CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203971Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	May 14, 2013
From	Robert L. Justice, M.D., M.S.
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	203971
Applicant Name	Bayer HealthCare Pharmaceuticals, Inc.
Date of Submission	December 14, 2012
PDUFA Goal Date	August 14, 2013
Proprietary Name / **Established (USAN) Name**	Xofigo Injection/ radium Ra-223 dichloride
Dosage Forms / Strength	Single-use 6 mL vial/1000 kBq/mL (27 microcurie/mL) with a total radioactivity of 6,000 kBq/vial
Proposed Indication(s)	Xofigo is indicated for the treatment of patients with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastatic disease.
Action/Recommended Action for NME:	*Approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Paul Kluetz, William Pierce
Statistical Review	Hui Zhang, Shenghui Tang, Rajeshwari Sridhara
Pharmacology Toxicology Review	Wei Chen, Todd Palmby, John Leighton
CMC Review/OBP Review	Martin Haber, Eldon Leutzinger, Denise Miller, Ali Al Hakim
Microbiology Review	N/A
Clinical Pharmacology Review	Pengfei Song, John Christy, Qi Liu, Nitin Mehrotra
OPDP	Michelle Safarik
OSI	Lauren Iacono-Connors, Janice Pohlman, Susan Thompson
CDTL Review	Ellen Maher
OSE/DMEPA	Jibril Abdus-Samad
OSE/DRISK	Bob Pratt
DMIP	Cynthia Welsh, Lucie Yang
SEALD	Jessica Voqui
QT-IRT	Justin Earp, Kevin Krudys, Janice Brodsky, Qianyu Dang, Monica Fiszman, Norman Stockbridge.

Division Director Summary Review

1. Introduction

This NDA for Xofigo Injection (radium Ra-223 dichloride) was submitted on 12/14/12 and was given an expedited review. The PDUFA date for a priority review is 8/14/13. The final indication is for the treatment of patients with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastatic disease. This review will summarize the recommendations of each review discipline and the clinical trial efficacy and safety results that support approval.

2. Background

The mechanism of action of Xofigo is provided in the following summary from the agreed-upon package insert.

> The active moiety of Xofigo is the alpha particle-emitting isotope radium-223 (as radium Ra 223 dichloride), which mimics calcium and forms complexes with the bone mineral hydroxyapatite at areas of increased bone turnover, such as bone metastases (see Table 2). The high linear energy transfer of alpha emitters (80 keV/micrometer) leads to a high frequency of double-strand DNA breaks in adjacent cells, resulting in an anti-tumor effect on bone metastases. The alpha particle range from radium-223 dichloride is less than 100 micrometers (less than 10 cell diameters) which limits damage to the surrounding normal tissue.

3. CMC/Device

The CMC Review recommended approval and stated that there are no pending CMC deficiencies to resolve. The microbiology review recommended approval from a quality microbiology standpoint.

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports a shelf-life of 28 days stored below 40 ℃. There are no CMC outstanding issues.

4. Nonclinical Pharmacology/Toxicology

The Pharmacology/Toxicology Review stated concluded that the nonclinical studies adequately support the safety of radium-223 dichloride by intravenous administration in patients with castration-resistant prostate cancer with bone metastases and that there are no outstanding nonclinical issues that would preclude the approval of Xofigo for the proposed indication.

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology of Xofigo is summarized in the following excerpt from the Executive Summary of the Clinical Pharmacology Review.

> Xofigo demonstrated linear pharmacokinetics in blood in terms of dose proportionality and time independence in a dose range of 46-250 kBq/kg total body weight. After intravenous injection, Radium-223 is rapidly cleared from blood and distributed to bone and intestine. At 10 minutes post injection, radioactivity was observed in bone and intestine. The fraction of the injected radioactivity remained in blood, bone, and intestine was 4 ±1%, 61 ± 10%, and 49 ±16%, respectively, at 4 hours post injection. Approximately 63% of administered radioactivity was excreted from the body within 7 days, primarily via fecal route. Dosimetry data suggested that bone, red marrow, and intestine wall received the highest absorbed radiation doses. Radium-223 is not metabolized, and there was no evidence of hepato-biliary excretion based on imaging data.
>
> Exploratory analyses suggested that the proposed dosing regimen may not be optimal. In the pivotal trial BC1-06, the separation of OS Kaplan-Meier curves stratified by body weight quartiles suggested that higher body weight was related with better overall survival in the Xofigo arm but not in the placebo control arm. Patients whose body weight = 73 kg did not have improved OS from the Xofigo treatment compared to the control arm. The incidence of Grade 3 or worse (Grade 3+) adverse events (AEs) is similar across body weight range, with slightly lower incidence of Grade 3+ AEs in Xofigo arm. Furthermore, a trend was observed for ideal body weight (IBW)-normalized dose: the larger the IBW-normalized dose, the lower OS hazard ratio.
>
> Furthermore, Xofigo has a favorable safety profile, and no maximum tolerated dose (MTD) was determined at a cumulative dose up to 250 kBq/kg. Therefore, a dose higher than 50 kBq/kg may improve the OS in the subpopulation especially with body weight lower than 73 kg (25% of the overall population), or even in the overall patient

> population. A post-marketing clinical trial will be recommended to evaluate the safety and efficacy of Xofigo at a higher dose.
>
> Based on subgroup analyses of the trial BC1-06, no dose adjustment is needed for patients with mild hepatic impairment, or patients with mild/moderate renal impairment. No dose adjustments can be recommended for patients with moderate/severe hepatic impairment, or severe renal impairment due to limited data available. Furthermore, subgroup analyses suggested that the concurrent use of calcium channel blockers or bisphosphonates did not affect the OS and safety in the trial BC1-06. No large changes in mean QTc intervals (i.e., > 20 ms) were detected at up to 4 hours post-injection at the proposed dose.

The review recommended approval with one post-marketing commitment.

I concur with the conclusions reached by the clinical pharmacology reviewers. There are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

N/A

7. Clinical/Statistical-Efficacy

The design and results of the clinical trial used to support approval are summarized in the following excerpt from the agreed-upon package insert.

> The efficacy and safety of Xofigo were evaluated in a double-blind, randomized, placebo-controlled phase 3 clinical trial of patients with castration-resistant prostate cancer with symptomatic bone metastases. Patients with visceral metastases and malignant lymphadenopathy exceeding 3 cm were excluded. The primary efficacy endpoint was overall survival. A key secondary efficacy endpoint was time to first symptomatic skeletal event (SSE) defined as external beam radiation therapy (EBRT) to relieve skeletal symptoms, new symptomatic pathologic bone fracture, occurrence of spinal cord compression, or tumor-related orthopedic surgical intervention. There were no scheduled radiographic assessments performed on study. All patients were to continue androgen deprivation therapy. At the cut-off date of the pre-planned interim analysis, a total of 809 patients had been randomized 2:1 to receive Xofigo 50 kBq (1.35 microcurie)/kg intravenously every 4 weeks for 6 cycles (n = 541) plus best standard of care or matching placebo plus best standard of care (n = 268). Best standard of care included local EBRT, corticosteroids, antiandrogens, estrogens, estramustine or ketoconazole. Therapy was continued until unacceptable toxicity or initiation of cytotoxic chemotherapy, other systemic radioisotope, hemi-body EBRT or other investigational drug. Patients with Crohn's disease, ulcerative colitis, prior hemibody radiation or untreated imminent spinal cord compression were excluded

from the study. In patients with bone fractures, orthopedic stabilization was performed before starting or resuming treatment with Xofigo.

The following patient demographics and baseline disease characteristics were balanced between the arms. The median age was 71 (range 44-94) with a racial distribution of 94% Caucasian, 4% Asian, 2% Black and <1% Other. Patients were enrolled predominantly from Europe (85%) with 4% of patients enrolled from North America. ECOG performance status was 0-1 in 86% of patients. Eighty-five percent of patients had 6 or more bone scan lesions and of those 40% had > 20 lesions or a superscan. Opiate pain medications were used for cancer-related pain in 54% of patients, non-opiate pain medications in 44% of patients and no pain medications in 2% of patients. Patients were stratified by baseline ALP, bisphosphonate use, and prior docetaxel exposure. Prior bisphosphonates were used by 41% of patients and 58% had received prior docetaxel. During the treatment period, 83% of Xofigo patients and 82% of placebo patients received gonadotropin-releasing hormone agonists and 21% of Xofigo patients and 34% of placebo patients received concomitant antiandrogens. Use of systemic steroids (41%) and bisphosphonates (40%) was balanced between the arms.

The pre-specified interim analysis of overall survival revealed a statistically significant improvement in patients receiving XOFIGO plus best standard of care compared with patients receiving placebo plus best standard of care. An exploratory updated overall survival analysis performed before patient crossover with an additional 214 events resulted in findings consistent with the interim analysis (Table 5).

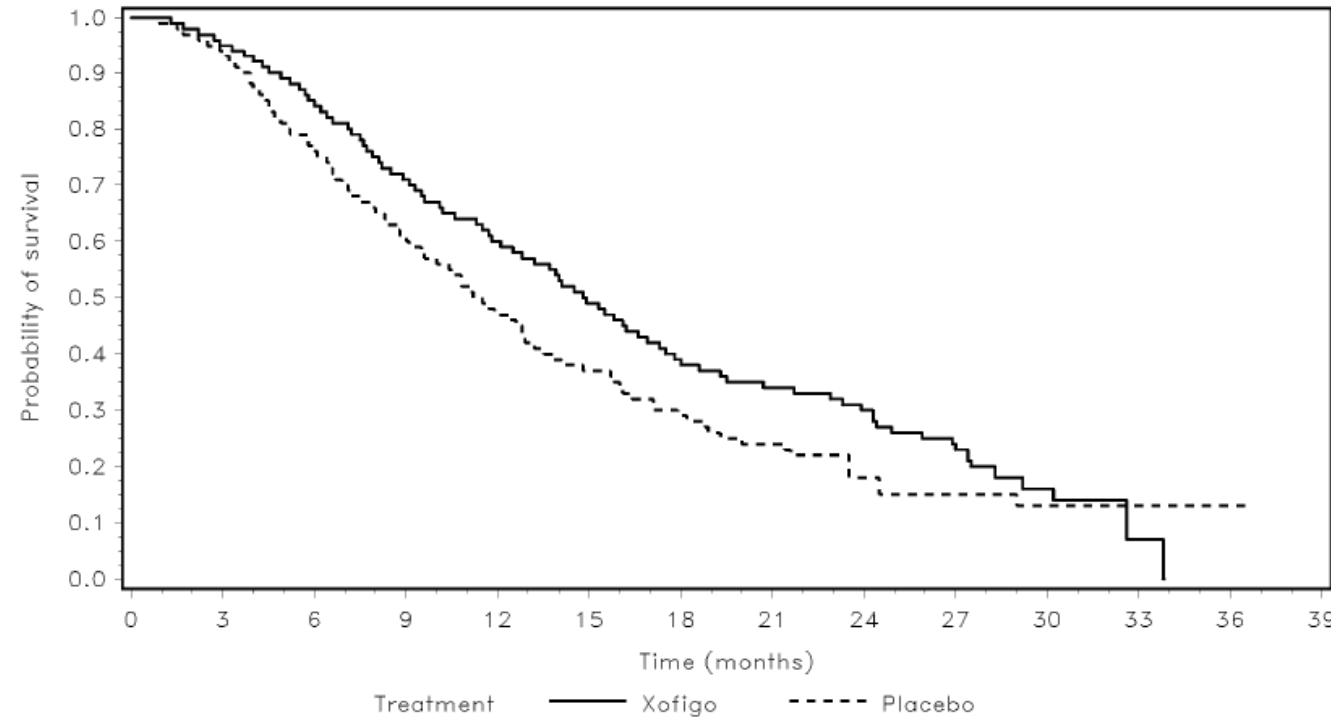
Table 5: Overall Survival Results from the Phase 3 Clinical Trial

	Xofigo	Placebo
Interim Analysis		
Subjects randomized	541	268
Number of deaths	191 (35.3%)	123 (45.9%)
Censored	350 (64.7%)	145 (54.1%)
Median survival (months) [a] (95% CI)	14.0 (12.1, 15.8)	11.2 (9.0, 13.2)
p-value[b]	0.00185	
Hazard ratio (95% CI)[c]	0.695 (0.552, 0.875)	
Updated Analysis		
Subjects randomized	614	307
Number of deaths	333 (54.2%)	195 (63.5%)
Censored	281 (45.8%)	112 (36.5%)
Median survival (months) [a] (95% CI)	14.9 (13.9, 16.1)	11.3 (10.4, 12.8)
Hazard ratio (95% CI)[c]	0.695 (0.581, 0.832)	

[a] Survival time is calculated as months from date of randomization to date of death from any cause. Subjects who are not deceased at time of analysis are censored on the last date subject was known to be alive or lost to follow-up.
[b] p-value is from a log-rank test stratified by total ALP, current use of bisphosphonates, and prior use of docetaxel.
[c] Hazard ratio is from a Cox proportional hazards model adjusted for total ALP, current use of bisphosphonates, and prior use of docetaxel. Hazard ratio < 1 favors radium-223 dichloride.

The Kaplan-Meier curves for overall survival based on the updated survival results are shown in Figure 1.

Figure 1: Kaplan-Meier Overall Survival Curves from the Phase 3 Clinical Trial



Number of patients at risk

Xofigo	614	578	504	369	277	178	105	60	41	18	7	1	0	0
Placebo	307	288	228	157	104	67	39	24	14	7	4	2	1	0

The survival results were supported by a delay in the time to first SSE favoring the Xofigo arm. The majority of events consisted of external beam radiotherapy to bone metastases.

8. Safety

The adverse reactions from the randomized trial are summarized in the following excerpt from the agreed-upon package insert.

In the randomized clinical trial in patients with metastatic castration-resistant prostate cancer with bone metastases, 600 patients received intravenous injections of 50 kBq/kg (1.35 microcurie/kg) of Xofigo and best standard of care and 301 patients received placebo and best standard of care once every 4 weeks for up to 6 injections. Prior to randomization, 58% and 57% of patients had received docetaxel in the Xofigo and

placebo arms, respectively. The median duration of treatment was 20 weeks (6 cycles) for Xofigo and 18 weeks (5 cycles) for placebo.
The most common adverse reactions (≥ 10%) in patients receiving Xofigo were nausea, diarrhea, vomiting, and peripheral edema (Table 3). Grade 3 and 4 adverse events were reported among 57% of Xofigo-treated patients and 63% of placebo-treated patients. The most common hematologic laboratory abnormalities in Xofigo-treated patients (≥ 10%) were anemia, lymphocytopenia, leukopenia, thrombocytopenia, and neutropenia (Table 4).

Treatment discontinuations due to adverse events occurred in 17% of patients who received Xofigo and 21% of patients who received placebo. The most common hematologic laboratory abnormalities leading to discontinuation for Xofigo were anemia (2%) and thrombocytopenia (2%).

Table 3 shows adverse reactions occurring in ≥ 2% of patients and for which the incidence for Xofigo exceeds the incidence for placebo.

Table 3: Adverse Reactions in the Randomized Trial

System/Organ Class Preferred Term	Xofigo (n=600)		Placebo (n=301)	
	Grades 1-4 %	Grades 3-4 %	Grades 1-4 %	Grades 3-4 %
Blood and lymphatic system disorders				
Pancytopenia	2	1	0	0
Gastrointestinal disorders				
Nausea	36	2	35	2
Diarrhea	25	2	15	2
Vomiting	19	2	14	2
General disorders and administration site conditions				
Peripheral edema	13	2	10	1
Renal and urinary disorders				
Renal failure and impairment	3	1	1	1

Laboratory Abnormalities

Table 4 shows hematologic laboratory abnormalities occurring in ≥ 10% of patients and for which the incidence for Xofigo exceeds the incidence for placebo.

Table 4: Hematologic Laboratory Abnormalities

Hematologic Laboratory Abnormalities	Xofigo (n=600)		Placebo (n=301)	
	Grades 1-4 %	Grades 3-4 %	Grades 1-4 %	Grades 3-4 %
Anemia	93	6	88	6
Lymphocytopenia	72	20	53	7
Leukopenia	35	3	10	<1
Thrombocytopenia	31	3	22	<1
Neutropenia	18	2	5	<1

Laboratory values were obtained at baseline and prior to each 4-week cycle.

As an adverse reaction, grade 3-4 thrombocytopenia was reported in 6% of patients on Xofigo and in 2% of patients on placebo. Among patients who received Xofigo, the laboratory abnormality grade 3-4 thrombocytopenia occurred in 1% of docetaxel naïve patients and in 4% of patients who had received prior docetaxel. Grade 3-4 neutropenia occurred in 1% of docetaxel naïve patients and in 3% of patients who have received prior docetaxel.

Fluid Status
Dehydration occurred in 3% of patients on Xofigo and 1% of patients on placebo. Xofigo increases adverse reactions such as diarrhea, nausea, and vomiting which may result in dehydration. Monitor patients' oral intake and fluid status carefully and promptly treat patients who display signs or symptoms of dehydration or hypovolemia.

Injection Site Reactions
Erythema, pain, and edema at the injection site were reported in 1% of patients on Xofigo.

Secondary Malignant Neoplasms
Xofigo contributes to a patient's overall long-term cumulative radiation exposure. Long-term cumulative radiation exposure may be associated with an increased risk of cancer and hereditary defects. Due to its mechanism of action and neoplastic changes, including osteosarcomas, in rats following administration of radium-223 dichloride, Xofigo may increase the risk of osteosarcoma or other secondary malignant neoplasms *[see Nonclinical Toxicology (13.1)]*. However, the overall incidence of new malignancies in the randomized trial was lower on the Xofigo arm compared to placebo (<1% vs. 2%; respectively), but the expected latency period for the development of secondary malignancies exceeds the duration of follow up for patients on the trial.

Subsequent Treatment with Cytotoxic Chemotherapy
In the randomized clinical trial, 16% patients in the Xofigo group and 18% patients in the placebo group received cytotoxic chemotherapy after completion of study

treatments. Adequate safety monitoring and laboratory testing was not performed to assess how patients treated with Xofigo will tolerate subsequent cytotoxic chemotherapy.

There is one Warning and Precaution about bone marrow suppression.

In the randomized trial, 2% of patients on the Xofigo arm experienced bone marrow failure or ongoing pancytopenia compared to no patients treated with placebo. There were two deaths due to bone marrow failure and for 7 of 13 patients treated with Xofigo, bone marrow failure was ongoing at the time of death. Among the 13 patients who experienced bone marrow failure, 54% required blood transfusions. Four percent (4%) of patients on the Xofigo arm and 2% on the placebo arm permanently discontinued therapy due to bone marrow suppression.

In the randomized trial, deaths related to vascular hemorrhage in association with myelosuppression were observed in 1% of Xofigo-treated patients compared to 0.3% of patients treated with placebo. The incidence of infection-related deaths (2%), serious infections (10%), and febrile neutropenia (<1%) were similar for patients treated with Xofigo and placebo. Myelosuppression; notably thrombocytopenia, neutropenia, pancytopenia, and leukopenia; has been reported in patients treated with Xofigo. In the randomized trial, complete blood counts (CBCs) were obtained every 4 weeks prior to each dose and the nadir CBCs and times of recovery were not well characterized. In a separate single-dose phase 1 study of Xofigo, neutrophil and platelet count nadirs occurred 2 to 3 weeks after Xofigo administration at doses that were up to 1 to 5 times the recommended dose, and most patients recovered approximately 6 to 8 weeks after administration *[see Adverse Reactions (6)]*.

Hematologic evaluation of patients must be performed at baseline and prior to every dose of Xofigo. Before the first administration of Xofigo, the absolute neutrophil count (ANC) should be $\geq 1.5 \times 10^9$/L, the platelet count $\geq 100 \times 10^9$/L and hemoglobin ≥ 10 g/dL. Before subsequent administrations of Xofigo, the ANC should be $\geq 1 \times 10^9$/L and the platelet count $\geq 50 \times 10^9$/L. If there is no recovery to these values within 6 to 8 weeks after the last administration of Xofigo, despite receiving supportive care, further treatment with Xofigo should be discontinued. Patients with evidence of compromised bone marrow reserve should be monitored closely and provided with supportive care measures when clinically indicated. Discontinue Xofigo in patients who experience life-threatening complications despite supportive care for bone marrow failure.

The safety and efficacy of concomitant chemotherapy with Xofigo have not been established. Outside of a clinical trial, concomitant use with chemotherapy is not recommended due to the potential for additive myelosuppression. If chemotherapy, other systemic radioisotopes or hemibody external radiotherapy are administered during the treatment period, Xofigo should be discontinued.

9. Advisory Committee Meeting

The application for Xofigo® (radium Ra 223 dichloride) Injection was not referred to an FDA advisory committee because the application showed improvement in overall survival and did not raise significant safety or efficacy issues.

10. Pediatrics

The pediatric study requirement for this application was waived because necessary studies are impossible or highly impracticable as this indication does not occur in children.

11. Other Relevant Regulatory Issues

DSI Audits: The Clinical Inspection Summary stated that "Based on the review of preliminary inspectional findings for clinical investigators Dr. Johannessen, Dr. Helle, Dr. Parker, and Dr. O'Sullivan, and study sponsor, Bayer HealthCare Pharmaceuticals Inc., the study data collected appear reliable."

There are no other unresolved relevant regulatory issues.

12. Labeling

- Proprietary name: Acceptable
- Physician labeling: Agreement has been reached on the physician labeling.
- Carton and immediate container labels: Agreement has been reached on the carton and container labels
- Patient labeling/Medication guide: Patient labeling or a medication guide are not required.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

  Approval

- Risk Benefit Assessment

  The risk benefit assessment is clearly favorable for the indicated patient population. The improvement in overall survival is clinically and statistically significant with a

median survival of 14.0 and 11.2 months in the Xofigo and placebo arms, respectively. The toxicity profile is acceptable for this improvement in overall survival. The most common adverse reactions in patients receiving Xofigo were nausea, diarrhea, vomiting, and peripheral edema. The most common hematologic laboratory abnormalities in Xofigo-treated patients were anemia, lymphocytopenia, leukopenia, thrombocytopenia, and neutropenia. Grade 3 and 4 adverse events and drug discontinuations were slightly greater in the placebo arm. There is one warning and precaution for bone marrow suppression. Concerns about long-term bone marrow suppression and the potential for secondary malignancies are being addressed by the PMR's.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

  None

- Recommendation for other Postmarketing Requirements and Commitments

  There are three PMR's recommended by the clinical review team.

2041-1 An observational study (N = 1200) to assess the long-term safety of radium Ra 223 dichloride 50 kBq/kg every 4 weeks for 6 doses in patients with castration-resistant prostate cancer with bone metastases.

Final Protocol Submission:	09/2013
First Interim Report Submission:	09/2017
Second Interim Report Submission:	09/2019
Study Completion:	12/2023
Final Report Submission:	09/2024

2041-2 A randomized clinical trial to assess the safety of radium Ra 223 dichloride in patients with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastatic disease.

Final Protocol Submission:	12/2013
Trial Completion:	12/2017
Interim Report Submission:	09/2018
Final Report Submission:	03/2025

2041-3 A trial of the short and long-term safety of re-treatment of patients with castration-resistant prostate cancer with bone metastases with radium Ra 223 dichloride.

Final Protocol Submission:	08/2013
Trial Completion:	09/2016
Interim Report	03/2017
Final Report Submission:	01/2024

There is one postmarketing commitment recommended by the clinical pharmacology review team.

2041-4 Optimize the dosing regimen of Xofigo by conducting a randomized Phase 2 clinical trial to evaluate the efficacy and safety of Xofigo at a dose higher than 50 kBq/kg in patients with castration-resistant prostate cancer with bone metastases.

Depending on the results of the Phase 2 trial, a randomized Phase 3 trial may be needed to further confirm the appropriateness of the dosing regimen determined in the Phase 2 trial.

Final Protocol Submission:	09/2013
Trial Completion:	09/2018
Final Report Submission:	03/2019

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/s/

ROBERT L JUSTICE
05/14/2013