BLA 125477
IND 011856

WRITTEN REQUEST – AMENDMENT 3

Eli Lilly and Company
Attention: Nancy C. Cress, BSc
Associate Director, Global Regulatory Affairs-NA
Lilly Corporate Center
Drop Code 2543
Indianapolis, IN 46285

Dear Ms. Cress:[1]

Please refer to your correspondence dated May 12, 2023, requesting changes to FDA's December 16, 2017, Written Request for pediatric studies for Cyramza (ramucirumab).

We have reviewed your proposed changes and are amending the Written Request. All other terms stated in our Written Request issued on December 16, 2017, and as amended on March 21, 2019, and March 8, 2022, remain the same. (Text added is underlined. Text deleted is strikethrough.)

- *Timeframe for submitting reports of the study(ies):* Reports of the studies that meet the terms of the Written Request dated December 16, 2017, as amended by this letter and by previous amendment(s) dated March 21, 2019, must be submitted to the Agency on or before January 1, 2021 (Study 1), and on or before January 1, ~~2024~~2025 (Study 2), in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act. Please keep in mind that pediatric exclusivity can attach only to existing exclusivity, if any, 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.

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 December 16, 2017, as amended by this letter and by previous amendments dated March 21, 2019, and March 8, 2022, must be submitted to the Agency on or before January 1, 2025, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

If FDA has not determined whether ramucirumab is eligible for reference product exclusivity under section 351(k)(7) of the PHS Act, you may submit a request for reference product exclusivity with supporting data and information to the Agency. Note that neither the issuance of this Written Request amendment, nor any request for exclusivity made by you, confers or otherwise implies that you are eligible for reference product exclusivity under section 351(k)(7) of the PHS Act.

Submit reports of the studies as a supplement to an approved BLA 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 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.[2]

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.

[2] https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm316937.htm

If you have any questions, contact Amy Sessums, Regulatory Project Manager, at Amy.Sessums@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Martha Donoghue, MD
Acting Associate Director, Pediatric Oncology
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURE:

- Complete Copy of Written Request as Amended

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We have reviewed your proposed changes and are amending the Written Request. All other terms stated in our Written Request issued on December 16, 2017, and as amended on March 21, 2019, and March 8, 2022, remain the same.

Despite the dramatic improvement in survival observed in the last 3-4 decades as a result of the multidisciplinary approach applied overall to pediatric solid malignancies, the outcome of patients with recurrent synovial sarcoma and desmoplastic round cell tumors remains poor. Synovial sarcoma accounts for approximately 6% of all soft tissue sarcomas and can occur at all ages, however, there is a predilection for young adults in their third decade. The incidence is approximately 0.5 to 0.7/million people younger than 20 years of age. The tumor can arise at all sites throughout the body but is most often located in the extremities. Synovial sarcomas show a range from indolent to highly aggressive behavior, resulting in an overall poor prognosis, with a 5-year cancer-specific survival of 66%. The standard, multimodality treatment includes surgical resection, radiation therapy and/or chemotherapy. Synovial sarcomas are only moderately responsive to ifosfamide-based chemotherapy (typically in combination with doxorubicin). Despite initial treatment, approximately 25% to 40% of pediatric patients with synovial sarcoma who initially present with local tumors develop recurrent or progressive disease, and in these patients, the 5-year survival is only 30% to 42%.

DSRCT is a rare disease of children, adolescents, and young adults that begins and spreads on the peritoneal surfaces. Less than 200 cases are reported in the world literature. Despite multimodal treatment, including aggressive surgical excision, chemotherapy, and radiotherapy, DSRCT has only a 15% overall survival rate at 5

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

years. Patients typically are aged 5–30 years at presentation. Desmoplastic small round cell tumor is almost always disseminated regionally; patients usually present with diffuse abdominal metastatic disease similar in gross appearance to carcinomatosis. There is no standard approach for the treatment of desmoplastic small round cell tumor; aggressive surgical debulking is the mainstay of the treatment strategy generally followed by multimodality treatment with radiation and/or chemotherapy.

Ramucirumab is a human receptor-targeted monoclonal antibody that specifically binds Vascular Endothelial Growth Factor (VEGF) Receptor 2. The binding of ramucirumab to VEGF Receptor 2 prevents its interaction with activating ligands (VEGF-A, VEGF-C, and VEGF-D). As a result, ramucirumab inhibits ligand-stimulated activation of VEGF Receptor 2 and its downstream signaling components.

The safety, pharmacokinetics (PK), and clinical activity of ramucirumab have been assessed in adults in a completed dose-finding study and several clinical studies which resulted in the approval of ramucirumab for the treatment of metastatic colorectal cancer, non-small cell lung cancer, and gastric cancer; further investigations are ongoing in adult patients with several diseases. A dose-finding study in the pediatric population which includes a limited expansion component in patients with primary central nervous system (CNS) tumors was initiated prior to the receipt of the PPSR and is included in this Written Request, as data will be used for dose determination in the subsequent combination study and contribute to informative pediatric labeling.

Ramucirumab is administered intravenously. The excipients used in the formulation are suitable for pediatric use.

There have been no clinical trials conducted for ramucirumab in adults with synovial sarcoma or DSRCT. The clinical experience in pediatric patients is limited and is still under investigation. Efficacy in pediatric patients aged ≥4 months to <18 years cannot be extrapolated from adult data and will be determined by the studies outlined in the Written Request.

FDA is not requesting studies in neonates because relapsed solid tumors, including those primary in the CNS, and both synovial sarcoma or DSRCT are not diagnosed in neonates.

To obtain needed pediatric information on ramucirumab and its potential role in the treatment of synovial sarcoma and DSRCT, 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 FD&C Act), as amended by the Food and Drug Administration Amendments Act of 2007, and pursuant to section 351(m) of the Public Health Service Act (the PHS Act), as amended by the Biologics Price Competition and Innovation Act of 2009, that you submit information from the studies described below.

- Nonclinical study(ies):

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.

- Clinical studies:

Study 1 (JVDA- ADVL1416): Multicenter, open-label, dose-finding study of ramucirumab monotherapy in children ages ≥12 months old and ≤ 21 years of age with recurrent solid tumors. The study being conducted by the Children's Oncology Group Phase 1 Consortium and consists of two parts. Part A is a PK, dose-finding, safety, and preliminary efficacy study in patients with recurrent or refractory non-CNS solid tumors using a rolling 6 design.

Part B includes additional safety and imaging evaluation in approximately 6 patients with recurrent or refractory CNS solid tumors.

Indication to be studied:
- Part A: patients with non-CNS refractory solid tumors
- Part B: Patients with recurrent or refractory CNS solid tumors.

Number of patients to be studied:
- Part A: Minimum of 23 patients
- Part B: Minimum of 6 patients

Age groups in which studies will be performed:
Patients ≥12 months to ≤21 years of age

Objectives of the study:
- Primary Objectives
  - To estimate the maximum tolerated dose and/or recommended Phase 2 dose of ramucirumab administered as an intravenous infusion over 60 minutes, every 2 weeks, to children with recurrent or refractory solid tumors.
  - To define and describe the toxicities of ramucirumab administered on this schedule.
  - To characterize the pharmacokinetics and immunogenicity of ramucirumab in children with recurrent or refractory solid tumors including CNS tumors.

- Secondary Objectives
  - To preliminarily define the antitumor activity of ramucirumab.

- Exploratory Objectives
  - To explore the pharmacodynamics effects of ramucirumab in this pediatric population.

- To explore potential predictive biomarkers relevant to pediatric cancers, cancer related conditions, ramucirumab and angiogenesis.

Regimen:
The study has already enrolled 18 patients who received intravenous ramucirumab 8 mg/kg or 12 mg/kg every 2 weeks. A third dosing level may be considered after analysis of PK data.

Drug-specific safety concerns:
Standard vital-sign and laboratory parameter monitoring will be included in all pediatric studies.

The following adverse events are adverse events of special interest for ramucirumab:
infusion-related reactions, hypertension, proteinuria, arterial thromboembolic events, venous thromboembolic events, bleeding/hemorrhagic events, gastrointestinal perforation, congestive heart failure, wound healing complications, fistula, live failure/liver injury, and reversible posterior leukoencephalopathy syndrome. These adverse events are associated with the administration of monoclonal antibodies (infusion-related reactions) or inhibition of the VEGF- or VEGF Receptor 2-mediated angiogenesis and reported for other agents inhibiting this pathway. These adverse events will be actively monitored.

Based on its mechanism of action, ramucirumab could cause fetal harm. Females of reproductive potential should be advised of the potential risk for maintaining pregnancy, risk to the fetus, and risk to newborn and infant development and to use effective contraception during ramucirumab therapy and for at least 3 months following the last dose of ramucirumab.

In addition to these specific safety concerns associated with the use of ramucirumab in adults, in preclinical toxicology studies in cynomolgus monkeys, the key adverse effects were identified in the kidney and long bone growth plate.

Additional monitoring for growth and development including detailed, protocol-specified radiographic studies of long bone growth plates will be performed longitudinally to assess any effect on bone growth.

Study 2 DSRCT: J1S-MC-JV01 (JV01) and SS: J1S-MC-JV02 (JV02): Multicenter, randomized, controlled study in pediatric and young adult patients with relapsed, recurrent or refractory synovial sarcoma or DSRCT. A total of 30 patients will be enrolled in each disease-specific cohort and randomized 2:1 to receive ramucirumab at the dose determined in Study 1 plus the selected backbone therapy or chemotherapy alone. Patients must have received at least one prior line of systemic therapy.

Indications to be studied:
- Relapsed, recurrent of refractory synovial sarcoma
- Relapsed, recurrent of refractory DSRCT.

Number of patients to be studied:
A minimum of 60 patients (30 in each disease-specific cohort)

Age groups in which the indications will be studied:
Patients older than 12 months and ≤29 years of age. The study must enroll a minimum of 5 patients ≤17 years old with synovial sarcoma and 10 patients ≤17 years old with DSRCT.

Objectives and endpoints of the study:
To evaluate the clinical benefit of ramucirumab when added to chemotherapy relative to chemotherapy alone for the treatment of patients with relapsed or recurrent synovial sarcoma and DSRCT. The primary study endpoint is progression- free survival (PFS) in each disease-specific cohort as assessed by the RECIST 1.1 criteria. Secondary endpoints include common measures of safety/tolerability and additional efficacy endpoints of overall response rate, duration of response and complete response. Exploratory endpoints include overall survival and the difference in proportion of patients who become eligible for surgical resection of lesions due to documented tumor response while on study therapy.

Treatment:
DSRCT: Ramucirumab dosing regimen of 12 mg/kg IV once every 2 weeks (Q2W) in combination with vinorelbine (25 mg/m2 IV on Days 1, 8, 15 of a 28-day [4-week] cycle) and cyclophosphamide (25 mg/m2 PO once daily [QD]).

SS: Ramucirumab dosing regimen of 9 mg/kg IV on Days 1 and 8 of a 3-week cycle in combination with gemcitabine (900 mg/m2 IV on Days 1 and 8 of a 3-week cycle) and docetaxel (75 mg/m2 IV on Day 8 of a 3-week cycle).

To rule out excessive toxicity associated with the experimental ramucirumab-based combinations, safety lead-in periods will be observed separately per tumor cohort via the rolling-six decision.

Timing of assessments:
Progression-free survival (PFS) will be assessed every 2 cycles for patients with DSRCT. PFS will be assessed every 3 cycles for patients with SS.

Drug-specific safety concerns:
Refer to previous section under Study 1.

Statistical information, including power of study and statistical assessments:

PFS will be evaluated using a Bayesian analysis. At least thirty patients per disease-specific cohort will be concurrently randomized (2:1) to treatment versus control, with Bayesian augmentation of the control arms based on outcomes observed in historical control subjects. Randomization and subsequent comparative efficacy analysis (experimental versus control) will be performed separately within each tumor cohort to facilitate histology-specific conclusions and treatment with tumor-specific backbone/control therapies.

The primary endpoint is PFS and the primary analysis of PFS must be based upon a prespecified number of events in each cohort. The study success criteria were calibrated to target a clinically meaningful improvement in median PFS of at least 3 months.

An interim futility analysis is planned and will be triggered when approximately 24 total PFS events (defined as an objective response of progression of disease or death from any cause) have been observed across Study JV01 and Study JV02, with a minimum of 8 events from each study. As designed, a minimum of 8 patients must be enrolled in each disease-specific cohort. While a single joint Bayesian hierarchical model will be fit to the PFS data from both Studies JV01 and JV02, study-specific futility conclusions will be made based on tumor-specific output obtained from the Bayesian model as described in the protocol and statistical analysis plan.

- If futility criteria for either study are met, the FDA will be consulted regarding review of the results, including a descriptive analysis of the observed number of both patients with disease progression and deaths by arm. The FDA's concurrence will be obtained prior to stopping the study. If futility criteria are met, there is potential that less than 30 patients may be enrolled in either or both disease-specific cohorts.
- If futility criteria are not met, each study will continue to its planned primary analysis of PFS which will be triggered when PFS events have occurred for approximately 80% of the enrolled patients (across both Study JV01 and Study JV02), as described in the statistical analysis plan. A progress update for obtaining real-world data will be provided to the FDA in advance of the planned primary analysis.

- 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.

- 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.

- Biological product information:
  - dosage form: ramucirumab is supplied in 50 mL single use vials. Each vial contains 500 mg of ramucirumab at a concentration of 10 mg/mL in a sterile, preservative-free solution.
  - route of administration: intravenous administration
  - regimen
    - Study 1: intravenous ramucirumab 8 mg/kg or 12 mg/kg every 2 weeks.
    - Study 2: intravenous ramucirumab 9 mg/kg or 12 mg/kg every 2 weeks.

- Labeling that may result from the study(ies): You must submit proposed pediatric labeling to incorporate the findings of the study(ies). Under section 505A(j) of the FD&C Act, regardless of whether the study(ies) demonstrate ramucirumab is safe, pure, and potent, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study(ies). Under section 505A(k)(2) of the FD&C Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the study(ies).

- 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 study(ies) 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 FD&C 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 600.80 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 https://www.fda.gov/media/83880/download 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 https://www.fda.gov/regulatory-information/search-fda-guidance- documents/providing-regulatory-submissions-electronic-format-certain-human- pharmaceutical-product-applications.

- Timeframe for submitting reports of the study(ies): Reports of the studies that meet the terms of the Written Request dated December 16, 2017, as amended by this letter and by previous amendment(s) dated March 21, 2019, must be submitted to the Agency on or before January 1, 2021 (Study 1), and on or before January 1, 2025 (Study 2), in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act. Please keep in mind that pediatric exclusivity can attach only to existing exclusivity, if any, 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, if there is unexpired exclusivity that 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 exclusivity is otherwise due to expire.

Submit reports of the studies as a supplement to an approved BLA 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 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:

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- 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.[2]

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, contact Amy Sessums, Regulatory Project Manager, at Amy.Sessums@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Martha Donoghue, MD
Acting Associate Director, Pediatric Oncology
Office of Oncologic Diseases
Center for Drug Evaluation and Research

[2] https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm316937.htm

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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/

MARTHA B DONOGHUE
08/04/2023 07:41:38 AM