

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761090Orig1s000

OTHER REVIEW(S)

MEMORANDUM
NONPROPRIETARY NAME SUFFIX

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	June 28, 2018
Responsible OND Division:	Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Application Type and Number:	BLA 761090
Product Name and Strength:	Takhzyro (lanadelumab-flyo) Injection [REDACTED] (b) (4) 300 mg/2 mL (150 mg/mL)
Product Type:	Single Ingredient, Combination Product (Drug-Device)
Applicant/Sponsor Name:	Dyax Corp.
FDA Received Date:	December 26, 2017
OSE RCM #:	2018-947
DMEPA Primary Reviewer:	Carlos M Mena-Grillasca, BS Pharm
DMEPA Deputy Director:	Danielle Harris, PharmD, BCPS

1 PURPOSE OF MEMO

This memorandum summarizes our evaluation of the four-letter suffixes proposed by Dyax Corp. for inclusion in the nonproprietary name and communicates our recommendation for the nonproprietary name for BLA 761090.

1.1 Regulatory History

Dyax Corp. was notified of the Agency's intention to designate a nonproprietary name that includes a four-letter distinguishing suffix that is devoid of meaning for their product in an Advice Letter^a.

2 ASSESSMENT OF THE NONPROPRIETARY NAME

On May 4, 2018, Dyax Corp. submitted a list of ten suffixes, in their order of preference, to be used in the nonproprietary name of their product^b. Dyax Corp. also provided findings from an external study conducted by (b) (4), evaluating the proposed four-letter suffixes for our consideration. Table 1 presents a list of suffixes submitted by Dyax Corp.:

1.	-flyo
2.	(b) (4)
3.	
4.	
5.	
6.	
7.	
8.	
9.	
10.	

We reviewed Dyax Corp.'s proposed suffixes in order of preference listed by Dyax Corp., along with the with the supporting data they submitted, using the principles described in the applicable guidance.^d

2.1 lanadelumab-flyo

Dyax Corp's proposed suffix -flyo, is comprised of four distinct letters. We note that the suffix -flyo is similar to the marketed product Zyflo (zileton, 300 mg and 600 mg tablets) and Glydo (lidocaine HCl, 2% jelly). We considered whether the name similarity with the suffix could be misleading or a source of confusion and errors, but we could not identify a plausible risk based on the expected use of this product or, based upon known causes of medication errors.

We determined that the proposed suffix -flyo, is not too similar to any other products' suffix designation, that the suffix is devoid of meaning, does not include any abbreviations that could be misinterpreted, and does not make any misrepresentations with respect to safety or efficacy of this product.

^a Harris, D. General Advice Letter for BLA 761090. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 MAR 23.

^b Request for Non-Proprietary Name Suffix (BLA 761090). Lexington (MA): Dyax Corp.; 2018 MAY 04. Available from: \\cdsesub1\evsprod\bla761090\0025\m1\us\non-proprietary-name-suffix-request.pdf

(b) (4)

^d See Section VI which describes that any suffixes should be devoid of meaning in Guidance for Industry: Nonproprietary Naming of Biological Products. 2017. Available from: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM459987.pdf>

3 COMMUNICATION OF DMEPA'S ANALYSIS

These findings were shared with OPDP, TBBS, and ORP. Per an email correspondence dated June 15, 2018, OPDP did not identify any concerns that would render this proposed suffix unacceptable. In email correspondence dated June 25, 2018, the workgroup concurred with DMEPA's and OPDP's assessment and conclusion. DMEPA also communicated our findings to the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) via e-mail on June 25, 2018.

4 CONCLUSION

We find Dyax Corp.'s proposed suffix -flyo acceptable and recommend the nonproprietary name be revised throughout the draft labels and labeling to lanadelumab-flyo.

4.1 Recommendations for Dyax Corp.

We find the nonproprietary name, lanadelumab-flyo, conditionally acceptable for your proposed product. Should your 351(a) BLA be approved during this review cycle, lanadelumab-flyo will be the proper name designated in the license and you should revise your proposed labels and labeling accordingly. However, please be advised that if your application receives a complete response, the acceptability of your proposed suffix will be re-evaluated when you respond to the deficiencies. If we find your suffix unacceptable upon our re-evaluation, we would inform you of our finding.

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

/s/

DANIELLE M HARRIS on behalf of CARLOS M MENA-GRILLASCA
06/28/2018

DANIELLE M HARRIS
06/28/2018

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: June 4, 2018

To: Sally Seymour, MD
Acting Director
**Division of Pulmonary, Allergy, and Rheumatology
Products (DPARP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Sharon Williams, MSN, BSN, RN
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

From: Kelly Jackson, PharmD
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Kyle Snyder, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)
and Instructions for Use (IFU)

Drug Name (established name): TAKHZYRO (lanadelumab)

Dosage Form and Route: injection, for subcutaneous use

Application Type/Number: BLA 761090

Applicant: Dyax Corp.

1 INTRODUCTION

On December 26, 2017, Dyax Corp. submitted for the Agency's review a Biologics Licensing Application (BLA) 761090 for TAKHZYRO (lanadelumab) injection, for subcutaneous use. The proposed indication is for prophylaxis to prevent attacks ^{(b) (4)} of hereditary angioedema (HAE) in patients 12 years or older.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) on February 21, 2018 and February 13, 2018, for DMPP and OPDP, respectively to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for TAKHZYRO (lanadelumab) injection, for subcutaneous use.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU will be forthcoming.

2 MATERIAL REVIEWED

- Draft TAKHZYRO (lanadelumab) PPI and IFU received on December 26, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on May 22, 2018.
- Draft TAKHZYRO (lanadelumab) Prescribing Information (PI) received on December 26, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on May 22, 2018.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss. We reformatted the PPI and IFU document using the Arial font, size 10.

In our collaborative review of the PPI and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

- ensured that the PPI and IFU is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI and IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI and IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI and IFU.

Please let us know if you have any questions.

21 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

KELLY D JACKSON
06/04/2018

KYLE SNYDER
06/04/2018

SHARON W WILLIAMS
06/04/2018

LASHAWN M GRIFFITHS
06/04/2018

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: May 30, 2018

To: Colette Jackson
Senior Regulatory Health Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

From: Kyle Snyder, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Kathleen Klemm, PharmD
Team Leader (OPDP)

Subject: OPDP Labeling Comments for TAKHZYRO™ (lanadelumab) injection, for subcutaneous use

BLA: 761090

In response to DPARP's consult request dated February 13, 2018, OPDP has reviewed the proposed prescribing information (PI), patient package insert (PPI), Instructions for Use (IFU), and carton and container labels for BLA 761090, TAKHZYRO™ (lanadelumab) injection, for subcutaneous use.

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DPARP on May 21, 2018. Comments on the proposed PI are provided below.

PPI and IFU: A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed for the PPI and IFU, and comments will be sent under separate cover.

Carton and Container Labels: OPDP's comments on the proposed labels are based on the draft carton and container labels received on March 29, 2018. OPDP has no comments at this time.

Thank you for your consult. If you have any questions, please contact Kyle Snyder at (240) 402-8792 or kyle.snyder@fda.hhs.gov.

14 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

KYLE SNYDER
05/30/2018

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: May 2, 2018

Requesting Office or Division: Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

Application Type and Number: BLA 761090

Product Name and Strength: Takhzyro
(lanadelumab-xxxx^a)
Injection
(b) (4)
300 mg/2 mL (150 mg/mL)

Total Product Strength: (b) (4) 300 mg/2 mL

Product Type: Single-Ingredient Product

Rx or OTC: Rx

Applicant/Sponsor Name: Dyax Corp.

FDA Received Date: December 26, 2017 and March 29, 2018

OSE RCM #: 2017-2629

DMEPA Safety Evaluator: Lissa C. Owens, PharmD

DMEPA Team Leader: Sarah K. Vee, PharmD

^a FDA has not yet designated a nonproprietary name for Dyax’s proposed biologic product that includes a distinguishing suffix (see Guidance on Nonproprietary Naming of Biological Products). FDA is using “-xxxx” as a placeholder for the suffix. “-xxxx” is not intended to be included in the final printed labels and labeling.

1 REASON FOR REVIEW

This review evaluates the proposed labels and labeling for Takhzyro (lanadelumab-xxxx) Injection for areas of vulnerability that could lead to medication errors. The Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) requested this review as part of their evaluation of BLA 761090.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B-N/A
Human Factors Study	C-N/A
ISMP Newsletters	D-N/A
FDA Adverse Event Reporting System (FAERS)*	E-N/A
Other	F-N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Dyax submitted a 351(a) BLA 761090 on October 31, 2017, with the proposed indication of prophylaxis to prevent attacks (b) (4) of hereditary angioedema (HAE) in patients 12 years and older.

DMEPA evaluated the proposed container labels, carton labeling, instructions for use, and prescribing information to determine whether there are any vulnerabilities that may lead to medication errors. We note that the terms 'single-dose' and (b) (4) appear to be used interchangeably in the labeling and the prescribing information contains abbreviations in the dosage and administration section. We make recommendations in section 4.1 and 4.2.

4 CONCLUSION & RECOMMENDATIONS

We reviewed the proposed container labels, carton labeling, instructions for use, and prescribing information and determined that the labeling can be improved to increase the clarity of important information.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information

1. Under Section 2.1 'Recommended Dosing' remove the terms [REDACTED] (b) (4)
2. Revise the strength presentation [REDACTED] (b) (4)

4.2 RECOMMENDATIONS FOR DYAX CORP.

We recommend the following be implemented prior to approval of this BLA:

B. Carton Labeling, Prescribing Information, and Instructions for Use

1. We note that you use the terms [REDACTED] (b) (4) and 'single-dose' interchangeably. Replace [REDACTED] (b) (4) with 'single-dose' to maintain consistency throughout the labeling.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Takhzyro received on December 26, 2017 and March 29, 2018 from Dyax Corp.

Table 2. Relevant Product Information for Takhzyro	
Initial Approval Date	N/A
Active Ingredient	lanadelumab-xxxx
Indication	prophylaxis to prevent attacks (b) (4) of hereditary angioedema (HAE) in patients 12 years and older
Route of Administration	Subcutaneous
Dosage Form	Injection
Strength	(b) (4) <ul style="list-style-type: none"> • 300 mg/2 mL solution in a single-dose vial
Dose and Frequency	300 mg every 2 weeks
How Supplied	A ready-to-use solution supplied in an individually packaged glass vial with chlorobutyl rubber stopper, aluminum crimp seal and polypropylene flip-off cap. Each vial contains a slight overfill.
Storage	<ul style="list-style-type: none"> • Vials must be stored under refrigerated conditions at 2°C to 8°C (36°F to 46°F) • (b) (4) • Do not freeze • Keep the vial in the original carton in order to protect the vial from light

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^b along with postmarket medication error data, we reviewed the following Takhzyro labels and labeling submitted by Dyax Corp.

- Carton labeling received on March 29, 2018
- Container label received on March 29, 2018
- Instructions for Use (Image not shown) received on March 29, 2018
- Prescribing Information (Image not shown) received on March 29, 2018

G.2 Label and Labeling Images

(b) (4)



^b Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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

/s/

LISSA C OWENS
05/02/2018

SARAH K VEE
05/03/2018

CLINICAL INSPECTION SUMMARY

Date	March 20, 2018
From	Min Lu, M.D., M.P.H., Medical Officer Janice Pohlman, M.D., M.P.H., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Stacy Chin, M.D., Medical Officer Badrul Chowdhury, M.D., Ph.D., Division Director Colette Jackson, Senior Regulatory Project Manager Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
BLA	761090
Applicant	Dyax Corp.
Drug	Lanadelumab
NME	Yes
Therapeutic Classification	Human immunoglobulin G1 (IgG1) kappa light chain monoclonal antibody against plasma kallikrein
Proposed Indication	Prophylaxis to prevent attacks (b) (4) of hereditary angioedema (HAE) in patients 12 years and older
Consultation Request Date	January 29, 2018
Summary Goal Date	April 1, 2018
Action Goal Date	June 26, 2018
PDUFA Date	August 26, 2018

1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Two clinical sites (Drs. Anderson and Craig) were selected for inspection for Protocol DX-2930-03, entitled “HELP Study®: A Multicenter, Randomized, Double-blind, Placebo-Controlled Efficacy and Safety Study to Evaluate DX-2930 For Long-Term Prophylaxis Against Acute Attacks of Hereditary Angioedema (HAE).” The study data derived from these clinical sites, based on the inspections, are considered reliable in support of the requested indication under this BLA.

The preliminary classification for the inspections of both above clinical sites is No Action Indicated (NAI). Preliminary classifications are based on communications with the ORA investigator. Inspection classification becomes final when the Establishment Inspection Report is received from the field, has been reviewed, and a letter is issued to the inspected entity. A clinical inspection summary addendum will be provided if review of the inspection report(s) indicates significant change in the classification for the inspection.

2. BACKGROUND

Lanadelumab is a human immunoglobulin G1 (IgG1) kappa light chain monoclonal antibody expressed in Chinese hamster ovary cells. It is a potent and specific inhibitor of active plasma kallikrein activity that rapidly binds both soluble and membrane-bound forms of the enzyme.

Hereditary angioedema (HAE) is a long-term, debilitating, and life-threatening disease caused by mutations in the C1 (esterase) inhibitor (C1-INH) gene, resulting in deficiency or dysfunction of C1-INH protein. Hereditary angioedema manifests clinically as unpredictable, intermittent attacks of subcutaneous or submucosal edema of the face, larynx, gastrointestinal tract, limbs, and/or genitalia. Lanadelumab is intended to prevent the release of bradykinin from high molecular weight kininogen, thereby preventing the vascular leak and swelling during an angioedema attack that is initiated when bradykinin binds to the B2 receptor. The sponsor proposes lanadelumab for routine prophylaxis to prevent attacks [REDACTED]^{(b) (4)} of hereditary angioedema (HAE) in patients 12 years and older.

Lanadelumab for hereditary angioedema is an orphan product developed under Fast Track. It was granted Breakthrough Therapy designation in May 2017. The sponsor conducted a Phase 3 study (DX-2930-03) to support the proposed indication. CDER DPARP requested two clinical sites for inspections for the Phase 3 clinical trial based on high enrollment and better efficacy at these sites.

Protocol DX-2930-03

This was a Phase 3, multicenter, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of DX-2930 in preventing acute angioedema attacks in patients with Type I and Type II HAE.

The primary objective of this study was to evaluate the efficacy of lanadelumab (DX-2930) in preventing HAE attacks. The secondary objective was to evaluate the safety of repeated subcutaneous (SC) administrations of lanadelumab.

The primary efficacy endpoint was the number of investigator-confirmed HAE attacks during the treatment period (Day 0 through Day 182). The secondary efficacy endpoints included the number of investigator-confirmed HAE attacks requiring acute treatment during the treatment period, the number of moderate or severe investigator-confirmed HAE attacks during the treatment period, and the number of investigator-confirmed HAE attacks occurring on Day 14 after administration of study drug through Day 182.

The study main inclusion criteria included subjects 12 years of age or older at the time of screening; documented diagnosis of HAE (Type I or II) based upon documented clinical history consistent with HAE (subcutaneous or mucosal, nonpruritic swelling episodes without accompanying urticaria), diagnostic testing results obtained during screening that confirm HAE Type I or II; and at least one of the following: age at reported onset of first angioedema symptoms \leq 30 years, a family history consistent with HAE Type I or II, or C1q within normal range. Subjects must also have experienced a baseline rate of at least 1 investigator-confirmed HAE attack per 4 weeks as confirmed during the run-in period.

Screened subjects who were either not on long-term prophylactic therapy for HAE or who had completed the required minimum 2-week washout period, entered a run-in period of 4 weeks to determine the baseline HAE attack rate. Only subjects meeting a minimum baseline rate of at least 1 investigator-confirmed HAE attack per 4 weeks were eligible for enrollment and randomization. After verification of eligibility, subjects were randomized 2:1 to receive repeated subcutaneous administrations of lanadelumab or placebo in a double-blind fashion. Subjects who were randomized to lanadelumab were assigned in a 1:1:1 ratio to one of 3 dose regimens: 150 mg every 4 weeks, 300 mg every 4 weeks, or 300 mg every 2 weeks. Randomization into all treatment groups was stratified by the baseline attack rate observed during the run-in period into the following groups: 1 to <2 attacks per 4 weeks, 2 to <3 attacks per 4 weeks, and ≥ 3 attacks per 4 weeks. Each subject entered a treatment period consisting of 13 doses of blinded investigational product for a period of 26 weeks. Subjects who completed the treatment period were given the option to enroll in an open-label HELP Study Extension (Study DX-2930-04). Subjects who elected not to participate in Study DX-2930-04 were to undergo safety and additional pharmacokinetic and pharmacodynamic evaluations during an 8-week follow-up period. Subjects were instructed to inform the site of any HAE attack experienced for up to 30 days after the final follow-up visit.

The study screened 159 subjects and enrolled 126 subjects from the clinical sites in six countries including United States, United Kingdom, Italy, Germany, Canada, and Jordan. The study enrolled the first subject on March 3, 2016 and the last subject completed the last visit on April 13, 2017.

3. RESULTS (by site):

Name of CI, Address	Site #, Protocol #, and # of Enrolled Subjects	Inspection Date	Classification
John Anderson, M.D. Clinical Research Center of Alabama 504 Brookwood Blvd., Suite 250 Birmingham, AL 35209	Site #101 DX-2930-03 Subjects: 9	February 26-28, 2018	*NAI
Timothy Craig, M.D. Penn State Hershey Medical Center, Pulmonary/Allergy/Critical Care 500 University Drive, C5860 Hershey, PA 17033	Site #106 DX-2930-03 Subjects: 5	March 5-9, 2018	*NAI

Key to Compliance Classifications

NAI (No Action Indicated) = No deviation from regulations.

VAI (Voluntary Action Indicated) = Deviation(s) from regulations.

OAI (Official Action Indicated) = Significant deviations from regulations. Data unreliable.

*Pending = Preliminary classification based on information in Form FDA 483 or preliminary communication with the field; EIR has not been received from the field, and

complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

Clinical Study Site Investigators

1) John Anderson, M.D. (Site #101, Birmingham, AL)

The site screened and enrolled nine subjects for Study Protocol DX-2930-03. All nine subjects completed the study. An audit of the nine enrolled subjects' records was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, eligibility criteria, randomization and blinding procedure, case report forms, electronic files, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected. Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and BLA subject line listings. There were no limitations during conduct of the clinical site inspection.

Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of adverse events was noted.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. No objectionable findings were noted and a Form FDA 483 (Inspectional Observations) was not issued. Data submitted by this clinical site appear reliable in support of this specific indication.

2) Timothy Craig, M.D. (Site # 106, Hershey, PA)

The site screened and enrolled five subjects for Study Protocol DX-2930-03. Among the five enrolled subjects, four subjects completed the study and one subject discontinued due to adverse events (Subject # (b) (6), elevated AST/ALT). The discontinuation data listing provided in the NDA were verified by review of source documents. An audit of all 5 enrolled subjects' records was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, eligibility criteria, randomization and blinding procedure, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected. Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and BLA subject line listings. There were no limitations during conduct of the clinical site inspection.

Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of adverse events was noted.

The following two protocol deviation were noted during the inspection:

- Subject (b) (6) was incorrectly stratified to the 1 to < 2 HAE attacks per 4 weeks, rather than the 2 to < 3 HAE attacks per 4 weeks at randomization. Although this subject had two HAE attacks during the run-in period prior to randomization, the second attack was not entered on the eCRF until after the randomization.
- Subject (b) (6) received a protocol prohibited medication (lisinopril for 34 days), prescribed by primary care physician.

OSI reviewer comments:

Angiotensin-converting enzyme (ACE) inhibitors, such as lisinopril, have been associated with drug-related angioedema events. Subject (b) (6), randomized into DX-2930 150 mg every 4 weeks group had no HAE attacks reported during the lisinopril treatment period. These observations appear unlikely to have significant impact on the primary efficacy endpoint and safety results of the study. The above observations were reported as protocol deviations in the NDA submission. Corrective/preventive actions were subsequently taken at the site.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (Inspectional Observations) was not issued. Data submitted by this clinical site appear reliable in support of this specific indication.

{See appended electronic signature page}

Min Lu, M.D., M.P.H.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Janice Pohlman, M.D., M.P.H.
Team Leader, Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H.
Branch Chief, Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:

Central Doc. Rm.

Review Division /Division Director/ Badrul Chowdhury

Review Division/Medical Officer/ Stacy Chin

Review Division /Project Manager/ Colette Jackson

OSI/DCCE/ Division Director/Ni Khin

OSI/DCCE/Branch Chief/Kassa Ayalew

OSI/DCCE/Team Leader/ Susan Thompson

OSI/DCCE/Team Leader/Janice Pohlman

OSI/DCCE/GCP Reviewer/Min Lu

OSI/ GCP Program Analyst/Yolanda Patague

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

/s/

MIN LU
03/20/2018

JANICE K POHLMAN
03/20/2018

KASSA AYALEW
03/20/2018