Labeling supplement – Clinical Review

Application Number	BLA 125477
Supplement Number	S39
Submission Date	December 18, 2020
Received Date	January 5, 2020
PDUFA Goal Date	June 18, 2021
Labeling Meeting(s)	May 14, 2021
Proper Name	Cyramza
Non-proprietary Name	Ramucirumab
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This supplement is to include pediatric information in Section 8 of the Cyramza label. The changes are supported by the results of an open-label, safety and pharmacokinetic study [NCT02564198] , I4T-MC-JVDA (ADVL1416), "A Phase 1 Study of Ramucirumab, A Human Monoclonal Antibody Against the Vascular Endothelial Growth Factor-2 (VEGFR-2) Receptor In Children With Refractory Solid Tumors, Including CNS Tumors". Study ADVL1416 was conducted in response to a Written Request approved in December 16, 2017 and amended in March 21, 2019 (IND 11856) Lilly does not propose to include an indication for pediatric patients. This study was conducted by the Children's Oncology Group and participation in the study was limited to the COG Phase 1 Consortium.

1. Study design

ADVL1416 was a two-part trial. In Part A, a rolling 6 design was used to determine the maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D) of ramucirumab given intravenously every other week in children with solid tumors, excluding CNS tumors. Once the RP2D was determined in Part A, Part B was opened to enroll children with recurrent or refractory CNS solid tumors who received ramucirumab at the MTD or RP2D.

The primary objectives were to

- estimate the MTD and/or RP2D of ramucirumab administered as an intravenous infusion over 60 minutes, every 2 weeks, to children with recurrent or refractory solid tumors.
- determine the tolerability of the MTD and/or RP2D of ramucirumab in children with recurrent or refractory CNS tumors.
- define and describe the toxicities of ramucirumab administered on this schedule.
- characterize the pharmacokinetics and immunogenicity of ramucirumab in children with recurrent or refractory solid tumors including CNS tumors.

The secondary objectives were to

- preliminarily define the antitumor activity of ramucirumab within the confines of a Phase 1 study.
- explore changes in tumor perfusion and vascularity evaluated by dynamic contrast-enhanced magnetic resonance imaging (DC-MRI).

Main eligibility criteria were

- Ages ≥ 12 months and ≤ 21 years of age
- Diagnosis:
    - Part A: recurrent or refractory non-CNS solid tumors are eligible.
    - Part B: Patients with recurrent or refractory CNS tumors
- Measurable or evaluable disease
- Patient's current disease state must be one for which there is no known curative therapy or therapy proven to prolong survival with an acceptable quality of life.
- Karnofsky ≥ 50% for patients > 16 years of age and Lansky ≥ 50 for patients ≤ 16 years of age.
- Adequate bone marrow function defined as ANC ≥ 1000/mm^3, platelet count ≥ 100,000/mm^3 (transfusion independent), hemoglobin ≥ 8.0 g/dL at baseline (may receive RBC transfusions).
- Adequate renal function defined as: urine protein: ≤ 30 mg/dl in urinalysis or ≤ 1+ on dipstick, unless quantitative protein is < 1000 mg in a 24 h urine sample; creatinine clearance or radioisotope GFR ≥ 70ml/min/1.73 m^2 or serum creatinine based on age/gender following the Schwartz formula.
- Adequate liver function defined as: bilirubin ≤ 1.5 x ULN for age, ALT ≤ 110 U/L and serum albumin ≥ 2 g/dL.
- Adequate cardiac function defined as: shortening fraction of ≥ 27% by echocardiogram, or ejection fraction of ≥ 50% by gated radionuclide study.
- Adequate blood pressure function defined as: BP ≤ the 95th percentile for age, height, and gender and not receiving medication for treatment of hypertension.
- Adequate coagulation defined as INR ≤ 1.5
- Patients who were receiving anti-hypertensive medications for control of blood pressure; therapeutic anticoagulation with heparin, low-molecular weight heparin or coumadin; belimumab; bisphosphonate derivatives were not eligible.
- Standard criteria for ramucirumab were included.

Patients were premedicated with diphenhydramine (1 mg/kg, maximum dose 50 mg) (or alternative antihistamine) within 30 to 60 minutes prior to each infusion with ramucirumab. Ramucirumab was administered as an intravenous infusion over 60 minutes every other week for 3 infusions over a 6-week period (42 days). Up to 8 cycles were allowed.

The rolling six phase 1 trial design was used for the conduct of this study. The starting dose of ramucirumab was 8 mg/kg (dose level 1) with dose levels for subsequent escalation to 12 mg/kg.

After accrual to dose level 2 was completed, PK comparisons from dose levels 1 and 2 were performed to determine the expansion cohort, planned at the lowest tolerable dose at which Cmin of ≥ 50 ug/mL has been achieved in at least 5 out of 6 evaluable patients to acquire PK data in a representative number of young patients (i.e. patients < 12 years old). If at least 10 out of the total 12 evaluable patients have a steady state concentration of ramucirumab greater than 50 μg/mL, then the RP2D had been defined.

The safety monitoring included assessment of growth toxicity. Patients with an open tibial growth plate underwent repeat plain AP radiographs of the same tibial growth plate prior to cycles 2, 5 and every 6 months. Patients with evidence of growth plate thickening or other changes had a knee MRI performed to further assess the degree of physeal pathology and underwent more frequent x-ray follow up at least every 3 cycles or as clinically indicated. MRI was performed without contrast.

2. Study results

A total of 29 patients were treated: 8 patients in Part 8 at dose level 1 (8 mg/kg IV Q2W): 15 patients at dose level 2 (12 mg/kg IV Q2W), and 6 patients in Part B. At the time of data cut-off, all 29 patients were off study treatment. One patient in Part A Dose Level 2 completed all 8 cycles (1 cycle = 42 days) of study treatment defined by the protocol.

Of the 23 patients with recurrent or refractory non-CNS solid tumors treated in Part A, 13 were male and 10 were female. The median age of the patients was 15 years (range 3 to 21 years) with 15 patients (65.2%) who were 12 years and above and 8 patients (34.8%) less than 12 years. The median body weight of the patients was 47.6 kg (11.3 - 91.4). Of the 6 patients with recurrent or refractory CNS solid tumors treated in Part B, 4 were male and 2 were female with a median age of 11.5 years (range 1 to 15 years) with 3 patients (50%) who were 12 years and above and 3 patients (50%) less than 12 years. The median body weight of the patients was 35.2 kg (8.7-77.5).

In Part A1, patients received a median of 4.5 doses of ramucirumab. The relative median dose intensity of ramucirumab was 99.96% (range 98.79 to 100.49). In Part A2, patients received a median of 3 doses of ramucirumab. The relative median dose intensity of ramucirumab was 99.96% (range 98.79 to 100.49). For PK analyses, please refer to the clinical pharmacology review.

Table 1, copied from the submission, summarizes the major safety results.

Table 1: Overview of Adverse Events

Number of Patients[a]	Dose Level 1 (8 mg/kg) N=8	Dose Level 2 (12 mg/kg) N=21			Overall Total N=29
	Part A N=8 n (%)	Part A N=15 n (%)	Part B N=6 n (%)	Total N=21 n (%)	n (%)
Patients with ≥1 TEAE	8 (100)	15 (100)	6 (100)	21 (100)	29 (100)
Related to study treatment[b]	7 (87.5)	14 (93.3)	6 (100)	20 (95.2)	27 (93.1)
Patients with ≥1 CTCAE Grade ≥3 TEAE	5 (62.5)	8 (53.3)	3 (50.0)	11 (52.4)	16 (55.2)
Related to study treatment[b]	1 (12.5)	3 (20.0)	1 (16.7)	4 (19.0)	5 (17.2)
Patients with ≥1 SAE	3 (37.5)	7 (46.7)	2 (33.3)	9 (42.9)	12 (41.4)
Related to study treatment[b]	2 (25.0)	2 (13.3)	1 (16.7)	3 (14.3)	5 (17.2)
Patients who discontinued study treatment due to an AE	0	1 (6.7)	0	1 (4.8)	1 (3.4)
Related to study treatment[b]	0	1 (6.7)	0	1 (4.8)	1 (3.4)
Patients who discontinued study treatment due to SAE	0	0	0	0	0
Patients who died due to AE on study treatment	0	0	0	0	0
Subjects who died due to AE within 30 days of discontinuation from study treatment	0	0	0	0	0

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; N = number of patients in safety population; n = number of patients in the specified category; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

[a] Subjects may be counted in more than 1 category.

[b] Includes events that were considered to be related to study treatment as judged by the investigator.

Source: smae1.rtf.

The overall TEAE profile observed in pediatric and young adult patients at both dose levels generally reflects the known safety profile of ramucirumab monotherapy in adult patients and/or events expected to occur within the disease setting of advanced cancer (CNS and non-CNS). While the types of TEAEs are similar and consistent with the safety profile of ramucirumab, there was a tendency for a higher frequency of TEAEs with the higher dose, which was chosen for the dose expansion and currently ongoing studies in patients with synovial sarcoma and small round cell desmoplastic tumors (Study 2 of the Written Request). The only TEA that resulted in treatment discontinuation was a Grade 2 DLT of proteinuria reported in Part A at Dose Level 2. The most common any-grade TEAEs across the study were AST increased (15 patients, 51.7%), anemia (13 patients, 44.8%) and, vomiting and nausea (12 patients, 41.4% each). Of the 16 patients (55.2%) who experienced Grade ≥3 TEAEs, only 1 patient experienced a Grade 4 event and the remaining were Grade 3 events. Grade 3 TEAEs observed in 2 or more patients were lymphocyte count decreased (4 patients, 13.8%), pyrexia, hypoxia, and dyspnea (2 patients, 6.9% each).

Adverse events of special interest

A total of 11 (37.9%) experienced any-grade bleeding/hemorrhage events(3 [37.5%] at Dose Level 1 and 8 [38.1%] at Dose Level 2). All were low-grade events. Events

observed in 2 or more patients were hematuria (7 patients, 24.1%), epistaxis and contusion (2 patients, 6.9% each).

A total of 10 (34.5 %) of the 29 patients experienced any-grade hypertension (2 [25%] at Dose Level 1 and 8 [38.1%] at Dose Level 2). Of the 2 patients with hypertension at Dose Level 1, 1 patient experienced a Grade 3 event that was controlled with antihypertensive medications. Each of the 8 patients who experienced hypertension at Dose Level 2 had low-grade events for which 1 patient received antihypertensive medication.

A total of 9 (31.0%) of the 29 patients experienced any-grade proteinuria (2 [25%] at Dose Level 1 and 7 [33.3%] at Dose Level 2). All were low-grade events.

One patient in Part A at Dose Level 2 experienced a Grade 2 ejection fraction decreased One patient in Part A Dose Level 1 experienced a healing complication event of Grade 1 impaired healing.

Of the 29 patients treated, 11 (37.9%) had closed growth plates and 18 (62.1%) had open growth plates at baseline. Of the 18 patients with an open growth plate, 13 patients had a follow-up growth plate radiograph prior to starting Cycle 2. Of these 13 patients, 1 patient in Part B had a progressive widening of the distal femoral growth plate that was apparent in 2 successive follow up radiographs. Long-term outcome remains unknown.

No tumor responses were observed in this study.

Summary

- Lilly identified 12 mg/kg IV when given Q2W as the RP2D for ramucirumab in children and young adults. Although the safety profile is consistent across doses, there was a tendency to higher rate of AEs in the 12 mg/kg dose when compared to the 8 mg/kg dose.
  Reviewer's note: On November 14, 2018, a Type B teleconference (under preIND 141186) between Lilly and FDA was held to discuss the available ramucirumab data from Part A of Study 1, reach agreement on dose selection and design for Study 2 (CAMPFIRE, Study NCT04145700), and discuss the proposed changes to the ramucirumab pediatric WR (please refer to the meeting minutes). FDA expressed concerns regarding the selection of the RP2D but based on the observed PK profile and monitoring measures, Lilly and COG/ CAMPFIRE are using the 12 mg/kg dose in combination with chemotherapy.

- Overall, no new safety signals were observed in this study as compared to the known safety profile of ramucirumab monotherapy in the adult population. These findings were consistent for patients with CNS and non-CNS recurrent/refractory tumors.

- The PK profile of ramucirumab in pediatric patient population was consistent with the established PK profile of ramucirumab in studies with adult patients. Ramucirumab exposure in pediatric patients were similar to ramucirumab exposure reached in adult patients at the corresponding 8 mg/kg and 12 mg/kg doses. Ramucirumab exposure following 12 mg/kg dose was similar across the age range (≥12 months to ≤21 years) of the pediatric patient enrolled at this dose.

- The immunogenicity profile of ramucirumab was consistent with the low rate of immunogenicity established for ramucirumab in adults.

3. Labeling

The following table summarizes Lilly's proposed changes to the label and FDA's edits.

Lilly's proposed language
8.4 Pediatric Use The safety and effectiveness of CYRAMZA in pediatric patients have not been established. The safety and pharmacokinetics (PK) of CYRAMZA, as a single agent, were (b) (4) in a multicenter, open-label, (b) (4) study (b) (4) . (b) (4) . (b) (4) .
Agreed upon language*
The safety and effectiveness of CYRAMZA in pediatric patients have not been established. The safety and effectiveness of CYRAMZA as a single agent were assessed but not established in a single-arm, multicenter, open-label study [NCT02564198] in 23

pediatric patients aged x months to 16 years with relapsed or refractory solid tumors. The effect on open tibial growth plates in pediatric patients who received CYRAMZA has not been adequately studied; however, one patient in this study had progressive widening of distal femoral growth plate. The pharmacokinetics for these pediatric patients was within the range of the values previously observed in adults given the same dose per body weight.

* At the time of completion of this review, labeling negotiations were ongoing. This is draft proposed language. The approved labeling may be found at drugs@FDA.

4. Action

The clinical review team recommends approval of the supplement. This approval does not fulfill the terms of the Written Request. The approved labeling may be found at drugs@FDA.

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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