CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217700Orig1s000
218033Orig1s000

OTHER REVIEW(S)

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)

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Date of This Review:	April 16, 2024
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	NDA 217700 and NDA 218033
Product Name, Dosage Form, and Strength:	Ojemda (tovorafenib) Tablet, 100 mg (NDA 217700) Ojemda (tovorafenib) Powder for Oral Suspension, 300 mg (25 mg/mL when reconstituted) (NDA 218033)
Applicant Name:	Day One Biopharmaceuticals
FDA Received Date:	April 15, 2024
TTT ID #:	2023-5162-2, 2023- 5216-2
DMEPA 2 Safety Evaluator:	Janine Stewart, PharmD
DMEPA 2 Team Leader:	Ashleigh Lowery, PharmD

1 PURPOSE OF MEMORANDUM

Day One Biopharmaceuticals submitted revised container labels and carton labeling received on April 15, 2024 for Ojemda Tablets (NDA 217700) and Ojemda Powder for Oral Suspension (NDA 218033). The Division of Oncology 2 (DO2) requested that we review the revised container labels and carton labeling for Ojemda (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

Day One Biopharmaceuticals implemented all of our container label and carton labeling recommendations and we have no additional recommendations at this time.

3 ADDITIONAL COMMENT FOR DIVISION OF ONCOLOGY 2 (DO2)

Regarding our recommendation for DO2 to consider issuing a Post-market Commitment (PMC) for the Applicant to develop blister wallets containing five 100 mg tablets for the 500 mg weekly dose packaging configuration[b], we had further discussions with the DO2 review team. From our discussions, we determined that Enhanced Pharmacovigilance (EPV) was the appropriate approach. Subsequently, on March 27, 2024, DMEPA consulted DMAMES to draft EPV language for inclusion in the "Postmarketing Safety Reports" section of the action letter and to review the future reports.

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

[a] Stewart, J. Label and Labeling MEMO for Ojemda (NDA 217700 and NDA 218033). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2024 MAR 29. TTT ID: 2023-5162-1, 2023- 5216-1.

[b] Stewart, J. Label and Labeling Review for Ojemda (NDA 217700 and NDA 218033). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2024 MAR 13. TTT ID: 2023-5162, 2023- 5216

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JANINE A STEWART
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ASHLEIGH V LOWERY
04/16/2024 03:18:51 PM

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

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

Memorandum

Date: **April 3, 2024**

To: Opeyemi Udoka, Senior Regulatory Health Project Manager, DO2

Barbara Scepura, Associate Director for Labeling, DO2

From: Mispa Ajua-Alemanji, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Rachael Conklin, Team Leader, OPDP

Subject: OPDP Labeling Comments for OJEMDA® (tovorafenib**)** tablets, for oral use and OJEMDA® (tovorafenib**)** for oral suspension

NDA: 217700; 218033

Background:
In response to DO2's consult request dated September 27,2023, OPDP has reviewed the proposed Prescribing Information (PI), Patient Package Insert (PPI)/Instructions for Use (IFU), and carton and container labeling for the original NDA 217700 and NDA 218033 submission for OJEMDA® (tovorafenib**)** tablets, for oral use and OJEMDA® (tovorafenib**)** for oral suspension

PI:
OPDP's comments on the proposed labeling are based on the draft PI and PPI accessed from SharePoint on March 26, 2024, and are provided below.

PPI /IFU:
A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed and comments on the proposed PPI and IFU were sent under separate cover on April 1,2024.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling emailed to OPDP on April 2, 2024, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Mispa Ajua-Alemanji at Mispa.Ajua-Alemanji@fda.hhs.gov.

APPEARS THIS WAY ON ORIGINAL

PI:

Section	Statement from Draft (if applicable)	OPDP Comment
HIGHLIGHTS OF PRESCRIBING INFORMATION: DOSAGE AND ADMINISTRATION	"Recommended dosage of OJEMDA is based on body surface area (***see Table 1***). (2.2)" (emphasis added)	We note that the Highlights only references Table 1 for dosing recommendations; however, Table 2 includes the recommended dosage for the oral suspension based on BSA. We recommend revising to include a reference to Table 2.
HIGHLIGHTS OF PRESCRIBING INFORMATION: WARNINGS AND PRECAUTIONS	"Effect on Growth: Reductions in growth velocity have been reported. Routinely monitor growth. (5.4)"	OPDP notes that section 5.4 includes the specific population of patients at risk for reduction in growth velocity (patients 18 years of age or younger). Should this information regarding the at-risk population be included in the Highlights section? We note that labels for Alvesco and Dymista include a warning and precaution for potential reduction in growth velocity and that the Highlights includes the information that this risk is specific to "children."
HIGHLIGHTS OF PRESCRIBING INFORMATION: WARNINGS AND PRECAUTIONS	Embryo-Fetal Toxicity: Can cause fetal harm. Advise (b) (4) of the potential risk to a fetus and to use effective non-hormonal contraception. (5.4, 8.1,8.3)"	ODPD notes that the information in the HL for this warning does not address (b) (4) consistent with sections 5.4 and 8.3. We note that other oncology labels (e.g., Piqray, Ibrance) with similar recommendations for contraceptive use in female and male patients include the more general language "Advise patients of potential risk to a fetus and to use effective contraception." OPDP recommends revising this recommendation to either be consistent with the more general recommendation made in other oncology labels or to include the recommendations specific to (b) (4) consistent with 8.3.
HIGHLIGHTS OF PRESCRIBING	" (b) (4)	OPDP notes the sponsor's comment on the AR presentation in the Highlights stating that the cutoff and list of common ARs has been

INFORMATION: ADVERSE REACTIONS **6.1 Clinical Trials Experience**	(b) (4) "The most common adverse reactions **(≥30%)** were rash, hair color changes, fatigue, vomiting, headache, hemorrhage, pyrexia, dry skin, constipation, nausea and upper respiratory tract infection" (emphasis added)	revised to meet the ≥ (b) (4) % cutoff proposed by the Agency. However, we note that the cutoff rate in the HL is not consistent with the ≥ 30% cutoff that is presented in section 6.1, which includes a number of additional ARs that are not included in the Highlights. OPDP recommends revising the labeling to ensure consistency between the most common ARs presented in the HL and described in section 6.1
DOSAGE AND ADMINISTRATION: **2.3 Administration**	" If a dose is missed by: • 3 days or less, take the missed dose as soon as possible, and take the next dose on its regularly scheduled day. • More than 3 days, skip the missed dose and take the next dose on its regularly scheduled day. • (b) (4) "	As it is currently written the information for the timing of missed doses may be confusing for providers as the recommendation to (b) (4) seems separate from the rest of the information here. For clarity, we recommend revising to integrate this information. e.g., " (b) (4)
14 CLINICAL TRIALS EXPERIENCE	"The ORR was 52% among patients with BRAF fusion or rearrangement (n=64), and 50% among patients with BRAF V600E mutation (n=12), respectively. The ORR was 49% among patients who had received prior MAPK-targeted therapy (n=45), and 55% among patients who had not received prior MAPK-targeted therapy (n=31)."	Were these subgroup analyses pre-specified? Were they considered exploratory? Depending on the nature of the analyses and if appropriate, OPDP recommends including some description to characterize this subgroup data. e.g., "in an exploratory subgroup analysis …" "in an exploratory post-hoc analysis …"

Carton and Container:

Applicable Carton and Container Labeling AND Applicable Strength	Statement from Proposed Carton/Container (If applicable)	OPDP Comment
Ojemda Draft PfOS Bottle Label **Ojemda draft 16c carton label** **Ojemda draft 20c carton label** **Ojemda draft 24c carton label** **Draft 1 x 4 Wallet Label** **Draft 1 x 6 Wallet Label**	"[redacted] (b) (4)	We note that this information was recently revised in the PI. Please revise the information with regards to vomiting on all applicable carton and container labeling for both the tablet and powder for oral suspension dosage forms, so that it is consistent with the current recommendations in section 2.3 of the PI.
Draft 1 x 4 Wallet Label and Draft 1 x 6 Wallet Label for Ujemda tablet formulation		As currently presented, there is no lot number /control number and name of manufacturer, packer or distributor of the drug. OPDP recommends including the missing information as required per *21 CFR 201.10 (i).*

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/s/

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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:	April 1, 2024
To:	Opeyemi Udoka, DPT, CSM Regulatory Project Manager **Division of Oncology II (DO2)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Maria Nguyen, MSHS, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Helen Young, MSN, MPH, CRRN, PHN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Mispa Ajua-Alemanji, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI) and Instructions for Use (IFU)
Drug Name (established name), Dosage Form and Route, Application Type/Number	• OJEMDA (tovorafenib) tablets, for oral use, NDA 217700 • OJEMDA (tovorafenib) for oral suspension, NDA 218033
Applicant:	Day One Biopharmaceuticals, Inc.

1 INTRODUCTION

On August 31, 2023, Day One Biopharmaceuticals, Inc. submitted for the Agency's review an original 505(b)(1) New Drug Application (NDA) 217700 for OJEMDA (tovorafenib) tablets and NDA 218033 OJEMDA (tovorafenib) for oral suspension. The proposed indication for OJEMDA (tovorafenib) is for the treatment of pediatric patients 6 months of age and older with relapsed or refractory pediatric low-grade glioma (LGG) harboring a BRAF fusion or rearrangement, or BRAF V600 mutation.

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 Oncology II (DO2) on September 27, 2023, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for OJEMDA (tovorafenib) tablets and OJEMDA (tovorafenib) for oral suspension.

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

2 MATERIAL REVIEWED

- Draft OJEMDA (tovorafenib) tablets and OJEMDA (tovorafenib) for oral suspension PPI received on August 31, 2023, and received by DMPP and OPDP on March 11, 2024.
- Draft OJEMDA (tovorafenib) for oral suspension IFU received on August 31, 2023, and received by DMPP and OPDP on March 11, 2024 and March 13, 2024, respectively.
- Draft OJEMDA (tovorafenib) tablets and OJEMDA (tovorafenib) for oral suspension Prescribing Information (PI) received on August 31, 2023, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 11, 2024, March 18, 2024, March 26, 2024, and March 29, 2024 respectively.
- Approved MEKINIST (trametinib) tablets and MEKINIST (trametinib) for oral solution comparator labeling dated March 16, 2023 and February 27, 2024.
- Approved TAFINLAR (dabrafenib) capsules and TAFINLAR (dabrafenib) tablets for oral suspension comparator labeling dated March 16, 2023 and February 27, 2024.

3 REVIEW METHODS

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

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more

accessible for patients with vision loss. We reformatted the PPI and IFU document using the Arial font, size 10.

In our collaborative review of the PPI and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are consistent with the PI
- removed unnecessary or redundant information
- ensured that the PPI and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the IFU meets the criteria as specified in the Instructions for Use-Patient Labeling for Human Prescription Drug and Biological Products (published July 2022)
- ensured that the PPI and IFU are consistent with the approved comparator labeling where applicable

4 CONCLUSIONS

The PPI and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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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)

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Date of This Review:	March 29, 2024
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	NDA 217700 and NDA 218033
Product Name, Dosage Form, and Strength:	Ojemda (tovorafenib) Tablet, 100 mg (NDA 217700) Ojemda (tovorafenib) Powder for Oral Suspension, 300 mg (25 mg/mL when reconstituted) (NDA 218033)
Applicant Name:	Day One Biopharmaceuticals
FDA Received Date:	March 19, 2024
TTT ID #:	2023-5162-1, 2023- 5216-1
DMEPA 2 Safety Evaluator:	Janine Stewart, PharmD
DMEPA 2 Team Leader:	Ashleigh Lowery, PharmD

1 PURPOSE OF MEMORANDUM

Day One Biopharmaceuticals submitted revised container labels and carton labeling received on March 19, 2024 for Ojemda Tablets (NDA 217700) and Ojemda Powder for Oral Suspension (NDA 218033). The Division of Oncology 2 (DO2) requested that we review the revised container labels and carton labeling for Ojemda (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

Day One Biopharmaceuticals acknowledged most of our recommendations regarding the product identifiers that are required under the Drug Supply Chain Security Act (DSCSA) and affirm that the required product identifier information (including NDC, serial number, lot number, and expiration date) in both human readable and 2-dimensional (2-D) data matrix barcode formats will be included on the carton labeling for NDA 217700 and NDA 218033 in the placeholder areas labeled "unvarnished area for variable text" as are the smallest saleable unit for this product. They also clarified that the container labels for the tablet blister packs and the bottles containing the powder for oral suspension will be printed with the lot number and expiration date in the placeholder areas labeled "unvarnished area for variable text". Further, Day One affirmed that the expiration date format on all the container labels and carton labeling will conform to the YYYY-MM-DD format. We find these proposals acceptable.

However, we have identified areas of vulnerability on the Ojemda Tablets container labels and carton labeling, and an area for improvement on the Ojemda carton labeling. We provide recommendations in Section 3 below.

3 RECOMMENDATIONS FOR DAY ONE BIOPHARMACEUTICALS

NDA 217700 Ojemda Tablets:

A. General Comments (Container Labels & Carton Labeling)

1. The statement of dosage is missing from the container labels and carton labeling. Before the storage information, add a statement of dosage that reads "Recommended Dosage: see Prescribing Information" in accordance with 21 CFR 201.55.

B. Container Label(s)

1. The linear barcode is missing on the container label. We acknowledge the rationale you provided in your Response to FDA IR[b]; however, as drug barcodes

[a] Stewart, J. Label and Labeling Review for Ojemda (NDA 217700 and NDA 218033). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2024 MAR 13. TTT ID: 2023-5162, 2023- 5216.

[b] Response to FDA Information Request dated 2024-03-13 for Ojemda Tablets (NDA 217700) 2024 MAR 19. Link to IR Response: \\CDSESUB1\EVSPROD\nda217700\0041\m1\us\response-to-fda-ir-2024-03-13.pdf

are an important safely feature in verification during the medication use process, we request that you add the product's linear barcode to each individual container label in accordance with 21CFR 201.25(c)(2). Note the regulation for barcodes and NDCs is different from the product identifier requirements under the DSCSA. We understand that the 4-count blister card is packaged in both the 16-count and 20-count carton configurations and the 6-count blister card is packaged in the 24-count carton configuration. Please be advised that both the 4-count and 6-count blister cards can be assigned a unique NDC number that uses the corresponding quantity code (last 2 digits) and can be packaged as proposed in cartons. In this instance, the NDC assigned to each carton configuration would not change as the quantity codes accurately reflect the number of tablets each contains.

NDA 218033 Ojemda Powder for Oral Suspension

A. Carton Labeling

1. Revise the "1 bottle" statement in the Contents list on principal display panel of the carton labeling to read "1 bottle of Ojemda". We recommend this revision for improved clarity of the carton contents.

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/s/

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LABEL AND LABELING REVIEW
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)

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Date of This Review:	March 13, 2024
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	NDA 217700 and NDA 218033
Product Name, Dosage Form, and Strength:	Ojemda (tovorafenib) Tablet, 100 mg (NDA 217700) Ojemda (tovorafenib) Powder for Oral Suspension, 300 mg (25 mg/mL when reconstituted) (NDA 218033)
Product Type:	Single Ingredient Product (NDA 217700) Combination Product (NDA 218033)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Day One Biopharmaceuticals
FDA Received Date:	June 21, 2023, August 31,2023, November 13, 2023, November 17, 2023, January 8, 2024 January 30, 2024, February 26, 2024
TTT ID #:	2023-5162, 2023- 5216
DMEPA 2 Safety Evaluator:	Janine Stewart, PharmD
DMEPA 2 Team Leader:	Ashleigh Lowery, PharmD

1 REASON FOR REVIEW

As part of the approval process for Ojemda (tovorafenib) Tablet (NDA 217700) and powder for oral suspension (NDA 218033) the Division of Oncology 2 (DO2) requested that we review the proposed Ojemda prescribing information (PI), container labels, and carton labeling, Patient Information and instructions for use (IFU) for areas of vulnerability that may lead to medication errors. Day One Biopharmaceuticals seeks to co-label both dosage forms under a single Ojemda labeling.

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 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	E– N/A
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

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the proposed Ojemda PI, Patient Information, container label, and carton labeling and determined that they may be improved to ensure safe product use. Our review of Ojemda tablets (NDA 217700), identified a packaging configuration that was incongruent with product dosing. On January 23, 2024, we issued an Information Request (IR) to inform our review of the proposed packaging configurations. Based on the Applicant's response[a] dated January 30, 2024, we recommend a post-marketing consideration and also provide recommendations below in section 4.2 which aim to minimize the risk of wrong dose errors.

We also reviewed the Ojemda IFU for the powder for oral suspension (NDA 218033). A human factors evaluation was documented under a separate cover[b]and advice was issued under IND

[a] Response to Information Request for Ojemda Tablets (NDA 217700) 2023 JAN 30. Link to IR Response: \\CDSESUB1\EVSPROD\nda205434\0088\m1\us\response-to-information-request-24jul2023.pdf.

[b] Srivastava, I. Use Related Risk Analysis and Comparative Analysis Review (IND 108340). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2023 OCT 21. TTT ID No.: 2023-5210.

108340[c]. The Applicant addressed all of our comments and we did not identify additional areas of concern.

4 CONCLUSION & RECOMMENDATIONS

The proposed Ojemda IFU is acceptable from a medication error perspective. However, the proposed Ojemda PI, Patient Information, container label, and carton labeling may be improved to ensure safe product use. We provide specific recommendations in Sections 4.1 and 4.2 below.

4.1 RECOMMENDATIONS FOR DIVISION OF ONCOLOGY 2 (DO2)

A. Post-marketing consideration (Container labels & Carton Labeling)-

1. We recommend communicating the following to the Applicant:

The 500 mg weekly dose carton of Ojemda (tovorafenib) tablets contains five blister wallets, where each blister wallet contains four 100 mg tablets. To achieve the 500 mg weekly dose, users must use one blister wallet (4 tablets) plus 1 tablet taken from another wallet. Thus, we are concerned that the current 500 mg weekly dose packaging configuration may contribute to wrong dose medication errors. Based on post marketing experience with similar product package design, we recommend that each blister wallet contains five 100 mg tablets to support the 500 mg weekly dose packaging configuration. Additionally, whereas placing the four 100 mg tablets blister wallets in both the 400 mg weekly dose and the 500 mg weekly dose cartons, having a separate five 100 mg tablets blister wallet product package design will allow Ojemda container labels and the carton labeling to include a weekly dose statement to support accurate product dose/strength selection (e.g., 400 mg once weekly dose, 500 mg once weekly dose, and 600 mg once weekly dose). Therefore, we recommend a Post-market Commitment (PMC) to develop a blister wallet containing five 100 mg tablets for the 500 mg weekly dose packaging configuration.

Develop blister wallets containing five 100 mg tablets for the 500 mg weekly dose packaging to prevent the risk of wrong dose medication errors and to support accurate product dose/strength selection, and commit to submit a prior approval supplement for this change within 1 year post-approval.

B. General Comment (Prescribing Information and Patient Information)

1. We note the storage temperature statement in PI Section 16 and in the Patient Information is inconsistent with the storage temperature statements that appear on the container label and carton labeling for the tablets and the powder for oral suspension. Revise the storage temperature information for accuracy and consistency across all labeling components.

[c] Ford, L. Human Factors Use Related Risk Analysis Advice Letter for tovorafenib (IND 108340). Silver Spring (MD): FDA, CDER, OSE (US); 2023 OCT 17.

C. Prescribing Information

1. Dosage Forms and Strengths

a. Consider revising the description of the dosage forms to read as follows:

OJEMDA Tablets:

100 mg: orange, film-coated, oval tablets debossed with "100" on one side and "D101" on the opposite side.

OJEMDA Powder for Oral Suspension:

25 mg/mL: White to off white powder (b) (4) . Each mL of (b) (4) strawberry-flavored tovorafenib suspension contains 25 mg of tovorafenib.

2. How Supplied/Storage and Handling Section

a. Revise the statement that reads "Suspension must be used immediately after reconstitution" to read " (b) (4)

4.2 RECOMMENDATIONS FOR DAY ONE BIOPHARMACEUTICALS

We recommend the following be implemented prior to approval of NDA 217700.

A. General Comments (Container labels & Carton Labeling)- Tablets

1. The statement of dosage is missing from the container labels and carton labeling. Before the storage information, add a statement of dosage that reads "Recommended Dosage: see Prescribing Information" in accordance with 21 CFR 201.55.
2. We note the storage temperature statement in PI Section 16 and in the Patient Information is inconsistent with the storage temperature statements that appear on the container label and carton labeling for the tablets and the powder for oral suspension. Revise the storage temperature information for accuracy and consistency across all labeling components.
3. In June 2021, FDA finalized the Guidance for Industry on product identifiers required under the Drug Supply Chain Security Act (DSCSA). The Act requires manufacturers and re-packagers 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. The product identifier includes the NDC, serial number, lot number, and expiration date in both a human-readable form and machine-readable (2D data matrix barcode) format. We recommend that you review the guidance to determine if the product identifier requirements apply to your product's labeling. See Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021). If you

determine that the product identifier requirements apply to your product's labeling, we request you add a place holder to the carton labeling.

Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers, June 2021

4. As currently presented, the format for the expiration date is not defined. We are unable to assess the proposed expiration date format from a medication safety perspective. To minimize confusion and reduce the risk for deteriorated drug medication errors, we recommend identifying 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 forward slash to separate the portions of the expiration date. See Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021).
5. The linear barcode is missing on the container label and carton labeling. The drug barcode is often used as an additional verification during the medication use process; therefore, it is an important safety feature that should be part of the label and is a requirement per 21 CFR 201.25(c)(2). Add the product's linear barcode to each individual container label and carton labeling in accordance with 21CFR 201.25(c)(2). The bar code should be placed in a conspicuous location where it will not be difficult to read because of distorted text. Additionally, the barcode should be placed in an area where it will not be damaged because it appears at the point of label separation (e.g., perforation).
6. Revise the statement in the Administration section that reads "Do not cut or crush tablets" to read "Do not chew, cut, or crush tablets."
7. Revise the statement in the Administration section that reads "(b) (4) " to read "Store tablets in original packaging until time of use". We recommend this revision to state the action in the affirmative.
8. Revise the header that reads "If a dose is missed" to read "If a dose is vomited or missed" to align the header with the information that is provided.
9. Revise the instructions for managing a dose of tablets that is vomited to provide the timing for when a vomited dose should be repeated or not. Ensure the information is consistent with the information provided in the PI and in the Patient Information labeling.

B. Container Labels- Blister Card

1. Revise the "[redacted]" strength statement on the principle display panel of the blister card label to read "[redacted]". We recommend this revision to make it clear that the designated strength is per tablet so there is no confusion as to how much product is contained in a single tablet as compared to the total contents of the blister card.

    a. To the inside panel where the storage statement appears, add the following statement to clarify the milligram strength is per-tablet and not per-blister card: "[redacted]."

C. Carton Labeling- Tablets

1. We understand that, for the 500 mg dose, patients would have to use 1 of the 4-count blister cards plus 1 tablet taken from another card to achieve their dose. We are concerned that the proposed 500 mg packaging configuration (5- 400 mg cards) is incongruent with the dose to be administered and could lead to wrong dose errors. Therefore, we recommend the following revisions be applied consistently across all 3 of the packaging configurations for Ojemda tablets:
    a. Increase the prominence of the "100 mg" strength statement on the carton labeling for each of the proposed packaging configurations for the tablet formulation.
    b. Remove the statement on the lower left corner of the principal display panel that reads "[redacted]".
2. To reduce clutter on the back panel of the carton labeling, we recommend the following revisions:
    a. Remove [redacted] from the carton labeling. This information is provided in the PI.
    b. Relocate [redacted] to appear on a side panel.

We recommend the following be implemented prior to approval of NDA 218033.

A. General Comments (Container labels & Carton Labeling)- <u>Powder for Oral Suspension</u>

1. We note the storage temperature statement in PI Section 16 and in the Patient Information is inconsistent with the storage temperature statements that appear on the container label and carton labeling for the tablets and the powder for oral suspension. Revise the storage temperature information for accuracy and consistency across all labeling components.
2. In June 2021, FDA finalized the Guidance for Industry on product identifiers required under the Drug Supply Chain Security Act (DSCSA). The Act requires manufacturers and re-packagers 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. The product identifier includes the NDC, serial number, lot number, and expiration date in both a human-readable form and machine-readable (2D data matrix barcode) format.
We recommend that you review the guidance to determine if the product identifier requirements apply to your product's labeling. See Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021). If you determine that the product identifier requirements apply to your product's labeling, we request you add a place holder to the carton labeling.

Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers, June 2021

3. As currently presented, the format for the expiration date is not defined. We are unable to assess the proposed expiration date format from a medication safety perspective. To minimize confusion and reduce the risk for deteriorated drug medication errors, we recommend identifying 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 forward slash to separate the portions of the expiration date. See Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021).
4. The linear barcode is missing on the container label and carton labeling. The drug barcode is often used as an additional verification during the medication use process; therefore, it is an important safety feature that should be part of the label and is a requirement per 21 CFR 201.25(c)(2). Add the product's linear barcode to each individual container label and carton labeling in accordance with 21CFR 201.25(c)(2). The bar code should be placed in a conspicuous location where it will not be difficult to read because of distorted text. Additionally, the barcode should be placed in an area where it will not be damaged because it appears at the point of label separation (e.g., perforation).
5. Revise the statement "(b) (4)", to read "Recommended Dosage: See Prescribing Information" in accordance with 21 CFR 201.55.
6. Revise the "(b) (4)" statement on the back panel to read: (b) (4)

B. Container Labels- Powder for Oral Suspension

1. For brevity, revise the statement that appears below the strength statement, "[redacted]", to read "[redacted]".

B. Carton Labeling- Powder for Oral Suspension

1. To reduce redundancy on the PDP, remove the "[redacted]" and "[redacted]" statements in the lower left corner.
2. To improve the prominence of the list of contents of each carton, revise the list to read as follows:

Contents:

1 bottle

1 oral dosing syringe

1 bottle adapter

1 Instructions for Use

3. To reduce clutter on the back panel of the carton labeling, we recommend the following revisions:
   a. Remove the [redacted] from the carton labeling. This information is provided in the PI.
   b. Relocate the [redacted] statement to appear on a side panel.
   c. To eliminate redundancy, remove the "[redacted]" statement that appears above the manufacturer information. It appears twice on the back panel.
4. Relocate the "[redacted]" statement to appear above the "Administration: ..." information. Revise the statement to read "Preparation: See enclosed Instructions for Use for instructions on preparing and administering OJEMDA oral suspension for the first time."
5. For improved clarity, revise the "Administration: ..." information on the back panel to read as follows:

   - Take OJEMDA once a week on the same day each week.
   - OJEMDA may be taken with or without food.
   - Prepare and administer OJEMDA suspension by mouth or via nasal or gastric feeding tube using the dosing syringe that is provided.
   - Administer OJEMDA suspension within 15 minutes of preparation. Discard unused suspension if not administered within 15 minutes of preparation.

- Store OJEMDA in the original container until ready to take (or give) a dose.

6. Revise the header that reads "If a dose is missed" to read "If a dose is vomited or missed" to align the header with the information that is provided.
7. Revise the instructions for managing a dose that is vomited for consistency with the PI as follows:

(b) (4)

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Ojemda received on February 26, 2023 from Day One Biopharmaceuticals.

Table 2. Relevant Product Information for Ojemda	
Initial Approval Date	NDA 217700-N/A NDA 218033-N/A
Active Ingredient	tovorafenib
Indication	for the treatment of pediatric patients 6 months of age and older with relapsed or refractory pediatric low-grade glioma (LGG) harboring a BRAF fusion or rearrangement, or BRAF V600 mutation
Route of Administration	Oral
Dosage Form	• Tablet (NDA 217700) • powder for oral suspension (NDA 218033)
Strength	Tablet: 100 mg Powder for Oral Suspension: 300 mg/bottle (25mg/mL after reconstitution)
Dose and Frequency	380 mg/m^2 once weekly, with a maximum weekly dose of 600 mg. Continue until disease progression. • Oral Tablet: up to six 100 mg oral tablets given in a single dose once weekly or every 7 days. • Power for Oral Suspension: contents of up to two 300 mg bottles given in a single dose once weekly or every 7 days.

Table 2. Relevant Product Information for Ojemda	
How Supplied	Tablets: • 16-count carton: 4 blister cards (4 tablets each) per box, NDC 82950-0001-16. • 20 count carton: 5 blister cards (4 tablets each) per box, NDC 82950-0001-20. • 24 count carton: 4 blister cards (6 tablets each) per box, NDC 82950-0001-24. Powder for Oral Suspension: Carton contains 1 bottle containing 300 mg powder for oral suspension, 1- 20 mL oral syringe and 1 bottle adapter.
Storage	Store at (b) (4)°C to 25°C ((b) (4)°F to 77°F). Excursions permitted between (b) (4)°C to (b) (4)°C ((b) (4)°F to (b) (4)°F) (b) (4) .
Container Closure	Foil blister packs packaged in paperboard cards packaged in paperboard cartons.

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,[d] along with postmarket medication error data, we reviewed the following Ojemda labels and labeling submitted by Day One Biopharmaceuticals.

- Container label received on August 31, 2023
- Carton labeling received on August 31, 2023
- Prescribing Information (Image not shown) received on February 26, 2024, available from: \\CDSESUB1\EVSPROD\nda217700\0035\m1\us\draft-uspi.docx
- Patient Package Insert received on February 26, 2024, available from: \\CDSESUB1\EVSPROD\nda217700\0035\m1\us\draft-ppi.docx
- Instructions for Use received on November 13, 2023, available from: \\CDSESUB1\EVSPROD\nda218033\0008\m1\us\ifu-pfos-word.docx

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

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

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

/s/

JANINE A STEWART
03/13/2024 04:04:31 PM

ASHLEIGH V LOWERY
03/13/2024 05:15:33 PM

Clinical Inspection Summary

Date	February 9, 2024
From	Lee Pai-Scherf, MD Michele Fedowitz, MD, Team Leader Jenn Sellers, MD, PhD, Branch Chief Good Clinical Practice Assessment Branch (GCPAB) DCCE, OSI
To	Sonia Singh, MD, Medical Officer Diana Bradford, MD, Team Leader (CDTL) Division of Oncology 2 (DO2), Office of Oncology Products
NDA #	NDA 217700
Applicant	Day One Biopharmaceuticals Inc.
Drug	Tovorafenib
NME (Yes/No)	Yes
Therapeutic Classification	Tyrosine Kinase Inhibitor
Proposed Indication(s)	Treatment of patients with pediatric low-grade glioma (pLGG) harboring an activating RAF alteration
Consultation Request Date	September 25, 2023
Summary Goal Date	February 15, 2024
Action Goal Date	April 23, 2024
PDUFA Date	April 30, 2024

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from Study DAY101-001 were submitted to the Agency in support of New Drug Application (NDA 217700) for tovorafenib (DAY101) for the treatment of pediatric patients with low-grade glioma harboring an activating RAF alteration that has progressed after one or more prior systemic therapies. Three clinical investigators, Drs. Lindsay Kilburn (Site # 1014), Daniel Landi (Site # 1019), and Dong Khung Quang (Site # 61002), as well as the imaging Contract Research Organization (CRO) Imaging Endpoints II, LLC and the study sponsor, Day One Pharmaceuticals, Inc (Day One), were inspected.

Inspections of the CIs, Drs. Kilburn, Landi, and Quang, the sponsor, DAY ONE, and the imaging CRO, Imaging Endpoints, revealed no discrepancies or regulatory violations. Based on these inspections, Study DAY101-001 appears to have been conducted adequately and the data generated by the inspected clinical investigators and the imaging CRO and submitted by the applicant, Day One, appear acceptable in support of the proposed indication.

II. BACKGROUND

Day One Biopharmaceuticals Inc. submitted NDA 217700 seeking approval for tovorafenib (DAY101) for the above indication based on the efficacy and safety results from Study DAY101-001, an ongoing Phase 2, open-label, multicenter study of tovorafenib in pediatric patients with RAF-altered, recurrent, or progressive low-grade glioma (LGG) and advanced solid tumors.

Eligible patients were enrolled in one of the 3 treatment arms:

- Arm 1 (pivotal, LGG): Patients with relapsed or progressive LGG harboring an activating BRAF alteration, including BRAF V600 mutations and KIAA1549: BRAF fusion.
- Arm 2 (expanded access cohort, LGG): Patients with relapsed or progressive LGG harboring an activating or expected to be activating RAF alteration (e.g., BRAF or CRAF/RAF1 fusion or BRAF V600 mutations)
- Arm 3 (advanced solid tumor): Patients with advanced solid tumors harboring an activating or expected to be activating RAF fusion.

At the time of the data cut-off date (June 5, 2023), at total of 140 subjects had been enrolled across the 3 arms (77 subjects in Arm 1, 60 in Arm 2 and 3 in Arm 3). The efficacy population to support the proposed indication consists of 77 subjects with LGG enrolled in Arm 1. The safety population consists of 137 subjects with LGG enrolled in Arms 1 and 2.

All subjects were to receive tovorafenib at the recommended phase 2 dose (RP2D) of 420 mg/m^2 (not to exceed 600 mg), orally, once weekly of a 28-day cycle until radiographic evidence of disease progression as determined by the treating investigator, unacceptable toxicity, decision to enter a "drug holiday" period, patient withdrawal of consent, or death.

The key efficacy endpoints are overall response rate (ORR) and duration of response (DOR) as assessed by blinded independent central review (BICR) using the RANO criteria.

Subjects were to sign the informed consent form before any study-specific procedures were to be performed. MRI of the brain and spine for tumor assessment were to be performed at screening, at the end of C3, C6 and then every 3 cycles thereafter. MRIs were to be performed per the protocol-defined schedule regardless of whether study treatment is reduced, held, or discontinued. For patients who discontinue study treatment before radiographic progressive disease, every effort was to be made to document progressive disease with subsequent imaging. All scans were to be submitted to Imaging Endpoints for blinded central imaging assessment.

Drs. Lindsay Kilburn (Site # 1014), Daniel Landi (Site # 1019), and Dong Khung Quang (Site # 61002), as well as Imaging Endpoints II, LLC and the study sponsor, Day One, were inspected.

III. RESULTS (by site):

1. **Dr. Lindsay Kilburn (Site # 1014)**
   111 Michigan Ave
   NW, DC 20010

   Inspection dates: December 4 – 8, 2023

   Dr. Kilburn was inspected as a routine PDUFA inspection for Study DAY101-001. This was the first FDA inspection for this investigator.

   At the time of the inspection, the site had screened 13 subjects and had enrolled 11 subjects in the study. Of the 11 subjects enrolled, 4 subjects are on active treatment, 3 subjects completed 26 cycles of tovorafenib and are on drug holiday, 3 are off treatment due to disease progression, and 1 subject was transferred to another center to continue study treatment.

   Source records for 13 subjects were reviewed. Records reviewed included: informed consent forms, medical records, eligibility criteria, investigational drug administration, adverse events reporting, protocol deviations, and subject dispositions. Records were compared with data listing tables submitted to the NDA and no meaningful discrepancies were noted.

   All protocol required MRIs were performed by the clinical site both pre-treatment and at each required treatment cycle. The electronic scans and associated radiology reports were reviewed by the Dr. Kilburn and the subject's tumor status per the RANO criteria (PD, SD, PR, CR), was determined by the investigator. All electronic scans were available at the site as were the associated radiology reports. Per the study protocol, the electronic scans for each subject were sent to the sponsor's central imaging CRO, Imaging Endpoints, for evaluation.

   Based on the results of the inspection, data generated at Kilburn's site appear acceptable in support of the proposed indication in the NDA.

2. **Dr. Daniel Landi (Site #1019)**
   B 2301 Erwin Rd.
   Durham, NC 27705

   Inspection dates: November 6 - 8, 2023

   Dr. Landi was inspected as a routine PDUFA inspection for Study DAY101-001. This was the first FDA inspection for this investigator.

   At the time of the inspection, the site had screened and enrolled 10 subjects in the study, of which 5 subjects are on active treatment, 2 subjects completed study and are

in follow-up phase, and 3 subjects discontinued study treatment due to disease progression.

Source records for all 10 subjects were reviewed in full and compared with data listings submitted to the NDA. Records reviewed included informed consent documents, inclusion and exclusion criteria, adverse events reporting, investigational product administration, protocol deviations, laboratory reports, and concomitant medications. No discrepancies were observed.

There were no non-adherences of the protocol noted during the conduct of the inspection. It appeared that tumor assessments for the primary efficacy endpoint of ORR were performed according to the protocol, with no discrepancies when compared to the data listing.

Additional records reviewed during the inspection included, but not limited to, IRB correspondence, training records, monitoring reports, electronic records, and investigational product accountability.

Based on the results of the inspection, the DAY101-001 study data generated at Dr. Landi's site appear acceptable in support of the proposed indication in the NDA.

3. Dr. Dong Khung Quang (Site # 61002)
Ahn 50 Flemington Rad
Parkville, Victoria 3052
Australia

Inspection dates: November 13 - 17, 2023

Dr. Quang was inspected as a routine PDUFA inspection for Study DAY101-001. This is Dr. Quang's initial FDA inspection.

At the time of the inspection, the site had screened and enrolled 11 subjects in the study. At the time of the data cut-off date, 2 subjects completed the study, 6 subjects remain on study, 2 subjects withdrew consent, and 1 subject discontinued treatment due to an adverse event.

Source records for all 11 subjects were reviewed and compared with data listing submitted to the NDA. Records reviewed included informed consent forms, eligibility criteria, adverse events reporting, study drug administration, protocol deviations, laboratory reports, and concomitant medications. No discrepancies were observed.

Tumor imaging scans were performed according to protocol specified time points and all scans were submitted to the imaging CRO for central assessment.

The inspection also reviewed CI and co-investigator's financial disclosures, IRB

approval and communications, staff training records, monitoring reports and communication, and investigational product accountability.

Based on the results of the inspection, the DAY101-001 study data generated at Dr. Quang's site appear acceptable in support of the proposed indication in the NDA.

4. **Day One Pharmaceuticals, Inc**
2000 Sierra Point Parkway, Suite 501
Brisbane, CA 94005

Inspection dates: November 7 - 10, 2023

This inspection assessed Day One's oversight responsibilities for DAY101-001 study. This was the first FDA inspection for Day One.

Documents reviewed during the inspection included, but not limited to, DAY101-001 study documents, data management plans, data collection and handling procedures, safety reporting and handling, selection of clinical site investigators and monitors, form FDA 1572s, financial disclosures, data monitoring committee activities, investigational product disposition, and vendor, contract, and service agreements.

The inspection reviewed site records in full for 5 clinical sites (Sites # 1010, #1014, #1019, #61002, and #972001). Records reviewed included, site staff training and monitoring visit logs. Day One's monitoring practices of the clinical sites appear appropriate and critical issues were addressed or followed up on in a timely manner.

Overall, the inspection did not observe issues with the staff qualifications, training, experience, or compliance with the investigational plan. No issues related to safety/adverse event handling and reporting for Study DAY101-001 were observed.

Based on the results of the inspection, Day One's oversight of the study and monitoring of the clinical investigator's appear adequate.

5. **Imaging Endpoints II, LLC**
7150 E Camelback Rd Ste 120
Scottsdale, AZ 85251-1240

Inspection dates: October 23 – 25, 2023

Imaging Endpoints was inspected as a routine PDUFA inspection for Study DAY101-001. The firm was previously inspected in June 2018 and February 2021.

This inspection reviewed Imaging Endpoints' responsibilities to perform an independent central imaging review for Study DAY101-001. Records reviewed

included Trial Master File, imaging source data, data collection and handling procedures, electronic databases, associate radiologist selection and training records. In addition, blinding and adjudication procedures were reviewed and found to be adequate.

As per email communication with the review team on October 10, 2023, the inspection focused on tumor response results for subjects who were reported as have achieved a complete tumor response (CR), partial tumor response (PR), or minor response (MR) per RANO-LGG and/or RAPNO-LGG. Tumor response source data for a total of 37 subjects were verified and compared with the data submitted to the NDA. The inspection also verified that tumor responses were confirmed by imaging at least 28 days after the initial response. No discrepancies were identified.

The ID of the subjects whose tumor measurements were verified are as follows: (b) (6)

Imaging Endpoints' procedures in performing image analysis, compliance with the Imaging Review Charter, clinical protocol, and appropriate regulations were reviewed and appeared adequate.

Based on the results of the inspection, the imaging review data generated by Imaging Endpoints appear acceptable in support of the proposed indication in the NDA.

{See appended electronic signature page}

Lee Pai-Scherf, MD
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Michele Fedowitz, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: {*See appended electronic signature page}*

Jenn Sellers, M.D., Ph.D.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CC:

DARRTS: NDA 217700
Review Division /Project Manager/Opeyemi Udoka
OSI/DCCE/GCPAB/Program Analyst/Yolanda Patague

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/

LEE HONG PAI SCHERF
02/09/2024 12:26:12 PM

MICHELE B FEDOWITZ
02/09/2024 12:29:56 PM

JENN W SELLERS
02/09/2024 01:07:49 PM

Interdisciplinary Review Team for Cardiac Safety Studies

QT Study Review

Submission	NDA 217700 / 218033
Submission Number	002 (New NDA)
Submission Date	8/31/2023
Date Consult Received	10/5/2023
Drug Name	Tovorafenib (DAY101)
Indication	Pediatric low-grade glioma
Therapeutic Dose	(b) (4) mg/m2 once weekly (not to exceed 600 mg)
Clinical Division	DO2
Protocol Review	Link (extracted from SP)

Note: Any text in the review with a light background should be considered to be copied from the sponsor's document.

This review responds to your consult dated 10/5/2023 regarding the sponsor's QT evaluation. We reviewed the following materials:

- Previous IRT review dated 02/12/2021, 04/19/2022 and 11/10/2022 in DARRTS;
- CQT report (NDA217700 / SDN0002; link);
- CQT SAP (NDA217700 / SDN0002; link);
- Clinical study report of study C28001 (NDA217700 / SDN0002; link);
- Clinical study report of study FIREFLY-1 (NDA217700 / SDN0002; link);
- Drafted label (NDA217700 / SDN0005; link);
- QT evaluation checklist (NDA217700 / SDN0002; link); and
- Highlights of clinical pharmacology and cardiac safety (NDA217700 / SDN0002; (link).

1 SUMMARY

Tovorafenib does not cause mean QTc interval prolongation ≥ 20 msec based on the results of Study DAY101-001/PNOC026 (FIREFLY-1) – see Table 1 for results. Without a positive control or a large exposure margin, we are reluctant to conclude that tovorafenib has no effect on QTc (E14 Q&A 6.1).

Study DAY101-001/PNOC026 (FIREFLY-1) is an ongoing Phase 2 multicenter, efficacy, safety, and pharmacokinetic (PK) study in 114 pediatric patients 6 months to 25 years of age with relapsed or progressive low-grade glioma and advanced solid tumors harboring an activating RAF alteration. 97% of patients ranged from neonates to adolescents and 3% of patients were adults. The (b) (4) (b) (4) dosing regimen in pediatric

patients has a geometric mean steady state C_{max} of 7542 ng/mL. C_{max} of tovorafenib is predicted to increase by 40% when it's coadministered with strong or moderate CYP2C8 inhibitors; [redacted]. The Applicant's Product Label states that coadministration of tovorafenib with strong or moderate CYP2C8 inhibitors is to be avoided. [redacted]

Data were analyzed using exposure-response analysis as the primary analysis, which did not suggest that tovorafenib is associated with large mean increases (≥ 20 msec) in the QTcF interval (refer to section 4.5). The findings of the primary analysis are further supported by the lack of QTc prolongation in by-time analysis (section 4.3) and categorical analysis (section 4.4).

Table 1: Summary of findings

<table>
<tr><td>QT assessment pathway</td><td>☐ Thorough QT study
☐ Substitute for thorough QT study (5.1)
☒ Alternative QT study when a thorough QT study is not feasible (6.1)</td></tr>
<tr><td>Clinical QT study findings</td><td>[redacted] The C_{max} seen at 420 mg/m$_2$ is 7637 ng/ml. The high clinical exposure scenario predicted based on modeling is [redacted]
<table>
<tr><th>ECG parameter</th><th>Treatment</th><th>Concentration</th><th>ΔQTcF (msec)</th><th>90% CI (msec)</th></tr>
<tr><td>ΔQTcF</td><td>Tovorafenib 420mg/m^2 QW</td><td>7637 ng/ml</td><td>-1.0</td><td>-2.6 to 0.5</td></tr>
</table></td></tr>
<tr><td>In vitro findings</td><td rowspan="2">Integrated non-clinical and clinical QT assessment was not conducted.</td></tr>
<tr><td>In vivo findings</td></tr>
</table>

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION

Not applicable.

2 RECOMMENDATIONS

2.1 ADDITIONAL STUDIES

Not applicable.

2.2 PROPOSED LABEL

Below are proposed edits to the label submitted to SDN 0005 (link) from the CSS-IRT.

Our changes are highlighted (addition, ~~deletion~~). Each section is followed by a rationale for the changes made. Additionally, we are omitting section x, as we do not have any edits to that section. Please note that this is a suggestion only and that we defer final labeling decisions to the Division.

12.2 Pharmacodynamics Cardiac Electrophysiology [redacted] (b) (4) *At the recommended TRADENAME [redacted] (b) (4) mg/m^2 orally once weekly (not to exceed 600 mg), a mean increase in the QTc interval > 20 milliseconds (ms) was not observed.*
Reviewer's comment: We propose to use labeling language for this product consistent with the "QTc Information in Human Prescription Drug and Biological Product Labeling Guidance for Industry" draft guidance (link).

3 SPONSOR'S SUBMISSION

3.1 OVERVIEW

The sponsor, Day One Biopharmaceuticals, is developing Tovorafenib (also known as DAY 101, molecular weight 506.29) as an oral, selective, Type II pan-rapidly accelerated fibrosarcoma (RAF) kinase inhibitor for treatment of patients (aged 6 months to 25 years) with low grade gliomas (LGGs) harboring an activating RAF alteration that has relapsed or progressed after 1 or more prior systemic therapies. Glioma is a common type of tumor originating in the brain. Tovorafenib is a central nervous system (CNS)-penetrant, selective, small molecule, which directly inhibits BRAF V600 monomers and BRAF fusions, blocking downstream MEK/ERK signaling. The recommended dose is (b) (4) mg/m^2 orally once weekly according to body surface area and it is not to exceed 600 mg. The sponsor has submitted the tovorafenib application under NDA 217700 for the tablet formulation (100 mg strength) and under NDA 218033 for the powder for oral reconstituted suspension (PFOS) (25 mg/ml). The sponsor claims that the tablet and the suspension formulations have comparable exposures, and no dose adjustment is necessary between the two formulations. Tovorafenib may be taken with or without food.

We have previously reviewed this product under IND 108340, in which we agreed (02/12/2021 and 04/19/2022) with the sponsor's plan to characterize the QT effects of tovorafenib as per ICH14 Q&A 6.1 using sparsely collected ECGs and time matched PK data from study DAY101-001 (FIREFLY-1) which was a Phase 2 monotherapy study conducted in *pediatric* patients. [redacted] (b) (4)

With these NDA applications the sponsor mentions that as part of the clinical development path of new drugs, evaluation of QT prolongation risk is required per

regulatory guidance (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use [ICH] E14 [2]) to support new drug application (NDA). The traditional approach is to assess corrected QT interval (QTc) prolongation risk with a thorough QT (TQT) study where typically a study in healthy volunteers with a positive control is required. However recent recommendations from ICH-E14 Q&A allow concentration-QTc modeling to replace the TQT study in specific situations. Further, according to the sponsor a traditional thorough QT/QTc Study in a pediatric population is not feasible because this type of a trial would not offer the prospect of direct benefit and involves more than minimal risk. Further, due to the safety profile observed in healthy adult subjects after a single dose of 300 mg in study (b) (4)205140, a traditional thorough QT/QTc study at supratherapeutic dose in healthy adult population is also not feasible. Therefore, the Sponsor followed the general recommendations outlined in the 6.1 pathway described in the August 2022 E14 and S7B Clinical and Nonclinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential—Questions and Answers, as a substitute for a Thorough QT/QTc Study.

The rationale for the present concentration-corrected QT interval (QTc) modeling was based on (i) in vitro studies that showed minimal effect of tovorafenib in hERG inhibition studies, (ii) no ECG changes in telemetered cynomolgus monkeys, (iii) as well as no serious cardiovascular events from clinical study C28001 in adult oncology patients. This was further supported by the absence of clinically meaningful QT interval prolongation at the clinical dose (600 mg once weekly (QW)) based on the concentration-QTc analysis in adults. The present evaluation of the relationship of the QTc interval to observed plasma tovorafenib concentration in pediatric oncology patients is intended to serve as an alternative to the thorough QT (TQT) study under E14, 6.1 pathway.

In this submission, the sponsor provides data from Study DAY101-001/PNOC026 (FIREFLY-1) which is an ongoing Phase 2 efficacy, safety, and pharmacokinetic (PK) study in pediatric patients 6 months to 25 years of age with relapsed or progressive low-grade glioma and advanced solid tumors harboring an activating RAF alteration.

There were 114 patients in the study where 97.6 % were from the age of neonates to adolescents (< 18 years of age), i.e., the pediatric category, and 3 patients (2.6 %) were adults.

The sponsor has submitted concentration-QTc analysis based on time-matched plasma tovorafenib pharmacokinetic (PK) concentration and triplicate ECG data (mixed digital and paper ECGs, read semi-automatically) from open-label Phase study FIREFLY-1 (DAY101-001/PNOC026) in patients aged 6 months to 25 years. Baseline ECG was average of pre-dose measurements. The primary analysis was concentration-QTc analysis following the white paper model. Automatic reading of the paper ECGs are not available in electronic format (sponsor's response to IR dated 10/24/2023). We will conduct sensitivity analysis using digital data only.

Study Number, Phase, Type	Subject Population	Number of Subjects	Drug Dose and Regimen	Time-Matched PK and ECG Sampling
FIREFLY-1 Phase 2 Open-label safety and efficacy study	Pediatric patients (6 months to 25 years of age) with the following tumor types: Arm 1: BRAF altered pLGG Arm 2: RAF altered pLGG Arm 3: RAF fusion advanced solid tumor	Planned: Arm 1: N = 60 Arm 2: N = up to 60 Arm 3: N = up to 20 Actual: Arm 1: N = 77 Arm 2: N = 59 Arm 3: N = 3	Patients initiated treatment at the RP2D of 420 mg/m^2, PO, QW (not exceeding 600 mg QW), on Cycle 1 Day 1. Tovorafenib was administered on Days 1, 8, 15, and 22 of a 28-day cycle.	Cycle 1 Day 1: 1, 2, and 4 hours postdose. Cycle 1 Day 15 (±3-day window: a sample between 1 and 4 hours postdose Cycle 2 Day 1 (±3-day window): within 1 hour predose Cycle 4 Day 1 (±3-day window): a sample between 1 and 4 hours postdose Day 1 (±3-day window) of every subsequent 3rd cycle through C13 (e.g., Cycle 7, Cycle 10 etc.): a sample between 1 and 4 hours postdose

3.1.1 Clinical Pharmacology

See Highlights of Clinical Pharmacology and Cardiac Safety (link)

Recommended dose for the proposed pediatric indication is (b) (4) mg/m^2 QW (not to exceed 600 mg). The steady state (C1D22) geometric mean (%CV) Cmax at 600 mg QW in Study C28001 (Phase 1 monotherapy in *adult* patients with cancer) is 5650 (36%) ng/mL (n=20). The population PK model-predicted steady state geometric mean (%CV) Cmax at 420 mg/m2 QW (not to exceed 600 mg) in Study DAY101-001/PNOC026 (FIREFLY-1) (Phase 2 monotherapy in *pediatrics*) is 7542 (25%) ng/mL. Median Tmax ~ 3 hours; terminal half-life ~48 hours. There is no accumulation with once weekly dosing. Primary elimination route is through biliary-fecal excretion (66%) and renal excretion is a minor route (29%).

Tovorafenib was the most abundant circulating component in plasma. Oxy-tovorafenib metabolites M3, M26 and glucuronide conjugate oxy-tovorafenib glucuronide M16 were the most abundant although minor (<10% of total plasma radioactivity exposure). Tovorafenib is primarily metabolized by aldehyde oxidase (AO) and by several CYP isozymes with no single CYP dominating the metabolism of tovorafenib.

Population PK analyses indicate that pharmacokinetic differences are not clinically relevant based on sex, race, or age (range: 1 to 94 years, after accounting for body surface area).

Organ impairment studies have not been conducted to date. Renal impairment and mild hepatic impairment are not expected to result in clinically relevant PK differences, based on population PK analyses. The impact of moderate and severe hepatic impairment is unknown. However, the prevalence of moderate and severe hepatic impairment in the intended patient population (i.e., pediatric low-grade glioma) is likely to be low.

Clinical drug interaction studies have not been conducted to date. Based on PBPK modeling, coadministration of tovorafenib with strong CYP2C8 inhibitor gemfibrozil is predicted to increase tovorafenib Cmax and AUC0-168 by 40% and 100%, respectively and to an almost similar extent by 35% and 100% respectively, when coadministered with clopidogrel (a moderate CYP2C8 inhibitor). Labeling is indicating that coadministration of tovorafenib with both strong or moderate CYP2C8 inhibitors is to be avoided, (b) (4) . Food (high fat meal) did not result in clinically meaningful effect on the exposure of tovorafenib.

The sponsor's current high clinical exposure scenario is (b) (4)

Reviewer's Comment: *The population PK model-predicted geometric mean steady state (cycle 1 day 22) Cmax of tovorafenib at the dose of 420 mg/m2 QW (not to exceed 600 mg) in Study DAY101-001/PNOC026 (FIREFLY-1) (Phase 2 monotherapy in pediatrics) is 7542 ng/mL. Strong or moderate CYP2C8 inhibitors like gemfibrozil or clopidogrel are predicted to increase the Cmax of Tovorafenib by about 40 %* (b) (4) *. It should be noted that the sponsor's Labeling is mentioning in both the Highlights and Full Prescribing Information sections that coadministration of Tovorafenib with strong or moderate CYP2C8 inhibitors is to be avoided.* (b) (4) *Examples of strong and moderate CYP2C8 inhibitors are gemfibrozil and clopidogrel and predicted tovorafenib Cmax increases are 40% and 35 %, respectively when coadministered.*

Table 2: Summary of dose and exposure assessment

		GeoMean C_{max}
Highest therapeutic or clinical trial dosing regimen	420 mg/m2 QW, oral tablets or powder for oral suspension in pediatric patients	7542 ng/mL ($C_{max,ss}$)
Sponsor's High clinical exposure scenario	(b) (4)	
Highest dose in QT assessment	420 mg/m2 QW, oral tablets or powder for oral suspension in pediatric patients	7542 ng/mL
C_{max} Ratio	(b) (4)	

3.1.2 Nonclinical Safety Pharmacology Assessments

In the GLP in vitro study using patch-clamp electrophysiology in HEK293 cells stably transfected with hERG cDNA, tovorafenib IC50 for hERG potassium current was 8.9 μM (free-drug concentration).

The potential effects of tovorafenib on the cardiovascular system were also evaluated in a GLP study with conscious, telemetered cynomolgus monkeys. A total of 6 monkeys (3 males and 3 females) were dosed by oral gavage at 0, 10, 30 and 60 mg/kg of tovorafenib in each dosing session. There were at least 4 days between each dosing session to ensure an appropriate washout period. The sex combined Cmax was 12,700 ng/mL in monkeys at 60 mg/kg, which corresponds to unbound Cmax of 635 ng/mL (monkey plasma fu of 5.0% and molecular weight of 506.29). There were no clinical signs directly attributed to tovorafenib at doses up to 60 mg/kg. Any changes in HR, QRS, PR, QT interval, and blood pressure were mild, and values remained within normal ranges. There was no clear or consistent evidence of a gender difference in any of the effects observed.

Reviewer's comment: *The hERG safety margin is (b)(4)-fold over free clinical exposure and (b)(4)-fold over free high clinical exposure in pediatric patients. The free Cmax at 60 mg/kg (at which level normal ECG parameters were observed) in monkeys was equivalent to (b)(4) fold of free geometric mean Cmax at high clinical exposure in pediatric patients.*

3.2 SPONSOR'S RESULTS

3.2.1 By-Time Analysis

In the sponsor's by-time analysis, the mean estimate of ΔQTcF was below 10 msec for Tovorafenib.

The primary analysis for Tovorafenib was based on exposure-response analysis, please see section 3.2.3 for additional details.

Reviewer's comment: *Results from FDA reviewer's analysis are similar to sponsor's results. Please see Section 4.3 for additional details.*

3.2.1.1 Assay Sensitivity

Not applicable.

3.2.1.1.1 QT Bias Assessment

Not applicable

3.2.2 Categorical Analysis

There were no significant outliers per the sponsor's analysis for QTc (i.e., QTc >500 msec or ΔQTc>60 msec over baseline) and QRS (>120 msec and 25% over baseline). A total of 24 subjects had at least 1 post-baseline HR > 100 beats/min and ≥ 25% increase from baseline. Two subjects had PR >200 msec and 25% over baseline.

Reviewer's comment: *We used slightly different cutoffs for HR, PR, and QRS. The sponsor's results are similar to the reviewer's results. FDA reviewer's analysis shows no significant outliers for QTc and QRS intervals. A total of 84 subjects had at least 1 post-*

baseline HR > 100 beats/min. One subject had PR >220 msec and 25% over baseline. Please see Section 4.4 for additional details.

3.2.3 Exposure-Response Analysis

The sponsor had previous experience with concentration-QTc analysis having conducted it for the study in adult cancer patients (Study C28001). Linear mixed effects models were able to adequately describe the data and were able to predict drug concentration-driven baseline-adjusted in QTcF (ΔQTcF) and baseline-adjusted population-corrected QT interval (ΔQTcP). Concentration-QTcF or concentration-QTcP analysis suggested no statistically significant relationship between tovorafenib concentration and ΔQTcF or ΔQTcP.

In this submission analysis is from data from Study FIREFLY-1 only (pediatric patients). The sponsor considered the appropriateness of conducting concentration-ECG analysis by pooling Study FIREFLY-1 with the previous Study C28001. Given that the 2 studies were from 2 different patient populations (pediatric versus adult), data pooling would be considered inappropriate. Additional potential between-study variability could be attributed to differences in the study design (e.g., sampling times and food restrictions) and ECG acquisition (baseline measurement was not associated with a pre-first dose PK sample in Study FIREFLY-1). Therefore, a single study analysis based on Study FIREFLY-1 alone was considered preferable to assess the relationship between tovorafenib and ECG parameters.

Both Cardiodynamic ECG and Pharmacokinetic collection time points are mentioned in the Appendix.

The increase in heart rate (HR) was generally below the 10 beats/min threshold and it was therefore considered that the HR effect was not large enough to impact the concentration-QTc analysis. Of the 3 HR correction methods, Fridericia, Bazett and population corrected (QTcP), only QTcP fully resolved the dependency between HR and QTc and therefore QTcP analysis was conducted in addition to the primary analysis of QTcF.

In the linear concentration-QTc relationship the linear regression and the loess regression lines were overlapping across the observed ranges of tovorafenib concentrations indicating that a linear model for the concentration-QTc relationship should appropriately describe the observed data.

Primary Analysis is C-QTc Analysis: The primary analysis was tovorafenib concentration-QTc analysis and the model development followed the approach described in the scientific White Paper. An LME model with parameters for intercept, slope, and additive subject-level random effects on both the intercept and slope terms was used. Nominal time, cycle and baseline effects were also tested and included if found significant during model development.

Based on ΔQTcF: The estimated population slope of the concentration-QTcF relationship was -0.000135 msec per ng/mL (95% CI: -0.000441, 0.00017; p = 0.387), indicating no statistically significant relationship between plasma tovorafenib concentration and QTcF prolongation (negative slope).

The final concentration-QTcF model was used to predict the mean and 90% CIs of ΔQTcF at the clinical concentration range for the *geometric mean* steady-state maximum concentration (Cmax,ss of 7542 ng/ml) for the 420 mg/m2 (not to exceed 600 mg) QW dose. The mean predicted ΔQTcF decreased by 1.70 msec (i.e., minus 1.70 msec) with the upper bounds of the 90% CI below 10 msec. The 90% CI (-3.76, 0.360 msec) encompassed zero, suggesting the change in ΔQTcF at the Cmax was not statistically significant from zero and the predicted upper bound as shown here for ΔQTcF was 0.36 msec.

According to the sponsor at the maximum population PK model-predicted steady-state *individual* concentration (approximately 12,600 ng/mL) following 420 mg/m2 (not to exceed 600 mg) QW dose, the upper 90% CI of the model predictions remained below 10 msec.

Based on ΔQTcP: Like the concentration-QTcF model, there was no statistically significant relationship between plasma tovorafenib concentration and ΔQTcP prolongation (slope = 4.57×10-5 msec per ng/mL [95% CI: -0.000288, 0.00038]; p = 0.789).

The final concentration-QTcP model was used to predict the mean and 90% CIs of ΔQTcP at the clinical concentration range for the *geometric mean* steady-state Cmax (Cmax,ss of 7542 ng/ml) for the 420 mg/m2 (not to exceed 600 mg) QW dose. The mean predicted ΔQTcP decreased by 0.323 msec (i.e., minus 0.323 msec) with the upper bounds of the 90% CI below 10 msec. The 90% CI (-2.55, 1.91 msec) encompassed zero, suggesting the change in ΔQTcP at the Cmax was not statistically significant from zero and the predicted upper bound as shown here for ΔQTcP was 1.91 msec.

At the maximum population PK model-predicted steady-state *individual* concentration (12,600 ng/ml) following 420 mg/m2 (not to exceed 600 mg) QW dose, the upper 90% CI of the model predictions remained below 10 msec.

There is no apparent delay between the time to reach peak QTc effect and Tmax indicating the absence of hysteresis.

Reviewer's comment: *The results of the sponsor's analysis and the reviewer's analysis are slightly different numerically but are quite comparable.*

3.2.4 Safety Analysis

As of 22 December 2022 six clinical trials with a total of 432 unique individuals had systemic exposure to at least one dose of tovorafenib. The sponsor's safety review focused on two studies: study C28001 in 149 adult patients (relapsed/refractory solid

tumors or metastatic melanoma) with median exposure of 44 days (2 22-day cycles) and study FIREFLY-1 with 139 pediatric patients (RAF altered, recurrent or progressive low-grade glioma and advanced solid tumors) with median exposure of 217 days (8 28-day cycles). At the time of the data cut off, 110 (81%) patients remain on study. See Table 3 for the number of subjects in each dose group.

Table 3. Dosing Strength and Number of Subjects in Study C28001 and FIREFLY-1

	Q2D						QW			
Dose (mg)	**20**	**40**	**80**	**135**	**200**	**280**	**420/m²***	**400**	**600**	**800**
Escalation N	4	3	3	3	10	7		3	13	4
Expansion N					80				19	
FIREFLY-1 (all three arms) N							139			

Source: C28001 CSR Table 10.b and Table 10.c; FIREFLY-1 CSR Synopsis; * not to exceed 600 mg

Study C280001

There were 45 cardiac-associated treatment emergent events per the screening algorithm. Most events were Grade 1 or 2 (5 patients with Grade 3 events, no Grade 4 or 5). The most common events were flushing (5.4%), atrial fibrillation (4.7%), and tachycardia (4.7%). No patients required a dose reduction due to cardiac-associated events.

There were 2 patients with reported SAEs of cardiac failure and 1 patient with a reported SAE of ejection fraction decreased. Both cases the cardiac failure occurred in very ill patients with complex medical histories including past histories of angina pectoris, ischemic heart disease, and atrial fibrillation.

The single event of electrocardiogram QTc prolonged occurred on C1D29 in a patient with coronary artery disease, hypothyroidism, adrenal insufficiency, and hypopituitarism with hyponatremia. The event resolved and the patient continued treatment with no change in dose and no recurrence of the event.

Study FIREFLY-1

There were 55 cardiac- associated treatment emergent events per the screening algorithm. All events were Grade 1 or 2.

Dose reductions occurred in 3 patients due to cardiac-associated AEs (pericardial effusion, left ventricular hypertrophy [by ECG voltage criteria only], and ventricular extrasystoles). The event of ventricular extrasystoles (maximum Grade 2; serious) also led to treatment discontinuation. Other SAEs were hypotension and seizures (5 events all associated with patient's CNS tumor and present at baseline). One AE of electrocardiogram QT prolonged was reported.

Reviewer's comment: *See section 4.6 for the reviewer's analysis.*

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF for the primary analysis. This is acceptable, as no large increases or decreases in heart rate (i.e., |mean| >10 beats/min) were observed (see section 4.3.2).

4.2 ECG ASSESSMENTS

4.2.1 Overall

Both digital ECG waveforms and non-digital ECG waveforms (i.e., scanned, or digitized ECGs) were submitted for review. Digitized ECG waveforms were semi-automatically read. Since the submission includes digitized ECG waveforms, sensitivity analysis was performed using the automatic measurements as provided by the ECG devices at the clinical sites. The results of the sensitivity analysis using the automatic measurements are similar to the results of the primary analysis using all the data.

4.2.2 QT Bias Assessment

Not applicable.

4.3 BY-TIME ANALYSIS

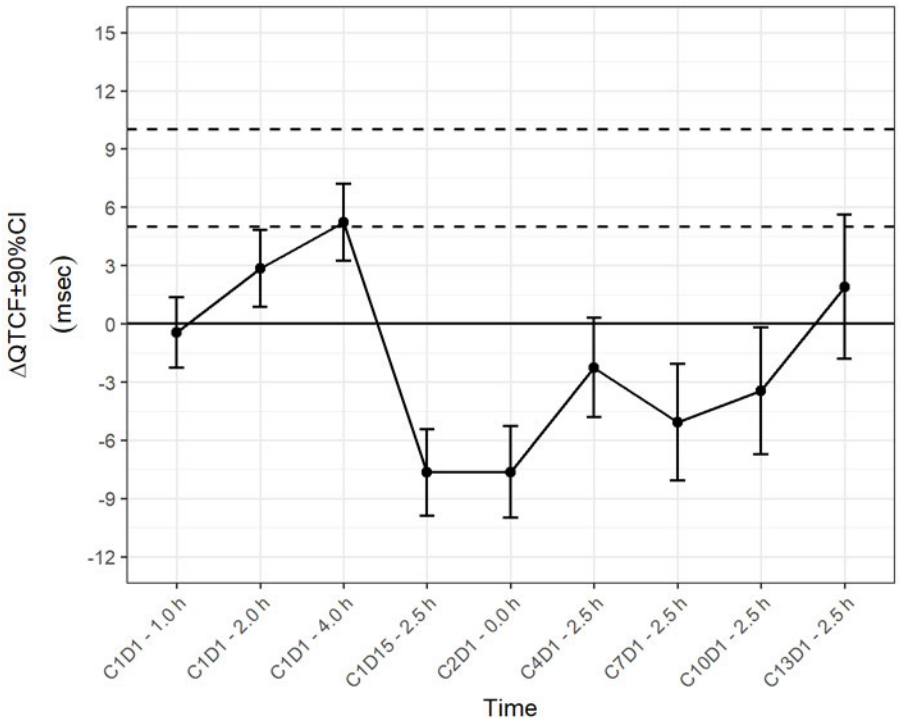
The analysis population used for by-time analysis included all subjects with a baseline and at least one post-dose ECG. Cycles and days that less than three subjects had ECG data on were excluded to avoid extremely large CI intervals displayed in the plot.

The statistical reviewer evaluated the ΔQTcF effect using descriptive parametric statistics.

4.3.1 QTc

Figure 1 displays the time profile of ΔQTcF for different treatment groups.

Figure 1: Mean and 90% CI of ΔQTcF Time-course (unadjusted CIs).



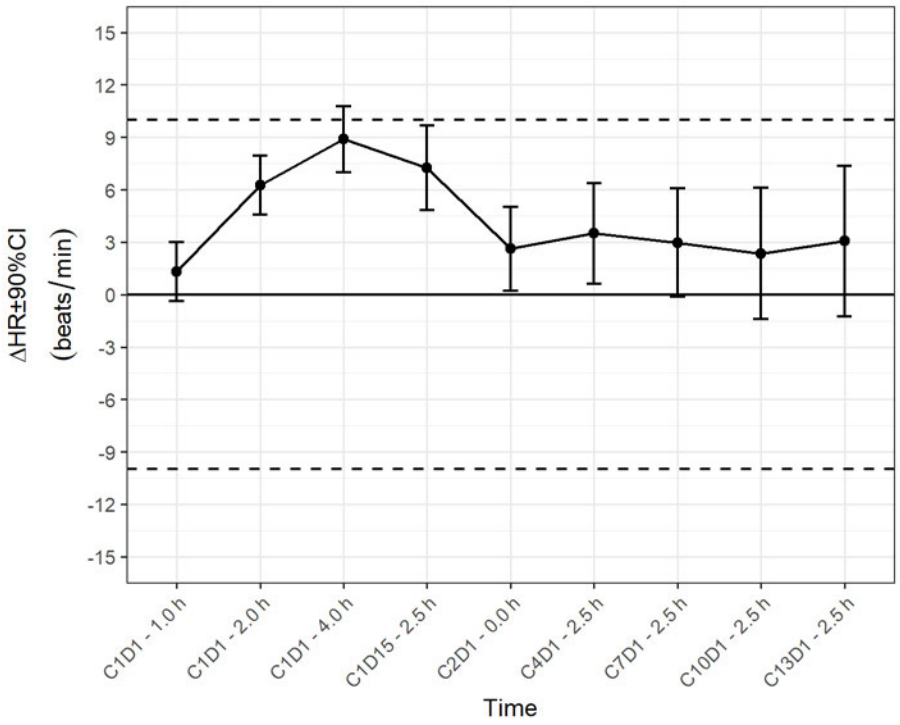
4.3.1.1 Assay Sensitivity

Not applicable.

4.3.2 HR

Figure 2 displays the time profile of ΔHR for different treatment groups.

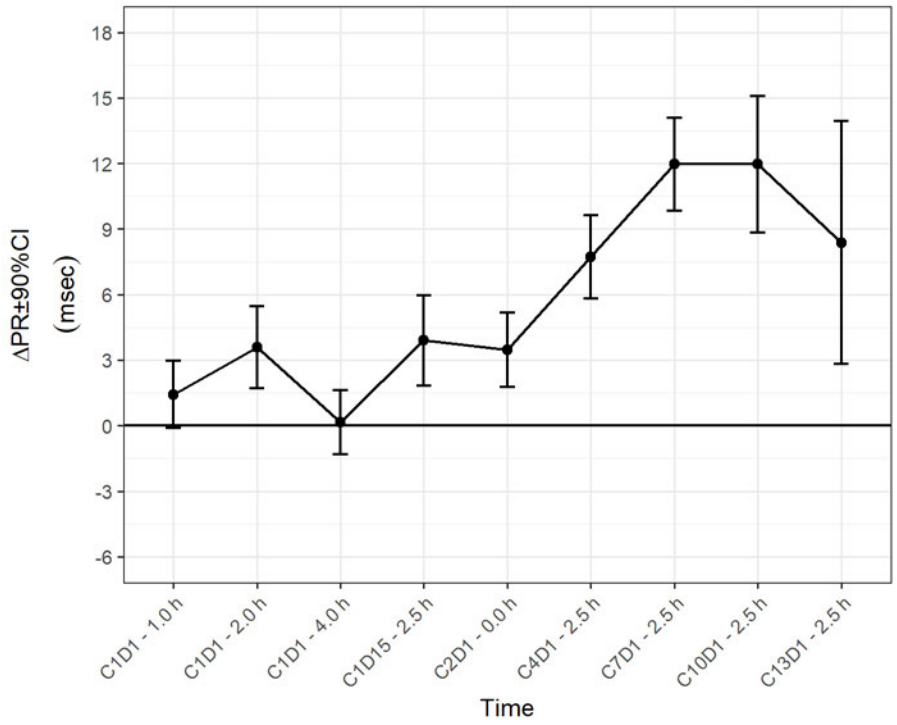
Figure 2: Mean and 90% CI of ΔHR Time-course



4.3.3 PR

Figure 3 displays the time profile of ΔPR for different treatment groups.

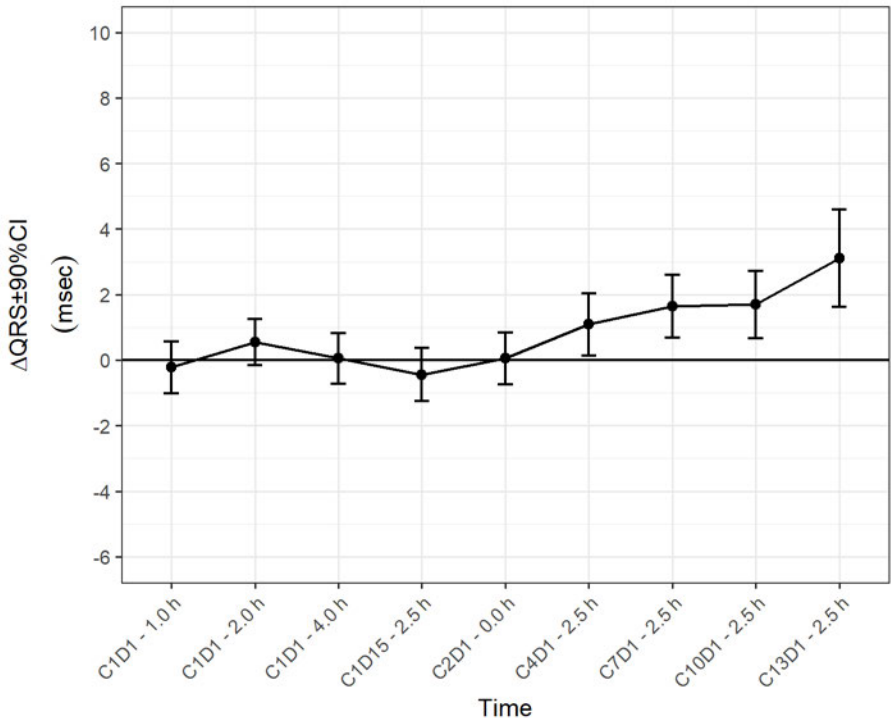
Figure 3: Mean and 90% CI of ΔPR Time-course



4.3.4 QRS

Figure 4 displays the time profile of ΔQRS for different treatment groups.

Figure 4: Mean and 90% CI of ΔQRS Time-course



4.4 CATEGORICAL ANALYSIS

Categorical analysis was performed for different ECG measurements, either using absolute values, change from baseline, or a combination of both. The analysis was conducted using the safety population, which includes both scheduled and unscheduled ECGs. In the following categorical tables, an omitted category means that no subjects had values in that category.

4.4.1 QTc

None of the subjects had QTcF value >450 msec. None of the subjects had ΔQTcF value >60 msec.

4.4.2 HR

Table 4 lists the categorical analysis results for maximum HR (<100 beats/min and >100 beats/min). There were 84 subjects who experienced HR >100 beats/min for the treatment of Tovorafenib.

Table 4: Categorical Analysis for HR (maximum)

Actual Treatment	Total (N)		Value <=100 beats/min		Value >100 beats/min	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Tovorafenib 420mg/m2 QW	133	800	49 (36.8%)	486 (60.8%)	84 (63.2%)	314 (39.2%)

4.4.3 PR

Table 5 lists the categorical analysis results for PR (<200 msec, >200 and ≤220 msec, and >220 msec; with and without 25% increase over baseline). There was one subject who experienced PR >220 msec with >=25% increase over baseline for the treatment of Tovorafenib.

Table 5: Categorical Analysis for PR

Actual Treatment	Total (N)		Value <=220 msec		Value >220 msec & <25%		Value >220 msec & >=25%	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Tovorafenib 420mg/m2 QW	132	797	130 (98.5%)	792 (99.4%)	1 (0.8%)	4 (0.5%)	1 (0.8%)	1 (0.1%)

4.4.4 QRS

None of the subjects had QRS value >120 msec and 25% over baseline.

4.5 Exposure-Response Analysis

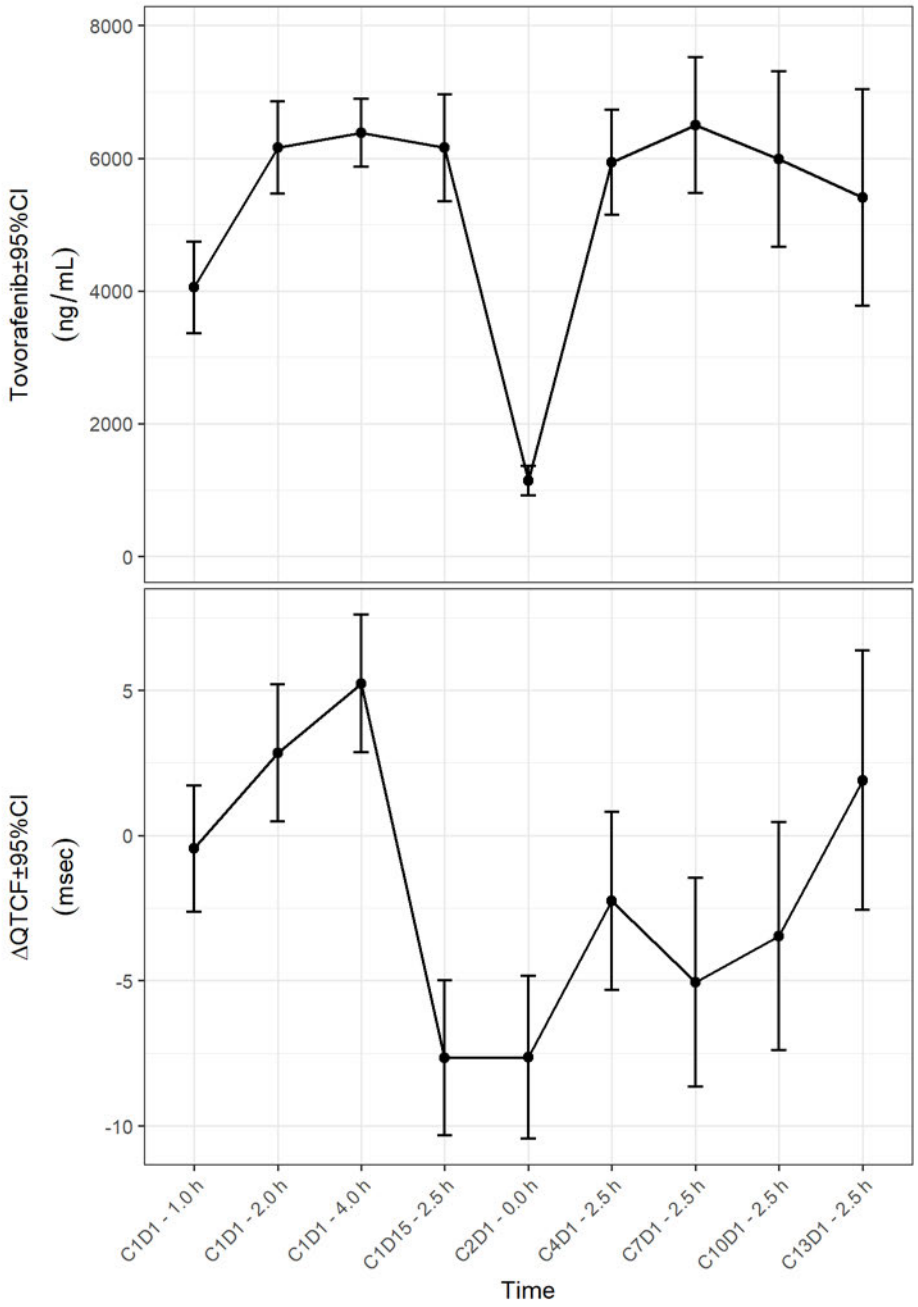
Exposure-response analysis was conducted using all subjects with baseline and at a least one post-baseline ECG, with time-matched PK.

4.5.1 QTc

Prior to evaluating the relationship between drug concentration and QTcF using a linear model, the three key assumptions of the model were evaluated using exploratory analysis: 1) absence of significant changes in heart rate (more than a 10 beats/min increase or decrease in mean HR); 2) absence of delay between plasma concentration and ΔΔQTcF; and 3) absence of a nonlinear relationship.

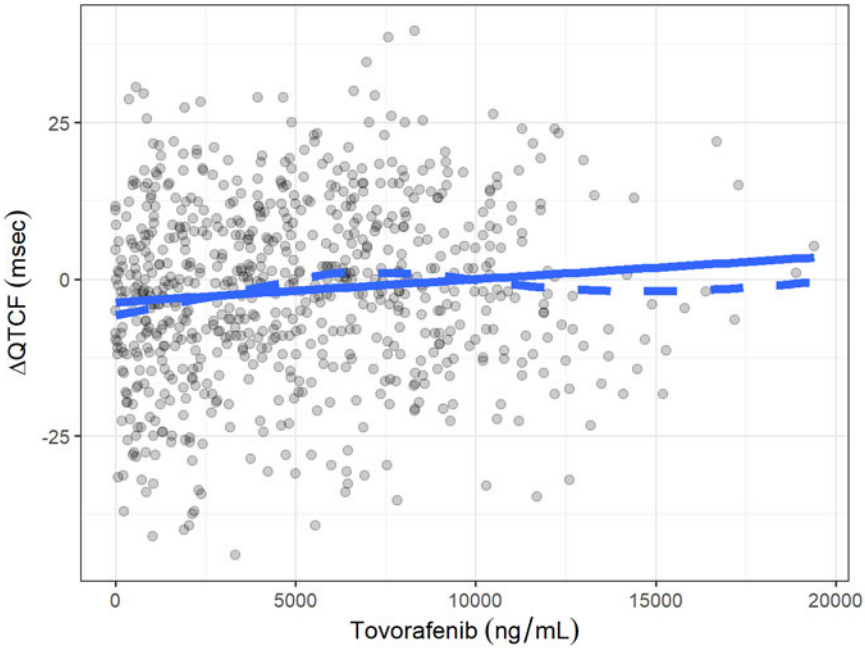
Figure 2 shows the time-course of ΔHR, with an absence of significant ΔHR changes. Figure 5 offers an evaluation of the relationship between time-course of drug concentration and ΔQTcF, with no appearance of significant hysteresis. Figure 6 shows the relationship between drug concentration and ΔQTcF and supports the use of a linear model.

Figure 5: Time-course of Drug Concentration (top) and QTcF (bottom)[1]



[1] ΔQTcF shown were obtained via descriptive statistics and might differ from Figure 1

Figure 6: Assessment of Linearity of the Concentration-QTcF Relationship



Finally, the linear model was applied to the data, and the goodness-of-fit plot is shown in Figure 7. Predictions from the concentration-QTcF model are provided in Table 6.

Figure 7: Goodness-of-fit Plot for QTcF

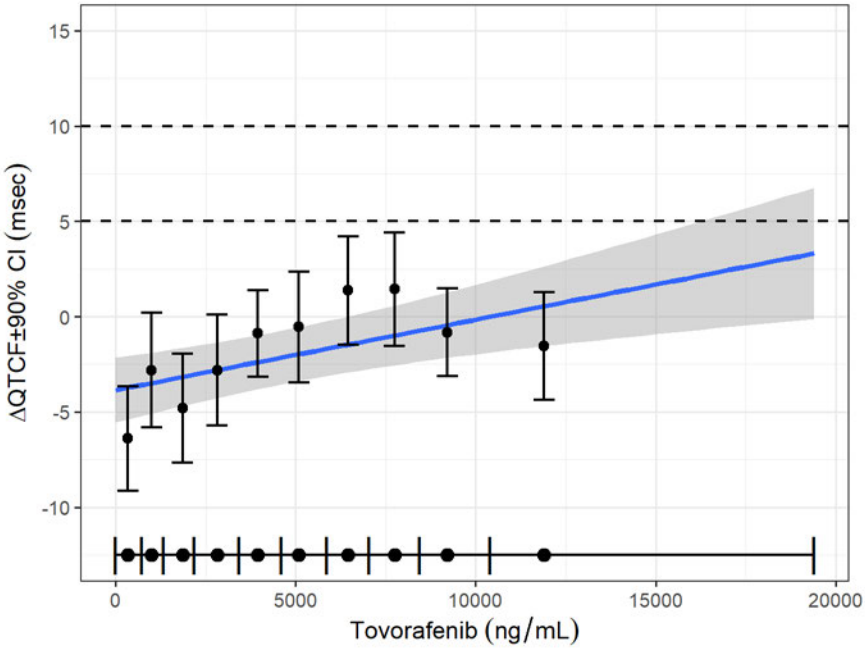


Table 6: Predictions from Concentration-QTcF Model

Actual Treatment	Analysis Nominal Period Day (C)	Tovorafenib (ng/mL)	ΔQTCF (msec)	90.0% CI (msec)
Tovorafenib 420mg/m2 QW	1	7,637.4	-1.0	(-2.6 to 0.5)

4.5.1.1 Assay Sensitivity

Not applicable.

4.6 SAFETY ASSESSMENTS

The reviewer's safety analysis focused on study FIREFLY-1, which was conducted in the targeted pediatric population and had longer exposure than the adult study (study C28001, see section 3.2.4).

In total, 139 patients received treatment of tovorafenib at therapeutic dose (420 mg/m^2, not to exceed 600 mg).

Forty-seven patients (34%) experienced SAEs. One patient experienced 2 SAEs of cardiac disorders (PT: ventricular extrasystoles, both Grade 2), one of which led to drug discontinuation. It was the only cardiac disorder AE that led to drug discontinuation and *based on the timing of the events, it was likely related to tovorafenib*.

- Patient (b) (6), an 8-year-old white male, experienced AEs of premature ventricular extrasystole starting 14 days after the first dose of tovorafenib. ECGs were normal on Day 1 (1, 2, and 4 hour post-dose). At the time of the second dose (Day 15), *the 1-hour post-dose ECG showed 40% ventricular premature beats (VPBs)* with bigeminy and trigeminy. The patient was admitted for observation on telemetry and had no symptoms or changes in vital signs. On Day 20, the patient's VPBs decreased to 10% VPBs and the patient was discharged. On Day 22, dose was reduced to 50%. *Pre-dose ECG showed 10% VPBs. One hour post the 50% reduced dose (3rd dose of study drug), ECG again showed worsening of VPBs with an increase to 40% VPBs* including recurrent trigeminy and bigeminy. The patient was asymptomatic with a normal blood pressure. Repeat ECG 5 hours post study drug demonstrated approximately 20% VPBs. *Labs were notable for a sodium of 135 mEq/L (low)*. On Day 25, the Holter monitor continued to be abnormal with very frequent isolated monomorphic premature ventricular contractions (9% of QRS complexes), some in trigeminy and bigeminy patterns. Study drug was discontinued.

Two subjects experienced non-SAEs within the broad SMQ 'torsade de pointes/QT prolongation' (MedDRA version 23.1, PT: electrocardiogram QT prolonged and syncope). *The event of electrocardiogram QT prolonged was likely related to the acute electrolyte abnormalities.*

- Patient (b) (6), a 5-year-old white female, experienced SAEs of Grade 3 clostridium difficile colitis and Grade 3 gastrointestinal hemorrhage; and a nonserious AE of Grade 1 electrocardiogram QT prolonged on Day 133, 5 days after the most recent dose of tovorafenib. Concomitant medications at the onset of the events included unknown bleach bath, topical clindamycin, and mupirocin for treatment of

folliculitis and paronychia. The patient presented to the emergency room (ER) with shock, a one-week history of fevers, and bloody diarrhea. The patient was hypotensive to 70s/30s and improved after 10 cc/kg normal saline IV bolus. Laboratory examination showed phosphorus of 1 mg/dL (3.0-6.0) and Hgb of 6.0 g/dL (11.5-15.5) (worsened from ongoing G2 anemia). An AE of Grade 1 ECG QT prolonged was reported and ECG showed ventricular rate 119 bpm, PR interval 134 ms, QRS duration 76 ms, P-R-T axes 70-77-80 and *QTcF 422 ms*; and normal sinus rhythm. When compared to ECG of Day 84, QT had lengthened and was 40 ms longer than baseline but still within normal limits for age. Per the laboratory values, the patient was additionally noted to have *hypokalemia*, *hypocalcemia*, hypoalbuminemia. The patient received PRBC transfusion for GI hemorrhage, antibiotics for C. difficile colitis, and treatment for electrolyte abnormalities. On Day 134, tovorafenib was interrupted due to the SAEs of C. difficile colitis and GI hemorrhage. *The prolonged QTc resolved with treatment of the acute electrolyte abnormalities and the patient did not experience any further events of prolonged QTc.*

- Patient (b) (6), a 11-year-old male, experience a non-serious AE of syncope. On Day 5, the patient, *with a history of convulsions*, developed a nonserious Grade 2 event of syncope (reported as social circumstances, breath-holding spell). Concomitant medications at the onset of the event included levothyroxine, methylcellulose (otic), dexamphetamine, calcium, macrogol, desmopressin, hydrocortisone, and mometasone. No action was taken with tovorafenib. Treatment included IV hydrocortisone and the event was considered resolved on the same day.

Five patients experienced SAEs of seizure, all with a medical history of seizure, epilepsy, or convulsion.

5 APPENDIX

5.1 EVALUATION OF THE SPONSOR'S CLINICAL QT STUDIES

1. QT Studies					
Study	**ECG Quality**	**Treatments**		**Sample Size**	**ECG & PK Assessments**
		Arms	**Dose Coverage**		
Protocol DAY101-001/PNOC026 (FIREFLY-1) Population: Patients Design: Other	Digital: Yes Central Read? Yes Blinded? No Replicates? No	Highest Dose: 420 mg/m2 Placebo: No Positive Control: No	Therapeutic	114 patients	Baseline: Pre-dose baseline Timing: See Reviewer's Comment below for details of sample collections.
Reviewer's Comment: FIREFLY-1, a Phase 2, open-label safety, and efficacy study. Pediatric patients (6 months to 25 years of age) with the following tumor types: Arm 1: BRAF altered pLGG; Arm 2: RAF altered pLGG; Arm 3: RAF fusion advanced solid tumor. Drug Dose and Regimen: Patients initiated treatment at the RP2D of 420 mg/m2, PO, QW (not exceeding 600 mg QW), on Cycle 1 Day 1. Tovorafenib was administered on Days 1, 8, 15, and 22 of a 28-day cycle. Time-Matched PK and ECG Sampling:					

Cycle 1 Day 1: 1, 2, and 4 hours postdose

Cycle 1 Day 15 (±3-day window: a sample between 1 and 4 hours postdose

Cycle 2 Day 1 (±3-day window): within 1-hour predose

Cycle 4 Day 1 (±3-day window): a sample between 1 and 4 hours postdose

Day 1 (±3-day window) of every subsequent 3rd cycle through C13 (e.g., Cycle 7, Cycle 10 etc.): a sample between 1 and 4 hours postdose

Reviewer's Comment: *The time to achieve peak plasma concentration (Tmax) is 3 hours. Sampling times as shown above cover the Tmax of tovorafenib.*

5.2 EVALUATION OF THE SPONSOR'S CLINICAL QT ANALYSIS PLAN

1. Analysis plan	
1.1 Study Objectives Related to QT	
What QTc effect size is the analysis trying to exclude?	20 ms
1.2 Data Pooling	
Data pooling?	No
Did sponsor propose an assessment for heterogeneity?	N/A
Is the data pooling appropriate?	N/A
1.3 QT Correction Method	
Is an HR increase or decrease greater than 10 beats/min?	No
Primary method for QT correction	QTcF
1.4 Assay Sensitivity	
Assay sensitivity methods proposed by sponsor	☐ Moxifloxacin ☐ Exposure-margin

	☐ QT bias assessment ☐ Other ☒ Not applicable (objective is large mean effects)
1.5 By-Time Analysis	
1.5.1 Investigational Drug	
Primary analysis	No
Did the sponsor use IUT or descriptive statistics?	Descriptive statistics
For IUT: Does the sponsor use MMRM to analyze longitudinal values that consider the correlation across time-points, or use ANCOVA by-time-point without considering correlation?	N/A
For IUT: Is the MMRM model specified correctly with regard to covariance structure, covariates, or if ANCOVA, is the model specified correctly with regard to covariates?	N/A
N/A.	
1.5.2 Positive Control	
Primary analysis	N/A
Did the sponsor adjust for multiplicity?	N/A
N/A.	
1.6 Exposure-Response Analysis	
1.6.1 Investigational Drug	
Primary analysis	Yes
What is the dependent variable in the sponsor's model?	Single delta
White paper model?	Yes
Which concentration covariate(s) are included in the model?	Parent
Which methods did the sponsor use for predicting the QT effect?	☒ Model-based confidence intervals

		☐ Bootstrap-derived confidence intervals	
1.6.2 Positive Control			
Primary analysis		N/A	
Same model as investigational drug		N/A	
1.7 Categorical Analysis			
QTcF / ΔQTcF?	Yes	QRS?	Yes
PR?	Yes	HR?	Yes

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/s/

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12/19/2023 01:46:39 PM

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XUTONG ZHAO
12/20/2023 11:12:06 AM

YU-TING WENG
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DALONG HUANG
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MICHAEL Y LI
12/20/2023 11:24:39 AM

YANYAN JI
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CHRISTINE E GARNETT
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