DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021660

WRITTEN REQUEST – AMENDMENT 2

Abraxis BioScience, LLC, a wholly-owned subsidiary of Celgene Corporation
Attention: Joycelyn Seymour, R.A.C.
Associate Director, Regulatory Affairs
Celgene Corporation
9225 Indian Creek Parkway; Suite 900
Overland Park, KS 66210

Dear Ms. Seymour:

Please refer to your correspondence dated March 27, 2017, requesting changes to FDA's October 29, 2014, Written Request for pediatric studies for Abraxane (paclitaxel).

We have reviewed your proposed changes and are amending the below-listed sections of the Written Request. All other terms stated in our Written Request issued on October 29, 2014, and as amended on April 17, 2015, remain the same. (Text added is underlined. Text deleted is marked as ~~strikethrough~~.)

BACKGROUND

Paclitaxel protein-bound particles for injectable suspension (paclitaxel protein-bound particles) is an albumin-bound formulation of paclitaxel currently approved for the treatment of refractory breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy, first line locally advanced or metastatic non-small cell lung cancer in combination with carboplatin, and first line treatment of metastatic adenocarcinoma of the pancreas in combination with gemcitabine. Paclitaxel, the cytotoxic ingredient in paclitaxel protein-bound particles, is an anti-microtubule agent. Compared to conventional paclitaxel, paclitaxel protein-bound particles increase the tissue bioavailability of paclitaxel by exploiting the natural properties of albumin to enhance the selective uptake of paclitaxel by tumor tissue.

The requested studies investigate the potential use of paclitaxel protein-bound particles for the treatment of pediatric patients with recurrent or refractory solid tumors with planned expansion cohorts to include pediatric patients with neuroblastoma, rhabdomyosarcoma and Ewing sarcoma. Solid tumors account for approximately 60% of all pediatric malignancies. Overall cure rates for children with solid tumors are greater than 50% with surgery, chemotherapy, and radiation; however there is still a need for more effective treatment, especially in patients who present with or develop metastatic disease.

Preclinical data suggests paclitaxel protein-bound particles may be effective in patients with neuroblastoma and rhabdomyosarcoma. In seven neuroblastoma and three rhabdomyosarcoma cell lines, paclitaxel protein-bound particles exhibited dose-dependent cytotoxicity in vitro as measured by cell viability. In all neuroblastoma cell lines tested, paclitaxel protein-bound particles were more effective than an equivalent dose of paclitaxel after 72-hours of treatment. In neuroblastoma xenograft models, paclitaxel protein-bound particles treatment (10mg/kg/day IV for 5 consecutive days or 50mg/kg weekly) resulted in greater antitumor activity compared to DMSO-paclitaxel (20mg/kg IV weekly). In rhabdomyosarcoma (RD) xenograft models, animals treated with DMSO-paclitaxel had earlier tumor relapses, which could be suppressed by rechallenging with paclitaxel protein-bound particles but not DMSO-paclitaxel. Paclitaxel protein-bound particles were more effective in suppressing RD tumor growth compared to DMSO-paclitaxel. The Pediatric Preclinical Testing Program at the NCI showed that paclitaxel protein-bound particles administered IV at 50mg/kg every 4 days for a total of three times was well tolerated in xenograft mice. Two Ewing sarcoma xenografts and a RD xenograft maintained complete responses. No tumor regression was observed in osteosarcoma or neuroblastoma xenografts, where only minimal tumor growth delay was observed.

Paclitaxel protein-bound particles have been established to have a statistically significant higher overall response rate in adult patients with metastatic breast cancer and lung cancer compared to solvent-based paclitaxel. In second line or greater metastatic breast cancer and metastatic adenocarcinoma of the pancreas, paclitaxel protein-bound particles have been shown to result in a statistically significant improvement in overall survival compared to solvent-based paclitaxel (in combination with gemcitabine in patients with pancreatic disease).

Pharmacokinetic (PK) studies show paclitaxel protein-bound particles to have a higher total clearance and larger volume of distribution compared to solvent-based paclitaxel in patients with advanced solid tumors. The sponsor states that the PK difference is likely to contribute to the difference seen in safety and activity.

Reduced levels of neurotoxicity and infusion related reactions are expected compared to conventional taxanes, because paclitaxel protein-bound particles do not require detergents/ethanol vehicle of solubilization of the active substance. The most common NCI CTCAE Grade 3 or higher adverse events reported with paclitaxel protein-bound particles include neutropenia, fatigue, and neuropathy. Reported Grade 3 sensory neuropathy is typically reversible within 3-4 weeks. Incidence of febrile neutropenia did not differ from comparison arms in Phase 3 clinical trials in adults.

The first pediatric clinical trial using paclitaxel protein-bound particles (ABI-007-PST-001) is ongoing and as of June 19, 2014, (b) (4)

Additional investigation of paclitaxel protein-bound particle activity in pediatric patients with relapsed/refractory solid tumors as well as those associated with increased risk of failure with current treatments is warranted given the lack of alternative effective therapy.

To obtain needed pediatric information on paclitaxel protein-bound particles, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, that you submit information from the studies described below.

- **Nonclinical studies:**

  Based on review of the available non-clinical toxicology, no additional animal studies are required at this time to support the clinical studies described in this written request. As the drug development program progresses, juvenile animal toxicology studies may be requested in order to assess the potential for toxicities for which stage of development may be associated with increased risk.

- **Clinical studies:**

  – **Study 1:** Open label, multicenter dose-finding study in pediatric patients with recurrent or refractory solid tumors with cohort expansion to pediatric patients with neuroblastoma, rhabdomyosarcoma, and Ewing sarcoma.

  – **Study 2:** Randomized, multi-center, open-label study in pediatric patients with recurrent or refractory neuroblastoma, rhabdomyosarcoma, and/or Ewing sarcoma.

  – **Study 3:** Randomized, multi-center, open-label study in pediatric patients with first relapse/high-risk newly diagnosed neuroblastoma, rhabdomyosarcoma, and/or Ewing sarcoma.

  Protocols from Studies 2 and 3 must be submitted for FDA review and approval prior to patient enrollment. Plans for expansion cohorts must be reviewed and approved by the FDA prior to patient enrollment.

  Efficacy in pediatric patients ~~less than 21~~ 24 ~~years of age~~ cannot be extrapolated and will be determined by the studies outlined in the WR.

Objective of Each Study:

Study 1: Phase 1/2, multi-center, open-label, dose-finding study to determine the maximum tolerated dose (MTD) and to assess the safety, tolerability, PK and efficacy of paclitaxel protein-bound particles administered to pediatric patients with recurrent or refractory solid tumors.

- **Primary Objectives:**
  - *Phase 1 portion*: determine the pediatric MTD /recommended phase 2 dose (RP2D) and characterize the safety and tolerability of paclitaxel protein-bound particles in patients ≥ 6 months and < 18 years old with recurrent or refractory solid tumors.
  - *Phase 2 portion*: determine the anti-tumor activity assessed by the overall response rate (ORR) of paclitaxel protein-bound particles given at the RP2D in patients ≥ 6 months and ≤ ~~21~~ 24 years old with several discrete recurrent or refractory solid tumor types including neuroblastoma, rhabdomyosarcoma, and Ewing sarcoma.

    The age range will be extended to ≤ ~~21~~ 24 years old (young adults) in the Phase 2 portion of the study to increase accrual and expedite assessment of activity.

- **Secondary Objectives:**
  - *Phase 1 portion:*
    - Early efficacy determination by characterizing the ORR.
  - *Phase 2 portion:*
    - Characterize duration of response (DOR).
    - Characterize progression-free survival (PFS).
    - Characterize 1-year survival.
    - Further characterize safety.
  - Pharmacokinetic Objectives:
    - Assess the pharmacokinetics (PK) of paclitaxel protein-bound particles in pediatric patients with solid tumors who are refractory to standard therapy.

Study 2: Randomized, multi-center, open-label study to assess the efficacy, safety, and tolerability of paclitaxel protein-bound particles in combination with standard treatment compared to standard treatment alone in pediatric patients with recurrent or refractory neuroblastoma, rhabdomyosarcoma, and/or Ewing sarcoma.

- Primary objective:
  - Determine the efficacy of paclitaxel protein-bound particles in combination with standard treatment compared with standard treatment assessed by event-free survival (EFS) in pediatric patients with recurrent or refractory neuroblastoma and/or rhabdomyosarcoma.
- Secondary objectives:
  - ORR
  - DOR
  - Survival at 2 years
  - Safety of the paclitaxel protein-bound particles combination
- Pharmacokinetic Objective:
  - Assess the PK of paclitaxel protein-bound particles, administered intravenously, in pediatric patients with recurrent or refractory neuroblastoma or rhabdomyosarcoma.

Study 3: Randomized, multi-center, open-label study to assess the efficacy, safety, and tolerability of weekly paclitaxel protein-bound particles in combination with standard treatment compared to standard treatment alone in pediatric patients with first relapse/high-risk newly diagnosed neuroblastoma, rhabdomyosarcoma and/or Ewing sarcoma.

- Primary Objective:
  - To determine the efficacy of paclitaxel protein-bound particles in combination with standard treatment compared with standard treatment assessed by EFS in first relapse/high-risk newly diagnosed neuroblastoma and/or rhabdomyosarcoma.
- Secondary Objectives:
  - ORR
  - DOR
  - Survival at 2 years
  - Safety of the paclitaxel protein-bound particles combination

- Pharmacokinetic Objective:
  - Assess the PK of paclitaxel protein-bound particles administered intravenously, in pediatric patients with first relapse/high-risk newly diagnosed neuroblastoma or rhabdomyosarcoma.

Patients to be Studied:

Study 1: Phase 1 portion: ≥ 6months to < 18 years of age

Phase 2 portion: ≥ 6months and ≤ ~~21~~ 24 years of age

Study 2: 6 months to ~~21~~ 24 years old

Study 3: 1 month to ~~21~~ 24 years old

Note: Neonates and infants < 6 months of age will not be enrolled on Studies 1 and 2 since relapsed and refractory tumors requiring therapeutic intervention rarely occur in this age group. Neonates will be excluded from Study 3 since high-risk tumors requiring intensive chemotherapy are extremely rare in this population. Study sample size will be agreed upon as part of the protocol and statistical analysis plan.

Representation of Ethnic and Racial Minorities: The studies must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

Endpoints for Each Study:

Efficacy Endpoints

Study 1:

Primary Endpoints:

- Phase 1 portion is a dose-finding stage and has no efficacy endpoints
- Phase 2 portion: ORR, which is the combined incidence of complete response (CR) and partial response (PR), confirmed no less than 4 weeks after the criteria for response are first met, based on Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. In the Phase 2 portion neuroblastoma group, the ORR will be determined by RECIST and the Curie scale (MIBG response) when possible. The corresponding Clopper-Pearson 95% confidence interval calculated about the ORR.

Secondary Endpoints:

- Phase 1 portion:
  - ORR and the corresponding Clopper-Pearson 95% confidence interval will be calculated about the ORR.
- Phase 2 portion:
  - DOR in patients with a confirmed objective CR or PR
  - PFS based on investigator assessment of response using RECIST 1.1 guidelines. In the Phase 2 portion neuroblastoma group the PFS will be determined by RECIST and the Curie scale (MIBG response) when possible.
  - Survival at 1 year

Studies 2 and 3:

Primary Endpoint:

- Event-free survival (EFS)

Secondary Endpoints:

- ORR and the corresponding Clopper-Pearson 95% confidence interval calculated about the ORR.
- DOR
- 2-year survival rate

Safety Endpoints

Study 1:

Primary Endpoints:

- Phase 1 portion: Determine MTD of paclitaxel protein-bound particles, incidence of DLTs, and the incidence of treatment-emergent adverse events (TEAEs)

Secondary Endpoints:

- Phase 2 portion: Incidence of TEAEs

Study 2:

- Safety of the paclitaxel protein-bound particles combination
- Incidence and severity of TEAEs

Study 3:

- Safety of the paclitaxel protein-bound particles combination
- Incidence and severity of TEAEs

Pharmacokinetic/Pharmacodynamic Endpoints

Studies 1, 2 and 3:

- Estimated paclitaxel clearance (CL) and volume of distribution (Vd) from PK samples obtained across all studies from a minimum of 14 patients in each of the following age groups: 2 to 5 years, 6 to 11 years and 12 to 18 years. Data from studies 1, 2 and 3 must be combined to develop PK and pharmacodynamics models to explore exposure-response relationships for measures of safety and activity.

Known Drug Safety Concerns and Monitoring:

The tolerability and safety of paclitaxel protein-bound particles has been well established in adults. The most clinically significant adverse reactions associated with the use of paclitaxel protein-bound particles across all studied indications are neutropenia, peripheral neuropathy, arthralgia, myalgia, nausea, vomiting, and constipation.

Throughout the studies, all patients will be monitored for safety evaluations. These data will be assessed periodically, along with all other safety parameters, for any potential risks that may not be foreseeable from the known risk/benefit in adults, or from preclinical findings. A patient whose symptoms are not manageable with allowable medications throughout the study will be discontinued from the study and treated according to local treatment guidelines.

A Data Monitoring Committee (DMC) or Safety Monitoring Committee (SMC) must be included. See FDA Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees
http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126578.pdf

Extraordinary Results:

In the course of conducting these studies, you may discover evidence to indicate that there are unexpected safety concerns, unexpected findings of benefit in a smaller sample size, or other unexpected results. In the event of such findings, there may be a need to deviate from the requirements of this Written Request. If you believe this is the case, you must contact the

Agency to seek an amendment. It is solely within the Agency's discretion to decide whether it is appropriate to issue an amendment.

Drug Information:

- *Dosage form:* paclitaxel protein-bound particles are available as a lyophilized powder for suspension for infusion. Each vial contains 100 mg of paclitaxel. Each vial is to be reconstituted with 20 mL of sodium chloride (0.9%) for injection. The lyophilized powder for suspension is considered an age-appropriate formulation for the studies described above.

- *Route of administration:* Intravenous

- *Regimen:* To be agreed upon as part of the final protocols

Statistical Information, including Power of Studies and Statistical Assessments:

Study 1: Dose escalation will be based on a rolling-6 study design. A Simon two-stage minimax design will be used to monitor patient enrollment for the expansion cohorts of neuroblastoma, Ewing's sarcoma, rhabdomyosarcoma.

Studies 2 and 3: The statistical plan for Studies 2 and 3 will be agreed upon as part of the protocol review by FDA.

Pharmacokinetic Analysis: Population PK analysis will be performed using paclitaxel concentration data obtained from all studies. Effect of age and body size on paclitaxel protein-bound particles PK will be assessed. The relationship between systemic drug exposure and selected efficacy and toxicity endpoints may be explored.

Labeling that May Result from the Studies:

You must submit proposed pediatric labeling to incorporate the findings of the studies. Under section 505A(j) of the Act, regardless of whether the studies demonstrate that paclitaxel protein-bound particles are safe and effective, or whether such study results are inconclusive in the studied pediatric populations or subpopulation(s), the labeling must include information about the results of the studies. 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 studies.

- *Format and types of reports to be submitted*: You must submit full study reports (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 reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the studies 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 choose to use other categories, you should obtain agency agreement.

- Under section 505A(d)(2)(B) of the Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. All post-market reports that would be reportable under section 21 CFR 314.80 should include adverse events occurring in an adult or a pediatric patient. In general, the format of the post-market adverse event report should follow the model for a periodic safety update report described in the Guidance for Industry E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs and the Guidance addendum. You are encouraged to contact the reviewing Division for further guidance.

  Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on the http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM199759.pdf and referenced in the FDA Guidance for Industry, *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at http://www.fda.gov/Cder/guidance/7087rev.htm.

- *Timeframe for submitting reports of the study(ies):* Final study reports for all studies should be submitted to the FDA on or before December. 31, 2024. ~~Reports of the above studies must be submitted to the Agency on or before the following dates.~~

- ~~Study 1: September 30, 2017~~ ~~December 31, 2019~~

- ~~Studies 2 & 3: December 31, 2022~~ ~~December 31, 2024~~

  Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

- *Response to Written Request:* Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you must indicate

why you are declining to conduct the study(ies). If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed.

Furthermore, if you agree to conduct the study(ies), but have not submitted the study reports on or before the date specified in the Written Request, the Agency may utilize the process discussed in section 505A(n) of the Act.

For ease of reference, a complete copy of the Written Request, as amended, is attached to this letter.

Reports of the studies that meet the terms of the Written Request dated October 29, 2014, as amended by this letter and by previous amendment(s) dated April 17, 2015, must be submitted to the Agency on or before December 31, 2019 (for Study 1) and December 31, 2024 (for Studies 2 and 3), in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit reports of the studies as a supplement to an approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. In addition, send a copy of the cover letter of your submission, via fax (240-276-9327) or messenger, to the Director, Office of Generic Drugs, CDER, FDA, Document Control Room, Metro Park North VII, 7620 Standish Place, Rockville, MD 20855-2773.

In accordance with section 505A(k)(1) of the Act, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following:

- the type of response to the Written Request (i.e., complete or partial response);
- the status of the application (i.e., withdrawn after the supplement has been filed or pending);
- the action taken (i.e., approval, complete response); or
- the exclusivity determination (i.e., granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049872.

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

If you have any questions, call Norma Griffin, Lead Regulatory Health Project Manager, at 301-796-4255.

Sincerely,

{See appended electronic signature page}

Gregory Reaman, M.D.
Associate Director
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE(S):
Attachment 1 - Clean Copy of Written Request as Amended – Amendment 2

ATTACHMENT 1

WRITTEN REQUEST - AMENDMENT 2

Paclitaxel protein-bound particles for injectable suspension (paclitaxel protein-bound particles) is an albumin-bound formulation of paclitaxel currently approved for the treatment of refractory breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy, first line locally advanced or metastatic non-small cell lung cancer in combination with carboplatin, and first line treatment of metastatic adenocarcinoma of the pancreas in combination with gemcitabine. Paclitaxel, the cytotoxic ingredient in paclitaxel protein-bound particles, is an anti-microtubule agent. Compared to conventional paclitaxel, paclitaxel protein-bound particles increase the tissue bioavailability of paclitaxel by exploiting the natural properties of albumin to enhance the selective uptake of paclitaxel by tumor tissue.

The requested studies investigate the potential use of paclitaxel protein-bound particles for the treatment of pediatric patients with recurrent or refractory solid tumors with planned expansion cohorts to include pediatric patients with neuroblastoma, rhabdomyosarcoma and Ewing sarcoma. Solid tumors account for approximately 60% of all pediatric malignancies. Overall cure rates for children with solid tumors are greater than 50% with surgery, chemotherapy, and radiation; however there is still a need for more effective treatment, especially in patients who present with or develop metastatic disease.

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- **Clinical studies:**

  - **Study 1:** Open label, multicenter dose-finding study in pediatric patients with recurrent or refractory solid tumors with cohort expansion to pediatric patients with neuroblastoma, rhabdomyosarcoma, and Ewing sarcoma.
  - **Study 2:** Randomized, multi-center, open-label study in pediatric patients with recurrent or refractory neuroblastoma, rhabdomyosarcoma, and/or Ewing sarcoma.
  - **Study 3:** Randomized, multi-center, open-label study in pediatric patients with first relapse/high-risk newly diagnosed neuroblastoma, rhabdomyosarcoma, and/or Ewing sarcoma.

  Protocols from Studies 2 and 3 must be submitted for FDA review and approval prior to patient enrollment. Plans for expansion cohorts must be reviewed and approved by the FDA prior to patient enrollment.

  Efficacy in pediatric patients cannot be extrapolated and will be determined by the studies outlined in the WR.

Objective of Each Study:

Study 1: Phase 1/2, multi-center, open-label, dose-finding study to determine the maximum tolerated dose (MTD) and to assess the safety, tolerability, PK and efficacy of paclitaxel protein-bound particles administered to pediatric patients with recurrent or refractory solid tumors.

- Primary Objectives:
  - *Phase 1 portion*: determine the pediatric MTD /recommended phase 2 dose (RP2D) and characterize the safety and tolerability of paclitaxel protein-bound particles in patients ≥ 6 months and < 18 years old with recurrent or refractory solid tumors.
  - *Phase 2 portion*: determine the anti-tumor activity assessed by the overall response rate (ORR) of paclitaxel protein-bound particles given at the RP2D in patients ≥ 6 months and ≤ 24 years old with several discrete recurrent or refractory solid tumor types including neuroblastoma, rhabdomyosarcoma, and Ewing sarcoma.

    The age range will be extended to ≤ 24 years old (young adults) in the Phase 2 portion of the study to increase accrual and expedite assessment of activity.

- Secondary Objectives:
  - *Phase 1 portion*:
    - Early efficacy determination by characterizing the ORR.
  - *Phase 2 portion*:
    - Characterize duration of response (DOR).
    - Characterize progression-free survival (PFS).
    - Characterize 1-year survival.
    - Further characterize safety.
- Pharmacokinetic Objectives:
  - Assess the pharmacokinetics (PK) of paclitaxel protein-bound particles in pediatric patients with solid tumors who are refractory to standard therapy.

Study 2: Randomized, multi-center, open-label study to assess the efficacy, safety, and tolerability of paclitaxel protein-bound particles in combination with standard treatment compared to standard treatment alone in pediatric patients with recurrent or refractory neuroblastoma, rhabdomyosarcoma and/or Ewing sarcoma.

- Primary objective:
  - Determine the efficacy of paclitaxel protein-bound particles in combination with standard treatment compared with standard treatment assessed by event-free survival (EFS) in pediatric patients with recurrent or refractory neuroblastoma and/or rhabdomyosarcoma.
- Secondary objectives:
  - ORR
  - DOR
  - Survival at 2 years
  - Safety of the paclitaxel protein-bound particles combination
- Pharmacokinetic Objective:
  - Assess the PK of paclitaxel protein-bound particles, administered intravenously, in pediatric patients with recurrent or refractory neuroblastoma or rhabdomyosarcoma.

Study 3: Randomized, multi-center, open-label study to assess the efficacy, safety, and tolerability of weekly paclitaxel protein-bound particles in combination with standard treatment compared to standard treatment alone in pediatric patients with first relapse/high-risk newly diagnosed neuroblastoma, rhabdomyosarcoma and/or Ewing sarcoma.

- Primary Objective:
  - To determine the efficacy of paclitaxel protein-bound particles in combination with standard treatment compared with standard treatment assessed by EFS in first relapse/high-risk newly diagnosed neuroblastoma and/or rhabdomyosarcoma.
- Secondary Objectives:
  - ORR
  - DOR

- Survival at 2 years
- Safety of the paclitaxel protein-bound particles combination

Pharmacokinetic Objective:

- Assess the PK of paclitaxel protein-bound particles administered intravenously, in pediatric patients with first relapse/high-risk newly diagnosed neuroblastoma or rhabdomyosarcoma.

Patients to be Studied:

Study 1: Phase 1 portion: ≥ 6months to < 18 years of age
Phase 2 portion: ≥ 6months and ≤ 24 years of age
Study 2: 6 months to 24 years old
Study 3: 1 month to 24 years old

Note: Neonates and infants < 6 months of age will not be enrolled on Studies 1 and 2 since relapsed and refractory tumors requiring therapeutic intervention rarely occur in this age group. Neonates will be excluded from Study 3 since high-risk tumors requiring intensive chemotherapy are extremely rare in this population. Study sample size will be agreed upon as part of the protocol and statistical analysis plan.

Representation of Ethnic and Racial Minorities: The studies must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

Endpoints for Each Study:

Efficacy Endpoints

Study 1:
PrimaryEndpoints:
- Phase 1 portion is a dose-finding stage and has no efficacy endpoints
- Phase 2 portion: ORR, which is the combined incidence of complete response (CR)

and partial response (PR), confirmed no less than 4 weeks after the criteria for response are first met, based on Response Evaluation Criteria in Solid Tumors (RECIST version 1.1 In the Phase 2 portion neuroblastoma group, the ORR will be determined by RECIST and the Curie scale (MIBG response) when possible. The corresponding Clopper-Pearson 95% confidence interval calculated about the ORR.

Secondary Endpoints:

- Phase 1 portion:
  - ORR and the corresponding Clopper-Pearson 95% confidence interval will be calculated about the ORR.
- Phase 2 portion:
  - DOR in patients with a confirmed objective CR or PR
  - PFS based on investigator assessment of response using RECIST 1.1 guidelines. In the Phase 2 portion neuroblastoma group the PFS will be determined by RECIST and the Curie scale (MIBG response) when possible.
  - Survival at 1 year

Studies 2 and 3:

PrimaryEndpoint:

- Event-free survival (EFS)

SecondaryEndpoints:

- ORR and the corresponding Clopper-Pearson 95% confidence interval calculated about the ORR.
- DOR
- 2-year survival rate

Safety Endpoints

Study 1:

Primary Endpoints:

- Phase 1 portion: Determine MTD of paclitaxel protein-bound particles, incidence of DLTs, and the incidence of treatment-emergent adverse events (TEAEs)

Secondary Endpoints:

- Phase 2 portion: Incidence of TEAEs

Study 2:

- Safety of the paclitaxel protein-bound particles combination
- Incidence and severity of TEAEs

Study 3:

- Safety of the paclitaxel protein-bound particles combination
- Incidence and severity of TEAEs

Pharmacokinetic/Pharmacodynamic Endpoints

Studies 1, 2 and 3:

- Estimated paclitaxel clearance (CL) and volume of distribution ($V_{d)}$ from PK samples obtained across all studies from a minimum of 14 patients in each of the following age groups: 2 to 5 years, 6 to 11 years and 12 to 18 years. Data from studies 1, 2 and 3 must be combined to develop PK and pharmacodynamics models to explore exposure-response relationships for measures of safety and activity.

Known Drug Safety Concerns and Monitoring:
The tolerability and safety of paclitaxel protein-bound particles has been well established in adults. The most clinically significant adverse reactions associated with the use of paclitaxel protein-bound particles across all studied indications are neutropenia, peripheral neuropathy, arthralgia, myalgia, nausea, vomiting, and constipation.

Throughout the studies, all patients will be monitored for safety evaluations. These data will be assessed periodically, along with all other safety parameters, for any potential risks that may not be foreseeable from the known risk/benefit in adults, or from preclinical findings. A patient whose symptoms are not manageable with allowable medications throughout the study will be discontinued from the study and treated according to local treatment guidelines.

A Data Monitoring Committee (DMC) or Safety Monitoring Committee (SMC) must be included. See FDA Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126578.pdf

Extraordinary Results:
In the course of conducting these studies, you may discover evidence to indicate that there are unexpected safety concerns, unexpected findings of benefit in a smaller sample size, or other unexpected results. In the event of such findings, there may be a need to deviate from the requirements of this Written Request. If you believe this is the case, you must contact the Agency to seek an amendment. It is solely within the Agency's discretion to decide whether it is appropriate to issue an amendment.

Drug Information:

- *Dosage form:* paclitaxel protein-bound particles are is available as a lyophilized powder for suspension for infusion. Each vial contains 100 mg of paclitaxel. Each vial is to be reconstituted with 20 mL of sodium chloride (0.9%) for injection. The lyophilized powder for suspension is considered an age- appropriate formulation for the studies described above.
- *Route of administration:* Intravenous
- *Regimen:* To be agreed upon as part of the final protocols

Statistical Information, including Power of Studies and Statistical Assessments:

Study 1: Dose escalation will be based on a rolling-6 study design. A Simon two-stage minimax design will be used to monitor patient enrollment for the expansion cohorts of neuroblastoma, Ewing's sarcoma, rhabdomyosarcoma.

Studies 2 and 3: The statistical plan for Studies 2 and 3 will be agreed upon as part of the protocol review by FDA.

Pharmacokinetic Analysis: Population PK analysis will be performed using paclitaxel concentration data obtained from all studies. Effect of age and body size on paclitaxel protein-bound particles PK will be assessed. The relationship between systemic drug exposure and selected efficacy and toxicity endpoints may be explored.

Labeling that May Result from the Studies:
You must submit proposed pediatric labeling to incorporate the findings of the studies. Under section 505A(j) of the Act, regardless of whether the studies demonstrate that paclitaxel protein-bound particles are safe and effective, or whether such study results are inconclusive in the studied pediatric populations or subpopulation(s), the labeling must include information about the results of the studies. 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 studies.

- *Format and types of reports to be submitted*: You must submit full study reports (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 reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the studies 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 choose to use other categories, you should obtain agency agreement.

- Under section 505A(d)(2)(B) of the Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. All post-market reports that would be reportable under section 21 CFR 314.80 should
include adverse events occurring in an adult or a pediatric patient. In general, the format of the post-market adverse event report should follow the model for a periodic safety update report described in the Guidance for Industry E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs and the Guidance addendum. You are encouraged to contact the reviewing Division for further guidance.

Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on the http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequire ments/ElectronicSubmissions/UCM199759.pdf and referenced in the FDA Guidance for Industry, *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at http://www.fda.gov/Cder/guidance/7087rev.htm.

- *Timeframe for submitting reports of the study(ies):* Final study reports for all studies should be submitted to the FDA on or before December. 31, 2024.

  Please keep in mind that pediatric exclusivity attaches only to existing patent protection or
  exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity
  is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

- *Response to Written Request:* Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the study(ies). If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed.

  Furthermore, if you agree to conduct the study(ies), but have not submitted the study reports on or before the date specified in the Written Request, the Agency may utilize the process discussed in section 505A(n) of the Act.

Submit protocols for the above study(ies) to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the study(ies) must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS - PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission to the Director, Office of Generic Drugs, HFD-600, Metro Park North IV, 7519 Standish Place, Rockville, MD 20855-2773. If you wish to fax it, the fax number is 240-276-9327.

In accordance with section 505A(k)(1) of the Act, *Dissemination of Pediatric Information*, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following circumstances:

1. the type of response to the Written Request (i.e. complete or partial response);
2. the status of the application (i.e. withdrawn after the supplement has been filed or pending);
3. the action taken (i.e. approval, complete response); or
4. the exclusivity determination (i.e. granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049872.

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

Please note that, if your trial is considered an "applicable clinical trial" under section 402(j)(1)(A)(i) of the Public Health Service Act (PHS Act), you are required to comply with the provisions of section 402(j) of the PHS Act with regard to registration of your trial and submission of trial results. Additional information on submission of such information can be found at www.ClinicalTrials.gov.

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

/s/

GREGORY H REAMAN
07/27/2017