CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210854Orig1s000

OTHER REVIEW(S)

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:	October 17, 2018
To:	Debra Birnkrant, MD Director **Division of Antiviral Products (DAVP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Ruth Lidoshore, PharmD Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Nima Ossareh, PharmD, RAC Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	XOFLUZA (baloxavir marboxil)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 210854
Applicant:	Shionogi Inc.

1 INTRODUCTION

On April 24, 2018, Shionogi Inc. submitted for the Agency's review an original New Drug Application (NDA) 210854 for XOFLUZA (baloxavir marboxil) tablets. The proposed indication for XOFLUZA (baloxavir marboxil) tablets is for the treatment of acute uncomplicated influenza in patients 12 years of age and older who have been symptomatic for no more than 48 hours.

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 Antiviral Products (DAVP) on April 30, 2018, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for XOFLUZA (baloxavir marboxil) tablets.

2 MATERIAL REVIEWED

- Draft XOFLUZA (baloxavir marboxil) tablets PPI received on April 24, 2018, and received by DMPP and OPDP on October 9, 2018.
- Draft XOFLUZA (baloxavir marboxil) tablets Prescribing Information (PI) received on April 24, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 9, 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 APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is 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 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.

Please let us know if you have any questions.

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/s/

RUTH I LIDOSHORE
10/17/2018

SAMUEL M SKARIAH on behalf of NIMA OSSAREH
10/17/2018

BARBARA A FULLER
10/17/2018

LASHAWN M GRIFFITHS
10/17/2018

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

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

Memorandum

Date: 10/15/18

To: Victoria Tyson
Senior Regulatory Health Project Manager
Division of Antiviral Products (DAVP)

From: Nima Ossareh, PharmD, RAC
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sam Skariah, Team Leader, OPDP

Subject: OPDP Labeling Comments for XOFLUZA™ (baloxavir marboxil) tablets, for oral use

NDA: 210854

In response to DAVP's consult request dated April 30, 2018, OPDP has reviewed the proposed product labeling (PI) and patient package insert (PPI) for XOFLUZA™ (baloxavir marboxil) tablets, for oral use.

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DAVP on October 9, 2018, and are provided below.

PPI: A combined OPDP and Division of Medical Policy Programs (DMPP) review of the PPI will be completed under a separate cover.

Thank you for your consult. If you have any questions, please contact Nima Ossareh at (240) 402-2769 or nima.ossareh@fda.hhs.gov.

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/s/

NIMA OSSAREH
10/15/2018

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
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)

Date of This Memorandum:	October 1, 2018
Requesting Office or Division:	Division of Antiviral Products (DAVP)
Application Type and Number:	NDA 210854
Product Name and Strength:	Xofluza (baloxavir marboxil) tablet, 20 mg and 40 mg
Applicant/Sponsor Name:	Shionogi, Inc.
FDA Received Date:	September 27, 2018
OSE RCM #:	2018-838-2
DMEPA Safety Evaluator:	Valerie S. Wilson, PharmD
DMEPA Team Leader (Acting):	Teresa McMillan, PharmD

1 PURPOSE OF MEMORANDUM

The Division of Antiviral Products (DAVP) requested that we review the revised carton labeling for Xofluza (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised carton labeling for Xofluza are acceptable from a medication error perspective. We have no further recommendations at this time.

[a] Wilson, V. Label and Labeling Review Memo for Xofluza (NDA 210854). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 SEP 24. RCM No.: 2018-838-1.

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/s/

VALERIE S WILSON
10/01/2018

TERESA S MCMILLAN
10/01/2018

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
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)

Date of This Memorandum:	September 24, 2018
Requesting Office or Division:	Division of Antiviral Products (DAVP)
Application Type and Number:	NDA 210854
Product Name and Strength:	Xofluza (baloxavir marboxil) Tablets, 20 mg and 40 mg
Applicant/Sponsor Name:	Shionogi, Inc.
FDA Received Date:	September 18, 2018
OSE RCM #:	2018-838-1
DMEPA Safety Evaluator:	Valerie S. Wilson, PharmD
DMEPA Team Leader (Acting):	Teresa McMillan, PharmD

1 PURPOSE OF MEMORANDUM

The Division of Antiviral Products (DAVP) requested that we review the revised container labels and carton labeling for Xofluza (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

Our evaluation of the revised container labels and carton labeling for Xofluza determined the container labels are acceptable; however, we find the revised carton labeling is unacceptable from a medication error perspective. (b) (4) We previously recommended the Applicant present the net quantity/total dose statement as shown in figure 1.

Figure 1. Previous DMEPA recommendation

[a] Wilson, V. Label and Labeling Review for Xofluza (NDA 210854). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 SEP 10. RCM No.: 2018-838.

(b) (4)

The applicant did not provide rationale (b) (4) which increases the risk for underdose and overdose medication errors.

Figure 2. Comparison of Principal Display Panels for each Dose Configuration of Xofluza

To mitigate the risk of underdose and overdose errors, we recommend the Applicant revise the carton labeling to provide adequate differentiation between the packaging configurations, for example, by removing (b) (4) (see Figure 3).

Figure 3. Contains 40 mg total dose (2 x 20 mg tablets)
Contains 80 mg total dose (4 x 20 mg tablet)
Contains 40 mg total dose (1 x 40 mg tablet)
Contains 80 mg total dose (2 x 40 mg tablets)

3 RECOMMENDATIONS FOR SHIONOGI, INC.

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

A. The carton labeling lacks adequate differentiation across the packaging configurations. You did not provide a rationale (b) (4) his increases the risk for underdose and overdose medication errors. To mitigate the risk of underdose and overdose errors, we recommend you revise the carton labeling to provide adequate differentiation between the packaging configurations, for example, by removing (b) (4) (see example below).

Contains 40 mg total dose (2 x 20 mg tablets)
Contains 80 mg total dose (4 x 20 mg tablet)
Contains 40 mg total dose (1 x 40 mg tablet)
Contains 80 mg total dose (2 x 40 mg tablets)

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/s/

VALERIE S WILSON
09/24/2018

TERESA S MCMILLAN
09/24/2018

LABEL, LABELING, AND PACKAGING 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:	September 10, 2018
Requesting Office or Division:	Division of Antiviral Products (DAVP)
Application Type and Number:	NDA 210854
Product Name and Strength:	Xofluza (baloxavir marboxil) Tablets, 20 mg and 40 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Shionogi, Inc.
FDA Received Date:	April 24, 2018, July 5, 2018, and August 20, 2018
OSE RCM #:	2018-838
DMEPA Safety Evaluator:	Valerie S. Wilson, PharmD
DMEPA Team Leader (Acting):	Teresa McMillan, PharmD

1 PURPOSE OF REVIEW

As part of the approval process for Xofluza (baloxavir marboxil) Tablets, 20 mg and 40 mg, the Division of Division of Antiviral Products (DAVP) requested that we review the proposed DosePak [redacted] (b) (4) label and carton labeling, prescribing information, and patient information for areas that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label, Labeling, and Packaging Review	
Material Reviewed	**Appendix Section (for Methods and Results)**
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B (N/A)
ISMP Newsletters	C (N/A)
FDA Adverse Event Reporting System (FAERS)*	D (N/A)
[redacted] (b) (4)	E
Labels and Labeling	F

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 FINDINGS AND RECOMMENDATIONS

Tables 2 and 3 below include the identified medication error issues with the submitted prescribing information, container labels, and carton labeling, DMEPA's rationale for concern, and the proposed recommendation to minimize the risk for medication error.

The Applicant initially submitted [redacted] (b) (4) an evaluation of the DosePak is included in this review.

Table 2: Identified Issues and Recommendations for Division of Antiviral Products

Prescribing Information			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
Highlights of Prescribing Information (HPI)			
1.	In the DOSAGE AND ADMINISTRATION section of the HPI, the symbols "<" and "≥" are used.	These symbols may result in misinterpretation and confusion, which could lead to medication errors.[a]	Consider replacing the error prone symbols "<" and "≥" with their intended meanings to prevent misinterpretation and confusion.
Full Prescribing Information (FPI)			
1.	In the DOSAGE AND ADMINISTRATION section of the FPI, symbols "<" and "≥" are used.	These symbols may result in misinterpretation and confusion which could lead to medication errors.[a]	Consider replacing the error prone symbols "<" and "≥" with their intended meanings to prevent misinterpretation or confusion.

Table 3: Identified Issues and Recommendations for Shionogi, Inc. (entire table, figure 1, and figure 2 to be conveyed to Applicant)

	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
Container Label (Inner Card)			
1.	The dose of the full package presents more prominently than the strength of each individual tablet. (b) (4)	End users may misinterpret the dose as the strength of each tablet, which could lead to underdose errors.	To provide clarity and mitigate underdose errors, we recommend revising the strength and dose presentations on the container label. Additionally, the same revisions should be applied to the carton. See proposed revisions in blue in figures 1 and 2.
Carton Labeling			

[a] ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2015 [cited 2018 JUL 10]. Available from: https://www.ismp.org/tools/errorproneabbreviations.pdf

2.	There is inadequate differentiation between the 20 mg and 40 mg strengths.	(b) (4)	(b) (4) to provide adequate differentiation between the strengths.
3.	An area for the lot number and expiration date is not designated on the outer carton labeling. Additionally, the format of the expiration date is not defined.	The lot number and expiration date are required on the immediate container and carton labeling per 21 CFR 201.10(i)(1) and 21 CFR 201.17, respectively.	To comply with 21 CFR 201.10(i)(1) and 21 CFR 201.17, ensure the lot number and expiration date are included on the immediate container and carton labeling. Additionally, to minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use to express the expiration date. We recommend using a format like either: DDMMMYYYY (e.g., 31JAN2013) MMMYYYY (e.g., JAN2013) YYYY-MMM-DD (e.g., 2013-JAN-31) YYYY-MM-DD (e.g., 2013-01-31)

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Figure 1. Proposed Recommended Revisions for the DosePak Inner Card

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/s/

VALERIE S WILSON
09/10/2018

IRENE Z CHAN on behalf of TERESA S MCMILLAN
09/11/2018

CLINICAL INSPECTION SUMMARY

Date	September 11, 2018
From	Sharon Gershon, Pharm.D, Reviewer Susan Thompson, M.D., Team Leader, Kassa Ayalew, M.D., M.P.H., Branch Chief, OSI /DCCE/GCPAB
To	Melisse Baylor, M.D, DAVP/Medical Officer Mary Singer, M.D, DAVP/Medical Team Leader Debra Birnkrant, M.D, DAVP/Division Director Victoria Tyson, PharmD, DAVP/Regulatory Project Manager Division of Anti-Viral Products (DAVP)
NDA #	NDA 210854
Applicant	Shionogi
Drug	XOFLUZA™ (baloxavir marboxil) Tablets 20 mg and 40 mg (S-033188)
NME	Yes
Therapeutic Classification	Priority Review
Proposed Indication	Treatment of acute uncomplicated influenza in patients 12 years and older who have been symptomatic for no more than 48 hours
Consultation Request Date	05/18/2018
Summary Goal Date	09/24/2018
Action Goal Date	10/24/2018
PDUFA Date	12/24/2018

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATION

The data from Phase 3 Study 1601T0831 and Phase 2 Study 151T0831 were submitted to the Agency in support of NDA 210854. For Study 1601T0831, three inspections (two in the U.S., one in Japan) were conducted, and for Study 151T0831, one inspection (in Japan) was conducted. No regulatory violations were found during inspections at any investigator site. The inspections are classified as No Action Indicated (NAI). The studies were conducted adequately, and data from these sites are acceptable in support of the pending application.

II. BACKGROUND

Shionogi Inc. submitted NDA 210854, XOFLUZA™ (proposed) (baloxavir marboxil) 20 mg and 40 mg tablets, expedited priority review, for the treatment of acute uncomplicated influenza in patients 12 years of age and older who have been symptomatic for no more than 48 hours. The data from two pivotal studies were submitted to support safety and efficacy.

The following two protocols were conducted in support of efficacy under this NDA:

Study 1518T0821: A randomized, double-blind, placebo-controlled, phase 2 study of S-033188 in otherwise healthy adult patients with influenza.

Study duration: 22 days
Dates of Study: November 2015 to June 2016

Four-hundred patients diagnosed with influenza virus infection were randomized in a ratio of 1:1:1:1 to receive S-033188 10 mg, S-033188 20 mg, S-033188 40 mg, or placebo.

The primary objective was to evaluate the efficacy of S-033188 (10, 20, and 40 mg) versus placebo as measured by the time to alleviation of influenza symptoms in patients with influenza virus infection.

The primary efficacy endpoint was the time to alleviation of influenza symptoms defined as time when all symptoms are assessed as 0 (none) or 1 (mild). Secondary endpoints included:

- Change from baseline in the total score of 7 influenza symptoms
- Time to alleviation of each influenza symptom
- Time to resolution of fever (axillary temperature < 37° C)
- Percentage of subjects with resolution of fever
- Percentage of subjects with virus titer detected

Study 1601T0831: A Phase 3, Multicenter, Randomized, Double-blind Study of a Single Dose of S-033188 Compared with Placebo or Oseltamivir 75 mg Twice Daily for 5 Days in Otherwise Healthy Patients with Influenza

This was a randomized, double-blind, multicenter, parallel-group, placebo- and active-controlled study enrolling approximately 1494 patients diagnosed with influenza. Approximately 1350 patients aged 20 to 64 years and 144 patients aged 12 to 19 years were enrolled.

For this study, eligible adult (aged ≥20 and 64 years) patients were randomized in a ratio of 2:2:1 to a single dose of S-033188 (for 1 day, S-033188 group), repeated doses of oseltamivir (75 mg twice daily for 5 days, oseltamivir group), or placebo (placebo group). Eligible adolescent (aged ≥12 and <19 years) patients were randomized in a ratio of 2:1 to a single dose of S-033188 (S-033188 group) or placebo (placebo group). For each age stratum, the patients were also stratified by the following 3 factors: region (Japan/Asia or the rest of the world), patient's weight (< 80 kg or ≥80 kg), and the composite symptom score (a total of 7 influenza symptoms scored (none = 0, mild = 1, moderate = 2, and severe = 3) at baseline (11 or ≥ 12).

Subjects were followed for 14 days for efficacy and 22 days for safety. The primary endpoint was time to alleviation of symptoms (cough, sore throat, headache, nasal congestion, feverishness or chills, muscle or joint pain, and fatigue), defined as the time from the start of treatment to the time when all influenza symptoms are rated as absent or mild.

Reasons for Site Selection:

This is a New Molecular Entity (NME), first-in-class oral antiviral drug for treatment of influenza. Two domestic sites and two foreign sites were inspected. U.S. Site #128 (McLean) enrolled the highest number of subjects overall with the highest number of pediatric subjects. This site had a high number of screen failures and premature discontinuations. U.S. Site #201 (Dever) had a better outcome for study drug (baloxavir/S-033188) than for placebo.

Japan Site #307 (Yamada) enrolled a large number of study subjects, the outcome was better for study drug (baloxavir/S-033188) than for the placebo, and there was a low number of adverse events compared to other sites. Japan Site #2KB (Kitada, Study 1518T0831) conducted a non-IND study that enrolled a large number of subjects, with no subjects having adverse events and no screen failures. Many subjects in both studies were enrolled at Japanese sites. The pharmacokinetics of baloxavir reportedly differs significantly between Japanese and non-Japanese patients, which has the potential to affect both efficacy and safety findings.

III. RESULTS (by site):

CI Name and Address	Protocol #, Site #, and # of Subjects enrolled	Inspection Dates	Compliance Classification
Barry McLean Birmingham, AL	Study 1601T0831 Site #128 40 subjects	6/25/18 - 6/28/18	NAI
Kouta Yamada Tsuchiura City, Japan	Study 1601T0831 Site #307 21 subjects	8/06/18 - 8/08/18	NAI
Michael Dever Orlando, FL	Study 1601T0831 Site #201 19 subjects	6/25/18 - 6/29/18	NAI
Hirokazu Kitada Osaka, Japan	Study 1518T0831 Site #2KB 18 subjects	7/30/18 - 8/02/18	NAI

Key to Compliance Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
*Pending = Preliminary classification based on information in 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.

1. Barry McLean
Central Alabama Research
10 Old Montgomery Highway, Suite 100
Birmingham, AL 35209

Dr. Barry McClean is listed with 53 IND studies in the COMIS CDER database. A prior inspection conducted 8/16-18/16 revealed no deficiencies, and no FDA-483 was issued.

The current inspection audited Protocol No. 1601T0831. Dr. McLean enrolled 40 of 57 screened subjects between 1/11/17 and 3/13/17. Reasons for the 17 screen failures were: failure to have enough test article on hand at the time of screening (4 subjects), lack of appropriate symptoms (6 subjects), exclusionary medical history (5). Two subjects withdrew and were recorded as screen failures: #132 withdrew because the blood collections were too numerous, and the subject did not want to participate; and Subject #148 withdrew because the rapid flu test resulted as negative, and the subject did not want to participate further.

The field investigator reviewed the source data worksheets, randomization emails, electronic diary (diary) symptoms, lab reports, electrocardiograms, adverse events, protocol deviations, concomitant medications, and quality of life questionnaires for 25 of the 40 enrolled subjects and compared applicable data points with the data line listings included with the assignment. The informed consent documents (ICD) for the 57 screened subjects were reviewed, along with the IRB approvals, drug accountability records, monitoring visit logs and emails, and financial disclosure documents.

Source records consisted of signed informed consent forms and assent forms; electronic medical records; worksheets (eligibility checklists, medical histories, physical exams, vital signs, concomitant medications, and follow-up visit records); questionnaires; laboratory test result printouts (serum chemistry, hematology, urine pregnancy, and viral marker - hepatitis and HIV); nasopharyngeal swab collection data; pharmacokinetic sample collection documentation (results were not received from the lab); electrocardiograms; randomization emails for dosing of blinded test article; test article dispensing and accounting; adverse event information

All protocol deviations were reported to the sponsor and IRB. Most protocol deviations involved Dr. McLean treating subjects with injectable steroids for various symptoms resulting from the flu. Steroids were a prohibited medication.

Two protocol deviations were due to improper enrollment of subjects into the study. These deviations were not included in the data line listings. These included:

> Subject # (b) (6) was enrolled in the study on (b) (6) and was subsequently found to be positive for Hepatitis C, which is an exclusion criterion. The lab reported the subject's viral status on (b) (6), eleven days after collection of the blood

sample and seven days after the last dose of test article. Dr. McLean notified the sponsor of the status by fax on (b) (6), and the CRO responded by telling Dr. McLean to keep the subject in the study.

Subject # (b) (6) was enrolled in the study on (b) (6) with a history of spherocytosis, a sign of hemolytic anemia, and a resultant splenectomy as treatment. The subject should have been excluded, as the subject would be considered high-risk; however, the subject could have been enrolled in the companion study #1601T0832 for high-risk subjects. Dr. McLean reported the error to the sponsor on (b) (6) stating that he did not believe the subject was high risk due to the splenectomy resolving the exclusionary condition. This protocol deviation was reported to the sponsor and the IRB.

Financial disclosure forms were reviewed. The ORA investigator found that everyone listed on the FDA-1572 had completed the form and submitted it to the sponsor prior to the enrollment of the first subject on (b) (6). No deficiencies in these documents were noted.

No deficiencies were noted, and no FDA-483 was issued.

2. Michael E. Dever
Family Medical Center
618 E. South Street, Suite 100
Orlando, FL 32801-2987

This was the initial FDA inspection for Michael E. Dever, and covered Protocol 1601T0831. The following documentation was reviewed: source documents and case report forms (CRFs) which included medical records, ext listse-diaries, and worksheets; correspondence with the Institutional Review Board (IRB) and sponsor; Informed Consent Documents (ICD) for all screened subjects; monitoring visits; test article accountability records.

The site screened 20 subjects, enrolled 19 subjects, and 16 subjects completed the study. Three subjects discontinued, and there was one screen failure. Reasons for subjects who discontinued were:

- Subject (b) (6) withdrew consent after Visit 1.
- Subject (b) (6) was incarcerated for 30 days and dropped from the study after the Visit 3.
- Subject (b) (6) was lost to follow-up after Visit 3.

All 20 enrolled subjects met the inclusion eligibility criteria. For the sixteen subjects who completed the study, the source documents for the primary endpoint (time to alleviation of 7 symptoms cough, sore throat, headache, nasal congestion, fever, muscle, and joint pain and fatigue) matched the data listings provided with the assignment. All secondary endpoints reviewed in the source records corroborated with the data listings.

The records appeared to be well organized, legible, and complete. The subject's records provided ample documentation of observations from the follow-up visits

The source documents corroborated with the listings for adverse events. There was no underreporting of adverse events. The most common adverse event was nausea. Dr. Dever classified all other adverse events as mild or moderate and not caused by the test article.

There was a total of ten protocol deviations reported among seven subjects. All were reported to the sponsor. The following are examples of deviations:

- Subject (b) (6) was prescribed Benzonatate due to influenza complication.
- Subject (b) (6) was prescribed prednisone due to influenza complication.
- Subject (b) (6) – the influenza antibody titer was not collected (Visit 7 - day 22).
- Subject (b) (6) – the subject was prescribed Benzonatate due to influenza complication (Visit 5 - day 9), and Valtrex due to influenza complication (Visit 7 - day 22).
- Subject (b) (6) - pharmacokinetics sample was not collected (Visit 2 - day 2).

Financial disclosure forms were reviewed. The forms were appropriately completed and signed by the principal investigator.

No Form FDA-483 was issued. The inspection is classified as NAI.

3. Kouta Yamada
Tsuchiura eryl Clinic,
4-4022-2, Tsuwa, Tsuchiura City
Ibaraki, 300-0062, Japan

This was the first FDA inspection for Dr. Yamada in Japan. He has two IND studies in the CDER COMIS database. The inspection covered Protocol 1601T0831.
The site screened 22 subjects and enrolled 21 subjects into the study. A total of 20 subjects completed the study.

The ORA investigator reviewed records and procedures related to the authority and administration of the clinical trial; the clinical trial protocol and amendments; Institutional Review Board (IRB) submissions and approvals; subject selection criteria and informed consent documents; test article controls, including blinding and accountability; source data evaluation; adverse event reports; clinical source data; monitoring; laboratory samples; concomitant medications and procedures; sponsor activities at the clinical site; financial disclosure forms; and corroborated relevant source data with the data submitted to the agency.

The first subject was screened and signed the ICD on (b) (6), and the last subject follow-up visit was on (b) (6).

The ORA investigator reviewed source records for all 22 subjects screened. Study records were organized and legible. The documentation was adequate to assure subjects were alive and present during the conduct of this clinical study. The Sponsor contracted with a contract research organization (CRO) A2 Healthcare Corporation, located in Tokyo, to provide oversight and monitoring of this clinical trial. A2 Healthcare was responsible for ensuring the clinical trial was performed in such a way as to ensure the study's scientific integrity; quality of the data; compliant with ethical principles and adherence to sponsor requirements.

At the end of the inspection no Form FDA-483 was issued. The following item was discussed: Failure to document all procedures completed. Specifically, no documentation was present in subject case histories if no observations for the symptom physical were present at a visit. For example, if a subject had no cough or fever, the CI did not document that the assessments were made. Rather, no documentation was provided because the symptoms did not exist.

Dr. Yamada acknowledged the verbal observation and provided the following response:

He and his research personnel always consulted the subject and performed the assessment, this was only a documentation error that will be corrected in the future. Dr. Yamada stated that he would document any assessments performed going forward.

No other concerns were found. No Form FDA-483 was issued, and the inspection was classified as No Action Indicated (NAI).

4. Hirokazu Kitada
Kitada Clinic
2-4-1, Hanatenhigashi, Tsurumi-ku, Osaka City
Osaka, 538-0044, Japan

This was the first FDA inspection of Dr. Kitada in Japan. Dr. Kitada has one IND study listed in the COMIS CDER database. The site screened 18 subjects and enrolled 18 subjects for this study. A total of 17 subjects completed the study.

The inspection covered the review of records and procedures related to the authority and administration of the clinical trial, the clinical trial protocol and amendments, Institutional Review Board (IRB) submissions and approvals; subject selection criteria and informed consents; test article controls, including blinding and accountability; source data evaluation; adverse event reports; clinical source data; monitoring; laboratory samples; concomitant medications and procedures; sponsor activities at the clinical site; financial disclosures; and the data submitted to the agency.

The ORA investigator reviewed source data and records for all 18 subjects enrolled in the study. All study records were observed as being organized and legible.

The sponsor contracted with CRO Linical Co., Ltd., located in Osaka, Japan, to monitor this clinical trial. Linical was also responsible for ensuring the study's scientific integrity; quality of

the data; compliance with ethical principles; local and regulatory adherence; adherence with sponsor requirements.

In addition to a site initiation visit, there were 9 intermediate monitoring visits occurred each week to one month between December 2015 through April 2016. No FDA 483 was issued, and the inspection is classified is NAI.

The following verbal observation was presented at closeout:

Failure to document all procedures completed. Specifically, no documentation was present in subject case histories if no observations for adverse events and concomitant medication were present at a visit.

Dr. Kitada acknowledged the verbal observation and provided the following response:

Adverse event and concomitant medications were reviewed with each subject at each visit, but their policy was to not record anything if there were no observations. Dr. Kitada promised that all procedures will be changed to document observations.

SIGNED: {See appended electronic signature page}

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CONCURRENCE: {See appended electronic signature page}

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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