

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

213182Orig1s000

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: December 18, 2019

To: Peter Franks, Regulatory Project Manager
Division of Metabolism and Endocrinology Products (DMEP)

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

Marcia Williams, PhD
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Maria Nguyen, MSHS, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Samantha Bryant, PharmD, BCPS
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): RYBELSUS (semaglutide)

Dosage Form and Route: tablets, for oral use

Application Type/Number: NDA 213182

Applicant: Novo Nordisk, Inc.

1 INTRODUCTION

On March 20, 2019, Novo Nordisk, Inc., submitted for the Agency's review New Drug Application (NDA) 213182 RYBELSUS (semaglutide) tablets, for oral use. The proposed indication is to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus (T2DM) [REDACTED] (b) (4) [REDACTED]

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 Metabolism and Endocrinology Products (DMEP) on April 11, 2019, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for RYBELSUS (semaglutide) tablets, for oral use.

2 MATERIAL REVIEWED

- Draft RYBELSUS (semaglutide) tablets MG received on March 20, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on December 10, 2019.
- Draft RYBELSUS (semaglutide) tablets Prescribing Information (PI) received on March 20, 2019, revised by the Review Division throughout the review cycle, and received by DMPP on December 10, 2019.
- Approved OZEMPIC (semaglutide) injection, for subcutaneous use, labeling dated April 9, 2019.
- Approved RYBELSUS (semaglutide) tablets, for oral use, labeling dated September 20, 2019.

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%.

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.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- rearranged information due to conversion of the PI to Physicians Labeling Rule (PLR) format
- removed unnecessary or redundant information

- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved labeling where applicable.

4 CONCLUSIONS

The MG 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 MG 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 MG.

Please let us know if you have any questions.

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/s/

MARIA T NGUYEN
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DMPP-OPDP review of semaglutide (RYBELSUS) NDA 213182 MG

SAMANTHA E BRYANT
12/18/2019 10:21:30 AM

MARCIA B WILLIAMS
12/18/2019 10:33:09 AM

LASHAWN M GRIFFITHS
12/18/2019 02:04:46 PM

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

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

Memorandum

Date: December 17, 2019

To: Peter Franks, Regulatory Project Manager
Division of Metabolism and Endocrinology Products (DMEP)

Monika Houstoun, Associate Director for Labeling, (DMEP)

From: Samantha Bryant, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Melinda McLawhorn, Team Leader, OPDP

Subject: OPDP Labeling Comments for RYBELSUS (semaglutide) tablets, for oral use

NDA: 213182

In response to DMEP's consult request dated April 11, 2019, OPDP has reviewed the proposed product labeling (PI), and Medication Guide for the original NDA for RYBELSUS (semaglutide) tablets, for oral use (Rybelsus). Specifically, it provides updates in section 14.4 for the PIONEER 6 study in support of a proposed indication for cardiovascular risk reduction.

PI and Medication Guide: OPDP's comments on the proposed labeling are based on the draft PI and Medication Guide received by electronic mail from DMEP (Peter Franks) on December 9, 2019 and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed Medication Guide will be sent under separate cover.

Thank you for your consult. If you have any questions, please contact Samantha Bryant at (301) 348-1711 or Samantha.Bryant@fda.hhs.gov.

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SAMANTHA E BRYANT
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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:	October 7, 2019
Requesting Office or Division:	Division of Metabolism and Endocrinology Products (DMEP)
Application Type and Number:	NDA 213182
Product Name and Strength:	Rybelsus (semaglutide) tablet, 3 mg, 7 mg, and 14 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Novo Nordisk Inc. (Novo)
FDA Received Date:	March 20, 2019 and September 26, 2019
OSE RCM #:	2019-642
DMEPA Safety Evaluator:	Ariane O. Conrad, PharmD, BCACP, CDE
DMEPA Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

This review evaluates the proposed labeling for Rybelsus (semaglutide), submitted under NDA 213182 on March 20, 2019, to determine if they are acceptable from a medication error perspective.

1.1 BACKGROUND INFORMATION

Novo Nordisk currently markets Ozempic (semaglutide) injection which is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (NDA 209637). In addition, Rybelsus, a tablet dosage form of semaglutide, was approved on September 20, 2019 (under NDA 213051) as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Novo Nordisk is proposing to add an indication for Rybelsus (semaglutide) “to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes and established cardiovascular ^{(b) (4)} disease” under NDA 213182.

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.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	N/A
ISMP Newsletters*	N/A
FDA Adverse Event Reporting System (FAERS)*	N/A
Other	N/A
Labels and Labeling	C

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters 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

Novo Nordisk submitted revised prescribing information (PI) and medication guide on September 26, 2019, following the approval of NDA 213051 on September 20, 2019, which incorporated changes from the approved labeling for Rybelsus. We note the product characteristics for NDA 213182 are the same as the recently approved NDA 213051.

We performed a risk assessment of the updated PI and medication guide to identify areas of vulnerability that may lead to medication errors and other areas of improvement. The Applicant implemented all of our recommendations during our prior reviews of the Rybelsus labeling^a and we have no additional recommendations at this time.

4 CONCLUSION & RECOMMENDATIONS

The proposed labeling for Rybelsus is acceptable from a medication error perspective and we have no recommendations at this time.

^a Conrad A. Label and Labeling Review for Rybelsus (NDA 213051). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 Aug 2. RCM No.: 2019-643.

Conrad A. Review of Revised Label and Labeling Memorandum for Rybelsus (NDA 213051). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 Sept 3. RCM No.: 2019-643-1.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Rybelsus received on September 26, 2019 from Novo Nordisk Inc. (Novo), and Ozempic.

Table 2. Relevant Product Information for Rybelsus and Ozempic		
Product Name	Rybelsus (NDA 213051) ^b	Ozempic ^c (NDA 209637)
Initial Approval Date	September 20, 2019	December 5, 2017
Active Ingredient	semaglutide	
Indication	<ul style="list-style-type: none"> adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes Proposed for NDA 213182: to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes and established cardiovascular ^{(b) (4)} disease 	<ul style="list-style-type: none"> adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes
Route of Administration	Oral	Subcutaneous
Dosage Form	tablet	injection
Strength	3 mg, 7 mg, and 14 mg	2 mg per 1.5 mL (1.34 mg/mL) and 4 mg per 3 mL (1.34 mg/mL)
Dose and Frequency	<ul style="list-style-type: none"> 3 mg, 7 mg or 14 mg by mouth once daily at least 30 minutes before first food, beverage, or other medications 3 mg once daily for 30 days, then increase to 7 mg daily. If additional benefit is needed after 30 days on 	<ul style="list-style-type: none"> Inject subcutaneously in the abdomen, thigh, or upper arm once weekly at any time of the day, with or without meals 0.25 mg once weekly then increase to 0.5 mg once weekly after 4 weeks; if after 4 weeks on the 0.5

^b Rybelsus [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2019 Sept. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/213051s000lbl.pdf.

^c Ozempic [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2019 Apr. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/209637s001lbl.pdf.

	<p>the 7 mg dose, then can increase to 14 mg daily.</p> <ul style="list-style-type: none"> • The maximum daily dose is 14 mg. 	<p>mg dose, increase to 1 mg once weekly</p>
How Supplied	<ul style="list-style-type: none"> • Trade Packs: 30-day supply (3x10) of 3 mg, 7 mg, or 14 mg blister pack • Sample Pack: 30-day supply (3x10) of 3 mg in blister pack 	<p>Single use pens containing a total of 2 mg/1.5 mL and delivers</p> <ul style="list-style-type: none"> • 0.25 mg or 0.5 mg per injection <u>OR</u> • 1 mg per injection <p>Single use pen containing a total of 4 mg/3 mL and delivers</p> <ul style="list-style-type: none"> • 1 mg per injection
Storage	<p>Store at 68° to 77°F (20 to 25°C); excursions permitted to 59° to 86°F (15° to 30°C) [see USP Controlled Room Temperature].</p> <p>Store and dispense in the original carton.</p>	<p><u>Prior to first use:</u> Refrigerated 36°F to 46°F (2°C to 8°C) until expiration date</p> <p><u>After first use:</u> Room Temperature 59°F to 86°F (15°C to 30°C) <u>OR</u> Refrigerated 36°F to 46°F (2°C to 8°C) for up to 56 days</p>
Container Closure	Blister packs	pre-filled, disposable, single-patient-use pens

APPENDIX B. PREVIOUS DMEPA REVIEWS

On October 2, 2019, we searched for previous DMEPA reviews relevant to this current review using the terms, “semaglutide and (IND) 114464” and “semaglutide and (NDA) 213051 or (NDA) 213182”. Our search identified 3 previous reviews^d and we confirmed that our previous recommendations were implemented.

^d Conrad A. Review of Revised Label and Labeling Memorandum for Rybelsus (NDA 213051). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 Sept 3. RCM No.: 2019-643-1.

Conrad A. Label and Labeling Review for Rybelsus (NDA 213051). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 Aug 2. RCM No.: 2019-643.

Conrad A. Human Factors Use Related Risk Analysis Review for semaglutide (IND 114464). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 June 11. RCM No.: 2017-251-1.

APPENDIX C. LABELS AND LABELING

C.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^e along with postmarket medication error data, we reviewed the following Rybelsus labels and labeling submitted by Novo Nordisk Inc. (Novo).

- Medication Guide received on September 26, 2019
 - <\\cdsesub1\evsprod\nda213182\0006\m1\us\proposed-med-guide-clean.doc>
- Prescribing Information received on September 26, 2019
 - <\\cdsesub1\evsprod\nda213182\0006\m1\us\proposed-physician-insert.pdf>

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

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Clinical Inspection Summary

Date	8/14/2019
From	Cynthia F. Kleppinger, M.D., Senior Medical Officer Min Lu, M.D., M.P.H., Acting 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	Andreea (Ondina) Lungu, M.D., Clinical Reviewer Mitra Rauschecker, M.D., Clinical Team Leader Peter Franks, M.S., Regulatory Project Manager Division of Metabolism and Endocrinology Products (DMEP)
NDA	213051; 213182; 209637/s003
Applicant	Novo Nordisk Inc.
Drug	Semaglutide
NME	Yes
Therapeutic Classification	Antidiabetic Agents, Non-Insulin (3031400)
Proposed Indication	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus and to reduce the risk of major adverse cardiovascular events
Consultation Request Date	4/26/2019
Summary Goal Date	8/15/2019
Action Goal Date	9/20/2019
PDUFA Date	9/20/2019

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The inspection for this new drug application (NDA) consisted of five domestic and five foreign clinical sites covering three studies.

In general, based on the inspections of the ten clinical sites, the inspectional findings support validity of data as reported by the sponsor under this NDA.

All classifications are considered preliminary until the final communication letter is sent to the inspected entity. An inspection summary addendum will be generated if conclusions change upon receipt and review of the pending Establishment Inspection Reports.

II. BACKGROUND

Novo Nordisk submitted an original new drug application (NDA 213051) for Rybelsus® (semaglutide) tablets indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes. If approved, this would be the first glucagon-like peptide-1 (GLP-1) receptor agonist in a pill form.

Novo Nordisk is also seeking an indication for Rybelsus® to reduce the risk of major adverse cardiovascular events (cardiovascular death, nonfatal myocardial infarction or non-fatal stroke) in adults with type 2 diabetes mellitus and established cardiovascular disease (b) (4)

The NDA to support this indication was also filed on March 20, 2019 and has an NDA number of 213182. The once-a-week injectable form of semaglutide was approved in December 2017 and is sold as Ozempic®. Outcome data was also submitted to NDA 209637/S-003.

Inspections were requested for three studies:

NN9924-4221 A trial investigating the cardiovascular safety of oral semaglutide in subjects with type 2 diabetes – PIONEER 6

This was a randomized, double-blind, placebo-controlled, multinational, multi-center, cardiovascular outcomes trial (CVOT) designed to assess the cardiovascular safety of oral semaglutide versus placebo when added to standard-of-care in subjects with type 2 diabetes at high risk of cardiovascular events. The primary endpoint is time from randomization to first occurrence of a MACE composite endpoint consisting of: cardiovascular death, non-fatal myocardial infarction or non-fatal stroke.

The trial was conducted at 214 sites in 21 countries. A total of 3418 subjects were screened, 3183 subjects were randomized, and 3172 subjects completed the study. The trial began January 17, 2017 and concluded September 25, 2018, with database lock as of November 2, 2018.

NN9924-4222 Efficacy and long-term safety of oral semaglutide versus sitagliptin in subjects with type 2 diabetes – PIONEER 3

The trial was a 78-week, randomized, double-blind, double-dummy, active-controlled, trial with four arms comparing the efficacy and safety of oral semaglutide 3 mg, 7 mg and 14 mg once-daily with sitagliptin 100 mg once-daily. Randomized trial product was given with metformin alone or in combination with a sulphonylurea. The primary endpoint was change from baseline to Week 26 in HbA1c.

The trial was conducted at 206 sites in 14 countries. There were 2463 subjects screened, 1864 subjects randomized, and 1566 subjects completed the trial. The trial began February 15, 2016 and concluded March 28, 2018. Database lock was May 29, 2018.

NN9924-4233 A 26-week, randomized, double-blind, placebo-controlled trial to investigate the efficacy and safety of oral semaglutide vs placebo in subjects with type 2 diabetes mellitus treated with diet and exercise only – PIONEER 1

This was a randomized, double-blind, placebo-controlled multinational, multi-center efficacy and safety trial with a 26-week treatment period (including an 8-week dose escalation period) and a 5-week follow-up period. Eligible subjects had to have been treated with diet and exercise for at least 30 days and not received anti-diabetic medication at least 90 days prior to screening. The primary endpoint was change from baseline to Week 26 in HbA1c.

The trial was conducted at 93 sites in 9 countries. In total, 1006 subjects were screened, 703 subjects were randomized, and 663 subjects completed the trial. The trial began September 20, 2016 and concluded December 8, 2017. Database lock was January 30, 2018.

III. RESULTS (by Site):

NOTE: Site inspections focused on review of informed consent documents (ICDs), institutional review board (IRB)/ ethics committee (EC) correspondences, 1572s/investigator agreements, financial disclosures, training records, CVs and licenses, delegation of duties, monitoring logs and reports, inclusion/exclusion criteria, enrollment logs, subject source documents including medical history records, drug accountability, concomitant medication records, and adverse event reports. Source records were compared to the sponsor's data line listings that were submitted with the application.

1. Freddy Goldberg Eliaschewitz, M.D.

Avenida Angélica, 2162 Higienópolis São Paulo, Sao Paulo 01228-200, Brazil

Study: NN9924-4221

Site Number: 160

Study: NN9924-4222

Site Number: 480

Dates of inspection: August 5 – 9, 2019

For Study NN9924-4221, there were 116 subjects screened and 101 subjects enrolled into the study; 99 subjects completed the study. (The study ended at the site before all subjects completed all study visits due to the sponsor closing the study for meeting the required number of subjects with endpoint criteria). Two subjects died. There were 45 subject records reviewed.

For Study NN9924-4222, there were 35 subjects screened and 23 subjects enrolled into the study; 23 subjects completed the study (one subject ended treatment with the study drug early due to a serious adverse event but remained in the study). There were 35 subject records reviewed.

All enrolled subjects had corresponding source study records and signed informed consents. The records were organized and legible. Source documents were compared against the sponsor data line listings. No discrepancies were noted. The primary endpoint was verifiable. There was no under-reporting of adverse events.

The full Establishment Inspection Report was not available for review. Preliminary inspection results were communicated by the FDA ORA field investigator.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

2. Yasushi Fukushima, M.D.
3-3-11 Nihombashi, Chuo-ku, Tokyo 103-0027, Japan

Study: NN9924-4233
Site Number: 804

Dates of inspection: July 22 – 26, 2019

There were 20 subjects screened and 20 subjects enrolled into the study; 19 subjects completed the study. One subject discontinued the study drug early due to an adverse event (Subject (b) (6)) but completed the subsequent study visits and procedures. There were 20 subject records reviewed.

All enrolled subjects had corresponding source study records and signed informed consents. The records were organized and legible. Additionally, the site had visit notes that supplemented the study records that were printed and signed/dated by the investigator (showing his review date) and placed in the study binders. These notes were generated electronically and showed the name of the investigator who entered the information but not an electronic signature and date/time stamp, although this information was available in the electronic medical records system and confirmed. Source documents were compared against the sponsor data line listings. Minor discrepancies were noted (one transcription error [blood pressure] and one example where a hypoglycemic episode was not reported [Subject (b) (6)]). The primary endpoint was verifiable. There was no under-reporting of adverse events.

The full Establishment Inspection Report was not available for review. Preliminary inspection results were communicated by the FDA ORA field investigator.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

3. Satoshi Inoue, M.D., Ph.D.
4-12-11 Kasuga Suita-shi, Osaka 565-0853, Japan

Study: NN9924-4233
Site Number: 806

Dates of inspection: July 29 – August 2, 2019

There were 33 subjects screened and 29 subjects enrolled into the study; 27 subjects completed the study. Two subjects discontinued the study drug early due to adverse events but completed their subsequent study visits and procedures. There were 33 subject records reviewed.

All enrolled subjects had corresponding source study records and signed informed consents. The records were organized and legible. Source documents were compared against the sponsor data line listings. No discrepancies were noted. The primary endpoint was verifiable. There was no under-reporting of adverse events.

The full Establishment Inspection Report was not available for review. Preliminary inspection results were communicated by the FDA ORA field investigator.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

4. Adriana Gabriela Onaca, M.D.
Republicii nr. 32 Oradea, Bihor 410025, Romania

Study: NN9924-4222
Site Number: 209

Study: NN9924-4221
Site Number: 532

Dates of inspection: July 29 – August 8, 2019

For Study NN9924-4222, there were 18 subjects screened and 18 subjects enrolled into the study; 15 subjects completed the study. There were 18 subject records reviewed.

For Study NN9924-4221, there were 25 subjects screened and 25 subjects enrolled into the study; 25 subjects completed the study. There were 25 subject records reviewed.

All enrolled subjects had corresponding source study records and signed informed consents. The records were organized and legible. Source documents were compared against the sponsor data line listings. A few minor discrepancies were noted (such as lack of source for a waist

circumference and one missing lab report). The primary endpoint was verifiable as well as all secondary endpoints. There was no under-reporting of adverse events. There were no MACE events for PIONEER 6.

The full Establishment Inspection Report was not available for review. Preliminary inspection results were communicated by the FDA ORA field investigator.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

5. Plamen Popivanov, M.D.

**University Multi-Profile Hospital for Active Treatment (UMHAT) Aaleksandrovskaa,
UMHAT Aleksandrovska, 1 Sv. Georgi Sofiyiski Str., Sofia 1431, Bulgaria**

Study: NN9924-4233
Site Number: 102

Dates of inspection: July 22 – 24, 2019

There were 20 subjects screened and 12 subjects enrolled into the study; 11 subjects completed the study. Subject ^{(b) (6)} was lost to follow-up. There were 12 subject records reviewed. A translator was present throughout the inspection.

Dr. Popivanov has been at the site since 1980. He allocates approximately 5-10% of his resources to clinical trials; 30% to associate professorship at the hospital university; and 60% to medical practice. Subjects were recruited within the hospital network and physician referrals.

The ^{(b) (4)} was the ethics committee of record.

All enrolled subjects had corresponding source study records and signed informed consents. The records were organized and legible. Source documents were compared against the sponsor data line listings. A couple minor discrepancies were noted (two eCRF transcription errors with the subject surveillance questionnaire). The primary endpoint was verifiable. There was no under-reporting of adverse events.

The full Establishment Inspection Report was submitted for review.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

6. Jeanne-Elyse Cedeño, M.D.
1601 North Palm Ave. Suite 102, Pembroke Pines, FL 33026
Study: NN9924-4233
Site Number: 753

Dates of inspection: May 22 – 30, 2019

There were 15 subjects screened and 11 subjects enrolled into the study; 10 subjects completed the study. One subject (Subject (b) (6)) was lost to follow-up. There were seven subject records reviewed.

This study was conducted by Dr. Cedeño at Family Clinical Trials. The site was established for research in 2010 by Dr. Cedeño, and the site is also utilized for her private practice where she practices as a family physician. The subjects for this study were either patients of Dr. Cedeño or a local referring physician.

(b) (4) was the IRB of record.

All enrolled subjects had corresponding source study records and signed informed consents. The records were organized and legible. Source documents were compared against the sponsor data line listings. Discrepancies were noted (as discussed below). The primary endpoint was verifiable. There was no under-reporting of adverse events.

The full Establishment Inspection Report was submitted for review.

At the conclusion of the inspection, a Form FDA-483, Inspectional Observations, was issued for failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation and informed consent. Specifically, the protocol required Patient Reported Outcome (PRO) questionnaires be completed and transcribed into the electronic data capture system (EDC). Each subject was required to be administered a PRO questionnaire at Visit 2 (Randomization), Visit 5 (During Treatment Phase), and Visit 8 (End of Treatment). A total of 62 questions were to be answered at Visit 1 and Visit 8; and 60 questions were to be answered at Visit 5. Of the 10 subjects that completed the study, there were a total of 1951 answers completed in the questionnaires. Each entry was transcribed by the Study Coordinators to the EDC. However, when comparing 100% of the source documents to the eCRF records, a total of 96 discrepancies were observed across 7 of the 10 subjects.

OSI Reviewer Comment: The monitoring plan was risk-based and did not include 100% data verification. The total percentage of discrepancies compared to datapoints total is low. Of the 1951 answers, 96 (4.9%) had discrepancies between the source document and the CRF. Except for the PRO data, there were no other discrepancies during the data verification comparing source and EDC data.

Dr. Cedeno responded to the inspectional observations with acknowledgement of the discrepancies. The root cause for the observation was the entry of responses from a Spanish PRO

questionnaire into an English eCRF. The alignment of the response choices, horizontally for the Spanish PRO and vertically for the eCRF, caused confusion. Additionally, no adequate quality control (QC) process was in place. A second quality review of all data has been implemented and includes a verified signature confirming the review took place for all ongoing trials.

Although regulatory violations were noted as described above, they are unlikely to significantly impact primary safety and efficacy analyses. Data from this site appear acceptable.

7. Charles Lovell, M.D.
142 W. York St., Suite 905, Norfolk, VA 23510-2015

Study: NN9924-4221
Site Number: 812

Study: NN9924-4233
Site Number: 735

Dates of inspection: July 29 – August 2, 2019

For Study NN9924-4221, there were 26 subjects screened and 22 subjects enrolled into the study; 21 subjects completed the study. There were 9 subject records reviewed.

For Study NN9924-4233, there were 4 subjects screened and 2 subjects enrolled into the study; one subject completed the study. There were 4 subject records reviewed.

All enrolled subjects had corresponding source study records and signed informed consents. The records were organized and legible. Source documents were compared against the sponsor data line listings. No discrepancies were noted. The primary endpoint was verifiable. There was no under-reporting of adverse events. It was noted that the cholesterol laboratory units were provided in mmol/L in the data line listing; however, the source records were reported using mg/dL. These cholesterol laboratory test results had to be verified manually by converting mg/dL to mmol/L using methods provided from internet searches.

The full Establishment Inspection Report was not available for review. Preliminary inspection results were communicated by the FDA ORA field investigator.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

8. Ildiko Lingvay, M.D.
5323 Harry Hines Blvd, Suite G4.100, Dallas, TX 75390-9302

Study: NN9924-4221

Site Number: 862

Study: NN9924-4222
Site Number: 856

Dates of inspection: July 1 – 12, 2019

For Study NN9924-4221, there were 25 subjects screened and 23 subjects enrolled into the study; 23 subjects completed the study. There were 23 subject records reviewed.

For Study NN9924-4222, there were 25 subjects screened and 13 subjects enrolled into the study; 9 subjects completed the study. Four subjects did not return for the final visit. There were 25 subject records reviewed.

All enrolled subjects had corresponding source study records and signed informed consents. The records were organized and legible. Source documents were compared against the sponsor data line listings. No discrepancies were noted. The primary endpoint was verifiable. There was no under-reporting of adverse events.

The full Establishment Inspection Report was not available for review. Preliminary inspection results were communicated by the FDA ORA field investigator.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

9. Zeeshan Shaikh
5900 Chimney Rock Road, Suite X, Houston, TX 77081

Study: NN9924-4222
Site Number: 879

Dates of inspection: July 11 – 19, 2019

There were 28 subjects screened and 19 subjects enrolled into the study; 18 subjects completed the study. There were 12 subject records reviewed. Of note, one of the subjects was a transfer from another site in May 2017.

Dr. Zeeshan Shaikh works at SW Clinical Trials Research. She was on extended vacation in Pakistan and not present during the inspection. The research coordinators involved with the study were no longer employed at the firm. The study closed a year ago at the site and the documents had to be retrieved from storage. The Office Manager provided the documents and was in touch with Dr. Shaikh regarding any questions during the inspection.

All enrolled subjects had corresponding source study records and signed informed

consents. The records were organized and legible. Source documents were compared against the sponsor data line listings. No discrepancies were noted. The primary endpoint was verifiable. There was no under-reporting of adverse events.

The full Establishment Inspection Report was not available for review. Preliminary inspection results were communicated by the FDA ORA field investigator.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

10. Eileen M. Palace, Ph.D.

3500 N. Causeway Blvd. Suite 1145, Metairie, LA 70002

Study: NN9924-4222

Site Number: 870

Study: NN9924-4233

Site Number: 727

Dates of inspection: June 10 – 13, 2019

For Study NN9924-4222, there were 28 subjects screened and 24 subjects enrolled into the study; 14 subjects completed the study (eight subjects withdrew consent, one was lost to follow-up and one terminated early). There were 28 subject records reviewed.

For Study NN9924-4233, there were 7 subjects screened and 5 subjects enrolled into the study; 3 subjects completed the study (one subject withdrew consent and one terminated early). There were 7 subject records reviewed.

Although Dr. Palace was the Principal Investigator at the site, she is a family therapist and not a physician; all the study procedures were done by her sub-investigator who was a physician. After the study closed at the site, the sub-investigator died. Dr. Palace then closed her site to clinical research and transferred all study files to the sponsor. The sponsor arranged to have the records shipped for review by the FDA ORA inspector. Dr. Palace and a sponsor representative were available for any questions.

None of the subjects were patients at the site and all were seen by private physicians for their medical care. All enrolled subjects had corresponding study records and signed informed consents. The records were organized and legible. Source documents were compared against the sponsor data line listings. No discrepancies were noted. The primary endpoint was verifiable. There was no under-reporting of adverse events.

The full Establishment Inspection Report was not available for review. Preliminary inspection results were communicated by the FDA ORA field investigator.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

{See appended electronic signature page}

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OSI/DCCE/GCPAB/Acting Team Leader/Min Lu
OSI/DCCE/GCPAB Reviewer/Cynthia Kleppinger
OSI/DCCE/GCPAB/Program Analyst/Yolanda Patague
OSI/DCCE/Database Project Manager/Dana Walters

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/s/

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