DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761090

WRITTEN REQUEST – AMENDMENT #1

Dyax Corporation
300 Shire Way
Lexington, MA 02421

Attention: Ms. Joyel C. Morris
Associate Director, Global Regulatory Affairs

Dear Ms. Morris:

Please refer to your correspondence dated December 18, 2018, requesting changes to FDA's July 20, 2018, Written Request for pediatric studies for lanadelumab.

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 July 20, 2018, remain the same. (Text added is underlined. Text deleted is strikethrough.)

- *Clinical studies:*

Study 1: A 12 month, open-label safety, pharmacokinetics (PK), and clinical outcome study
in children ages 2 to ~~11~~ <12 years with Type I or II hereditary angioedema with ≥ 1 hereditary angioedema attack per 3 months during an observation run-in period. The study design shall be specified in an agreed-upon protocol with the Division.

☐ Efficacy in 2 to ~~11~~ <12year old patients will be supported by PK exposure matching and extrapolation of efficacy from adolescent patients 12 to 17 years of age and adults. The pathophysiology of HAE due to C1-INH deficiency in children is similar to that of adults; therefore, the efficacy of lanadelumab is expected to be similar in the pediatric population with comparable exposure.

- *Objective of the study:*

To evaluate the safety, PK, and clinical outcomes of lanadelumab in children 2 to ~~11~~ <12 years of age with HAE.

- *Patients to be studied:*

  - *Age group in which study will be performed*: 2 to ~~11~~ <12 years of age

  - *Number of patients to be studied:* At least ~~20~~ ~~10~~20 patients total with a minimum of 5~~10~~ patients in each age cohort of 2 to 8 years of age and 9 to <12~~11~~ years of age. A minimum of ~~15~~ 15~~7~~ patients must complete 1 year of treatment.

- *Study endpoints:*

☐ *Pharmacokinetic/Pharmacodynamic (PD) Endpoints:*

The pharmacokinetic endpoints for this study must include maximum observed plasma concentration (C_{max}) at steady-state, average plasma concentration (C_{avg}) at steady-state, trough plasma concentration (C_{trough}) at steady-state, time to reach maximum plasma concentration (t_{max}), area under the plasma concentration time curve over the dosing interval (AUC_{tau}) at steady-state, elimination half-life ($t_{1/2}$), apparent total plasma clearance after extravascular administration (CL/F), apparent volume of distribution (V/F). The pharmacodynamic endpoints for this study should include plasma levels of cleaved high molecular weight kininogen (cHMWK), C1 esterase inhibitor (C1-INH), complement component 4 (C4), and anti-drug antibody titers. PK sampling must enable estimation of primary PK parameters with reasonable precision.

☐ *Clinical Outcome Endpoints:*

☐ The primary clinical outcome endpoint will be the number of investigator confirmed HAE attacks during the entire treatment period and must be assessed by parent/caregiver reporting with verification by the investigator.

☐ Important secondary endpoints must include normalized number of investigator-confirmed HAE attacks during each ~~dosing interval treatment~~efficacy evaluation period by dosing regimen and overall as well as time to first HAE attack, number of investigator-confirmed HAE attacks requiring acute therapy, number of moderate or severe investigator-confirmed HAE attacks, and proportion of attack-free patients ~~during the entire treatment period and~~ during each ~~dosing interval treatment~~efficacy evaluation period by dosing regimen and overall. HAE attacks will be monitored daily and recorded as they occur, and must be assessed by parent/caregiver reporting with verification and confirmation by the investigator.

☐ Measures of compliance must include ~~monitoring~~ monitoring of a ~~daily~~ diary to be completed by parents/caregivers to record symptoms and HAE attacks as they occur and medication administration as well as tracking all used and unused vials for drug accountability.

☐ *Safety Endpoints:*
☐ Safety outcomes must include: adverse events, adverse events of special interest (hypersensitivity reactions, ~~injection site reactions,~~ abnormal bleeding events), vital signs (blood pressure, heart rate, temperature, respiratory rate), ~~physical exam,~~ clinical labs (hematology, clinical chemistry including LFTs, coagulation).

☐ The following adverse events must be actively monitored: elevated liver function tests. AST, ALT, and total bilirubin should be assessed at least every 2 months. Liver function abnormalities must be monitored until resolution or stabilization.

☐ The following adverse events of special interest must be captured when spontaneously reported: ~~injection site reactions,~~ hypersensitivity reactions, bleeding or hypercoagulable events

- *Biological product information:*
- ~~*d*~~*osage form:* 1mL (150mg/mL) solution for injection in a 2mL glass vial. Each vial contains a slight overfill.
- *route of administration:* subcutaneous
- *regimen:* ~~to be agreed upon with the Division~~
  6 to <12 years: 150mg every 2 weeks (q2w)
  2 to <6 years: 150mg every 4 weeks (q4w)

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 July 20, 2018, as amended by this letter must be submitted to the Agency on or before September 1, 2023, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

If FDA has not determined whether lanadelumab 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 addition, send a copy of the cover letter of your submission to the Office of New Drugs, Immediate Office, Therapeutic Biologics and Biosimilars Team, 10903 New Hampshire Ave, Building 22, Mail Stop 6411, Silver Spring, MD 20993. If you wish to fax it, the fax number is 301-796-9855.

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 Colette Jackson, Senior Regulatory Health Project Manager, at 301-796-1230.

Sincerely,

{See appended electronic signature page}

Mary Thanh Hai, M.D.
Office Director
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure: Complete Text of Written Request as Amended

COMPLETE TEXT OF WRITTEN REQUEST AS AMENDED

Hereditary angioedema (HAE) is a rare, genetic disease caused by mutations in the C1 inhibitor (C1-INH) *SERPING1* gene that result in deficient or dysfunctional C1-INH plasma protein and subsequent dysregulation of the plasma kallikrein-kinin pathway. HAE disease is characterized by intermittent, spontaneous attacks of submucosal or subcutaneous edema at various anatomic sites, such as the face, gastrointestinal tract, limbs, genitalia, and/or larynx. The attacks are painful and potentially life-threatening, particularly in cases of upper airway/laryngeal involvement. With an estimated prevalence of 1:10,000-1:50,000, HAE affects approximately 6,000-31,000 people in the US. Given that children comprise ~23% of the US population, the applicant has estimated the US pediatric HAE population (diagnosed and undiagnosed) to be 1,766 to 1,798 patients < 18 years of age and 1,268 to 1,286 patients ≤12 years of age. The diagnosis is confirmed by low or absent levels of functional C1-INH. Despite an autosomal dominant pattern of inheritance, symptoms are extremely uncommon during infancy and typically do not manifest until later childhood or adolescence with a median age of first symptom onset ranging from 6 to 11 years of age reported in the literature. Though the severity and frequency of HAE attacks is generally milder in pediatric patients compared to adolescents and adults, the underlying pathophysiology is the same. While the prevalence of patients who have HAE attacks is extremely low in the pediatric population under 6 years of age, symptomatic patients in this younger age group may exist; therefore, patients down to 2 years of age are included. However, the rarity of symptoms in patients under 2 years of age make studies in the youngest pediatric patients, including neonates, infeasible. Because clinical trials in the pediatric ages group 12 years and older have already been submitted, this age group will not be included.

Approved medications for children less than 12 years of age with HAE include the plasma derived C1-INH replacement therapies, Berinert and Cinryze, indicated for treatment of acute attacks and for prophylaxis, respectively, and danazol, an attenuated androgen, indicated for prophylaxis. While danazol is approved for prevention of HAE attacks in all ages, safety concerns limit its use in pediatric patients. For pediatric patients with more severe disease, there is a need for safe and effective approved prophylactic therapies. Lanadelumab is a human IgG1 monoclonal antibody that inhibits active plasma kallikrein to prevent the release of bradykinin from high molecular weight kininogen and thus prevent the vascular leak and swelling during an angioedema attack.

To obtain needed pediatric information on lanadelumab, 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: A 12 month, open-label safety, pharmacokinetics (PK), and clinical outcome study in children ages 2 to <12 years with Type I or II hereditary angioedema with ≥ 1 hereditary angioedema attack per 3 months during an observation run-in period. The study design shall be specified in an agreed-upon protocol with the Division.

☐ Efficacy in 2 to <12year old patients will be supported by PK exposure matching and extrapolation of efficacy from adolescent patients 12 to 17 years of age and adults. The pathophysiology of HAE due to C1-INH deficiency in children is similar to that of adults; therefore, the efficacy of lanadelumab is expected to be similar in the pediatric population with comparable exposure.

- *Objective of the study:*
To evaluate the safety, PK, and clinical outcomes of lanadelumab in children 2 to <12 years of age with HAE.

- *Patients to be studied:*

  - *Age group in which study will be performed*: 2 to <12 years of age

  - *Number of patients to be studied:* At least 20 patients total with 5 patients in each age cohort of 2 to 8 years of age and 9 to <12 years of age. A minimum of 15 patients must complete 1 year of treatment.

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.

- *Study endpoints:*

☐ *Pharmacokinetic/Pharmacodynamic (PD) Endpoints:*

The pharmacokinetic endpoints for this study must include maximum observed plasma concentration (C_{max}) at steady-state, average plasma concentration (C_{avg}) at steady-state, trough plasma concentration (C_{trough}) at steady-state, time to reach

maximum plasma concentration (t_{max}), area under the plasma concentration time curve over the dosing interval (AUC_{tau}) at steady-state, elimination half-life ($t_{1/2}$), apparent total plasma clearance after extravascular administration (CL/F), apparent volume of distribution (V/F). The pharmacodynamic endpoints for this study should include plasma levels of cleaved high molecular weight kininogen (cHMWK), C1 esterase inhibitor (C1-INH), complement component 4 (C4), and anti-drug antibody titers. PK sampling must enable estimation of primary PK parameters with reasonable precision.

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☐ The primary clinical outcome endpoint will be the number of investigator confirmed HAE attacks during the entire treatment period and must be assessed by parent/caregiver reporting with verification by the investigator.

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☐ Measures of compliance must include monitoring of a diary to be completed by parents/caregivers to record symptoms and HAE attacks as they occur and medication administration as well as tracking all used and unused vials for drug accountability.

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☐ Safety outcomes must include: adverse events, adverse events of special interest (hypersensitivity reactions, abnormal bleeding events), vital signs (blood pressure, heart rate, temperature, respiratory rate), clinical labs (hematology, clinical chemistry including LFTs, coagulation).

☐ The following adverse events must be actively monitored: elevated liver function tests. AST, ALT, and total bilirubin should be assessed at least every 2 months. Liver function abnormalities must be monitored until resolution or stabilization.

☐ The following adverse events of special interest must be captured when spontaneously reported: hypersensitivity reactions, bleeding or hypercoagulable events

- *Known safety concerns and monitoring:*
  Safety concerns include injection site and hypersensitivity reactions, elevated liver function tests, and bleeding/coagulation disorders. Monitoring for safety concerns will be performed in the clinical trial as listed under Safety Endpoints above.

- *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:* 1mL (150mg/mL) solution for injection in a 2mL glass vial. Each vial contains a slight overfill.
- *route of administration:* subcutaneous
- *regimen:*
  6 to <12 years: 150mg every 2 weeks (q2w)
  2 to <6 years: 150mg every 4 weeks (q4w)

Use an age-appropriate formulation in the study described above. If an age appropriate formulation is not currently available, you must develop and test an age appropriate formulation and, if it is found safe, pure, and potent in the studied pediatric population(s), you must seek marketing approval for that age-appropriate formulation.

In accordance with section 505A(e)(2), if

1) you develop an age-appropriate formulation that is found to be safe, pure, and potent in the pediatric population(s) studied (i.e., receives approval);

2) you have unexpired reference product exclusivity or orphan exclusivity to which pediatric exclusivity can attach and the Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(1) of the FD&C Act; and

3) you have not marketed the formulation within one year after the Agency publishes such notice, the Agency will publish a second notice indication you have not marketed the new pediatric formulation

If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be prepared by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients. Under these circumstances, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for preparing an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using such a formulation, the following information must be provided for inclusion in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step preparation instructions; packaging and storage requirements; and formulation stability information.

Bioavailability of any formulation used in the studies must be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age appropriate formulation may be conducted in adults.

- *Statistical information, including power of study and statistical assessments:* Safety and efficacy analyses will be based on all patients that receive at least one dose of lanadelumab.

The sample size is based on feasibility considerations, and all statistical analyses will be qualitative and descriptive in nature. At least 20 subjects will be enrolled to ensure 15 subjects complete the study.

Safety and clinical outcome endpoints:

- Continuous endpoints will be summarized using number of subjects, mean, standard deviation, median, minimum value and maximum value. Raw values, changes from baseline and percent changes from baseline will be summarized overall and at each scheduled time point as appropriate.

- Categorical endpoints will be summarized using counts and percentages.

- Time to event endpoints will be analyzed using Kaplan-Meier estimates.

PK/PD endpoints:

Descriptive analyses will be performed for plasma concentrations and PK/PD parameters.

- *Labeling that may result from the study*: You must submit proposed pediatric labeling to incorporate the findings of the study. Under section 505A(j) of the FD&C Act, regardless of whether the study demonstrate that lanadelumab 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. 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.

- *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 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/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM312964.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 https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm333969.pdf.

- *Timeframe for submitting reports of the study(ies):* Reports of the above studies must be submitted to the Agency on or before September 1, 2023. 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.

If FDA has not determined whether lanadelumab 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 formal pediatric Written Request, 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.

- *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. 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.

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

Reports of the study must be submitted as a biologics license application (BLA) or as a supplement to your approved BLA 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 Office of New Drugs, Immediate Office, Therapeutic Biologics and Biosimilars Team, 10903 New Hampshire Ave, Building 22, Mail Stop 6411, Silver Spring, MD 20993. If you wish to fax it, the fax number is 301-796-9855.

In accordance with section 505A(k)(1) of the FD&C 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 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. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MARY T THANH HAI
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