 2 years to < 12 years, ≥ 12 years to < 18 years, ≥18 years to ≤ 24 years) is provided in Table 14.3.1.5. A summary of TEAEs related to the study drug by age group is provided in Table 14.3.1.7. Summaries of Grade 3 or 4 TEAEs by age group and Grade 3 or 4 TEAEs related to the study drug by age group are provided in Table 14.3.1.15 and Table 14.3.1.17, respectively. The limited numbers of different subgroups however precludes meaningful conclusions regarding these TEAEs.

Serious adverse events

SAEs

Serious TEAEs reported during Phase 2 are summarised in Table 31.

For the Ewing's sarcoma group, 6 patients (43%) experienced at least 1 serious TEAE. The majority of serious TEAEs were reported in 1 patient each. Serious TEAEs reported in > 1 patient were pneumothorax (2 patients [14%]) and pyrexia (2 patients [14%]). The only treatment-related serious TEAE reported in > 1 patient was pyrexia (2 patients [14%]).

For the neuroblastoma group, 6 patients (43%) experienced at least 1 serious TEAE. The majority of serious TEAEs were reported in 1 patient each. Serious TEAEs reported in > 1 patient were general physical health deterioration (2 patients [14%]), pyrexia (2 patients [14%]), and thrombocytopaenia (2 patients [14%]). No treatment-related serious TEAEs were reported in > 1 patient.

For the rhabdomyosarcoma group, 11 patients (79%) experienced at least 1 serious TEAE. The majority of serious TEAEs were reported in 1 patient each. Serious TEAEs reported in > 1 patient were febrile neutropaenia (3 patients [21%]), general physical health deterioration (2 patients [14%]), headache (2 patients [14%]), and pyrexia (2 patients [14%]). The only treatment-related serious TEAE reported in > 1 patient was febrile neutropaenia (3 patients [21%]).

The RP2D group included all patients in Phase 1 and Phase 2 treated at 240 mg/m2. Twenty-six patients (52%) experienced at least 1 serious TEAE. The majority of serious TEAEs were reported in 1 patient each. Serious TEAEs reported in > 1 patient were pyrexia (7 patients [14%]), general physical health deterioration (5 patients [10%]), febrile neutropaenia (4 patients [8%]), acute kidney injury (2 patients [4%]), headache (2 patients [4%]), pneumothorax (2 patients [4%]), seizure (2 patients [4%]), and thrombocytopaenia (2 patients [4%]). Treatment-related serious TEAEs reported in > 1 patient were pyrexia (4 patients [8%]) and febrile neutropaenia (4 patients [8%]).

Table 31. Treatment-emergent Serious Adverse Events by System Organ Class and Preferred Term – Phase 2 (Safety Population)

System Organ Class Preferred Term[a]	Phase 2 Group			RP2D[b] N = 50 n (%)	Overall[c] N = 106 n (%)
	Ewing's Sarcoma N = 14 n (%)	Neuroblastoma N = 14 n (%)	Rhabdomyosarcoma N = 14 n (%)		
Patients With at Least 1 Serious TEAE	6 (43)	6 (43)	11 (79)	26 (52)	58 (55)
General Disorders and Administration Site Conditions	2 (14)	3 (21)	4 (29)	11 (22)	24 (23)
Pyrexia	2 (14)	2 (14)	2 (14)	7 (14)	17 (16)
General Physical Health Deterioration	0	2 (14)	2 (14)	5 (10)	6 (6)
Oedema Peripheral	0	0	0	0	3 (3)
Chills	0	0	0	0	1 (1)
Generalised Oedema	0	0	0	0	1 (1)
Blood and Lymphatic System Disorders	1 (7)	2 (14)	4 (29)	7 (14)	13 (12)
Febrile Neutropenia	1 (7)	0	3 (21)	4 (8)	6 (6)
Neutropenia	0	0	1 (7)	1 (2)	3 (3)
Thrombocytopenia	0	2 (14)	0	2 (4)	3 (3)
Leukopenia	0	0	0	0	1 (1)
Respiratory, Thoracic, and Mediastinal Disorders	2 (14)	1 (7)	1 (7)	4 (8)	8 (8)
Pleural Effusion	1 (7)	0	0	1 (2)	3 (3)
Dyspnoea	0	1 (7)	0	1 (2)	2 (2)
Pneumothorax	2 (14)	0	0	2 (4)	2 (2)
Hypoxia	0	0	0	0	1 (1)
Pneumonitis	0	0	0	0	1 (1)
Pulmonary Embolism	0	0	0	0	1 (1)
Respiratory Failure	0	0	1 (7)	1 (2)	1 (1)
Gastrointestinal Disorders	0	1 (7)	1 (7)	2 (4)	7 (7)
Vomiting	0	1 (7)	0	1 (2)	4 (4)
Abdominal Pain	0	0	1 (7)	1 (2)	2 (2)
Diarrhoea	0	0	0	0	2 (2)
Nausea	0	0	0	0	1 (1)
Infections and Infestations	2 (14)	1 (7)	1 (7)	4 (8)	7 (7)
Cellulitis	0	0	0	0	1 (1)
Device-related Infection	1 (7)	0	0	1 (2)	1 (1)
Gastroenteritis	1 (7)	0	0	1 (2)	1 (1)
Lower Respiratory Tract Infection Bacterial	0	0	1 (7)	1 (2)	1 (1)
Pneumonia	0	0	0	0	1 (1)
Soft Tissue Infection	0	0	0	0	1 (1)
Staphylococcal Bacteraemia	0	1 (7)	0	1 (2)	1 (1)
Varicella	0	1 (7)	0	1 (2)	1 (1)

Nervous System Disorders	0	1 (7)	2 (14)	4 (8)	7 (7)
Dizziness	0	1 (7)	0	1 (2)	2 (2)
Headache	0	0	2 (14)	2 (4)	2 (2)
Intracranial Pressure Increased	0	0	1 (7)	1 (2)	2 (2)
Seizure	0	0	1 (7)	2 (4)	2 (2)
Slow Speech	0	0	1 (7)	1 (2)	1 (1)
Somnolence	0	0	0	0	1 (1)
Tremor	0	1 (7)	0	1 (2)	1 (1)
Musculoskeletal and Connective Tissue Disorders	1 (7)	0	0	1 (2)	5 (5)
Back Pain	0	0	0	0	3 (3)
Pain in Extremity	1 (7)	0	0	1 (2)	2 (2)
Bone Pain	1 (7)	0	0	1 (2)	1 (1)
Neoplasms Benign, Malignant, and Unspecified (Including Cysts and Polyps)	0	0	0	0	5 (5)
Cancer Pain	0	0	0	0	1 (1)
Osteosarcoma	0	0	0	0	1 (1)
Osteosarcoma Metastatic	0	0	0	0	1 (1)
Refractory Anaemia With an Excess of Blasts	0	0	0	0	1 (1)
Tumour Pain	0	0	0	0	1 (1)
Renal and Urinary Disorders	1 (7)	0	1 (7)	2 (4)	5 (5)
Acute Kidney Injury	1 (7)	0	1 (7)	2 (4)	3 (3)
Anuria	0	0	0	0	1 (1)
Urinary Retention	0	0	0	0	1 (1)
Urinary Tract Obstruction	0	0	0	0	1 (1)
Skin and Subcutaneous Tissue Disorders	0	1 (7)	0	2 (4)	3 (3)
Dermatitis Acneiform	0	0	0	0	1 (1)
Dermatitis Bullous	0	0	0	1 (2)	1 (1)
Erythema	0	1 (7)	0	1 (2)	1 (1)
Skin Exfoliation	0	1 (7)	0	1 (2)	1 (1)
Vascular Disorders	0	0	0	0	3 (3)
Hypotension	0	0	0	0	2 (2)
Hypertension	0	0	0	0	1 (1)
Metabolism and Nutrition Disorders	0	0	0	0	2 (2)
Hyponatraemia	0	0	0	0	2 (2)
Dehydration	0	0	0	0	1 (1)
Hypercreatininaemia	0	0	0	0	1 (1)
Cardiac Disorders	0	0	0	0	1 (1)
Tachycardia	0	0	0	0	1 (1)
Injury, Poisoning, and Procedural Complications	0	0	1 (7)	1 (2)	1 (1)
Anaphylactic Transfusion Reaction	0	0	1 (7)	1 (2)	1 (1)
Psychiatric Disorders	0	0	0	0	1 (1)
Restlessness	0	0	0	0	1 (1)

RP2D = Recommended Phase 2 Dose; TEAE = treatment-emergent adverse event.

Treatment-emergent adverse events were defined as adverse events (AEs) that began or worsened in severity on or after the date of the first dose of study drug and within 28 days of the date of the last dose of study drug.

[a] Adverse events were coded using Medical Dictionary for Regulatory Activities, Version 20.0. Patients with multiple AEs were counted once for each system organ class and/or preferred term using worst reported grade.

[b] The RP2D column includes all patients in Phase 1 and Phase 2 treated at 240 mg/m^2.

[c] The Overall column includes all patients in Phase 1 and Phase 2 in this table.

Source: Table 14.3.2.1.

Deaths

A summary of deaths and causes of death by category is presented in Table 32. During Phase 2, 6 patients (43%), 8 patients (57%), and 11 patients (79%) died in the Ewing's sarcoma, neuroblastoma, and rhabdomyosarcoma groups, respectively; all were attributed to "death from malignant disease under study, or complication due to malignant disease under study." None of these deaths were related to treatment. Five patients experienced TEAEs with the outcome of death during Phase 2. Two patients experienced an event of general physical health deterioration due to disease progression (1 patient each in the neuroblastoma [verbatim term: worsening deterioration due to progression disease] and rhabdomyosarcoma [verbatim term: symptomatic deterioration due to progression of disease] groups). Two patients experienced an event of general physical health deterioration (1 patient each in the neuroblastoma [verbatim term: physical deterioration] and rhabdomyosarcoma [verbatim term: symptomatic deterioration] groups). One patient in the rhabdomyosarcoma group experienced an event of respiratory failure due to disease progression.

Table 32. Summary of Deaths and Causes of Death Category – Phase 2 (Safety Population)

Primary Cause	Phase 2 Group			RP2D[a] N = 50 n (%)	Overall[b] N = 106 n (%)
	Ewing's Sarcoma N = 14 n (%)	Neuroblastoma N = 14 n (%)	Rhabdomyosarcoma N = 14 n (%)		
Number of Deaths	6 (43)	8 (57)	11 (79)	33 (66)	75 (71)
Cause of Death					
Death From Malignant Disease Under Study, or Complication Due to Malignant Disease Under Study	6 (43)	8 (57)	11 (79)	33 (66)	75 (71)

RP2D = Recommended Phase 2 Dose.
[a] The RP2D column includes all patients in Phase 1 and Phase 2 treated at 240 mg/m^2.
[b] The Overall column includes all patients in Phase 1 and Phase 2 in this table.
Source: Table 14.3.2.5.

Discontinuations

Study drug discontinuations

For the Ewing's sarcoma group, 3 patients (21%) had a TEAE leading to study drug discontinuation. The TEAEs leading to study drug discontinuation were pneumothorax (2 patients [14%]), disease progression (1 patient [7%]), peripheral sensorimotor neuropathy (1 patient [7%]), and pleural effusion (1 patient [7%]). One patient (7%) had a TEAE (peripheral sensorimotor neuropathy) related to the study drug leading to drug discontinuation.

For the neuroblastoma group, 1 patient (7%) had a TEAE (general physical health deterioration) leading to study drug discontinuation. No patients had a TEAE related to the study drug leading to drug discontinuation.

For the rhabdomyosarcoma group, 3 patients (21%) had a TEAE leading to study drug discontinuation. The TEAEs leading to study drug discontinuation were peripheral sensory neuropathy (2 patients [14%]) and neuralgia (1 patient [7%]). In 3 patients (21%) the TEAE leading to drug discontinuation was related to the study drug. The TEAEs related to the study drug leading to study drug discontinuation were peripheral sensory neuropathy (2 patients [14%]) and neuralgia (1 patient [7%]).

For the RP2D group, 9 patients (18%) had a TEAE leading to study drug discontinuation. The majority of TEAEs leading to study drug discontinuation were reported in 1 patient each. The TEAEs leading to study drug discontinuation reported in > 1 patient were peripheral sensorimotor neuropathy (2 patients [4%]) and pneumothorax (2 patients [4%]). 6 patients (12%) had a TEAE related to the study drug leading to drug discontinuation. The majority of TEAEs related to the study drug leading to

drug discontinuation were reported in 1 patient each. The TEAE related to the study drug leading to study drug discontinuation reported in > 1 patient was peripheral sensory neuropathy (2 patients [4%]).

Dose reductions

For the Ewing's sarcoma group, 4 patients (29%) had a TEAE leading to dose reduction. The TEAEs leading to dose reduction were reported in 1 patient each and were erythema, febrile neutropaenia, hyperchromasia, and neutropaenia. 4 patients (29%) had a TEAE related to the study drug leading to dose reduction. The TEAEs related to the study drug leading to dose reduction were reported in 1 patient each and were erythema, febrile neutropaenia, hyperchromasia, and neutropaenia.

For the neuroblastoma group, 5 patients (36%) had a TEAE leading to dose reduction. The TEAEs leading to dose reduction were neutropaenia (3 patients [21%]), stomatitis (1 patient [7%]), and thrombocytopaenia (1 patient [7%]). 4 patients (29%) had a TEAE related to the study drug leading to dose reduction. The TEAEs related to the study drug leading to dose reduction were neutropaenia (3 patients [21%]) and stomatitis (1 patient [7%]).

For the rhabdomyosarcoma group, 4 patients (29%) had a TEAE leading to dose reduction. The TEAEs leading to dose reduction were neutropaenia (3 patients [21%]), febrile neutropaenia (1 patient [7%]), peripheral sensory neuropathy (1 patient [7%]), and thrombocytopaenia (1 patient [7%]). 4 patients (29%) had a TEAE related to the study drug leading to dose reduction. The TEAEs related to the study drug leading to dose reduction were neutropaenia (3 patients [21%]), febrile neutropaenia (1 patient [7%]), peripheral sensory neuropathy (1 patient [7%]), and thrombocytopaenia (1 patient [7%]).

For the RP2D group, 16 patients (32%) had a TEAE leading to dose reduction. The majority of TEAEs leading to dose reduction were reported in 1 patient each. The TEAEs leading to dose reduction reported in > 1 patient were neutropaenia (9 patients [18%]), febrile neutropaenia (2 patients [4%]), and thrombocytopaenia (2 patients [4%]). In 15 patients (30%) the TEAE leading to dose reduction was related to the study drug. The majority of TEAEs related to the study drug leading to dose reduction were reported in 1 patient each. The TEAEs related to the study drug leading to dose reduction reported in > 1 patient were neutropaenia (9 patients [18%]) and febrile neutropaenia (2 patients [4%]).

Study drug interruption

For the Ewing's sarcoma group, 5 patients (36%) had a TEAE leading to study drug interruption. The TEAEs leading to study drug interruption were reported in 1 patient each and were gamma-glutamyltransferase increased, neuralgia, rash maculo-papular, pneumonitis, pruritus, and pyrexia. 3 patients (21%) had a TEAE related to the study drug leading to study drug interruption. The TEAEs related to the study drug leading to dose interruption were reported in 1 patient each and were gamma-glutamyltransferase increased, neuralgia, rash maculo-papular, and pruritus.

For the neuroblastoma group, 3 patients (21%) had a TEAE leading to study drug interruption. The TEAEs leading to study drug interruption were skin exfoliation (2 patients [14%]), dizziness (1 patient [7%]), dyspnoea (1 patient [7%]), erythema (1 patient [7%]), neuralgia (1 patient [7%]), neutropaenia (1 patient [7%]), tremor (1 patient [7%]), and varicella (1 patient [7%]). 3 patients (21%) had a TEAE related to the study drug leading to study drug interruption. The TEAEs related to the study drug leading to study drug interruption were skin exfoliation (2 patients [14%]), dizziness (1 patient [7%]), dyspnoea (1 patient [7%]), erythema (1 patient [7%]), neuralgia (1 patient [7%]), neutropaenia (1 patient [7%]), and tremor (1 patient [7%]).

For the rhabdomyosarcoma group, 4 patients (29%) had a TEAE leading to study drug interruption. The TEAEs leading to study drug interruption were reported in 1 patient each and were increased intracranial pressure, neutropaenia, rash maculo-papular, respiratory failure, and thrombocytopaenia. 2 patients (14%) had a TEAE related to the study drug leading to study drug interruption. The TEAEs related to the study drug leading to dose interruption were reported in 1 patient each and were neutropaenia, rash maculo-papular, and thrombocytopaenia.

For the RP2D group, 15 patients (30%) had a TEAE leading to study drug interruption. The majority of TEAEs leading to study drug interruption were reported in 1 patient each. The TEAEs leading to study drug interruption reported in > 1 patient were neutropaenia (5 patients [10%]), neuralgia (2 patients [4%]), rash maculo-papular (2 patients [4%]), and skin exfoliation (2 patients [4%]). 11 patients (22%) had a TEAE related to the study drug leading to study drug interruption. The majority of TEAEs related to the study drug leading to study drug interruption were reported in 1 patient each. The TEAEs related to the study drug leading to study drug interruption reported in > 1 patient were neutropaenia (5 patients [10%]), neuralgia (2 patients [4%]), rash maculo-papular (2 patients [4%]), and skin exfoliation (2 patients [4%]).

AEs of special interest

Adverse events of special interest (AESI) for the Phase 2 part are summarised in Table 33.

Table 33. Treatment-emergent Adverse Events of Special Interest – Phase 2 (Safety Population)

Event of Interest	Phase 2 Group			RP2D[a] N = 50 n (%)	Overall[b] N = 106 n (%)
	Ewing's Sarcoma N = 14 n (%)	Neuroblastoma N = 14 n (%)	Rhabdomyosarcoma N = 14 n (%)		
Patients With at Least 1 TEAE	14 (100)	14 (100)	14 (100)	50 (100)	104 (98)
General Myelosuppression	11 (79)	13 (93)	11 (79)	43 (86)	86 (81)
Neutropenia	7 (50)	10 (71)	9 (64)	33 (66)	65 (61)
Anaemia	9 (64)	9 (64)	9 (64)	33 (66)	64 (60)
Gastrointestinal Events	9 (64)	6 (43)	9 (64)	29 (58)	60 (57)
Hypersensitivity Reactions	6 (43)	5 (36)	9 (64)	24 (48)	55 (52)
Skin Toxicity	7 (50)	7 (50)	7 (50)	27 (54)	50 (47)
Peripheral Neuropathy	4 (29)	1 (7)	3 (21)	13 (26)	23 (22)
Hepatic Toxicity (Drug-induced Liver Injury)	2 (14)	2 (14)	2 (14)	7 (14)	22 (21)
Thrombocytopenia	0	6 (43)	3 (21)	11 (22)	21 (20)
Myalgia and Arthralgia	3 (21)	0	0	5 (10)	17 (16)
Acute Renal Failure Including HUS	2 (14)	1 (7)	2 (14)	5 (10)	10 (9)
Cardiotoxicity	1 (7)	0	0	1 (2)	5 (5)
Clinically Severe Infection-sepsis	0	1 (7)	0	1 (2)	2 (2)
Pneumonitis	1 (7)	0	0	1 (2)	2 (2)
Congestive Heart Failure/Left Ventricular Dysfunction	1 (7)	0	0	1 (2)	1 (1)

HUS = hemolytic-uremic syndrome; RP2D = Recommended Phase 2 Dose; TEAE = treatment-emergent adverse event. Treatment-emergent adverse events were defined as adverse events that began or worsened in severity on or after the date of the first dose of study drug and within 28 days of the date of the last dose of study drug.
[a] The RP2D column includes all patients in Phase 1 and Phase 2 treated at 240 mg/m^2.
[b] The Overall column includes all patients in Phase 1 and Phase 2 in this table.
Source: Table 14.3.2.6.1.

Myelosuppression

Grade 3 or 4 myelosuppression AESIs were reported for 10 patients (71%), 13 patients (93%), 10 patients (71%), and 41 patients (82%) in Ewing's sarcoma, neuroblastoma, rhabdomyosarcoma, and RP2D groups, respectively. Serious myelosuppression AESIs were reported for 1 patient (7%), 2 patients (14%), 4 patients (29%), and 7 patients (14%) in the Ewing's sarcoma, neuroblastoma,

rhabdomyosarcoma, and RP2D groups. None of the cases had a fatal outcome. Study drug discontinuation was reported in 1 patient (2%) in the RP2D group. Dose reduction were reported for 2 patients (14%), 4 patients (29%), 3 patients (21%), and 12 patients (24%) in the Ewing's sarcoma, neuroblastoma, rhabdomyosarcoma, and RP2D groups. Study drug interruption were seen for 1 patient (7%), 2 patients (14%), and 6 patients (12%) in the neuroblastoma, rhabdomyosarcoma, and RP2D groups.

Neutropenia

Neutropenia AESIs were reported for 7 patients (50%), 10 patients (71%), 9 patients (64%), and 33 patients (66%) in the Ewing's sarcoma, neuroblastoma, rhabdomyosarcoma, and RP2D groups, respectively. The AESI of febrile neutropenia was seen in 1 patient (7%), 3 patients (21%), and 5 patients (10%) in Ewing's sarcoma, rhabdomyosarcoma, and RP2D groups. Grade 3 or 4 neutropenia AESIs were reported for 6 patients (43%), 10 patients (71%), 8 patients (57%), and 31 patients (62%) in Ewing's sarcoma, neuroblastoma, rhabdomyosarcoma, and RP2D groups. Serious neutropenia AESIs were seen in 1 patient (7%), 4 patients (29%), and 5 patients (10%) in Ewing's sarcoma, rhabdomyosarcoma, and RP2D groups, respectively. No fatal cases were observed. Neutropenia AESIs leading to study drug discontinuation was reported for 1 patient (2%) in the RP2D group. Neutropenia AESIs leading to dose reduction were reported for 2 patients (14%), 3 patients (21%), 3 patients (21%), and 11 patients (22%) in Ewing's sarcoma, neuroblastoma, rhabdomyosarcoma, and RP2D groups. Study drug interruption was reported for 1 patient (7%), 1 patient (7%), and 5 patients (10%) in the neuroblastoma, rhabdomyosarcoma, and RP2D groups, respectively. The time to first occurrence of Grade 3 or higher neutropenia is shown in Table 34.

Table 34. Time to First Occurrence of Grade 3 or Higher Treatment-emergent Neutropaenia – Phase 2 (Safety Population)

	Phase 2 Group			RP2D[a] N = 50 n (%)	Overall[b] N = 106 n (%)
	Ewing's Sarcoma N = 14 n (%)	Neuroblastoma N = 14 n (%)	Rhabdomyosarcoma N = 14 n (%)		
Number of Subjects With Grade 3 or Higher Treatment-emergent Neutropenia	6 (43)	9 (64)	8 (57)	30 (60)	57 (54)
Time to Onset (days), n	6	9	8	30	57
Mean (Standard Deviation)	43.5 (58.93)	21.8 (18.25)	8.3 (2.71)	21.3 (29.68)	19.7 (22.75)
Median	21.5	15.0	8.0	11.5	15.0
Minimum, Maximum	5, 162	8, 55	3, 12	3, 162	3, 162

RP2D = Recommended Phase 2 Dose.
Analysis was only on subjects with Grade 3 or higher treatment-emergent neutropenia. Time to onset was defined as the time from the first dose of study drug to the first occurrence of Grade 3 or higher treatment-emergent neutropenia. Adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA), Version 20.0. Classification for neutropenia was based on MedDRA, Version 20.0 preferred terms 'Neutropenia' and 'Neutrophil count decreased'.
[a] The RP2D column includes all patients in Phase 1 and Phase 2 treated at 240 mg/m².
[b] The Overall column includes all patients in Phase 1 and Phase 2 in this table.
Source: Table 14.3.3.2.

Anaemia

Anaemia AESIs were reported for 9 patients (64%), 9 patients (64%), 9 patients (64%), and 33 patients (66%) in the Ewing's sarcoma, neuroblastoma, rhabdomyosarcoma, and RP2D groups, respectively. Grade 3 or 4 anaemia AESIs were reported for 5 patients (36%), 8 patients (57%), 7 patients (50%), and 22 patients (44%) in the Ewing's sarcoma, neuroblastoma, rhabdomyosarcoma, and RP2D groups. No serious or fatal anaemia AESIs were observed. Study drug discontinuation or dose reductions were not needed. Anaemia AESIs leading to study drug interruption was reported for 1 patient (2%) in the RP2D group (which was also in the Phase 1 group).

Thrombocytopaenia

Thrombocytopaenia AESIs were reported for 6 patients (43%), 3 patients (21%), and 11 patients (22%) in the neuroblastoma, rhabdomyosarcoma, and RP2D groups, respectively. Grade 3 or 4 thrombocytopaenia AESIs were described for 5 patients (36%), 2 patients (14%), and 8 patients (16%) in the neuroblastoma, rhabdomyosarcoma, and RP2D groups. Serious thrombocytopaenia AESIs were reported for 2 patients (14%), and 2 patients (4%) in the neuroblastoma, and RP2D groups. There were no fatal cases. No thrombocytopaenia AESIs led to study drug discontinuation. Dose reductions were reported for 1 patient (7%), 1 patient (7%), and 2 patients (4%) in the neuroblastoma, rhabdomyosarcoma, and the RP2D groups, respectively. Thrombocytopaenia AESIs leading to study drug interruption were reported for 1 patient (7%) and 1 patient (2%) in the rhabdomyosarcoma and RP2D groups. The time to first occurrence of Grade 3 or higher thrombocytopaenia in Phase 1 and 2 is presented Table 35.

Table 35. Time to First Occurrence of Grade 3 or Higher Treatment-emergent Thrombocytopaenia – Phase 2 (Safety Population)

	Phase 2 Group			RP2D[a] N = 50 n (%)	Overall[b] N = 106 n (%)
	Ewing's Sarcoma N = 14 n (%)	Neuroblastoma N = 14 n (%)	Rhabdomyosarcoma N = 14 n (%)		
Number of Subjects With Grade 3 or Higher Treatment-emergent Thrombocytopenia	0	5 (36)	2 (14)	8 (16)	10 (9)
Time to Onset (days), n	0	5	2	8	10
Mean (Standard Deviation)	-	22.6 (18.72)	9.5 (7.78)	26.0 (25.53)	32.6 (27.07)
Median	-	15.0	9.5	15.0	18.5
Minimum, Maximum	-	10, 55	4, 15	4, 76	4, 76

RP2D = Recommended Phase 2 Dose.
Analysis was only on subjects with Grade 3 or higher treatment-emergent thrombocytopenia. Time to onset was defined as the time from the first dose of study drug to the first occurrence of Grade 3 or higher treatment-emergent thrombocytopenia. Adverse Events were coded using Medical Dictionary for Regulatory Activities (MedDRA), Version 20.0. Classification for thrombocytopenia was based on MedDRA, Version 20.0 preferred terms 'Thrombocytopenia' and 'Platelet count decreased'.
[a] The RP2D column includes all patients in Phase 1 and Phase 2 treated at 240 mg/m².
[b] The Overall column includes all patients in Phase 1 and Phase 2 in this table.
Source: Table 14.3.3.4.

Peripheral neuropathy

Peripheral neuropathy AESIs were presented in 4 patients (29%), 1 patient (7%), 3 patients (21%), and 13 patients (26%) in Ewing's sarcoma, neuroblastoma, rhabdomyosarcoma, and RP2D groups, respectively. Grade 3 or 4 peripheral neuropathy AESIs were reported for 2 patients (14%), and 3 patients (6%) in rhabdomyosarcoma and RP2D groups. No serious or fatal peripheral neuropathy AESIs were reported. Peripheral neuropathy AESIs leading to study drug discontinuation were reported for 1 patient (7%), 3 patients (21%), and 5 patients (10%) in the Ewing's sarcoma, rhabdomyosarcoma, and RP2D groups. Dose reductions was observed in 1 patient (7%) and 1 patient (2%) in the rhabdomyosarcoma and RP2D groups. Drug interruption was observed in 1 patient (7%), 1 patient (7%), and 3 patients (6%) in the Ewing's sarcoma, neuroblastoma, and RP2D groups. The overall incidence of Grade 2 or higher peripheral neuropathy and the time to improvement to Grade 1 or better peripheral neuropathy are presented in Table 36.

Table 36. Time to First Occurrence of Grade 2 or Higher Treatment-emergent Peripheral Neuropathy and Time to Improvement of CTCAE Grade 2 or Higher Treatment-emergent Peripheral Neuropathy to Grade 1 or Better – Phase 2 (Safety Population)

	Phase 2 Group			RP2D[a] N = 50 n (%)	Overall[b] N = 106 n (%)
Number of Subjects With	Ewing's Sarcoma N = 14 n (%)	Neuroblastoma N = 14 n (%)	Rhabdomyosarcoma N = 14 n (%)		
Grade 2 or Higher Treatment-emergent Peripheral Neuropathy	1 (7)	1 (7)	3 (21)	9 (18)	13 (12)
Time to Onset (days), n	1	1	3	9	13
Mean (Standard Deviation)	43.0 (NE)	36.0 (NE)	50.7 (42.16)	67.7 (37.30)	55.6 (36.90)
Median	43.0	36.0	62.0	62.0	52.0
Minimum, Maximum	43, 43	36, 36	4, 86	4, 116	4, 116
Improvement to Grade 1 or Better	0	1 (7)	1 (7)	4 (8)	4 (4)
Time to Improvement (days), n	0	1	1	4	4
Mean (Standard Deviation)	-	26.0 (NE)	5.0 (NE)	24.0 (19.95)	24.0 (19.95)
Median	-	26.0	5.0	20.0	20.0
Minimum, Maximum	-	26, 26	5, 5	5, 51	5, 51

CTCAE = Common Terminology Criteria for Adverse Events; NE = not estimated; RP2D = Recommended Phase 2 Dose.
Analysis was only on subjects with Grade 2 or higher treatment-emergent peripheral neuropathy. Time to onset was defined as the time from the first dose of study drug to the first occurrence of Grade 2 or higher treatment-emergent peripheral neuropathy. Adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA), Version 20.0. Classification for peripheral neuropathy was based on MedDRA, Version 20.0 broad scope standardized MedDRA query (SMQ) (SMQ term = "Peripheral Neuropathy", SMQ number = "20000034").
Analysis was only on subjects with Grade 2 or higher treatment-emergent peripheral neuropathy. Time to Improvement was defined as the time from the first occurrence of Grade 2 or higher treatment-emergent peripheral neuropathy to improvement to Grade 1 or better. Adverse events were coded using MedDRA, Version 20.0. Classification for peripheral neuropathy was based on MedDRA, Version 20.0 broad scope SMQ (SMQ term = "Peripheral Neuropathy", SMQ number = "20000034").
[a] The RP2D column includes all patients in Phase 1 and Phase 2 treated at 240 mg/m².
[b] The Overall column includes all patients in Phase 1 and Phase 2 in this table.
Source: Table 14.3.3.1 and Table 14.3.3.5.

Gastrointestinal events

Gastrointestinal AESIs were reported for 9 patients (64%), 6 patients (43%), 9 patients (64%), and 29 patients (58%) in the Ewing's sarcoma, neuroblastoma, rhabdomyosarcoma, and RP2D groups, respectively. Grade 3 or 4 gastrointestinal AESIs were seen in 1 patient (7%), 1 patient (7%), and 2 patients (4%) in the neuroblastoma, rhabdomyosarcoma, and RP2D groups, respectively. Serious gastrointestinal AESIs were reported for 1 patient (7%), and 1 patient (2%) in the neuroblastoma and RP2D groups. None of the cases were fatal. Study drug discontinuations, dose reduction or drug interruptions were not reported.

Myalgia and arthralgia

Myalgia and arthralgia AESIs were reported for 3 patients (21%) and 5 patients (10%) in the Ewing's sarcoma and RP2D groups. None of the cases were Grade 3 or 4, serious or fatal. Also no dose adjustments were needed.

Hypersensitivity reactions

Anaphylactic transfusion reaction was reported in 1 patient (7%) in the rhabdomyosarcoma group, who was also classified in the RP2D group (1 patient [2%]). The event was serious, Grade 3, and did not lead to study drug discontinuation, dose reduction, or dose interruption. Periorbital oedema was reported for 1 patient (7%), 2 patients (14%), and 3 patients (6%) in the neuroblastoma, rhabdomyosarcoma, and RP2D groups, respectively. All events were Grade 1 or 2, non-serious, and did not lead to study drug discontinuation, dose reduction, or dose interruption. Face oedema presented in 1 patient (7%), 1 patient (7%), and 2 patients (4%) in the neuroblastoma, rhabdomyosarcoma, and RP2D groups. All events were Grade 1, non-serious, and did not lead to study drug discontinuation, dose reduction, or dose interruption. Eyelid oedema was reported for 1 patient (7%) in the rhabdomyosarcoma group, who was also classified in the RP2D group (1 patient [2%]. The event was

Grade 2, non-serious, and did not lead to study drug discontinuation, dose reduction, or dose interruption. Rash erythematous was reported for 1 patient (7%) in the neuroblastoma group. The neuroblastoma patient was also classified in the RP2D group (1 patient [2%]). The event was Grade 1, non-serious, and did not lead to study drug discontinuation, dose reduction, or dose interruption. A hypersensitivity reaction AESI with an outcome of death (respiratory failure) was reported for 1 patient with rhabdomyosarcoma (7%), who was also classified in the RP2D group (1 patient [2%]). The event of respiratory failure was described as related to disease progression from pulmonary metastasis.

Pneumonitis

Pneumonitis AESIs were reported for 1 patient (7%), and 1 patient (2%) in the Ewing's sarcoma, and RP2D groups, respectively. No Grade 3 or 4 pneumonitis AESIs were reported, as also was the case for serious or fatal pneumonitis. No pneumonitis led to study drug discontinuation or dose reduction. Pneumonitis AESIs leading to study drug interruption were reported for 1 patient (7%) and 1 patient (2%) in the Ewing's sarcoma and RP2D groups.

Hepatic toxicity

Hepatic toxicity AESIs were reported for 2 patients (14%), 2 patients (14%), 2 patients (14%), and 7 patients (14%) in the Ewing's sarcoma, neuroblastoma, rhabdomyosarcoma, and RP2D groups, respectively. No PTs related to more severe hepatic toxicity (hepatic failure, fibrosis, cirrhosis, and other liver damage-related conditions) were reported. Grade 3 or 4 hepatic toxicity AESIs were reported for 1 patient (7%), 1 patient (7%), 1 patient (7%), and 4 patients (8%) in the Ewing's sarcoma, neuroblastoma, rhabdomyosarcoma, and RP2D groups. No serious or fatal hepatic toxicity AESIs were observed. Study drug discontinuation and dose reduction were not seen. Hepatic toxicity AESIs leading to study drug interruption were reported for 1 patient (7%) and 1 patient (2%) in the Ewing's sarcoma and RP2D groups.

Acute renal failure and haemolytic uremic syndrome

Acute renal failure AESIs including HUS were reported for 2 patients (14%), 1 patient (7%), 2 patients (14%), and 5 patients (10%) in the Ewing's sarcoma, neuroblastoma, rhabdomyosarcoma, and RP2D groups, respectively. No PTs of renal failure acute or haemolytic-uremic syndrome were reported. Acute kidney injury was reported for 1 patient (7%), 1 patient (7%), and 2 patients (4%) in the Ewing's sarcoma, rhabdomyosarcoma, and RP2D groups. Blood creatinine increased was observed in 1 patient (7%) in the rhabdomyosarcoma group. s, respectively. The patient with rhabdomyosarcoma was also classified in the RP2D group (1 patient [2%]) and the event was Grade 1, non-serious, and did not lead to study drug discontinuation, dose reduction, or interruption. Grade 3 or 4 acute renal failure AESIs including HUS were reported for 1 patient (7%) and 1 patient (2%) in the neuroblastoma and RP2D groups. Serious acute renal failure AESIs including HUS presented in 1 patient (7%), 1 patient (7%), and 2 patients (4%) in the Ewing's sarcoma, rhabdomyosarcoma, and RP2D groups. None of the cases were fatal. Study drug discontinuations, dose reductions or study drug interruptions were not observed.

Clinically severe infections-sepsis

Clinically severe infections-sepsis AESIs were reported for 1 patient (7%) and 1 patient (2%) in the neuroblastoma and RP2D groups. Grade 3 or 4 clinically severe infections-sepsis AESIs were reported for 1 patient (7%) and 1 patient (2%) in the neuroblastoma and RP2D groups. Serious clinically severe infections-sepsis AESIs were reported for 1 patient (7%) and 1 patient (2%) in the neuroblastoma and RP2D groups. No fatal cases were observed. No dose modifications were needed.

Cardiotoxicity

Cardiotoxicity AESIs presented in 1 patient (7%) in the Ewing's sarcoma group, which was also classified in the RP2D group (1 patient [2%]). The PTs reported were primarily related to abnormal rhythms. No Grade 3 or 4, serious or fatal cases were seen. No dose modifications were needed.

Congestive heart failure and left ventricular dysfunction

Congestive heart failure and left ventricular dysfunction AESIs was reported for 1 patient (7%) in the Ewing's sarcoma group, which was also classified in the RP2D group (1 patient [2%]). No Grade 3 or 4, serious or fatal cases were seen. No dose modifications were needed.

Skin toxicity

Skin toxicity AESIs were reported for 7 patients (50%), 7 patients (50%), 7 patients (50%), and 27 patients (54%) in the Ewing's sarcoma, neuroblastoma, rhabdomyosarcoma, and RP2D groups, respectively. The most frequently reported skin toxicity AESIs (≥ 10% of patients in the Overall group including Phase 1) were erythema (13 patients [12%]) and pruritus generalised (12 patients [11%]). Grade 3 or 4 skin toxicity AESIs were reported for 1 patient (7%) and 2 patients (4%) in the Ewing's sarcoma and RP2D groups. Serious skin toxicity AESIs were reported for 1 patient (7%) and 2 patients (4%) in the neuroblastoma and RP2D groups. No skin toxicity AESIs with an outcome of death were reported. Skin toxicity AESIs leading to study drug discontinuation were not observed. Dose reduction were reported for 1 patient (7%) and 1 patient (2%) in Ewing's sarcoma and RP2D groups. Study drug interruption were observed in 2 patients (14%), 2 patients (14%), 1 patient (7%), and 5 patients (10%) in the Ewing's sarcoma, neuroblastoma, rhabdomyosarcoma, and RP2D groups. The time to first occurrence of Grade 2 and Grade 3 or higher skin toxicity is presented in Table 37.

Table 37. Time to First Occurrence of Grade 2 and Grade 3 or Higher Treatment-emergent Skin Toxicity – Phase 2 (Safety Population)

| Number of Subjects With | Phase 2 Group | | | RP2D[a] N = 50 n (%) | Overall[b] N = 106 n (%) |
	Ewing's Sarcoma N = 14 n (%)	Neuroblastoma N = 14 n (%)	Rhabdomyosarcoma N = 14 n (%)		
Grade 2 or Higher Treatment-emergent Skin Toxicity	5 (36)	3 (21)	5 (36)	16 (32)	31 (29)
Time to Onset (days), n	5	3	5	16	31
Mean (Standard Deviation)	44.8 (19.38)	42.3 (3.06)	33.4 (25.70)	39.7 (18.48)	45.0 (58.40)
Median	48.0	43.0	23.0	42.0	39.0
Minimum, Maximum	22, 71	39, 45	7, 74	7, 74	1, 340
Grade 3 or Higher Treatment-emergent Skin Toxicity	1 (7)	0	0	2 (4)	6 (6)
Time to Onset (days), n	1	0	0	2	6
Mean (Standard Deviation)	22.0 (NE)	-	-	39.0 (24.04)	40.2 (11.09)
Median	22.0	-	-	39.0	40.5
Minimum, Maximum	22, 22	-	-	22, 56	22, 56

NE = not estimated; RP2D = Recommended Phase 2 Dose.
Analysis was only on subjects with Grade 2 or higher treatment-emergent skin toxicity. Time to onset was defined as the time from the first dose of study drug to the first occurrence of Grade 2 or higher treatment-emergent skin toxicity. Adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA), Version 20.0. Classification for skin toxicity was based on a search of 430 MedDRA, Version 20.0 preferred terms within the skin system organ class.
[a] The RP2D column includes all patients in Phase 1 and Phase 2 treated at 240 mg/m².
[b] The Overall column includes all patients in Phase 1 and Phase 2 in this table.
Source: Table 14.3.3.3.

Laboratory evaluations

In the Ewing's sarcoma group for each of the haematology parameters, the majority of the patients experienced worst CTCAE values of Grade 1 or 2, with the exception of leukocytes with 8 patients (57%) having worst CTCAE values of Grade 3 and 1 patient (7%) having worst CTCAE values of Grade

4; and neutrophils with 7 patients (50%) having worst CTCAE values of Grade 3 and 2 patients (14%) having worst CTCAE values of Grade 4.

In the neuroblastoma group for each of the haematology parameters, the majority of the patients experienced worst CTCAE values of Grade 1 or 2 with the exception of haemoglobin with 9 patients (64%) having worst CTCAE values of Grade 3; leukocytes with 6 patients (43%) having worst CTCAE values of Grade 3 and 2 patients (14%) having worst CTCAE values of Grade 4; and neutrophils with 4 patients (29%) having worst CTCAE values of Grade 3 and 6 patients (43%) having worst CTCAE values of Grade 4.

In the rhabdomyosarcoma group for each of the haematology parameters, the majority of the patients experienced worst CTCAE values of Grade 1 or 2 with the exception of haemoglobin with 5 patients (36%) having worst CTCAE values of Grade 3; leukocytes with 5 patients (36%) having worst CTCAE values of Grade 3 and 3 patients (21%) having worst CTCAE values of Grade 4; and neutrophils with 4 patients (29%) having worst CTCAE values of Grade 3 and 4 patients (29%) having worst CTCAE values of Grade 4.

For each of the chemistry parameters, the majority of the patients experienced worst CTCAE values of Grade 1 or 2 in all groups. The majority of patients did not experience shifts from baseline or maintained or experienced improvements from baseline during treatment for haematology and chemistry laboratory parameters.

There were no SAEs related to laboratory parameters reported. For both the Ewing's sarcoma and rhabdomyosarcoma groups, all clinical laboratory-related TEAEs were reported in 1 patient each. For the neuroblastoma group, the majority of clinical laboratory-related TEAEs were reported in 1 patient each, except the event of aspartate aminotransferase increased (2 patients [14%]).

Vital signs, physical finding and other observations related to safety

– **Vital signs**- The majority of patients had no changes from baseline to the worst classification during treatment. No notable changes from baseline in vital sign measurements were observed.
– **Electrocardiogram**- The majority of patients had no clinically meaningful changes in ECG overall interpretation or ECG values from baseline to the final evaluation. No patients had "abnormal, clinically significant" ECG findings at either baseline or worst post baseline evaluation. No notable trends in abnormal post baseline QTc values were observed.

– **Left ventricular shortening fraction assessment**- There were few shifts from baseline LVEF values and no worst post baseline visit value was abnormal and clinically significant. The majority of patients had no clinically meaningful changes in the LVEF values from baseline to the final evaluation.

– **Lansky and Karnofsky performance status**- No notable changes from baseline in Lansky and Karnofsky performance status measurements were observed.

– **Pregnancy status**- No pregnancies were reported in female patients of childbearing potential during the study.

Updated 1-year survival follow-up

At the time of the first database cutoff date of 05 Dec 2017, a total of 10 patients (6 patients in the Ewing's sarcoma group, 3 patients in the neuroblastoma group, and 1 patient in the rhabdomyosarcoma group) were ongoing in the survival follow-up period. As of the final database cutoff date of 06 Nov 2018, all patients had completed the 1-year survival follow-up period or discontinued from the study.

Median overall survival results observed at the final database cutoff date were similar to those seen at the first database cutoff date. At the 06 Nov 2018 cutoff date, the median overall survival was 32.1 weeks, 32.0 weeks, and 19.6 weeks for the Ewing's sarcoma, neuroblastoma, and rhabdomyosarcoma groups, respectively, versus the median overall survival of 32.1 weeks, 26.7 weeks, and 19.6 weeks for the Ewing's sarcoma, neuroblastoma, and rhabdomyosarcoma groups, respectively, at the 05 Dec 2017 database cutoff. Median duration of response and progression-free survival results remained unchanged between the two database cutoff dates.

Data collection for TEAEs had been completed by the time of the first database cutoff date. Thus, no new safety concerns emerged during the remaining follow-up period for the 10 patients ongoing in the study on 05 Dec 2017.

During the 1-year follow-up period, an additional 5 patients from the Ewing's sarcoma group, 2 patients from the neuroblastoma group, and 1 patient from the rhabdomyosarcoma group died. Similarly to what had been reported for the deaths recorded until the first database cutoff date, these patient deaths were attributed to "death from malignant disease under study, or complication due to malignant disease under study". In total, eleven patients (79%) from the Ewing's sarcoma group, 10 patients (71%) from the neuroblastoma sarcoma group, and 12 patients (86%) from the rhabdomyosarcoma group died during the study.

4.3.4. Discussion

Background

nab-Paclitaxel (also called Abraxane or ABI-007) is a protein formulation of a noncrystalline, amorphous form of paclitaxel in an insoluble particle state and was designed to improve the chemotherapeutic effects of paclitaxel and decrease toxicity. *nab*-Paclitaxel is approved in adults for the treatment of metastatic breast cancer (monotherapy), metastatic adenocarcinoma of the pancreas (in combination with gemcitabine), and first-line treatment of NSCLC (in combination with carboplatin). The most common clinically significant adverse reactions associated with the use of *nab*-paclitaxel in adults are neutropaenia, peripheral neuropathy, arthralgia/myalgia, and gastrointestinal disorders.

In this type II variation, the results of the paediatric ABI-007-PST-001 study are submitted. The Applicant updated the SmPC to reflect these results, but does not apply for an indication in the paediatric population. ABI-007-PST-001 was a Phase 1/2 study designed to establish the recommended dose of *nab*-paclitaxel in the paediatric population (phase 1) and to determine its clinical activity in three distinct paediatric solid tumour types (Ewing's sarcoma, neuroblastoma, and rhabdomyosarcoma; phase 2).

At 14 August 2018 the PDCO accepted a modification of an agreed paediatric investigation plan for *nab*-paclitaxel (EMEA-001308-PIP01-12-M02) based on the results of ABI-PST-001. The Applicant requested to discontinue the currently agreed paediatric development due to lack of efficacy. The PDCO agreed that given the results of study ABI-PST-001 it is very unlikely that the product can be useful for the paediatric tumours considered. The proposal not to continue the development appeared reasonable to the PDCO. Studies planning to investigate *nab*-paclitaxel as add-on to best standard of anti-cancer therapy were therefore deleted.

Efficacy

Phase 1

The primary objective of the Phase 1 portion of the study was to determine the maximum tolerated dose (MTD)/recommended Phase 2 dose (RP2D) in paediatric patients (≥6 months and <18 years) with recurrent or refractory solid tumours who progressed on standard therapy or for whom no standard

anticancer therapy existed. The Phase 1 portion used a rolling-6 dose escalation and six dose levels of *nab*-paclitaxel were tested: 120 mg/m2 (n=16), 150 mg/m2 (n=8), 180 mg/m2 (n=14), 210 mg/m2 (n=11), 240 mg/m2 (n=8), and 270 mg/m2 (n=7), with a total of 64 patients enrolled. Of these, 37 patients (58%) constituted the Dose-determining Set (DDS) including 6 patients in each dose level except for 270 mg/m2, which included 7 patients.

All patients discontinued from the study. The most frequently reported reasons for study treatment discontinuation were progressive disease, AE, and symptomatic deterioration. A total of 13 patients completed the 1-year survival follow-up portion of the study, 50 patients died prior to 1 year, and 1 patient was lost to follow-up.

The Phase 1 patients were 2 years to 17 years old, and predominantly in the age category 12–17 years (n=37, 58%), with the following diagnosis: rhabdomyosarcoma (n=14, 22%), Ewing's sarcoma (n=13, 20%), neuroblastoma (n=10, 16%), osteosarcoma (n=8, 13%), Wilm's tumour (n=4, 6%), hepatoblastoma (n=3, 5%), and other tumours (less than 3 patients). These patients received 1 to 12 cycles (median 2 cycles) of *nab*-paclitaxel.

The primary endpoint of Phase 1 was to determine the incidence of DLTs and TEAEs in paediatric patients who received *nab*-paclitaxel. The 240 mg/m2 dose level was selected as the RP2D. The safety profile will be further discussed in the safety section.

The secondary endpoint was ORR and best overall response based on RECIST version 1.1. The Efficacy Evaluable Population included 59 patients. The ORR was 3.4%, with 1 patient with rhabdomyosarcoma in the 240 mg/m2 (lasting 8.6 weeks) cohort and 1 Ewing's sarcoma patient in the 270 mg/m2 cohort (lasting 38.1 weeks) having had a confirmed PR. There were 5 unconfirmed best responses, with 1 CR and 4 PRs. The unconfirmed CR was observed in 1 patient in the 210 mg/m2 cohort. The unconfirmed PRs were observed in the 240 mg/m2 (3 patients) and 270 mg/m2 (1 patient) cohorts.

Phase 2

The primary objective of the Phase 2 portion was to evaluate the anti-tumour activity of *nab*-paclitaxel administered at the RP2D in paediatric patients (≥6 months and ≤24 years) with recurrent or refractory neuroblastoma, rhabdomyosarcoma, and Ewing's sarcoma. Phase 2 implemented a two-stage enrollment design where patients were to be recruited in each of the 3 cohorts. Initiation of Stage 2 was based on the review of predefined efficacy results of Stage 1. The protocol design required ≥ 2 responders (i.e., patients with a confirmed CR or PR) based on RECIST version 1.1 (and/or MIBG for the neuroblastoma patients) in the first 14 patients in the Efficacy Evaluable Population for the disease group to proceed to Stage 2. During Stage 2, enrollment was expanded to include up to 23 patients per disease group. This requirement was not met in any of the 3 cohorts. The study did not proceed to Stage 2 and ended with 14 enrolled and treated patients in each of the 3 groups.

The Phase 2 portion of the study enrolled 42 patients aged 1 year to 24 years, predominantly 2 to less than 12 years old (n=27) and 12 to less than 18 years (n=12). During the study, patients received 1 to 6 cycles of *nab*-paclitaxel at the recommended dose of 240 mg/m2 administered weekly for 3 weeks in a 28-day cycle. The median number of *nab*-paclitaxel cycles administered was higher in Ewing's sarcoma patients (4.0) than in neuroblastoma and rhabdomyosarcoma patients (2.0). All but 1 patients in the Ewing's sarcoma group were Efficacy Evaluable. All patients discontinued, mostly due to PD.

One patient in the rhabdomyosarcoma group had a confirmed PR resulting in an ORR of 7.1% (95% CI: 0.2, 33.9). The response lasted 6.14 weeks. No confirmed CR or PR was observed in either the Ewing's sarcoma group or the neuroblastoma group based on RECIST version 1.1 and/or MIBG response (neuroblastoma group only). There were 5 unconfirmed PRs reported: 3 patients (21.4%)

and 2 patients (15.4%) in the rhabdomyosarcoma and Ewing's sarcoma groups, respectively. Responses were not confirmed due to no subsequent tumour evaluations or because PD developed after an initial response. No unconfirmed best response of CR or PR was seen in the neuroblastoma group based on RECIST version 1.1 and/or MIBG response. Disease control rate was 30.8% (4 patients; 95% CI: 9.1, 61.4) for the Ewing's sarcoma group; 7.1% (1 patient; 95% CI: 0.2, 33.9) for the neuroblastoma group; and 7.1% (1 patient; 95% CI: 0.2, 33.9) for the rhabdomyosarcoma group. Of note, there was one patient in the Ewing's sarcoma group that had an unconfirmed best response of PR, but also met the criteria of confirmed SD ≥ 16 weeks and was therefore counted in the DCR rate as SD. Median PFS was 13 weeks (95% CI: 7.4, 16.1) for the Ewing's sarcoma group, 7.4 weeks (95% CI: 4.6, 8.1) for the neuroblastoma group, and 5.1 weeks (95% CI: 2.1, 7.9) for the rhabdomyosarcoma group. The estimated Kaplan-Meier overall survival at 1 year was 48% (95% CI: 14, 76), 25% (95% CI: 4, 54), and 15% (95% CI: 2, 39) for the Ewing's sarcoma, neuroblastoma, and rhabdomyosarcoma groups, respectively. The median overall survival was 32.1 weeks, 26.7 weeks, and 19.6 weeks for the Ewing's sarcoma, neuroblastoma, and rhabdomyosarcoma groups, respectively. At the time of data cutoff 10 patients were still in survival follow-up. Median overall survival results observed at the final database cutoff date were similar to those seen at the first database cutoff date. At the 06 Nov 2018 cutoff date, the median overall survival was 32.1 weeks, 32.0 weeks, and 19.6 weeks for the Ewing's sarcoma, neuroblastoma, and rhabdomyosarcoma groups.

In conclusion, based on this Phase 1/2 study with an acceptable study design *nab*-paclitaxel monotherapy seems to have limited anti-tumour activity in the studied paediatric tumours. The low response rate implies that no clinical benefit of *nab*-paclitaxel in the paediatric population is to be expected. Although the use of *nab*-paclitaxel as add-on therapy might have activity it is agreed with the PDCO that further development of *nab*-paclitaxel in the paediatric population does not seem justified. The demonstrated results cannot support an indication in children and the approach to update the SmPC to reflect the results of the study is supported, as information in the SmPC regarding the results in paediatric patients is considered important for physicians. Theoretically physicians might consider to prescribe *nab*-paclitaxel because of the high unmet medical need in solid paediatric tumours, the higher dosing due to lower toxicity than classical taxanes, and the off label use of docetaxel in Ewing's sarcoma, osteosarcoma, and other recurrent/refractory solid tumours.

Safety

Phase 1

Overall, 2 patients (5%) experienced a protocol-defined DLT during Phase 1. One patient in the 120 mg/m2 cohort experienced Grade 3 dizziness that lasted 19 days, which met the DLT definition of Grade 3 or 4 non-haematologic toxicity. One patient in the 270 mg/m2 cohort experienced Grade 4 neutropaenia that lasted 13 days, which met the DLT definition of Grade 4 uncomplicated neutropaenia lasting >7 days. The DMC established the RP2D, 240 mg/m2, after reviewing the safety data from the 270 mg/m2 cohort where one DLT was reported combined with an increase in skin toxicity events in this cohort.

Overall, all 64 patients (100%) experienced at least 1 TEAE during the study. Serious TEAEs, Grade 3 or 4 TEAEs, and TEAEs leading to death were reported in 55%, 88%, and 8%, respectively. All deaths were contributed to the malignant disease under study. Treatment-emergent AEs related to the study drug were reported in 92%. 16% experienced a TEAE leading to dose reduction, 25% had a TEAE leading to drug interruption, and 17% had a TEAE leading to drug discontinuation. The low number of patients in each cohort precludes meaningful conclusions regarding any dose-dependent trends, but the number of dose reductions seemed to increase with increasing dosing.

The most frequently reported TEAEs were neutropaenia, anaemia, pyrexia, and leukopaenia. The incidence of neutropaenia and thrombocytopaenia appeared to increase as the dose escalated.

Peripheral neuropathy was reported in 23%, Grade 3 or 4 in 3%. Grade 3 or 4 peripheral neuropathies were only seen in the 240 mg/m2 and 270 mg/m2 cohorts.

Phase 2

In Phase 2, all patients experienced an TEAE. The majority of the TEAEs were Grade 1 (95%) and Grade 2 (86%) in severity. All deaths were attributed to "death from malignant disease under study, or complication due to malignant disease under study0." None of these deaths were related to treatment. Next, the separate groups will be described in more detail.

For the Ewing's sarcoma group, serious TEAEs, Grade 3 or 4 TEAEs, and TEAEs leading to death were reported in 43%, 86%, and 0%, respectively. Treatment-emergent AEs related to the study drug were reported in 93%. TEAEs led to dose reduction in 29%, drug interruption in 36%, and discontinuation in 21%. The most frequently reported TEAEs were anaemia, pain in extremity, neutropaenia, leukopaenia, and diarrhoea. Peripheral neuropathy was presented 29%, none was Grade 3 or 4, and 7% led to study drug discontinuation.

For the neuroblastoma group, serious TEAEs, Grade 3 or 4 TEAEs, and TEAEs leading to death were reported in 43%, 93%, and 14%, respectively. Treatment-emergent AEs related to the study drug were reported in 86%. Dose reduction due to a TEAE was seen in 36%, drug interruption in 21%, and drug discontinuation in 7%. Anaemia, neutropaenia, leukopaenia, thrombocytopaenia, pain in extremity, and headache were the most frequently reported TEAEs. Peripheral neuropathy was observed in 7%, none was Grade 3 or 4 or led to study drug discontinuation.

In the rhabdomyosarcoma group, serious TEAEs, Grade 3 or 4 TEAEs, and TEAEs leading to death were reported in 79%, 86%, and 21%, respectively. Treatment-emergent AEs related to the study drug were reported in 86%. 29% experienced a TEAE leading to dose reduction, 29% leading to drug interruption, and 21% leading to drug discontinuation. The most frequently reported TEAEs were anaemia, neutropaenia, leukopaenia, vomiting, constipation, nausea, and pyrexia. Peripheral neuropathy was seen in 21%, Grade 3 or 4 in 14%, and study drug discontinuation in 21%.

The RP2D group included all patients in Phase 1 and Phase 2 treated at 240 mg/m2 (n=50). For the RP2D group, serious TEAEs, Grade 3 or 4 TEAEs, and TEAEs leading to death were reported in 52%, 90%, and 12%, respectively. Treatment-emergent AEs related to the study drug were reported in 88%. In 32% the TEAE led to dose reduction, 30% to drug interruption, and 18% to drug discontinuation. Most frequently reported TEAEs were anaemia, neutropaenia, leukopaenia, pyrexia, and pain in extremity. Peripheral neuropathy presented in 26%, Grade 3 or 4 in 6%, and led to study drug discontinuation in 10%.

The limited numbers per tumour group hamper proper comparisons, but there does not seem to be large differences in the toxicity profiles between the investigated tumour types. Also the comparison with the approved indications in the adult population is difficult due the combination with other chemotherapeutics used in adults (pancreatic carcinoma, NSCLC) or the different treatment schedule for monotherapy (Q3W in adult breast cancer versus QW in the paediatric study). However, based on the provided safety results, the TEAE profile in the paediatric population seems to be consistent with the expected events reported in adult patients and no new safety signals were detected. Most frequently reported AEs were related to cytopaenia with neutropaenia, anaemia, and leukopaenia. It was noted that the recommended dose of *nab*-paclitaxel in the paediatric population is higher than the one established for adults, in whom a dose of 150 mg/m2 was selected for administration as a single agent in a weekly schedule for 3 weeks in a 28-day cycle. In adults, the DLT at higher doses of *nab*-paclitaxel was neuropathy (25% of adult patients who received 150 mg/m2 *nab*-paclitaxel in a Phase 3 metastatic melanoma study had at least 1 Grade ≥ 3 event of neuropathy). In the paediatric population, peripheral neuropathy was manageable at 240 mg/m2.

5. Request for supplementary information

Other concerns

Clinical aspects

1. The planned non-compartmental and POP-PK methods to establish PK are in general acceptable. However, no validation, bioanalytical, statistical or POP-PK reports were submitted. The applicant should submit these reports.

2. The non-linearity in PK is suggested as being due to saturation of clearance and this is incorporated into the PopPK model, but apparently inconsistent with this, the clearance increases with dose and exposure decreases, or at least at the highest dose. In the literature it has also been postulated that there is also saturable tissue uptake (https://ascopubs.org/doi/abs/10.1200/jco.1994.12.3.532). The applicant should provide a discussion whether this additional non-linear process would explain the presented data and should be included in the model. If deemed necessary after discussion, the model should be updated with this process.

3. The Applicant is asked how the number of 4 patients with DCR is calculated in the Ewing's sarcoma group, since the results show only 3 patients with SD ≥16 weeks and no patients with confirmed CR or PR.

4. The Applicant is asked when the final report with the completed 1 year-survival follow-up is expected to be submitted.

6. Assessment of the responses to the request for supplementary information

6.1. Other concerns

Clinical aspects

Question 1

The planned non-compartmental and population pharmacokinetic (PopPK) methods to establish pharmacokinetics (PK) are in general acceptable. However, no validation, bioanalytical, statistical or PopPK reports were submitted. The applicant should submit these reports.

Summary of the MAH's response

The reports related to PK analysis and validation of bioanalytical methods are listed below and included in Section 5.3.1.4 and Section 5.3.3.5 of the electronic common technical document (eCTD).

- ABI-007-PST-001-BA – Study title: Pharmacokinetic Human Whole Blood Sample Analysis Report for "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

- ARPAC21 – ABI-007-DMPK-1744 – Study title: Method Validation Report for the Determination of Abraxane (Paclitaxel) in Human Whole Blood (K3EDTA) Using LC-MS/MS

- ABI-007-PST-001-PK – Study title: Population Pharmacokinetics and Exposure-response Analysis of nab®-Paclitaxel in Pediatric Patients with Recurrent or Refractory Solid Tumors.

To capture the information provided by these reports, addenda for 2.7.1. Summary of Biopharmaceutic Studies and Associated Analytical Methods and 2.7.2. Summary of Clinical Pharmacology Studies were prepared and are included in Module 2.

Assessment of the MAH's response

The applicant submitted the requested reports.

The validation, bioanalytical, statistical or PopPK reports are of sufficient quality and support the reported results. **Issue solved.**

Conclusion

☐ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒ No need to update overall conclusion and impact on benefit-risk balance

Question 2

The non-linearity in PK is suggested as being due to saturation of clearance and this is incorporated into the PopPK model, but apparently inconsistent with this, the clearance increases with dose and exposure decreases, or at least at the highest dose. In the literature it has also been postulated that there is also saturable tissue uptake (https://ascopubs.org/doi/abs/10.1200/jco.1994.12.3.532). The applicant should provide a discussion whether this additional non-linear process would explain the presented data and should be included in the model. If deemed necessary after discussion, the model should be updated with this process.

Summary of the MAH's response

The sponsor acknowledges and appreciates the CHMP comments on the PopPK analysis. Non-linearity in paclitaxel PK, specifically mentioned by the Rapporteurs at the highest dose, was shown in the following submitted PK table (Table 2). Of note, a total of 9 patients were excluded from the descriptive statistics in this table due to blood draw time deviations. Given that the blood draw time deviations did not have significant impact on clearance estimation, the sponsor summarized the descriptive statistics of PK parameters including all patients (Table 3) and compared to those in Table 6 of ABI-007-PST-001-PK. Inclusion of the initially excluded subjects at the highest dose of 270 mg/m2 brings down the CL from 32 L/hr to 24 L/hr. In addition, ANOVA testing indicates a lack of significant difference of clearance across different dose levels (p = 0.2173), which can be explained by large inter-subject variability and limited number of subjects enrolled from different dose levels. Taken together, there is limited nonlinear PK behavior of paclitaxel exposure from 120 mg/m2 to 270 mg/m2 in pediatric patients.

Table 2: Summary Pharmacokinetic Parameters of Whole Blood Paclitaxel Following a Single 30-minute Intravenous Infusion of *nab*-Paclitaxel in Pediatric Patients with Recurrent or Refractory Solid Tumors - Cycle 1, Day 1 (Phase 1)

Geometric Mean (Geometric CV%); N	Age Group	*nab*-Paclitaxel Dose					
		120 mg/m²	150 mg/m²	180 mg/m²	210 mg/m²	240 mg/m²	270 mg/m²
N		16	8	14	11	8	7
Dose (mg)[a]	Overall	156 (24.8); 13	224 (25.5); 7	213 (27.6); 12	265 (44.2); 9	295 (33.0); 7	389 (14.4); 6
	2 - <6	60 (NC); 1	102 (NC); 1	153 (NC); 1	160 (16.4); 3	125 (NC); 1	NA (NA)
	6 - <12	140 (19.3); 4	NA (NA)	163 (13.1); 5	180 (0.0); 2	220 (NC); 1	319 (6.0); 2
	12 - ≤18	176 (10.6); 8	244 (8.6); 6	264 (11.3); 6	387 (6.5); 4	344 (14.6); 5	424 (3.2); 4
AUC_t (ng.h/mL)		7844 (73.4); 13	10374 (91.8); 7	9690 (37.1); 12	11817 (64.0); 9	12706 (29.2); 7	11245 (22.6); 6
AUC_{24} (ng.h/mL)		6392 (79.0); 13	8944 (85.9); 7	8365 (37.7); 12	10932 (66.3); 8	11167 (27.4); 7	9768 (20.7); 6
AUC_∞ (ng.h/mL)		8867 (85.4); 9	11992 (99.8); 6	10087 (38.4); 10	14361 (72.1); 6	14242 (29.2); 6	12424 (28.5); 5
C_{max} (ng/mL)		3488 (73.7); 13	5468 (38.0); 7	5597 (33.4); 12	5616 (63.9); 9	7831 (23.1); 7	8078 (41.5); 6
t_{max} (h)[b]		0.48 (0.47; 1.52); 13	0.47 (0.47; 3.58); 7	0.48 (0.47; 0.78); 12	0.47 (0.47; 0.75); 9	0.47 (0.47; 0.52); 7	0.47 (0.47; 0.52); 6
t_{last} (h)[b]		48.50 (5.62; 72.90); 16	59.48 (21.68; 74.88); 8	47.45 (22.42; 72.42); 14	47.92 (21.63; 73.58); 11	47.75 (24.50; 72.67); 8	48.50 (46.58; 72.50); 7
$t_{½}$ (h)		11.0 (101); 11	17.9 (13.4); 6	11.8 (38.6); 11	11.3 (52.3); 7	13.5 (41.9); 7	20.5 (43.6); 6
CL (L/h)		16.1 (75.6); 9	20.3 (101); 6	20.9 (39.9); 10	15.4 (25.4); 6	19.1 (67.4); 6	31.9 (35.0); 5
V_{ss} (L)		127 (145); 9	266 (78.3); 6	146 (106); 10	89.8 (45.1); 6	175 (117); 6	446 (17.6); 5
V_z (L)		253 (154); 9	526 (90.9); 6	345 (73.0); 10	236 (45.0); 6	393 (125); 6	992 (33.9); 5
Dose-Normalized							
AUC_{24} /Dose (ng.h/mL/(mg))		42.7 (77.4); 13	41.6 (87.0); 7	40.8 (39.7); 12	43.3 (63.6); 8	40.2 (65.4); 7	25.4 (26.1); 6
AUC_∞ /Dose (ng.h/mL/(mg))		62.0 (75.7); 9	49.2 (101); 6	47.8 (39.8); 10	64.8 (25.4); 6	52.3 (67.4); 6	31.3 (34.9); 5

Table 2: Summary Pharmacokinetic Parameters of Whole Blood Paclitaxel Following a Single 30-minute Intravenous Infusion of *nab*-Paclitaxel in Pediatric Patients with Recurrent or Refractory Solid Tumors - Cycle 1, Day 1 (Phase 1) (Continued)

Geometric Mean (Geometric CV%); N	Age Group	*nab*-Paclitaxel Dose					
		120 mg/m²	150 mg/m²	180 mg/m²	210 mg/m²	240 mg/m²	270 mg/m²
N		16	8	14	11	8	7
BSA- Normalized							
CL (L/h per m²)		13.5 (85.1); 9	12.5 (99.3); 6	17.8 (38.3); 10	14.6 (72.3); 6	16.7 (29.2); 6	21.8 (28.4); 5
V_{ss} (L per m²)		106 (95.3); 9	164 (78.4); 6	124 (82.8); 10	84.9 (49.7); 6	154 (56.5); 6	304 (29.0); 5
V_z (L per m²)		213 (101); 9	323 (90.1); 6	294 (64.7); 10	223 (76.1); 6	344 (61.2); 6	676 (46.7); 5

AUC_{24} = area under the concentration-time curve from time 0 to 24 hours; AUC_t = area under the concentration-time curve from time zero to the last sample collected (t_{last}); the planned t_{last} was 24 h for patients 2 to < 6 years, and was 72 h for patients ≥ 6 years; AUC_∞ = Area under the concentration-time curve from time 0 to infinity; CL = clearance; C_{max} = peak (maximum) concentration; CV = coefficient of variation; NA = not applicable; NC = not calculated; Max = maximum; Min = minimum; t_{last} = time of last blood sample collected; t_{max} = time of maximum concentration; $t_{\frac{1}{2}}$ = elimination half-life; V_{ss} = volume of distribution at steady state; V_z = volume of distribution based on area.
[a] Mean (CV%); N
[b] Median (Min; Max); N
Note: A total of 9 patients were excluded from the descriptive statistics of PK parameters over the 120 to 240 mg/m² dose levels due to blood draw time deviations related to the end of infusion.
Source: Report ABI-007-PST-001-PK, Table 6.

Table 3: Summary Clearance Data for All Patients Included

Geometric Mean (Geometric CV%); N	*nab*-Paclitaxel Dose					
	120 mg/m²	150 mg/m²	180 mg/m²	210 mg/m²	240 mg/m²	270 mg/m²
CL (L/h)	15.7 (66.66); N = 11	19.0 (92.26); N = 7	19.6 (48.09); N = 12	14.3 (29.96); N = 8	21.2 (68.46); N = 7	24.4 (83.0); N = 6

CL = clearance; CV = coefficient of variation.

Nevertheless, per the suggestion from the reviewer, the sponsor has re-run the PopPK model using the three-compartment model with both saturable distribution and saturable elimination as a starting point to fit sparse and rich whole blood concentrations collected from ABI-007-PST- 001 pediatric patients. The model was eventually reduced to only saturable elimination indicating that the current data did not support the identification of saturable distribution. Model discrimination results comparing models with only saturable elimination and models with both saturable distribution and elimination are summarized in Table 4. The results of models including both saturable distribution and elimination show an increase in objective function value compared to models with only saturable elimination and confirm that the current data did not support the identification of saturable distribution. Typical values of PK parameters derived with Model 2 (saturable elimination; used in Report ABI-007-PST-001-PK) and Model 3 (saturable distribution and elimination; proposed by CHMP) are presented in Table 5.

Table 4: Structural Population Pharmacokinetic Model Discrimination Table for *nab*-Paclitaxel

Model	Description	MOF	ΔMOF
3CMT_BLOCKALL (reference model) – Model 1	Base model, 3 compartment, BLOCKALL ETAs, prop. error	7645.736	--
3CMT_MMEL_BLOCKNOV2_SAMEALLO (Base/Final Model submitted) – **Model 2**	Base model, 3 compartment, saturated elimination	7526.034	-119.702
3CMT_MMEL_MMTR_BLOCKALLNOV2_SAMEALLO – **Model 3**	Base model, 3 compartment, saturated elimination, saturated distribution	8166.411	520.675

ETA = random effect on PK parameter; MOF = minimum objective function; ΔMOF = differential of MOF; PK = pharmacokinetic; prop. = proportional; V2 = volume of distribution of the first peripheral compartment.

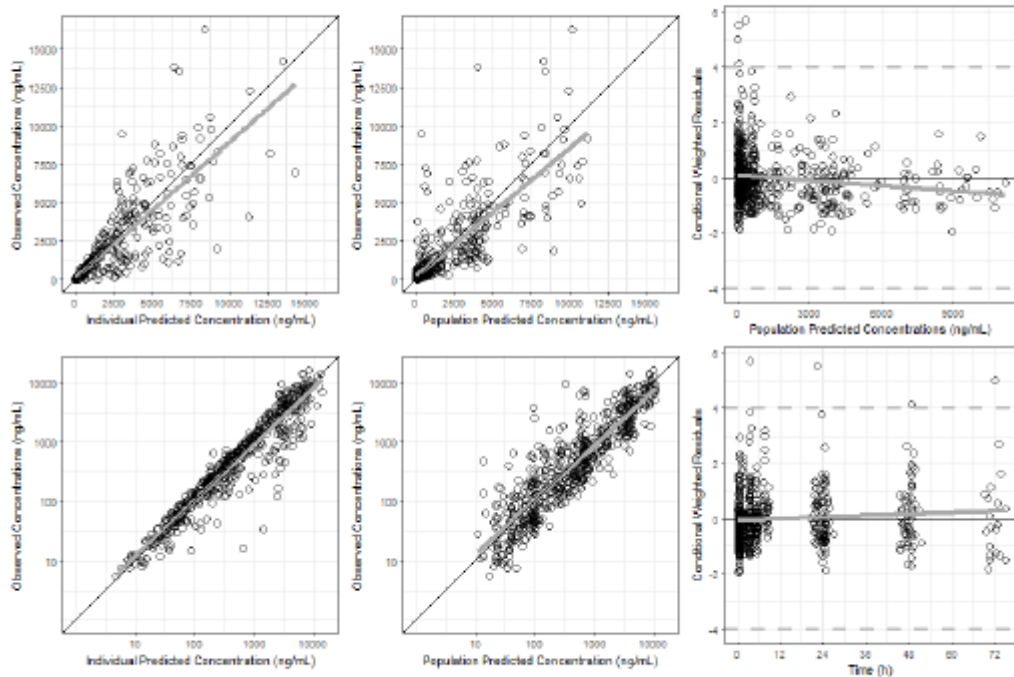**Table 5:** **Population Pharmacokinetic Parameters of *nab*-Paclitaxel**

Parameter	Model Term	Model 2 (Saturable Elimination) ABI-007-PST-001-PK		Model 3 (Saturable Distribution and Elimination) proposed by CHMP	
		Parameter Scale (θ)		Parameter Scale (θ)	
		Estimate	RSE (%)	Estimate	RSE (%)
VM_{EL} (µg/h)	θ	31983	42.6	12209	NA
BSA	$\times (BSA/1.25)^{\theta}$	1.12	12.5	-0.0949	NA
KM_{EL} (µg/L)	θ	951	54.6	575	NA
VM_{TR} (µg/h)	θ	NA	NA	342049	NA
BSA	$\times (BSA/1.25)^{\theta}$	NA	NA	-0.0949	NA
KM_{TR} (µg/L)	θ	NA	NA	3975	NA
V1 (L)	θ	11.8	14.5	57.1	NA
BSA	$\times (BSA/1.25)^{\theta}$	0.888	16.3	1.39	NA
Q2 (L/h)	θ	22.4	17.8	NA	NA
BSA	$\times (BSA/1.25)^{\theta}$	1.12	12.5	NA	NA
V2 (L)	θ	545	7.78	145	NA
BSA	$\times (BSA/1.25)^{\theta}$	0.888	16.3	1.39	NA
Q3 (L/h)	θ	34.8	7.99	14.0	NA
BSA	$\times (BSA/1.25)^{\theta}$	1.12	12.5	-0.0949	NA
V3 (L)	θ	45.3	5.04	398	NA
BSA	$\times (BSA/1.25)^{\theta}$	0.888	16.3	1.39	NA

Table 5: **Population Pharmacokinetic Parameters of *nab*-Paclitaxel (continued)**

Parameter	Model Term	Model 2 (Saturable Elimination) ABI-007-PST-001-PK		Model 3 (Saturable Distribution and Elimination) proposed by CHMP	
		Parameter Scale (θ)		Parameter Scale (θ)	
		Estimate	RSE (%)	Estimate	RSE (%)
Between Subject Variability	**Model Term**	Parameter Scale (ω)			
		Estimate	RSE (%)	Estimate	RSE (%)
On VM_{EL}	$\omega = SD(\eta_{VMEL,i})$	0.773	10.3	1.04	NA
On VM_{TR}	$\omega = SD(\eta_{VMTR,i})$	NA	NA	0.954	NA
On V1	$\omega = SD(\eta_{V1,i})$	0.417	36.6	0.657	NA
On Q2	$\omega = SD(\eta_{Q2,i})$	0.855	12.6	NA	NA
Correlation VM_{EL}, V1	$\omega = Corr(\eta_{VMEL,i}, \eta_{V1,i})$	0.966	25.0	NA	NA
Correlation VM_{EL}, Q2	$\omega = Corr(\eta_{VMEL,i}, \eta_{Q2,i})$	0.599	12.8	NA	NA
Correlation V1, Q2	$\omega = Corr(\eta_{V1,i}, \eta_{Q2,i})$	0.785	25.6	NA	NA
Residual Variability	**Model Term**	Parameter Scale (σ or θ)		Parameter Scale (σ or θ)	
		Estimate	RSE (%)	Estimate	RSE (%)
Proportional Error (%)	$\sigma = SD(\varepsilon_{i,j})$	0.453	4.94	0.825	NA

BSA = body surface area at baseline (m²); CHMP = Committee for Medicinal Products for Human Use; KM_{EL} = concentration in the central compartment at 50% of VM_{EL}; KM_{TR} = concentration in the central compartment at 50% of VM_{TR}; NA = not applicable; PK = pharmacokinetic; Q2 = intercompartmental clearance between the central compartment and the first peripheral compartment; Q3 = intercompartmental clearance between the central compartment and the second peripheral compartment; RSE = relative standard error; V1 = volume of distribution of the central compartment; V2 = volume of distribution of the first peripheral compartment; V3 = volume of distribution of the second peripheral compartment VM_{EL} = maximum elimination rate from the central compartment; VM_{TR} = maximum intercompartmental distribution rate between the central compartment and the first peripheral compartment.
Source for Model 2: Report ABI-007-PST-001-PK, Table 9.

In addition, goodness-of-fit plots were provided for Model 2 (saturable elimination) and Model 3 (saturable distribution and elimination) in Figure 1 and Figure 2, respectively. The individual and population predicted concentrations versus observed concentrations show a clear bias and underprediction for Model 3 when compared to Model 2.

Figure 1: Diagnostic Plots for the Final Population Pharmacokinetic Model for *nab*-Paclitaxel Including Saturable Elimination (Model 2)

Black line = identity line (upper panel) or zero line (lower panel); Gray line = locally weighted scatterplot smoothing (LOESS).
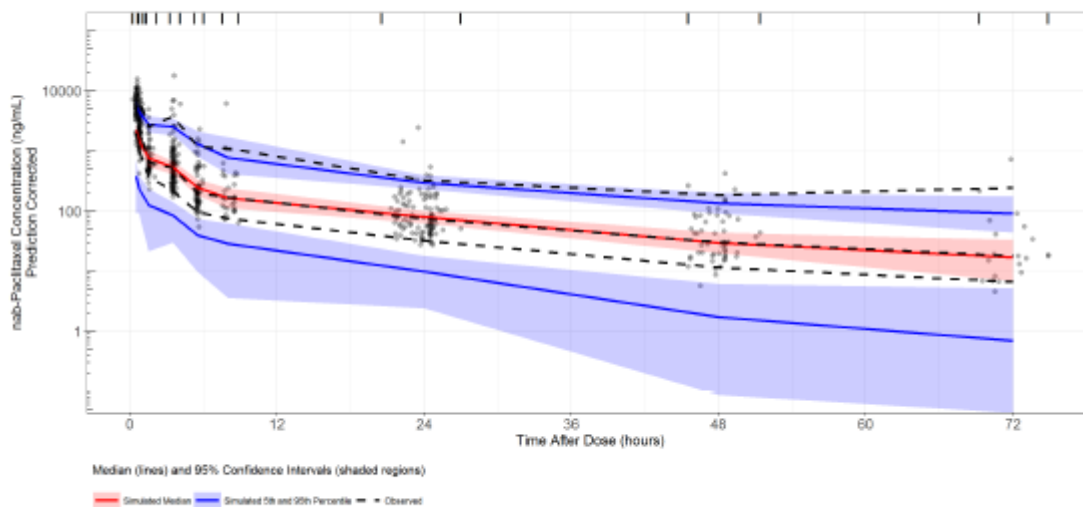Source: Report ABI-007-PST-001-PK, Figure 3.

Figure 2: Diagnostic Plots for the Population Pharmacokinetic Model for *nab*-Paclitaxel Including Saturable Distribution and Elimination (Model 3)
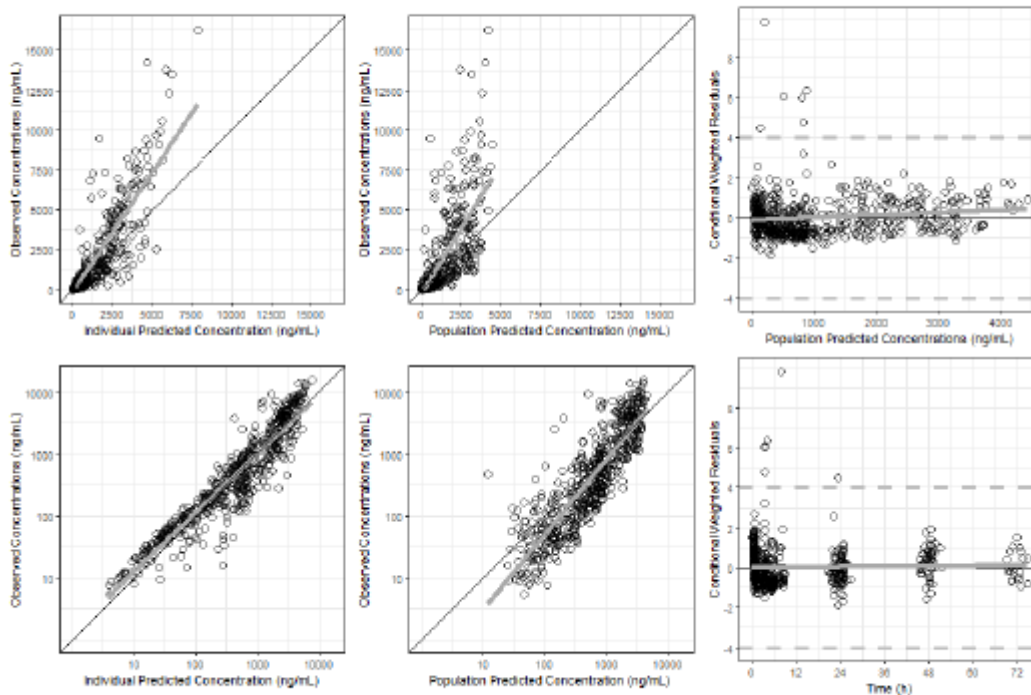
Black line = identity line (upper panel) or zero line (lower panel); Gray line = locally weighted scatterplot smoothing (LOESS).
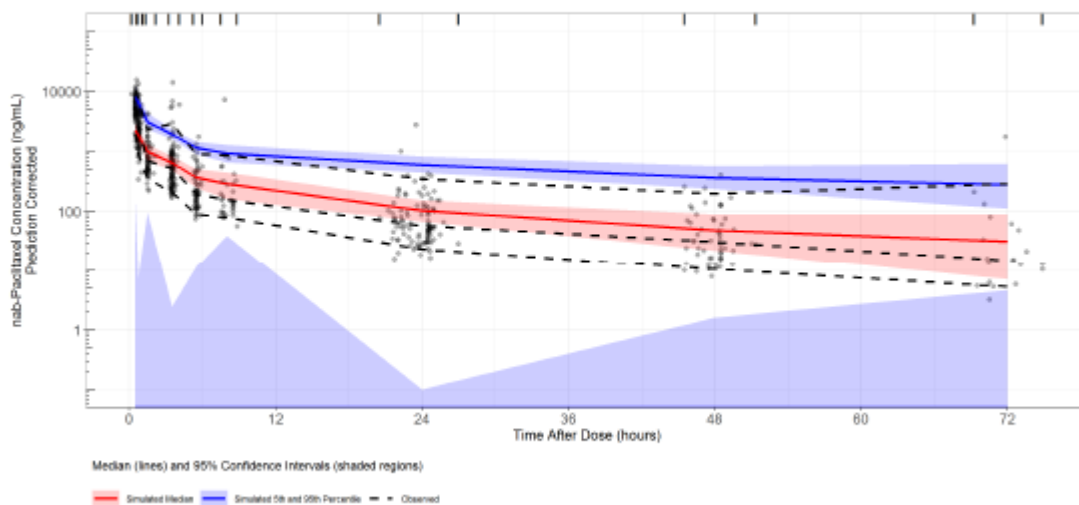
Finally, Models 2 and 3 were evaluated using the method of prediction corrected visual predictive check. The models were used to generate PK profiles for a simulated subject population with the same characteristics and observed sampling times as the observed subject population. Both the observed and the simulated data were separated into 8 bins according to the sampling times. These simulations were replicated a total of 1000 times so that within each bin, nonparametric 95% confidence intervals of the 5th, 50th and 95th prediction percentiles of concentration could be computed. These were displayed graphically and overlaid with the corresponding percentiles of the observed data. Results of the visual predictive check are presented in Figure 3 for Model 2 and in Figure 4 for Model 3. Observed median and upper 90th percentile of paclitaxel concentrations were contained within the model-predicted ranges (shaded areas) for Model 2 with only saturable elimination (Figure 3). However, only upper 90th percentile of paclitaxel concentrations were contained within the model-predicted ranges and for Model 3 with saturable distribution and elimination and median concentrations were overpredicted (Figure 4). Lower 90th percentile of paclitaxel concentrations were underpredicted in both models but with a larger bias for Model 3 with saturable distribution and elimination.

Figure 3: Prediction Corrected Visual Predictive Check for the Concentration-Time Profiles of Paclitaxel – Final Model Including Saturable Elimination (Model 2)

Median (lines) and 95% Confidence Intervals (shaded regions)

Simulated Median —— Simulated 5th and 95th Percentile —— Observed

Black dots are individual observed concentrations.
Source: Report ABI-007-PST-001-PK, Figure 4.

Figure 4: Prediction Corrected Visual Predictive Check for the Concentration-Time Profiles of Paclitaxel – Model Including Saturable Distribution and Elimination (Model 3)

Median (lines) and 95% Confidence Intervals (shaded regions)

Simulated Median —— Simulated 5th and 95th Percentile —— Observed

Black dots are individual observed concentrations.

In summary, there is limited nonlinear PK behavior of paclitaxel exposure from 120 mg/m2 to 270 mg/m2 in pediatric patients. In addition, the current work confirms that the model with three compartments and only saturable elimination, as used in ABI-007-PST-001-PK, adequately escribed the concentrations of paclitaxel in pediatrics and the current data don't support the identification of a saturable distribution component. The proposed wording on PK in the Summary of Product Characteristics (SmPC), Section 5.2, remains unchanged.

Assessment of the MAH's response

The applicant showed sufficiently that the observed non-linearity in PK is adequately described with the initial proposed model with three compartments and only saturable elimination. **Issue solved.**

Conclusion

☐ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒ No need to update overall conclusion and impact on benefit-risk balance

Question 3

The Applicant is asked how the number of 4 patients with DCR is calculated in the Ewing's sarcoma group, since the results show only 3 patients with SD ≥16 weeks and no patients with confirmed CR or PR.

Summary of the MAH's response

As noted, Table 14: Disease Control Rate – Phase 2 (Efficacy Evaluable Population) in Study Report ABI-007-PST-001 indicates that 4 patients are included in the DCR for the Ewing's sarcoma group. The source for this information, Table 14.2.1.1.1 (Summary of Overall Response by RECIST 1.1 and/or Curie Score, Efficacy Evaluable Population), shows that 3 patients in the Ewing's sarcoma group had a Best Overall Response of SD ≥ 16 weeks, and no patients exhibited confirmed PR or confirmed CR.

Table 14.2.1.1.1 also indicates that 2 patients had a Best Overall Response of PR; please note that these were not confirmed responses. It can be seen on page 9 in Listing 16.2.5.5 (see ABI-007-PST-001 Listing of Individual Laboratory Measurements by Patients) (Best Confirmed Overall Response and Duration of Response by RECIST 1.1, Safety Population) that one of these 2 patients with a Best Overall Response of (unconfirmed) PR also met the requirements for a Best Confirmed Overall Response of SD ≥ 16 weeks; in accordance with the ABI-007-PST-001 Statistical Analysis Plan, SD duration was calculated as the time from first study drug administration until first observed disease progression. This brings to 4 the total number of patients with SD ≥ 16 weeks.

Assessment of the MAH's response

The MAH explained that in addition to the three patients with confirmed SD, there were two patients who had an unconfirmed best response of PR, of which one also met the criteria of confirmed SD ≥16 weeks and was therefore counted in the DCR rate as SD. **Issue resolved.**

Conclusion

☒ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☐ No need to update overall conclusion and impact on benefit-risk balance

Question 4

The Applicant is asked when the final report with the completed 1 year-survival follow-up is expected to be submitted.

Summary of the MAH's response

Please note that the final report including 1-year overall survival (OS) follow-up data, dated 26 Apr 2019, was part of the initial submission made on 28 Jun 2019. The report was included in eCTD section m-5-3-3-2-patient-PK-and-initial-tolerability-study-reports, ABI-007-PST-001-Study Report Body – OS Follow-Up.

The clinical overview (Section 2.5), summary of clinical efficacy (Section 2.7.3), and summary of clinical safety (Section 2.7.4) were updated to include data on the 1-year OS follow-up period and are submitted in Module 2. Below, the results are summarised of the 1-year survival follow-up period.

Results 1-year survival follow-up

Patients completing or discontinuing treatment in Study ABI-007-PST-001 were included in a 1-year survival follow-up period.

At the time of the first database cutoff date of 05 Dec 2017, a total of 10 patients (6 patients in the Ewing's sarcoma group, 3 patients in the neuroblastoma group, and 1 patient in the rhabdomyosarcoma group) were ongoing in the survival follow-up period. As of the final database cutoff date of 06 Nov 2018, all patients had completed the 1-year survival follow-up period or discontinued from the study.

Median overall survival results observed at the final database cutoff date were similar to those seen at the first database cutoff date. At the 06 Nov 2018 cutoff date, the median overall survival was 32.1 weeks, 32.0 weeks, and 19.6 weeks for the Ewing's sarcoma, neuroblastoma, and rhabdomyosarcoma groups, respectively, versus the median overall survival of 32.1 weeks, 26.7 weeks, and 19.6 weeks for the Ewing's sarcoma, neuroblastoma, and rhabdomyosarcoma groups, respectively, at the 05 Dec 2017 database cutoff. Median duration of response and progression-free survival results remained unchanged between the two database cutoff dates.

Data collection for TEAEs had been completed by the time of the first database cutoff date. Thus, no new safety concerns emerged during the remaining follow-up period for the 10 patients ongoing in the study on 05 Dec 2017.

During the 1-year follow-up period, an additional 5 patients from the Ewing's sarcoma group, 2 patients from the neuroblastoma group, and 1 patient from the rhabdomyosarcoma group died. Similarly to what had been reported for the deaths recorded until the first database cutoff date, these patient deaths were attributed to "death from malignant disease under study, or complication due to malignant disease under study". In total, eleven patients (79%) from the Ewing's sarcoma group, 10 patients (71%) from the neuroblastoma sarcoma group, and 12 patients (86%) from the rhabdomyosarcoma group died during the study.

Assessment of the MAH's response

The MAH clarified that during the submission in June 2019 both the original CSR and an addendum of the CSR with 1-year follow-up survival data were submitted. The first CSR dated from 29 May 2018. The last patient completed the study on 06 Nov 2018 and an update of the OS data was performed on 26 April 2019. The 1-year follow-up survival data were not added to the clinical overview, summary of clinical efficacy, or the summary of clinical safety. In this response the MAH updated these documents accordingly.

The 1-year follow-up survival data were comparable to the results of the first database cutoff. PFS and DOR did not change with the new cutoff data. Collection of safety data was already completed at the first data cutoff. **Issue resolved.**

Conclusion

☒ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☐ No need to update overall conclusion and impact on benefit-risk balance