CLINICAL REVIEW

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Reviewer Name(s)	Amy Barone, MD Suzanne Demko, PA-C (CDTL)
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Established Name	Cabazitaxel
(Proposed) Trade Name	Jevtana
Therapeutic Class	Taxane
Applicant	Sanofi
Formulation(s)	Intravenous
Dosing Regimen	Not applicable
Indication(s)	None
Intended Population(s)	None

Template Version: March 6, 2009

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1 Recommendations

The clinical reviewer recommends that Pediatric Exclusivity be granted for Jevtana (cabazitaxel) and that relevant information obtained from pediatric studies of cabazitaxel be incorporated into the Jevtana package insert. This recommendation is based on the review finding that the Application Holder fairly responded to all of the elements in the Written Request (WR).

The adverse event profile of cabazitaxel in the pediatric population studied appears to be similar to that of the adult population. However, the pediatric studies failed to demonstrate that cabazitaxel is effective in the treatment of pediatric patients with recurrent or refractory high-grade glioma or diffuse pontine glioma. Therefore, use of cabazitaxel in this population is not recommended.

2 Introduction and Regulatory Background

2.1 Product Information

Established name: Cabazitaxel
Proprietary Name: Jevtana®
Applicant: Sanofi.
Pharmacological Class: Taxane
Mechanism of Action: Microtubule inhibitor
Proposed Indication: There is no proposed pediatric indication.

2.2 Rationale for Pediatric Studies of Cabazitaxel

Brain tumors are the second most common pediatric cancer, after hematological malignancies, accounting for approximately 20% of all childhood cancers and gliomas are the most common type of childhood CNS tumor[1]. Using the World Health Organization (WHO) classification criteria, gliomas are classified as low grade (WHO Grade I and II) and high grade (WHO Grade III and IV) tumors. High grade glioma (HGG) represents about 8-10% of all pediatric CNS tumors. In pediatric oncology, HGGs include Grade III and IV anaplastic astrocytoma, anaplastic oligodendroglioma, oligoastrocytoma, anaplastic ependymoma, and glioblastoma. Diffuse intrinsic pontine gliomas (DIPG) are the most common pediatric brainstem cancers[2]. Histologically, DIPG are usually high grade anaplastic astrocytomas or glioblastoma multiforme. According to the Central Brain Tumor Registry of the United States, the incidence of high-grade gliomas (any location) among patients <19 years of age was approximately 0.63 per 100,000 person years[1]. Based on SEER 17 registries from 1995-2007, the 5-year relative survival rate is 34% for anaplastic astrocytoma and 19% for glioblastoma multiforme in patients 0-19 years of Age[3].

Depending on the subtype, location and grade of the brain tumor, a combination of surgery, radiation therapy, and chemotherapy is often used in treating brain tumors in children greater than 3 years of age. Younger children do not normally receive radiotherapy because of the severe neurological sequelae. Surgery and radiation remain the cornerstones of treatment of HGG. Concomitant temozolomide and radiation are the standard treatment for adult patients with HGG, but this regimen has failed to demonstrate benefit in children. Although HGG consists of several tumor subtypes, each associated with a unique molecular profile, the treatment and prognosis do not differ significantly. Despite multimodality treatment, long term survival rates for HGGs remain poor. Most patients with HGGs will have tumor recurrence and will die of the disease within 3 years of the diagnosis[3]. Given the tumor location, DIPG are particularly difficult to treat and a majority of patients with DIPG tumors progress rapidly and die of the disease within one year of diagnosis.

Cabazitaxel is a microtubule inhibitor which binds to tubulin and promotes its assembly into microtubules while simultaneously inhibiting disassembly. This leads to the stabilization of microtubules, which results in the inhibition of mitotic and interphase cellular functions. Cabazitaxel is structurally similar to docetaxel; the hydroxyl groups present in docetaxel are replaced with methoxy groups in cabazitaxel. A limitation of paclitaxel and docetaxel for the treatment of HGG is the inability of these compounds to cross the blood-brain barrier (BBB). Based on nonclinical data, the sponsor proposed that cabazitaxel may have the ability to cross the BBB..

2.3 Summary of Pre-submission Regulatory Activity

Cabazitaxel is FDA approved in combination with prednisone for treatment of patients with hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing treatment regimen.

Table 1 provides a brief summary of the regulatory history of the pediatric development of cabazitaxel.

Table 1 Pediatric Regulatory History

Date	Action
December 6, 2011	Sanofi submitted an initial Proposed Pediatric Study Request (PPSR) for cabazitaxel with the goal of obtaining a Written Request (WR)
March 20, 2012	FDA issued a WR for development of cabazitaxel in pediatric patients with recurrent or refractory high grade glioma (defined as WHO Grade III or Grade IV astrocytic or oligodendroglial tumor; HGG) or recurrent or refractory diffuse intrinsic pontine glioma (DIPG) for whom no further effective therapy is available
July 20, 2012	Sanofi agreed to conduct the studies as detailed in the WR and submitted the protocol
May 8, 2013	WR Amended to clarify study design and to further define the age groups and number of patients to be studied.
March 3, 2015	WR Amended to 1) extend the due date for the final study reports submission from September 30, 2016 to December 15, 2017 and 2) use modified RANO criteria instead of Macdonald criteria for the evaluation of the primary endpoint in patients with CNS tumors in phase 2 of the study.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

This submission contained sufficient datasets and relevant case report forms. The quality and integrity of the submission were adequate to permit a comprehensive review.

3.2 Compliance with Good Clinical Practices

According to the ethics sections of the submission, the relevant study was performed in compliance with Good Clinical Practices, including the archiving of essential documents. The study report was prepared in accordance with the ICH Harmonized Tripartite Guideline on the Structure and Content of Clinical Study Reports, dated July 1996, using QSOP-004712 Version 3.0.

3.3 Financial Disclosures

This submission contained the required financial disclosure information for clinical investigators who participated in the TED12689 study. There were no clinical investigators with disclosure financial interests and/or arrangements who participated in the TED12689 study.

4 Significant Efficacy/Safety Issues Related to Clinical Pharmacology

The expectations of the WR were met from a clinical pharmacology perspective. Please see review by Dr. Ruby Leong for full detail on the issues related to clinical pharmacology.

5 Sources of Clinical Data

This submission contains the results of one clinical trial (TED12689, "A Phase 1-2 Dose Finding, Safety and Efficacy Study of Cabazitaxel in Pediatric Patients with Refractory Solid Tumors including Tumors of the Central Nervous System") and a pharmokinetic analysis conducted in response to the WR. The study was conducted by Sanofi US Services Inc.

Monitoring of all investigator sites was performed by (b) (4) according to Sanofi procedures. Management of clinical trial data was performed according to the following rules and procedures. Data entry and validation were carried out using standard validated remote data capture computer software (Oracle Clinical version 4.6). Data were stored in an Oracle database on a UNIX machine. Data entry was performed directly at the Investigator site from the data source documents and signed electronically by the authorized site personnel. Moreover, any modification in the database was traced using an audit trail. Sanofi conducted Investigator meetings and training sessions for clinical research associates as well as individual site initiation meetings to develop a common understanding of the clinical study protocol, case report form,

and study procedures, in compliance with GCP. An audit certificate for a site audit conducted during the study is provided in the submission.

5.1 Tables of Studies/Clinical Trials

Table 2 Clinical Trials of Cabazitaxel Conducted in Response to the PWR

Study Number	Title	Design	Number of Patients
TED12689	A Phase 1-2 Dose Finding, Safety and Efficacy Study of Cabazitaxel in Pediatric Patients with Refractory Solid Tumors including Tumors of the Central Nervous System	12 clinical sites in the United States of America and Canada Open label, multi-center study conducted in two parts: Phase 1 Part using dose escalation to establish the maximum tolerated dose (MTD) of cabazitaxel in pediatric patients with recurrent or refractory solid tumors based on related dose limiting toxicities (DLTs); and Phase 2 Part to evaluate the activity and safety of cabazitaxel at the MTD in pediatric patients with recurrent or refractory high grade glioma (HGG) or diffuse intrinsic pontine glioma (DIPG).	**Number of patients:** Planned: 9-28 patients for Phase 1 part; 10-29 patients for Phase 2 part Enrolled: 23 patients for Phase 1 part; 16 patients for Phase 2 part Treated: 39 patients **Evaluated:** Safety: 39 patients Efficacy: 33 patients Pharmacokinetics: 36 patients

5.2 Review Strategy

The objectives of this review were two-fold: 1) to determine if the Applicant fairly responded to the elements outlined in Amendment 2 of the WR and 2) to provide recommendations for incorporation into the Jevtana package insert of relevant pediatric information derived from the conduct of the studies outlined in the WR. To accomplish these objectives, data from the clinical trials submitted with this supplement were comprehensively reviewed. Documentation from previous interactions with FDA regarding the pediatric development plan for cabazitaxel, the WR, and relevant published literature were also reviewed.

5.3 Discussion of Individual Clinical Trials

Study Title
TED12689: A Phase 1-2 Dose Finding, Safety and Efficacy Study of Cabazitaxel in Pediatric Patients with Refractory Solid Tumors including Tumors of the Central Nervous System

Study Milestones
This clinical trial was conducted by Sanofi at 12 sites in the United States and Canada from February 19, 2013 to July 3, 2015.

Study Objectives
PRIMARY

Phase 1 Part:

- To determine the dose limiting toxicity (DLT) and the maximum tolerated dose (MTD) of cabazitaxel as a single agent in patients with recurrent or refractory solid tumors including tumors of the central nervous system.

Phase 2 Part:

- To determine the objective response rate (complete and partial response) and the duration of response to cabazitaxel as a single agent in patients with recurrent or refractory high grade glioma (HGG) or diffuse intrinsic pontine glioma (DIPG).

SECONDARY

Phase 1 Part:

- To characterize the safety and tolerability of cabazitaxel in patients with recurrent or refractory solid tumors including tumors of the central nervous system
- To characterize the PK profile of cabazitaxel in patients with recurrent or refractory solid tumors including tumors of the central nervous system.
- To evaluate preliminary anti-tumor activity that may be associated with cabazitaxel in patients with recurrent or refractory solid tumors including tumors of the central nervous system.

Phase 2 Part:

- To characterize the safety and tolerability of cabazitaxel in patients with recurrent or refractory HGG or DIPG.
- To estimate progression free survival (PFS) in patients with recurrent or refractory HGG or DIPG.
- To estimate overall survival (OS) in patients with recurrent or refractory HGG or DIPG.
- To characterize the plasma PK profile of cabazitaxel in patients with recurrent or refractory HGG or DIPG.

Study Design

Methodology**:** This was an open label, multi-center study conducted in two parts: Phase 1 Part using dose escalation to establish the maximum tolerated dose (MTD) of cabazitaxel in pediatric patients with recurrent or refractory solid tumors based on related dose limiting toxicities (DLTs); and Phase 2 Part to evaluate the activity and safety of cabazitaxel at the MTD in pediatric patients with recurrent or refractory high grade glioma (HGG) or diffuse intrinsic pontine glioma (DIPG).

Inclusion criteria

- Phase 1 Part (dose escalation): Patients with a histologically confirmed solid tumor, including tumors of the central nervous system, that was recurrent or refractory and for which no further effective standard treatment was available. All patients must have had measurable or non-measurable (but evaluable) disease. Patients with diffuse pontine glioma were eligible without a biopsy after evidence of progressive disease post radiation therapy.
- Phase 2 Part (safety and activity): Patients with recurrent or refractory high grade glioma(defined as WHO Grade III or Grade IV astrocytic or oligodendroglial tumor) or diffuse intrinsic pontine glioma for whom no further effective therapy was available. All patients must have had measurable disease. Patients with diffuse pontine glioma were eligible without a biopsy after evidence of progressive disease post radiation therapy. Patients with a Grade III or Grade IV glioma must have had pathologic conformation either at the time of initial diagnosis or at the time of recurrence.
- Patients aged ≥2 years and ≤18 years
- Patients should have met the body surface area (BSA) requirements to be eligible:
    - a) Minimal BSA requirements for a particular dose level
    - b) During the Phase 1 part, patients must have had a BSA <2.1m2 at the time of enrollment;.
    - c) During the Phase 2 part, patients with a BSA ≥2.1 m2 were eligible, however the actual dose of cabazitaxel for these patients was to be adjusted to a maximum dose calculated with (capped at) the BSA of 2.1 m^2.
- Performance status by:
    - Lansky score ≥60 (patients ≤10 years of age);
    - Karnofsky score ≥60% (patients >10 years of age);

  Patients who were unable to walk because of paralysis, but who were mobile in a wheelchair, were considered ambulatory for the purpose of assessing the performance score.
- Patients must have had adequate liver, renal and marrow function as defined below:
    - Total bilirubin ≤1.0 x the upper limit of normal (ULN) for age;
    - AST (SGOT) and ALT (SGPT) ≤2.5xULN;
    - Serum creatinine ≤1.5xULN for age or creatinine clearance ≥60 mL/min/1.73 m2 (calculated according to Schwartz formula);
    - Absolute neutrophil count ≥1.0x109/L;
    - Platelets ≥75x109/L (transfusion independent);
    - Hemoglobin ≥8.0 g/dL (can be transfused).
- Female patients of child-bearing potential (reproductive or child bearing potential was to be defined as per local site practice) must have had a negative pregnancy

test ≤ 7 days before starting cabazitaxel treatment. Should a female patient have become pregnant or suspected she was pregnant while participating in this study, she was to inform her treating physician immediately.

- Male and female patients of reproductive potential must have agreed to use adequate contraception (hormonal and/or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation, and for 6 months following the last dose of cabazitaxel.
- Written informed consent/assent prior to any study-specific procedures: Consent must have been obtained from the patient and/or parent(s) or legal guardian(s) and the signature of at least one parent or guardian was required. Investigators were also to obtain assent of patients according to local, regional or national guidelines.
- Patients must have recovered from the acute toxic effects of all prior therapy to ≤ grade 1 before entering this study.

Exclusion criteria

- Prior treatment within the following timeframes:
    - Systemic anti-cancer treatment within 3 weeks (6 weeks for nitrosurea, mitomycin and monoclonal antibodies)
    - Surgery or smaller field radiation therapy within 4 weeks
    - Treatment with an investigational agent within 4 weeks or within half-lives of the agent, whichever is longer
- Craniospinal or other large field radiation therapy (defined as >25% of bone marrow irradiated) within 6 months prior to the first dose.
- Prior systemic radioisotope therapy (this does not include diagnostic imaging) or total body irradiation
- Prior bone marrow or stem cell transplant
- Patients with any clinically significant illness that, in the investigator's opinion cannot be adequately controlled with appropriate therapy, would compromise a patient's ability to tolerate cabazitaxel or result in inability to assess toxicity. This includes, but is not limited to uncontrolled intercurrent illness including ongoing or active infection, cardiac disease, renal impairment, planned surgery or psychiatric illness/social situations that would limit compliance with study requirements.
- Known human immunodeficiency virus (HIV) infection or acquired immunodeficiency syndrome (AIDS)-related disease
- Active hepatitis
- Pregnant or breast feeding women
- Treatment with strong inhibitors or strong inducers of CYP3A4 within 14 days prior to first dose of cabazitaxel and for the duration of study
    - Treatment with continuous daily dexamethasone is not permitted during the first cycle of study treatment. Dexamethasone is permitted during

the study for premedication and for symptomatic management of acute events
- Treatment with enzyme inducing anti-epileptic drugs (EIAED) during the study. Non-EIAEDs are permitted (see Section 20, Appendix A).

- Known history of hypersensitivity to taxanes or polysorbate 80.
- Participation in another interventional clinical trial and/or concurrent treatment with any investigational drug.
- Patients not able to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures.

Treatment Plan

Treatment was administered on an inpatient or outpatient basis. All patients were administered cabazitaxel by intravenous (IV) infusion over 1 hour (+/- 15 minutes) on Day 1 every 21 days (up to 3 days delay was allowed for logistics). Patients in the Phase 1 part of the study received cabazitaxel according to the 3+3 dose escalation schema described in Figure 1. The starting dose corresponded to 80% of the cabazitaxel recommended dose determined in adults (25 mg/m2 IV) on an every 3 week basis.

Table 3 Proposed Dose Levels

Dose level	Cabazitaxel mg/m²
-1	15
1 (starting dose)	20
2	25
3	30
4	35
5	40

Patients in the Phase 2 part of the study were administered cabazitaxel at the MTD established in the Phase 1 part. As of Protocol Amendment 4, 24 hours (+/- 1 hour) and 12 hours (+/- 1 hour) before each dose of cabazitaxel, the patient was to be administered steroid (dexamethasone 0.05 mg/kg – 0.10 mg/kg, 10 mg maximum, or equivalent [both dose and half-life needed to be taken into consideration]).

At all times during the study, the following premedications were to be administered within 30-60 minutes of each dose of cabazitaxel:

- Antihistamine (diphenhydramine 1 mg/kg, maximum dosage 25 mg, or other antihistamines),
- Steroid (prior to Protocol Amendment 4, dexamethasone 0.01-0.25 mg/kg or equivalent; and as of Protocol Amendment 4, dexamethasone 0.05-0.10 mg/kg, 10

mg maximum or equivalent [both dose and half-life were to be taken into consideration]),
- H2 antagonist (ranitidine 2-4 mg/kg, maximum dosage 50 mg, or other H2 antagonist).

Prophylactic G-CSF or pegylated granulocyte-colony stimulating factor (PEG G-CSF) (per institutional guidelines) was required for all patients to reduce the duration of taxane-induced neutropenia and prevent neutropenic complications. G-CSF (5 μg/kg/day) was to be administered at least 24 hours post cabazitaxel and continued until the absolute neutrophil count (ANC) ≥1.0x109/L. PEG G-CSF could have been used in place of G-CSF as per institutional use and dosing guidelines. Patients may have received supportive care (eg, packed red blood cells, platelets) as per local institutional guidelines, at any time during the study; however, as of Protocol Amendment 3, platelet transfusion during Cycle 1 was to be considered a DLT.

Patients were to be removed from study treatment when any of the criteria listed below applied:
- Clinical or radiological evidence of disease progression;
- Intercurrent illness that prevented further administration of treatment;
- Unacceptable adverse events(s);
- Patient, parent(s) or legal guardian(s) wished to withdraw from the study treatment;
- General or specific changes in the patient's condition that rendered the patient unacceptable for further treatment in the judgment of the investigator;
- Pregnancy;
- A treatment delay >2 weeks before the start of Cycle 2;
- A treatment delay >2 weeks beyond Cycle 2 not related to safety if the patient was NOT considered to be receiving benefit from the study treatment;
- 0The requirement of >2 dose reductions

Dose-Limiting Toxicity Criteria

DLTs were assessed according to NCI CTCAE (v4.0). For the purposes of dose escalation and determination of the MTD, only DLTs that occurred during Cycle 1 of treatment were considered for decisions regarding dose escalation.

A DLT was defined as an adverse event (AE) or abnormal laboratory value causally related to therapy with cabazitaxel (ie, assessed as unrelated to disease progression, intercurrent illness, or concomitant medications), that met any of the criteria below.

Definition of hematologic dose-limiting toxicity
- Any Grade 4 hematologic toxicity with the specific exception of:
  - Neutropenia Grade 4 lasting ≤7 days
- Grade 3 or 4 febrile neutropenia with the specific exception of:
  - Grade 3 or 4 febrile neutropenia in the absence of G-CSF prophylaxis.
- Grade 4 thrombocytopenia was to be considered a DLT.

- As of Protocol Amendment 3, if a patient received a platelet transfusion during Cycle 1, such an event was to be considered a DLT.

Non-hematologic dose-limiting toxicity was defined as any grade ≥3 non-hematologic toxicity with the specific exception of:

- Grade 3 nausea or Grade 3 or 4 vomiting that in the opinion of the investigator occurred in the setting of inadequate treatment with supportive care measures;
- Grade 3 or 4 diarrhea that in the opinion of the investigator occurred in the setting of inadequate treatment with supportive care measures;
- Grade 3 or 4 dehydration that in the opinion of the investigator occurred in the setting of inadequate treatment of other toxicity (such as management of diarrhea, nausea, vomiting, etc.);
- Grade 3 fatigue lasting ≤7 days;
- Inadequately treated hypersensitivity reactions. Patients with anaphylaxis reactions during
- Cycle 1 cabazitaxel administration were to be removed from study but these idiopathic reactions were not to be considered DLTs. These patients were to be replaced.
- Elevated transaminases <10xULN of ≤7 days in duration.

In addition, the following was also to be considered a DLT:

- Re-treatment delay of >2 weeks due to delayed recovery from a toxicity related to study treatment to baseline grade or ≤ Grade 1 (except for alopecia). If there was a treatment delay >2 weeks before the start of Cycle 2, patient was to discontinue study treatment.

Concomitant Therapies

The following concomitant treatments were not permitted during the study treatment period:

- Concurrent treatment with other investigational drugs.
- Concurrent treatment with any other anticancer therapy including radiation therapy to the involved tumor being assessed, immunotherapy, targeted therapy or biological therapies.
- Palliative radiotherapy for pain control was not allowed to the primary lesion being assessed for response.
- Concurrent treatment with strong inhibitors of CYP3A4 (eg, ketoconazole, itraconazole, clarithromycin, etc.). For patients who were receiving treatment with such agents, a 14-day washout period was required prior to enrollment.
- Concurrent treatment with potent strong inducers CYP3A4, such as the antiepileptic drugs carbamazepine, phenytoin, phenobarbital, and St. John's Wort (millepertuis). For patients who were receiving treatment with such agents, a 14-day washout period was required prior to enrollment.

The following concomitant treatments were permitted during the study treatment period:

- As of Protocol Amendment 1 (15 November 2012), the use of dexamethasone was allowed during the study treatment period.

- The use of bisphosphonates was allowed, however the dose must have been stable for 12 weeks prior to enrollment and during the study treatment period (though bisphosphonate treatment may have been discontinued during the study treatment period).
- Ancillary treatments were to be given as medically indicated; they must have been specified in the electronic case report form (eCRF).
- G-CSF or PEG G-CSF was to be given at least 24 hours after cabazitaxel administration to prevent hematological toxicity and was continued following each investigational medicinal product (IMP) administration throughout the duration of the study treatment.
- Standard anti-diarrheal treatments (eg, loperamide) were recommended for patients with ongoing diarrhea as per institutional guidelines.
- Supportive treatment as medically indicated for the patient's well-being (including hyperalimentation and blood transfusion) may have been prescribed at the Investigators discretion. Every medication or treatment taken by the patient during the trial and the reason for its administration were to be recorded on the eCRF.
- Patients on hormone replacement for central pituitary dysfunction could have been on appropriate hormone replacement therapy.

Dose Delays and Dose Modification

Treatment may have been delayed no more than 2 weeks to allow recovery from acute toxicity. If there was a treatment delay >2 weeks before Cycle 2, due to delayed recovery from an acute toxicity related to study treatment, to baseline or ≤ Grade 1 (except for alopecia), the patient was to discontinue study treatment. If there was a treatment delay >2 weeks and the patient was considered to be receiving benefit from the study treatment, the patient may have continued to receive study treatment if deemed appropriate by the Study Committee. For patients who were assessed by the investigator to be receiving benefit from cabazitaxel, dose modifications for toxicity were allowed according to recommendations provided in Table 3. The cabazitaxel dose could have been reduced when necessary the dose reduction levels detailed in Table 4. The dose, which had been reduced for toxicity, was not to be re-escalated. Up to a maximum of 2 dose reductions were allowed per patient. If a third dose reduction was required per the modifications above, the patient was to discontinue study treatment.

Table 4 Dose Modifications (copied from Study Report)

Toxicity	Grade 2	Grade 3	Grade 4
Neutropenia	If not recovered on D21, delay** next infusion until recovery to grade ≤2 (neutrophil ≥1.0 x 10^9/L). - 1st episode: No dose reduction required. - 2nd episode; reduce by 1 dose level	No dose reduction if isolated and duration ≤7 days. If duration more than 7 days or not recovered on D21 Delay** next infusion until ANC ≥1.0 x 109/L and: - 1st episode: Reduce dose by 1 dose level - 2nd episode: Reduce dose by 1 more dose level, if available. - 3rd episode: Withdraw from study treatment	
Febrile neutropenia or neutropenic infection	Not applicable	Delay** next infusion until recovery and ANC ≥1.0 x 109/L and: - 1st episode: Reduce dose by 1 dose level - 2nd episode: Reduce dose by 1 more dose level, if available. - 3rd episode: Withdraw from study treatment	
Thrombocytopenia	Delay** next infusion until recovery to grade ≤1 (platelets ≥75 x 109/L). No dose reduction required.	Delay** infusion until platelets ≥75 x 109/L: If grade 3 without delay, no dose reduction required. If grade 4, or grade 3 with dose delay or platelet transfusion - 1st episode: reduce dose by 1 dose level. - 2nd episode: reduce dose by 1 more dose level. - 3rd episode: Withdraw from study treatment.	
Diarrhea§	Delay** next infusion until recovery (grade ≤1) No dose reduction required.	- 1st episode: Reduce dose by 1 dose level. - 2nd episode: Reduce dose by 1 more dose level. - 3rd episode: Withdraw from study treatment.	
Stomatitis§	Delay** next infusion until recovery (grade ≤1) No dose reduction required.	- 1st episode: Reduce dose by 1 dose level. - 2nd episode: Reduce dose by 1 more dose level. - 3rd episode: Withdraw from study treatment.	
Cutaneous Reactions§	Delay** next infusion until recovery (grade ≤1) No dose reduction required.	Delay** next infusion until recovery (grade ≤1): - 1st episode: Reduce dose by 1 dose level. - 2nd episode: Withdraw from study treatment.	Withdraw from study treatment.

Toxicity	Grade 2	Grade 3	Grade 4
Creatinine increase	No delay, perform actual creatinine clearance - if ≥ 60 ml/min, no dose modification - if clearance ≥40 ml/min and <60 ml/min, reduce dose by one dose level - if clearance <40 ml/min, Withdraw from study treatment.		
Neurological toxicity***	No delay Reduce dose by 1 dose level	Stop study treatment.	
Bilirubin Elevation	Delay** until recovery to bilirubin ≤1.0xULN and reduce dose by 1 dose level	Withdraw from study treatment.	
Transaminases Elevation	Delay** until recovery to AST/ALT <2.5xULN	Delay** until recovery to AST/ALT <2.5xULN and reduce dose by 1 dose level	Withdraw from study treatment.
Hypersensitivity	No dose reduction. Withdraw from study treatment in case of 2nd grade 3 episode.		Withdraw from study treatment.

*Dose reduction levels provided in Table 3.

** Maximum of 2 weeks delay, the patient will be withdrawn from study treatment unless deemed to benefit from the study treatment by Study Committee

*** Including hearing disorders

§ Delay infusion by maximum of 2 weeks until recovery to grade ≤1 and apply dose reduction according to worst grade observed

Table 5 Dose Reduction Levels (copied from Study Report)

Dose (mg/m^2)	Initial dose		Dose reduction 1		Dose Reduction 2
Cabazitaxel	40 mg/mg^2	→	35 mg/mg^2	→	30 mg/mg^2
Cabazitaxel	35 mg/mg^2	→	30 mg/mg^2	→	25 mg/mg^2
Cabazitaxel	30 mg/mg^2	→	25 mg/mg^2	→	20 mg/mg^2
Cabazitaxel	25 mg/mg^2	→	20 mg/mg^2	→	15 mg/mg^2
Cabazitaxel	20 mg/mg^2	→	15 mg/mg^2	→	12 mg/mg^2
Cabazitaxel	15 mg/mg^2	→	12 mg/mg^2	→	NA

NA=not applicable

Criteria for Evaluation

For the purposes of endpoint analysis, tumor response was assessed by study investigators using standard criteria (Response Evaluation Criteria in Solid Tumors [RECIST] 1.1 for patients with solid tumors and modified RANO criteria for patients with CNS tumors).Patients were to be evaluated every 9 weeks (±7 days) from the date of first cabazitaxel administration. If a complete response (CR) or partial response (PR) was observed, confirmation was required via subsequent scans performed at least 4 weeks later. If a confirmed response was documented, response was to be re-assessed every 9 weeks. Patients removed from study treatment for any reason other than disease progression were to have tumor assessments performed 12 weeks after the latest assessment, and then again every 12 weeks until disease progression was documented. The same imaging modality was to be used for each assessment. Imaging studies (scans) were centrally collected and stored for potential central review.

Objective response rate (ORR) and duration of response (DOR) were the primary endpoints in the Phase 2 part. The ORR was defined as the proportion of efficacy evaluable patients with a CR or PR after 3 cycles of cabazitaxel treatment and maintained for at least 4 weeks. The DOR was defined as the time (in days) from the date of first response until the date of first documented progressive disease or death (from any cause), whichever came first. If progression or death was not observed, the patient was censored at the date of the patient's last progression-free tumor assessment prior to the study cut-off date.

Statistical Methods

The following analysis populations were defined:

- The safety population (**all treated population**) in the Phase 1 and Phase 2 parts was defined as registered patients who actually received at least one dose or part of a dose of the IMP.
- Patients evaluable for DLT assessment (**DLT evaluable population**) were the subset of patients in the Phase 1 part of the study from the all treated (AT) population who received

the first dose of cabazitaxel and had sufficient safety evaluations or experienced a DLT during Cycle 1. Patients who did not experience a DLT during the first cycle were considered to have sufficient safety evaluations if they had been observed for at least 21 days following the first dose and were considered by both the Sponsor and the Investigators to have sufficient safety data to conclude whether or not a DLT had occurred. In practice, a DLT-specific form was to be completed at the end of the first cycle. Patients who were ineligible for DLT assessment were to be replaced after discussion and confirmation by the Sponsor and Investigator. Any Phase 1 patient who initiated treatment after the occurrence of the second DLT in a cohort was excluded from the DLT evaluable population but included in the Safety population. Patients were analyzed according to their dose level.

- In the Phase 1 part, the efficacy evaluable population was the subset of the AT population with measurable or non-measurable but evaluable disease with a baseline and at least one post-baseline tumor evaluation. Any patient who progressed or died from disease progression prior to the first tumor evaluation at the end of Cycle 3 was to be classified as early progression and considered evaluable for efficacy. A patient who permanently discontinued treatment prior to the first tumor evaluation at the end of Cycle 3 for a reason other than disease progression was not to be included in the efficacy evaluable population.
- In the Phase 2 part, the efficacy evaluable population was the subset of the AT population with measurable disease with a baseline and at least one post-baseline tumor evaluation. Any patient who progressed or died from disease progression prior to the first tumor evaluation at the end of Cycle 3 was to be classified as early progression and considered evaluable for efficacy. A patient who permanently discontinued treatment prior to the first tumor evaluation at the end of Cycle 3 for a reason other than disease progression was not to be included in the efficacy evaluable population.

The Phase 2 part utilized a Simon's two-stage design to test the null hypothesis that the true ORR is ≤10% versus the alternative hypothesis that the true ORR is ≥30% assuming a one-sided significance level of 5% and power of 80%. Objective response rate per the modified RANO for stages 1 and 2 combined and its associated 90% confidence interval (CI) and the one-sided p-value from the test of the null hypothesis (H0; p ≤10%) are estimated in the efficacy evaluable population and the AT population. For DOR, the analysis is based on the cohort of responders in the efficacy evaluable population and the AT population. Kaplan-Meier estimates of the 25th, 50th, and 75th percentiles and their associated 95% CIs are estimated for DOR, when estimable. In addition, a time-to-event curve is estimated using the Kaplan-Meier method.

The primary focus of adverse event reporting is on treatment-emergent adverse events (TEAE). Treatment-emergent AEs were defined as AEs that developed or worsened in grade (according to the Investigator opinion) or became serious during the on-treatment period. Pretreatment and post treatment adverse events are described separately. The grade and cycle (if relevant) are taken into account in the summary. For patients with multiple occurrences of the same event, the maximum grade was used. The denominator used for the summary by cycle is the total number of cycles administered in a treatment group. For a given event, a patient contributes 1 to the

numerator for each cycle in which an episode occurred. An episode occurred during a cycle if the date of onset was on or after the first day of the cycle, but prior to the first day of the next cycle.

Study Schedule

Table 6 Schedule of Assessments for Study TED12689 (copied from Study Report)

9.1 STUDY FLOWCHART

Evaluation[a]	Screening	Treatment period					End of Treatment	Follow-up period[p]
		Cycle 1				Subsequent Cycles		
	Within N days before first dose	D1[b]	D4	D8	D15	D1		Every 12 weeks
Assessment window in days		-1	±1	±1	±1	+3	±7	±7
Inclusion/exclusion criteria, informed consent[c], contraception counseling, demographic and medical/ disease history	21 days							
Pregnancy test[d]	8 days	X				X	X	
Height, performance status, body weight[e]	8 days	X				X	X	
Physical examination[f]	8 days	X		X	X	X	X	
Hematology[g]	8 days	X		X	X	X	X	
Blood chemistry[h]	8 days	X		X	X	X	X	
Coagulation[i]	8 days					X	X	
Urinalysis[j]	8 days	X				X	X	
12-lead ECG[k]		X					X	
Cabazitaxel administration[l]		X				X		
AE assessment[m]	Continuously throughout the study period							
Concomitant Medication	21 days	Continuously throughout the study treatment period						
PK assessment[n]		X	X					
Tumor assessment[o]	21 days					X	X	
Survival status								X
Post-treatment anti-cancer therapy								X

a Evaluation: should be performed prior to first administration of cabazitaxel unless otherwise indicated. Results should be reviewed by the investigator prior to the administration of the next dose

b D1 of cycle 1 refers to the day the patient receives the initial dose of cabazitaxel (assessments can be done within 24hrs of receiving cabazitaxel). D1 of cycle 2 and of each subsequent cycle corresponds to d22 of the previous cycle (up to 3 days will be allowed for logistics).

c The informed consent will have to be signed by the patient and/or parent(s) or legal guardian(s) before any procedure specific to the study is performed.

d Serum pregnancy test: To be performed prior to cabazitaxel administration during screening, D1 of every cycle and at end of treatment for female patients of child-bearing potential (reproductive or child bearing potential will be defined as per local site practice).

e Body height at screening only, body weight and Karnofsky/Lansky performance status assessed during screening, D1 of every cycle and at end of treatment visit.

f Physical examination will include: vital signs (temperature, blood pressure, heart rate, respiration rate) and examination of major body systems. Only clinically relevant signs and symptoms will be reported in the eCRF as AEs. To be performed prior to cabazitaxel administration during screening, D1, D8, D15 of cycle 1, then D1 of subsequent cycles and end of treatment (examination on day of administration is acceptable).

g Hematology: To be performed prior to cabazitaxel administration during screening, D1, D8, D15 of cycle1, then D1 of subsequent cycles and end of treatment. Complete blood count (CBC) consisting of red blood cells (RBC), hemoglobin, WBC with differential, platelet counts. If Grade 4 neutropenia, assess ANC approximately twice weekly until ANC ≥0.5 x 109/L and at least weekly thereafter until ANC ≥1.0 x 109/L. To be performed also in the case of fever or suspected infection.

h Blood chemistry: To be performed prior to cabazitaxel administration during screening, D1, D8, D15 of cycle 1, then D1 of subsequent cycles and end of treatment. Liver function tests: SGOT (AST), SGPT (ALT), alkaline phosphatase, total bilirubin, conjugated bilirubin. Renal function tests: Sodium, potassium, calcium, phosphate, bicarbonate, BUN, uric acid, creatinine and, if creatinine value > 1.5 x ULN then creatinine clearance should be performed (24 hour urine collection or calculated eGFR are acceptable). Glucose, LDH, albumin and total proteins to be done. Additional tests will be performed when clinically appropriate. If abnormal liver or renal function tests are Grade 3 or higher, additional tests will be done twice weekly until recovery to baseline value.

i Coagulation: INR. To be performed prior to cabazitaxel administration during screening, D1 of cycle 1 and end of treatment.

j Urinalysis: (dipstick) pH, blood, proteins during screening, D1 of every cycle and at end of treatment visit. In addition urine electrolytes, cell count and urine protein/creatinine ratio (UPCR) will be performed at screening and when serum creatinine increase >1.5 above the baseline value.

k 12-lead ECG is required prior to cabazitaxel administration during screening, D1 of cycle 1 and at end of treatment visit. To be repeated as clinically indicated.

l Cabazitaxel administration: Cabazitaxel will be administered on Day 1 (up to 3 days will be allowed for logistics) of each 21-day cycle. Cycle administration will be repeated every 3 weeks. Cabazitaxel may be delayed up to 14 days to permit resolution of any drug-related toxicity.

m Adverse Event assessment: The period of observation for collection of adverse events, extends from informed consent signed, until at least 30 days following the last study treatment administration. Serious adverse events should be followed as described in Section 11.5. Serious adverse event and related AE ongoing 30 days after last study treatment administration or new related adverse event should be followed during follow-up period until recovery or stabilization or further anticancer therapy.

n Pharmacokinetics (PK): See Section 9.2 for details.

o Tumor Assessment: CT-scan or MRI within 21 days prior to first infusion of cabazitaxel and other (e.g. PET-scan, SPECT, X-ray), if applicable. Antitumor activity will be assessed at the end of cycle 3 (± 7 days; imaging scan by CT or MRI of the primary tumor site and area of metastatic disease) and then every 3 cycles thereafter (i.e, cycle 6, 9, etc) using the criteria defined in Section 12. If a response is seen, a confirmation scan will be performed at least 4 weeks later (scans should thereafter be performed every 3 cycles). The same method should be used for each assessment to follow all target and/or non target lesions present at baseline. If patient discontinued study treatment for any reason other than disease progression, tumor assessments will be performed every 12 weeks until disease progression is documented.

p Follow-up period: All patients will be followed every 12 weeks for survival status and documentation of post-treatment anti-cancer therapy until the final study cut-off (6 months following the first dose of study treatment for the last patient enrolled in the study). This assessment can be conducted by telephone.

Changes in the Conduct of the Study

Table 7 Summary of Protocol Amendments (copied from Study Report)

Amendment Number	Date Approved	Purpose of amendments
1	15 November 2012	• Change in exclusion criterion 9 to allow patients being treated with continuous daily dexamethasone into the study, based on results from TCD10870 study indicating that CYP3A inducers have a limited impact on the PK of cabazitaxel. • Clarification of timing for: coagulation and ECG assessments; end of treatment visit, PK sampling; and G-CSF administration.
2	30 July 2013	The main intent of this amendment was to implement revisions from Pediatric Written Request issued by FDA on 08 May 2013: • Phase 2 part (efficacy) added after Phase 1 part (dose escalation) completion. • Enrollment opened for children 2-4 years old in Phase 1 part. • Addition of optional CSF collection. • Clarification of: reporting timelines; DLT definition; inclusion and exclusion criteria; and PK analysis parameters.
3	31 January 2014	• The DLT definition was changed to avoid underreporting of thrombocytopenia as DLT. • Clarification of: dose escalation rules; exclusion criteria; concomitant medications; and the management of cabazitaxel-related toxicity.
4	03 April 2015	The main intent of this amendment was to better manage infusion-related reactions, which were observed in 5 of the first 10 patients treated at the MTD in the Phase 2 part. The study committee decided to implement the following changes: • Decrease the concentration of cabazitaxel infusion by lowering the high end of the range from 0.26 mg/mL to 0.18 mg/mL. • Add pre-steroid treatment at 24 hours and 12 hours before each cabazitaxel infusion (pre-steroid treatment was to be given at 24 hours, 12 hours and 30 minutes – 60 minutes before each cabazitaxel dosing). • Adjust the dose (0.5 mg/kg) and the range (from 0.01 - 0.25 mg/kg to 0.05 - 0.1 mg/kg) of dexamethasone. • Cap each dose of dexamethasone to 10 mg maximum.

CSF= cerebrospinal fluid; DLT= dose limiting toxicity; ECG= electrocardiogram; FDA= Food and Drug Administration (United States of America); G-CSF= granulocyte-colony stimulating factor; MTD=maximum tolerated dose; PK= pharmacokinetics

Table 8 Summary of Protocol Amendment Statistical Changes (copied from Study Report)

Amendment Number	Date Approved	Rationale	Description of statistical changes
1	15 November 2012	In analyses of TEAEs, TEAEs leading to death are analyzed as Grade 5 events.	The text 'TEAE leading to death' was changed to Grade 5 TEAE.
2	30 July 2013	Study design was modified to add a Phase 2 efficacy part after the Phase 1 dose escalation study.	The determination of sample size was updated to include the justification of the sample size for Phase 2. Efficacy endpoints for Phase 2, overall response rate, duration of response, overall survival, and progression free survival were added. Statistical methods were updated to include analyses for Phase 2 data.
3	31 January 2014	Clarification of dose escalation rules, change to the definition of DLT, clarification of eligibility criteria, clarification of the use of concomitant medications, and clarification of the management of cabazitaxel toxicities.	Minor word changes.

TEAE = Treatment emergent adverse events, DLT = Dose Limiting Toxicity

Evaluation of the Applicant's Fulfillment of the Requirements of the Pediatric Written Request

Table 9 outlines the items contained in the WR and the information and responses submitted by the Applicant with this sNDA. After conducting a thorough interdisciplinary review of the data submitted, the clinical and clinical pharmacology reviewers concluded that the Applicant fulfilled the requirements for the WR and recommended that pediatric exclusivity be awarded to the Applicant.

Table 9 Summary of the Applicant's Response to the Written Request (WR)

Written Request Items	Information Submitted/Sponsor's Response	DOP2 Assessment
Types of studies/Study Design: 1. Phase 1-2: The Phase 1 part is a dose-finding and safety study of cabazitaxel monotherapy in pediatric patients with refractory solid tumors, including pharmacokinetics, with doses determined for all appropriate age groups. This will be followed by a Phase 2 part to determine the response rates with and safety of cabazitaxel monotherapy in pediatric patients with recurrent or refractory high grade glioma or diffuse intrinsic pontine glioma. The Phase 2 part will be conducted at the dose determined by the Phase 1 portion of the study.	**Types of studies:** 1. TED12689: A Phase 1-2 Dose Finding, Safety and Efficacy Study of Cabazitaxel in Pediatric Patients with Refractory Solid Tumors including Tumors of the Central Nervous System The sponsor conducted an open label, multi-center study in two parts: Phase 1 Part using dose escalation to establish the maximum tolerated dose (MTD) of cabazitaxel in pediatric patients with recurrent or refractory solid tumors based on related dose-limiting toxicities (DLTs); and Phase 2 Part to evaluate the activity and safety of cabazitaxel at the MTD in pediatric patients with recurrent or refractory high grade glioma (HGG) or diffuse intrinsic pontine glioma (DIPG).	The response fulfils the requirements of the WR.
Indication(s) to be studied: 1. Phase 1 Part (dose escalation): Pediatric patients with metastatic or locally advanced solid tumors for whom no further effective therapy is available.	**Indication(s) studied:** 1. Phase 1 Part: Patients with a histologically confirmed solid tumor, including tumors of the central nervous system, that was recurrent or refractory and for which no further effective standard treatment was available. All patients must have had measurable or non-measurable (but evaluable) disease. Patients with diffuse pontine glioma were eligible without a biopsy after evidence of progressive disease post radiation therapy	The response fulfils the requirements of the WR.

<table>
<tr><th>Written Request Items</th><th>Information Submitted/Sponsor's Response</th><th>DOP2 Assessment</th></tr>
<tr><td>2. Phase 2 Part (safety and activity): Pediatric patients with recurrent or refractory high grade glioma defined as WHO Grade III or Grade IV astrocytic or oligodendroglial tumor or recurrent or refractory diffuse intrinsic pontine glioma for whom no further effective therapy is available</td><td>2. Phase 2 Part: Patients with recurrent or refractory high grade glioma (defined as WHO Grade III or Grade IV astrocytic or oligodendroglial tumor) or diffuse intrinsic pontine glioma for whom no further effective therapy was available. All patients must have had measurable disease. Patients with diffuse pontine glioma were eligible without a biopsy after evidence of progressive disease post radiation therapy. Patients with a Grade III or Grade IV glioma must have had pathologic conformation either at the time of initial diagnosis or at the time of recurrence.</td><td></td></tr>
<tr><th>Written Request Items</th><th>Information Submitted/ Sponsor's response</th><th></th></tr>
<tr><td>Age group and population in which study will be performed:

1. Phase 1 Part (dose escalation): ≥2 years and <18 years (with at least four children 2-4 years old treated at the recommended Phase 2 dose)

2. Phase 2 Part (safety and activity): ≥2 years and < 18 years</td><td>Age group and population in which study was performed:

1. Phase 1 Part: ≥2 years and ≤18 years
<table><tr><th>Age Group (years)</th><th>Number of patients included in Phase 1 Part</th></tr><tr><td>2-4</td><td>2</td></tr><tr><td>5-6</td><td>4</td></tr><tr><td>7-11</td><td>10</td></tr><tr><td>12-18</td><td>7</td></tr></table>
2. Phase 2 Part: ≥2 years and ≤18 years
<table><tr><th>Age Group (years)</th><th>Number of patients</th></tr></table></td><td>The maximum tolerated dose was determined to be 30mg/m^2. A recommended phase 2 dose was not established. Four patients in the age group of 2-4 years were treated at the MTD (two in each Phase). The response fulfils the requirements of the WR.</td></tr>
</table>

<table>
<tr><th>Written Request Items</th><th>Information Submitted/Sponsor's Response</th><th>DOP2 Assessment</th></tr>
<tr><td></td><td><table><tr><td></td><td>included in Phase 1 Part</td></tr><tr><td>2-4</td><td>2</td></tr><tr><td>5-6</td><td>4</td></tr><tr><td>7-11</td><td>4</td></tr><tr><td>12-18</td><td>6</td></tr></table></td><td></td></tr>
<tr><td>Number of patients to be studied or power of study to be achieved:

1. Phase 1 Part (dose escalation): >9 patients treated

2. Phase 2 Part (safety and activity): Use a Simon optimal two stage design with 10 patients treated in the first stage. If >1 response is seen in the first 10 patients, treat an additional 19 patients (with at least four children 2-4 years old of the 29 patients to be studied).

3. Pharmacokinetics: At least 7 patients within each of the following specified age groups (2-6, 7-11 and 12-18 years old) must be evaluated. The number of patients may include patients from Part 1 and Part 2 of the study.</td><td>Number of patients studied or power achieved:

1. Phase 1 Part: 23 patients studied total. See above for break-down by age group.

2. Phase 2 Part: There were no objective responses observed in the first 10 patients and thus the null hypothesis that the true response rate was ≤10% could not be rejected. There was also no response in the one additional evaluable patient. There was one patient with a best response of stable disease: Patient 840-014-103, a 9-year-old female with DIPG.

3. In Study TED12689, pharmacokinetic data were available from 31 pediatric patients: 9 in 2-6 year, 10 in 7-11 year, and 12 in 12-18 year age groups.</td><td>The response fulfils the requirements of the WR.</td></tr>
</table>

Written Request Items	Information Submitted/Sponsor's Response	DOP2 Assessment
Written Request Items	**Information Submitted/ Sponsor's response**	
Clinical endpoints: 1. Primary Endpoint: • Phase 1 Part (dose escalation): To estimate the maximum tolerated dose (MTD) and recommend a Phase 2 dose of cabazitaxel administered intravenously once every 21 days as a single agent in patients >2 to <18 years of age. • Phase 2 Part (safety and activity): To determine the objective response rate (complete and partial response) and the duration of response using the Modified Response Assessment in Neuro-Oncology Working Group criteria. 2. Secondary Endpoints (will include, but not limited to the following): Phase 1 and Phase 2: • To characterize the safety and tolerability of cabazitaxel • To characterize the pharmacokinetics of cabazitaxel	**Clinical endpoints used:** 1. Primary Endpoint *Phase 1 Part:* To determine the dose limiting toxicity (DLT) and the maximum tolerated dose (MTD) of cabazitaxel as a single agent in patients with recurrent or refractory solid tumors including tumors of the central nervous system. *Phase 2 Part:* To determine the objective response rate (complete and partial response) and the duration of response to cabazitaxel as a single agent in patients with recurrent or refractory high grade glioma (HGG) or diffuse intrinsic pontine glioma (DIPG). 2. Secondary Endpoint Phase 1 Part: • To characterize the safety and tolerability of cabazitaxel in patients with recurrent or refractory solid tumors including tumors of the central nervous system • To evaluate preliminary anti-tumor activity that may be associated with cabazitaxel in patients with recurrent or refractory solid tumors including tumors of the central nervous system. Phase 2 Part: • To characterize the safety and tolerability of cabazitaxel in patients with recurrent or refractory HGG or DIPG.	The response fulfils the requirements of the WR.

Written Request Items	Information Submitted/Sponsor's Response	DOP2 Assessment
	• To estimate progression free survival (PFS) in patients with recurrent or refractory HGG or DIPG. • To estimate overall survival (OS) in patients with recurrent or refractory HGG or DIPG.	
3. Pharmacokinetic Endpoints: Pharmacokinetic samples must be collected through approaches such as rich sampling or optimal sparse sampling in patients. Such data must then be appropriately analyzed using methods such as nonlinear mixed effects modeling or non- compartmental analysis. If appropriate, develop pharmacokinetic and pharmacodynamics (PK-PD) models to explore exposure-response relationships as measures of safety and activity.	3. Pharmacokinetic Endpoints: • To characterize the PK profile of cabazitaxel in patients with recurrent or refractory solid tumors including tumors of the central nervous system. • Available data from Study TED12689 were used to explore exposure-response relationships for safety. Given that objective responses were not observed in pediatric patients treated with cabazitaxel, the planned exposure-response analysis for activity/efficacy was not conducted	
Written Request Items	**Information Submitted/ Sponsor's response**	
Drug specific safety concerns: In adult patients treated with cabazitaxel, the most common (≥10%) grade 1-4 adverse reactions were anemia, leukopenia, neutropenia, thrombocytopenia, diarrhea, fatigue, nausea, vomiting, constipation, asthenia, abdominal pain, hematuria, back pain, anorexia, peripheral neuropathy, pyrexia, dyspnea, dysgeusia, cough, arthralgia, and alopecia. The most common (≥5%) grade 3-4 adverse reactions were neutropenia, leukopenia, anemia, febrile neutropenia, diarrhea, fatigue, and asthenia. Deaths due to causes other than disease progression within 30 days of last study drug dose were reported in 18 (5%) of cabazitaxel-treated patients. The most common fatal	**Drug specific safety concerns evaluated:** Safety evaluations included routine clinical examinations, evaluation of symptomatic adverse events, and laboratory studies including complete blood counts (CBCs), electrolytes, assessments of renal and hepatic function, and pregnancy. Toxicity was monitored and graded according to the Cancer Therapy Evaluation Program Common Terminology Criteria for Adverse Events version 4.0 (CTCAEv4.0).	The response fulfils the requirements of the WR.

Written Request Items	Information Submitted/Sponsor's Response	DOP2 Assessment
adverse reactions were infections (n=5) and renal failure (n=4). The majority (4 of 5 patients) of fatal infection-related adverse reactions occurred after a single dose of cabazitaxel. Other fatal adverse reactions in cabazitaxel-treated patients included ventricular fibrillation, cerebral hemorrhage, and dyspnea.		
Drug information: **Dosage Form:** Cabazitaxel Injection in single use vial 60 mg/1.5 mL, supplied with diluent (5.7 mL) **Route of Administration:** Intravenous infusion **Regimen:** Phase 1 Part (dose escalation): The starting dose of cabazitaxel will be 20 mg/m2 administered intravenously on Day 1 of each 21 day cycle. If this dose is not tolerated, cabazitaxel 15 mg/m2 will be administered intravenously using the same schedule. Doses below 15 mg/m2 will not be given. If the 20 mg/m2 dose is tolerated, additional dose levels of cabazitaxel will be explored using standard (3+3) dose escalation rules. The maximum Body Surface Area for the actual cabazitaxel dose calculation will be 2.1 m2 for safety reasons. Following cycle 1, patients may receive additional cycles as clinically appropriate. Phase 2 Part (safety and activity): The maximum tolerated dose or recommended Phase 2 dose, as determined in the Phase 1 study, will be administered intravenously on Day 1 of	**Drug information:** **Dosage Form:** Single-dose vials contained a total of 60 mg of cabazitaxel, expressed as anhydrous and solvent-free basis, per 1.5 mL of solution. **Route of Administration:** Oral Intravenous infusion **Regimen:** In the Phase 1 part, dose escalation was used: starting at 20 mg/m2 and then escalating to 35 mg/m2. In the Phase 2 part, all patients received cabazitaxel at the MTD determined in the Phase 1 part (30 mg/m2). Cabazitaxel was	The response fulfils the requirements of the WR.

Written Request Items	Information Submitted/Sponsor's Response	DOP2 Assessment
each 21 day cycle.	administered on Day 1 of each 3-week cycle; premedication included an antihistamine, steroid, and H2 antagonist.	
Statistical information (statistical analyses of the data to be performed): 1. Phase 1 Part (dose escalation): The maximum tolerated dose of cabazitaxel will be determined in pediatric patients (age 2-18 years old) with advanced solid tumors using a 3+3 design. The minimum sample size required to identify the maximum tolerated dose is 9 patients. At least 4 patients should be treated at the MTD in the younger age group (2-4 years old). 2. Phase 2 Part (safety and activity): Patients will be treated at the recommended Phase 2 dose established in the Phase 1 study. The anti-tumor activity of cabazitaxel will be examined by employing a Simon optimal two-stage design. Ten patients will be accrued in the first stage. If only one or no patient experiences an objective response (partial or complete response based on the Modified RANO criteria) in the first stage, the trial will be stopped for lack of efficacy. If 2 or more patients out of the first 10 patients achieve an objective response, then an additional 19 patients will be enrolled in the second stage. With a null hypothesis of a true response rate of 10%, the study is designed to have 80% power to detect a true response rate of 30% using a one-sided alpha level of 0.05. The response rate will be calculated as the percent of patients whose best confirmed response is a complete response or partial response and a confidence interval for the	**Statistical information (statistical analyses of the data to be performed):** 1. Phase 1 Part: The maximum tolerated dose of cabazitaxel will be determined in pediatric patients (age 2-18 years old) with advanced solid tumors using a 3+3 design. Safety and PK analyses are summarized with descriptive statistics. 2. Phase 2 Part: The Phase 2 part utilized a Simon's two-stage designed to test the null hypothesis that the true ORR is ≤10% versus the alternative hypothesis that the true ORR is ≥30 assuming a one-sided significance level of 5% and power of 80%. The ORR per the modified RANO for stages 1 and 2 combined and its associated 90% confidence interval (CI) and the one-sided p-value from the test of the null hypothesis (H0: p ≤10%) are estimated.	The response fulfils the requirements of the WR.

Written Request Items	Information Submitted/Sponsor's Response	DOP2 Assessment
response rate will be calculated. The median duration of response will be estimated for patients with an objective response.		
Written Request Items	**Information Submitted/ Sponsor's response**	
Labeling that may result from the studies: You must submit proposed pediatric labeling to incorporate the findings of the study(ies). Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that cabazitaxel is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study. Under section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the study(ies).	**Labeling that may result from the studies:** *The sponsor proposes the following labeling changes to Section 8.4 Pediatric Use:* **Current label:** The safety and effectiveness of Jevtana in pediatric patients have not been established. **Sponsor Proposed label:** See Appendix I **New Label:** See Appendix II	The response fulfils the requirements of the WR.
Format of reports to be submitted: You must submit full study report (which have not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the report must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity, you should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you	**Format of reports submitted:** Full study reports not previously submitted to the Agency including full analysis, assessment, and interpretation of the data were submitted. The reports included information on the representation of pediatric patients of ethnic and racial minorities according to the categories and designations in the WR. A population PK and PK/PD report was also submitted.	The response fulfils the requirements of the WR.

Written Request Items	Information Submitted/Sponsor's Response	DOP2 Assessment
choose to use other categories, you should obtain agency agreement. Under section 505A(d)(2)(B) of the Act, when you submit the study report, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. These postmarketing adverse event reports should be submitted as narrative and tabular reports.		
Timeframe for submitting reports of the studies: Report of the above study must be submitted to the Agency on or before December 15, 2017.	**Timeframe for submitting reports of the studies:** The clinical study reports, associated data sets and proposed labeling changes were submitted on November 21, 2016.	The response fulfils the requirements of the WR.

6 Review of Efficacy

Efficacy Summary

The data submitted with this application did not provide evidence of a treatment benefit from administration of cabazitaxel to pediatric patients with relapsed/recurrent high grade glioma (HGG) or intrinsic pontine glioma (DIPG).

The Phase 2 part of the study did not meet the primary objective of demonstrating efficacy as determined by objective response rate (complete or partial response) in this pediatric population with DIPG or HGG: there were no objective responses observed in the first 10 evaluable patients (Stage 1), and thus the null hypothesis that the true response rate was ≤10% could not be rejected and the alternative hypothesis that the true response rate was ≥30% was very unlikely. There was also no response in the one additional evaluable patient. There was one patient with a best response of stable disease, a 9-year-old female with DIPG. The median survival was 2.7 months (95% confidence interval [CI]: 1.7-4.5 months), and the median PFS was 1.3 months (95% CI: 0.6-2.1 months).

In the Phase 1 part, there was one objective partial response in a patient with ependymoma, which was observed at assessments from Cycle 4 through Cycle 15.

6.1 Methods

Clinical review was based primarily upon the clinical study report for study TED12689, case report forms, and primary datasets submitted by the Applicant.

6.2 Demographics

Patients ranged in age from 4 to 18 years, with a median age of 9 years. The median ages were generally similar among the 4 dose levels tested, with the exception of the median age of the 7 patients treated at 35 mg/m2, which was 7 years. The majority of patients were male and Caucasian (65.2% for both).

The disease characteristics for the Phase 1 patients are summarized in Table 9. Solid tumors with a location other than the CNS were the primary tumor for 4 patients (17.4%). The most common histology was ependymoma (9 patients [39.1%]), and there were 4 patients (17.4%)with DIPG and one patient (4.3%) with HGG. The median time from initial diagnosis to the first dose of cabazitaxel in this study was 26.7 months. All patients had disease that was either refractory to standard therapy (69.6%) or for which no standard therapy exists (30.4%).

Table 10 Summary of Patient Disease Characteristics for Study TED12689, Part 1, adapted from Sponsor submitted Study Synopsis, verified by clinical reviewer)

	XRP6258				
	20 mg/m^2 (N=6)	25 mg/m^2 (N=3)	30 mg/m^2 (N=7)	35 mg/m^2 (N=7)	All (N=23)
Primary tumor [n (%)]					
Number	6	3	7	7	23
Brain / CNS	4 (66.7%)	3 (100%)	5 (71.4%)	7 (100%)	19 (82.6%)
Other	2 (33.3%)	0	2 (28.6%)	0	4 (17.4%)
Histology [n (%)]					
Number	6	3	7	7	23
Brain Other: Anaplastic Astrocytoma With Pnet Features	0	0	0	1 (14.3%)	1 (4.3%)
Brain Other: Fibrillary Astrocytoma	0	1 (33.3%)	0	0	1 (4.3%)
Brain Other: Pilomyxoid Astrocytoma	0	0	1 (14.3%)	0	1 (4.3%)
Diffuse Intrinsic Pontine Glioma	2 (33.3%)	0	0	2 (28.6%)	4 (17.4%)
Ependymoma	2 (33.3%)	2 (66.7%)	2 (28.6%)	3 (42.9%)	9 (39.1%)
Glioma High Grade: Glioblastoma Multiforme G4	0	0	1 (14.3%)	0	1 (4.3%)
Medulloblastoma	0	0	1 (14.3%)	1 (14.3%)	2 (8.7%)
Osteosarcoma	0	0	2 (28.6%)	0	2 (8.7%)
Other: Grade III Teratoma With Yolk Sac Component	1 (16.7%)	0	0	0	1 (4.3%)
Other: Wilms' Tumor	1 (16.7%)	0	0	0	1 (4.3%)
Time from initial diagnosis to first cabazitaxel dose (months)					
Number	6	3	7	7	23
Mean (SD)	52.70 (52.85)	48.65 (25.83)	28.94 (15.98)	29.25 (21.58)	37.80 (31.89)
Median	26.12	42.12	25.53	20.30	26.68
Min : Max	6.9 : 134.6	26.7 : 77.1	6.1 : 51.0	7.8 : 62.9	6.1 : 134.6
Extent of disease for solid/CNS tumor [n (%)]					
Number	6	3	7	7	23
Metastatic	4 (66.7%)	3 (100%)	3 (42.9%)	1 (14.3%)	11 (47.8%)
Locally Advanced	2 (33.3%)	0	3 (42.9%)	4 (57.1%)	9 (39.1%)
Loco Regional	0	0	1 (14.3%)	2 (28.6%)	3 (13.0%)
Refractory status [n (%)]					
Refractory To Standard Therapy	4 (66.7%)	2 (66.7%)	4 (57.1%)	6 (85.7%)	16 (69.6%)
No Standard Therapy Exists	2 (33.3%)	1 (33.3%)	3 (42.9%)	1 (14.3%)	7 (30.4%)
Time from last progression to first cabazitaxel dose (months)					
Number	6	3	7	7	23
Mean (SD)	1.16 (1.07)	1.24 (0.95)	1.66 (1.38)	1.16 (0.36)	1.32 (0.97)
Median	0.59	0.72	1.31	1.22	1.12
Min : Max	0.3 : 2.9	0.7 : 2.3	0.3 : 4.4	0.7 : 1.6	0.3 : 4.4

CNS: Central Nervous System
Note: Number corresponds to the count of patients with non missing data used for the calculation of the percentage.
PGM=PRODOPS/XRP6258/TED12689/CSR/REPORT/PGM/dem_bl_dis_s_t.sas OUT=REPORT/OUTPUT/dem_bl_dis_s_t_pl_i.rtf
(19NOV2015 - 23:22)

Table 11 Summary of Patient Disease Characteristics for Study TED12689, Part 2, adapted from Sponsor submitted Study Synopsis, verified by clinical reviewer)

	XRP6258 30 mg/m^2 (N=16)
Primary tumor [n (%)]	
Number	16
Brain / CNS	16 (100%)
Histology [n (%)]	
Number	16
Diffuse Intrinsic Pontine Glioma	8 (50.0%)
Glioma High Grade: Anaplastic Astrocytoma	1 (6.3%)
Glioma High Grade: Anaplastic Astrocytoma Who Grade III/IV	1 (6.3%)
Glioma High Grade: Glioblastoma G4	1 (6.3%)
Glioma High Grade: Glioblastoma Grade IV	1 (6.3%)
Glioma High Grade: Glioblastoma Who Grade IV	1 (6.3%)
Glioma High Grade: High Grade Astrocytoma Who Grade III	1 (6.3%)
Glioma High Grade: High Grade Glioma Most Consistent With Glioblastoma, Who Grade IV	1 (6.3%)
Glioma High Grade: Infiltrating High Grade Astrocytoma, Who Grade III	1 (6.3%)
Time from initial diagnosis to first cabazitaxel dose (months)	
Number	15
Mean (SD)	16.05 (11.16)
Median	11.37
Min : Max	6.4 : 39.1
Extent of disease for solid/CNS tumor [n (%)]	
Number	16
Metastatic	2 (12.5%)
Locally Advanced	11 (68.8%)
Loco Regional	3 (18.8%)
Refractory status [n (%)]	
Refractory To Standard Therapy	15 (93.8%)
No Standard Therapy Exists	1 (6.3%)
Time from last progression to first cabazitaxel dose (months)	
Number	16
Mean (SD)	0.77 (0.44)
Median	0.69
Min : Max	0.1 : 1.8

6.3 Concomitant Medications

All patients received concomitant medications. The most frequently used concomitant medications that were administered included corticosteroids, epinephrine, lidocaine, paracetamol, nystatin, macrogol, diphenhydramine, bactirm, lorazepam, salbutamol, and ondansetron.

6.4 Patient Disposition

Patients enrolled in 12 institutions in the United States and Canada. Reasons for discontinuation of treatment for patients in the cabazitaxel arm include disease progress (13 of 13 patients). The most common reason for treatment discontinuation was disease progression, in 91.3% of patients in Phase 1 and 68.8% of patients in Phase 2. There were 4 patients who discontinued treatment due to an AE, all in the Phase 2 part; additional details are provided in Section 7.1.

6.5 Analysis of Primary Endpoint(s)

In the Phase 2 part of the study, there were no objective responses observed in the first 10 patients (Stage 1), as summarized in Table 30, and thus the null hypothesis that the true response rate was ≤10% could not be rejected. There was also no response in the one additional evaluable patient. There was one patient with a best response of stable disease: a 9-year-old female with DIPG.

Table 12 Objective Response Rate (CR+PR) by Investigator Assessment, FAS and EES (adapted from Sponsor submitted Study Synopsis, verified by clinical reviewer)

Stage/Category	XRP6258 30 mg/m^2 (N=11)
Stage 1	
Number	10
Objective response (confirmed CR + confirmed PR)	0
Complete response	0
Partial response	0
Stable disease	1 (9.1%)
Progressive disease	9 (81.8%)
Non CR/non PD	0
Not evaluable	0
Not assessed	0

6.6 Analysis of Secondary Endpoints(s)

The Kaplan-Meier curve for OS in the Phase 2 efficacy evaluable population is provided in Figure 2. The median OS was 2.7 months (95% CI: 1.7-4.5 months). The median PFS was 1.3 months (95% CI: 0.6-2.1 months).

Reviewer Comment: Time-to-event endpoints such as PFS and OS cannot be interpreted in the context of a single-arm trial.

In the Phase 1 part, there was one patient with a partial response (PR): Patient 840-007-001, a 15-year-old female with ependymoma treated at 20 mg/m2. At the Cycle 3 assessment, the patient's target lesion showed a reduction in size of 27.5%. However, because a new pontine lesion was observed the overall response was considered not evaluable. After a confirmatory scan at Cycle 4, the decision was made to continue treatment and include the pontine lesion as an additional target lesion. The assessment at Cycle 4 resulted in determination of PR, which was maintained through Cycle 15 and which included reduction in size of the pontine lesion first observed at Cycle 3; progressive disease was noted at Cycle 18.

Reviewer Comment: Most patients with recurrent or refractory ependymoma do not typically respond to chemotherapy; therefore, a description of this response will be included in Section 8.4 of the label (See Appendix II).

No other objective responses were observed in the Phase 1 part. This resulted in an ORR of 4.5% (95% CI: 0.1-22.8%). There were 5 patients (22.7%) with a best response of stable disease (or nonCR/nonPD). This includes one patient who exhibited stable disease at assessments from Cycle 3 through Cycle 24, and who was still undergoing study treatment at the time of the study cut-off.

Table 13 Phase 1 Best Objective Responses per RECIST 1.1 and modified RANDO criteria (adapted from Sponsor submitted Study Synopsis, verified by clinical reviewer)

	XRP6258				
	20 mg/m^2 (N=5)	25 mg/m^2 (N=3)	30 mg/m^2 (N=7)	35 mg/m^2 (N=7)	All (N=22)
Category					
Complete response	0	0	0	0	0
Partial response	1 (20.0%)	0	0	0	1 (4.5%)
Stable disease or Non CR/Non PD	1 (20.0%)	1 (33.3%)	2 (28.6%)	1 (14.3%)	5 (22.7%)
Progressive disease	3 (60.0%)	2 (66.7%)	4 (57.1%)	6 (85.7%)	15 (68.2%)
Not assessed/Not evaluable	0	0	1 (14.3%)	0	1 (4.5%)

CR: Complete response, PD: Progressive disease
PGM=PRODOPS/XRP6258/TED12689/CSR/REPORT/PGM/eff_or_e_t.sas OUT=REPORT/OUTPUT/eff_or_e_t_p1_i.rtf (19NOV2015 - 23:37)

6.7 Other Endpoints

An analysis of biomarkers was not conducted in this study. Please see the clinical pharmacology review performed by Ruby Leong, Pharm.D. for a review of the pharmacokinetic endpoints.

7 Review of Safety

7.1 Safety Summary

Overall, the adverse reaction profile of cabazitaxel is consistent with the known adverse reaction profile in adults. There were 23 patients treated in the Phase 1 part of the study: 6 patients at the 20 mg/m^2 dose level, 3 patients at the 25 mg/m^2 dose level, 7 patients at the 30 mg/m^2 dose level and 7 patients at the 35 mg/m^2 dose level. The median number of cycles of treatment received is 3 cycles for all dose levels (range: 1 to 25 cycles). One patient enrolled at the 30 mg/m2 dose level remains on treatment and will continue to be followed. There were 16 patients treated in the Phase 2 part of the study, all at the 30 mg/m^2 dose level. The median number of cycles of treatment received is 2 cycles (range: 1 to 4 cycles).

Three dose limiting toxicities (DLTs) during Cycle 1 were observed in the Phase 1 part of the study, all Grade 3 febrile neutropenia. One DLT was reported at the 20 mg/m2 dose level, and per protocol 3 additional patients were enrolled at this dose level. No DLTs during Cycle 1 were reported at the 25 mg/m2 or 30 mg/m2 dose levels. The incidence of 2 DLTs at the 35 mg/m2 dose level established the maximum tolerated dose (MTD) at the 30 mg/m2 dose level.

Cumulative deaths due to progression of the patients' underlying disease during the treatment emergent adverse event (TEAE) period and post-TEAE follow-up period included 15 patients (65.2%) in the Phase 1 part of the study and 12 patients (75%) in the Phase 2 part of the study. No deaths were attributed to TEAEs possibly related to study treatment.

The most frequent TEAEs (≥25%) of any grade were fatigue (39.1%), headache, diarrhea, nausea (all 34.8%), vomiting (30.4%), cough, and constipation (26.1%) in Phase 1 patients; and diarrhea (43.8%), dysphagia (37.5%), nausea (31.3%), vomiting, and headache (both 25.0%) in Phase 2 patients. Treatment emergent serious adverse events (SAEs) of Grade ≥ 3 were reported in 12 patients (52.2%) in the Phase 1 part of the study and 10 patients (62.5%) in the Phase 2 part of the study. SAEs reported in >2 patient in either part of the study included febrile neutropenia in 5 patients (21.7%) in Phase 1; and febrile neutropenia, anaphylactic reaction, and disease progression, all reported in 3 patients (18.8%) in Phase 2. The 3 serious events of anaphylactic reaction and 1 non-serious Grade 2 elevated liver transaminases in Phase 2 were the 4 TEAEs reported as leading to treatment discontinuation. In the Phase 1 part of the study, Grade 4 neutropenia was reported in 15 of 23 patients (65.2%): 3 of 6 patients (50%) at the 20 mg/m2

dose level, 2 of 3 patients (66.7%) at the 25 mg/m2 dose level, 5 of 7 patients (71.4%) at the 30 mg/m2 dose level and 5 of 7 patients (71.4%) at the 35 mg/m2 dose level. In the Phase 2 part of the study, neutropenia ≥ Grade 3 was reported in 8 of 15 patients (53.3%).

Analyses of vital signs, ECGs, and performance status did not reveal any significant safety findings.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Clinical review of the safety of cabazitaxel in pediatric patients was based primarily on the clinical study report for TED 12689, case report forms and primary datasets submitted by the Applicant.

Reviewer Comment: Care should be taken with interpretation of safety data derived from small trials, particularly in the context of a patient population with life-threatening brain tumors who typically require concomitant corticosteroid therapy

7.1.2 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

N/A

7.2 Analysis of Adverse Events

7.2.1 Deaths

From first dose of study treatment through 30 days following the last dose of study treatment, one death was reported in the Phase 1 part of the study and 5 deaths were reported in the Phase 2 part of the study. All deaths were attributed to progression of the patients' underlying disease.

Cumulative deaths including the follow-up period were 15 patients (65.2%) in the Phase 1 part of the study (Table 49) and 12 patients (75%) in the Phase 2 part of the study (Table 50). No deaths were attributed to TEAEs reported as possibly related to study treatment.

7.2.2 Treatment Emergent Adverse Events

In the Phase 1 part of the study, treatment-emergent adverse events (TEAEs) of Grade 3 or 4 occurred in 4 of 6 patients (66.7%) at the 20 mg/m2 dose level, in 1 of 3 patients (33.3%) at the 25 mg/m2 dose level, in 5 of 7 patients (71.4%) at the 30 mg/m2 dose level, and in 3 of 7

patients (42.9%) at the 35 mg/m2 dose level. In the Phase 2 part of the study, treatment-emergent adverse events (TEAEs) of Grade 3 or 4 occurred in 11 of 16 patients (68.8%), all treated at the 30 mg/m2 dose level.

The most frequent TEAEs (any grade) in the Phase 1 patients were fatigue (39.1%), headache, diarrhea, nausea (all at 34.8%), vomiting (30.4%), cough, and constipation (both at 26.1%). The most frequent TEAEs (any grade) in the Phase 2 patients were diarrhea (43.8%), dysphagia (37.5%), nausea (31.3%), vomiting, and headache (both at 25.0%).

Infusion related/hypersensitivity reactions were seen in 5 patients (21.7%) in Phase 1 and 5 patients (50%) in Phase 2. Three Phase 2 patients experienced serious adverse events of anaphylaxis. The Study Committee analyzed the cases and amended the protocol (Amendment 4, April 3, 2015) to provide additional steroid premedication.

Reviewer Comment: Hypersensitivity is a known adverse reaction and currently included in Warnings/Precautions section in the label.

Table 14 Summary of treatment emergent infusion related/hypersensitivy reactions (adapted from Sponsor submitted Study Synopsis, verified by clinical reviewer)

	Phase 1 (N=23)		Phase 2 (N=16)		All Phases (N=39)	
Preferred term n[%]	Before (N=23)	After (N=1)	Before (N=10)	After (N=7)	Before (N=33)	After (N=8)
Any TEAE	5 (21.7%)	0	5 (50.0%)	1 (14.3%)	10 (30.3%)	1 (12.5%)
Anaphylactic reaction	0	0	3 (30.0%)	0	3 (9.1%)	0
Hypersensitivity	1 (4.3%)	0	1 (10.0%)	0	2 (6.1%)	0
Infusion related reaction	4 (17.4%)	0	1 (10.0%)	1 (14.3%)	5 (15.2%)	1 (12.5%)

N is the number of patients who were treated in that period, n is the number of these patients who had treatment emergent infusion related/hypersensitivity reactions. The date of protocol amendment implementation is 26 December 2014.

7.2.3 Dropouts and/or Discontinuations

No patients experienced a TEAE that lead to permanent discontinuation of study drug in either study. No patients in the Phase 1 part of the study and 4 patients in the Phase 2 part of the study were withdrawn from study treatment due to adverse events. Three were due to SAEs of anaphylactic reaction. One patient, 840011102, was withdrawn from study treatment due to non-serious Grade 2 elevated liver transaminases.

7.2.4 Significant Adverse Events

Treatment emergent SAEs of Grade ≥ 3 were reported in 12 patients (52.2%) in the Phase 1 part of the study and 10 patients (62.5%) in the Phase 2 part of the study. In Part 1, the most common SAEs were febrile neutropenia (21.7%), hydrocephalus (8.7%), and intracranial tumor hemorrhage (8.7%). The most common >Grad3 event was febrile neutropenia (21.7%). In Part 2, the most common SAEs (>10%), all Grade ≥ 3 included anaphylactic reaction, disease progression, febrile neutropenia and diarrhea.

Table 15 Incidence of SAEs in Part 1 (adapted from Sponsor submitted Study Report, verified by clinical reviewer)

	XRP6258									
	20 mg/m² (N=6)		25 mg/m² (N=3)		30 mg/m² (N=7)		35 mg/m² (N=7)		All (N=23)	
Preferred term	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Any serious TEAE	4 (66.7%)	4 (66.7%)	1 (33.3%)	1 (33.3%)	5 (71.4%)	4 (57.1%)	3 (42.9%)	3 (42.9%)	13 (56.5%)	12 (52.2%)
Febrile neutropenia	1 (16.7%)	1 (16.7%)	1 (33.3%)	1 (33.3%)	1 (14.3%)	1 (14.3%)	2 (28.6%)	2 (28.6%)	5 (21.7%)	5 (21.7%)
Hydrocephalus	0	0	0	0	1 (14.3%)	1 (14.3%)	1 (14.3%)	1 (14.3%)	2 (8.7%)	2 (8.7%)
Intracranial tumour haemorrhage	1 (16.7%)	0	0	0	1 (14.3%)	0	0	0	2 (8.7%)	0
Bone pain	0	0	0	0	1 (14.3%)	1 (14.3%)	0	0	1 (4.3%)	1 (4.3%)
Cystitis noninfective	1 (16.7%)	1 (16.7%)	0	0	0	0	0	0	1 (4.3%)	1 (4.3%)
Diarrhoea	0	0	0	0	0	0	1 (14.3%)	1 (14.3%)	1 (4.3%)	1 (4.3%)
Disease progression	1 (16.7%)	1 (16.7%)	0	0	0	0	0	0	1 (4.3%)	1 (4.3%)
Fatigue	0	0	0	0	0	0	1 (14.3%)	1 (14.3%)	1 (4.3%)	1 (4.3%)
Gastroenteritis	1 (16.7%)	1 (16.7%)	0	0	0	0	0	0	1 (4.3%)	1 (4.3%)
Herpes zoster	0	0	1 (33.3%)	1 (33.3%)	0	0	0	0	1 (4.3%)	1 (4.3%)
Hypoventilation	0	0	0	0	1 (14.3%)	1 (14.3%)	0	0	1 (4.3%)	1 (4.3%)
Nerve root compression	0	0	0	0	0	0	1 (14.3%)	1 (14.3%)	1 (4.3%)	1 (4.3%)
Neutropenia	0	0	0	0	1 (14.3%)	1 (14.3%)	0	0	1 (4.3%)	1 (4.3%)
Paraesthesia	0	0	0	0	1 (14.3%)	0	0	0	1 (4.3%)	0
Platelet count decreased	0	0	1 (33.3%)	1 (33.3%)	0	0	0	0	1 (4.3%)	1 (4.3%)
Stoma site infection	0	0	0	0	1 (14.3%)	1 (14.3%)	0	0	1 (4.3%)	1 (4.3%)
Upper respiratory tract infection	0	0	0	0	1 (14.3%)	0	0	0	1 (4.3%)	0

SAE: Serious adverse event, PT: Preferred term, TEAE: Treatment emergent adverse event
MedDRA 18.0
n (%) = number and percentage of patients with at least one treatment-emergent SAE.
N= number of patients
Note: Table sorted by decreasing frequency of PT for all grades in the All group.

Table 16 Incidence of SAEs in Part 2 (adapted from Sponsor submitted Study Report, verified by clinical reviewer)

	XRP6258 30 mg/m² (N=16)	
Preferred term	**All Grades**	**Grade ≥3**
Any serious TEAE	12 (75.0%)	10 (62.5%)
Anaphylactic reaction	3 (18.8%)	3 (18.8%)
Disease progression	3 (18.8%)	3 (18.8%)
Febrile neutropenia	3 (18.8%)	3 (18.8%)
Diarrhoea	2 (12.5%)	2 (12.5%)
Aspiration	1 (6.3%)	1 (6.3%)
Brain herniation	1 (6.3%)	1 (6.3%)
Cardiac arrest	1 (6.3%)	1 (6.3%)
Death	1 (6.3%)	1 (6.3%)
Dehydration	1 (6.3%)	1 (6.3%)
Dyspnoea	1 (6.3%)	1 (6.3%)
Hydrocephalus	1 (6.3%)	1 (6.3%)
Hypotension	1 (6.3%)	1 (6.3%)
Intracranial tumour haemorrhage	1 (6.3%)	0
Neoplasm progression	1 (6.3%)	0
Neutropenic sepsis	1 (6.3%)	1 (6.3%)
Pneumonia aspiration	1 (6.3%)	1 (6.3%)
Tumour pain	1 (6.3%)	1 (6.3%)

SAE: Serious adverse event, PT: Preferred term, TEAE: Treatment emergent adverse event
MedDRA 18.0
n (%) = number and percentage of patients with at least one treatment-emergent SAE.
N= number of patients

8 Labeling Recommendations

I recommend that the following information be include in Section 8.4 (Pediatric Use) of the Jevtana package insert.

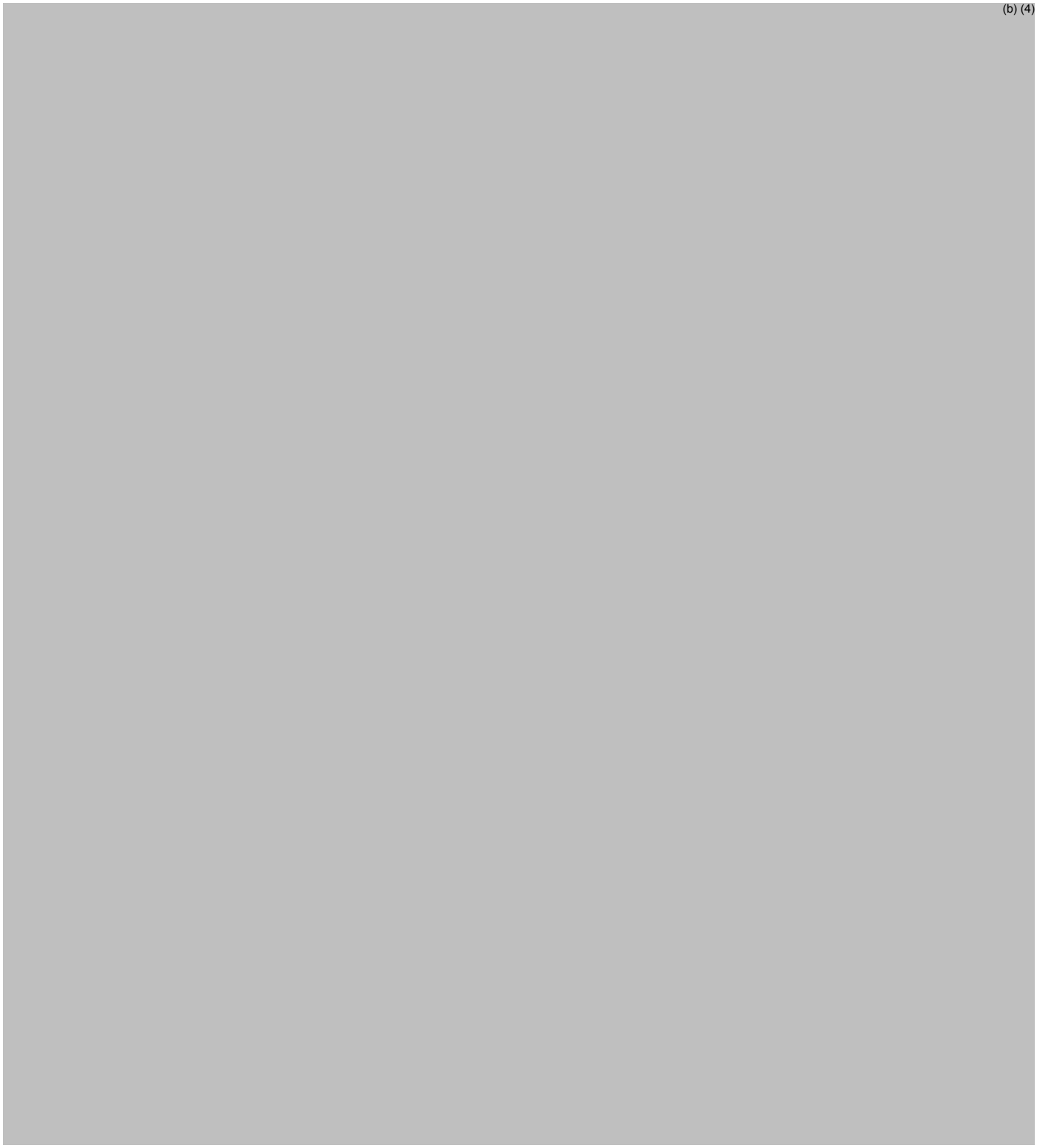
See Appendix II

9 References

1. Ostrom, Quinn T., et al. "CBTRUS statistical report: Primary brain and central nervous system tumors diagnosed in the United States in 2006-2010." *Neuro-oncology* 15.suppl 2 (2013): ii1-ii56.
2. Louis DN, Perry A, Reifenberger G, et al.: The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. Acta Neuropathol 131 (6): 803-20, 2016
3. Qaddoumi I, Sultan I, Gajjar A: Outcome and prognostic features in pediatric gliomas: a review of 6212 cases from the Surveillance, Epidemiology, and End Results database. Cancer 115 (24): 5761-70, 2009

Appendix I: Sponsor Proposed Changes to the Label, Section 8.4

(b) (4)



Appendix II: FDA Proposed Label, Section 8.4

The safety and effectiveness of JEVTANA in pediatric patients have not been established. JEVTANA was evaluated in 39 pediatric patients receiving prophylactic G-CSF. The maximum tolerated dose (MTD) was 30 mg/m^2 intravenously over 1 hour on Day 1 of a 21 day cycle (doses studied ranged from 20 mg/m^2 and 35 mg/m^2) in pediatric patients (ages 4 to 18 years) with solid tumors based on the dose-limiting toxicity (DLT) of febrile neutropenia. No objective responses were observed in 11 patients with refractory high grade glioma (HGG) or diffuse intrinsic pontine glioma (DIPG) One partial response was observed in a patient with ependymoma.

Infusion related/hypersensitivity reactions were seen in 10 patients (26%). Three patients experienced serious adverse events of anaphylactic reaction. The incidence of infusion related/hypersensitivity reactions decreased with steroid pre-medication. The most frequent treatment-emergent adverse events were similar to those reported in adults.

Based on the population pharmacokinetics analysis conducted with data from 31 pediatric patients with cancer (ages 3 to 18 years), the geometric mean clearance by body surface area was comparable to those in adults

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/s/

AMY K BARONE
04/27/2017

SUZANNE G DEMKO
04/27/2017