CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214962Orig2s000

OTHER REVIEW(S)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 28, 2021

From: CAPT Anissa Davis-Williams, RN, BSN MPH, Regulatory Health Project Manager, Division of Pediatrics and Maternal Health (DPMH)

To: Rania Younes, PharmD, Senior Regulatory Health Project Manager, Division of Regulatory Operations for Neuroscience (DRON)

NDA Number: NDA 214962 (Original 2)

Drug: Tascenso ODT (fingolimod) orally disintegrating tablet

Applicant: Handa Neuroscience, LLC

Indication: Treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in pediatric patients 10 years of age and older and weighing less than or equal to 40 kg.

DRON submitted a consult to DPMH dated November 29, 2021, requesting our participation in the review of draft labeling submitted for Tascenso ODT which utilized the 505(b)(2) pathway and relied on the listed drug product, Gilenya (Novartis). The Division is seeking review of proposed changes to the labeling as the exclusivity for the Gilenya 0.25 mg dose has now expired. The Applicant is seeking final approval of Tascenso ODT for the treatment of multiple sclerosis in pediatric patients 10 years of age and older and weighing less than or equal to 40 kg.

DPMH held a discussion with Office of Chief Counsel (OCC) on December 10, 2021, regarding the now expired exclusivity and any potential impact this may have on labeling.\DPMH also participated in the internal meeting and offered advice to the Division on December 21, 2021.

DRON issued the Approval letter to the Applicant on December 23, 2021. The official labeling represents DPMH current thinking and no further comment/edits are needed at this time.

This memorandum will close out the consult request.

DPMH RPM- CAPT Anissa Davis-Williams, RN, B.S.N., M.P.H.
DPMH- Supervisory, Consumer Safety Officer- George Greeley, M.S., M.B.A.
DPMH Pediatrics MO Reviewer- Charlotte Jones, M.D.
DPMH Pediatrics Team Leader- Mona Khurana, M.D.
DPMH Deputy Director- John Alexander, M.D., M.P.H.

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/s/

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

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

Memorandum

Date: December 13, 2021

To: Laura Baldassari, M.D., Clinical Reviewer
Division of Neurology-2 (DN-II)

Rania Younes, PharmD, Regulatory Project Manager, (DN-II)

Tracy Peters, PharmD, Associate Director for Labeling, (DN-II)

From: Domenic D'Alessandro, PharmD, MBA, BCPS, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Aline Moukhtara, RN, MPH, Team Leader, OPDP

Subject: OPDP Labeling Comments for TASCENSO ODT™ (fingolimod) orally disintegrating tablets

NDA: 214962

In response to DN-II's consult request dated December 7, 2021, OPDP has reviewed the proposed product labeling (PI) for the original NDA submission for TASCENSO ODT™ (fingolimod) orally disintegrating tablets.

PI: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DN-II (Rania Younes) on December 7, 2021, and are provided below.

Thank you for your consult. If you have any questions, please contact Domenic D'Alessandro at (301) 796-3316 or domenic.dalessandro@fda.hhs.gov.

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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
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:	November 15, 2021
Requesting Office or Division:	Division of Neurology 2 (DN 2)
Application Type and Number:	NDA 214962
Product Name and Strength:	Tascenso ODT (fingolimod) orally disintegrating tablets, 0.25 mg
Applicant/Sponsor Name:	Handa Neuroscience, LLC
OSE RCM #:	2020-2700-4
DMEPA 2 Safety Evaluator:	Justine Kalonia, PharmD
DMEPA 2 Acting Team Leader:	Stephanie DeGraw, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised prescribing information (PI), Medication Guide (MG) labeling received on October 27, 2021 for Tascenso ODT as part of a Class 1 Resubmission. The Division of Neurology 2 (DN 2) requested that we review the revised PI and MG labeling for Tascenso ODT (Appendix A) to determine if they are acceptable from a medication error perspective. We evaluated the labels and labeling for the 0.25 mg [(b) (4)] in previous label and labeling review, and memoranda.[a, b, c, d]

The sponsor and patent holder for the RLD NDA filed patent infringement suits against Handa for the 0.5 mg strength of Tascenso ODT. These lawsuits are currently pending. Thus, Handa submitted revised PI and MG labeling [(b) (4)] as a Minor Amendment to request final approval for the 0.25 mg strength of Tascenso ODT under NDA 214962.

[a] Kalonia, J. Label and Labeling Review for fingolimod orally disintegrating tablets (NDA 214962). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 JUN 01. RCM No.: 2020-2700.
[b] Kalonia, J. Label and Labeling Review for fingolimod orally disintegrating tablets (NDA 214962). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 JUN 28. RCM No.: 2020-2700-1.
[c] Kalonia, J. Label and Labeling Review for Tascenso ODT (NDA 214962). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2021 OCT 05. RCM No.: 2020-2700-2.
[d] Kalonia, J. Label and Labeling Review for Tascenso ODT (NDA 214962). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2021 OCT 18. RCM No.: 2020-2700-3.

2 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the proposed revisions to the Tascenso ODT Prescribing Information (PI) and Medication Guide (MG) to identify risks that may lead to medication errors. We note the sponsor is seeking final approval for the 0.25 mg strength only, and as such revised the indication to reflect that the product should only be used in pediatric patients 10 years of age and older weighing less than 40 kg (i.e., the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in pediatric patients 10 years of age and older and weighing less than or equal to 40 kg). (b) (4) the proposed revisions are acceptable from a medication error perspective.

As part of our review, we considered whether the changes proposed in this Minor Amendment would require revisions to the carton labeling, or blister (container) label to ensure consistency and decrease risk of confusion and medication errors. We note no changes were proposed or required to the name, strength, or route of administration for Tascenso ODT 0.25 mg. As such, our evaluation did not identify any necessary revisions to the container label or carton labeling as a result of the changes proposed in this Minor Amendment.

3 CONCLUSION

Our evaluation of the proposed revisions to the Tascenso ODT PI and Medication Guide did not identify areas of vulnerability that may lead to medication errors. We have no recommendations at this time. (b) (4)

APPENDIX A. LABELS AND LABELING

A.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 revised Tascenso ODT labels and labeling submitted by Handa Neuroscience, LLC.

- Medication Guide (image not shown) received on October 27, 2021
  \\CDSESUB1\evsprod\nda214962\0031\m1\us\114-labeling\draft\labeling\tascenso-odt-25mg-med-guide-word.doc
- Prescribing Information (image not shown) received on October 27, 2021
  \\CDSESUB1\evsprod\nda214962\0031\m1\us\114-labeling\draft\labeling\tascenso-odt-25mg-pi-word.doc

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

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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
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 18, 2021
Requesting Office or Division:	Division of Neurology 2 (DN 2)
Application Type and Number:	NDA 214962
Product Name and Strength:	Tascenso ODT (fingolimod) orally disintegrating tablets, 0.25 mg (b) (4)
Applicant/Sponsor Name:	Handa Neuroscience, LLC
OSE RCM #:	2020-2700-3
DMEPA 2 Safety Evaluator:	Justine Kalonia, PharmD
DMEPA 2 Acting Team Leader:	Stephanie DeGraw, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised prescribing information (PI), Medication Guide (MG), container labels and carton labeling received on October 15, 2021 and October 18, 2021 for Tascenso ODT. Division of Neurology 2 (DN 2) requested that we review the revised container labels and carton labeling for Tascenso ODT (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, and memoranda.[a, b, c]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Kalonia, J. Label and Labeling Review for fingolimod orally disintegrating tablets (NDA 214962). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 JUN 01. RCM No.: 2020-2700.
[b] Kalonia, J. Label and Labeling Review for fingolimod orally disintegrating tablets (NDA 214962). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 JUN 28. RCM No.: 2020-2700-1.
[c] Kalonia, J. Label and Labeling Review for Tascenso ODT (NDA 214962). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2021 OCT 05. RCM No.: 2020-2700-2.

APPENDIX A. LABELS AND LABELING

A.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[d] along with postmarket medication error data, we reviewed the following revised Tascenso ODT labels and labeling submitted by Handa Neuroscience, LLC.

- Container labels received on October 15, 2021
- Carton labeling received on October 15, 2021
- Medication Guide (image not shown) received on October 18, 2021 \\CDSESUB1\evsprod\nda214962\0030\m1\us\114-labeling\draft\labeling\med-guide-word.doc
- Prescribing Information (image not shown) received on October 18, 2021 \\CDSESUB1\evsprod\nda214962\0030\m1\us\114-labeling\draft\labeling\proposed-word.doc

A.2 Label and Labeling Images

Container labels

0.25 mg Blister

[d] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

STEPHANIE L DEGRAW
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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 7, 2021
To:	Rania Younes Regulatory Project Manager **Division of Neurology II (DN2)**
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:	Kelly Jackson, PharmD Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
	Samuel Fasanmi, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	TASCENSO (fingolimod)
Dosage Form and Route:	orally disintegrating tablets, for oral use
Application Type/Number:	NDA 214962
Applicant:	Handa Neuroscience, LLC

1 INTRODUCTION

On December 18, 2020, Handa Neuroscience, LLC submitted for the Agency's review a New Drug Application (NDA) for TASCENSO (fingolimod) orally disintegrating tablets, (ODT) for oral use. The proposed indication for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, (b) (4) This submission is a 505(b)(2) application, relying on the Agency's previous findings for the reference listed drug (RLD) GILENYA (fingolimod) capsules, for oral use NDA 22527.

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 Neurology II (DN2) on February 4, 2021 and February 5, 2021 respectively, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for TASCENSO (fingolimod).

2 MATERIAL REVIEWED

- Draft TASCENSO (fingolimod) MG received on December 18, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 22, 2021.
- Draft TASCENSO (fingolimod) Prescribing Information (PI) received on December 18, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 22, 2021.
- Approved GILENYA (fingolimod) capsules, for oral use dated December 26, 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%. 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.

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)
- 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)

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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MARCIA B WILLIAMS
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MEMORANDUM

REVIEW OF REVISED LABELS AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)

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 5, 2021
Requesting Office or Division:	Division of Neurology 2 (DN 2)
Application Type and Number:	NDA 214962
Product Name and Strength:	Tascenso ODT (fingolimod) orally disintegrating tablets, 0.25 mg (b) (4)
Applicant/Sponsor Name:	Handa Neuroscience, LLC
OSE RCM #:	2020-2700-2
DMEPA 2 Safety Evaluator:	Justine Kalonia, PharmD
DMEPA 2 Acting Team Leader:	Stephanie DeGraw, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised carton labeling received on July 27, 2021 and August 25, 2021 for fingolimod orally disintegrating tablets. The Division of Neurology 2 (DN 2) requested that we review the revised carton labeling for fingolimod orally disintegrating tablets (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, and memorandum. [a,b]

2 DISCUSSION

The Applicant implemented our recommendation to change the strength statement to state "XX mg per orally disintegrating tablet" in the revised carton labeling received on July 27, 2021. However, upon further evaluation, the Office of Pharmaceutical Quality (OPQ) found the format of the established name statement unacceptable because it must include both the USAN name and the dosage form, and as presented, the “strength” split this statement into two fragments. Thus, OPQ recommended switching the order such that the established name appears as

[a] Kalonia, J. Label and Labeling Review for fingolimod orally disintegrating tablets (NDA 214962). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 JUN 01. RCM No.: 2020-2700.

[b] Kalonia, J. Label and Labeling Review for fingolimod orally disintegrating tablets (NDA 214962). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 JUN 28. RCM No.: 2020-2700-1.

"(fingolimod) orally disintegrating tablet" with the strength after it. This conflicted with our previous recommendation to include the "strength per orally disintegrating tablet." OPQ shared their recommendations with us prior to sending them to the Sponsor, and we requested they notify the sponsor that "we recognize this recommendation conflicts with a previous recommendation the Agency provided", and that they recommend the strength statement is presented as either "X mg per tablet", or "X mg per orally disintegrating tablet" on the PDP and side panels of the carton labeling.

Subsequently, the Applicant submitted revised carton labeling received on August 25, 2021. However, it appears that the Applicant overlooked our recommendation to add "per tablet" or "per orally disintegrating tablet" after the strength. Typically we recommend adding the strength per tablet to blister package labeling to make it clear that the designated strength is per unit to prevent confusion about how much product is contained in a single unit (i.e., one tablet) as compared to the total contents of the entire blister pack.

Upon further evaluation, given the fact that this is a 30-count blister pack and the strength is stated on each blister cell, we expect it to be unlikely for someone to mistake all tablets in the pack as one dose. (b) (4) Therefore, users should be familiar with taking just one solid oral dosage form (capsule or tablet) as a single dose. Thus, we find that the revisions made to the carton labeling received on August 25, 2021 are acceptable from a medication error perspective.

3 CONCLUSION

The Applicant implemented all of our recommendations. However, we have an additional recommendation related to the proprietary name on the labels and labeling. We provide our recommendation for Handa in Section 4 below.

4 RECOMMENDATIONS FOR HANDA NEUROSCIENCE, LLC

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

A. We refer to the Proprietary Name Decision Letter dated October 04, 2021 finding the proposed proprietary name, Tascenso ODT, conditionally acceptable.[c] Thus, we recommend you replace the placeholder "TRADENAME" with the proprietary name "Tascenso ODT" on all applicable areas of the labels and labeling.

[c] Killen, M. Proprietary Name Granted for Tascenso ODT. Silver Spring (MD): FDA, CDER, OSE (US); 2021 OCT 04. NDA214962.

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

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

Memorandum

Date: October 01, 2021

To: Laura Baldassari, M.D.
Office of Neuroscience/Division of Neurology II (ON/DN II)

Rania Younes, Regulatory Project Manager, (ON/DN II)

Tracy Peters, Associate Director for Labeling, (DN II)

From: Samuel Fasanmi, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Aline Moukhtara, RN, MPH, Team Leader, OPDP

Subject: OPDP Labeling Comments for fingolimod orally disintegrating tablets, for oral use

NDA: 214962

In response to DN II consult request dated February 5, 2021, OPDP has reviewed the proposed product labeling (PI), Medication Guide, and carton and container labeling for the original NDA submission for fingolimod orally disintegrating tablets, for oral use.

PI: OPDP's comments on the proposed labeling are based on the draft PI and Medication Guide received by electronic mail from DN II (Rania Younes) on September 22, 2021, and are provided below.

Medication Guide: 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.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on August 25, 2021, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Samuel Fasanmi at (301) 796-5188 or samuel.fasanmi@fda.hhs.gov.

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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:	June 28, 2021
Requesting Office or Division:	Division of Neurology 2 (DN 2)
Application Type and Number:	NDA 214962
Product Name and Strength:	fingolimod orally disintegrating tablets, 0.25 mg (b) (4)
Applicant/Sponsor Name:	Handa Neuroscience, LLC
OSE RCM #:	2020-2700-1
DMEPA Safety Evaluator:	Justine Kalonia, PharmD
DMEPA Acting Team Leader:	Celeste Karpow, PharmD, MPH

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on June 21, 2021 for fingolimod orally disintegrating tablets. Division of Neurology 2 (DN 2) requested that we review the revised container labels and carton labeling for fingolimod orally disintegrating tablets (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 Applicant implemented most of our recommendations and we have no additional recommendations at this time. However, we note that the strength statement on the Principal Display Panel (PDP) was not revised to state the strength in terms of "mg per orally disintegrating tablet." Below, we provide further information to clarify our concern to the Sponsor and request they consider revising this statement.

3 RECOMMENDATIONS FOR HANDA NEUROSCIENCE, LLC

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

[a] Kalonia J. Label and Labeling Review for fingolimod orally disintegrating tablets (NDA 214962). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 JUN 01. RCM No.: 2020-2700.

A. We note you implemented our recommendation to change the strength statement to state "XX mg per orally disintegrating tablet" on most parts of the carton labeling. However, you did not made this change on the Principal Display Panel (PDP). We are concerned a user may erroneously interpret the statement of strength (b) (4) Consider revising the strength statement on your PDP to say “XX mg per orally disintegrating tablet” for consistency with the rest of the carton labeling.

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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:	June 1, 2021
Requesting Office or Division:	Division of Neurology 2 (DN 2)
Application Type and Number:	NDA 214962
Product Name and Strength:	fingolimod orally disintegrating tablets, 0.25 mg (b) (4)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Handa Neuroscience, LLC
FDA Received Date:	December 18, 2020 February 9, 2021 February 25, 2021
OSE RCM #:	2020-2700
DMEPA Safety Evaluator:	Justine Kalonia, PharmD
DMEPA Acting Team Leader:	Celeste Karpow, PharmD, MPH

1 REASON FOR REVIEW

As part of the approval process for fingolimod orally disintegrating tablets, the Division of Neurology 2 (DN 2) requested that we review the proposed fingolimod prescribing information (PI), Medication Guide (MG), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

2 BACKGROUND

NDA 214962 is a 505(b)(2) NDA and the listed drug product is Gilenya, NDA 022527.

3 MATERIALS 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 – N/A
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other – Information Request	E
Labels and Labeling	F

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

4 FINDINGS AND RECOMMENDATIONS

4.1 (b) (4) PACKAGE DESIGN

Handa proposes to supply fingolimod in cartons containing 30 orally disintegrating tablets. The cartons are (b) (4)

(b) (4)

(b) (4)

We note that Handa proposes packaging 30 fingolimod orally disintegrating tablets within one (b) (4) carton. (b) (4)

To better inform our review, we issued an information request (see Appendix E) to the Sponsor requesting they provide:

1. Any human factors (HF) formative studies or testing they may have completed to support the use of (b) (4) packaging in the intended patient population.
2. Clarification for whether the design incorporates considerations for the user population with limitations in motor skill.
3. Clarification for how they plan to mitigate the risk of unintentional exposure to children (b) (4)
4. Five (5) placebo only intend-to-market samples of product.

Subsequently, the Sponsor submitted a response and 5 empty sample cartons. We reviewed the information submitted to support the safe and effective use of the product in the intended population and we find Handa's justifications reasonable. Upon evaluation of the samples, we identified two findings:

1. (b) (4)
2.

We are not aware of any postmarket errors indicating this packaging has led to accidental exposure to product medication errors. We note Handa's response to our IR states that the (b) (4) . We considered our review recommendations (b) (4)

(b) (4)

(b) (4)

(b) (4) we determined that we do not need human factors data to support the proposed packaging, and below in Table 3 we provide recommendations to the carton labeling for fingolimod ODT.

4.2 LABELS AND LABELING

Tables 2 and 3 below include the identified medication error issues with the submitted prescribing information (PI), Medication Guide (MG), container labels, and carton labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2. Identified Issues and Recommendations for Division of Neurology 2 (DN 2)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information – General Issues			
1.	The proposed proprietary name, (b) (4) is used throughout the Prescribing Information, Medication Guide, and container labels and carton labeling.	The proprietary name, (b) (4) was found unacceptable by DMEPA.	Remove the proposed proprietary name, (b) (4) throughout the Prescribing Information, Medication Guide, and container labels and carton labeling. Until a new name is found to be conditionally acceptable, the placeholder "TRADENAME" may be used. Replace (b) (4) with the proprietary name that is eventually found acceptable.
Highlights of Prescribing Information –Dosage and Administration			
1.	The second and last bullet points describing initiation or re-initiation of fingolimod treatment could be combined for brevity and clarity.	We are concerned that users may overlook the last bullet point about reinitiating treatment.	Consider combining the second bullet point with the last bullet point to read: (b) (4)

(b) (4)

Table 2. Identified Issues and Recommendations for Division of Neurology 2 (DN 2)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			(b) (4) [redacted]
2.	The statement: (b) (4) [redacted] in the fifth bullet could be revised for consistency with the fourth bullet and Section 2.3 (Recommended Dosage) of the Full Prescribing Information (FPI), which state "10 years of age and older."	We are concerned that readers will be confused with varying word choice.	Consider revising the fifth bullet to read: "Recommended dosage for pediatric patients (10 years of age and older) weighing less than or equal to 40 kg: 0.25 mg orally once-daily, with or without food (2.2, 2.3)."
Full Prescribing Information – Section 3 Dosage Forms and Strengths			
1.	Section 3 (Dosage Forms and Strengths) does not include information about the shape of the drug product.	This information facilitates the identification of the dosage form and is required per 21 CFR 201.57(c)(4)(ii).	We recommend adding the description of the shape of the drug product to this section in accordance with 21 CFR 201.57(c)(4)(ii).
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	Section 16 (How Supplied/Storage and Handling) does not include information about the shape of the drug product.	This information facilitates the identification of the dosage form and is required per 21 CFR 201.57(c)(4)(ii).	We recommend adding the description of the shape of the drug product to this section in accordance with 21 CFR 201.57(c)(4)(ii).

Table 3. Identified Issues and Recommendations for Handa Neuroscience, LLC (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
General Recommendations (All Labels and Labeling)			

Table 3. Identified Issues and Recommendations for Handa Neuroscience, LLC (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	The proposed proprietary name, (b) (4) is used throughout the Prescribing Information, Medication Guide, and container labels and carton labeling.	The proprietary name, (b) (4) was found unacceptable by DMEPA.	Remove the proposed proprietary name, (b) (4) throughout the Prescribing Information, Medication Guide, and container labels and carton labeling. Until a new name is found to be conditionally acceptable, the placeholder "TRADENAME" may be used. Replace (b) (4) with the proprietary name that is eventually found acceptable.
Container (Blister) Labels and Carton Labeling			
1.	The format of the expiration date is not defined.	Clearly define the expiration date to minimize confusion and risk for deteriorated drug medication errors.	Identify the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
Carton Labeling			
1.	The carton labeling does not include step-by-step instructions for opening	We are concerned that users may not understand how to open the carton and may	Revise the carton labeling to include instructions for opening the (b) (4) packaging. In developing

Table 3. Identified Issues and Recommendations for Handa Neuroscience, LLC (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	the (b) (4) packaging. The statements, "push" and (b) (4) pull out tray" lack prominence on the principal display panel and it is unclear how to apply these statements when opening the packaging. (b) (4)	attempt to destroy the carton to remove the blisters, or otherwise manipulate the packaging (b) (4) (b) (4)	instructions, consider the use of text and graphics. Additionally, consider increasing the prominence of the statements "push" and (b) (4) pull out tray" taking into account all pertinent factors, including typography, layout, contrast, and other printing features Additionally, you may wish to consider including a statement advising the user to ensure that both hooks have clicked back into place each time they slide the tray back into the carton.
2.	The product strength is not expressed in mg per orally disintegrating tablet.	We are concerned there may be dosing errors.	Consider revising the statement of strength to read "XX mg per tablet".
3.	The route of administration is not specifically stated on the principal display panel.	The route of administration is critical information that should appear on the principal display panel according to FDA draft guidance.[c]	Include the route of administration on the principal display panel.
4.	The "Dosage" statement can be improved.	Labels for prescription drugs are required to bear a statement of the recommended or usual dosage per 21 CFR 201.100(b)(2). Furthermore, to ensure consistency with the Physician Labeling Rule (PLR)	Revise the statement: (b) (4) to read "Recommended Dosage: See prescribing information."

[c] Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

Table 3. Identified Issues and Recommendations for Handa Neuroscience, LLC (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		formatted prescribing information, we recommend the phrase "Recommended Dosage: See prescribing information."	
5.	As currently presented, the human-readable lot number is absent.	The lot number statement is required on carton labeling when there is sufficient space per 21 CFR 201.10(i)(1).	Ensure the lot number is clearly differentiated from the expiration date.[d] Also, ensure that the lot number and expiration date are not located in close proximity to other numbers where the numbers can be mistaken as the lot number or expiration date.[e]
6.	The colors (b) (4)	The use of (b) (4)	Revise the color (b) (4)
7.	As currently presented, there is no product identifier on the carton labeling.	In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act (DSCSA)*. The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning	We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product's labeling. If you determine that the product identifier requirements apply to your product's labeling, add a placeholder for the human- and machine-readable product identifiers to your product's labeling.

[d] Institute for Safe Medication Practices. Safety briefs: Lot number, not expiration date. ISMP Med Saf Alert Acute Care. 2014;19(23):1-4.

[e] Institute for Safe Medication Practices. Safety briefs: The lot number is where? ISMP Med Saf Alert Acute Care. 2009;14(15):1-3.

Table 3. Identified Issues and Recommendations for Handa Neuroscience, LLC (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		November 27, 2017, and November 27, 2018, respectively. * The draft guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf	The DSCSA guidance on product identifiers recommends that the human-readable portion be located near the 2D data matrix barcode and recommends the following format: NDC: [insert product's NDC] SERIAL: [insert product's serial number] LOT: [insert product's lot number]
8.	The carton labeling (b) (4) [redacted]	We are concerned that dispensing pharmacists (b) (4) [redacted]	Include an alert on the principal display panel of the carton labeling. For example, consider revising your (b) (4) alert to "Pharmacist", such that it reads: "Pharmacist: (b) (4) [redacted] Provide the accompanying Medication Guide to each patient"

5 CONCLUSION

Our evaluation of the proposed fingolimod prescribing information (PI), Medication Guide (MG), container labels, and carton labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Division and Table 3 for the Applicant. We ask that the Division convey Table 3 in its entirety to Handa Neuroscience, LLC so that recommendations are implemented prior to approval of this NDA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for fingolimod that Handa Neuroscience, LLC submitted on February 9, 2021, and the listed drug (LD).

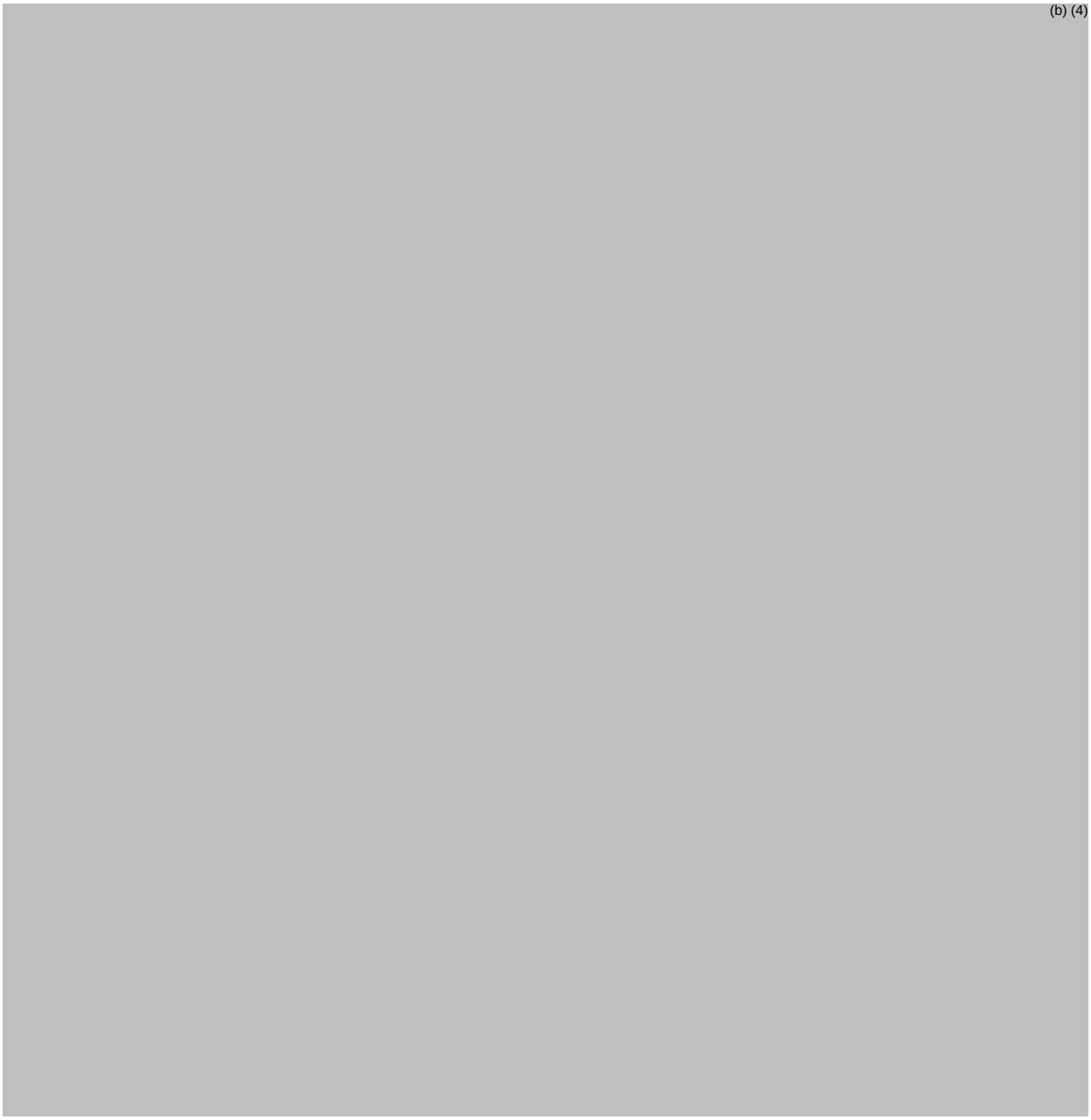
Table 4. Relevant Product Information for Listed Drug and fingolimod

Product Name	Gilenya	fingolimod
Initial Approval Date	9/21/2010	N/A
Active Ingredient	fingolimod	fingolimod
Indication	treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in patients 10 years of age and older	treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, (b) (4)
Route of Administration	oral	oral
Dosage Form	capsule	orally disintegrating tablet
Strength	0.25 mg and 0.5 mg	0.25 mg (b) (4)
Dose and Frequency	• Adults and pediatric patients (10 years of age and older) weighing more than 40 kg: 0.5 mg orally once daily • Pediatric patients (10 years of age and above) weighing less than or equal to 40 kg: 0.25 mg orally once daily	(b) (4) • Pediatric patients (10 years of age and above) weighing less than or equal to 40 kg: 0.25 mg orally once daily
How Supplied	• Bottle of 30 capsules • Carton of 7 capsules containing 1 blister of 7 capsules per blister card	Each (b) (4) carton contains 30 orally disintegrating tablets total. Each carton contains 3 blister cards, and each blister card contains 10 orally disintegrating tablets.
Storage	Stored at 20ºC to 25ºC (68ºF-77ºF); excursions permitted to 15ºC to 30ºC (59ºF-86ºF).	Stored at 20ºC to 25ºC (68ºF-77ºF); excursions permitted to 15ºC to 30ºC (59ºF-86ºF).
Container Closure	Bottle or carton	Carton (b) (4)

APPENDIX E. INFORMATION REQUEST

E.1 Agency's Information Request (Issued February 19, 2021)

(b) (4)



Sponsor's response to Information Request (Received February 25, 2021)

The response can be accessible in EDR via: \\CDSESUB1\evsprod\nda214962\0011\m1\us\111-information-amendment\response-rfi-dated-20210219.pdf

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[f] along with postmarket medication error data, we reviewed the following fingolimod labels and labeling submitted by Handa Neuroscience, LLC.

- Container label(s) received on December 18, 2020
- Carton labeling received on December 18, 2020
- Medication Guide received on December 18, 2020
- Prescribing Information (Image not shown) received on December 18, 2020 and February 9, 2021

F.2 Label and Labeling Images

Container labels

0.25 mg Blister

[f] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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

JUSTINE H KALONIA
05/28/2021 03:08:02 PM

CELESTE A KARPOW
06/01/2021 12:12:09 PM

Division of Cardiology and Nephrology

From: Charu Gandotra, MD, MS, FACC, FASE Clinical Reviewer
Division of Cardiology and Nephrology/ CDER

Through: Fortunato Senatore, MD, PhD, FACC, Team Leader
Division of Cardiology and Nephrology/ CDER

Norman Stockbridge, MD, PhD, Division Director
Division of Cardiology and Nephrology/ CDER

To: Rania Younes, RPM
Division of Neurology 2, Office of Neuroscience / CDER

Subject: NDA 214962, Fingolimod orally disintegrating tablet (b) (4)
Sponsor: Handa Neuroscience, LLC
Referenced IND 13054

Division of Neurology 2 (DN2) requests the assistance from the Division of Cardiology and Nephrology (DCN) with a new 505(b)(2) NDA for fingolimod orally disintegrating tablet (ODT), relying on the listed drug, Gilenya capsule. DN2 stated: "*Please review and comment on the cardiovascular adverse events that occurred in the single-dose studies FGL-P01 and FGL-P02 for fingolimod ODT (NDA 214962, a 505(b)(2) NDA using fingolimod as the reference listed drug), given the known safety profile of sphingosine 1-phosphate (S1P) receptor modulators. Despite Agency recommendations provided in PIND 13054 Written Responses Only (WRO) dated 7/14/2016 to include continuous cardiac monitoring for at least 144 hours post-dose due to unknown pharmacokinetics (PK) of fingolimod ODT, the sponsor performed only 7 hours of post-dose monitoring in some patients in one study only. Both studies contain ECG data at screening, 6- and 24-hours post-dose, and end of study (day 7). Vital signs were also recorded through 24 hours post-dose. Both studies involved the administration of single doses of either fingolimod ODT 1mg (pooled n = 69) or fingolimod (Gilenya) 1mg (pooled n = 44). Our preliminary review of recorded adverse events indicates that 1st degree AV block occurred in 6/69 (8.7%) of patients on fingolimod ODT vs 1/44 (2.3%) on fingolimod, 2nd degree AV block in 4/69 (5.8%) on fingolimod ODT vs 2/44 (4.5%) on fingolimod, nodal arrythmia in 2/69 (2.9%) on fingolimod ODT vs 0/44 on fingolimod, and bradycardia in 1/69 (1.4%) on fingolimod ODT vs 0/44 on fingolimod. Since this is a 505(b)(2), we are concerned that this product may result in increased cardiac events compared to Gilenya given the differential incidence between the groups in two single-dose studies, and that the data may not be fully capturing this information because of inadequate cardiac monitoring. Please note that the sponsor's proposed*

(b) (4)

Additionally, the dose used in these trials (1mg) is higher than the approved dose of Gilenya (0.5mg)".

Date received: March 5, 2021

Date Completed: May 10, 2021

Background

The Sponsor has submitted a New Drug Application (NDA) 214962 under 505(b)(2) pathway for HND-020 (fingolimod orally disintegrating tablets, (b) (4) developed as an alternative dosage form to Gilenya. Gilenya is a sphingosine 1-phosphate (S1P) receptor modulator approved for the treatment of relapsing forms of multiple sclerosis (MS). Key cardiac safety issues with Gilenya include transient bradyarrhythmia and atrioventricular blocks associated with the first dose. Hence, the Label for Gilenya provides detailed pre-dose cardiac assessment and first-dose cardiac monitoring guidance for initiation or re-initiation of treatment.

To support NDA 214962, the Sponsor conducted two bioavailability/bioequivalence (BA/BE) studies - FGL-P01 (fasting) and FGL-P02 (fed) to establish a scientific bridge to the reference listed drug (RLD), Gilenya. These studies exposed 69 and 44 healthy volunteers to a single 1 mg dose of fingolimod, orally disintegrating tablets (ODT) and Gilenya, respectively. In these studies, a higher incidence of atrioventricular blocks was reported in the fingolimod, ODT arm(s) compared to Gilenya. There was limited cardiac safety monitoring in these studies. The Division of Neurology 1 is concerned that fingolimod, ODT may be associated with a higher incidence of cardiac conduction abnormalities than Gilenya and seek input from DCN regarding cardiac safety assessment of fingolimod, ODT.

On April 10, 2010 the Division of Cardiorenal Products (DCRP) provided a consult response to the Division of Neurology addressing the cardiovascular safety of fingolimod (NDA 022527). DCRP acknowledged that heart rate reduction was observed in the first human study and in all subsequent clinical studies of Gilenya as an effect related to initial stimulation of S1P receptors in the heart. Gilenya induces a dose-dependent reduction in heart rate that is maximal within hours after the first dose, and then attenuates over days-weeks despite increasing blood levels with continued dosing. A review of available echocardiographic data with Gilenya did not raise a safety concern regarding structural heart disease.

Materials Reviewed

a) PIND 130544 Meeting Request – Written Responses dated July 14, 2016
b) Response to Sponsor Clarification of the Agency's Response dated December 22, 2016
c) Label for GILENYA (fingolimod) capsules, for oral use Initial U.S. Approval: 2010
d) NDA 214962 Summary of Clinical Efficacy
e) Relevant sections of protocol and clinical study reports of FGL-P01 and FGL-P02
f) NDA 022527, Gilenya, DCRP Consult Response to Division of Neurology dated April 10, 2010

Regulatory Background

Table 1 summarizes relevant clinical issues discussed with the FDA at PIND stage for fingolimod, ODT.

Table 1. Summary of Relevant Clinical Issues addressed in Meeting Minutes of PIND 13054 (Source: Reviewer Compilation)

IND/NDA; Date; Meeting Type	Issue	FDA Advice
PIND 130544; July 14, 2016; Meeting Request – Written Responses	Proposed pharmacokinetic clinical study design in healthy volunteers to demonstrate bioequivalence of fingolimod to Gilenya	Conduct two bioequivalence studies, fasting and fed, to compare the bioavailability of the proposed drug product (fingolimod ODT) to Gilenya and one study to compare the bioavailability of the proposed drug (ODT) with and without water. Bioequivalence based on 90% confidence interval needs to be established for both fingolimod and its active metabolite fingolimod-phosphate. Using truncated area under the curve (AUC) is not appropriate to characterize the drug and the active metabolite exposures because the intra-subject variability in AUC for both fingolimod and fingolimod-phosphate is moderate to high; hence, you will need to collect some blood samples at least 144 hours post-dose for both fingolimod and fingolimod-phosphate.
	It is understood from published literature that initiation of fingolimod treatment may result in bradyarrhythmia transient AV conduction delays. Therefore, subjects will be observed for 24 hours for signs and symptoms of bradycardia with hourly pulse and blood pressure measurement until 6 hours post-dose, and at 8, 10, 12, 14, and 24 hours post-dose. In addition, an electrocardiogram ("ECG") will be performed before dosing and approximately 6 and 24 hours post-dose.	You should incorporate 144 hours of post-dose cardiac monitoring because the pharmacokinetics of ODT fingolimod and its metabolites are unknown. The cardiac safety monitoring should follow the recommendations for first dose monitoring in the label of Gilenya.
PIND 130544; December 22, 2016; Sponsor Request for Clarification of FDA Response	Instead of 3 studies, can the requirement be completed with 2 studies by adding a third arm in the fasting study to include the ODT with water?	Your proposal to conduct two instead of three studies is acceptable; however, please provide the draft protocols for our review.

Reference Listed Drug (RLD) Label Review

Gilenya was approved by US FDA in 2010 with recent major changes dated 12/2019 for the **indication** - "Gilenya is a sphingosine 1-phosphate receptor modulator indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in patients 10 years of age and older."

Recommended dosage for adults and pediatric patients (10 years of age and older) weighing more than 40 kg: 0.5 mg orally once-daily, with or without food.

The **mechanism of action** of Gilenya is described as follows: Fingolimod is metabolized by sphingosine kinase to the active metabolite, fingolimod-phosphate. Fingolimod phosphate is a sphingosine 1-phosphate receptor modulator and binds with high affinity to sphingosine 1-phosphate receptors 1, 3, 4, and 5. Fingolimod-phosphate blocks the capacity of lymphocytes to egress from lymph nodes, reducing the number of lymphocytes in peripheral blood. The mechanism by which fingolimod exerts therapeutic effects in multiple sclerosis is unknown but may involve reduction of lymphocyte migration into the central nervous system.

The **pharmacokinetic profile** of Gilenya as described in the Label is as follows:

- Tmax is approximately 12–16 hours.
- Apparent absolute oral bioavailability 93%.

- Steady-state blood concentrations are reached within 1 to 2 months following once-daily administration and steady-state levels are approximately 10 times the Cmax following the initial dose .
- Average apparent terminal half-life (t1/2) of fingolimod and fingolimod-phosphate is 6 to 9 days.
- Food intake does not alter Cmax or (AUC) of fingolimod or fingolimod-phosphate. Therefore, Gilenya may be taken without regard to meals.
- Fingolimod and fingolimod-phosphate are > 99.7% protein bound. Fingolimod and fingolimod-phosphate protein binding is not altered by renal or hepatic impairment.
- The biotransformation of fingolimod in humans occurs by 3 main pathways: by reversible stereoselective phosphorylation to the pharmacologically active (S)-enantiomer of fingolimod-phosphate, by oxidative biotransformation catalyzed mainly by the cytochrome P450 4F2 (CYP4F2) and possibly other CYP4F isoenzymes with subsequent fatty acid-like degradation to inactive metabolites, and by formation of pharmacologically inactive non-polar ceramide analogs of fingolimod.
- After oral administration, about 81% of the dose is slowly excreted in the urine as inactive metabolites.
- In adult patients with severe renal impairment, fingolimod Cmax and AUC are increased by 32% and 43%, respectively, and fingolimod-phosphate Cmax and AUC are increased by 25% and 14%, respectively, with no change in apparent elimination half-life. Based on these findings, the GILENYA 0.5 mg dose is appropriate for use in adult patients with renal impairment. GILENYA 0.25 mg and 0.5 mg are appropriate for use in pediatric patients with renal impairment. The systemic exposure of 2 metabolites (M2 and M3) is increased by 3-and 13-fold, respectively. The toxicity of these metabolites has not been fully characterized.
- In subjects with mild, moderate, or severe hepatic impairment (Child-Pugh class A, B, and C), no change in fingolimod Cmax was observed, but fingolimod AUC0-∞ was increased respectively by 12%, 44%, and 103%. No dose adjustment is needed in patients with mild or moderate hepatic impairment (Child-Pugh class A and B). Patients with severe hepatic impairment (Child-Pugh class C) should be closely monitored, as the risk of adverse reactions is greater.

The **safety database** for Gilenya comprised of 1212 patients with relapsing forms of multiple sclerosis who received 0.5 mg dose of Gilenya, including 783 and 429 patients in 2-year and 1-year controlled trials, respectively. In all clinical studies, overall exposure to 0.5 mg of Gilenya was approximately 4119 person-years. The incidence of bradycardia and atrioventricular blocks with Gilenya 0.5 mg once daily has been reported to be up to approximately 5%.

Cardiac Warnings and Precautions include:

- Bradyarrhythmia and Atrioventricular Blocks: After the first dose of GILENYA, the heart rate decrease starts within an hour. On Day 1, the maximum decline in heart rate generally occurs within 6 hours and recovers, although not to baseline levels, by 8 to 10 hours post dose. Because of physiological diurnal variation, there is a second period of heart rate decrease within 24 hours after the first dose. In some patients, heart rate decrease during the second period is more pronounced than the decrease observed in the first 6 hours. Heart rates below 40 beats per minute (bpm) in adults, and below 50 bpm in pediatric patients occurred rarely. In controlled clinical trials in adult patients, adverse reactions of symptomatic bradycardia following the first dose were reported in 0.6% of patients receiving GILENYA 0.5 mg and in 0.1% of patients on placebo. Patients who experienced bradycardia were generally asymptomatic, but some patients experienced hypotension, dizziness, fatigue, palpitations, and/or chest pain that usually resolved within the first 24 hours on treatment.

  Since initiation of Gilenya treatment, results in decreased heart rate and may prolong the QT interval, patients with a prolonged QTc interval (> 450 msec adult and pediatric males, > 470 msec adult females, or > 460 msec pediatric females) before dosing or during 6-hour observation, or at additional risk for QT prolongation (e.g., hypokalemia, hypomagnesemia, congenital long-QT syndrome), or on concurrent therapy with QT prolonging drugs with a known risk of torsades de pointes (e.g., citalopram, chlorpromazine, haloperidol, methadone, erythromycin) should be monitored overnight with continuous ECG in a medical facility. In a thorough QT interval study of doses of 1.25 or 2.5 mg fingolimod at steady-state, when a negative chronotropic effect of fingolimod was still present, fingolimod treatment resulted in a prolongation of QTc, with the upper boundary of the 90% confidence interval (CI) of 14.0 msec. There is no consistent signal of increased incidence of QTc outliers, either absolute or change from baseline, associated with fingolimod treatment. In MS studies, there was no clinically relevant prolongation of the QT interval, but patients at risk for QT prolongation were not included in clinical studies.

  Following the second dose, a further decrease in heart rate may occur when compared to the heart rate prior to the second dose, but this change is of a smaller magnitude than that observed following the first dose. With continued dosing, the heart rate returns to baseline within 1 month of chronic treatment. Clinical data indicate effects of Gilenya on heart rate are maximal after the first dose although milder effects on heart rate may persist for, on average, 2 to 4 weeks after initiation of therapy at which time heart rate generally returns to baseline. Physicians should continue to be alert to patient reports of cardiac symptoms.

  In controlled clinical trials in adult patients, first-degree AV block after the first dose occurred in 4.7% of patients receiving GILENYA and 1.6% of patients on placebo. In a study of 697 patients with available 24-hour Holter monitoring data after their first dose (N = 351 receiving GILENYA and N = 346 on placebo), second-degree AV blocks (Mobitz Types I [Wenckebach] or 2:1 AV blocks) occurred in 4% (N = 14) of patients receiving GILENYA and 2% (N = 7) of patients on placebo. Of the 14 patients receiving GILENYA, 7 patients had 2:1 AV block (5 patients within the first 6 hours post dose and 2 patients after 6 hours post dose). All second degree AV blocks on placebo were Mobitz Type I and occurred after the first 12 hours post dose. The conduction

abnormalities were usually transient and asymptomatic, and resolved within the first 24 hours on treatment, but they occasionally required treatment with atropine or isoproterenol.

In the post marketing setting, third-degree AV block and AV block with junctional escape have been observed during the first-dose 6-hour observation period with Gilenya. Isolated delayed onset events, including transient asystole and unexplained death, have occurred within 24 hours of the first dose. These events were confounded by concomitant medications and/or preexisting disease, and the relationship to Gilenya is uncertain. Cases of syncope were also reported after the first dose of Gilenya.

- Increased Blood Pressure (BP): Monitor BP during treatment.

Given cardiac safety issues, cardiac evaluation is recommended prior to initiating Gilenya in patients with certain pre-existing conditions, e.g., ischemic heart disease, history of myocardial infarction, congestive heart failure, history of cardiac arrest, cerebrovascular disease, uncontrolled hypertension, history of symptomatic bradycardia, history of recurrent syncope, severe untreated sleep apnea, AV block, sinoatrial heart block. If treated with Gilenya, these patients should be monitored overnight with continuous ECG in a medical facility after the first dose. Prior to starting treatment, determine whether patients are taking drugs that could slow heart rate or atrioventricular (AV) conduction.

The following **First-Dose Monitoring** is recommended (including reinitiating after discontinuation greater than 14 days and dose increases):

- Observe all patients for bradycardia for at least 6 hours; monitor pulse and blood pressure hourly. Electrocardiograms (ECGs) prior to dosing and at end of observation period required.
- Monitor until resolution if heart rate < 45 beats per minute (bpm) in adults, < 55 bpm in patients aged 12 years and above, or < 60 bpm in pediatric patients aged 10 to below 12 years, atrioventricular (AV) block, or if lowest post dose heart rate is at the end of the observation period.
- Monitor symptomatic bradycardia with ECG until resolved. Continue overnight if intervention is required; repeat first-dose monitoring for second dose.
- Observe patients overnight if at higher risk of symptomatic bradycardia, heart block, prolonged QTc interval, or if taking drugs with known risk of torsades de pointes.

Within the first 2 weeks of treatment, first-dose procedures are recommended after interruption of 1 day or more; during Weeks 3 and 4 of treatment, first-dose procedures are recommended after treatment interruption of more than 7 days.

Cardiac Contraindications for Gilenya include:

- Recent (in last 6 months) myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure with hospitalization, or Class III/IV heart failure.
- History or presence of Mobitz Type II 2nd degree or 3rd degree AV block or sick sinus syndrome, unless patient has a pacemaker.
- Baseline QTc interval ≥ 500 msec.
- Cardiac arrhythmias requiring anti-arrhythmic treatment with Class Ia or Class III anti-arrhythmic drugs.

Proposed Label for Fingolimod orally disintegrating tablets (b) (4)

The proposed **indication** statement for fingolimod, ODT (b) (4) is a sphingosine 1-phosphate receptor modulator indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, (b) (4)

The proposed dosage and administration are as follows:

(b) (4)

The (b) (4) cardiac contraindications, pre-dose cardiac assessment, first-dose monitoring recommendations for initial Fingolimod treatment, and warnings and precautions are similar to those with Gilenya.

Pivotal Trial Findings with Fingolimod orally disintegrating tablets (b) (4)

The sponsor conducted **two pivotal PK studies** in healthy volunteers – FGL-P01 and FGL-P02 to demonstrate bioavailability (BA) and bioequivalence (BE) of fingolimod, ODT to the RLD, Gilenya. Table 2 displays a tabular listing of clinical studies conducted with fingolimod, ODT.

Table 2 List of Clinical Studies Conducted with Fingolimod, ODT (Source: Sponsor Table)

Study	Study Objective	Study Design; Type of Control	Fingolimod Dosage Regimen; Route of Administration	Number of Subjects	Duration of Treatment
FGL-P01	The primary objectives: to compare the bioavailability between a new orally disintegrating tablet (ODT) formulation (Test, administered without water) of fingolimod and the Reference Gilenya® capsule and to compare the bioavailability between the Test administered with and without water after a single oral dose administration under fasting conditions. The secondary objective of this study was to evaluate the safety and tolerability of the Test and Reference formulations in healthy subjects.	Single period, 3-treatment, 3-arm, parallel study; Fasting conditions	One ODT formulation (Test) and one capsule formulation (Reference); Treatment-1: 1 mg single dose with 240 mL of water (2 × 0.5 mg ODT [Test]) Treatment-2: 1 mg single dose without water (2 × 0.5 mg ODT [Test]) Treatment-3: 1 mg single dose without water (2 × 0.5 mg hard capsule [Reference]); oral	75	Single Dose

Study	Study Objective	Study Design; Type of Control	Fingolimod Dosage Regimen; Route of Administration	Number of Subjects	Duration of Treatment
FGL-P02	The primary objective of this study was to compare the bioavailability between 2 different formulations of fingolimod after a single oral dose administration under fed conditions. The secondary objective of this study was to evaluate the safety and tolerability of the Test and Reference formulations in healthy subjects.	Parallel; Fed conditions	One ODT formulation (Test); Single 1 mg dose (2 × 0.5 mg ODT); Oral One capsule formulation (Reference); Single 1 mg dose (2 × 0.5 mg capsule); Oral	38	Single Dose

A determination of bioequivalence of fingolimod, ODT to Gilenya is beyond the scope of this review. The Sponsor reports that for both studies, the AUC0-144 and Cmax were not significantly different between each treatment group as the geometric mean ratios and associated confidence intervals (CIs) were within the predefined range of 80.00 to 125.00%. Almost similar results were reported for PK parameters for fingolimod phosphate. Table 3 displays a summary of whole blood fingolimod pharmacokinetic parameters in Study FGL-P01. Figure 1 displays the mean concentration-time profiles by treatment for Studies FGL-P01 and FGL-P02.

Table 3. Summary of Whole Blood Fingolimod Pharmacokinetic Parameters in Study FGL-P01 (Source: Sponsor Table)

Parameter	Treatment-1 (n=25)		Treatment-2 (n=25)		Treatment-3 (n=25)	
	Mean	CV (%)	Mean	CV (%)	Mean	CV (%)
C_{max} (pg/mL)	722.7	17.6	689.0	13.9	761.6	14.8
T_{max} (hours)[a]	32.00	(12.00 – 59.82)	32.00	(10.00 – 58.87)	28.00	(12.00 – 59.03)
AUC_{0-144} (pg·h/mL)	74521.7	20.4	70875.8	14.4	77952.1	15.4

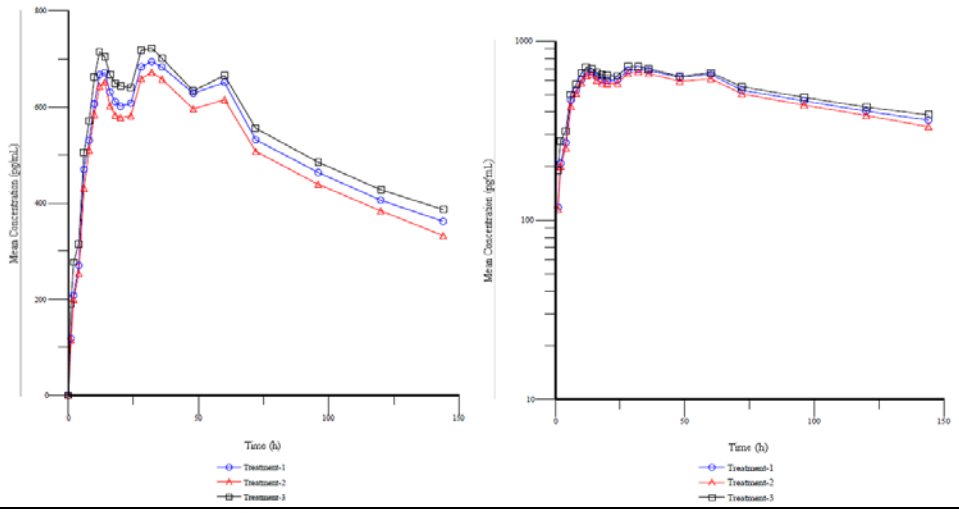
Treatment-1: 1 mg (b) (4) with water; Treatment-2: 1 mg (b) (4) without water; Treatment-3: 1 mg Gilenya with water

Abbreviations: CV = coefficient of variation; n = number of subjects

a. Median and range (minimum-maximum) are presented.

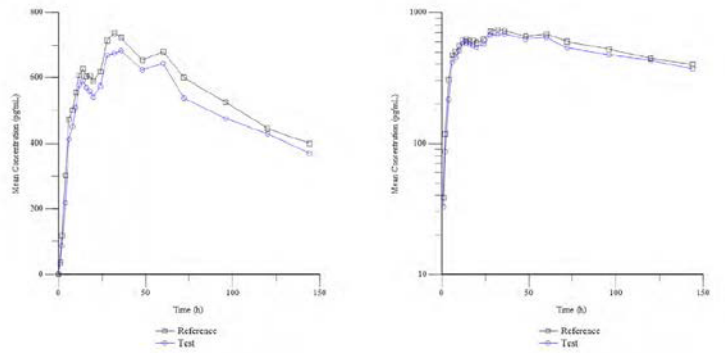
Figure 1. Mean Fingolimod Concentration-Time Profiles After Single-Dose Administration – Pharmacokinetic Population (Linear and Semi-Logarithmic Scales)

Study FGL-P01



Treatment-1: fingolimod, ODT 1 mg with water; Treatment-2: fingolimod, ODT 1 mg without water; Treatment-3: 1 mg Gilenya with water

Study FGL-P02



Reference: Glenya 1 mg; Test: (b) (4) 1 mg

Cardiac safety monitoring was conducted as follows:

- Vital signs were obtained pre-dose and 1, 2, 3, 4, 5, 6, 8, 10, 12, 14, and 24 hours post dose on Day 1; Days 2 and 7 in FGL-P01 and FGL-P02.
- 12-lead electrocardiograms (ECGs) were obtained pre-dose, 6 and 24 hours post-dose on Day 1; Days 2 and 7 in FGL-P01. ECGs were obtained pre-dose, 6, 2 and 14 hours post-dose in FGL-P02.
- Continuous cardiac monitoring from at least 30 minutes prior to dosing until at least 7 hours post dose was conducted in FGL-P01.

In both studies combined, no deaths, serious adverse events or severe treatment emergent adverse events (TEAEs) were reported. No subjects were withdrawn by the investigator due to a TEAE. The incidence of TEAEs was lower in fingolimod, ODT compared to Gilenya arm, 23 and 34%, respectively. Clinically significant ECG assessments were observed in 10 subjects (7/69, 10.1% for fingolimod, ODT and 3/44, 6.8% for Gilenya). All were considered mild TEAEs except for 1 TEAE (AV block 2nd degree) which was considered moderate in intensity. All TEAEs were considered drug-related and resolved by the end of the study.

Table 4 summarizes key cardiac safety findings of studies FGL-P01 and FGL-P02.

Table 4. Key Cardiac Safety Findings of Single Dose Pharmacokinetic Studies of (b) (4) FGL-P01 and FGL-P01

N	Safety Findings			
FGL-P01				
75 (25 in each study arm)		Fingolimod, ODT with water	Fingolimod, ODT without water	Gilenya with water
	TEAEs n (%)	11 (44)	10 (40)	10 (40)
	Cardiac Disorders n (%)	4 (16)	2 (8)	3 (12)
	AV block first degree n (%)	3 (12)	2 (8)	1 (4)
	AV block second degree n (%)	1 (4)	2 (8)	2 (8)
	Dizziness n (%)	1 (4)	2 (8)	-
	Somnolence n (%)	-	-	2 (8)
	Nodal arrhythmia n (%)	2 (8)	-	-
FGL-P02				
38 (19 in each study arm)		Fingolimod, ODT	Gilenya	
	TEAEs n (%)	8 (42)	10 (53)	
	Dizziness n (%)	-	2 (11)	
	Sinus bradycardia with second degree AV Block Mobitz 1	1 (5)	-	

Source: Reviewer compilation

Reviewer Comments: *The BA/BE studies of fingolimod, ODT used a single 1 mg dose which is higher that the intended dose for clinical use (0. 5mg). The size of studies FGL-P01 and FGL-P02 is small. Hence, the numerical differences in the incidence of cardiac adverse events between fingolimod, ODT and Gilenya need to be interpreted with caution. The observed cardiac adverse events with fingolimod, ODT are similar to previous findings of safety with Gilenya. The label for Gilenya and the proposed label for fingolimod, ODT delineate cardiac safety issues and the necessary cardiac monitoring. If fingolimod, ODT is determined to be bioequivalent to Gilenya, the proposed label for fingolimod, ODT adequately describes the observed cardiac adverse events and the approach to cardiac risk mitigation.*

DCN's Response

Request: The Division of Neurology 1 has requested input from DCN on potential increased risk of cardiac adverse events with fingolimod, ODT compared to Gilenya.

DCN Response: The numerically higher incidence of cardiac conduction disorders observed with 1 mg dose of fingolimod, ODT compared to 1 mg dose of Gilenya in the pivotal bioavailability/bioequivalence studies FGL-P01 and FGL-P02 does not indicate a new safety signal, and it is implausible that it represents worsening of the known cardiac effects, if the ODT is bioequivalent to Gilenya. The cardiac effects at a first dose of 1 mg are likely to be worse than at 0.5 mg, but neither product is supposed to be initiated at 1 mg. (b) (4) If it is concluded that fingolimod, ODT is bioequivalent to Gilenya, the cardiac warnings and precautions, cardiac contraindications, pre-dose cardiac assessment and first-dose cardiac monitoring described in the proposed label are considered adequate.

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/s/

CHARU GANDOTRA
05/10/2021 09:28:53 AM

FORTUNATO F SENATORE
05/10/2021 09:50:20 AM

NORMAN L STOCKBRIDGE
05/10/2021 09:51:37 AM

M E M O R A N D U M **DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE**
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 2/18/2021

TO: Division of Neurology II (DN II)
Office of Neuroscience (ON)

FROM: Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: NDA 214962

The Division of New Drug Study Integrity (DNDSI) within the Office of Study Integrity and Surveillance (OSIS) determined that inspections are not warranted at this time for the sites listed below. The rationale for this decision is noted below.

Rationale

The clinical inspection was conducted in June 2019 and the analytical inspection was conducted in (b) (4), which falls within the surveillance interval. The inspections were conducted under the following submissions: NON-RESPONSIVE

The final classification for the inspections was No Action Indicated (NAI).

Therefore, based on the rationale provided above, inspections are not warranted at this time.

Inspection Sites

Facility Type	Facility Name	Facility Address
Clinical	Altasciences	1200 Beaumont Avenue, Mount-Royal, Quebec, Canada
Analytical	(b) (4)	

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/s/

FOLAREMI ADEYEMO
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