Clinical Review of Efficacy Supplement

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Executive summary:

This submission is an efficacy supplement containing a final Clinical Study Report (CSR) that includes studies conducted in accordance with a pediatric Written Request (WR) for pomalidomide. Two clinical studies were conducted:

- PBTC-043: A dose-finding study to determine the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) of pomalidomide in children with recurrent, progressive, or refractory CNS tumors (n=29)
- BRN-001: An activity-estimating study of pomalidomide in children with recurrent or progressive brain tumors and to identify types of brain tumors most sensitive to pomalidomide treatment (n=46)

FDA issued a WR on November 20, 2015. FDA amended the WR (Amendment #1) on July 13, 2016 to remove the subgroup of patients with low-grade glioma due to limited benefit in the context of available therapy, to update the response criteria, and to add a statement about the inclusion of neonates. On August 30, 2019, FDA amended the WR (Amendment #2) to remove Study 3 based on lack of meaningful antitumor activity observed in Studies 1 and 2 and to change the minimum number of patients needed in the age group 1 to less than 6 years of age (minimum of 4 patients). According to the WR, the CSR was due to FDA by July 19, 2020.

The overall safety data in the two pediatric studies were consistent with the known and well-established safety profile of pomalidomide in adults with multiple myeloma (MM), and no new or unexpected risks were observed. The efficacy results of the two pediatric studies indicate pomalidomide is not effective as a monotherapy in children and young adults with recurrent, progressive, or refractory CNS tumors. No complete responses (CR) were observed in either study; one partial response (PR) was observed in a single patient with a high-grade glioma in BRN-001.

This submission contains a prior approval supplement (PAS) with proposed pediatric labeling to incorporate the findings from the studies above included in the WR. The Division assessed that the

terms of the WR were met by submission of the CSR and proposed labeling changes. The Pediatric Exclusivity Board agreed with granting exclusivity based on fulfillment of the terms of the WR. See the Pediatric Determination Checklist and Template uploaded to DARRTS on October 16, 2020 for additional details.

1. Description of the Pediatric Trials

PBTC-043

Study PBTC-043 was a single-arm, dose escalation trial of pomalidomide in children with recurrent, progressive, or refractory CNS tumors. The study population included patients who were ≥ 3 years and < 21 years of age at study entry with a histologically-confirmed diagnosis of a primary CNS tumor that was evaluable by magnetic resonance imaging (MRI) and was recurrent, progressive, or refractory to standard therapy. Patients must have received standard therapy (or generally accepted upfront therapy if no standard existed) and must have had no curative therapy options available.

The study employed a rolling-six design and initially planned to enroll 36 to 42 patients across treatment sites within the United States (see Table 2 for dosing cohorts). Pomalidomide was administered orally once daily for 21 consecutive days followed by a 7-day rest period, constituting a 28-day cycle. Cycles were repeated every 28 days and could continue for up to 26 cycles unless any of the treatment discontinuation criteria were met. Once the MTD was reached, an expansion cohort was opened where enrollment was stratified based on age (< 12 years versus ≥ 12 years) and steroid use (not on steroids [or on physiologic doses alone] versus those taking therapeutic doses of steroids). The expansion cohort included a minimum of 4 patients in each of the 4 steroid/age strata.

Table 2: Pomalidomide Dosing Regimen (copied from CSR)

Dose Level	Dose
0	1.3 mg/m^2
1[a]	1.9 mg/m^2
2	2.6 mg/m^2
3	3.4 mg/m^2
4	4.4 mg/m^2

[a] Starting dose.

Disease response was assessed by standard MRI of the brain, with gadolinium, performed prior to initiation of therapy, after Cycles 2, 4, 6, and every 3 cycles thereafter until the time of disease progression or completion of treatment. Efficacy was a secondary objective of Study PBTC-043. The

secondary endpoint of response rate was calculated as the percentage of confirmed responders among all response-assessable patients and was summarized by each response category.

BRN-001

Study BRN-001 was a multicenter, open-label, parallel-group study to assess the efficacy, safety, and tolerability of pomalidomide in children and young adults aged 1 year to < 21 years with recurrent or progressive primary brain tumors after at least 1 prior standard therapy.

The study population included patients with a diagnosis of high-grade glioma, medulloblastoma, ependymoma, or diffuse intrinsic pontine glioma (DIPG) that was recurrent or progressive with the primary location in the CNS. Patients were aged 1 year to < 21 years and had received at least 1 prior standard therapy (or generally accepted upfront therapy if no standard therapy existed) and had no known curative therapy. The complete eligibility criteria are described in BRN-001.

The starting dose of pomalidomide in Study BRN-001 was 2.6 mg/m^2/day on Days 1 to 21 of a 28-day cycle. Four consecutive weeks constituted 1 cycle and subsequent cycles immediately followed as long as criteria to continue pomalidomide therapy were met. A cycle may have been repeated every 28 days, for up to 24 cycles or until documented progressive disease (PD), withdrawal of consent/assent, treatment became intolerable, or death, whichever came first.

The study consisted of 4 parallel strata, 1 stratum for each of the following primary brain tumor types: DIPG, ependymoma, high-grade glioma, and medulloblastoma. A Simon's Optimal Two-Stage study design was applied to each stratum, conducted in parallel.

Patients received oral pomalidomide once daily for the first 21 days, followed by a 7-day rest period, in each 28-day treatment cycle for up to 24 cycles or until documented PD, withdrawal of consent/assent, treatment became intolerable, or death, whichever occurred first. Patients who discontinued treatment entered a Follow-up Period which continued with visits (or telephone contact) every 3 months (± 14 days) for up to 5 years from enrollment of the last patient, unless consent/assent was withdrawn, the patient was lost to follow-up, or the patient died.

Brain MRI assessments were conducted during screening (within 21 days prior to the first dose of study drug) and then on Day 1 of Cycles 3, 5, 7, 10, 13, 16, 19, and 22 (or within 7 days prior to dosing), after completion of Cycle 24 (or within 7 days prior), and as clinically indicated. For DIPG patients only, postbaseline brain MRI assessments were performed on Day 1 of Cycles 4, 7, 10, 13, 16, 19, and 22 (or within 7 days prior to dosing), after completion of Cycle 24 (or within 7 days prior), and as clinically indicated.

Spine MRI assessments were also performed during screening (within 21 days prior to the first dose of study drug) for all patients. If no spinal or leptomeningeal disease was present at screening, subsequent spine MRIs were obtained on Day 1 of Cycles 7, 13, and 19 (or within 7 days prior to dosing), after completion of Cycle 24 (or within 7 days prior), and as clinically indicated.

The primary efficacy endpoint, overall response (OR) and long-term stable disease (SD) rate, was defined as the percentage of patients who achieved a CR, PR, or SD maintained for ≥ 6 cycles (≥ 3 cycles for DIPG) as their best response, divided by the total number of patients available for the analysis within the given population.

2. Summary of Trial Results

PBTC-043

A total of 29 patients were enrolled in Study PBTC-043; all 29 enrolled patients received pomalidomide and were evaluable for efficacy, safety, and pharmacokinetic (PK) endpoints.

The most common reason for treatment discontinuation was PD (radiological and/or clinical), which occurred in 24 patients (83%). At the time of the February 28, 2017 cutoff date, 1 patient remained on treatment.

Overall, 16 patients (55%) were female and 13 patients (45%) were male. Patient age at the time of enrollment ranged from 5 to 20 years, with a mean of 12.3 years. The most common initial cancer diagnosis among the 29 enrolled patients was glioblastoma multiforme (5 patients [7%]). Karnofsky/Lansky performance status had a mean (range) of 79.3 (50.0 to 100.0).

Of the 29 treated patients, no patients (0%) experienced a CR or PR (Table 3, copied from CSR). Two patients (6.9%) experienced long-term SD lasting ≥ 6 cycles.

Table 3: Study PBTC-043 Summary of Best Responses by Dose Level

	1.9 mg/m²/day		2.6 mg/m²/day		3.4 mg/m²/day		Total	
	N	% (95% CI[a])	N	% (95% CI[a])	N	% (95% CI[a])	N	% (95% CI[a])
Treated	6	100	18	100	5	100	29	100
Complete Response	0	0 (0.0, 46)	0	0 (0.0, 19)	0	0 (0.0, 52)	0	0 (0.0, 12)
Partial Response	0	0 (0.0, 46)	0	0 (0.0, 19)	0	0 (0.0, 52)	0	0 (0.0, 12)
Stable Disease ≥ 6 Cycles	1	17 (0.4, 64)	1	5.6 (0.1, 27)	0	0 (0.0, 52)	2	6.9 (0.8, 23)
Stable Disease < 6 Cycles	1	17 (0.4, 64)	3	17 (3.6, 41)	0	0 (0.0, 52)	4	14 (3.9, 32)
Progressive Disease[b]	4	67 (22, 96)	13	72 (47, 90)	5	100 (48, 100)	22	76 (57, 90)
Disease Not Assessed	0	0 (0.0, 46)	1[c]	5.6 (0.1, 27)	0	0 (0.0, 52)	1	3.4 (0.1, 18)
Clinical Benefit (CR + PR + [SD ≥ 6 cycles])	1	17 (0.4, 64)	1	5.6 (0.1, 27)	0	0 (0.0, 52)	2	6.9 (0.8, 23)

CI = confidence interval; CR = complete response; N = number of subjects; PR = partial response; SD = stable disease.
[a] Clopper-Pearson 95% CI.
[b] Disease progression included clinical and radiological progression.
[c] The subject expired before a disease assessment was performed.
Source: PBTC-043 Clinical Study Report, Table 11-1.

The RP2D was determined to be 2.6 mg/m^2/day on Days 1 to 28 of a 28 day cycle. The most common adverse events (AE) included decreased lymphocyte count, decreased WBC, decreased neutrophil count, decreased platelet count, anemia, hypocalcemia, hypokalemia, hypoalbuminemia, increase AST/ALT, benign or malignant neoplasms (includes cysts and polyps) and headache. Grade 3 AEs included decreased neutrophil count and decreased lymphocyte count. No deaths were considered treatment related. One patient discontinued due to an AE (decreased platelet count). Overall, the AE profile was as expected for this class of drug and patient population and was similar between dose levels. No new safety signals were identified.

BRN-001

Overall, a total of 57 patients were screened for inclusion in the study and 52 patients received at least one dose of study drug. A total of 46 patients were included in the efficacy population, defined as all patients who received a minimum of 1 cycle of study drug if not discontinued earlier due to disease progression or relapse. The most common reason for treatment discontinuation was PD, which was reported in 42 patients (84.0%) overall. At the time of the March 15, 2019 cutoff date, 2 patients (3.8%) remained on treatment.

In the Safety Population, 33 patients (63.5%) were male and 19 patients (36.5%) were female. The median age (range) was 11.5 years (4 to 18 years), and half of patients (26 patients [50.0%]) were in the age category ≥ 12 years. The majority of patients were white (38 patients [73.1%]). Lansky performance status baseline scores (for patients < 16 years) had a median (range) of 90.0 (50 to 100). Karnofsky performance status baseline scores (for patients ≥ 16 years) had a median (range) of 85.0 (60 to 100). Baseline corticosteroid use was reported for 14 patients (26.9%) (all 14 patients with therapeutic dosing).

None of the groups met the primary endpoint. Two patients (10.5%) in the high-grade glioma group and 1 patient (11.1%) in the ependymoma group had OR (PR) or long-term SD (Table 4, copied from CSR).

Table 4: Study BRN-001 Objective Response and Long-term Stable Disease According to Independent Central Review (Response Population)

Parameter	DIPG (N = 9)	Ependymoma (N = 9)	High-grade Glioma (N = 19)	Medulloblastoma (N = 9)
Objective Response and Long-term Stable Disease Rate – n (%)[a]	0	1 (11.1)	2 (10.5)	0
95% Confidence Interval[b]	(0.0, 33.6)	(0.3, 48.2)	(1.3, 33.1)	(0.0, 33.6)
Objective Response Rate – n (%)[c]	0	0	1 (5.3)	0
95% Confidence Interval[b]	(0.0, 33.6)	(0.0, 33.6)	(0.1, 26.0)	(0.0, 33.6)
Long-term Stable Disease Rate – n (%)[d]	0	1 (11.1)	1 (5.3)	0
95% Confidence Interval[b]	(0.0, 33.6)	(0.3, 48.2)	(0.1, 26.0)	(0.0, 33.6)
Best Overall Response – n (%)				
Complete Response	0	0	0	0
Partial Response	0	0	1 (5.3)	0
Stable Disease	0	3 (33.3)	1 (5.3)	1 (11.1)
SD < 3 Cycles	0	0	0	0
SD ≥ 3 Cycles	0	3 (33.3)	1 (5.3)	1 (11.1)
SD ≥ 6 Cycles	0	1 (11.1)	1 (5.3)	0
Disease Progression	6 (66.7)	6 (66.7)	11 (57.9)	5 (55.6)
Not Evaluable	3 (33.3)	0	6 (31.6)	3 (33.3)

CR = complete response; DIPG = diffuse intrinsic pontine glioma; PR = partial response; SD = stable disease.
[a] Objective response and long-term SD rate were defined as the proportion of subjects who achieved either a CR or PR within the first 6 cycles of study drug (within 3 cycles for DIPG) or a long-term SD, defined as a SD maintained for ≥ 6 cycles (≥ 3 cycles for DIPG), divided by the total number of subjects evaluable for analysis in the disease indication.
[b] Confidence interval obtained using Clopper-Pearson method.
[c] Objective response rate was defined as the proportion of subjects who achieved either a CR or PR within the first 6 cycles of study drug (within 3 cycles for DIPG), divided by the total number of subjects evaluable for analysis in the disease indication.
[d] Long-term SD rate was defined as the proportion of subjects who achieved a long-term SD, defined as a SD maintained for ≥ 6 cycles (≥ 3 cycles for DIPG), divided by the total number of subjects evaluable for analysis in the disease indication.
Source: BRN-001 Clinical Study Report, Table 14.2.1.1.

The common AEs were similar to those observed in the PBTC study described above. Grade 3 or 4 AEs included neutropenia and headache. One death was reported as related to an AE (sepsis) but determined to not be caused by treatment. Five patients discontinued due to an AE (anorectal infection, pneumonia, sepsis, neutropenia, pain, increased intracranial pressure). No secondary malignancies were reported. Overall safety data in Study BRN-001 were consistent with the known safety profile of pomalidomide, and no unexpected safety signals were observed.

3. Proposed Labeling

The following text represents the Sponsor's proposed addition to Section 8.4, Pediatric Use (new text in blue).

~~Safety and effectiveness have not been established in pediatric patients.~~ The safety and effectiveness of POMALYST have not been established in pediatric patients (b) (6)

Reviewers comments:

According to FDA's March 2019 *Guidance for Industry - Pediatric Information Incorporated Into Human Prescription Drug and Biological Products Labeling*: "When it is determined that available evidence regarding safety or effectiveness does not support a pediatric indication, relevant pediatric information related to the unapproved use that is included in labeling generally should be placed only in the Pediatric Use subsection. Negative studies and inconclusive studies should be briefly summarized in this subsection... Furthermore, when the data from negative or inconclusive pediatric studies suggest clinically significant differences in responses (e.g., adverse reactions, pharmacodynamic/pharmacokinetic data) in pediatric patients (either all pediatric patients or in specific pediatric age group(s)) compared with adults, a summary of this information should be included in the Pediatric Use subsection." Therefore, DO2 agrees a description of the inconclusive or negative study should be included in Subsection 8.4.

As per 21 CFR 201.57(c)(9)(iv)(E)): When substantial evidence does not exist to support an indication in a particular pediatric population, or the drug has not been studied in a particular pediatric population, an appropriate statement must be included, such as "Safety and effectiveness in pediatric patients have not been established." Given the lack of evidence to support an indication of POMALYST in pediatric patients, DO2 agrees with the inclusion of this language in section 8.4.

According to 21 CFR 201.57(c)(9)(iv)(A): The terms pediatric population(s) and pediatric patient(s) are defined as the pediatric age group, from birth to 16 years, including age groups often called neonates, infants, children, and adolescents. Therefore, the text was modified to include only patients < 17 years enrolled in the study. The description of the study was modified to provide a more clinically useful description of the study design.

The Guidance for Industry - Pediatric Information Incorporated Into Human Prescription Drug and Biological Products Labeling March 2019 states, "when the data from negative or inconclusive

pediatric studies suggest clinically significant differences in responses (e.g., adverse reactions, pharmacodynamic/pharmacokinetic data) in pediatric patients compared with adults, a summary of this information should be included in the Pediatric Use subsection." Although no clinically significant differences were observed, FDA recommended including a statement that no new adverse reactions were observed to provide additional information to healthcare providers and recommended to modify the proposed statement describing the safety profile so as not to imply a cross-study comparison from adults to pediatrics.

FDA's *Guidance for Industry - Pediatric Information Incorporated Into Human Prescription Drug and Biological Products Labeling* recommends including pharmacokinetic data when data reflect safety concerns related to dosing (e.g., the clearance of the drug is low, resulting in higher exposure). Additionally, if the number of pediatric patients or age range for the pediatric patients in the pharmacokinetic assessment is different than those of the study, it is recommended to include the number of pediatric patients and their age range in these statements. Therefore, FDA recommended additional changes to comply with these recommendations.

The agreed-upon labeling is as follows:

> *The safety and effectiveness of POMALYST have not been established in pediatric patients. The safety and effectiveness were assessed but not established in two open-label studies: a dose escalation study in 25 pediatric patients aged 5 to <17 with recurrent, progressive or refractory CNS tumors [NCT02415153] and a parallel-group study conducted in 47 pediatric patients aged 4 to <17 years with recurrent or progressive high-grade glioma, medulloblastoma, ependymoma, or diffuse intrinsic pontine glioma (DIPG) [NCT03257631]. No new safety signals were observed in pediatric patients across these studies.*
>
> *At the same dose by body surface area, pomalidomide exposure in 55 pediatric patients aged 4 to < 17 years old was within the range observed in adult patients with MM but higher than the exposure observed in adult patients with KS [see Clinical Pharmacology (12.3)].*

4. Fulfillment of the Written Request

The Division of Oncology 2 reviewed the primary Clinical Study Report (CSR) and the labeling supplement submitted to NDA 204026 on May 20, 2020. The Division assessed that the terms of the Written Request had been met based on the information in the primary CSR and the Pediatric Exclusivity Board determined that exclusivity could be granted.

5. Conclusions and Regulatory Action

The Division agrees with approval of the supplement with the agreed-upon labeling and with the Pediatric Exclusivity Board's recommendation that pediatric exclusivity be granted based upon fulfillment of the terms of the Written Request.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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