CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761090Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 116647

MEETING PRELIMINARY COMMENTS

Dyax Corporation
55 Network Drive
Burlington, MA 01803

Attention: Ms. Joyel C. Morris
Manager, Regulatory Affairs

Dear Ms. Morris:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for lanadelumab (DX-2930).

We also refer to your May 26, 2017, correspondence, received May 26, 2017, requesting a meeting to discuss the format and content of the BLA submission planned for December 2017.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, call me at (301) 796-1230.

Sincerely,

{See appended electronic signature page}

Colette Jackson
Senior Regulatory Health Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE: Preliminary Meeting Comments

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type:	Type B
Meeting Category:	Pre-BLA
Meeting Date and Time:	August 23, 2017, 1:30 PM to 3 PM EST
Meeting Location:	WO22, Conference Room 1415
Application Number:	IND 116647
Product Name:	lanadelumab (DX-2930)
Indication:	Hereditary Angioedema
Sponsor Name:	Dyax Corporation

Introduction:
This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for August 23, 2017, from 1:30 PM to 3 PM EST, here at our White Oak facility between Dyax and the Division of Pulmonary, Allergy, and Rheumatology Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

Dyax Corporation sent in a Type B meeting request dated May 26, 2017, to discuss the format and content of the BLA submission planned for December 2017 for lanadelumab (DX-2930) for the prevention of angioedema attacks in hereditary angioedema (HAE) patients. Dyax has Breakthrough Therapy Designation and Fast Track Designation for this product. The Division granted the meeting on June 20, 2017. Dyax Corporation provided their briefing materials on July 20, 2016.

2.0 DISCUSSION

Question 1: Does the Agency agree that the nonclinical studies conducted are sufficient to support the BLA submission and the Agency review?

FDA Response:
Yes, we agree. The nonclinical studies conducted appear to be sufficient to support the BLA submission. The adequacy of these studies will be a review issue.

Question 2: Does the Agency agree with the locations and electronic format of the nonclinical reports within the current draft structure of Module 4?

FDA Response:
Yes, we agree with your proposed approach.

Question 3: The sponsor submitted a QT evaluation plan to QT-IRT review. Does the Agency have any additional requests to those made by QT-IRT?

FDA Response:
Your approach is reasonable, and we do not have additional requests.

Question 4: Does the Agency agree with the evaluations by modeling and simulation of population PK/PD/exposure-response to support the clinical analyses and prescribing information?

FDA Response:
In general, your approach to use population PK/PD and exposure-response analyses to assist the clinical analyses and dosing regimen proposal seems reasonable. The inferences from the PK/PD and E-R analyses will be a review issue.

For population PK analysis and exposure-response analysis, please submit the datasets and codes/scripts for all analyses. Data files should be submitted as SAS transport files with *.xpt extension (e.g., Data1.xpt) and other files be submitted as ASCII text files with *.txt extension (e.g., myfile_ctl.txt, myfile_out.txt).

Question 5: Dyax intends to submit a BLA package containing final data from the double-blind pivotal study (DX-2930-03) and interim data from the open label extension study (DX-2930-04) (including at least 12 months of lanadelumab exposure across both studies for lanadelumab rollover subjects from Study DX-2930-03). Dyax believes that this data, supplemented by lanadelumab PK/PD data from Studies DX-2930-02, DX-2930-03, and DX-2930-04, will support the BLA submission and clinical review. Does the Agency agree?

FDA Response:
Provided that your BLA package is complete upon submission, your plan for the clinical portion is reasonable. You will need to elaborate on how you envision the dose and dosing regimen will appear in your proposed label.

Question 6: Per the FDA guidance on integrated summary of efficacy (ISE) for simple drug development programs (single adequate, and well-controlled effectiveness trial), Dyax plans to summarize clinical efficacy data from Phase 1b and Phase 3

studies in the BLA package. Dyax intends to address the requirements for an ISE within Module 2.7.3, summary of clinical efficacy (SCE). Does the Agency agree?

FDA Response:
Yes, your plan is acceptable.

Question 7: ***Given that in Study DX2930-04 Dyax fully adhered to FDA feedback on data required for self-administration, Dyax believes self-administration of lanadelumab can be submitted in the submission package and in the proposed label. Does the Agency agree?***

FDA Response:
Yes, you may submit self-administration data for lanadelumab to the BLA. Any language regarding self-administration in the proposed labeling will be a review issue.

Question 8: ***Dyax intends to present a clinical data package including full results from the completed double-blind, pivotal Phase 3 Study DX-2930-03 and interim results from ongoing open label Phase 3 Study DX-2930-04, as well as an integrated safety analysis which will combine data from Study DX-2930-03 and Study DX-2930-04 to provide at least 12 months of safety data for all rollover subjects. Does the Agency agree that the integrated safety analysis plan is acceptable?***

FDA Response:
Your integrated safety analysis plan is acceptable; however, note that controlled data will likely provide the most useful information. Ensure that your ISS datasets include variables to indicate the specific study in which the adverse event occurred, the actual treatment arm at the time the adverse event occurred, whether or not subjects were rollover or non-rollover participants of Study DX-2930-04, and if and when subjects have self-administered treatment. For adverse events which occurred during the OLE, provide study days relative to both the first dose in Study DX-2930-03 as well as the first dose in Study DX-2930-04.

Question 9: ***Per the FDA guidance on the eCTD location of the integrated summary of safety (ISS), Dyax proposes to provide the summary tables, figures, and analysis datasets in Module 5.3.5.3. The narrative portions of the safety results will be provided in Module 2.7.4, Summary of Clinical Safety. Does the Agency agree?***

FDA Response:
Yes, we agree.

Question 10: ***Does the Agency agree with proposed approach and documentation to be submitted as part of the 4-Month Safety Update?***

FDA Response:
Yes, your plan to provide fully updated ISS tables and listings as well as an updated Summary of Clincal Safety without an additional interim CSR for study DX2930-04 is acceptable documentation for the 4-month safety update.

Question 11: Based on the current benefit-risk profile of the product, Dyax believes that the current safety concerns would be adequately addressed within the label and that a Risk Evaluation and Mitigation Strategy (REMS) would not be necessary to ensure that the benefits outweigh the risks. Dyax will continue to assess as additional data become available. Does the Agency concur with this approach?

FDA Response:
Whether or not a REMS will be necessary will be a review issue.

Question 12: Dyax believes that the continuation of Study DX2930-04 , to support 12 month safety for rollover subjects, and in addition, the proposed continuation of this study from 12 months up to 30 months, will not impact the content of BLA package being submitted for review. Does the Agency agree?

FDA Response:
Yes, your plan to extend Study DX2930-04 from 12 to 30 months is acceptable.

Question 13: Based on the well-known characteristics of HAE and the importance of preventing angioedema attacks, coupled with the favorable efficacy and safety profile of lanadelumab, Dyax does not believe an Advisory Committee is warranted. During the review if the Agency deems it necessary to convene an Advisory Committee, could the Agency please provide guidance on timing and process for planning purposes?

FDA Response:
If an advisory committee meeting is deemed necessary for an NDA/BLA submission, it is typically held during the second half of the review cycle, although the exact timing is subject to multiple factors such as availability of committee members, location sites, etc.

Question 14: Does the Agency agree with the content of the complete BLA application as provided in the proposed Table of Contents (TOC); and the minor components to be submitted within 30 days of original BLA submission?

FDA Response:
Yes, we agree.

Question 15: Dyax believes that lanadelumab is exempt from the PREA requirements for pediatric development based on its Orphan Designation and does not intend to submit a pediatric assessment, or waiver request? Does the Agency agree?

FDA Response:
Yes, products that have been granted orphan drug designation by the Agency are exempt from PREA requirements. If you do not intend to conduct a pediatric program, you may state the orphan designation status in your BLA submission. Please refer to the PREA Requirements in Section 3.0 below.

Question 16: Dyax intends to submit one Bioresearch Monitoring (BIMO) clinical site dataset for the single Phase 3 pivotal study (Study DX-2930-03) with the BLA submission. Dyax will submit the dataset in in SAS transport file format (.xpt) format as required per FDA document entitled "Specification for Preparing and Submitting Summary Level Clinical Site Data for Center for Drug Evaluation and Research, CDER's, Inspection Planning. Does the agency agree?

FDA Response:
Yes, we agree.

3.0 OTHER IMPORTANT MEETING INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION
As stated in our June 20, 2017, communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA V. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on PDUFA V and the Program is available at
http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.
This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

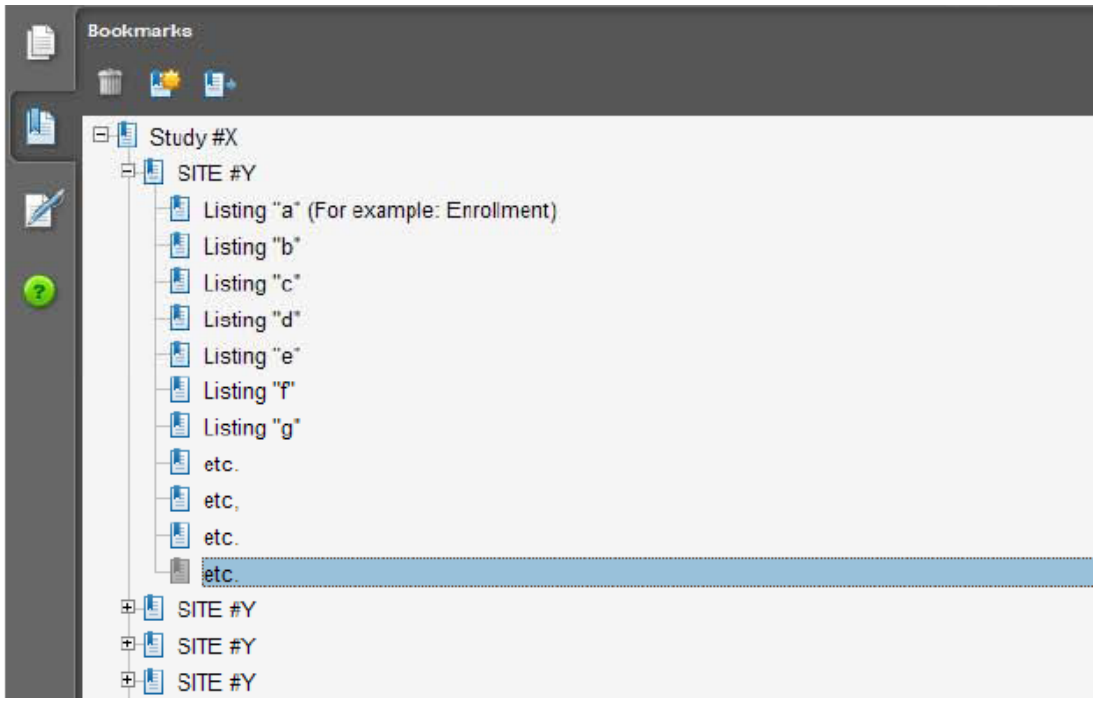
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
   c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
    a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
    b. Subject listing for treatment assignment (randomization)
    c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
    d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
    e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
    f. By subject listing, of AEs, SAEs, deaths and dates
    g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
    h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
    i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
    j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

Attachment 1
Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-NDA Request Item[1]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

[1] Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

COLETTE C JACKSON
08/22/2017

CDER Breakthrough Therapy Designation Determination Review Template

IND/NDA/BLA #	IND 116,647
Request Receipt Date	May 7, 2015
Product	DX-2930
Indication	Prevention of acute attacks of hereditary angioedema
Drug Class/Mechanism of Action	Monoclonal antibody; plasma kallikrein inhibitor
Sponsor	Dyax
ODE/Division	ODEII / DPARP
Breakthrough Therapy Request Goal Date (within 60 days of receipt)	July 6, 2015

Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.*Section I to be completed within 14 days of receipt for all BTDRs*

1. **Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):** The prevention of angioedema attacks in patients with type I and type II hereditary angioedema (HAE).

2. **Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?** ☐YES ☒NO

3. **Consideration of Breakthrough Therapy Criteria:**

   a. Is the condition serious/life-threatening[1])? ☒YES ☐NO

If 3a is checked "No," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:

   b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequeate and sufficiently complete to permit a substantive review?
      - ☒ YES the BTDR is adequate and sufficiently complete to permit a substantive review
      - ☐ Undetermined
      - ☐ NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore the request must be denied because (check one or more below):

         i. Only animal/nonclinical data submitted as evidence ☐
         ii. Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information about the protocol[s]) ☐
         iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression) ☐

[1] For a definition of serious and life threatening see Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease) ☐

v. No or minimal clinically meaningful improvement as compared to available therapy[2]/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval) ☐

4. Provide below a brief description of the deficiencies for each box checked above in Section 3b:

If 3b is checked "No", BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC's input is desired. If this is the case, proceed with BTDR review and complete Section II). If 3b is checked "Yes" or "Undetermined", proceed with BTDR review and complete Section II, as MPC review is required.

5. Clearance and Sign-Off (no MPC review)

Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.

6. **A brief description of the drug, the drug's mechanism of action (if known), the drug's relation to existing therapy(ies), and any relevant regulatory history.**

DX-2930 is a recombinant human IgG1 kappa light chain monoclonal antibody inhibitor of active plasma kallikrein being developed as long-term maintenance therapy (administered SC) for the prevention of acute attacks in patients with Types I and II hereditary angioedema (HAE). Its proposed mechanism of action is to bind the active form of plasma kallikrein, thereby blocking its action and preventing cleavage of high molecular weight kininogen and subsequent release of bradykinin. Ordinarily, kallikrein activity is regulated by C1 esterase inhibitor (C1-INH), but in HAE patients with low or absent levels of functional C1-INH, kallikrein activity goes unchecked, leading to widespread release of bradykinin. In turn, bradykinin increases vascular permeability which leads to the characteristic swelling of acute HAE attacks.

Hereditary angioedema is a rare, autosomal dominant, inheritable disease estimated to affect 1 in 10,000 to 50,000 individuals worldwide and is categorized as an orphan disease in the US. The disease is characterized by painful, self-limited attacks of subcutaneous or submucosal nonpitting edema affecting the face, larynx, gastrointestinal tract, limbs, or genitalia. Hereditary angioedema is considered a serious, potentially life-threatening disease given the possibility of upper airway compromise or significant hypotension to occur during an acute attack.

Although approved therapies are available for the treatment of acute attacks, patients with frequent attacks may benefit from prophylactic therapy. For prophylaxis, there are two approved products in the U.S.: Cinryze (a highly purified human plasma-derived C1-INH replacement product) and danazol (a synthetic androgenic steroid). In addition, tranexamic acid (an anti-fibrolytic) is occasionally used off-label for this indication. Due to its short half-life and large formulation volume, Cinryze must be administered by intravenous infusion every 3-4 days and may necessitate placement of an indwelling venous catheter, which carries known risks of thrombosis and infection. Danazol is associated with known dose-related androgen-associated adverse effects such as virilization, weight gain,

[2] For a definition of available therapy refer to Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

depression, hepatotoxicity, and dyslipidemia. Tranexamic acid off label use is commonly associated with nausea, diarrhea, fatigue, muscles cramps/weakness with increased muscle enzymes along with a potential for enhanced thrombosis. Its effectiveness has not been adequately evaluated.

7. Information related to endpoints used in the available clinical data:

a. Describe the endpoints considered by the sponsor as supporting the BTDR and any other endpoints the sponsor plans to use in later trials. Specify if the endpoints are primary or secondary, and if they are surrogates.

Data to support BTDR is derived from a proof-of-concept, safety/tolerability/PK study which captured HAE attacks as adverse events. For the interim analysis, the primary endpoint was the mean HAE attack rate per week compared to placebo which we would consider a meaningful clinical endpoint. Secondary endpoints in this study included the proportion of attack-free subjects as well as the number, severity, and location of attacks. The Sponsor also evaluated 2-chain high molecular weight kininogen (HMWK) levels as a surrogate measure of plasma kallikrein activity.

b. Describe the endpoint(s) that are accepted by the Division as clinically significant (outcome measures) for patients with the disease.

For the indication of long-term maintenance and prevention of HAE attacks, the Division considers the frequency of acute attacks, with attack severity taken into consideration, an acceptable primary endpoint for phase 3 trials. The time to first attack, hospitalizations due to an attack, and proportion of attack-free days are appropriate secondary endpoints. Patient-reported outcome measures for HAE have not been rigorously validated, but any positive findings may be judged supportive.

c. Describe any other biomarkers that the Division would consider likely to predict a clinical benefit for the proposed indication even if not yet a basis for accelerated approval.

The degree of plasma kallikrein inhibition, as measured by 2-chain HMWK levels or otherwise has been assessed but has not yet been directly correlated with a HAE disease activity or validated as a biomarker.

8. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population.

For prophylactic treatment of HAE attacks[1], there are two approved products in the U.S.: Cinryze[2] (a highly purified human plasma-derived C1-INH replacement product) and danazol[3] (a synthetic androgenic steroid). In addition, tranexamic acid (an anti-fibrolytic) is occasionally used off-label for this indication. Cinryze was approved on October 10, 2008, by CBER for adolescents and adults with HAE based on a reduction in the number of acute attacks over 12 weeks in 22 patients. The mean number of attacks was 6.1 during the Cinryze treatment period compared with 12.7 during the placebo treatment period, about a 50% reduction ($p<0.001$). Cinryze treatment also led to a significant reduction in days of swelling, average severity of swelling, and average duration of attacks. Danazol is approved for males and females with angioedema of all types; however, it is contraindicated during pregnancy/lactation and not recommended for use in children. Although efficacy data is not presented in the label, danazol has a long history of use in HAE[4], and the literature suggests a sizeable treatment effect. A recent study demonstrated that danazol treatment reduced the mean number of attacks per year from 33.3 to 5.4 in 118 patients[5]. Although widely used in Europe for long-term prophylaxis of HAE, tranexamic acid is generally felt to be less effective than androgens[1]; however, a recent study demonstrated a mean attack reduction of approximately 50% in 18 HAE patients treated with tranexamic acid over 6 months[6]. There are, however, disadvantages associated with each treatment option. Due to its short half-life and large formulation volume, Cinryze must be administered by intravenous infusion every 3-4 days and may necessitate placement of an indwelling venous catheter, which carries

known risks of thrombosis and infection. Danazol is associated with known dose-related androgen-associated adverse effects such as virilization, weight gain, depression, hepatotoxicity, and dyslipidemia. Tranexamic acid use is commonly associated with nausea, diarrhea, fatigue, muscles cramps/weakness with increased muscle enzymes along with a potential for enhanced thrombosis.

For the treatment of acute angioedema attacks, there are currently four approved therapies: Berinert (purified C1-INH), Ruconest (recombinant C1-INH), Firazyr (bradykinin B2 receptor antagonist), and Kalbitor (recombinant kallikrein inhibitor).

9. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation[3].

BCX4161 (b) (4) is a small molecule inhibitor of plasma kallikrein also being developed as prophylactic treatment of HAE attacks. (b) (4)

10. Information related to the preliminary clinical evidence:

a. Table of clinical trials supporting the BTDR (only include trials which were relevant to the designation determination decision), including study ID, phase, trial design[4], trial endpoints, treatment group(s), number of subjects enrolled in support of specific breakthrough indication, hazard ratio (if applicable), and trial results.

Dyax has conducted a single ascending dose study in healthy volunteers and one safety and efficacy study in HAE patients, which is summarized in the table below. While all doses of study drug have been administered in Study DX-2930-02, follow-up is ongoing.

Table 1. Studies to support BTDR

Study Number	Objectives	Design	Study population	Doses: number of subjects	Treatment duration	Efficacy endpoints
DX-2930-02 Phase 1b	Safety, tolerability, PK	R, DB, PC, PG, MAD	Type I and II HAE patients, ages ≥ 18 years	30 mg: 4 100 mg: 4 300 mg: 5 400 mg: 11* Placebo: 13	2 doses; 14 days apart	Primary: HAE attacks/week Secondary: Proportion of attack-free patients, HAE characteristics

R=randomized, DB=double-blind, PC=placebo-controlled, PG=parallel group, MAD=multiple ascending dose
*One subject who did not return for the second dose of study drug was lost to follow-up and subsequently replaced. Also includes one subject who was later found to have normal C1 inhibitor levels.

A total of 37 subjects were randomized and treated. One subject in the 400 mg dose cohort received a single dose of DX-2930, and was subsequently replaced after being lost to follow-up; except where noted, analyses included this subject. At the time of the interim analysis, 27 (71%) subjects had completed the study (remainder in follow-up). The pre-specified, primary efficacy analysis was based on subjects in the 300 mg and 400 mg dose cohorts compared to placebo from Days 8

[3] Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.
[4] Trial design information should include whether the trial is single arm or multi-arm, single dose or multi-dose, randomized or non-randomized, crossover, blinded or unblinded, active comparator or placebo, and single center or multicenter.

to 50. Only subjects with at least 2 attacks in the 3 months prior to enrollment were included. The baseline attack rate and results following treatment are shown in Table 2. In addition, the proportion of attack-free subjects and characteristics of HAE attacks are presented in Table 3 and Table 4.

Table 2. Study DX-2930-02: HAE Attack Rate per Week (Days 8 to 50)

Parameter	DX-2930 300 mg (N=5)	DX-2930 400 mg (N=11)	DX-2930 Combined 300 and 400 mg (N=16)	Placebo (N=13)
n[a]	4	11	15	11
Baseline HAE attack rate (attacks/week), mean (SD)[b]	0.33 (0.25)	0.55 (0.17)	0.49 (0.21)	0.39 (0.18)
Overall HAE attack rate, unadjusted (attacks/week), mean (SD)[c]	0	0.048 (0.15)	0.034 (0.13)	0.36 (0.36)
HAE attack rate GEE analysis[d]				
Estimated mean rate (attacks/week) (SE)	0	0.045 (0.033)	0.033 (0.024)	0.37 (0.098)
P value (vs placebo)	<0.0001	0.0050	0.0012	
% change in mean rate (vs placebo)	−100.0	−87.8	−91.1	
95% CI for % change	−100.0, −100.0	−97.2, −46.9	−97.9, −61.6	

Abbreviations: CI = confidence interval; GEE = General Estimating Equation; HAE = hereditary angioedema; SD = standard deviation; SE = standard error

[a] Number of subjects included in analysis. Only patients who have a baseline attack rate of at least 2 attacks in the last 3 months prior to enrollment are included.

[b] Baseline is defined as historical HAE attacks over the last 3 months prior to dosing.

[c] Weighted statistics, unadjusted for baseline attack rate.

[d] The result is based on General Estimating Equation analysis of repeated counts per week during the observation period (Day 8 to 50). Baseline HAE attack rate per week is a covariate, treatment group is a fixed effect and subject is a random effect in the GEE model with independence working correlation structure.

Table 3. Proportion of Attack-free Patients

Parameter	DX-2930 300 mg (N = 5)	DX-2930 400 mg (N = 11)	DX-2930 Combined 300 and 400 mg (N = 16)	Placebo (N = 13)
n[a]	4	11	15	11
Attack-free subjects, n (%)	4 (100)	9 (82)	13 (87)	3 (27)
P value vs placebo[b]	0.026	0.030	0.004	

[a] Number of subjects included in analysis. Only patients who have a baseline attack rate of at least 2 attacks in the last 3 months prior to enrollment are included.

[b] *P* value from Fisher exact test.

Table 4. Characteristics of HAE Attacks

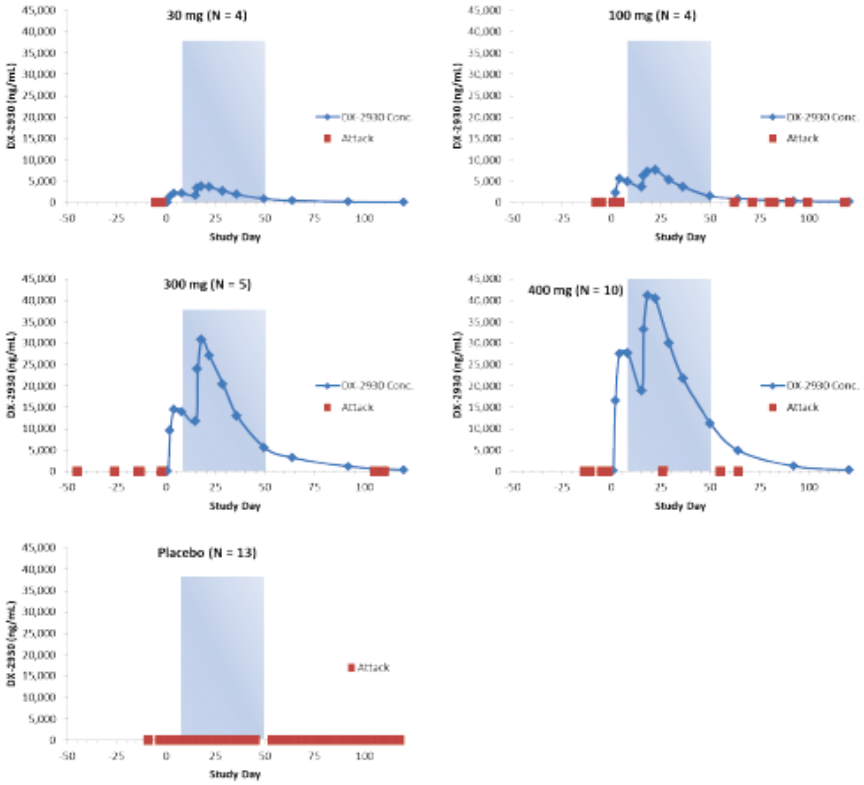
Parameter	DX-2930 300 mg (N = 5)	DX-2930 400 mg (N = 11)	Placebo (N = 13)
n[a]	4	11	11
Number of attacks	0	3	24
Primary attack location			
Peripheral		3	10
Abdominal		0	13
Laryngeal		0	1
Attack severity			
Mild		1	8
Moderate		1	6
Severe		1	10
Attacks requiring treatment		2	22

[a] Number of subjects included in analysis. Only patients who have a baseline attack rate of at least 2 attacks in the last 3 months prior to enrollment are included.

As a post-hoc analysis on the PK population (excludes Subject (b) (6) who only received 1 dose), the Sponsor evaluated the incidence of HAE attacks in relation to drug exposure over time for each dose group. As shown in the figure below,

relatively few HAE attacks occurred during periods of higher drug exposure, although by this account, 30 mg DX-2930 should have been ineffective. While the lack of a clear dose response may potentially be explained by the relatively low baseline attack rate in the low dose 30 mg cohort, this finding makes the results slightly less persuasive.

Figure 1. HAE Attack Rate by DX-2930 Plasma Concentration



Blue diamonds show mean DX-2930 plasma drug concentration by study day per dose group. Red squares indicate days on which an HAE attack was reported by a subject in the indicated dose group. Shaded area indicates the primary efficacy assessment period of Day 8 to Day 50. HAE attack events were collected from the time of informed consent, which could have occurred up to 28 days prior to dosing on study Day 1, through the data cutoff (08 March 2015), which includes data through the final 120 day follow-up visit for subjects treated with 30, 100, and 300 mg, and through at least Day 50 for subjects treated with 400 mg. One subject (b) (6) in the 400 mg dose group, who only received 1 dose of study drug and was subsequently lost to follow up, was excluded from the analysis due to lack of available samples for PK analyses. Conc. = concentration.

b. Include any additional relevant information.

Efficacy Compared to Existing Treatments

As mentioned above, existing treatments for the prevention of HAE attacks in patients with hereditary angioedema include Cinryze and danazol, which are approved for this indication, and off-label use of tranexamic acid. According to the Cinryze label, prophylaxis treatment reduced the frequency of HAE attacks by about half – mean attack frequency over a 12 week period of 12.7 with placebo compared to 6.1 with Cinryze (or 1 and 0.5 attacks/week, respectively). In addition, 4 out of 22 patients were attack-free during the Cinryze treatment period. With regard to danazol, in a large retrospective study[5] of 356 patients with HAE who received danazol for an average of 11 years (range 2 months to 30 years), treatment with danazol at a mean dose of 171 mg/day reduced the frequency of HAE attacks by 84% (reduction in mean yearly HAE attack rate from 33.3 to 5.4). A retrospective study of tranexamic acid as long-term maintenance treatment in 18 HAE patients demonstrated an average 50% reduction in attacks in the 6 months after starting therapy[6].

This is compared to a mean attack rate per week of 0 and 0.05 for DX-2930 300 mg and 400 mg, respectively, compared with 0.37 for placebo. Over a 6-week period, the percent reduction in mean HAE attack rate from placebo was 100% and 88% for DX-2930 300 mg and 400 mg, respectively, and 13 out of 15 DX-2930-treated patients were attack-free. These data provide preliminary clinical evidence of substantial improvement over the available Cinryze and tranexamic acid therapies which on average reduce the frequency of HAE attacks by about half and is approximately the same as was

observed in studies with Danazol, albeit without the worrisome side effect profile of androgenic steroids. While the preliminary efficacy results are somewhat limited by the study's brief treatment and observation period, relatively mild patient population, and lack of clear dose response, inhibition of plasma kallikrein has also shown to be an effective target for treating acute attacks with the approved therapy Kalbitor.

Preliminary Safety

The main treatment-emergent adverse events associated with DX-2930 were injection site pain/reactions, headache, and nausea. Anti-drug antibodies were detected in two patients, but had no apparent clinical effect on safety or efficacy. Although the immunogenicity assessment is currently limited to exposure to two doses, anti-drug antibodies are not anticipated to be a major safety issue given that DX-2930 is a fully humanized monoclonal antibody. There have been no deaths or treatment discontinuations due to an adverse event. While exposure data is limited to 120 days following two doses of DX-2930, preliminary safety data suggests that DX-2930 could potentially be a safer alternative to currently available therapies.

11. Division's recommendation and rationale (pre-MPC review):

☒ GRANT :

Provide brief summary of rationale for granting:

Based on the preliminary clinical evidence submitted, treatment with DX-2930 appears to provide a substantial improvement over available therapies on the clinically meaningful endpoint of reduction/prevention of HAE attacks. Although the data to support the BTDR has limitations (relatively short treatment and observation period, milder patient population, and lack of dose response relationship), the study did demonstrate a dramatic decrease in HAE attacks in patients treated with DX-2930 compared with placebo. Although safety data is limited, DX-2930 appears to represent a safety advantage over Cinyrze and danazol, given the significant drawbacks associated with each therapy.

☐ DENY:

Provide brief summary of rationale for denial:

12. Division's next steps and sponsor's plan for future development:

a. If recommendation is to grant the request, explain next steps and how the Division would advise the sponsor (for example, plans for phase 3, considerations for manufacturing and companion diagnostics, considerations for accelerated approval, recommending expanded access program):

An end-of-phase 2 meeting with the Sponsor is scheduled for June 30th. The Breakthrough Therapy process will be outlined at that time.

13. List references, if any:

1. Zuraw BL, Bernstein JA, Lang DM, et.al. A focused parameter update: hereditary angioedema, acquired C1 inhibitor deficiency, and angiotensin-converting enzyme inhibitor-associated angioedema. *J Allergy Clin Immunol*. 2013; 131(6):1491-3
2. Cinryze (human C1 esterase inhibitor) package insert. Approved October 10, 2008. Access at: http://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/ucm150480.htm
3. Danazol package insert. http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=f2c9b713-aafc-49ca-866e-334d9b5c2e2d
4. Gelfand JA, Sherins RJ, Alling DW, Frank MM. Treatment of hereditary angioedema with danazol. Reversal of clinical and biochemical abnormalities. *N Engl J Med*. 1976;295:1444-8

5. Bork K, Bygum A, Hardt J. Benefits and risks of danazol in hereditary angioedema: a long-term survey of 118 patients. *Ann Allergy Asthma Immunol.* 2008; 100:153-61
6. Wintenberger C, Boccon-Gibod I, Launay D, et.al. Tranexamic acid as maintenance treatment for non-histaminergic angioedema: analysis of efficacy and safety in 37 patients. *Clin Exp Immunol*. 2014; doi:10.1111/cei.12379 [Epub ahead of print]

14. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting? YES ☒ NO ☐

15. Clearance and Sign-Off (after MPC review):

The Division met with the MPC on June 26, 2015. During the MPC meeting discussion, it was noted that the preliminary efficacy for DX-2930 approximates that reported for danazol, and therefore the preliminary efficacy data for DX-2930, while showing a dramatically positive effect, does not necessarily represent a substantial improvement over danazol on one or more clinically significant endpoints. However, given the numerous, well-characterized side effects of danazol such as virilization, altered mood/depression, weight gain, dyslipidemia, LFT elevations, and hypertension, treatment with DX-2930 would offer a safety advantage over the best available therapies. While safety data for DX-2930 is limited, its mechanism of action would not lead to the dose-limiting androgenic side effects experienced with danazol treatment. Therefore, the MPC concurred with the Division to grant breakthrough therapy designation based on preliminary clinical evidence that treatment with DX-2930 not only appears to be as efficacious as the best currently available therapy for HAE attack prophylaxis, but also would represent a significant safety advantage.

Grant Breakthrough Therapy Designation ☒
Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

5-7-15/M. Raggio

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

STACY J CHIN
06/30/2015

ANTHONY G DURMOWICZ
06/30/2015

BADRUL A CHOWDHURY
06/30/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 116647

MEETING PRELIMINARY COMMENTS

Dyax Corporation
55 Network Drive
Burlington, MA 01803

Attention: Nicole D'Auteuil
Vice President, Regulatory Affairs

Dear Ms. D'Auteuil:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for DX-2930.

We also refer to your April 1, 2015, correspondence requesting an End-of-Phase 2 meeting to discuss the development of your recombinant human monoclonal antibody for inhibition of active plasma kallikrein, designated DX-2930, for prevention of angioedema attacks in hereditary angioedema (HAE) patients.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes. If you have any questions, call me at (301) 796-1230.

Sincerely,

{See appended electronic signature page}

Colette Jackson
Senior Regulatory Health Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE: Preliminary Meeting Comments

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: Type B
Meeting Category: End-of-Phase 2

Meeting Date and Time: June 30, 2015
Meeting Location: WO22, Building 22, Conference Room 1419

Application Number: IND 116647
Product Name: DX-2930
Indication: Hereditary Angioedema
Sponsor/Applicant Name: Dyax

Introduction:
This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for June 30, 2015, at 3 PM EST, here at our White Oak facility between Dyax and the Division of Pulmonary, Allergy, and Rheumatology Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the RPM if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

Dyax Corporation sent in a Type B End-of-Phase 2 meeting request dated April 1, 2015, to discuss the development of your recombinant human monoclonal antibody for inhibition of active plasma kallikrein, designated DX-2930, for prevention of angioedema attacks in hereditary angioedema (HAE) patients. The Division granted the meeting on April 23, 2015. Dyax Corporation provided their briefing materials on May 26, 2015.

2.0 DISCUSSION

Introductory Comments

We have concerns about your proposed dosing regimen. While the proposed every 2 week doses appear to have a positive effect based on limited data from the phase 1 studies, dosing regimens longer than every two weeks also appear to be efficacious and have not been adequately explored. One method to estimate the dosing interval would be to conduct a study comparing several doses of DX-2930 delivered every 2 weeks to placebo using an endpoint such as time to first HAE attack. After a predefined period of time, an interim analysis could be conducted and dose(s) which is efficacious would be selected. After the analysis, patients could be re-randomized into groups which would receive DX-2930 for an additional period of time either on a regular schedule or at the first signs of an attack, which, based on the mechanism of action we believe DX-2930 would be effective. In this way, the maximum dosing interval for DX-2930 could be estimated. Alternatively, a more conventional study could be performed to assess dosing interval comparing doses given at least every 2 weeks and every 4 weeks.

Question 1. ***Does the Division have comments regarding the two doses selected for the pivotal study given the rationale in Section 6.1.2?***

FDA Response:

See introductory comments.

Question 2. ***The Phase 3 pivotal study, DX-2930-03, is described in Section 6.1 and the protocol is located in Appendix 1.***

a. The clinical patient population is described in Section 6.1.3. Does the Division have any comments regarding our proposed study entry criteria?

FDA Response:

Your inclusion of adolescent patients is acceptable. We note that the eligibility requirement for baseline HAE attack frequency is relatively low and that patients must be managing their HAE disease while off long-term prophylactic therapy; these selection criteria call into question the need for HAE prophylaxis.

b. The primary and secondary endpoints and associated statistical analysis plan intended to demonstrate the efficacy of DX-2930 for prevention of acute attacks of HAE is located in Section 6.1.5 and Section 6.1.4. Does the Division concur with the endpoints, data collection methodology, and statistical analyses to demonstrate efficacy to support marketing approval?

FDA Response:

No, we do not necessarily agree. We have the following comments:

1. The rate of HAE attacks should be expressed as number of attacks per month or year to more easily interpret the clinical relevance of the results.

2. Your protocol states that "subjects that drop out of the study prior to receiving the second dose of study drug or placebo will be replaced." Please note that subjects should not be replaced as the drop out subjects could provide important information related to the study medication.

3. According to the protocol, the Investigator may withdraw a subject from the trial for certain reasons. Subjects should not be discontinued from the trial unless they self-withdraw consent or die. All subjects should continue to be followed as per protocol even if they are discontinued from the trial medication.

4. The protocol states that "If it is determined at any time that the higher dose group must be dropped due to an important safety signal, the Sponsor may increase the sample size of the remaining dosing arms and continue enrollment for the remainder of the study in a 1:1 ratio of 150 mg DX-2930 every 2 weeks or placebo every 2 weeks in a double-blind fashion."

   You will need to clarify how subjects who have already been randomized to the higher dose group would be treated or analyzed.

5. The protocol defines a Modified Intent-to-treat (mITT) Population which will include all randomized patients who receive at least the first two doses of active drug or placebo, a defined population to which we do not necessarily agree.

   You will need to provide the rationale for excluding patients who receive the first dose of study drug from the mITT population.

6. Submit a statistical analysis plan for review when available.

c. Does the Division agree the study duration of 6 months is suitable to support a marketing application?

FDA Response:
See introductory comments.

d. As described in Section 6.1.5.3, the study includes an interim analysis plan, which will be conducted when all of the following criteria have been met: at least 30% of subjects complete at least 24 weeks of efficacy assessment, at least 36 additional subjects complete at least 12 weeks of efficacy assessments, and at least 80 investigator-confirmed HAE attacks have occurred. Does the Division agree to the methodology for the interim analysis as well as its planned timing?

FDA Response:
No, we do not agree with conducting an interim analysis in your proposed trial in order to terminate the trial early due to efficacy.

e. Section 6.1.6 describes the safety evaluations and our approach to considering HAE attacks as study endpoints and therefore not subject to expedited reporting, as they are directly relevant to the efficacy evaluation. Does the Division concur or have any comments?

FDA Response:
All serious adverse events (SAEs), regardless of the nature or cause, must be reported in an expedited manner according to CFR 310.305. Although, HAE attacks are the efficacy outcome of interest, these should also be captured in the safety database for completeness with the explanations provided for any discrepancies.

f. Does the Division have any other comments regarding the study design of our Phase 3 pivotal study?

FDA Response:
We agree with your definition of an HAE attack, but note that for any subject-reported attack, even those not confirmed by an investigator, the complete information must be submitted for review by the Agency. In addition, emergency department visits for HAE attacks should be captured as a separate variable from HAE attacks hospitalization admissions.

Question 3. Dyax plans to conduct an open-label extension (OLE) study, DX-2930-04, following the double-blind study to further evaluate long-term exposure. The OLE is described in Section 6.2 and the protocol synopsis is located in Appendix 2. The OLE includes a broader patient population than allowed in the double-blind study. Additionally, in the future, we may seek to amend the OLE to evaluate self-administration. This would only occur after results of the double-blind study are available. Dyax anticipates that subjects may participate in the OLE until DX-2930 receives product approval or the development program is discontinued. Does the Division have any comments regarding the design of the OLE?

FDA Response:
We have reservations about your OLE in that it has no designated time frame or stopping point and has limited capacity to provide informative safety data.

Question 4. The Phase 3 pivotal study, DX-2930-03, is a multi-center, randomized, double-blind, placebo-controlled, and parallel-arm study to investigate two DX-2930 doses in comparison to placebo. The study is highly powered for efficacy to evaluate the important clinical benefit of prevention of attacks. Based on our current data, we anticipate greater than 75% attack reduction to be achieved. In

designing the study, we utilized several elements suggested for single pivotal studies as described in the Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products (FDA, 1998). Further rationale for the single study is provided in Section 7.1. Does the Division agree that Study DX-2930-03 is sufficiently designed to serve as a single pivotal trial for the BLA submission?

FDA Response:
Whether or not a single, well-controlled trial will be sufficient to provide substantial evidence of safety and efficacy of DX-2930 as a prophylactic treatment in patients with HAE will depend on the review of the data and robustness of the treatment effect.

Question 5. ***The proposed single trial and its OLE, together with the completed clinical studies will result in a safety database of approximately 170 subjects who have been exposed to DX-2930, of which approximately half will have received repeated treatments over 6 months or longer at the time of the BLA submission, including an estimated 25 subjects with a year or longer duration of exposure (Section 7.2). Because the OLE will continue until DX-2930 receives product approval or the development program is discontinued, data from this study would continue to be evaluated following submission of the BLA. Presuming that the clinical safety continues to be consistent with the safety profile based on results to date, does the anticipated exposure at the time of BLA submission appear reasonable?***

FDA Response:
The size and scope of your safety database will ultimately be a review issue. For a new monoclonal antibody intended for chronic, life-long use, your proposed safety database is rather limited in both size and length of treatment

Question 6. ***A CMC update is located in Section 8. Does the Division have any comments regarding our CMC plans?***

FDA Response:
Your plan to transfer the Drug Substance and Drug Product manufacturing process to another contractor seems reasonable. We will review your overall plans and your comparability results, once these are submitted. Your intention to request a DX2930, CMC meeting with the OBP Division in Q4, 2015 is also reasonable. You will need to contact the regulatory project manager to coordinate the scheduling this meeting.

3.0 OTHER IMPORTANT MEETING INFORMATION

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For

more information, please see CDER/CBER Position on Use of SI Units for Lab Tests (http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm).

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:

a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

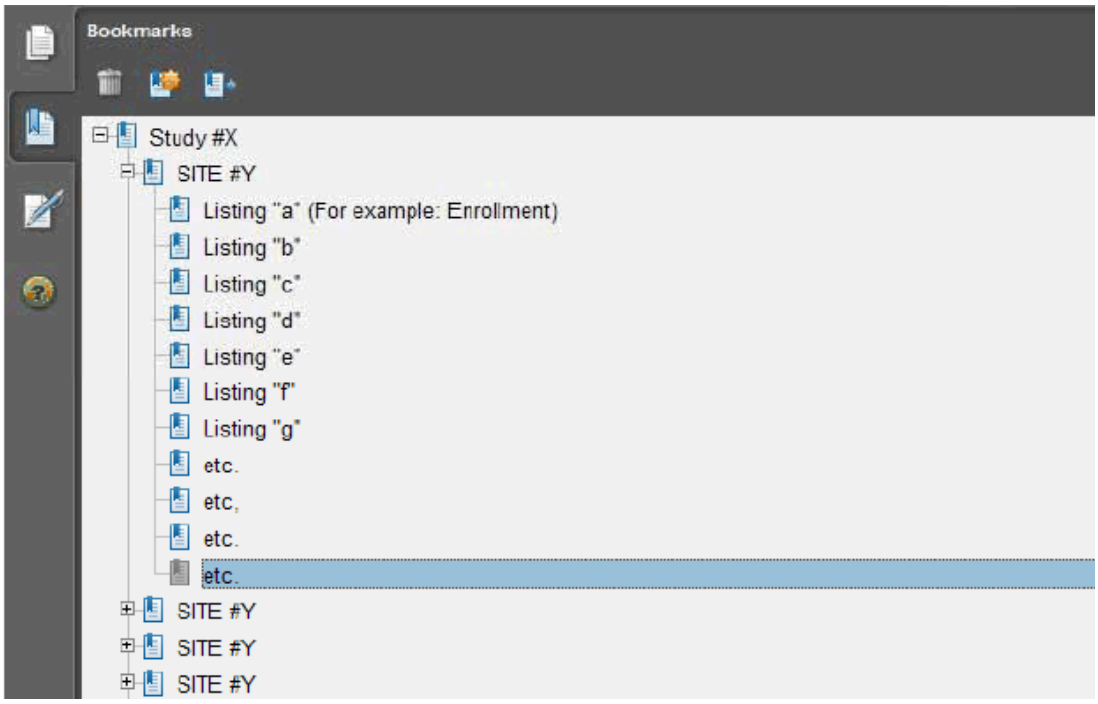
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).

5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)
   c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
   d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
   e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
   f. By subject listing, of AEs, SAEs, deaths and dates
   g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
   h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
   i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
   j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal phase 2 and phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft "Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

Attachment 1

Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-NDA Request Item[1]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

[1] Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LAURA MUSSE
06/26/2015