CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217865Orig1s000

OTHER REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
Epidemiology: ARIA Sufficiency Memorandum

Date:	March 20, 2024
Reviewer/Acting Team Leader:	Catherine Callahan PhD, MA Division of Epidemiology I
Division Director:	CAPT Sukhminder K. Sandhu, PhD, MPH, MS Division of Epidemiology I
Subject:	ARIA Sufficiency Memorandum
Drug Name:	DUVYZAT (givinostat)
Application Type/Number:	NDA 217865
Applicant/sponsor:	Italfarma S.p.A
TTT #:	2023-5012

EXECUTIVE SUMMARY *(place "X" in appropriate boxes)*

Memo type		
-Initial		
-Interim		
-Final	X	
Source of safety concern		
-Peri-approval	X	
-Post-approval		
Is ARIA sufficient to help characterize the safety concern?	Thrombocytopenia	Serious bleeding events
-Yes		
-No	X	X
If "No", please identify the area(s) of concern.		
-Surveillance or Study Population		
-Exposure		
-Outcome(s) of Interest	X	X
-Covariate(s) of Interest	X	X
-Surveillance Design/Analytic Tools		

1. BACKGROUND INFORMATION

1.1. Medical Product

Givinostat is a histone deacetylase (HDAC) inhibitor with the proposed indication for the treatment of Duchenne muscular dystrophy (DMD) in patients 6 years of age and older. The recommended dosage of givinostat is based on body weight and administered orally twice daily with food. DMD has a prevalence of 1 per 3,500-6,000 male births.[1] The proposed labeling for givinostat includes warnings and precautions statement for hematological changes, gastrointestinal disturbances, increased triglycerides, and QTc prolongation.[2]

1.2. Describe the Safety Concern

HDAC inhibitor-induced thrombocytopenia is a major dose-limiting toxicity of the class of drugs. In clinical trials of other HDAC inhibitors, thrombocytopenia was dose-related, asymptomatic, and reversible upon treatment discontinuation.(1) During the clinical development of givinostat, thrombocytopenia occurred in 33.1% of givinostat exposed patients and none of the placebo exposed patients.[3] None of the events of thrombocytopenia in Trial DSC/14/2357/48 led to serious bleeding events. There were three reports of subjects who experienced thrombocytopenia and also reported adverse events of contusions. One of these subjects also had an observed adverse event of epistaxis. Two subjects with thrombocytopenia also reported an adverse event of hematoma. There were two reported cases of hemorrhage identified (anal and ear bleeding), both in subjects with concomitant thrombocytopenia.[4]

The proposed labeling for givinostat as of March 20, 2024 contains a warning and precautions statement regarding thrombocytopenia. The current information regarding thrombocytopenia is as follows:

> **5.1 *Hematological Changes***
> *DUVYZAT can cause dose-related thrombocytopenia and other signs of myelosuppression, including decreased hemoglobin and neutropenia.*
>
> *In Study 1 [see Clinical Studies (14)], thrombocytopenia occurred in 33% of patients treated with DUVYZAT compared to no patients on placebo. The maximum decrease in platelets occurred within the first 2 months of therapy and remained low throughout the course of therapy. In a few patients, thrombocytopenia was associated with bleeding events including epistaxis, hematoma, or contusions. Low platelet counts resulted in DUVYZAT dose reduction in 28% of patients. Patients with baseline platelet counts below the lower limit of normal were excluded from the study.*
>
> *Decreased hemoglobin and decreased neutrophils were also observed in patients treated with DUVYZAT compared to placebo.*

[1] Duchenne Muscular Dystrophy and Related Dystrophinopathies: Developing Drugs for Treatment: Guidance for Industry. February 2018. Silver Spring (MD), U.S. Food and Drug Administration. https://www.fda.gov/media/92233/download accessed February 26, 2024.
[2] Proposed DUVYZAT (givinostat) labeling as of March 20, 2024.
[3] DUVYZAT (givinostat). DRAFT Clinical safety review IAMA as of March 15, 2024.
[4] DRAFT clinical safety review IAMA

Monitor blood counts every 2 weeks for the first 2 months of treatment, then monthly for the first 3 months, and every 3 months thereafter. Modify the dosage of DUVYZAT for confirmed thrombocytopenia [see Dosage and Administration (2.3)]. Treatment should be permanently discontinued if the abnormalities worsen despite dose modification. If a patient develops signs or symptoms of thrombocytopenia, obtain a platelet count as soon as possible, and hold dosing until platelet count is confirmed.

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

Assess a known serious risk	X
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	

1.4. Statement of Purpose

The Division of Neurology 1 (DN1) requested DEPI assess the sufficiency of ARIA to conduct a post-marketing requirement (PMR) study to characterize the incidence, frequency, and severity of thrombocytopenia and serious events of bleeding among givinostat exposed patients. While there were no clinical events such as serious bleeding events related to thrombocytopenia in the clinical development of givinostat, these events are a concern in the overall DMD population, especially given the muscle weakness and predisposition to falls. This PMR (b) (4) provide additional information regarding the reversibility of thrombocytopenia, impact of dosage changes and the incidence of serious bleeding events in a population with less monitoring and a larger sample size than the clinical trial for givinostat.

1.5. Effect Size of Interest or Estimated Sample Size Desired

The goal of this study would be to provide descriptive data on the incidence, frequency, and severity of thrombocytopenia and serious bleeding events. There is no specific effect size of interest as this is not a comparative study.

2. SURVEILLANCE OR DESIRED STUDY POPULATION

2.1 Population

The intended study population is patients with DMD treated with givinostat.

There is an ICD-10 diagnosis code for Becker/DMD G71.01. There was a validation study of this code using the U.S. Optum database that included males aged 40 years or younger on their first Becker/DMD diagnosis and met continuous enrollment and 1-day minimal clinical activities requirement in a 12-month measurement period. A broad definition of DMD (at least two claims with a DBMD diagnosis code (ICD-10-CM G71.01)) had positive predictive value (PPV) of 86.1% (95% Confidence Interval (CI) 80.6%-90.6%) when compared to electronic health record data. A narrow DMD definition included patients meeting the broad DMD definition who also had a prescription for glucocorticoids or exon-skipping therapy or evidence of ambulation assistance/support or nonambulatory status at 12 years of age or younger or evidence of ventilation support or dependence; if aged 30 years or older, patients were required to have evidence of ventilation support or dependence, this definition had a PPV of 91.0% (95%CI 85.2%-95.1%) (2).

2.2 Is ARIA sufficient to assess the intended population?

ARIA is sufficient to identify DMD patients.

DMD is a rare disease, which will make it difficult to enroll enough givinostat-exposed patients regardless of the study design.

3 EXPOSURES

3.1 Treatment Exposure

Givinostat is the exposure of interest. Givinostat is administered orally twice daily with food. The dosage of givinostat is based on the patient's body weight.

3.2 Comparator Exposure

This study will not require a comparator exposure.

3.3 Is ARIA sufficient to identify the exposure of interest?

ARIA is sufficient to identify patients with dispensings of givinostat.

4 OUTCOMES

4.1 Outcomes of Interest

The outcomes of interest are thrombocytopenia and serious bleeding events. The severity of these events is also of interest.

4.2 Is ARIA sufficient to assess the outcome of interest?

ARIA is not sufficient to assess thrombocytopenia. A literature review of algorithms or codes to identify thrombocytopenia identified studies that were not generalizable to the Mini-Sentinel distributed database (MSDD) because they were conducted in study populations receiving tertiary care or with chronic liver disease.[5] Further, the purpose of the study is to characterize the severity of thrombocytopenia which would require complete blood counts (CBC) with differential and platelet counts that are not available in Sentinel. Further, CBCs with differential and platelet counts need to be measured at baseline and during and after the event.

ARIA is not sufficient to assess serious bleeding events in this PMR. Although ARIA has been used to assess specific instances of bleeding (gastrointestinal bleeding, extracranial hemorrhage),[6] this PMR would require medical chart review or detailed case narratives to assess the severity of the outcomes.

5 COVARIATES

5.1 Covariates of Interest

Based on discussions with DN1, detailed case narratives regarding all instances of thrombocytopenia and serious bleeding would be needed for a complete assessment. The type of information that would be needed from these case narratives include dates of exposure; age; concomitant medications; baseline CBC with platelet count results, as well as CBC with platelet count results before, during, and after the event; disposition (e.g., was the givinostat dose reduced

[5] https://www.sentinelinitiative.org/sentinel/surveillance-tools/validations-lit-review (accessed March 1, 2024).
[6] https://www.sentinelinitiative.org/sites/default/files/Drugs/Assessments/Sentinel-Report_cder_mpl2p_wp009_Report-1-of-2.pdf (accessed March 6, 2024)

in response to the event, discontinued temporarily or permanently, and if the dose was reduced did event stop/resolve or if restarted did the event recur); what intervention, if any, was required.

5.2 Is ARIA sufficient to assess the covariates of interest?

ARIA is not sufficient to assess the covariates of interest as detailed case narratives are not available in Sentinel.

6 SURVEILLANCE DESIGN / ANALYTIC TOOLS

6.1 Surveillance or Study Design

The proposed study will provide estimates of the incidence, frequency, and severity of thrombocytopenia and serious bleeding events.

6.1.1 Is ARIA sufficient with respect to the design/analytic tools available to assess the question of interest?

Yes, ARIA is sufficient to provide incidence estimates, stratified analyses are also available.

7 NEXT STEPS

As ARIA is not sufficient to assess to characterize the incidence, frequency, and severity of thrombocytopenia and serious bleeding events among givinostat exposed patients. DN1 plans to issue the following PMR as of March 20, 2024:

> Conduct a prospective observational registry for a minimum of 5 years to characterize the incidence, frequency, and severity of thrombocytopenia and incidence, frequency, and severity of serious events of bleeding in patients with Duchenne muscular dystrophy exposed to givinostat. For each case of thrombocytopenia and severe bleeding identified, provide detailed case narratives that include~~s~~, but are not limited to, information on concomitant medications, CBC results at baseline, and during and after the event, and disposition (e.g., was the givinostat dose reduced in response to the event, discontinued temporarily or permanently, and outcomes if the dose was reduced).

8 REFERENCES

1. Subramanian S, Bates SE, Wright JJ, Espinoza-Delgado I, Piekarz RL. Clinical Toxicities of Histone Deacetylase Inhibitors. Pharmaceuticals (Basel). 2010;3(9):2751-67.
2. Schrader R, Posner N, Dorling P, Senerchia C, Chen Y, Beaverson K, et al. Development and electronic health record validation of an algorithm for identifying patients with Duchenne muscular dystrophy in US administrative claims. J Manag Care Spec Pharm. 2023;29(9):1033-44.

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/s/

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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 15, 2024
Requesting Office or Division:	Division of Neurology 1 (DN 1)
Application Type and Number:	NDA 217865
Product Name, Dosage Form, and Strength:	Duvyzat (givinostat) oral suspension, 8.86 mg/mL
Applicant Name:	Italfarmaco S.p.A
FDA Received Date:	March 14, 2024
TTT ID #:	2023-4562-2
DMEPA 2 Safety Evaluator:	Rina Patel, PharmD
DMEPA 2 Team Leader:	Stephanie DeGraw, PharmD

1 PURPOSE OF MEMORANDUM

Italfarmaco S.p.A submitted revised container label and carton labeling received on March 14, 2024 for Duvyzat. The Division of Neurology 1 (DN 1) requested that we review the revised container label and carton labeling for Duvyzat (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 memorandum.[a]

2 CONCLUSION

Italfarmaco S.p.A implemented all of our recommendations and we have no additional recommendations at this time.

[a] Patel, R. Label and Labeling Review Memo for Duvyzat (NDA 217865). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2024 March 12. TTT ID: 2023-4562-1.

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RINA N PATEL
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STEPHANIE L DEGRAW
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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

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

Memorandum

Date: March 13, 2024

To: Annie Nguyen, Regulatory Project Manager, Division of Neurology Products (DN1)

Peggy Lazerow, DN1

Tracy Peters, Associate Director for Labeling, DN

From: Lindsay McCann, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Susannah O'Donnell, Team Leader, OPDP

Subject: OPDP Labeling Comments for DUVYZAT (givinostat) oral suspension

NDA/BLA: 217865

Background: In response to DN1's consult request dated May 10, 2023, OPDP has reviewed the proposed Prescribing Information (PI), Medication Guide (MG), Instructions for Use (IFU), and carton and container labeling for the original NDA 217865 submission for DUVYZAT.

PI:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on February 29, 2024, and our comments are provided below.

Medication Guide/IFU
A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed Medication Guide/IFU, and comments were sent under separate cover.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling submitted by the sponsor to the electronic document room on March 6, 2024, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Lindsay McCann at 301-796-3719 or Lindsay.McCann@fda.hhs.gov.

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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:	March 11, 2024
To:	Annie Nguyen, RPh Regulatory Project Manager **Division of Neurology I (DN1)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Lonice Carter, MS, RN, CNL, NHDP-BC Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Lindsay McCann, PharmD, BCCCP Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG) and Instructions for Use (IFU)
Drug Name (established name):	DUVYZAT (givinostat)
Dosage Form and Route:	oral suspension
Application Type/Number:	NDA 217865
Applicant:	Freyr Inc., U.S. Agent for Italfarmaco S.p.A.,

1 INTRODUCTION

On April 21, 2023, Freyr Inc., U.S. Agent for Italfarmaco S.p.A., submitted for the Agency's review an Original New Drug Application (NDA)/New Molecular Entity 217865 for DUVYZAT (givinostat) oral suspension. Per the Applicant's cover letter, this NDA proposes an indication for the treatment of Duchenne Muscular Dystrophy (DMD).

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 DN1 on May 10, 2023, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for DUVYZAT (givinostat) oral suspension.

2 MATERIAL REVIEWED

- Draft DUVYZAT (givinostat) IFU received on April 21, 2023, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on February 29, 2024.
- Draft DUVYZAT (givinostat) MG received on February 27, 2024, and received by DMPP and OPDP on February 29, 2024.
- Draft DUVYZAT (givinostat) Prescribing Information (PI) received on April 21, 2023, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on February 29, 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.

In our collaborative review of the MG and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU are consistent with the PI
- removed unnecessary or redundant information
- ensured that the MG and IFU are free of promotional language or suggested revisions to ensure that they are free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20

- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the IFU meets the criteria as specified in both the FDA Guidance for Useful Written Consumer Medication Information (published July 2006) and Instructions for Use-Patient Labeling for Human Prescription Drug and Biological Products (published July 2022)

4 CONCLUSIONS

The MG 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 MG and IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFU.

Please let us know if you have any questions.

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/s/

LONICE J CARTER
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LINDSAY M MCCANN
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MARCIA B WILLIAMS
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LASHAWN M GRIFFITHS
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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

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

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	March 11, 2024
Requesting Office or Division:	Division of Neurology 1 (DN 1)
Application Type and Number:	NDA 217865
Product Name, Dosage Form, and Strength:	Duvyzat (givinostat) oral suspension, 8.86 mg/mL
Applicant/Sponsor Name:	Italfarmaco S.p.A
TTT ID #:	2023-4562-1
DMEPA 2 Safety Evaluator:	Rina Patel, PharmD
DMEPA 2 Team Leader:	Stephanie DeGraw, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted a Medication Guide (MG) received on February 27, 2024 and revised prescribing information (PI), container label and carton labeling received on March 6, 2024 for Duvyzat. The Division of Neurology 1 (DN 1) requested that we review the MG and revised container label and carton labeling for Duvyzat (Appendix A) to determine if they are acceptable from a medication error perspective. The MG was submitted in response to an information request submitted by the Division.[a] The revisions to the container label and carton labeling are in response to recommendations that we made during a previous label and labeling review.[b] In addition the recommended revisions, the Applicant modified the artwork and color scheme of the container label and carton labeling.

2 CONCLUSION

We note the addition of a graphic image in front of the proprietary name, Duvyzat, on the principal display panel (PDP) of the container label and carton labeling. The graphic does not

[a] Nguyen, A. FDA Communication: FDA Information Request - Email Communication. Silver Springs, (MD): FDA, CDER, DN1 (US); 2024 Feb 24. NDA 217865.

[b] Patel, R. Comparative Analyses, URRA, and Label and Labeling Review for Duvyzat (NDA 217865). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2024 Feb 16. TTT ID No.: 2023-4562 and 2023-4589.

interfere with the readability of the proprietary name; therefore, we do not object to the addition of the graphic image at this time.

The Applicant implemented all of our recommendations for the container label and carton labeling from our previous review. However, with the addition of the Medication Guide (MG), we have additional recommendations for the container label and carton labeling regarding the required MG statement, as well as recommendations for the prescribing information related to the MG. Additionally, the proposed MG may be improved to promote the safe use of this product from a medication error perspective.

We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 3 for the Division and in Section 4 for Italfarmaco S.p.A.

3 RECOMMEDATIONS FOR DIVISION OF NEUROLOGY 1 (DN 1)

A. Highlights of Prescribing Information (HPI)

1. The patient counseling information statement should be revised to "See 17 for PATIENT COUNSELING INFORMATION and Medication Guide" in accordance with 21 CFR 201.57(a)(14).

B. Full Prescribing Information – Section 17 Patient Counseling

1. Reference to the FDA-approved patient labeling should be updated to include the Medication Guide. For example, "Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use)."

C. Medication Guide (MG)

1. Multiple terms are used to describe the (b) (4) in the MG. To help prevent confusion, we recommend revising all references to the (b) (4) to be consistent by using the term (b) (4)

2. As currently presented, important administration information is missing from the MG. We recommend adding the following bullets to the "How should I take DUVYZAT?" section, or something similar:
    a. "Take DUVYZAT by mouth with food."
    b. "DUVYZAT should not be mixed with water or other liquids."

3. The "How should I take DUVYZAT?" section states " (b) (4) (b) (4) We are concerned that including the (b) (4) We recommend removing (b) (4)

4 RECOMMENDATIONS FOR ITALFARMACO S.P.A

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

A. General Comments (Container Label & Carton Labeling)

1. The font and font size for the proprietary name and established name appear to be different in the new proposed container label and carton labeling. As such, it is unclear if the established name is at least half the size of the proprietary name. Confirm that the established name is at least half the size of the proprietary name on both the container and carton in accordance with 21 CFR 201.10(g)(2) for the new presentation. Consider enlarging the established name to improve readability.

B. Carton Labeling

1. We note the inclusion of a Medication Guide (MG) as a part of the labeling submission; however, the MG statement is not stated on the principal display panel (PDP). Per 21 CFR 208.24(d), the label of each container or package, where the container label is too small, of drug product for which a Medication Guide is required under this part shall instruct the authorized dispenser to provide a MG to each patient to whom the drug product is dispensed and shall state how the MG is provided. These statements shall appear on the label in a prominent and conspicuous manner.

   We recommend the following:

   a. Relocate the medication guide statement on the back panel of the carton to the PDP. Ensure the statement is prominent and conspicuous, taking into account font size, font color, bolding, boxing, etc.
   b. As currently presented, the medication guide statement does not instruct the authorized dispenser to provide a MG to each patient. If a physical copy of the MG will not be provided as part of the labeling supplied with the product, modify the statement to read "Dispense a Medication Guide to each patient. Print Medication Guides at…" or something similar.

C. Container Label

1. The container label may be large enough to include the MG statement. We recommend adding MG statements as recommended above to the container label in accordance with 21 CFR 208.24(d). To allow room for this information, consider decreasing the size of the statement "For Oral Administration Only" on the container label.

APPENDIX A. IMAGES OF LABEL AND LABELING

A.1 List of Labels and Labeling Reviewed

- Container label received on March 6, 2024
- Carton labeling received on March 6, 2024
- Medication Guide (image not shown) received February 27, 2024, available from \\CDSESUB1\EVSPROD\nda217865\0054\m1\us\114-labeling\draft-labeling\draft-label-text\givinostat-med-guide.pdf
- Prescribing Information (image not shown) received March 6, 2024, available from \\CDSESUB1\EVSPROD\nda217865\0057\m1\us\114-labeling\draft-labeling\draft-label-text\givinostat-uspi-clean-version.pdf

A.2 Label and Labeling Images

Container label

(b) (4)

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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 Surveillance and Epidemiology Review (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)

Epidemiology: Real-World Evidence Review - Addendum

Date:	February 23, 2024
Reviewer:	Danielle Abraham, PhD, MPH Division of Epidemiology I (DEPI-I) Office of Surveillance and Epidemiology (OSE)
Team Leader:	Catherine Callahan, PhD, MA (Acting) DEPI-I, OSE
Associate Director for Real-World Evidence (RWE) & Oncology:	Kira Leishear White, PhD, MS DEPI-I, OSE
Drug Name:	Duvyzat (givinostat)
Subject:	Addendum to review of Applicant proposal to use real-world evidence (RWE) to support NDA 217865
Application Type/Number:	NDA 217865
Applicant/sponsor:	Italfarmaco S.p.A
TTT #:	2023-5012

The Division of Epidemiology I (DEPI-I) previously conducted a review on the strengths and limitations of the natural history data and quality of the real-world evidence (RWE) submitted as part of a New Drug Application (NDA) for Duvyzat (givinostat, Italfarmaco S.p.A) for the treatment of Duchenne muscular dystrophy (DMD).[1] The purpose of this amendment is to clarify DEPI-I's position regarding the use of the integrated analysis of long-term efficacy with natural history data as confirmatory evidence of effectiveness for givinostat.

The integrated analysis of long-term efficacy with natural history data indicated clinically meaningful delays in persistent loss of function among those treated with givinostat, compared to external controls. There are limitations to the external control analysis using natural history data, including the heterogeneity of DMD progression, lack of comparability between givinostat treated patients and natural history controls, potential for residual confounding, enrichment of the pivotal trial sample, differences in index date and follow-up, and use of effort-based outcomes that make the externally controlled study results difficult to interpret. Overall, DEPI-I agrees with using the natural history control analysis as confirmatory evidence of effectiveness for this rare disease indication.

[1] Abraham D, Callahan C, Leishear White K. Review of Applicant proposal to use real-word evidence (RWE) to support NDA 217865. September 19, 2023. Silver Spring (MD), U.S. Food and Drug Administration. DARRTS Reference ID: 5246869.

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/s/

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02/23/2024 01:51:27 PM

KIRA N LEISHEAR WHITE
02/23/2024 02:05:25 PM

COMPARATIVE ANALYSES, USE RELATED RISK ANALYSIS, 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:	February 16, 2024
Requesting Office or Division:	Division of Neurology 1 (DN 1)
Application Type and Number:	NDA 217865
Product Name, Dosage Form, and Strength:	Duvyzat (givinostat) oral suspension, 8.86 mg/mL
Product Type:	Combination Product (Drug-Device)
Device Constituent:	5 mL oral syringe
Rx or OTC:	Prescription (Rx)
Applicant Name:	Italfarmaco S.p.A
FDA Received Date:	04/21/2023, 06/13/2023, 07/12/2023, 07/26/2023, 11/09/2023, 11/15/2023, 01/24/2024
TTT ID #:	2023-4562 and 2023-4589
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1 REASON FOR REVIEW

This review evaluates the use-related risk analysis (URRA) and comparative analyses (CA) submitted for Duvyzat under NDA 217865 to determine whether the Applicant needs to submit the results of a human factors (HF) validation study as part of the marketing application.

In addition, as part of the approval process for Duvyzat (givinostat) suspension, the Division of Neurology 1 (DN 1) requested that we review the proposed Duvyzat prescribing information (PI), Instructions for Use (IFU), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

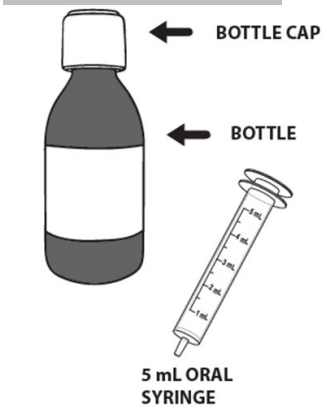
1.1 PRODUCT INFORMATION

Table 1 presents relevant product information for the proposed product, Duvyzat, received from Italfarmaco S.p.A on April 21, 2023 and January 24, 2024, and the comparator, Purixan[a].

Table 1. Relevant Product Information for the proposed product and comparator

Product Name	Duvyzat	Purixan (NDA 205919)
Initial Approval Date	N/A	04/28/2014
Active Ingredient	Givinostat	Mercaptopurine
Indication	Treatment of Duchenne muscular dystrophy (DMD)	Treatment of patients with acute lymphoblastic leukemia (ALL) as part of a combination chemotherapy maintenance regimen
Route of Administration	Oral	Oral
Dosage Form	Suspension	Suspension
Strength	8.86 mg/mL	20 mg/mL
Dose and Frequency	Weight based dosing range from 1.5 mL to 6 mL twice daily. (See Appendix A for detailed dosing information)	1.5 to 2.5 mg/kg (50 to 75 mg/m^2) orally once daily
How Supplied	Carton containing: - one bottle with 140 mL oral suspension - one 5 mL oral syringe	Carton containing: - one amber glass bottle with 100 mL oral suspension - one bottle adapter - one 1 mL oral syringe - one 5 mL oral syringe

[a] Purixan [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. Apr 2020. [cited 2023 Nov] 15. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/205919s004lbl.pdf

Storage	Store at 20°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Do not freeze. Store upright.	Store PURIXAN between 59°F to 77°F (15°C to 25°C). Store in a dry place.
Container Closure/Device Constituents	One amber polyethylene terephthalate (PET) bottle with a high-density polyethylene child-proof, (b) (4) screw cap. Bottle adapter is (b) (4) 	Child resistant closure. Bottle adapter is provided separately from the cap and is to be inserted by the user at the time of first use. 
Drug Disposal	N/A	Cytotoxic drug- follow special handling and disposal procedures
Intended Users	Healthcare professionals (HCPs), parents/caregivers of patients with DMD	Healthcare professionals (HCPs), parents/caregivers of patients with ALL
Intended Use Environment	Hospital, home	Hospital, home

2 MATERIALS REVIEWED

Table 2. Materials Considered for this Review

Material Reviewed	Appendix or Section
Product Information/Prescribing Information	Section 1.1 and A
Previous DMEPA Reviews	B- N/A
ISMP Newsletters*	C- N/A
FDA Adverse Event Reporting System (FAERS)*	D- N/A

Table 2. Materials Considered for this Review	
Material Reviewed	Appendix or Section
Information Requests Issued During the Review	E
Use Related Risk Analysis and Comparative Analyses	F
Labels and Labeling	G

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 post-market safety surveillance

3 OVERALL ASSESSMENT OF MATERIALS REVIEWED

The sections below provide our evaluation of the use-related risk analysis (URRA) and comparative analyses (CA). The URRA is evaluated to identify use-related hazards associated with the proposed product use and the measures implemented to reduce those risks. The CA was evaluated in the context of aiding the identification of design differences between the proposed Duvyzat and the Purixan comparator.

3.1 USE-RELATED RISK ANALYSIS

The Applicant submitted a URRA for their proposed product, Duvyzat (givinostat) suspension, 8.86 mg/mL which identified and evaluated the tasks involved in the use of the proposed product, the errors that users might commit, the tasks they might fail to perform, and the potential negative consequences of use errors. The Applicant concluded that the "URRA indicates that all the user related risks are mitigated, and no human factor study is required to be conducted" to support this combination product.

We reviewed the URRA for the proposed product, and we disagree that all of the use related risks have been considered and adequately mitigated. Based on our review of the URRA, we found one task that was not evaluated in the URRA which is the storage information for the product. We acknowledge that the details of this storage task is product specific, however as the product is to be stored under normal room temperature conditions, 20°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F), similar to many marketed products we anticipate that the intended users will be familiar with it based on their experiences with products that include similar labeling statements regarding storage. Thus, we find this does not preclude our ability to proceed with our review.

(b) (4)

(b) (4)

3.2 COMPARATIVE ANALYSES

The Applicant provided a physical comparison, comparative task analysis, and labeling comparison to identify any differences which may affect the safe and effective use of Duvyzat as compared to two comparators, Purixan and Banzel. For the purpose of our review, we considered a single comparator, Purixan. We find the use of Purixan appropriate as a comparator product because of the shared similarities between the intended users (i.e., lay caregivers of pediatric patients, and healthcare providers), use environment (i.e., home), (b) (4) (b) (4) and administration tasks. See Table 1 for relevant product information for the proposed product and comparator.

Per the Applicant,

> *Overall threshold analyses carried out to conduct the comparative analysis of the user interface of the proposed Duvyzat identified no meaningful difference in external critical design attributes that directly affect users' performance during drug product administration, therefore no comparative use Human Factor Study is required.*

3.2.1 Physical Comparison

The Applicant identified physical differences between the proposed product and Purixan. The Applicant stated that "no or minor differences have been identified". The Applicant did not specify if any of these differences impact critical tasks. The Applicant's identified physical differences include:

- Bottle adapter: The adapter for Duvyzat is (b) (4) The bottle adapter for Purixan is provided separately from the cap.
- Bottle type and volume: Duvyzat is proposed to be supplied in a plastic bottle containing 140 mL of product while Purixan is supplied in a glass bottle containing 100 mL of product.
- Oral syringes: (b) (4)

We reviewed the Applicant's identified physical differences and find the bottle type and oral syringe (b) (4) differences are driven by product specific characteristics. We also note the difference in the bottle adaptor but find the physical difference does not have a negative impact on the ability to measure or

administer the prescribed dose. As such, we don't anticipate these differences will negatively impact the intended user's ability to use the product as intended.

In addition, our independent review identified the following physical differences that were not identified by the Applicant.

- Graduation markings: The proposed oral syringes have graduation markings in milliliters (mL). (b) (4)
- Color of the oral syringe graduation markings: The graduation markings on proposed oral syringe for Duvyzat are black as compared to the blue graduation markings on the oral syringes co-packaged with Purixan.
- Color of the oral suspension: Duvyzat is a white to off-white or faintly pink oral suspension, and Purixan is a pink to brown oral suspension.
- Color of the plunger seal: The proposed oral syringe for Duvyzat has a (b) (4) plunger seal, and the oral syringe for Purixan has a black plunger seal.
- Orientation of the numerical graduation markings on the oral syringes: The numerical graduation markings on proposed oral syringes for Duvyzat are oriented right-side up when the tip is facing downwards. The numerical graduation markings on the oral syringes for Purixan are oriented right-side up when the tip is facing upwards.

We find that the physical differences regarding the plunger seal color and the color, type, and orientation of graduation markings may impact critical dose measurement tasks. However, based on our independent review of other approved products with same intended user group (i.e., lay caregivers of pediatric patients) and similar physical presentation, in this particular instance, we find these physical differences are acceptable. We find that the physical difference related to the color of the oral suspension is driven by product specific characteristics, and we don't anticipate this difference will negatively impact the intended user's ability to use the product as intended.

3.2.2 Comparative Task Analysis

For the Comparative Task Analysis, the Applicant compared the tasks provided in the intended use of the proposed product. Per the Applicant, "no or minor differences have been detected among the information reported for Duvyzat and the other products already on the market". The Applicant identified the following task differences but did not specify if any of these differences impact critical tasks.

- There is no use task to insert the bottle adapter ((b) (4) (b) (4) for Duvyzat while there is a use task to push the bottle adapter into the neck of the bottle by the user for Purixan.

- (b) (4) [redacted]

We reviewed the Applicant's identified task differences, and we disagree with the categorization by the Applicant of the task difference related to the interpretation of the (b) (4) [redacted]. Without additional data, we are unable to determine if the inclusion of these (b) (4) [redacted] introduces any new or unique risks in the intended use of the product in the intended user (e.g., lay caregivers). As such, we discussed this concern with the review Division to determine if the (b) (4) [redacted] are needed and appropriate to be included in the IFU. See Section 5 for additional discussion.

In addition, our independent review identified the following task differences that were not identified by the Applicant.

- Duvyzat does not have special handling instructions. When administering Purixan, hands should be washed with soap and water before and after administration, and gloves should be worn.
- Duvyzat should be shaken by continuously turning the bottle up and down while Purixan should be shaken vigorously.
- Purixan oral syringe should be aimed at the inside of the cheek to prevent risk of choking. This is not specified in the IFU for Duvyzat.

Based on our review of the Applicant's comparative task analysis, we anticipate the task difference of shaking the bottle will not impact the intended user's ability to use the product as intended. The task differences of special handling are product specific and a reasonable difference. The task difference of aiming the oral syringe at the inside of the cheek also impacts labeling. We discuss these differences below and provide recommendations to mitigate the risk of medication error in Table 3.

3.2.3 Labeling Comparison

The Applicant provided a labeling comparison between Duvyzat and the comparator, Purixan. The carton and container and Prescribing Information (PI) were compared, and the Applicant stated that "no or minor differences have been identified". The Applicant provided an IFU comparison with their Comparative Task Analysis, however, we relocated the differences here in the discussion of labeling differences.

- The Duvyzat proposed IFU does not contain an image which labels the components of the oral syringe (e.g., plunger, tip, barrel etc.) and bottle (e.g., bottle adapter).
- Duvyzat does not instruct on the preferred technique for administering the liquid in the patient's mouth. Purixan's IFU states that the oral syringe should be aimed at the inside of the cheek to prevent risk of choking.
- In use period: Duvyzat oral suspension should be used within 60 days after opening the bottle and any unused medicine should be disposed of after 60 days. Purixan should be used within 8 weeks after opening the bottle and any unused medicine should be disposed of after 8 weeks.
- Duvyzat does not instruct to drink water after each dose. The Purixan IFU states to drink water after swallowing the dose.
- Duvyzat's IFU provides an image of the packaging contents. Purixan's IFU does not contain an image of the packaging contents.
- Duvyzat does not contain specific disposal information in the IFU. The Purixan IFU includes disposal information stating to ask a pharmacist how to dispose of the medication and that the medication should not be disposed of via wastewater or household waste.

Based on the URRA for Duvyzat, we did not find the above differences in the labels and labeling introduces any new or unique risk. However, considering best practices to decrease risk of medication error, we provide recommendations in Table 3 to support safe use.

4 EVALUATION OF LABELS AND LABELING

Table 3 below include the identified medication error issues with the submitted label and labeling, our rationale for concern, and our proposed recommendations to minimize the risk for medication error.

Table 3. Identified Issues and Recommendations for Division of Neurology 1 (DN 1)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Highlights of Prescribing Information			
1.	The dosing regimen is not included under Dosage and Administration due	We are concerned that without a statement alerting the health care provider to additional	Consider including a statement under the Dosage and Administration heading in Highlights of PI to alert the

Table 3. Identified Issues and Recommendations for Division of Neurology 1 (DN 1)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	space limitations; however, there is no statement directing users to the full prescribing information for complete dosing instructions.	critical information, such as the recommended dosage and dose modifications, it may cause important dosing information to be overlooked and increase the risk of dosing errors.	healthcare provider that additional important information is in the FPI. Include: See Full Prescribing Information for recommended dosage and dose modifications. (2.2, 2.3).
2.	Under the Dosage and Administration section, the second bullet point reads, (b) (4) which may be confusing.	As presented, this information in the highlights can be simplified for improved clarity.	Consider re-wording the sentence. For example, "Administer orally twice daily with food. (2.1).
3.	The Dosage Forms and Strength section of the HPI includes a (b) (4) (b) (4)	As presented, this information may cause confusion regarding the strength and volume of the product.	We recommend removing (b) (4)
Full Prescribing Information – Section 2 Dosage and Administration			
1.	The administration statement, (b) (4) may be confusing.	As presented, the information in this section can be simplified for improved clarity.	Consider re-wording the sentence. For example, "DUVYZAT should be administered orally twice daily with food…"
2.	Multiple terms are used to describe the co-packaged graduated oral syringe in the PI.	Consistent terminology may help prevent confusion.	We recommend revising all references to the oral syringe to be consistent by using the term "graduated oral syringe".

Table 3. Identified Issues and Recommendations for Division of Neurology 1 (DN 1)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
3.	As currently presented, the dosing tables contain the following symbols: "<", ">", "≤", and "≥".	Error prone symbols may be mistaken as opposite of their intended meaning.	We recommend replacing the symbols in this section ("<", ">", "≤", and "≥") with their intended meanings. See Guidance for Industry: "*Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors.*"[b]
4.	Throughout the dosing tables, each dose is presented with a trailing zero (e.g., 5.0 mL).	Trailing zeros can lead to tenfold dosing errors when the decimal point goes unnoticed (e.g., 5.0 mL is seen as 50 mL).	We recommend revising the "Oral suspension volume (mL)" rows in the dosing tables to remove the trailing zeros. We also recommend including units of measurement (kg, mg, or mL) with each numerical unit in the dose and volume rows. For example, 5.0 should be 5 mL and 6.0 should be 6 mL. See Guidance for Industry: "*Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors.*"[b]
	In the dosing tables, the unit of measure for dose (mg), oral suspension volume (mL), and weight (kg) are located within the header of the rows instead of next to the dose.	Including units of measurement with each numerical unit will help mitigate potential medication dosing errors.	
Full Prescribing Information – Section 3 Dosage Forms and Strengths			
1.	This section includes a (b) (4) statement.	This information is not needed in this section and may cause confusion regarding the (b) (4)	We recommend removing (b) (4)

[b] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. May 2022. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safety-considerations-container-labels-and-carton-labeling-design-minimize-medication-errors.

Table 3. Identified Issues and Recommendations for Division of Neurology 1 (DN 1)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			We recommend adding the strength to the beginning of this section, so it reads "Oral suspension: 8.86 mg/mL givinostat as a white to…"
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	A description of the dosage form is not provided (e.g., color).	A description of identifying characteristics of the dosage form is required per 21 CFR 201.57(c)(17)(iii).	Provide a description of identifying characteristics of the oral suspension in accordance with 21 CFR 201.57(c)(17)(iii).
2.	As presented, the expression of strength does not clarify whether (b) (4)	To prevent confusion, the information should be presented in a manner that allows the reader to understand (b) (4)	We recommend removing the second sentence and modifying the first sentence to read "Duvyzat (givinostat) 8.86 mg/mL oral suspension is supplied in… adapter containing 140 mL of oral suspension (NDC XXXXXXXXXX)."
3.	(b) (4) information is stated twice.	To prevent confusion and decrease clutter, duplicative information should be simplified.	Consider removing (b) (4)
Full Prescribing Information – Section 17 Patient Counseling			
1.	Multiple terms are used to describe the co-packaged graduated oral syringe in the PI.	Consistent terminology may help prevent confusion.	We recommend revising (b) (4) to "graduated oral syringe".
2.	The last bullet point under the Administration Instructions combines administration information and BUD information.	Combined bullet points can lead to important information being overlooked.	We recommend splitting up the two sentences in this bullet, so a new fourth bullet reads, "Discard any unused DUVYZAT oral suspension remaining after 60 days of first opening the bottle."

Table 3. Identified Issues and Recommendations for Division of Neurology 1 (DN 1)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Instructions for Use (IFU)			
1.	As currently presented in the IFU submitted on January 24, 2024, the format of the IFU has steps and the corresponding figures on different pages.	We are concerned that presenting steps and corresponding figures on different pages may cause confusion.	Ensure that the steps and corresponding figures appear together on the same page when feasible. Consider eliminating some of the white space and reducing the size of the figures.
2.	The title of the IFU is (b) (4) Instructions for Use".	The title may be misleading because some tasks/steps are not related to the (b) (4)	Remove (b) (4) so the title reads "Instructions for Use".
3.	Your IFU includes (b) (4) information. However, it is not representative of actual use to expect lay user t (b) (4) .	We expect the healthcare provider to (b) (4) (b) (4) information is outside of the scope of the lay user's intended use of this product. Additionally, we are concerned the inclusion this information may lead to (b) (4) due to misinterpretation by lay users.	1. Remove the (b) (4) section from the IFU, (b) (4) 2. Revise Step 3 to remove the statement, (b) (4) (b) (4) 3. Revise Step 5 to now read "Step 5. Slowly pull the plunger down until the bottom of the plunger is even with the markings on the oral syringe for the prescribed dose of DUVYZAT (see Figure F)."
4.	The statement, (b) (4)	We are concerned users may interpreted the statement (b) (4)	Remove the phrase (b) (4) from the aforementioned statement.

Table 3. Identified Issues and Recommendations for Division of Neurology 1 (DN 1)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	(b) (4) can be improved since users may store the opened bottle and oral syringe in the carton during the in-use period.	(b) (4) to mean that the opened bottle and oral syringe cannot be stored in the carton during the in-use period.	
5.	Multiple terms are used to describe the co-packaged graduated oral syringe in the IFU (e.g., "graduated oral syringe", "syringe", "oral syringe).	Inconsistent terminology may result in confusion.	We recommend revising all references to the oral syringe (e.g., "syringe", "oral syringe", etc.) to "graduated oral syringe" throughout the IFU.
6.	As currently presented, your IFU includes important information in multiple sections (b) (4)	Presenting important information in multiple sections may cause some of this information to be overlooked and difficult to locate.	We recommend combining the aforementioned sections into a single section after Figure A. Consider titling the section "Important information you need to know before you take DUVYZAT".
7.	Step 1 includes the word, (b) (4)	The word (b) (4) may not be readily understood by lay users which could lead to confusion and misinterpretation regarding the appearance of your proposed product.	Replace the word (b) (4) with its intended meaning or a phrase to improve understanding.
8.	The parts of the oral syringe (i.e., tip, plunger, barrel, etc.) are not labeled in the IFU.	Lay users may not be able to identify the parts of the oral syringe mentioned in IFU, which may cause confusion and result in dosing errors.	To help guide users in the proper administration technique, revise the graphics in Figure A by identifying each part of the oral syringe, such as the plunger, barrel, markings, and tip.

Table 3. Identified Issues and Recommendations for Division of Neurology 1 (DN 1)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
9.	Step 3 does not indicate which part of the oral syringe the user should insert into the bottle.	Failure to provide clarity on the syringe part may result in administration errors.	We recommend clarifying which part of the oral syringe (i.e., syringe tip) will be inserted into the bottle.
10.	Step 5 can be improved to inform users who are intended to measure a dose volume greater than 5 mLs that multiple withdrawals with the same oral syringe will be needed to measure and administer a single dose.	Lack of clarity regarding how to measure dose volumes greater than 5 mLs with the co-packaged 5 mL oral syringe may lead to wrong dose medication errors.	Revise Step 5 to include the following statement: "If your prescribed dose is more than 5 mL, you will need to use the same oral dispensing syringe more than one time."
11.	Step 8 can be improved to provide instructions related to the correct orientation and location of the oral syringe during administration.	Lack of clarity regarding the correct location and orientation of the syringe in the patient's mouth could lead to administration errors and increase the risk of choking.	Revise (b) (4) to "Place the tip of the (b) (4) oral syringe against the inside of the (b) (4) cheek. Slowly push the plunger all the way down (b) (4) (b) (4)
12.	The statement (b) (4) in Step 8 can be improved to increase readability.	Lack of clarity may result in confusion and administration errors.	Revise the aforementioned statement to read "DUVYZAT should not be mixed with water or other liquids." Additionally, relocate this statement to the important information section of the IFU.
13.	Step 8 can be improved to clarify which prescribed doses will require users to repeat steps 3 to 8.	Lack of clarity may result in wrong dose errors.	Revise (b) (4) to read "If your prescribed dose is more than 5 mL, repeat Steps 3 through 8 to withdraw and give the remaining dose.
14.	The presentation of the numerical ranges in your	Inconsistent presentation of storage information may	Revise the storage statement to read (b) (4)

Table 3. Identified Issues and Recommendations for Division of Neurology 1 (DN 1)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	storage statement is inconsistent. (b) (4)	confusion and lead to improper storage medication errors.	(b) (4)

5 CONCLUSION AND RECOMMENDATIONS

Based on our overall review of the use related risk analysis, justifications, and comparative analyses for Duvyzat (givinostat) we find that there is a risk of (b) (4) (b) (4) are provided to the lay caregiver within the instructions for use (IFU) labeling. We find this risk may be addressed by removing the (b) (4) from the IFU. Upon discussion with the review team, it was determined the (b) (4) in the Prescribing Information and do not need to be included in the IFU. (b) (4)

We note the revised IFU still contained the (b) (4). As such we provide a recommendation in Table 3 above to remove the (b) (4) from the IFU as we do not anticipate lay caregivers to (b) (4)

Additionally, we note (b) (4) one 5 mL oral syringe will be required for dosing. Most all doses can be drawn up with the 5 mL oral syringe except for one dose which would require the user to repeat steps to draw up the full dose. We note the comparator products analyzed by the Applicant do not require using the same oral syringe to draw up the entire dose (e.g., using a 5 mL oral syringe to draw up a 6 mL dose by drawing up 5 mL first and then repeating steps to draw up 1 mL for a total of 6 mL). However, this task is not unique to this product and multiple products exist on the market which require the user to repeat steps using the same oral syringe in order to draw up and administer a full dose. We relied on our experiences as we reviewed the labels and labeling of those products in consideration for our recommendations for this product.

Our evaluation of the proposed label and labeling identified areas of vulnerability that may lead to medication errors. We have provided recommendations in Table 3 above for the Division and Table 4 below for the Applicant. We ask that the Division convey Table 4 in its entirety to the Applicant so that recommendations are implemented for this NDA.

5.1 RECOMMENDATIONS FOR ITALFARMACO S.P.A

We have reviewed your revised labels and labeling submitted on January 24, 2024 that proposed the administration of your product using one 5 mL oral syringe. We have the following additional recommendations for your labels and labeling.

Table 4. Identified Issues and Recommendations for Italfarmaco S.p.A (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label(s) and Carton Labeling			
1.	As currently presented, your proposed name presentation on the principal display panel (PDP) is: Duvyzat givinostat oral suspension We note that the established name "givinostat" is not enclosed in parentheses.	Per 21 CFR 201.10 (g)(1): *"…the established name shall be placed in direct conjunction with the proprietary name or designation, and the relationship between the proprietary name or designation and the established name shall be made clear by use of a phrase such as "brand of" preceding the established name, by brackets surrounding the established name, or by other suitable means."*	Revise the name presentations by adding parentheses surrounding the established name as follows to align with the product title in the prescribing information (PI): Duvyzat (givinostat) oral suspension
2.	The established name does not seem to be half the size of the proprietary name.	We refer you to 21 CFR 201.10(g)(2) which states that the established name shall be printed in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking	Confirm that the established name is at least half the size of the proprietary name on both the container and carton in accordance with 21 CFR 201.10(g)(2).

Table 4. Identified Issues and Recommendations for Italfarmaco S.p.A (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		into account all pertinent factors, including typography, layout, contrast, and other printing features.	
3.	The (b) (4) statement on the principal display panel (PDP) does not provide complete instructions.	This can be improved for clarity and to provide more detailed preparation information. Including this information on the PDP will help ensure this important instruction is not overlooked.	We recommend modifying this statement to read, "Shake bottle for 30 seconds before use".
4.	Some of the information in the "Storage and Use" section on the side panel is also present on the PDP of the container label and carton labeling.	Duplicative information and clutter may decrease readability and may cause confusion.	We recommend removing part of the "Storage and Use" section on the side panel of the carton labeling and container label. Specifically, (b) (4)
5.	The terminology within the Recommended Dosage statement is inconsistent with the terminology in the Prescribing Information.	To ensure consistency with the terminology in the Prescribing Information and to simplify the statement.	We recommend revising the recommended dosage statement to read, "Dosage: see Prescribing Information."
6.	The format for expiration date is not defined.	Clearly defining the expiration date will minimize confusion and risk for deteriorated drug medication errors.	Identify the expiration date format you intend to use in accordance with USP General Chapter <7>. When all-numeric dates are used, they must be formatted using the year, the month, and, if applicable, the day, separated by hyphens or

Table 4. Identified Issues and Recommendations for Italfarmaco S.p.A (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			forward slashes in one of the following formats: YYYY-MM-DD or YYYY-MM. When alphanumeric dates are used, months must be displayed using at least three letters in one of the following formats: YYYY-MMM-DD or YYYY-MMM.
7.	The storage statements do not contain a unit of measure after each temperature numerical value. Additionally, the symbol "-" is used in the temperature ranges in place of the word "to".	This may increase the risk for improper storage medication errors.	We recommend you revise the storage temperatures to read "Store Duvyzat at controlled room temperature between 20°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F)."
8.	Your product is supplied with an oral syringe and the statement "For Oral Administration" on the container label and carton labeling does not include "only".	To minimize the risk of wrong route of administration errors, the route of administration statement should be on the container label and carton labeling.	We recommend adding the word "Only" to the route of administration statement on both PDPs and carton back panel. For example, "For Oral Administration Only."
Container Label(s)			
1.	The manufacturer name and logo compete for prominence with critical product information (e.g., proprietary name, established name, strength).	Critical product information such as the proprietary name, established name, and product strength should appear as the most prominent information on the principal display panel in accordance with 21 CFR 201.15.	We recommend decreasing the prominence and font size (height) of the letters and logo within your manufacturer information or consider moving the manufacturer information and logo to the side panel. We also recommend removing the (b) (4) at the bottom of the PDP to decrease clutter.

Table 4. Identified Issues and Recommendations for Italfarmaco S.p.A (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
2.	[redacted] is displayed twice.	Duplicative information and clutter may decrease readability and may cause confusion.	To avoid redundancy, we recommend removing the statement [redacted] A similar statement is already present at the [redacted] of the container label.
3.	The statement [redacted] is duplicative and is not appropriate for end users.	End users (laypersons) of the product should refer to the enclosed Instructions for Use rather than the Prescribing Information, which is directed towards healthcare professionals.	We recommend you revise this statement to read "See enclosed Instructions for Use."
Carton Labeling			
1.	Some users may store the container within the carton. The date of first opening is an important component of the use process, but a space to write this information is not present on the carton.	Absence of this information may increase the risk for deteriorated drug medication errors.	We recommend adding the "Date of first opening: __/__/__" statement to the carton labeling in alignment with the container label.
2.	The PDP and back panel contain the statement [redacted] Similar information is stated elsewhere on the carton label.	Duplicative information and clutter may decrease readability and may cause confusion.	Consider removing these statements on both the PDP and back panel.
3.	The carton labeling contains the statement	End users (laypersons) of the product should refer to	Consider removing the statement on the side panel.

Table 4. Identified Issues and Recommendations for Italfarmaco S.p.A (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	(b) (4) This information is present on the PDP, back panel, and side panel.	the enclosed Instructions for Use rather than the (b) (4) Duplicative information and clutter may decrease readability and may cause confusion.	Additionally, we recommend you revise the remaining statements on the PDP and back panel to read "See enclosed Instructions for Use."

APPENDICES:

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 5 presents additional product information for Duvyzat that Italfarmaco S.p.A submitted on January 24, 2024.

Table 5. Additional Product Information for Duvyzat

Dose and Frequency

The dose of DUVYZAT is based on body weight, as shown in the table below. The volume indicated should be administered twice daily.

Dose A (Starting Dose; to be Administered Twice Daily)

Weight (kg)	≥10 and <20	≥20 and <40	≥40 and <60	≥60
Dose (mg)	22.2	31.0	44.3	53.2
Oral suspension volume (mL)	2.5	3.5	5.0	6.0

Dose B (To be Administered Twice Daily)

Weight (kg)	≥10 and <20	≥20 and <40	≥40 and <60	≥60
Dose (mg)	17.7	22.2	(b) (4)	
Oral suspension volume (mL)	2.0	2.5		

Dose C (To be Administered Twice Daily)

Weight (kg)	≥10 and <20	≥20 and <40	≥40 and <60	≥60
Dose (mg)	13.3	17.7	26.6	35.4
Oral suspension volume (mL)	1.5	2.0	3.0	4.0

APPENDIX E. INFORMATION REQUESTS ISSUED DURING THE REVIEW

On 06/07/ 2023, we issued an Information Request (IR) to request the Applicant submit Comparative Analyses in order to determine if a human factors (HF) validation study should be conducted. On 06/13/2023, the Applicant provided an acceptable response that can be accessed on EDR via: \\CDSESUB1\EVSPROD\nda217865\0011\m1\us\12-cover-letters\cover-letter.pdf.

On 07/09/2023, we issued an IR to request the Applicant to provide discussion on the critical tasks related to the preparation and administration of the proposed product. On 07/12/2023, the applicant provided a response that can the accessed on the EDR via: \\CDSESUB1\EVSPROD\nda217865\0015\m1\us\12-cover-letters\response-hf-information-request.pdf.

On 07/19/2023, we issued an IR to request the Applicant provide details regarding the administration instructions given to participants in the clinical studies. On 07/26/2023, the Applicant provided a response that can be accessed on the EDR via: \\CDSESUB1\EVSPROD\nda217865\0018\m5\53-clin-stud-rep\535-rep-effic-safety-stud\duchenmuscudystro\5354-other-stud-rep\urra\response-document-ir.pdf and \\CDSESUB1\EVSPROD\nda217865\0018\m5\53-clin-stud-rep\535-rep-effic-safety-stud\duchenmuscudystro\5354-other-stud-rep\urra\clinical-commercial-ifu-comparison-gc.pdf.

On 11/06/2023, we issued an IR to request the Applicant submit an updated URRA which categorizes each task as either critical or non-critical. On 11/09/2023, the Applicant provided a response that can be accessed on the EDR via: \\CDSESUB1\EVSPROD\nda217865\0032\m5\53-clin-stud-rep\535-rep-effic-safety-stud\duchenmuscudystro\5354-other-stud-rep\urra\urra-givinostat-dmd.pdf

APPENDIX F. THRESHOLD ANALYSES AND USE-RELATED RISK ANALYSIS

F.1 Comparative Analyses

The comparative analyses received on June 13, 2023, available from \\CDSESUB1\EVSPROD\nda217865\0011\m5\53-clin-stud-rep\535-rep-effic-safety-stud\duchenmuscudystro\5354-other-stud-rep\urra\threshold-analyses.pdf

F.2 Use-Related Risk Analysis

The use-related risk analysis received on April 21, 2023, available from \\CDSESUB1\EVSPROD\nda217865\0003\m5\53-clin-stud-rep\535-rep-effic-safety-stud\duchenmuscudystro\5354-other-stud-rep\urra\urra-givinostat-dmd.pdf

An updated use-related risk analysis received on November 9, 2023, available from \\CDSESUB1\EVSPROD\nda217865\0032\m5\53-clin-stud-rep\535-rep-effic-safety-stud\duchenmuscudystro\5354-other-stud-rep\urra\urra-givinostat-dmd.pdf

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[c] along with post-market medication error experiences with similar products, we reviewed the following Duvyzat labels and labeling submitted by Italfarmaco S.p.A.

- Container label(s) received on April 21, 2023
- Carton labeling received on January 24, 2024
- Prescribing Information and Instructions for Use (Image not shown) received on January 24, 2024, available from \\CDSESUB1\EVSPROD\nda217865\0048\m1\us\114-labeling\draft-labeling\draft-label-text\givinostat-uspi-final-version-clean.pdf

G.2 Label and Labeling Images

Container label

(b) (4)

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

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

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/s/

RINA N PATEL
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COLLEEN L LITTLE on behalf of STEPHANIE L DEGRAW
02/16/2024 11:35:16 AM

COLLEEN L LITTLE
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LOLITA G STERRETT
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HINA S MEHTA
02/16/2024 12:00:09 PM

Clinical Inspection Summary

Date	10/27/2023
From	Cara Alfaro, Pharm.D., Clinical Analyst Phillip Kronstein, M.D., Team Leader Jenn Sellers, M.D., Ph.D. Branch Chief Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Annie Nguyen, RPh, Regulatory Project Manager Peggy Lazerow, M.D., Medical Officer Emily Freilich, M.D., Team Leader Division of Neurology 1 Office of Neuroscience
NDA #/BLA #	NDA #217865
Applicant	Italfarmaco S.p.A.
Drug	Givinostat oral suspension
NME	Yes
Proposed Indication	Treatment of Duchenne Muscular Dystrophy
Consultation Request Date	5/26/2023
Clinical Inspection Summary Goal Date	10/20/2023, extended to 11/3/2023
Priority/Standard Review	Priority
Action Goal Date	12/21/2023
PDUFA Date	12/21/2023

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Drs. Mercuri (Site #15), Vilchez (Site #23), Zaidman (Site #30), and the contract research organization (CRO), (b) (4) were inspected in support of this NDA covering Protocol DSC/14/2357/48. Based on the inspection results, the study appears to have been conducted adequately, and the data generated by these sites and submitted by the sponsor appear acceptable in support of the respective indication.

Primary efficacy data, the Four Stairs Climb Test (4SC), and key secondary efficacy data, North Star Ambulatory Assessment (NSAA), Time to Rise from floor (TTR), and 6 Minute Walk Test (6MWT) were reviewed at the clinical investigator sites. There were no discrepancies identified for the 4SC or TTR data. Minor discrepancies in NSAA and 6MWT data were identified in 4 of 10 randomized subjects at Site #23 only. These discrepancies were due to transcription errors and did not appear to have impact on the overall efficacy results. Two unreported adverse events, fall and resulting right femur fracture, were identified for one subject at Site #23 only. These adverse events should be included in the overall assessment of efficacy and safety.

In the NDA submission, the sponsor had included a Serious Breach document describing good clinical practice (GCP) protocol deviations. The most significant deviation was that for 4 of 10 subjects randomized at Site #23, the back-up physiotherapists who performed the functional assessments (i.e., 4SC, NSAA, TTR, 6MWT) at some study visits were also the study coordinators. Per protocol, physiotherapists were to be blinded and not have access to subject data, specifically laboratory data, which could unblind the physiotherapist. During the clinical investigator and CRO inspections, there was no evidence that other subjects at other sites had similar protocol deviations. None of the functional assessments performed by the back-up physiologists involved the time points of interest for the efficacy analyses in the target population. Therefore, we defer to the review division whether sensitivity analyses are needed.

II. BACKGROUND

Givinostat oral suspension is being developed under IND #126598 for the treatment of Duchenne Muscular Dystrophy (DMD). The sponsor has submitted the results of a Phase 3 study (DSC/14/2357/48) to support the safety and efficacy of givinostat for this indication.

Protocol DSC/14/2357/48

Title: "Randomised, double blind, placebo controlled, multicentre study to evaluate the efficacy and safety of givinostat in ambulant patients with Duchenne Muscular Dystrophy"

Subjects: 179

Sites: 41 sites; Western Europe (24), North America (15), Eastern Europe (1), Middle East/Central Asia (1)

Study Initiation and Completion Dates: 6/6/2017 – 2/22/2022

This was a Phase 3, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of givinostat in subjects with Duchenne Muscular Dystrophy (DMD). Main inclusion criteria were:

- Males ≥6 years of age at randomization
- Ambulant with DMD characteristic clinical symptoms at screening
- DMD diagnosis confirmed by genetic testing
- Able to complete two Four Stairs Climb test (4SC) screening assessments, results within 1 second of each other with a mean value ≤8 seconds
- Time to Rise (TTR) from floor ≥3 and <10 seconds at screening
- Manual muscle testing (MMT) of quadriceps ≥Grade 3 at screening
- Having used systemic corticosteroids for a minimum of 6 months immediately prior to the start of study treatment with no significant change in corticosteroid type of dosage (excluding changes related to body weight change) with a reasonable expectation that dosage will not change significantly during study

Subjects were not to have used another investigational drug or idebenone within 3 months prior to the study or used any dystrophin restoration product (e.g., ataluren, exon-skipping) within 6 months prior to the study.

The study was comprised of three periods: Screening Period, Double-Blind Treatment Period, and Follow-up Period.

Screening (4 weeks ± 2 weeks; Visits 1 and 2)
The screening phase included study procedures to determine subject eligibility and included two separate screening visits. During screening Visit 1, study procedures included, but were not limited to, physical examination, ECG, echocardiogram, pulmonary function tests, genetic test (if not already available) and clinical assessments including 4SC, North Star Ambulatory Assessment (NSAA), 6 Minute Walk Test (6MWT), and muscle strength. During screening Visit 2, a second 4SC assessment and MRI (thigh)/MRS (vastus lateralis) were completed.

Treatment Period (18 months; Week 0/Visit 3 to Week 72/Visit 15)
Subjects were randomized (2:1), stratified for their concomitant use of corticosteroids, to one of the following study arms:

- Givinostat oral suspension twice daily in a fed state
- Placebo oral suspension twice daily in a fed state

Dosing was based on weight, with reductions specified due to tolerability or several lab indices (in particular, reduced platelet count).

Per protocol, there were two defined populations: Target and Off-Target Populations. A Target Population (Group A) was defined as subjects with a baseline vastus lateralis muscle fat fraction (VL MFF) assessed by MRS in the range >5% and $\leq$30%. An Off-Target Population (Group B) was defined as subjects with a baseline VL MFF assessed by MRS in the range $\leq$5% or $\geq$30%. The Target population was the population of interest for the efficacy analyses.

Follow-Up Visit (Week 76/Visit 16)
A safety follow-up visit occurred 7 days after the last dose of IP.

The *primary efficacy endpoint* was the mean change from baseline to 18 months in 4SC in the Target population (as defined above). Key secondary efficacy measures included the NSAA, TTR, and 6MWT.

III. RESULTS

1. Eugenio M. Mercuri, M.D., Ph.D.
Site #15
Fondazione Policlinico Universitario Agostino Gemelli
Largo Agostino Gemelli, 8
Rome, 00168 Italy
Inspection Dates: 7/31/2023 – 8/4/2023

At this site for Protocol DSC/14/2357/48, 28 subjects were screened, 16 subjects were randomized, and 15 subjects completed the study. Subject (b) (6) randomized to givinostat, withdrew consent.

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records for all randomized subjects was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, Independent Ethics Committee (IEC) communications, sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, key secondary efficacy data (North Star Ambulatory Assessment [NSAA], Time to Rise from floor [TTR], 6 Minute Walk Test [6MWT]), and primary efficacy data (Four Stairs Climb Test [4SC]).

Primary efficacy (4SC) and key secondary efficacy data (NSAA, TTR, 6MWT) recorded on paper as source documentation were reviewed against sponsor data line listings. Efficacy data were verified; no discrepancies were identified. There were two blinded physiotherapists at this site who conducted the functional assessments (e.g., 4SC, NSAA, 6MWT). No unblinding events were identified during the inspection. Additionally, there was no evidence of under-reporting of adverse events.

According to sponsor data line listings, Subject (b) (6) randomized to placebo, was unable to complete 4SC and 6MWT assessments for Week 60 (b) (6) and End of Study (b) (6) due to the subject's non-ambulatory status. The last 4SC and 6MWT that the subject completed was at Week 48 (b) (6) The review division requested that the subject's non-ambulatory status be verified during the inspection. The clinical investigator stated that in (b) (6) the subject's family reported that the subject had been unable to walk independently since (b) (6) (b) (6) could only take a few steps with bilateral support, and that a manual wheelchair was used inside and outside the home. This communication with the family was not contemporaneously documented. During the inspection, the clinical investigator wrote and signed a "note-to-file" document summarizing the conversation with the family. Study progress notes for the (b) (6) study visits documented that the subject was able to walk only with bilateral support.

Reviewer's comment: The inspection was able to verify the non-ambulatory status of Subject (b) (6) for the Week 60 and End of Study visits.

2. Juan J. Vilchez, M.D., Ph.D.
Site #23
Avenida De Fernando Abril
Martorell 106
Servicio De Neurologia
Valencia, 46026 Spain
Inspection Dates: 7/24/2023 – 7/28/2023

At this site for Protocol DSC/14/2357/48, 23 subjects were screened, 10 subjects were randomized, and all 10 subjects completed the study.

An audit of the study records for all randomized subjects was conducted. Records reviewed included, but were not limited to, informed consent forms, source documents, monitoring documents, Independent Ethics Committee (IEC) communications, sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, key secondary efficacy data (NSAA, TTR, 6MWT), and primary efficacy data (4SC).

Primary efficacy (4SC) and key secondary efficacy data (NSAA, TTR, 6MWT) recorded on paper as source documentation were reviewed against sponsor data line listings. A review of the 4SC and TTR data did not identify any data discrepancies. Minor discrepancies were identified in NSAA and 6MWT data for four of 10 randomized subjects. These errors were due to site personnel entering incorrect data into the electronic data capture (EDC) system and did not appear to have any impact on the overall efficacy results.

There were two unreported adverse events identified during the inspection. Subject (b) (6) randomized to givinostat, experienced a fracture of the right distal femur due to a fall on (b) (6) The subject went to the emergency room but was not admitted. Due to this adverse event, the study functional assessments could not be completed at the end of study visit on (b) (6) Of note, although not reported as an adverse event, the comment field in the sponsor data line listings for functional assessments note that for this visit the assessments were not completed due to this fracture.

Reviewer comments: The unreported adverse events of "fall" and "fracture of right distal femur" occurring in Subject (b) (6) randomized to givinostat, should be included in the overall assessment of efficacy and safety.

There were four blinded physiotherapists at this site who conducted functional assessments (e.g., 4SC, NSAA, 6MWT). Two additional individuals who were used as back-up physiotherapists. These two back-up physiotherapists also had roles as study coordinator, with access to laboratory data. Per protocol, physiotherapists were not to have access to potentially unblinding data, which included platelet counts and other laboratory data.

The subjects and study visits for which the back-up physiotherapists/study coordinators performed functional assessments are listed in Table 1. The sponsor identified this as a serious good clinical practice (GCP) breach and summarized the issue and corrective and preventive action plan (CAPA) implemented in a Serious Breach document submitted with the NDA (see CRO inspection summary below).

Table 1. Subjects with Functional Assessments Performed by Back-up Physiotherapists/Study Coordinators

Subject	Treatment Arm	Population	Visit (Date)
(b) (6)	Givinostat	Off-Target	V 15/End of Study (b) (6)
	Givinostat	Target	Screening (b) (6) V 11/Week 24 (b) (6)
	Givinostat	Target	Screening (b) (6) V 11/Week 24 (b) (6) V 12/Week 36 (b) (6) V 13/Week 48 (b) (6)
	Givinostat	Target	V 10/Week 12 (b) (6) V 11/Week 24 (b) (6) V 12/Week 36 (b) (6) V 13/Week 48 (b) (6)
	NA Screen Failure	NA	Screening (b) (6)

NA = not applicable

The site monitor met with the clinical investigator on 4/7/2021 to discuss this protocol deviation and the importance of maintaining the blind for the physiotherapists performing the functional assessments. At that time, only one of the back-up physiotherapists/study coordinators remained at the site. The clinical investigator confirmed that this back-up physiotherapist would be continuing in the role of study coordinator only and would no longer be performing functional assessments. The monitor provided retraining of the clinical investigator and study coordinator. Other blinded physiotherapists performed the remaining functional assessments for all subjects.

Reviewer comments: Although there was no evidence that the blind was broken for these subjects, the possibility exists since these back-up physiotherapists also served as study coordinators with access to subject data that could have unblinded them. The timepoints of interest for the primary and secondary efficacy endpoint analyses were baseline and Visit 15/Week 72. Only one of the subjects in Table 1 ((b) (6) *) had a functional assessment at Visit 15, and this subject was not in the Target population (the population of interest for the efficacy analyses). Therefore, we defer to the review division whether sensitivity analyses are needed.*

3. Craig Zaidman, M.D
Site #30
660 S. Euclid Avenue Campus
Box 8111
St. Louis, MO 63110
Inspection Dates: 10/2/2023 – 10/5/2023

At this site for Protocol DSC/14/2357/48, 14 subjects were screened, 8 subjects were randomized, and 7 subjects completed the study. One subject discontinued the study due to withdrawal of consent.

Signed informed consent forms, dated prior to participation in the study, were present for all subjects who were screened. An audit of the study records for all randomized subjects was conducted. Records reviewed included, but were not limited to, source documents, monitoring documents, IRB communications, sponsor communications, financial disclosure, test article accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, key secondary efficacy data (NSAA, TTR, 6MWT), and primary efficacy data (4SC).

Primary efficacy (4SC) and key secondary efficacy data (NSAA, TTR, 6MWT) recorded on paper as source documentation were reviewed against sponsor data line listings. Efficacy data were verified; no discrepancies were identified. There were three blinded physiotherapists at this site who conducted the function assessments (e.g., 4SC, NSAA, 6MWT). No unblinding events were identified during the inspection. Additionally, there was no evidence of under-reporting of adverse events.

There were missing concomitant medications in the sponsor data line listings for Subject (b) (6) (b) (6) randomized to placebo. This subject took the following concomitant medications prior to and throughout the study: gabapentin 250 mg daily (muscle cramps/DMD), lisinopril 2.5 mg daily (cardiac prophylaxis), cetirizine 5 mg daily (seasonal allergies), montelukast 5 mg daily (seasonal allergies), and fluticasone spray daily (seasonal allergies).

Reviewer comments: These unreported concomitant medications for Subject (b) (6) were not prohibited per protocol, were initiated prior to the study, and remained stable throughout study participation. It is unlikely that these unreported concomitant medications would impact efficacy or safety analyses.

4. (b) (4)

This inspection covered the responsibilities transferred to the contract research organization (CRO), (b) (4) from the sponsor, Italfarmaco S.p.A., related to Protocol DSC/14/2357/48 and focused on the three clinical investigator sites chosen for inspection (Sites #15, #23, #30).

Study records reviewed included, but were not limited to, transfer of regulatory obligation (TORO); SOPs; organization and personnel; personnel training; monitoring plan; selection of monitors; monitoring procedures and reports; DSMB documents including meeting minutes; quality assurance; data management; investigational product accountability; clinical investigator training and compliance; safety data collection and adverse event reporting; and financial disclosure.

The primary responsibilities transferred to (b) (4) included those related to clinical monitoring and pharmacovigilance. Clinical monitoring responsibilities included, but were not limited to, qualifying clinical investigators, selecting site monitors, assessing clinical investigator compliance, and obtaining financial disclosure information from clinical investigators. Pharmacovigilance responsibilities were outlined in the Safety Management Plan and included, but were not limited to, set up and maintenance of global safety database, serious adverse event (SAE) processing, medical review of adverse events (shared with sponsor), and submission of aggregate safety reports to IRBs/IECs/clinical investigators. No issues were identified with regard to pharmacovigilance responsibilities transferred to (b) (4)

The sponsor had submitted a Serious Breach document with the NDA submission that described good clinical practice (GCP) deviations occurring at Site #23 (as described in inspection summary above). Due to these GCP deviations, the focus of the inspection was clinical site monitoring and sponsor/CRO oversight of the clinical sites. It appears that monitoring visits were conducted according to the monitoring plan and SOPs. No sites were terminated for noncompliance. Three sites (Sites #20, #40, #42) were unable to enroll any subjects and were closed.

Site #23– Back-up Physiotherapists/Study Coordinator Roles
During the inspection, site visit monitoring reports were collected and reviewed to confirm the information in the Serious Breach document submitted to the NDA by the sponsor. Of note, this document did not indicate when this GCP breach was first identified. Monitoring visits occurred approximately every one to three months. A review of the monitoring reports noted the following:

- (b) (4) monitoring visit. The study coordinator had received the required training to perform functional assessments and wished to have both the study coordinator and

back-up physiotherapist roles. The site monitor noted this would be problematic due to potential unblinding and was to confirm with the study coordinator which one of the two roles she would have for this study.

- (b) (4) monitoring visit. The site monitor discussed the potential unblinding issue with the study coordinator who indicated that she had not yet performed any functional assessments and confirmed that her role will only be study coordinator and not back-up physiotherapist. A post-visit comment in the monitoring report stated that a Note-to-File (NTF) should be created and signed by the study coordinator confirming that she will have a study coordinator role only.
- (b) (4) monitoring visit. The NTF was obtained.
- (b) (4) monitoring visit. A different site monitor identified that the study coordinator performed functional assessments as the back-up physiotherapist for some subjects (refer to inspection summary for Site #23 above).
- (b) (4) monitoring visit. The site monitor noted one other study coordinator who also served as back-up physiotherapist. This back-up physiotherapist performed functional assessments for two screening visits in two subjects only and left the study team in 2019.

The clinical site monitor met with the clinical investigator and study coordinator on (b) (4) to discuss this protocol deviation. The clinical investigator stated that the study coordinator would be delegated the study coordinator role only. The site monitor re-trained the clinical investigator and study coordinator on the protocol and blinding plan. The site monitor communicated this protocol deviation to the sponsor via email on (b) (4) The sponsor discussed this issue with the clinical investigator on (b) (4)

After this breach of the blinding plan was discovered at Site #23, the sponsor asked (b) (4) to evaluate whether similar instances occurred at other clinical sites. Clinical monitors were retrained on blinding procedures on (b) (4) Clinical monitors ascertained whether the blinding plan was being followed at clinical sites during regular monitoring visits and/or phone calls from (b) (4) On (b) (4) informed the sponsor that there were no other quality issues "due to combination of study coordinator/sub-investigator and physiotherapist roles" at any other site. In their root cause analysis for Site #23, (b) (4) cited inappropriate clinical investigator oversight, inappropriate understanding of the blinding requirements and study role responsibilities by the clinical investigator and study coordinator, and inappropriate use of the site delegation of authority log (tasks not documented).

Reviewer comments: There appears to be a discrepancy between the (b) (4) *monitoring reports stating that the study coordinator agreed to perform only study coordinator tasks and the fact that the study coordinator performed functional assessments as back-up physiotherapist in* (b) (4) *The NTF mentioned in the monitoring reports was not collected during the inspection, so that information could not be verified. During the inspection, it was communicated that due to the COVID-19 pandemic, there wasn't enough staff at the*

hospital to perform the functional assessment tests since these physiotherapists provided assessments for patients not in the trial as well as study subjects. It is unclear if the clinical investigator and study coordinator understood the issues regarding maintaining the study blind and the necessity that the role of study coordinator and blinded physiotherapist be held by different study staff. (b) (4) *investigated and did not identify similar issues at other clinical sites.*

There was also inadequate follow-up by (b) (4) *to confirm that the study coordinator was not also serving as back-up physiotherapist since this potential issue was identified in 2019. It is unknown how these study coordinators were able to complete the functional assessment training provided by the vendor, there should have been more safeguards in place to prevent this from occurring.*

{See appended electronic signature page}

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Good Clinical Practice Assessment Branch
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/s/

CARA L ALFARO
10/27/2023 12:48:31 PM

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10/27/2023 01:13:49 PM

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10/27/2023 01:19:15 PM

Consulting Memorandum

FOR CONSULTED CENTER'S (CDER) USE ONLY

To: **Peggy Lazerow**
RPM: **Anhtu Nguyen**
From: Daniel Krainak, Ph.D.
CDRH/OPEQ/OHT8/DHT8C
Through: Julie Sullivan, Ph.D.
CDRH/ OPEQ/OHT8/DHT8C

Digital Signature Concurrence Table	
Reviewer Sign-Off	
Division Sign-Off	

Subject: **NDA 217865 003**
Sponsor: **ITALFARMACO SA**
Product: **Givinostat**

I. Summary

As the clinical team likely understands better than this engineer, fat fraction is generally correlated with muscle function. However, it is unclear if change in muscle fat fraction is responsible for or predictive of function. In other words, nothing in this consulting memo should be interpreted as commentary on the relationship to the causal pathway of the disease nor treatment mechanism of action. Based on the information reviewed, the difference between the placebo and experimental treatment arm in muscle fat fraction in the vastus lateralis (and other leg muscles) is of the same magnitude as or slightly greater the uncertainty in the muscle fat fraction measurement. Therefore, the change in muscle morphology appears to be a measurable observed difference between groups. I defer to the CDER review team for the relevance of this change in with respect to the mechanism of action of the treatment or predictive of clinically meaningful functional outcomes in terms of appropriateness for use as confirmatory evidence. Based on the information provided, the sponsor observed a measurable difference in the leg muscle morphology between the placebo and treatment arms based on MRI techniques used to measure fat fraction in study 48. The magnitude of the effect between groups was ~3% and the uncertainty of the fat fraction measurement may range from 1-5% (based on literature), with capability to achieve ~1-2% in a well-controlled study (that include consistent image acquisition and analysis procedures).

II. Background

The team requests: "Please review the use of MRI data for muscle morphology and if this could be used as confirmatory evidence for the NDA." Upon follow-up with the team, feedback on Study 48 was requested, where MRS and MRI data was used to measure vastus lateralis fat fraction.

Muscle morphology by MRI may be considered to include both volume (or cross-sectional area) and composition. The most relevant feature to the study based on this and similar studies in the population may be considered fat fraction (frequently acquired with a Dixon-based method) in a selected region.

ICCR link: https://force-dsc.lightning.force.com/lightning/r/Case/5003d000008jr5MAAQ/view
Document link: \\CDSESUB1\evsprod\NDA217865\0030

VL = vastus lateralis
MFF = muscle fat fraction

III. Magnetic resonance Fat Fraction measures

Magnetic resonance spectroscopy and proton density fat fraction
Essentially, the different molecular positions of protons lead to slightly different resonance frequencies in the magnetic field. Using different MR spectroscopy techniques (used over a large block of tissue to obtain a spectra of the various frequencies) or imaging techniques (by applying different magnetic and radio frequency pulses at different times to obtain water only and fat-only images), the differences in these peaks may be used to obtain a ratio of fat-to-water and therefore estimate the "fat fraction" in a particular volume of interest.

A more detailed explanation and summary of the technique is included in Peterson and others (2020). An excerpt provides a brief summary:

From Peterson and others 2020,

> "1H MR spectroscopy and chemical-shift-encoded imaging (CSE-MRI) are both based on the chemical shift between fat and water and are established methods for noninvasive quantification of fat concentration in tissue, also known as the proton density fat fraction (PDFF).[13,14] By measuring the relative amplitudes of the peaks in the fat spectrum, corresponding to different positions within the triglyceride molecule, the chemical composition of the fat can be assessed, which first was investigated using both 13C[15,16] and 1H MRS.[17-19]
>
> …
>
> "By comparing the total area of all fat peaks with the area of the water peak, after correcting for differences in T1- and T2-relaxation, it is possible to quantify the relative proton density fat fraction (PDFF)."

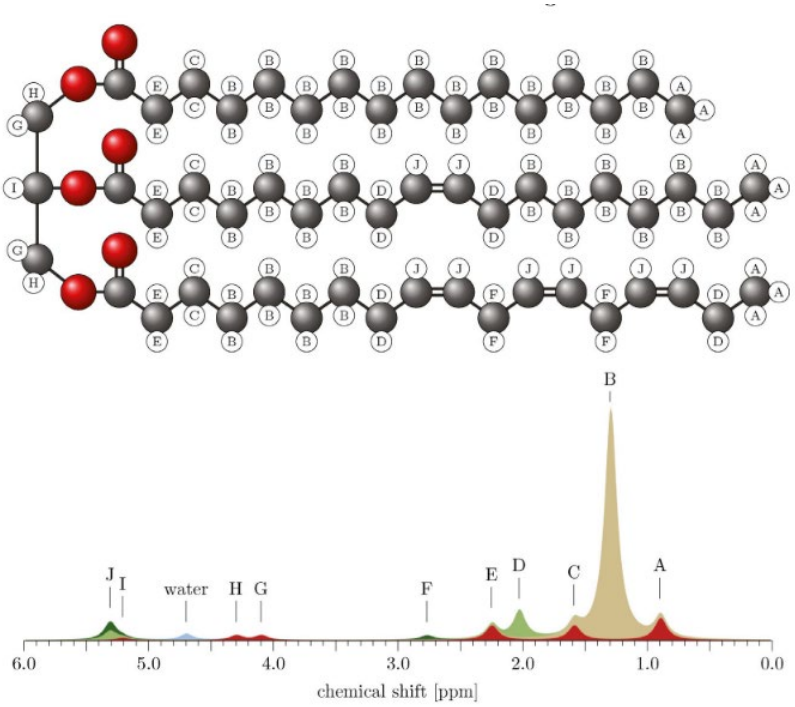

FIGURE 1 Schematic illustration of a triglyceride molecule (top) and the corresponding MR spectrum (bottom). Hydrogen atoms are shown in white, carbon in gray, and oxygen in red. The letters refer to the peak assignments in Table 2. Reproduced with permission from Berglund et al[20]

TABLE 2 Peak assignments, frequencies,[20,28] white adipose tissue relaxation times at 3T,[29] and theoretical amplitudes expressed in terms of the descriptive measures *ndb*, *nmidb*, and *cl*[28]

Peak	Chemical shift (ppm)	Type	Proton position	Theoretical amplitude	T_1 (ms)	T_2 (ms)
A	0.90	Methyl	-CH_2-$\mathbf{CH_3}$	9	543	80
B	1.30	Methylene	-$(\mathbf{CH_2})_n$-	6(*cl*-4)-8*ndb*+2*nmidb*	280	55[a]
C	1.59	β-Carboxyl	-$\mathbf{CH_2}$-CH_2-COO	6	240	55[a]
D	2.03	α-Olefin	-$\mathbf{CH_2}$-CH=CH-	4(*ndb*-*nmidb*)	249	52[b]
E	2.25	α-Carboxyl	-CH_2-$\mathbf{CH_2}$-COO	6	202	52[b]
F	2.77	Diacyl	-CH=CH-$\mathbf{CH_2}$-CH=CH-	2*nmidb*	284	46
G	4.10	Glycerol	-$\mathbf{CH_2}$-O-CO	2	154	–[c]
H	4.30	Glycerol	-$\mathbf{CH_2}$-O-CO	2	154	–[c]
I	5.21	Glycerol	-$\mathbf{CH}$-O-CO-	1	–[d]	–[d]
J	5.31	Olefin	-$\mathbf{CH}$=$\mathbf{CH}$-	2*ndb*	421	44

Note: The hydrogen atoms of interest are written in bold text.

[a]Estimated as one peak.

[b]Estimated as one peak.

[c]Not available due to J-coupling effects.

[d]Not available due to overlap with olefinic peak J.

These techniques are commonly used in the abdominal region to obtain an estimate of liver fat, but the technique may be similarly applied to other tissue (such as muscle) to obtain a fat/water ratio.

To contextualize the potential for a clinically meaningful difference, the characterization of the measurable difference and uncertainty of the measurement should be understood and described.

Uncertainty in the measurement

Some information about the uncertainty of the fat fraction method in the relevant population (DMD) is found in Forbes 2013.

Table 7

Day-to-Day Variability of MR Spectroscopy T2 and Lipid Fraction in the Soleus and VL Muscles of Control Boys and Boys with DMD

	Control Boys			Boys with DMD		
Parameter and Muscle	Day 1	Day 2	CV (%)	Day 1	Day 2	CV (%)
MR spectroscopy T2 (msec)						
Soleus	28.3 (27.7, 28.9)	28.1 (27.5, 28.6)	2.0 (0.8, 3.0)	32.4 (30.9, 33.1)	32.0 (31.0, 32.8)	3.4 (0.9, 4.5)
VL	28.4 (28.0, 29.0)	29.5 (28.4, 30.4)	3.9 (2.5, 4.9)	31.6 (29.9, 33.1)	32.4 (30.4, 34.2)	4.4 (2.1, 5.6)
Lipid fraction						
Soleus	0.18 (0.12, 0.23)	0.18 (0.14, 0.24)	11.0 (6.1, 16.0)	0.46 (0.26, 0.65)	0.44 (0.23, 0.64)	4.9 (0.6, 6.0)*
VL	0.17 (0.11, 0.22)	0.17 (0.12, 0.21)	6.9 (4.6, 8.9)	0.59 (0.36, 0.77)	0.58 (0.37, 0.77)	4.3 (0.7, 4.3)*

Note.—Data are means, with 25th and 75th percentiles in parentheses. All day 1 and day 2 values were significantly different ($P \leq .05$) between boys with DMD and control boys.

* Significantly different ($P \leq .05$) between boys with DMD and control boys.

The CV appears to be 1 – 9 %, but the absolute measurement repeatability appears closer to 1% within this particular study. In a well-controlled image acquisition and processing system, the MRI-based fat fraction measurement is likely capable of achieving measures within 5% in liver (see draft PDFF QIBA profile for liver QIBA_MRI-Based_PDFF_of_the_Liver_Profile-Stage_1-Public_Comment.pdf (rsna.org)). In a meta-analysis in liver, repeatability of ~3% and reproducibility of ~4% were observed for PDFF (Yokoo and others 2018). Similar, repeatability and reproducibility should be achievable in muscle tissue in the extremities.

IV. Description of Givinostat

"Givinostat hydrochloride monohydrate (laboratory code ITF2357), hereafter referred to as givinostat, is an orally active hydroxamic acid derivative possessing potent histone deacetylase (HDAC) inhibitory activity and a strong anti-inflammatory effect."

Indications for Use

Treatment of Duchenne Muscular Dystrophy

Study

Randomised, Double Blind, Placebo Controlled, Multicentre Study to Evaluate the Efficacy and Safety of Givinostat in Ambulant Patients with Duchenne Muscular Dystrophy
Protocol Number: DSC/14/2357/48

"The pivotal Phase 3 study (Study 48) was a double-blind, placebo-controlled study in ambulant male DMD patients aged ≥ 6 years, receiving stable corticosteroid treatment."

Primary Objective: To establish the effects of givinostat versus placebo administered chronically over 18 months to slow disease progression in ambulant DMD patients.

Secondary Objectives: To evaluate the impact on QoL and activities of daily living of givinostat versus placebo administered chronically.

Relevant methods to imaging:
Subjects who signed the assent form to participate in this study (if capable of doing so) and whose parent/legal guardian signed the informed consent form to participate underwent pre-study screening assessments up to 4 weeks before the first scheduled dose of study drug. At the randomisation visit, in

addition to the continued standard-of-care corticosteroids regimen, subjects with DMD were randomised (2:1 ratio) to receive givinostat oral suspension 10 mg/mL or placebo oral suspension twice daily (in a fed state).

A total of 110 subjects were planned to be randomised in the Target Population (Group A: subjects with a baseline vastus lateralis muscle fat fraction [VL MFF] assessed by magnetic resonance spectroscopy (MRS) in the range > 5% and ≤ 30%). Up to 50 subjects (about 35% of the Overall Population) outside of the target were planned to be recruited into the study (Group B: subjects with a baseline VL MFF assessed by MRS in the range of ≤ 5% to >30%). The overall subject population (Group A + Group B) provided supportive data. In the Target Population, a total of 81 subjects were enrolled in the givinostat group, of whom 77 (95.1%) subjects completed the study; and 39 subjects were enrolled in the placebo group, of whom 37 (94.9%) subjects completed the study.

Analysis population
The MR cohort included all subjects in the Target Population who were randomised to study treatment and completed at least one post-baseline MRI/MRS assessment.

Imaging
The baseline MRI/MRS test had to be performed when all inclusion/exclusion criteria had been already evaluated and the subject was eligible. At screening, all subjects underwent the MRI scan of thigh and MRS of vastus lateralis; then, the MRI scan of thigh and MRS of vastus lateralis was performed also at 12 and 18 months in a subgroup of subjects: the first 99 to 150 randomised subjects in the target population (ie, with MRS VL MFF between > 5% and ≤ 30%). The MRI evaluation using the Dixon technique and the MRS were performed at specialised sites.

The subjects underwent the Dixon MRI and MRS on the thigh muscles without receiving general anaesthesia. The MRI/MRS images were read to evaluate the FF of each muscle. A CSA of muscles was evaluated as well.

- With respect to VL MFF, a similar approach was applied; the within-treatment SD for the change from baseline was estimated as $\hat{\sigma}_{within} = \sqrt{(\hat{\sigma}^2_{overall} - (\Delta/2)^2)}$, where $\hat{\sigma}_{overall}$ was the overall SD for the change from baseline in VL MFF and Δ was the originally hypothesized treatment effect, ie, Δ=3.63% (ie, 55% of 6.6%). Dependent upon the blinded SD estimate, the sample size could have been decreased or increased to maintain 90% power. Any increase in sample size required to assess VL MFF was also limited to 1.5 times the required target population sample size stated in the preceding power calculation, to a maximum of $1.5 \times 99 \approx 150$ subjects.

For the MR cohort, the blinded SD estimate was 5.941%, which was in line with the SD assumed in the original power calculation for VL MFF; hence, all subjects in the target population were included in the analysis of the MR cohort.

Efficacy

Fat fraction of VL muscles evaluated by MRS technique (magnetic resonance [MR] cohort only)
Mean change in VL MFF

Note that other MRI-based parameters were included as exploratory efficacy assessments.

Treatment with givinostat delayed fat infiltration in VL muscle by approximately 30% (LS mean difference [givinostat-placebo]: -2.92%; p-value: 0.0354) (VL MFF). Subgroup analyses supported the results from the main analysis of the mean change in VL MFF.

Table 35. Analysis of Fat Fraction of Vastus Lateralis Muscle (VL MFF) Assessed by MRS (%), Change From Baseline at 18 Months (Magnetic Resonance Cohort – Target Population)

Statistics	Givinostat (N=77)	Placebo (N=37)
Number of subjects included in analysis, n (%)	77 (100.0)	37 (100.0)
LS mean	7.63	10.56
95% CI for LS mean	6.098, 9.172	8.331, 12.783
Difference in LS means (givinostat-placebo)	-2.92	
95% CI for difference in LS means	-5.641, -0.204	
P-value	0.0354	

Abbreviations: CI, confidence interval; LS, least square; MRS, magnetic resonance spectroscopy; N, number of subjects in the analysis set; n, number of subjects meeting the criterion; VL MFF, vastus lateralis muscle fat fraction.
Notes: Baseline was defined as the last nonmissing value recorded prior to or on the date of first study treatment. LS means, Cis, and p-values were obtained from an analysis of covariance model on change from baseline in VL MFF at Month 18 with baseline VL MFF and rederived age at first dose fitted as covariates, with concomitant steroid use and treatment group as independent classification factors.
Source: Table 14.2.6.2.1

Reviewer notes

In the trial report (dsc-14-2357-48-report-body.pdf), the sponsor notes that FF measures correlate with lower limb function. The questions for this consulting reviewer remains, how much change (gain) in fat fraction is necessary to predict a functional loss? And is fat fraction a leading or lagging indicator of functional loss? In others words, the magnitude of the effect is likely important.

Roughly, a ~3% difference in the change in fat fraction between baseline and follow-up was observed in the study. Based on the previous reports of measurement variability, this may be considered measurable difference between groups after accounting for the uncertainty associated with the measurement (i.e., at the edge of or just outside of what would need to be observed to have confidence that a real change in the measurement occurred). Individual data would be necessary to ensure that the group effect is largely consistent among study participants.

Although exploratory, similar results and effect sizes were observed for fat fraction in the muscles included in the exploratory analysis. See Table 50 in dsc-14-2357-48-report-body.pdf. Notably all

muscles in exploratory analysis trended in the same direction with similar differences between groups (roughly 4% difference).

V. References

Forbes SC, Walter GA, Rooney WD, Wang DJ, DeVos S, Pollaro J, Triplett W, Lott DJ, Willcocks RJ, Senesac C, Daniels MJ, Byrne BJ, Russman B, Finkel RS, Meyer JS, Sweeney HL, Vandenborne K. Skeletal muscles of ambulant children with Duchenne muscular dystrophy: validation of multicenter study of evaluation with MR imaging and MR spectroscopy. Radiology. 2013 Oct;269(1):198-207. doi: 10.1148/radiol.13121948. Epub 2013 May 21. PMID: 23696684; PMCID: PMC3781359.

Peterson P, Trinh L, Månsson S. Quantitative 1 H MRI and MRS of fatty acid composition. Magn Reson Med. 2021 Jan;85(1):49-67. doi: 10.1002/mrm.28471. Epub 2020 Aug 25. PMID: 32844500.

Triplett WT, Baligand C, Forbes SC, Willcocks RJ, Lott DJ, DeVos S, Pollaro J, Rooney WD, Sweeney HL, Bönnemann CG, Wang DJ, Vandenborne K, Walter GA. Chemical shift-based MRI to measure fat fractions in dystrophic skeletal muscle. Magn Reson Med. 2014 Jul;72(1):8-19. doi: 10.1002/mrm.24917. Epub 2013 Sep 4. PMID: 24006208; PMCID: PMC4307808.

Yokoo T, Serai SD, Pirasteh A, Bashir MR, Hamilton G, Hernando D, Hu HH, Hetterich H, Kühn JP, Kukuk GM, Loomba R, Middleton MS, Obuchowski NA, Song JS, Tang A, Wu X, Reeder SB, Sirlin CB; RSNA-QIBA PDFF Biomarker Committee. Linearity, Bias, and Precision of Hepatic Proton Density Fat Fraction Measurements by Using MR Imaging: A Meta-Analysis. Radiology. 2018 Feb;286(2):486-498. doi: 10.1148/radiol.2017170550. Epub 2017 Sep 11. PMID: 28892458; PMCID: PMC5813433.

Notes:

Primary efficacy endpoint: mean change in total fibrosis (%) comparing the histology of muscle biopsies before and after 12 months of treatment with givinostat versus placebo

This was a phase 2, randomised, double-blind, placebo-controlled study. Eligible patients were randomized in a 2:1 ratio to receive givinostat or placebo for 12 months. Randomization was stratified by concomitant steroid use at baseline (yes or no).

Relevant secondary endpoints

- Mean change in fat fraction of the vastus lateralis and soleus comparing MRS findings before and after 12 months of treatment with givinostat versus placebo.
- Mean change in fat fraction of the pelvic girdle, thigh and lower limb muscles comparing Dixon MRI findings before and after 12 months of treatment with givinostat versus placebo.
- Mean change in Cross Sectional Area (CSA) of the pelvic girdle and lower limb muscles comparing
  Dixon MRI findings before and after 12 months of treatment with givinostat versus placebo

Study did not meet primary endpoint

In the present study, Dixon MRI findings at baseline featured considerable fat infiltration of the whole thigh (56% for the givinostat group and 63% for the placebo group) and of the quadriceps (55% vs. 60%). After 12 months of treatment, the degree of fat infiltration remained practically unchanged in the givinostat group and increased in the placebo group.
Another noteworthy MRI finding was the lack of change in contractile CSA after 12 months in patients treated with givinostat and a decrease in all muscles of patients treated with placebo. The between-group difference was again statistically significant and in favor of givinostat for the whole thigh and quadriceps. Change from baseline in total CSA did not differ between the two groups.

Fat fraction assessments

9.5.3.2.2 Fat fraction evaluated by Dixon MRI

MRI scans were acquired in a 1.5T (b) (4) or 3T (b) (4) whole body magnet. To generate fat fraction maps, multi-echo axial gradient echo images were acquired in the thigh (TR = 430 ms or greater; TE = 4.61, 6.91, 9.21 ms [1.5T], 4.61, 5.76, 6.91 ms [3T]). Slices were chosen to include the origin of the short head of the biceps femoris, which served as landmark. MRI data were sent to and analyzed by ImagingDMD, University of Florida, through a Windows application that allowed secure transfer of data over the internet. Fat fraction maps were generated, and the borders of the quadriceps group (vastus lateralis, vastus medialis, vastus intermedius, rectus femoris), hamstrings group (biceps femoris, semitendinosus, semimembranosus), and medial compartment of the thigh (adductor magnus, adductor longus, gracilis, sartorius) were manually traced on three contiguous slices (landmark and two distal slices) using custom-written software with mean values reported for each muscle. Fat fraction for each compartment was calculated as the average of all pixels on the three slices, and whole-thigh fat fraction was calculated as the average fat fraction of the quadriceps, hamstrings, and medial thigh compartments. The same approach was used to calculate the average fat fraction of the pelvis girdle and the triceps surae.

9.5.3.2.3 Cross-sectional area evaluated by Dixon MRI
CSA of the pelvic girdle and lower limb muscles were determined by means of Dixon MRI

The protocol was amended, “Fat fraction and cross section evaluations by Dixon MRI were now performed on muscles of the lower leg, as well as those of the thigh and pelvic girdle as originally planned.”

11.4.1.2.2 Change in fat fraction of lower limb muscles after 12 months of treatment (Dixon MRI)

Mean changes from baseline of fat fraction in the medial thigh, hamstrings, triceps surae and pelvic girdle respectively for givinostat and placebo are as follows:
Medial thigh: 0.24 ± 2.14% (min; max: -3.0; 4.2%) and 1.71 ± 2.91% (min; max: -1.7; 8.5%).
Hamstrings: 1.50 ± 2.84% (min; max: -2.8; 8.4%) and 1.97 ± 2.46% (min; max: -2.3; 8.5%).
Triceps surae: 1.37 ± 2.67% (min; max: -4.1; 6.8%) and 3.13 ± 2.0% (min; max: 0.4; 6.3%).
Pelvic girdle: 0.32 ± 2.19% (min; max: -4.3; 4.3%) and 1.69 ± 1.78% (min; max: -1.9; 4.9%).

The sponsor notes
The between-group differences for fat fraction of the whole thigh and quadriceps indicate a significantly greater increase in fat fraction in the placebo group.

Least square means of mean MFF in the whole thigh were 0.642 (95% CI: -0.328, 1.611) for the givinostat group and 1.996 (95% CI: 0.813, 3.180) for the placebo group. The estimated betweengroup difference of -1.35 (95% CI: -2.43, -0.28) was statistically significant (p-value = 0.0149).

Least square means of mean MFF of the quadriceps were 0.610 (95% CI: -0.506, 1.726) for givinostat and 2.572 (95% CI: 1.227, 3.918) for placebo. The between-group difference was -1.96 (95% CI: -3.18, -0.75) and again statistically significant (p-value = 0.0022).

The between-group differences for fat fraction of the medial thigh, hamstrings, triceps surae and pelvic girdle were not statistically significant.

The changes observed are small. In well-controlled situations an estimate of the uncertainty would be between 3%. The method is generally considered a reliable assessment of fat within tissue.

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology Review (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)

Epidemiology: Real-World Evidence Review

Date:	September 19, 2023
Reviewer:	Danielle Abraham, PhD, MPH Division of Epidemiology I (DEPI-I) Office of Surveillance and Epidemiology (OSE)
Team Leader:	Catherine Callahan, PhD, MA (Acting) DEPI-I, OSE
Associate Director for Real-World Evidence (RWE) & Oncology:	Kira Leishear White, PhD, MS DEPI-I, OSE
Drug Name:	Duvyzat (givinostat)
Subject:	Review of Applicant proposal to use real-world evidence (RWE) to support NDA 217865
Application Type/Number:	NDA 217865
Applicant/sponsor:	Italfarma S.p.A
TTT #:	2023-5012

TABLE OF CONTENTS

EXECUTIVE SUMMARY

The Division of Neurology I (DN1) requested that the Division of Epidemiology I (DEPI-I) provide input on the strengths and limitations of the natural history data and quality of the real-world evidence (RWE) submitted as part of a New Drug Application (NDA) for Duvyzat (givinostat, Italfarmaco S.p.A) for the treatment of Duchenne muscular dystrophy (DMD).

The principal source of evidence for efficacy from the givinostat clinical development program stems from a randomized, double-blind, placebo-controlled study to assess the efficacy and safety of givinostat in DMD (Study 48). The Applicant submitted multiple sources of confirmatory evidence, including an integrated analysis of long-term efficacy with natural history data (RWE). The integrated analysis compared the age at persistent, functional disease milestones comparing patients treated with givinostat in Studies 48 or 51 (an open-label, long-term safety, tolerability, and efficacy study of givinostat) and external, natural history controls. The Applicant selected natural history controls from two cohort studies—Magnetic Resonance Imaging and Biomarkers for Muscular Dystrophy (ImagingDMD) and the Cooperative International Neuromuscular Research Group (CINRG). Natural history controls were restricted to patients with baseline characteristics that matched to patients from Study 48 on inclusion and exclusion criteria. Survival analysis was conducted on the entire sample (148 givinostat exposed patients and 197 natural history controls) due to poor performance of propensity score matching.

The natural history controls were younger at baseline with a lower body mass index, shorter time since diagnosis, shorter time since first corticosteroid initiation, and better functional performance (except for baseline time to climb 4 stairs [4SC]). Deflazacort use was more common in the givinostat group. The survival analysis results for the age at persistent loss of function analyses indicated that all milestones were significantly delayed in the givinostat group, compared to the natural history controls. In the unmatched analysis, for the givinostat group, compared to the natural history controls, the median age at persistent rise from floor > 10 seconds was delayed by 1.6 years, persistent 10-meter walk/run > 10 seconds was delayed by 3.5 years, persistent loss of rise from floor was delayed by 2.2 years, persistent loss of 4SC was delayed by 3.3 years, and persistent loss of ambulation was delayed by 2.7 years.

Although the integrated analysis of long-term efficacy with natural history data indicated meaningful delays in persistent loss of function among those treated with givinostat, compared to external controls, the analyses should be considered exploratory due to a lack of a priori study protocol and statistical analysis plan agreement with the FDA. Although the results from sensitivity analyses were somewhat consistent with primary analysis findings, the heterogeneity of DMD progression, lack of comparability between givinostat treated patients and natural history controls, potential for residual confounding, enrichment of the pivotal trial sample, differences in index date and follow-up, and use of effort-based outcomes make the externally controlled study results difficult to interpret. Overall, the RWE submitted as part of the NDA should be evaluated by DN1 considering these limitations and biases in the context of the rest of the NDA submission.

1 INTRODUCTION

On June 15, 2023, the Division of Neurology 1 (DN1) consulted the Division of Epidemiology I (DEPI-I) to provide input on the strengths and limitations of the natural history data and quality of the real-world evidence (RWE) submitted as part of a New Drug Application (NDA) for Duvyzat (givinostat, Italfarmaco S.p.A) for the treatment of Duchenne muscular dystrophy (DMD). The purpose of this review is for DEPI-I to advise DN1 on the strengths and limitations of the natural history data submitted as confirmatory evidence for this NDA.

1.1 BACKGROUND

DMD is caused by a genetic mutation in the dystrophin gene that results in muscle degeneration.[1] DMD is a rare disease that impacts males with a prevalence of 1 per 3,500-6,000 male births.[2] DMD is a progressive disease that results in loss of muscle function and premature death.[3] With long-term corticosteroid treatment, the average age at loss of ambulation is 12.3 years (1). Median survival has improved over time with improved clinical management and ventilatory support (2). In a meta-analysis, among patients with ventilatory support, the weighted pooled median survival was 31.8 years (95% CI: 29.3, 36.2) (2). The Applicant provided a figure (see Figure 1) to summarize their conceptualization of DMD progression, milestones, and outcomes.

Figure 1. Stages of DMD Progression, Disease Milestones, and Outcome Measures[4]

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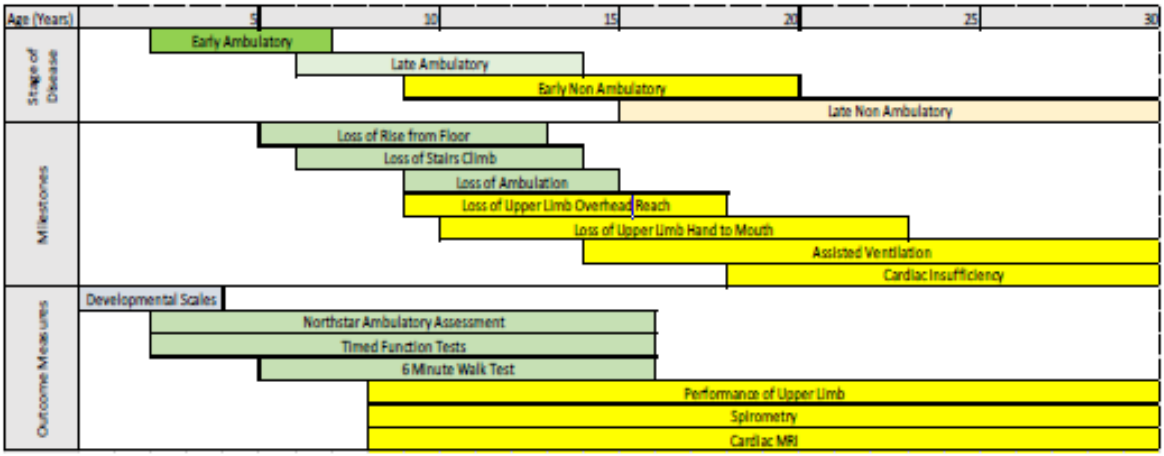

DMD = Duchenne muscular dystrophy; MRI =magnetic resonance imaging.
Source: Adapted from Lynn 2015.

[1] Duchenne Muscular Dystrophy and Related Dystrophinopathies: Developing Drugs for Treatment: Guidance for Industry. February 2018. Silver Spring (MD), U.S. Food and Drug Administration.

[2] Ibid.

[3] Ibid.

[4] Extracted Figure and title from Applicant submitted Clinical Overview Figure 1

Currently, DMD is treated with the corticosteroids prednisone and deflazacort (3). Deflazacort is an FDA approved corticosteroid for the treatment of DMD in patients five years of age and older.[5] Other therapies, such as eteplirsen[6], golodirsen[7], viltolarsen[8], and casimersen[9] have received FDA accelerated approval for the treatment of DMD in patients with specific DMD gene mutations. Recently, delandistrogene moxeparvovec-rokl, a gene therapy, received accelerated approval for the treatment of ambulatory pediatric patients aged 4 through 5 years with DMD with a confirmed mutation in the DMD gene.[10]

Per the Applicant, givinostat is an orally active hydroxamic acid derivative that inhibits histone deacetylase (HDAC); HDAC inhibitors are thought to impact DMD progression through multiple mechanisms.[11] There are three clinical trials that provide efficacy data in the NDA. The first is DSC/11/2357/43 (Study 43), a phase two single-arm open-label trial. The second is DSC/14/2357/48 (Study 48), a phase three randomized, placebo-controlled trial. The third is DSC/14/2347/51 (Study 51), an open-label, long-term extension study of subjects enrolled in Study 43 and enrolled or eligible[12] for Study 48. In study 51, all patients are treated with givinostat.

The principal source of evidence for efficacy from the givinostat clinical development program stems from Study 48. The study found that, in the target population, for the intention to treat (ITT) analysis, there was a statistically significant difference in time to 4 Stair Climb (4SC) at 18 months that favored givinostat, compared to placebo. To support findings from Study 48, the Applicant submitted multiple sources of confirmatory evidence including:

- Mechanistic evidence from histological findings in the *mdx* mouse model
- Mechanistic evidence from muscle histological findings in Study 43
- Mechanistic evidence from muscle magnetic resonance spectroscopy (MRS) imaging and vastus lateralis muscle fat fraction (VL MFF) findings in Study 48
- Long-term treatment effect evidence

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[5] NDA 208684 & NDA 208685 ORIG-1 Approval Letter. February 9, 2017. Silver Spring (MD), U.S. Food and Drug Administration. DARRTS Reference ID: 4053971.

[6] NDA 206488 ORIG-1 Approval Letter. September 19, 2016. Silver Spring (MD), U.S. Food and Drug Administration. DARRTS Reference ID: 3987286.

[7] NDA 211970 ORIG-1 Approval Letter. December 12, 2019. Silver Spring (MD), U.S. Food and Drug Administration. DARRTS Reference ID: 4532753.

[8] NDA 212154 ORIG-1 Approval Letter. August 12, 2020. Silver Spring (MD), U.S. Food and Drug Administration. DARRTS Reference ID: 4655432.

[9] NDA 213026 ORIG-1 Approval Letter. February 25, 2021. Silver Spring (MD), U.S. Food and Drug Administration. DARRTS Reference ID: 4752790.

[10] BL 124781/0 Accelerated Approval Letter. June 22, 2023. Silver Spring (MD), U.S. Food and Drug Administration. Accessed on August 8, 2023, at: fda.gov/media/169715/download

[11] Italfarmaco S.p.A. NDA 217865, Ed. 1.0 March 2023. Module 2.5 Clinical Overview.

[12] Met criteria for Study 48 but did not meet vastus lateralis muscle fat fraction percentage for On Target Population (>5% and ≤30%) and Off Target Population enrollment was already complete.

- Delayed start analysis in Study 51 comparing patients who received givinostat in Studies 43 and 48 to those from study 48 randomized to placebo who started givinostat after completion of Study 48
- Integrated summary of efficacy (ISE) – integrated analysis of long-term efficacy comparing those treated with givinostat in Studies 48 or 51 with controls from natural history data (RWE)

1.2 REGULATORY HISTORY

NDA 217865 was developed under IND 126598. NDA 217865 was submitted for FDA review on April 21, 2023. Givinostat has received the following designations:

- Orphan drug designation on April 12, 2013, for the treatment of DMD and Becker muscular dystrophy[13]
- Fast track designation August 29, 2016[14]
- Rare pediatric disease designation September 22, 2020[15]

Relevant to this review, on January 27, 2023, the FDA provided preliminary meeting comments for a Type C meeting request. The Applicant's question and FDA's response are provided below[16]:

> *Question 3: The Sponsor's nonclinical and clinical investigations provide a substantial body of evidence that demonstrates givinostat's ability to delay DMD disease progression by countering the hallmark feature of progressive degenerative muscle loss caused by inflammatory and fibroadipgenic processes. Multiple sources of clinical and nonclinical data provide mechanistic support for givinostat's effects in DMD and long-term data supported by comparisons to natural history demonstrate givinostat's ability to preserve function in an otherwise relentlessly progressive disease. Does the Agency agree that the Sponsor's mechanistic data and long-term data with comparisons to natural history could, (either independently or collectively), provide confirmatory evidence to substantiate the findings of the pivotal adequate and well-controlled Study 48 in accordance with FDA's December 2019 Draft Guidance?*
>
> *FDA Response to Question 3:*

[13] IND 126598 Meeting Preliminary Comments. January 27, 2023. Silver Spring (MD), U.S. Food and Drug Administration. DARRTS Reference ID: 5116859.

[14] Ibid.

[15] Filing Meeting: NDA 217865. Clinical Slides. June 2, 2023. Silver Spring (MD), U.S. Food and Drug Administration.

[16] See footnote 13.

The ability of the mechanistic data and the natural history analyses to support the effectiveness of your drug with be a matter of review. As indicated in the Type C meeting minutes on August 25, 2022, reliance on a single study plus confirmatory evidence to meet the standards of effectiveness still requires consideration of the persuasiveness of the single study in the context of the confirmatory evidence, and reliability of the treatment benefit from the result of that study.

Additional Statistical Comment:
As we communicated in an email on March 10, 2022, the CSR should also include the results of the analyses based on the methods prespecified prior to the interim analysis.

On August 17, 2023, the following information request[17] was sent to the Sponsor[18]:

We refer to pending NDA 217865. We request additional sensitivity analyses for the ISE Statistical Analysis:

- *Submit Tables and Figures for the ISE Statistical Analysis that present results for the age at persistent loss of ambulation, persistent rise from floor >10 seconds, persistent walk/run 10 meters >10 seconds, persistent loss of rise from floor, and persistent loss of 4 standard stairs climb comparing the ITT set and natural history data, restricted to matching subjects.*
- *Present ISE Tables and Figures for subject disposition, demographic and baseline characteristics, and persistent loss of function comparing subjects treated with givinostat in Study 48 and natural history data. Present the data overall as well as restricted to matching subjects.*
- *Present ISE Tables and Figures for subject disposition, demographic and baseline characteristics, and persistent loss of function comparing subjects who received placebo in Study 48 (prior to initiation of givinostat) and natural history data. Present the data overall as well as restricted to matching subjects.*

2 REVIEW METHODS AND MATERIALS

DEPI-I reviewed the following Applicant submitted documents, focusing on the sections that pertain to the natural history controls:

- Module 2.5 – Clinical Overview

[17] Information request from DEPI-I with Division of Biometrics I (DBI) input and DN1 concurrence

[18] Nguyen A. FDA information request: NDA 217865 17Aug2023. August 17, 2023. DARRTS Reference ID: 5228308.

- Module 2.7.3 – Summary of Clinical Efficacy
- Statistical Analysis Plan – Integrated Summary of Efficacy (ISE) for Givinostat in Duchenne Muscular Dystrophy (Version 2.0, November 7, 2022)
- Tables for ISE Statistical Analysis Version 3.0
- Figures for ISE Statistical Analysis Version 3.0

DEPI-I also considered the following documents submitted by the Applicant on August 31, 2023. These documents were submitted in response to the August 17, 2023, FDA IR:

- Tables for ISE Statistical Analysis – FDA Request #1
- Figures for ISE Statistical Analysis – FDA Request #1
- Tables for ISE Statistical Analysis – FDA Request #2
- Figures for ISE Statistical Analysis – FDA Request #2
- Tables for ISE Statistical Analysis – FDA Request #3
- Figures for ISE Statistical Analysis – FDA Request #3
- NDA 217865. Givinostat Oral Suspension. Italfarmaco S.p.A. Query Response on Integrated Summary of Efficacy.

For this review, DEPI-I also considered the following FDA guidance documents:

- Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products: Draft Guidance for Industry. December 2019. Silver Spring (MD), U.S. Food and Drug Administration.
- Duchenne Muscular Dystrophy and Related Dystrophinopathies: Developing Drugs for Treatment: Guidance for Industry. February 2018. Silver Spring (MD), U.S. Food and Drug Administration.
- Rare Diseases: Natural History Studies for Drug Development: Draft Guidance for Industry. March 2019. Silver Spring (MD), U.S. Food and Drug Administration.
- Rare Diseases: Common Issues in Drug Development: Draft Guidance for Industry. January 2019. Silver Spring (MD), U.S. Food and Drug Administration.
- Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products: Draft Guidance for Industry. February 2023. Silver Spring (MD), U.S. Food and Drug Administration.
- Considerations for the Use of Real-world Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products: Draft Guidance for Industry. December 2021. Silver Spring (MD), U.S. Food and Drug Administration.
- Real-World Data: Assessing Registries to Support Regulatory Decision-Making for Drug and Biological Products: Draft Guidance for Industry. November 2021. Silver Spring (MD), U.S. Food and Drug Administration.

3 REVIEW RESULTS

3.1 STUDY OVERVIEW

The ISE included an integrated analysis of long-term efficacy with natural history data. The analysis examined the age at persistent disease milestones comparing givinostat exposed subjects from clinical trials to external, natural history controls.

3.2 STUDY OBJECTIVE

The objective of the integrated analysis of long-term efficacy with natural history data was, "[T]o provide supportive analyses for the long-term efficacy evaluation of givinostat for the treatment of DMD, based on data from clinical studies…and [natural history] NH studies..."[19]

3.3 STUDY METHODS

3.3.1 Source Studies - Clinical Trials

3.3.1.1 Summary of Study 43

Study 43 was a two-part, phase 2, open-label study of safety, tolerability, pharmacokinetics, and muscle histology/clinical effects of givinostat in DMD. There was an extension phase of the study where subjects continued treatment. The primary study objective was, "To establish the histologic effects of givinostat administered chronically at the selected daily dose."[20] The study took place from April 2, 2013, to July 30, 2014, with extension phases through July 14, 2016, or November 17, 2017. There were four study sites in Italy.

The study inclusion criteria at screening were as follows:

- Males
- ≥7 to <11 years of age
- Diagnosis of DMD (immunohistochemical and molecular)
- Ambulatory (2 screening 6-minute walk test (6MWTs) ≥ 250 meters [± 30 meters of each other])
- On stable corticosteroids (≥6 months)

Givinostat was administered orally as a capsule or suspension. In part one, subjects received 25 mg, 37.5 mg, or 50 mg twice daily. In part two, subjects, depending on part

[19] Italfarmaco S.p.A. 2.7.3 Summary of Clinical Efficacy.

[20] Ibid.

one, received 25 mg or 37.5 mg twice daily. In extension one, subjects received the same dosage as part two. In extension two and three, dosage was weight-based.

The total study duration was 52 months (≥ 2 weeks for part one[21], 12 months for part two[22], and up to 12 months for each of the three extensions[23]). The primary study outcome was change in muscle fiber area (%) from pre-treatment to post-12 months of givinostat treatment. Additional outcome measures are summarized in Appendix A.

The study enrolled 20 subjects (20 in the ITT population, 19 completed the study).

3.3.1.2 Summary of Study 48

Study 48 was a phase 3, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of givinostat in DMD. The primary objective was, "To establish the effects of givinostat versus placebo administered chronically over 18 months to slow disease progression in ambulant DMD patients."[24] The multicenter study took place from June 6, 2017, to February 22, 2022, at sites in North America, Europe, and Israel.

The study selected an enriched population of patients who would be expected to have a decline in muscle function but not loss of muscle function during the study.[25] The study inclusion criteria were as follows:

- Males
- ≥6 years of age
- DMD diagnosis (signs or symptoms and diagnosis confirmed by genetic testing)
- Ambulatory (mean of 2 screening [± 1 second] 4SCs ≤ 8 seconds, time to rise from floor ≥3 to <10 seconds, manual muscle testing of quadriceps grade ≥3)
- On stable corticosteroids (≥6 months)

The target population included patients with MRS VL MFF >5% to ≤30%. The off-target population included patients with MRS VLF MFF ≤5% or >30%.

Subjects were randomized 2:1 (givinostat:placebo), stratified by steroid regimen (daily deflazacort, intermittent deflazacort, daily other steroids, intermittent other steroids). Givinostat was administered as a twice daily, 10 mg/mL oral suspension with weight-

[21] Per Clinical Study Report, visits every 7 days

[22] Per Clinical Study Report, visits every 1 month to 1.5 months

[23] Per Clinical Study Report, visits every 2 months for extension 1 and 2; visits every 6 months for extension 3

[24] Italfarmaco S.p.A. 2.7.3 Summary of Clinical Efficacy.

[25] Age, steroid type, baseline function, VL MFF considered predictors

based dosing. Earlier protocols used a starting dose (Dose A[26]) with a one-third dose reduction (Dose B) allowed. Later protocols used Dose B as the starting dose with an additional 20% dose reduction allowed (Dose C).

Patients were followed for 18 months after initiation of givinostat or placebo.[27] There were 15 planned study visits.[28] The primary endpoint was the change in baseline time to 4SC. Secondary endpoints are presented in Appendix A. For analysis, the ITT population included randomized patients who received one dose of the treatment assigned at randomization and had one post-baseline 4SC measure[29].

The study enrolled a total of 179 subjects with 118 randomized to givinostat (111 completed the study) and 61 randomized to placebo (59 completed the study).

3.3.1.3 Summary of Study 51

Study 51 is an ongoing, open-label, long-term safety, tolerability, and efficacy study of givinostat. The primary study objective is, "[T]o assess the long-term safety and tolerability of givinostat in patients with DMD previously treated in one of the givinostat studies (Study 43 and Study 48), and in givinostat-naïve DMD patients…".[30] The study began on October 25, 2017, and is ongoing, although the 48-week interim analysis cut-off date was December 31, 2021. The study is taking place at 39 sites in North America, Europe, and Israel.

The study inclusion criteria are as follows:

- Males, ≥6 years of age:
    - From Study 43
    - From Study 48 and attended end of study visit
    - Screened in Study 48 and met inclusion criteria with baseline VL MF (MRS) ≤5% or >30% (off-target population) but not randomized due to off-target enrollment being complete

Givinostat is administered as an oral suspension 10 mg/mL twice daily with dosage matching that from the end of Study 43 or Study 48, except for givinostat-naïve subjects

[26] ≥10-<12.5 kg: 20 mg givinostat hydrochloride monohydrate twice daily (b.i.d); ≥12.5-<20 kg: 25 mg b.i.d; ≥20-<25 kg: 30 mg b.i.d; ≥25-<30 kg: 35 mg b.i.d; ≥30-<40 kg: 40 mg b.i.d; ≥40-<50 kg: 50 mg b.i.d; ≥50-<60 kg: 55 mg b.i.d; ≥60-<70 kg: 60 mg b.i.d; ≥70 kg: 70 mg b.i.d

[27] 15 total visits (including screening and randomization) with final follow-up visit 4 weeks after last administration of treatment

[28] 2 screening visits, randomization (week 0), weeks 1, 2, 3, 4, 6, 8, 12, 24, 36, 48, 60, 72. Additional follow-up visit at 76 weeks for those who completed 18 months of treatment but did not participate in long-term study.

[29] Includes a missing measure due to a participant being non-ambulatory or unable to perform the 4SC.

[30] Italfarmaco S.p.A. 2.7.3 Summary of Clinical Efficacy.

who receive Dose B (one-third dose reduction from Dose A in Study 48). The study considers three treatment groups:

- Givinostat group – received givinostat in Study 43 or Study 48
- Delayed givinostat – received placebo in Study 48
- Givinostat naïve – Screened in Study 48 and met inclusion criteria with baseline VL MF (MRS) ≤5% or >30% (off-target population) but not randomized due to off-target group enrollment being complete

The study will continue until NDA approval or subject discontinuation.[31] The primary endpoints are long-term measures of safety and tolerability (adverse events, physical examination, vital signs, weight, height, echocardiogram, electrocardiogram, laboratory assessments). Additional outcomes, including effectiveness outcomes, are presented in Appendix A.

The study screened and enrolled 194 subjects (110 givinostat group, 54 delayed givinostat group, 30 givinostat-naïve group).

3.3.2 Source Studies – Natural History Studies

3.3.2.1 Study Selection

The Applicant considered seven natural history studies[32]:

- Magnetic Resonance Imaging and Biomarkers for Muscular Dystrophy (ImagingDMD)
- Cooperative International Neuromuscular Research Group (CINRG)
- Cincinnati Children's Hospital Medical Center (CCHMC)
- Leuven
- North Star UK
- DMD Italian Group
- iMDEX

Further details of the studies are available in Appendix B. The Applicant selected ImagingDMD and CINRG, which include a proportion of patients who met Study 48 eligibility criteria. CCHMC and Leuven were not selected due to being single center studies. CCHMC, North Start UK, and DMD Italian Group did not capture 4SC and time to rise from floor, which were used to assess eligibility for Study 48. iMDEX was not selected due to a small proportion of patients meeting Study 48 eligibility criteria.

[31] Per Clinical Study Report, visits at baseline (end of study visit from prior study for all except naïve givinostat); weeks 1, 2, 3, 4, 6, 8, 12, 16; and every 4 months thereafter.

[32] Studies available through the Collaborative Trajectory Analysis Project

3.3.2.2 Summary of Selected Study - ImagingDMD[33]

This ongoing study is a prospective, longitudinal, observational, natural history study.[34] Enrollment began in September 2010, and the anticipated study completion is August 2025. There are multiple study sites in the United States.

The primary study objective is, "[T]o validate the potential of noninvasive [magnetic resonance imaging] MRI and MRS to monitor disease progression and to serve as a noninvasive surrogate outcome measure for clinical trials in DMD and Becker Muscular Dystrophy (BMD)."[35] The study has a secondary objective, "[T]o characterize the progressive involvement of the lower extremity, upper extremity, trunk/respiratory muscles in boys/men with DMD and BMD guiding clinical trials."[36]

For DMD patients enrolled in the study, the study inclusion criteria are as follows:

- Males
- 5-30 years of age
- DMD based on clinical features (and symptom onset before 5 years of age), elevated serum creatine kinase level, or absence of dystrophin expression (immunostain or western blot and/or dystrophin mutation)

Participants are excluded for:

- Contraindications to MRI
- Other muscle disorders
- Unable to participate due to cognitive/behavioral problems

There is no exclusion of patients due to other study or trial participation. The study includes both ambulatory (walk ≥ 100 meters, able to 4SC) and non-ambulatory patients.

Patients undergo annual visits (12 months ± 2 months) [37] with follow-up for 7 years. Visits include MRI/MRS, anthropometric measurements, functional assessments, and assessment of medical history.

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[33] Summary study information extracted from: Applicant documents; Magnetic Resonance Imaging and Biomarkers for Muscular Dystrophy. NCT0148467. June 15, 2023. Accessed on August 16, 2023, at: https://clinicaltrials.gov/study/NCT01484678?id=NCT01484678&rank=1 ; Barnard AM, Willcocks RJ, Triplett WT, et al. MR biomarkers predict clinical function in Duchenne muscular dystrophy. Neurology. 2020 Mar 3;94(9):e897-e909.

[34] Clinicaltrials.gov website and Applicant documents state that this is a case-control study; however, it appears to be a cohort study.

[35] Italfarmaco S.p.A. 2.7.3 Summary of Clinical Efficacy.

[36] Ibid.

[37] Subset had follow-ups at 3 and 6 months post-baseline; if a visit was missed, data was collected at next study visit

Between 2010 and 2020, there were 160 DMD patients recruited. The mean baseline VL MFF was 20% (Standard Deviation [SD]=19%).

3.3.2.3 Summary of Selected Study - CINRG[38]

This ongoing[39] study is a prospective, longitudinal, observational, natural history study. [40] Enrollment began in September 2006 with a second enrollment period that commenced in September 2012. There are multiple study sites in the United States along with study sites in Argentina, Australia, Canada, India, Israel, Italy, and Sweden.[41]

The primary study objective is, "[T]o establish the largest long-term assessment of people with DMD."[42]

For DMD patients[43] enrolled in the study, the study inclusion criteria are as follows:

- Males
- 2 to 28 years of age[44]
- Documented DMD
    - 2-4 years of age – confirmed by immunofluorescence/immunoblot or genetic findings
    - ≥5 years of age – criteria above OR clinical symptoms + supportive evidence of the diagnosis

Participants are excluded for being:

- Steroid-naïve and ambulatory after 13 years of age
- Steroid exposed and ambulatory after 16 years of age
- Unwilling/unable to comply with study protocol

Physical abilities (including functional tests), quality of life, medical history/problems, and healthcare utilization are assessed for ≥ 8 years[45]. For ambulatory patients,

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[38] Summary study information extracted from: Applicant documents; Longitudinal Study of the Natural Histoyr of Duchenne Muscular Dystrophy (DMD). NCT00468832. April 21, 2016. Accessed on August 16, 2023, at: https://clinicaltrials.gov/study/NCT00468832?id=NCT00468832&rank=1#locations.; McDonald CM, Henricson EK, Abresch RT, et al.. Long-term effects of glucocorticoids on function, quality of life, and survival in patients with Duchenne muscular dystrophy: a prospective cohort study. Lancet. 2018 Feb 3;391(10119):451-461.

[39] Per clinicaltrials.gov, the estimated study completion is December 2019

[40] Applicant documents state that this is a case-control study; however, it appears to be a cohort study.

[41] Clinicaltrials.gov lists Japan and Puerto Rico as removed countries

[42] Italfarmaco S.p.A. 2.7.3 Summary of Clinical Efficacy.

[43] Study compares physical abilities of DMD patients to healthy controls

[44] Per clinicaltrials.gov, age eligibility extends to 30 years but other documents list maximum age as 28

[45] McDonald et al. (2018) states that follow-up occurred for 10 years

assessments occur at baseline, 3 months, 6 months, 9, months, and 12 months. For non-ambulatory patients, assessments occur at 6 months and 12 months. Additional visits occur at 18 months, 24 months, and subsequently every 12 months.

Between 2006 and 2016, 440 patients were enrolled (340 DMD patients between 2 and 28 years of age enrolled between 2006 and 2009; 100 DMD patients between 4 and 8 years of age enrolled between 2012 and 2015). Of the enrolled patients, 292 (66%) were ambulatory.

3.3.3 Integrated Analysis of Long-term Efficacy with Natural History Data

A study synopsis of the integrated analysis of long-term efficacy with natural history data, using an RWE framework, is presented in Appendix C.

3.3.3.1 Selection Criteria

For the integrated analysis of long-term efficacy with natural history data, the study included clinical trial subjects from Studies 48 and 51. From Study 51, the analysis excluded patients from the delayed givinostat group but included givinostat-naïve patients from their first day of givinostat dosing. Together, patients from Study 48 and the subset of patients from Study 51 are considered, by the Applicant, to be "Group 2".

For the natural history controls, the study sample was restricted to patients with baseline characteristics that matched to patients from Study 48 on inclusion and exclusion criteria:

- Males
- ≥6 years of age
- Confirmed DMD diagnosis
- Ambulant with baseline 4SC ≤8 seconds, time to rise from floor ≥3 to <10 seconds
- Stable corticosteroid treatment
- No exposure investigational drug or dystrophin restoration product
- No diagnosis of other uncontrolled neurological disease or uncontrolled somatic disorders

The analysis restricted to the ITT analysis set from Study 48 and Study 51. For the natural history studies, the analysis set included those with baseline and ≥1 follow-up assessment.

3.3.3.2 Exposures

The exposure was givinostat treatment (from the first day recruited to givinostat) versus no givinostat treatment.

3.3.3.3 Outcomes

For givinostat exposed patients, follow-up began from the day recruited to givinostat and for natural history controls, follow-up began on the day of study entry for CINRG and the day of first assessment for ImagingDMD. The outcomes for the natural history comparative analysis included:

- Age at persistent rise from floor > 10 seconds[46]
- Age at persistent 10-meter walk/run (10MWR) > 10 seconds[47]
- Age at persistent loss of rise from Floor (cannot perform due to physical inability)
- Age at persistent loss of 4SC (cannot perform due to physical inability)
- Age at persistent loss of ambulation (cannot perform 6MWT due to physical inability or cannot complete 10MWR in <30 seconds with our support/devices [10MWR grading ≤2])[48]

Age at outcome was based on age at the outcome event occurrence for clinical trials and age at first visit where the event was observed for natural history controls. Persistence was defined as the outcome event being noted in two consecutive assessments (or if the second assessment was missing or the event occurred at the last study timepoint).[49] Censoring occurred if the aforementioned outcomes were not reached or the patient was lost to follow-up.

3.3.3.4 Covariates

Covariates included:

- Body Mass Index (BMI)
- Age
- Race (not available for ImagingDMD)
- Time since diagnosis (years) (not available for CINRG)
- Time since first corticosteroid initiation (years)
- Use of corticosteroids at baseline (deflazacort versus other)
- Baseline functional tests

3.3.3.5 Sample Size/Power

The study pooled together multiple studies. There was no power calculation for the integrated analysis of long-term efficacy with natural history data.

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[46] For natural history controls, will also consider if patient is unable to perform due to physical inability

[47] Ibid.

[48] CINRG did not grade the 10MWR so ambulatory status=non-ambulatory was used

[49] If non-ambulatory at baseline of Study 51, will be defined by prior data.

3.3.3.6 Statistical Analysis

Descriptive analysis of subject disposition, demographics, and baseline characteristics was conducted. Results were analyzed overall and stratified by givinostat versus control group.

Propensity score matching was used for comparisons between givinostat exposed patients and natural history controls. The propensity score model included baseline age, 4SC, time to rise from floor, and steroid use (deflazacort versus other). Greedy, nearest neighbor matching with a caliper of 0.5 was used. Density plots, standardized differences, and variance ratios were generated. Survival analysis was conducted on the matched patients. If performance of the propensity score matching was poor (standardized mean difference ≥0.1, variance ratio deviates from 1), survival analysis was conducted on the entire sample.

The proportion of patients who reached the outcome events were calculated and Kaplan-Meier curves stratified by exposure were generated.

3.4 RESULTS OF INTEGRATED ANALYSIS OF LONG-TERM EFFICACY WITH NATURAL HISTORY DATA

3.4.1 Sample Size

There were 345 patients included in the integrated analysis of long-term efficacy with natural history data; 148 were exposed to givinostat and 197 were natural history controls. For the givinostat group, the median number of months in the study was 25.82 (minimum=2.9, maximum=50.1). For the controls, the median number of months was 36.61 (minimum 2.5, maximum 110.6). For the givinostat group, 18 received dose level A, 69 received dose level B, 37 received dose level A-B-C, and 24 received dose level B-C.

3.4.2 Baseline Characteristics

Demographic and other baseline characteristics are displayed in Table 1. The natural history controls were younger at baseline with a lower BMI, shorter time since diagnosis, shorter time since first corticosteroid initiation, and better functional performance (except for baseline time to climb 4 stairs). Deflazacort use was more common in the givinostat group.

Table 1. Demographic and baseline characteristics of study sample[50]

	Givinostat (n=148)		Controls (n=197)*	
	n (%)	Mean (SD)	n (%)	Mean (SD)
Age (years)		9.92 (2.08)		7.87 (1.66)
Age at last assessment (years)		12.25 (2.22)		11.74 (3.62)
Race				
Asian	6 (4.1)		13 (6.6)	
Black/African American	4 (2.7)		1 (0.5)	
White	128 (86.5)		111 (56.3)	
Other	10 (6.8)		7 (3.6)	
Unknown	0 (0.0)		3 (1.5)	
Missing	0 (0.0)		62 (31.5)	
Height (cm)		125.23 (8.33)		118.17 (8.35)
Weight (kg)		31.46 (9.01)		26.11 (8.14)
BMI (kg/m^2)		19.79 (4.08)		18.32 (3.52)
Time since diagnosis (years)		5.74 (2.69)		4.37 (1.88)
Time since first corticosteroids initiation (years)		3.80 (2.23)		2.10 (1.56)
Use of corticosteroids at baseline				
Deflazacort	118 (79.7)		94 (47.7)	
Other	30 (20.3)		101 (51.3)	
Baseline time to rise from floor (seconds)		6.62 (6.71)		4.97 (1.75)
Baseline time to climb 4 stairs (seconds)		3.58 (1.25)		3.58 (1.21)
Baseline time to walk/run 10 meters (seconds)		8.28 (33.60)		5.38 (1.58)
Baseline distance walked at 6 minutes (meters)		395.94 (71.03)		389.22 (56.26)

Abbreviations: SD, Standard Deviation; BMI, Body Mass Index

*Noted instances where sample size is reduced for controls: Height n=193; Weight n=195; BMI n=191; time since diagnosis n=62; time since corticosteroids n=192; use of corticosteroids at baseline n=195; baseline time to walk/run 10 meters n=196; baseline distance walked at 6 minutes n=58

3.4.3 Propensity Score Matching

The standardized mean difference and variance ratio of the logit score for the overall propensity score logistic regression sample (n=343 [195 from natural history controls]) was 0.93 and 5.79, respectively. Propensity score matching resulted in 126 matched pairs. After matching, the overall logit score standardized difference was 0.37 and the variance ratio was 1.68. Demographic and baseline characteristics for the matched sample are presented in Appendix D. The standardized differences after matching were 0.59 for age, 0.28 for use of corticosteroids at baseline, 0.04 for baseline time to rise from floor, and -0.10 for baseline 4SC. Matching was not perused because it resulted in the loss of 20 patients from the givinostat treated group and the standardized mean difference of the logit score and its variance ratio were not within defined thresholds (standardized mean difference <0.1, variance ratio approximately 1). A similar issue was noted for matching covariates. Analyses used the full, unmatched sample.

[50] Derived from Table 14.1.2.3.1.2 of ISE Statistical Analysis tables

3.4.4 Outcomes

The hazard ratio results for the age at persistent loss of function analyses indicated that all milestones were significantly delayed in the givinostat group, compared to the natural history controls. Results are displayed in Table 2. In the unmatched analysis, Kaplan-Meier analysis indicated that for the givinostat group, compared to the natural history controls, the median age at persistent rise from floor > 10 seconds was delayed by 1.6 years, persistent 10MWR > 10 seconds was delayed by 3.5 years, persistent loss of rise from floor was delayed by 2.2 years, persistent loss of 4SC was delayed by 3.3 years, and persistent loss of ambulation was delayed by 2.7 years.[51] Analysis was also conducted examining results by dose level. Detailed results are not displayed in this review.[52]

Table 2. Results of analyses of age in years at persistent loss of function comparing givinostat (givin.) (n=148) group to control (cont.) group (n=197)[53]

	Outcome									
	Persistent loss of ambulation		Persistent Rise from Floor > 10 Seconds		Persistent 10MWR > 10 seconds		Persistent Loss of Rise from Floor		Persistent Loss of 4SC	
Result	Givin.	Cont.	Givin.	Cont.	Givin.	Cont.	Givin.	Cont.	Givin.	Cont.
Outcome Reached, n (%)	16 (10.8)	44 (22.3)	66 (44.6)	99 (50.3)	35 (23.6)	84 (42.6)	49 (33.1)	76 (38.6)	23 (15.5)	62 (31.5)
KM Results, median (95% CI)	18.1 (18.09, NE)	15.4 (14.70, 18.31)	13.4 (12.47, 14.91)	11.8 (11.20, 12.26)	16.3 (14.32, NE)	12.8 (12.50, 13.70)	14.9 (13.40, 15.36)	12.7 (12.20, 14.15)	17.2 (15.65, NE)	13.9 (13.50, 14.70)
Hazard Ratio (95% CI)	0.48 (0.27, 0.86)	Ref	0.62 (0.45, 0.84)	Ref	0.43 (0.29, 0.64)	Ref	0.68 (0.47, 0.97)	Ref	0.42 (0.26, 0.67)	Ref

Abbreviations: 10MWR, 10-meter Walk/Run; 4SC, 4 Stair Climb; KM, Kaplan-Meier; CI, Confidence Interval; NE, Not Estimable; Ref, Reference

3.5 APPLICANT CONCLUSIONS

The Applicant concluded that, "[G]ivinostat can delay progression to clinically meaningful DMD disease milestones."[54]

[51] Confidence intervals for median age at loss of function overlapped for persistent loss of rise from floor and persistent loss of ambulation.

[52] The Applicant did not present the results of the analysis by dose in the Summary of Clinical Efficacy (although results are presented in the Tables for ISE Statistical Analysis). There were 18 exposed to Dose A, 69 to Dose B, 37 to Dose A-B-C, and 24 to Dose B-C. Per the DEPI-I reviewer, the results by dose are not particularly meaningful, result in smaller samples for comparative analysis, and are correlated with clinical study.

[53] Derived from Tables 14.2.3.2.1, 14.2.3.3.1, 14.2.3.4.1, 14.2.3.5.1, 14.2.3.6.1 from ISE Statistical Analysis Tables

[54] Italfarmaco S.p.A. 2.7.3 Summary of Clinical Efficacy.

3.6 FDA REQUESTED SENSITIVITY ANALYSES

In response to the FDA's IR from August 17, 2023[55], the Applicant submitted several sensitivity analyses on August 31, 2023.

3.6.1 FDA Request #1

> *Submit Tables and Figures for the ISE Statistical Analysis that present results for the age at persistent loss of ambulation, persistent rise from floor >10 seconds, persistent walk/run 10 meters >10 seconds, persistent loss of rise from floor, and persistent loss of 4 standard stairs climb comparing the ITT set and natural history data, restricted to matching subjects.*

The Applicant provided the requested tables and figures in their IR response. The hazard ratio results indicated a similar pattern to the unmatched results with estimates only slightly different than the original analyses (see Table 3). Some hazard ratio estimates were attenuated, while some were strengthened. Notably, the hazard ratio estimate was no longer statistically significant for persistent loss of ambulation.

Table 3. Results of analysis of age in years at persistent loss of function comparing matched givinostat (givin.) (n=126) group to control (cont.) group (n=126)[56]

	Outcome									
	Persistent loss of ambulation		Persistent Rise from Floor > 10 Seconds		Persistent 10MWR >10 seconds		Persistent Loss of Rise from Floor		Persistent Loss of 4SC	
Result	Givin.	Cont.	Givin.	Cont.	Givin.	Cont.	Givin.	Cont.	Givin.	Cont.
Outcome Reached, n (%)	12 (9.5)	36 (28.6)	46 (36.5)	77 (61.1)	27 (21.4)	65 (51.6)	32 (25.4)	56 (44.4)	17 (13.5)	49 (38.9)
KM Results, median (95% CI)	NE (NE, NE)	15.4 (14.70, 18.90	14.4 (12.47, NE)	12.0 (11.26, 12.50)	NE (13.78, NE)	13.2 (12.50, 14.01)	15.2 (14.32, NE)	13.2 (12.30, 14.47)	NE (NE, NE)	14.2 (13.70, 14.88)
Hazard Ratio (95% CI)	0.58 (0.30, 1.10)	Ref	0.58 (0.41, 0.81)	Ref	0.49 (0.33, 0.73)	Ref	0.66 (0.44, 0.98)	Ref	0.47 (0.28, 0.79)	Ref

Abbreviations: 10MWR, 10-meter Walk/Run ; 4SC, 4 Stair Climb; KM, Kaplan-Meier; CI, Confidence Interval; NE, Not Estimable; Ref, Reference

[55] Nguyen A. FDA information request: NDA 217865 17Aug2023. August 17, 2023. DARRTS Reference ID: 5228308.

[56] Derived from Tables 14.2.3.2.1.1, 14.2.3.3.1.1, 14.2.3.4.1.1, 14.2.3.5.1.1, 14.2.3.6.1.1 from Tables for ISE Statistical Analysis – FDA Request #1

As part of their IR response, the Applicant made additional efforts to improve the matching of the givinostat exposed patients and natural history controls. Per the Applicant, prior studies suggest that steroid treatment and functional status are the most important prognostic factors.[57] Thus, the Applicant conducted matching for baseline 4SC, baseline time to rise from the floor, baseline 10MWRT, and baseline steroid use (deflazacort, other). The updated matching approach excluded six patients treated with givinostat (total n=142 for givinostat group). The standardized mean difference of the logit score for the matched sample was improved to 0.23 with a variance ratio of 1.66. However, the absolute value of the standardized mean differences of baseline 4SC and steroid use still exceeded 0.10. All hazard ratios were statistically significant and favored the givinostat group (see Table 4). However, hazard ratios were attenuated, compared to the original results. As the updated matching analyses were conducted post hoc, not detailed in the statistical analysis plan (SAP), may be biased by prior analytic findings, and still suggest imbalance in matching covariates, this review will not focus further on these additional, updated matching analyses.

Table 4. Results of analysis of age in years at persistent loss of function comparing matched givinostat (givin.) (n=142) group to control (cont.) group (n=142) using updated matching approach[58]

	Outcome									
	Persistent loss of ambulation		Persistent Rise from Floor > 10 Seconds		Persistent 10MWR >10 seconds		Persistent Loss of Rise from Floor		Persistent Loss of 4SC	
Result	Givin.	Cont.	Givin.	Cont.	Givin.	Cont.	Givin.	Cont.	Givin.	Cont.
Outcome Reached, n (%)	14 (9.9)	39 (27.5)	61 (43.0)	82 (57.7)	33 (23.2)	70 (49.3)	45 (31.7)	61 (43.0)	21 (14.8)	52 (36.6)
KM Results, median (95% CI)	18.1 (18.09, NE)	15.2 (14.70, 18.31)	13.6 (12.56, 14.91)	11.9 (11.20, 12.44)	16.3 (14.32, NE)	13.0 (12.20, 13.80)	14.9 (13.60, 15.97)	12.9 (12.20, 14.33)	17.2 (15.65, NE)	13.9 (13.50, 14.88)
Hazard Ratio (95% CI)	0..42 (0.23, 0.76)	Ref	0.57 (0.42, 0.78)	Ref	0.42 (0.28, 0.61)	Ref	0.66 (0.45, 0.96)	Ref	0.39 (0.24, 0.65)	Ref

Abbreviations: 10MWR, 10-meter Walk/Run; 4SC, 4 Stair Climb; KM, Kaplan-Meier; CI, Confidence Interval; NE, Not Estimable; Ref, Reference

[57] Applicant provided references Mercuri E, Signorovitch JE, Swallow E, Song J, Ward SJ; DMD Italian Group; Trajectory Analysis Project (cTAP). Categorizing natural history trajectories of ambulatory function measured by the 6-minute walk distance in patients with Duchenne muscular dystrophy. Neuromuscul Disord. 2016;26(9):576-83. Erratum in: Neuromuscul Disord. 2017;27(5):e1.; Muntoni F, Domingos J, Manzur AY, Mayhew A, Guglieri M, UK NorthStar Network, et al. Categorising trajectories and individual item changes of the North Star Ambulatory Assessment in patients with Duchenne muscular dystrophy. PLoS One. 2019;14(9):e0221097.; Goemans N, Vanden Hauwe M, Signorovitch J, Swallow E, Song J. Individualized Prediction of Changes in 6-Minute Walk Distance for Patients with Duchenne Muscular Dystrophy. PLoS One. 2020;11(10):e0164684.

[58] Derived from Tables 14.2.3.2.1.2, 14.2.3.3.1.2, 14.2.3.4.1.2, 14.2.3.5.1.2, 14.2.3.6.1.2 from Tables for ISE Statistical Analysis – FDA Request #1

3.6.2 FDA Request #2

Present ISE Tables and Figures for subject disposition, demographic and baseline characteristics, and persistent loss of function comparing subjects treated with givinostat in Study 48 and natural history data. Present the data overall as well as restricted to matching subjects.

In the Applicant's response, the Applicant presented the requested data overall as well as using only the updated matching approach (standardized mean difference of logit score=0.16, variance ratio=1.91). Due to the rationale provided in Section 3.6.1, this review will focus on the overall data presentation. The demographic and clinical characteristics of the patients treated with givinostat in Study 48 are presented in Appendix E. Compared to the full sample of givinostat treated patients, those treated with givinostat in Study 48 were slightly younger. The most notable difference was in the baseline time to walk/run 10 meters, with baseline function worse in the full sample of givinostat treated patients, compared to givinostat treated patients in Study 48 alone (8.28 seconds versus 5.56 seconds). Hazard ratio findings were consistent with the full analysis findings, although hazard ratios were closer to the null and persistent loss of rise from floor was no longer statistically significant (Table 5).

Table 5. Results of analyses of age in years at persistent loss of function comparing givinostat (givin.) (n=118) group to control (cont.) group (n=197)[59]

	Outcome									
	Persistent loss of ambulation		Persistent Rise from Floor > 10 Seconds		Persistent 10MWR >10 seconds		Persistent Loss of Rise from Floor		Persistent Loss of 4SC	
Result	Givin.	Cont.	Givin.	Cont.	Givin.	Cont.	Givin.	Cont.	Givin.	Cont.
Outcome Reached, n (%)	15 (12.7)	44 (22.3)	57 (48.3)	99 (50.3)	31 (26.3)	84 (42.6)	44 (37.3)	76 (38.6)	21 (17.8)	62 (31.5)
KM Results, median (95% CI)	18.1 (18.09, NE)	15.4 (14.70, 18.31)	12.8 (11.99, 14.91)	11.8 (11.20, 12.26)	15.6 (14.32, NE)	12.8 (12.50, 13.70)	14.4 (13.01, 15.36)	12.7 (12.20, 14.15)	17.2 (15.65, NE)	13.9 (13.50, 14.70)
Hazard Ratio (95% CI)	0.55 (0.30, 1.00)	Ref	0.67 (0.48, 0.93)	Ref	0.46 (0.31, 0.70)	Ref	0.75 (0.52, 1.09)	Ref	0.47 (0.28, 0.77)	Ref

Abbreviations: 10MWR, 10-meter Walk/Run; 4SC, 4 Stair Climb; KM, Kaplan-Meier; CI, Confidence Interval; NE, Not Estimable; Ref, Reference

3.6.3 FDA Request #3

Present ISE Tables and Figures for subject disposition, demographic and baseline characteristics, and persistent loss of function comparing subjects who received placebo in Study 48 (prior to initiation of

[59] Derived from Tables 14.2.3.2.1.3, 14.2.3.3.1.3, 14.2.3.4.1.3, 14.2.3.5.1.3, 14.2.3.6.1.3 from Tables for ISE Statistical Analysis – FDA Request #2

givinostat) and natural history data. Present the data overall as well as restricted to matching subjects.

In the IR response, the Applicant presented data overall as well as using only the updated matching approach (standardized mean difference of logit score=0.07, variance ratio=1.68). Due to the rationale provided in Section 3.6.1, this review will focus on the overall data presentation. The Applicant interpreted the FDA request for comparative analysis on patients who received placebo in Study 48 to mean all data on those patients who were assigned placebo in Study 48 and givinostat in Study 51. The IR was intended to request data on those who were assigned placebo in Study 48, censoring at time of switch to givinostat.[60]

The demographic and clinical characteristics of the patients treated with placebo in Study 48 are presented in Appendix E. Comparative analyses are presented in Table 6. In general, compared to the full analysis, hazard ratios were attenuated toward the null and are no longer statistically significant, except for persistent 10MWR > 10 seconds and persistent loss of 4SC.

Table 6. Results of analysis of age in years at persistent loss of function comparing placebo (n=61) group to control (cont.) group (n=197)[61]

	Outcome									
	Persistent loss of ambulation		Persistent Rise from Floor > 10 Seconds		Persistent 10MWR >10 seconds		Persistent Loss of Rise from Floor		Persistent Loss of 4SC	
Result	Placebo	Cont.	Placebo	Cont.	Placebo	Cont.	Placebo	Cont.	Placebo	Cont.
Outcome Reached, n (%)	10 (16.4)	44 (22.3)	36 (59.0)	99 (50.3)	17 (27.9)	84 (42.6)	26 (42.6)	76 (38.6)	12 (19.7)	62 (31.5)
KM Results, median (95% CI)	NE (15.19, NE)	15.4 (14.70, 18.31)	12.9 (11.93, 14.57)	11.8 (11.20, 12.26)	15.2 (14.41, NE)	12.8 (12.50, 13.70)	14.0 (12.48, NE)	12.7 (12.20, 14.15)	NE (14.71, NE)	13.9 (13.50, 14.70)
Hazard Ratio (95% CI)	0.61 (0.30, 1.21)	Ref	0.72 (0.49, 1.06)	Ref	0.43 (0.25, 0.72)	Ref	0.77 (0.49, 1.21)	Ref	0.43 (0.23, 0.80)	Ref

Abbreviations: 10MWR, 10-meter Walk/Run; 4SC, 4 Stair Climb; KM, Kaplan-Meier; CI, Confidence Interval; NE, Not Estimable; Ref, Reference

4 DISCUSSION

4.1 RWE CRITIQUE

[60] A follow-up IR was not sent to the Applicant as the reviewer noted that only 18 months of follow-up data are available for the placebo group, before switch to givinostat. Eighteen months may not be an adequate amount of time to detect functional loss in patients and may result in inestimable median ages in Kaplan-Meier analyses.

[61] Derived from Tables 14.2.3.2.1.5, 14.2.3.3.1.5, 14.2.3.4.1.5, 14.2.3.5.1.5, 14.2.3.6.1.5 from Tables for ISE Statistical Analysis – FDA Request #3

4.1.1 DMD and Use of Natural History Controls

Per FDA Guidance for Industry, FDA may consider externally controlled studies to contribute to the evidence of efficacy to support approval for DMD.[62] Bias in external control studies may be lessened if the disease course is predictable and there is a large treatment effect.[63] DMD has a heterogeneous disease course (4-6) and improvements in outcomes can be noted in younger patients receiving standard-of-care (5). These may be a key limitation to using natural history controls as a comparator in DMD, in general. The Applicant did exclude younger patients <6 years of age from all studies reviewed, so the studies may be less likely to include patients that may improve. The Applicant provided references to two studies to support the assertion that placebo-controlled arms from clinical trials are similar to natural history controls for DMD.[64] Muntoni et el. (2022) compared 48-week change in the North Star Ambulatory Assessment (NSAA) in a pooled sample of patients from the placebo arm of phase three clinical trials and several real-world data/natural history data sources. Before matching, there was a greater decline in NSAA among patients from placebo-controlled arms (mean change in NSAA = -1.2 [95% CI: -2.0, -0.5]). There was no difference after successful matching on prognostic factors (mean change in NSAA = 0.2 [95% CI: -0.7, 1.0]). The Applicant's in text citation linked to the Goemans et al. (2016) article, which only examines the 6MWD in natural history data.

4.1.2 Statistical Analysis Plan

The document date for the SAP used for the integrated analysis of long-term efficacy with natural history data is relatively recent (November 7, 2022) and after completion of the pivotal study. Study 43 ended November 17, 2017, Study 48 ended February 22, 2022, and Study 51 had an interim analysis conducted on December 31, 2021. The natural history control analysis plan does not appear to have been discussed with the FDA prior to its execution and unblinding of the pivotal clinical trial (Study 48).[65] The

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[62] Duchenne Muscular Dystrophy and Related Dystrophinopathies: Developing Drugs for Treatment: Guidance for Industry. February 2018. Silver Spring (MD), U.S. Food and Drug Administration.

[63] Rare Diseases: Natural History Studies for Drug Development: Draft Guidance for Industry. March 2019. Silver Spring (MD), U.S. Food and Drug Administration.

[64] Applicant provided references: Muntoni F, Signorovitch J, Sajeev G, Goemans N, Wong B, Tian C, et al. Real-world and natural history data for drug evaluation in Duchenne muscular dystrophy: suitability of the North Star Ambulatory Assessment for comparisons with external controls. Neuromuscul Disord. 2022;32(4):271-283.; Goemans N, Vanden Hauwe M, Signorovitch J, Swallow E, Song J. Individualized Prediction of Changes in 6-Minute Walk Distance for Patients with Duchenne Muscular Dystrophy. PLoS One. 2016;11(10):e0164684. Reviewer noted that the Applicant had the incorrect year for the Goemans et al. study.

[65] E-mail communication with clinical reviewer (Peggy Lazerow) dated August 11, 2023.

Applicant did include their RWE datasets and programming code with their NDA submission.[66]

Per FDA guidance, if RWE is submitted in support of a NDA, draft protocols and SAPs should be submitted to the FDA for review and comment before finalizing documents and conducting analyses.[67] Study selection and analytic decisions may have been influenced by pivotal study findings. If the applicant had submitted their SAP[68] for FDA input, FDA would have had the opportunity to provide feedback. The Applicant also did not present power calculations or specify an anticipated effect size. As a result, the integrated analysis of long-term efficacy with natural history data should be considered exploratory.

4.1.3 Selection of Natural History Studies

FDA Guidance states that the Applicant should provide justification for their external control selection.[69] The Applicant provided reasonable justification for their selection of natural history studies from which to obtain natural history controls; however, the selection of studies was not included in a pre-specified protocol discussed with the FDA. The Applicant considered multiple studies. Final, selected studies were chosen based on the following characteristics: 1) multi-center studies, 2) availability of functional outcomes, and 3) similarity of study sample to Study 48 eligibility criteria. These selection criteria increased the likelihood of comparability between givinostat treated patients and natural history controls.

4.1.4 Baseline Characteristics - Comparability

Lack of comparability is a major threat to the validity of studies that leverage external controls.[70] Key areas of comparability concern are discussed below.

4.1.4.1 Time period and geographic region

[66] Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products: Draft Guidance for Industry. December 2021. Silver Spring (MD), U.S. Food and Drug Administration.

[67] Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products: Draft Guidance for Industry. December 2021. Silver Spring (MD), U.S. Food and Drug Administration.

[68] SAP included information relevant to a protocol

[69] Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products: Draft Guidance for Industry. February 2023. Silver Spring (MD), U.S. Food and Drug Administration.

[70] Ibid.

As noted in Table 7, the natural history control studies were not concurrent with the studies that included givinostat exposed patients. The natural history controls cover earlier years than the givinostat trials. If there have been improvements in the standard of care over time, outcomes for the earlier, natural history controls may be worse and bias results away from the null. Additionally, CINRG has a broader geographic capture than the givinostat exposed studies. Differences in DMD care by country or site could bias study results, and the Applicant did not consider country of residence in the integrated analysis of long-term efficacy with natural history data.

Table 7. Time Period and Geographic Region for Included Studies

Study	Start Date	End Date	Geographic Region
Givinostat Exposed			
Study 43	April 2013	November 2017	Italy
Study 48	June 2017	February 2022	North America, Europe, Israel
Study 51	October 2017	Data Cut December 2021	North America, Europe, Israel
Natural History Controls			
CINRG	September 2006	Data Cut 2016	Argentina, Australia, Canada, Israel, Italy, Sweden
Imaging DMD	September 2010	Data Cut 2020	United States

4.1.4.2 Prognostic Factors

The standardized differences for the logit of the matched sample suggest substantial imbalance on the matched covariates, which are key prognostic factors. The Applicant, due to poor matching, only presented baseline characteristics for the matched sample. No matched, comparative analyses were presented. The Applicant only presented the results of comparative analyses for the overall, unmatched sample.[71] Unmatched analyses did not control for confounding, resulting in biased estimates:

- The younger age, shorter time since diagnosis, and better functional status in controls may suggest that controls were earlier in their disease course and could possibly bias results of the integrated analysis of long-term efficacy with natural history data towards the null.
- The shorter time since corticosteroid initiation in controls could suggest that controls were earlier in their disease course (bias toward the null) but could also suggest a faster disease progression requiring earlier initiation of treatment (bias away from the null).
- There is some evidence that deflazacort is associated with better outcomes in DMD, compared to prednisone/prednisolone (7). The greater use of this corticosteroid in the givinostat group could bias results away from the null.

[71] In the Clinical Overview, the Applicant mistakenly labels analysis results as matched.

The FDA requested sensitivity analyses that compare age at persistent loss of function among matched patients which indicated a similar pattern to the unmatched results. However, there is still imbalance in the covariates after matching. In the Applicant's analyses using the updated matching approach, hazard ratios were all attenuated, suggesting that the prognostic factors included in the propensity score model biased results away from the null.

Several other potentially important prognostic factors were not measured or controlled for in the analyses either due to a lack of availability or not being considered. Example prognostic factors that could be important confounders include baseline VL MFF, steroid regimen, genetic mutations[72], and non-drug interventions. Time since diagnosis was not available in the CINRG and race was not available in ImagingDMD. It is difficult to assess the impact of residual confounding by such factors on the results.

Natural history controls were eligible for the integrated analysis of long-term efficacy if they matched eligibility criteria for Study 48. Study 43 had different eligibility criteria and a different target population of younger patients in an earlier disease stage than Study 48. The givinostat-naïve patients from Study 51 may not have met Study 48 eligibility criteria at the time of givinostat initiation due to elapsed time since baseline eligibility assessments. In the Applicant's Summary of Clinical Efficacy, the Applicant did not pool together Study 43, 48, and 51 in an integrated analysis of efficacy because baseline age and functional status differed across these three studies. However, these three studies were pooled, despite their differences, for the integrated analysis of long-term efficacy with natural history data. The selection criteria for the natural history controls may have limited their comparability to givinostat exposed patients from Study 43 and givinostat-naïve patients treated in Study 51. The FDA requested sensitivity analysis that restricts the givinostat treated patients to those from Study 48 indicated attenuated hazard ratios. The attenuated findings suggest that the natural history controls were likely more similar to treated patients from Study 48, compared to the full givinostat treated group.

Study 48 was enriched for a certain expected rate of disease progression[73] and natural history controls were not. This enrichment may result in selection bias. If the placebo group fared better than controls, it could suggest selection bias or poor choice of external controls. In the FDA requested sensitivity analyses that restricted to placebo exposed patients from Study 48, hazard ratios were attenuated toward the null and were only statistically significant for a subset of outcomes.

4.1.4.3 Index date and follow-up period/intervals

[72] Duchenne Muscular Dystrophy and Related Dystrophinopathies: Developing Drugs for Treatment: Guidance for Industry. February 2018. Silver Spring (MD), U.S. Food and Drug Administration.

[73] Expected not to lose ambulation in 18 months

The index date for the integrated analysis of long-term efficacy with natural history data was age at baseline[74]. However, the baseline age of patients exposed to givinostat was more than two years older than the natural history controls (Table 1). Per DMD-specific FDA guidance for industry, external control analyses may be sensitive to the age of patients at inception.[75] Follow-up intervals differed between the givinostat exposed patients and natural history controls. Follow-ups occurred less often for the natural history controls, which could have resulted in delayed recognition of loss of function in these patients. There was longer duration of follow-up of the natural history controls. Per the Applicant, "[T]he longer follow-up in the control group compensates for the younger age at baseline."[76] The Applicant may be suggesting that the longer follow-up in controls (despite younger age at baseline) allows for assessment of function at similar, older ages to givinostat treated patients.

4.1.4.4 Outcomes

The outcomes selected for the comparative analyses capture a range of functional outcomes, which may prevent floor and ceiling effects. However, the outcomes are all effort/function based. Outcome assessment should be standardized, including assessor encouragement. [77] If assessors were aware of which patients were assigned givinostat, those patients may receive more encouragement and patients may be more motivated while undertaking functional assessments. Increased motivation could lead to delayed capture of functional loss in givinostat treated patients. It is unknown if the assessments in the givinostat clinical development program and the two natural history control studies were conducted in the same manner and under identical conditions.

4.1.5 Overall Findings

The unmatched comparative analyses from the integrated analysis of long-term efficacy with natural history data indicated large magnitudes of effectiveness with median delays in persistent loss of function ranging from 1.6 years to 3.5 years in givinostat treated patients, compared to natural history controls (although not all Kaplan Meier results were statistically significant). These differences were likely clinically meaningful. Per FDA guidance, "[A]n external control is most interpretable when a treatment effect… is large in comparison to potential biases and known variability in progression." [78] Although the comparative analyses suggest that givinostat may delay progression of disease milestones

[74] For givinostat exposed patients, age on day recruited to givinostat. For natural history controls, age on the day of study entry for CINRG and the day of first assessment for ImagingDMD.

[75] Duchenne Muscular Dystrophy and Related Dystrophinopathies: Developing Drugs for Treatment: Guidance for Industry. February 2018. Silver Spring (MD), U.S. Food and Drug Administration.

[76] Italfarmaco S.p.A. 2.7.3 Summary of Clinical Efficacy.

[77] See footnote 75.

[78] Rare Diseases: Natural History Studies for Drug Development: Draft Guidance for Industry. March 2019. Silver Spring (MD), U.S. Food and Drug Administration.

by up to several years, it is not clear if these findings are large enough to exclude that findings are due to the aforementioned limitations and biases.

4.2 SUBSTANTIAL EVIDENCE OF EFFECTIVENESS

Pertinent to the review of the integrated analysis of long-term efficacy with natural history data, the Applicant is using the following substantial evidence of effectiveness statutory standard: "One adequate and well-controlled clinical investigation with compelling results, supported by additional data from the natural history of the disease."[79] Notably, DMD is a serious disease with unmet medical need where it is appropriate to exercise regulatory flexibility.[80] As noted previously, the Applicant presents multiple sources of confirmatory data in their application. DEPI-I defers to other disciplines to review and comment on the persuasiveness of the pivotal clinical trial as well as the strength of the other confirmatory evidence. The interpretability of the RWE is uncertain, given the limitations and potential biases detailed above.

5 CONCLUSION AND RECOMMENDATION

Although the integrated analysis of long-term efficacy with natural history data indicated meaningful delays in persistent loss of function among those treated with givinostat, compared to external controls, the analyses should be considered exploratory due to a lack of a priori protocol and SAP agreement with the FDA. Applicants should always submit both a protocol and SAP for RWE submissions. Although the results from sensitivity analyses were somewhat consistent with primary analysis findings the heterogeneity of DMD progression, lack of comparability between givinostat treated patients and natural history controls, potential for residual confounding, enrichment of the pivotal trial sample, differences in index date and follow-up, and use of effort-based outcomes make the externally controlled study results difficult to interpret. Overall, the RWE submitted as part of the NDA should be evaluated in the context of these limitations and biases as well as the rest of the NDA submission.

[79] Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products: Draft Guidance for Industry. December 2019. Silver Spring (MD), U.S. Food and Drug Administration.

[80] Duchenne Muscular Dystrophy and Related Dystrophinopathies: Developing Drugs for Treatment: Guidance for Industry. February 2018. Silver Spring (MD), U.S. Food and Drug Administration.

6 APPENDICES

APPENDIX A. SUMMARY OF FUNCTION, STRENGTH AND MORPHOLOGY ENDPOINTS IN GIVINOSTAT CLINICAL EFFICACY STUDIES[81]

	Ambulant Patients	Non-ambulant Patients	Lower Limb	Upper Limb	Whole Body	Study 48	Study 43	Study 51
Endpoints Assessing Function								
4SC	X		X			X		X
Time to rise from floor	X		X			X	X	X
10MWR	X		X			X	X	X
6MWT	X		X			X	X	X
NSAA	X		X			X	X	X
PUL	X	X		X			X[a]	X[a]
MFM	X	X			X			X
Egen Klassifikation Total Score		X			X			X
Barthel Index Total Score		X			X			X
Endpoints Assessing Strength								
Knee Extension	X		X			X		X
Elbow Flexion	X	X		X		X		X
Endpoints Assessing Muscle Morphology								
Histology	X			X			X	
VL MFF (MRS)	X		X			X		
FF (Dixon MRI)	X		X			X		

4SC, climb 4 standard stairs; 6MWT, 6-minute walk test; 10MWR, walk or run 10 metres; DMD, Duchenne muscular dystrophy; FF, fat fraction; MFM, motor function measure; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NSAA, North Star Ambulatory Assessment; PUL, performance of upper limb; VL MFF, vastus lateralis muscle fat fraction.

[a] Motor performance in the upper limb was evaluated using PUL version 1.2 in Study 43 and PUL version 2.0 in Study 51.

Source: Study 43 CSR, Study 48 CSR and Study 51 CSR.

APPENDIX B. SUMMARY OF NATURAL HISTORY STUDIES[82]

Data Source	Type	Location	Time Period	Unique Patients	Total Visits	Visit Frequency (months)	Follow-up (years)
CCHMC	Curated clinical data from electronic health records of boys with DMD from the Comprehensive Neuromuscular Center at CCHMC	1 centre in Cincinnati, USA	2004-2016	600	4,384	6-12	2-10
CINRG	Prospective, longitudinal, multicentre observational study at neuromuscular centres	22 clinical sites worldwide (incl. US, South America, Europe, Australia, India)	2006-2016	440	3559	3 monthly for Study Year 1; 6 monthly for Study Year 2; annually thereafter	0.25-10
DMD Italian Group	Routine clinical practice data from neuromuscular clinical centres	13 centres in Italy	2008-2013	96	381	12	3
Imaging DMD	Prospective, longitudinal natural history study at MRI centers in the USA	3 centres in the USA	2010-present	180	769	12 months in all participants *3 and/or 6 months in prespecified subpopulations*	1-10
iMDEX	Prospective, longitudinal, multicentre observational study at neuromuscular centres	5 centres in Europe	2012-2018	87	496	6	1-4
Leuven	Curated RWD from boys with DMD from routine clinical practice at the Universitaire Ziekenhuizen paediatric neurology clinic in Leuven, Belgium	1 centre in Belgium	2001-2016	155	2,262	6	1-3
NSUK	Prospective natural history study from specialist neuromuscular centres in the United Kingdom	24 centres in the United Kingdom	2005-2016	533	2,988	6	1-4

CCHMC, Cincinnati Children's Hospital Medical Center; CINRG, Cooperative International Neuromuscular Research Group; DMD, Duchenne Muscular Dystrophy; ImagingDMD, Magnetic Resonance Imaging and Biomarkers for Muscular Dystrophy; NSUK, North Star United Kingdom; RWD, real world data; USA, United States of America.

Sources: CTAP/CINRG/Imaging DMD, Data on file.

[81] Table and title extracted from Table 3 of Summary of Clinical Efficacy

[82] Table and title extracted from Table 39 of Summary of Clinical Efficacy

APPENDIX C. STUDY SYNOPSIS FOR RWE REVIEW

Product, therapeutic area, indication	Duchenne Muscular Dystrophy (DMD)	
Regulatory purpose	RWE submitted as part of an NDA for Duvyzat (givinostat, Italfarmaco S.p.A) for the treatment of DMD.	
Existing evidence from other sources	Study 48 (Phase three randomized, placebo control trial) with confirmatory evidence from: • Mechanistic evidence from histological findings in *mdx* mouse model • Mechanistic evidence from muscle histological findings in Study 43 (Phase two single-arm open-label trial) • Mechanistic evidence from magnetic resonance spectroscopy (MRS) imaging and vastus lateralis muscle fat fraction (VL MFF) from Study 48 • Long-term treatment effect evidence from Study 51 (open-label, long-term study of subjects enrolled in Study 43 or enrolled/eligible for Study 48)	
Regulatory need and gap	RWE study intended to provide one source of confirmatory evidence of effectiveness.	
Study objective	To examine long-term efficacy of givinostat for the treatment of DMD by comparing the age at persistent disease milestones between givinostat exposed subjects from clinical trials to natural history controls.	
Study design	Givinostat exposed patients from clinical development program (Study 48, Study 51)	External controls from two natural history studies (RWD)
Studied period: • Total duration • Date of first enrollment, date of last completed	Study 43: 52 months; April 2, 2023-November 17, 2017 Study 48: 18 months; June 6, 2017-February 22, 2022 Study 51: Ongoing (48-week interim analysis cut-off December 31, 2021); started October 25, 2017	Magnetic Resonance Imaging and Biomarkers for Muscular Dystrophy (ImagingDMD): September 2010-anticipated completion August 2025 (data cut-off 2020) Cooperative International Neuromuscular Research Group (CINRG): Started September 2006 (data cut-off 2016)
Design (e.g., parallel, cross-over)	Study 43: Single arm Study 48: Randomized, placebo-controlled Study 51: Single arm	Cohort studies
Blinding (e.g., open, double-blind, single-blind)	Study 43: Open-label study Study 48: Double-blind Study 51: Open-label study	N/A
Data source(s)	Clinical trials from givinostat clinical development program	ImagingDMD CINRG
Study population (inclusion and exclusion criteria)	The integrated analysis of long-term efficacy with natural history data includes clinical trial subjects from	The integrated analysis of long-term efficacy with natural history data includes

	Studies 48 and Studies 51 (except for those randomized to placebo in Study 48 [delayed givinostat group]). The inclusion criteria for the source studies are listed below: Study 43: Males, ≥7 to <11 years of age, DMD diagnosis, ambulatory 2 screening 6-minute walk test (6MWTs) ≥ 250 meters [± 30 meters of each other], stable corticosteroids Study 48: Males, ≥6 years of age, DMD diagnosis, ambulatory (mean of 2 screening [± 1 second] 4 Stair Climbs [4SCs] ≤ 8 seconds, time to rise from floor ≥3 to <10 seconds, manual muscle testing of quadriceps grade ≥3), stable corticosteroids. Target population MRS VL MFF >5% to ≤30%; off-target population MRS VLF MFF ≤5% or >30% Study 51: Males ≥6 years of age from Study 43, Study 48 (and attended end of study visit), screened Study 48 and met off-target criteria but not randomized due to off-target enrollment being complete	natural history controls with baseline characteristics matching study 48 inclusion/exclusion criteria (Males, ≥6 years of age, DMD, ambulant with baseline 4SC ≤8 seconds, time to rise from floor ≥3 to <10 seconds, stable corticosteroid treatment, no exposure to investigational drug or dystrophin restoration product, no diagnosis of other uncontrolled neurological disease or uncontrolled somatic disorders). The inclusion/exclusion criteria for the source studies are listed below: ImagingDMD: Males, 5-30 years of age, DMD, ambulatory and non-ambulatory. Excluded individuals with contraindications to MRI, other muscle disorders, unable to participate due to cognitive/behavioral problems. CINRG: Males, 2-28 years of age, DMD. Excluded individuals who were steroid-naïve and ambulatory after 13 years of age, steroid exposed and ambulatory after 16 years of age, unwilling/unable to comply with study protocols.
Causal Contrasts (ITT or PP)	ITT	Those with baseline and ≥1 follow-up assessment
Exposure definition (e.g., test product dose and mode of administration, batch number, duration), ascertainment, and validation	Givinostat exposure from two treatment groups from day recruited to givinostat: Givinostat group – received givinostat in Study 43 or Study 48 Givinostat naïve – Screened in Study 48 and met off-target criteria but not randomized due to off-target enrollment being complete	No givinostat exposure (natural history cohorts)
Comparator definition (e.g., reference therapy, dose and mode of administration, batch number, duration), ascertainment, and validation	N/A	N/A

Outcome definition, ascertainment, and validation	• Age at persistent Rise from Floor > 10 seconds • Age at persistent 10-meter Walk/Run (10MWR) > 10 seconds • Age at persistent loss of Rise from Floor • Age at persistent loss of 4SC • Age at persistent loss of ambulation	• Age at persistent Rise from Floor > 10 seconds • Age at persistent 10-meter Walk/Run (10MWR) > 10 seconds • Age at persistent loss of Rise from Floor • Age at persistent loss of 4SC • Age at persistent loss of ambulation
Key covariates: measured and unmeasured	Measured: Body Mass Index (BMI), age, race, time since diagnosis, time since first corticosteroid initiation, use of corticosteroids at baseline, baseline functional tests	Measured: Body Mass Index (BMI), age, race (not available Imaging DMD), time since diagnosis (not available for CINRG), time since first corticosteroid initiation, use of corticosteroids at baseline, baseline functional tests Unmeasured: VL MFF, steroid regimen, genetic mutations, non-drug interventions. Time since diagnosis not available in CINRG and race not available in ImagingDMD.
Index time	Age	Age
Start and End of Follow-up	Day recruited to givinostat – until NDA approval,	Day of study entry (CINRG) and ay of first assessment (ImagingDMD)
Statistical methods (primary analysis)	Stratified descriptive analysis Survival analysis (Kaplan-Meier curves, hazard ratios)	Stratified descriptive analysis Survival analysis (Kaplan-Meier curves, hazard ratios)
Sample size (planned and analyzed)	Pooled analysis of multiple studies. N=148	Pooled analysis of multiple studies. N=197
Methods to handle confounding, if applicable	Propensity score matching (not pursued due to poor performance)	Propensity score matching (not pursued due to poor performance)
Methods to handle missing data, if applicable	As addressed in source studies	No imputation
RWE results for confirmatory evidence of effectiveness	Persistent loss of ambulation: Hazard ratio (HR): 0.48 (95% Confidence Interval [CI]: 0.27, 0.86); Median age at loss of ambulation givinostat group=18.1 years (95% CI: 18.09, not estimable [NE]); control group=15.4 years (95% CI: 14.70, 18.31); difference=delay of 2.7 years	

	Persistent rise from floor > 10 seconds: HR: 0.62 (95% CI: 0.45, 0.84); Median age givinostat group=13.4 (95% CI: 12.47, 14.91); control group=11.8 (95% CI; 11.20, 12.25); difference=delay of 1.6 years Persistent 10MWR > 10 seconds: HR: 0.43 (95% CI: 0.29, 0.64); Median age givinostat group=16.3 (95% CI: 14.32, NE); control group=12.8 (95% CI: 12.50, 13.70); difference=delay of 3.5 years Persistent loss of rise from floor: HR: 0.68 (95% CI: 0.47, 0.97); Median age givinostat group=14.9 (95% CI: 13.40, 15.36); control group=12.7 (95% CI: 12.20, 14.15); difference=delay of 2.2 years Persistent loss of 4SC: HR: 0.42 (95% CI: 0.26, 0.67); Median age givinostat group=17.2 (95% CI: 15.65, NE); control group=13.9 (95% CI: 13.50, 14.70); difference=delay of 3.3 years

APPENDIX D. DEMOGRAPHIC AND BASELINE CHARACTERISTICS OF MATCHED STUDY SAMPLE[83]

	Givinostat (n=126)		Controls (n=126)*		Standardized Difference / Variance Ratio
	n (%)	Mean (SD)	n (%)	Mean (SD)	
Age (years)		9.57 (1.92)		8.46 (1.73)	0.59 / 1.23
Age at last assessment (years)		11.83 (1.98)		12.82 (3.65)	
Race					
Asian	5 (4.0)		9 (7.1)		
Black/African American	2 (1.6)		1 (0.8)		
White	111 (88.1)		65 (51.6)		
Other	8 (6.3)		2 (1.6)		
Unknown	0 (0.0)		1 (0.8)		
Missing	0 (0.0)		48 (38.1)		
Height (cm)		124.01 (7.71)		120.59 (8.31)	
Weight (kg)		30.53 (8.74)		27.63 (9.11)	
BMI (kg/m^2)		19.59 (4.06)		18.61 (4.04)	
Time since diagnosis (years)		5.42 (2.55)		4.62 (1.77)	
Time since first corticosteroids initiation (years)		3.63 (2.25)		2.39 (1.74)	
Use of corticosteroids at baseline					0.28 / 0.76
Deflazacort	98 (77.8)		82 (65.1)		
Other	28 (22.2)		44 (34.9)		
Baseline time to rise from floor (seconds)		5.53 (2.01)		5.33 (1.79)	0.04 / 1.27
Baseline time to climb 4 stairs (seconds)		3.49 (1.19)		3.61 (1.22)	-0.10 / 0.96
Baseline time to walk/run 10 meters (seconds)		8.65 (36.42)		5.59 (1.80)	
Baseline distance walked at 6 minutes (meters)		401.02 (69.39)		387.29 (58.19)	

Abbreviations: SD, Standard Deviation; BMI, Body Mass Index
Noted instances where sample size is reduced for controls: Height n=122; Weight n=125; BMI=121; time since diagnosis=48; time since first corticosteroids initiation n=121; baseline distance walked at 6 minutes n=45

[83] Derived from Table 14.1.2.3.1.1 and Table 14.2.3.1.1 of ISE Statistical Analysis tables

APPENDIX E. DEMOGRAPHIC CHARACTERISTICS OF PATIENTS TREATED WITH GIVINOSTAT AND PLACEBO IN STUDY 48[84]

	Study 48 – Givinostat Only (n=118)		Study 48 – Placebo Only (n=61)	
	n (%)	Mean (SD)	n (%)	Mean (SD)
Age (years)		9.78 (2.02)		9.97 (2.08)
Age at last assessment (years)		12.38 (2.20)		12.76 (2.15)
Race				
Asian	4 (3.4)		2 (3.3)	
Black/African American	3 (2.5)		0 (0.0)	
White	106 (89.8)		57 (93.4)	
Other	5 (4.2)		2 (3.3)	
Unknown	0 (0.0)		0 (0.0)	
Missing	0 (0.0)		0 (0.0)	
Height (cm)		125.09 (7.92)		126.70 (9.82)
Weight (kg)		31.22 (8.88)		32.58 (10.75)
BMI (kg/m^2)		19.69 (4.10)		19.91 (4.40)
Time since diagnosis (years)		5.45 (2.60)		5.62 (2.71)
Time since first corticosteroids initiation (years)		3.62 (2.09)		3.91 (2.18)
Use of corticosteroids at baseline				
Deflazacort	91 (77.1)		45 (73.8)	
Other	27 (22.9)		16 (26.2)	
Baseline time to rise from floor (seconds)		6.89 (7.43)		6.76 (7.31)
Baseline time to climb 4 stairs (seconds)		3.58 (1.25)		3.60 (1.27)
Baseline time to walk/run 10 meters (seconds)		5.56 (1.34)		5.30 (1.03)
Baseline distance walked at 6 minutes (meters)		398.27 (70.93)		393.72 (61.43)

Abbreviations: SD, Standard Deviation; BMI, Body Mass Index

[84] Derived from Table 14.1.2.3.1.2.3 from Tables for ISE Statistical Analysis – FDA Request #2 and Table 14.1.2.3.1.2.5 from Tables for ISE Statistical Analysis – FDA Request #3

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M E M O R A N D U M
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: September 14, 2023

To: Emily Freilich, MD, Director, Division of Neurology I

Through: Dominic Chiapperino, PhD, Director, Controlled Substance Staff
Chad Reissig, PhD, Supervisory Pharmacologist, Controlled Substance Staff

From: Neil Varshneya, PhD, Pharmacologist, Controlled Substance Staff

Subject: **NDA 217865** for Givinostat Oral Suspension (10 mg/ml)
Indication: Duchenne Muscular Dystrophy
Dosage and Route: (10.6 – 70) mg, PO, BID
Sponsor: Italfarmaco SpA

Materials Reviewed: Drug Abuse Liability Assessment of Givinostat (May 15, 2023)

I. Background

This memorandum is in response to a consult request dated May 17, 2023, from the Division of Neurology I (DNI) pertaining to NDA 217865 for givinostat. Givinostat is an orally active hydroxamic acid derivative possessing class I and class II histone deacetylase (HDAC) inhibitory activity in development by Italfarmaco SpA (Applicant) for the treatment of Duchenne Muscular Dystrophy (DMD). The Applicant submitted an NDA for givinostat dated May 17, 2023, with a document titled *Drug Abuse Liability Assessment of Givinostat*. DNI requested that the Controlled Substance Staff (CSS) review the Applicant's NDA from an abuse potential perspective. CSS has not previously reviewed givinostat.

CSS evaluated givinostat for chemical structural similarities to all drugs scheduled under the Controlled Substances Act (CSA) using open-source cheminformatics software and determined that it was not substantially similar to any scheduled substances (see the chemistry subsection of Section 4 [Discussion of Abuse and Dependence-Related Data] of this memorandum). The Applicant evaluated givinostat for its secondary pharmacology in vitro using competition radioligand binding tests and determined that it binds to the dopamine transporter (71% inhibition of control specific binding at 10 µM) among other non-abuse-related targets [Appendix – Table 3]. However, givinostat does not achieve CNS concentrations sufficient to

elicit abuse related-effects at abuse-related receptor targets at doses within the therapeutic range or exceeding it by 3x (see the pharmacology subsection of Section 4 [Discussion of Abuse and Dependence-Related Data] of this memorandum for rationale). Moreover, there were no reports of abuse-related TEAEs across the clinical development program (e.g., euphoria, high, feeling drunk, floating, rush, perceptual disturbances, hallucination, or dissociation). Although the in vitro studies demonstrate that givinostat binds to receptors associated with abuse-related effects, givinostat does not achieve CNS concentrations sufficient to elicit psychoactive or intoxicating effects and does not produce TEAEs associated with abuse potential. Therefore, additional studies including non-clinical abuse potential assessments and a human abuse potential study are not needed.

Overall, CSS has not identified any abuse- or dependence-related concerns with givinostat and did not identify any evidence to suggest that givinostat poses risks of addiction liability in humans. CSS concludes that givinostat is unlikely to be abused and therefore should not be controlled under the Controlled Substance Act (CSA). The proposed drug product, if approved under this NDA, will not require Section 9 (Drug Abuse and Dependence section) in its label.

II. Conclusions

- Givinostat is an orally active hydroxamic acid derivative and is not similar in chemical structure to any drugs scheduled under the CSA.

- Givinostat possesses class I and class II histone deacetylase (HDAC) inhibitory activity. HDAC inhibition is not known to be associated with abuse-related effects.

- Givinostat binds to the dopamine transporter at high concentrations. However, givinostat does not achieve CNS concentrations sufficient to elicit psychoactive or intoxicating effects, even at doses equivalent to, or substantially exceeding (e.g., 3x) the therapeutic dose.

- A review of TEAEs in the clinical studies did not reveal any evidence to suggest that givinostat poses risks of addiction liability in humans.

III. Recommendations (to the Division)

- Givinostat does not have abuse potential under the conditions in which it was tested and therefore does not require scheduling under the CSA nor a Section 9 (Drug Abuse and Dependence) in its label.

IV. Discussion of Abuse and Dependence-Related Data

Chemistry

Drug Substance. The chemical structure of givinostat is shown in **Figure 1**. Givinostat has an IUPAC name of [6-(diethylaminomethyl)naphthalen-2-yl]methyl N-[4-(hydroxycarbamoyl)phenyl]carbamate, a molecular formula of $C_{24}H_{27}N_3O_4$, and a molecular weight of 421.5 g/mol. The chemical properties and structural identifiers of givinostat including

the IUPAC Name, PubChem ID, CASRN, Molecular Formula, Molecular Weight, Canonical SMILES, InChI, and InChIKey are shown in **Table 1**.

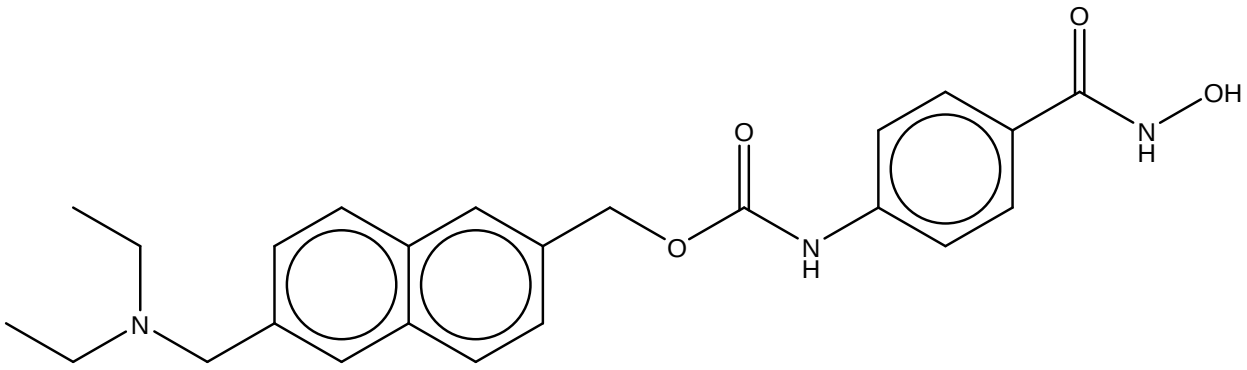

Figure 1. Chemical Structure of Givinostat.

Table 1. Chemical Properties and Structural Identifiers of Givinostat	
Property or Identifier	**Value**
Common Name	Givinostat
IUPAC Name	[6-(diethylaminomethyl)naphthalen-2-yl]methyl N-[4-(hydroxycarbamoyl)phenyl]carbamate
PubChem ID	9804992
CASRN	497833-27-9
Molecular Formula	C24H27N3O4
Molecular Weight	421.5 g/mol
Canonical SMILES	CCN(CC)CC1=CC2=C(C=C1)C=C(C=C2)COC(=O)NC3=CC=C(C=C3)C(=O)NO
InChI	InChI=1S/C24H27N3O4/c1-3-27(4-2)15-17-5-7-21-14-18(6-8-20(21)13-17)16-31-24(29)25-22-11-9-19(10-12-22)23(28)26-30/h5-14,30H,3-4,15-16H2,1-2H3,(H,25,29)(H,26,28)
InChIKey	YALNUENQHAQXEA-UHFFFAOYSA-N
IUPAC = International Union of Pure and Applied Chemistry CASRN = Chemical Abstract Service Registry Number SMILES = Simplified Molecular-Input Line-Entry System InChI = International Chemical Identifier InChIKey = InChIKey is a hashed version of the full InChI (using the SHA-256 algorithm)	

The Tanimoto coefficient (Tc), a measurement of chemical structure similarity, for givinostat and each substance in a CSA drug schedule was computed with the RDK7 molecular fingerprint (O'Boyle and Sayle, 2016) using open-source cheminformatics software (RDKit). A Tc value for molecular fingerprints ranges from '0' to '1', where '0' results from fingerprints with no similarities and '1' results from identical fingerprints. Givinostat is not substantially similar in chemical structure to any drugs controlled under the CSA (all Tc <0.45).

Drug Product. According to the Sponsor: "The proposed drug product Givinostat hydrochloride monohydrate 10 mg/mL Oral Suspension is a white to off-white or faintly pink, homogenous suspension when mixed (i.e., after shaking the bottle for at least 30 seconds). Each 1 mL contains 8.86 mg Givinostat, equivalent to 10 mg Givinostat hydrochloride monohydrate. The drug product is supplied in a 150 mL amber PET bottle closed with a (b) (4) HDPE childproof screw cap with LDPE (b) (4) syringe adapter). Each bottle contains 140 mL of Oral Suspension and is intended for multidose use. The drug product is supplied with (b) (4) graduated oral dispensers (Plunger (b) (4) /Barrel (b) (4) 5 mL capacity."

Pharmacology

Givinostat was evaluated in vitro against a comprehensive suite of abuse-related targets. Givinostat was determined to bind to the rat dopamine transporter (71% inhibition of control specific binding at 10 µM) in these tests [Appendix – Table 3]. In single oral dose studies in humans, the maximum (or peak) blood serum concentration observed was 542.1 ng/ml ± 92.7 ng/ml following the administration of 600 mg, PO givinostat which equates to an exposure of 1.29 µM (542.1 ng / ml * 1 mol / 421.5 g) [see Module 2.7.2 Summary of Clinical Pharmacology Studies]. The 600 mg, PO givinostat dose is 4.29 x greater than (600 mg / 140 mg) the maximum proposed therapeutic dosage (70 mg, PO, BID) and results in a peak exposure in humans that is 7.75 x less than (10 µM / 1.29 µM) the concentration required to produce 71% inhibition of control specific binding of the dopamine transporter. Given that givinostat is 95.9% bound in human plasma (TR1683/E, Module 4.2.2.3), and a substrate for efflux pumps such as p-glyocoprotein P (TR1608/E, TR1876/E, Module 4.2.2.2 and TR2329/E, Module 4.2.2.6), the maximum CNS concentrations achieved are likely to be substantially less than those observed in blood. Moreover, in single oral dose studies of [14C]-givinostat in Sprague Dawley rats, the observed peak brain tissue exposure concentration was C_{max} = 0.18 (µg equiv/g) following the administration of a 10 mg/kg, PO dose [Appendix – Table 2]. Assuming brain tissue has the same density as water, the expected peak givinostat concentration is 427 nM (0.18 µg / 1 ml * 1 mol / 421.5 g). The 10 mg/kg, PO givinostat rat dose equates to a 96 mg human dose for a 60 kg human (10 mg/kg * 0.16 * 60 kg) or approximately 68.5% (96 mg /140 mg *100 %) of the maximum proposed therapeutic dosage and results in a peak brain concentration in rats that is 23.42 x less than (10 µM / 427 nM) the concentration required to produce 71% inhibition of control specific binding of the dopamine transporter. Although givinostat binds to the dopamine transporter, it does not achieve CNS concentrations sufficient to elicit psychoactive or intoxicating effects, even at doses equivalent to, or substantially exceeding (e.g., >3x) the maximum proposed therapeutic dose.

Givinostat was also evaluated for signs of neurological worsening using an Irwin Functional Observation Battery (FOB). According to the Sponsor, "In the Irwin assay performed for the CNS safety assessment of givinostat (TR1534/E, Module 4.2.1.3), givinostat was administered as a single oral dose (gavage) to male CD-1 mice, at doses of 1, 10 and 100 mg/kg. The control group received the vehicle for givinostat (sterile water). Behavior of mice was scored at 30, 90, 150, 300 minutes, 24 hours and up to 7 days after dosing, to assess any changes in animal behavior or physiological state due to treatment. A panel of behavior-related parameters was systematically evaluated for each mouse using a standardized procedure. Givinostat produced no behavioral or physiological changes in mice, at any of the tested doses, at any time points. There were no mortalities or gross signs of toxicity observed during the study, up to the 7-day post-dose observation period. The No observed effect level (NOEL) was therefore greater than 100 mg/kg." From an abuse potential perspective, these data suggest that givinostat does not elicit CNS-related toxicity even at doses equivalent to, or substantially exceeding (e.g., >3x) the maximum proposed therapeutic dose.

Abuse-Related Adverse Events in Human Studies

Givinostat was investigated for various indications in clinical trials including chronic inflammatory disease, hematological malignancies, chronic myeloproliferative neoplasms, and muscular dystrophy. Treatment Emergent Adverse Events (TEAEs) observed in these studies were recorded and analyzed [Appendix – Table 6 & 7]. The Sponsor performed a search of the abuse-related terms. According to the Sponsor, "Some examples are: Euphoria-related terms (i.e., Dizziness, Elevated mood, Hallucination); Terms indicative of impaired attention, cognition and mood (i.e., Somnolence); Dissociative/psychotic terms (i.e., Aggression, Confusion, Psychosis). Only "Dizziness" has been reported in > 1% of DMD patients treated with givinostat (9 episodes reported in 7 patients out of 222 subjects treated)." From an abuse potential perspective, safety data obtained from clinical studies with givinostat are not suggestive of abuse potential.

Conclusions

The data collected from studies with givinostat showed little evidence indicative of abuse potential. No significant structural similarities were identified comparing givinostat to known drugs of abuse. Moreover, low penetration through BBB is expected, leading to brain concentrations of givinostat that do not translate into physiologically relevant binding of abuse-related targets (e.g., dopamine transporter). Furthermore, no evidence of abuse-related behaviors was identified for givinostat in the Irwin FOB even at doses equivalent to, or substantially exceeding (e.g., >3x) the maximum proposed therapeutic dose. Finally, evaluation of TEAEs from clinical safety and efficacy studies with givinostat also did not result in evidence of effects that will be sought out for abuse purposes. Based on the evaluation from the available data, givinostat does not warrant control under the CSA.

V. References

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Appendices. The following are data from the Applicant's document titled *Drug Abuse Liability Assessment of Givinostat* dated May 15, 2023. They are presented verbatim:

Table 2: Residual total radioactivity (µg eq/g) in organ/tissue after single and repeated oral administration of [14C]-givinostat to Sprague Dawley rat

Single Administration					
	0.5 hours	**4 hours**	**8 hours**	**24 hours**	**72 hours**
Intestinal tract	86.506	49.203	30.417	0.761	0.027
Duodenum	40.264	4.448	2.433	0.159	0.015
Stomach	21.331	1.532	0.669	0.037	0.012
Liver	8.442	1.879	1.292	0.311	0.117
Kidney	6.047	1.156	1.019	0.090	0.034
Urinary bladder	46.833	6.713	1.254	0.046	0.002
Brain	0.18	0.07	0.06	0.04	0.007
Repeated Administration					
	0.5 hours	**4 hours**	**8 hours**	**24 hours**	**72 hours**
Intestinal tract	67.140	83.391	81.043	2.316	0.283
Duodenum	16.072	7.327	4.213	0.234	0.051
Stomach	7.162	2.989	0.724	0.103	0.034
Liver	2.043	2.949	2.111	0.647	0.358
Kidney	1.452	1.792	1.170	0.308	0.117
Urinary bladder	0.527	2.919	1.741	0.229	0.054
Brain	0.045	0.072	0.069	0.013	0.009

Table 3: Effect of givinostat (concentration 10-5M) in the CNS-specific In Vitro Receptor Binding Assay

Binding Site	**% Inhibition of Control Specific Binding**
Cannabinoid CB1	26.6
Cannabinoid CB2	1.3
Dopamine D1	2.6
Dopamine D2S	32.3
GABAA1	2.5
NMDA	-3.4
δ-opioid	6.7
κ-opioid	25.1
µ-opioid	13.3
Serotonin 5HT1A	18.9

Serotonin 5HT2A	6
Serotonin 5HT2B	9.5
Serotonin 5HT2C	10.6
Serotonin 5HT3	-1.7
Ca^{2+} channel (N)	1.7
Cl- channel (GABA-gated)	-7.3
Dopamine transporter	44.3
GABA transporter	-7.9
Serotonin transporter	12.8

Table 6: Nervous system TEAEs occurring in all patients' studies

System Organ Class **Preferred Term**	**Givinostat Overall (n = 634)** **n (%)**	**Placebo Overall (n = 139)** **n (%)**
Nervous system disorders	120 (18.9)	27 (19.4)
Headache	78 (12.3)	21 (15.1)
Dizziness	15 (2.4)	1 (0.7)
Paresthesia	12 (1.9)	0 (0)
Dysgeusia	6 (0.9)	0 (0)
Migraine	4 (0.6)	1 (0.7)
Hypoesthesia	2 (0.3)	1 (0.7)
Lethargy	2 (0.3)	0 (0)
Loss of consciousness	2 (0.3)	0 (0)
Sciatica	2 (0.3)	0 (0)
Somnolence	2 (0.3)	0 (0)
Syncope	2 (0.3)	0 (0)
Tremor	2 (0.3)	1 (0.7)
Cerebral Hemorrhage	1 (0.2)	0 (0)
Cerebral ischemia	1 (0.2)	0 (0)
Cerebrovascular accident	1 (0.2)	0 (0)
Cervicobrachial syndrome	1 (0.2)	0 (0)
Disturbance in attention	1 (0.2)	0 (0)
Dizziness postural	1 (0.2)	1 (0.7)
Head discomfort	1 (0.2)	0 (0)
Memory impairment	1 (0.2)	0 (0)
Neurological symptom	1 (0.2)	0 (0)
Nystagmus	1 (0.2)	0 (0)
Parosmia	1 (0.2)	0 (0)
Peripheral sensory neuropathy	1 (0.2)	0 (0)
Presyncope	1 (0.2)	0 (0)
Taste disorder	1 (0.2)	0 (0)
Tension headache	1 (0.2)	0 (0)
Balance disorder	0 (0)	1 (0.7)
Hand-arm vibration syndrome	0 (0)	1 (0.7)

Hypotonia	0 (0)	1 (0.7)
Neuralgia	0 (0)	1 (0.7)
Psychomotor hyperactivity	0 (0)	1 (0.7)

Table 7: Psychiatric TEAEs occurring in all patients' studies.

System Organ Class **Preferred Term**	**Givinostat Overall (n = 634)** **n (%)**	**Placebo Overall (n = 139)** **n (%)**
Psychiatric disorders	39 (6.2)	5 (3.6)
Anxiety	11 (1.7)	0 (0)
Insomnia	7 (1.1)	2 (1.4)
Sleep disorder	3 (0.5)	1 (0.7)
Attention deficit hyperactivity disorder	2 (0.3)	0 (0)
Panic attack	2 (0.3)	0 (0)
Abnormal behavior	1 (0.2)	0 (0)
Affect lability	1 (0.2)	0 (0)
Aggression	1 (0.2)	0 (0)
Agitation	1 (0.2)	0 (0)
Behavior disorder	1 (0.2)	0 (0)
Confusional state	1 (0.2)	0 (0)
Delirium	1 (0.2)	0 (0)
Depressed mood	1 (0.2)	0 (0)
Depression	1 (0.2)	0 (0)
Dysphemia	1 (0.2)	0 (0)
Emotional disorder	1 (0.2)	0 (0)
Enuresis	1 (0.2)	0 (0)
Initial insomnia	1 (0.2)	0 (0)
Intermittent explosive disorder	1 (0.2)	0 (0)
Irritability	1 (0.2)	0 (0)
Libido decreased	1 (0.2)	0 (0)
Mixed anxiety and depressive disorder	1 (0.2)	0 (0)
Negativism	1 (0.2)	0 (0)
Nervousness	1 (0.2)	1 (0.7)
Neurosis	1 (0.2)	0 (0)
Nightmare	1 (0.2)	0 (0)
Obsessive-compulsive disorder	1 (0.2)	0 (0)
Oppositional defiant disorder	1 (0.2)	0 (0)
Restlessness	1 (0.2)	0 (0)
Sleep terror	1 (0.2)	0 (0)
Procedural anxiety	0 (0)	1 (0.7)

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/s/

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Interdisciplinary Review Team for Cardiac Safety Studies

QT Study Review

Submission	NDA 217865
Submission Number	003
Submission Date	4/21/2023
Date Consult Received	5/10/2023
Drug Name	Givinostat (DUVYZAT)
Indication	Indicated for the treatment of Duchenne muscular dystrophy (DMD)
Therapeutic Dose	Up to (b) (4) mg BID (weight based)
Clinical Division	DN1
Protocol Review	Link

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 5/10/2023 regarding the sponsor's QT evaluation. We reviewed the following materials:

- Previous IRT reviews under IND 126598 dated 11/20/2020 and 08/09/2022 in DARRTS;
- Thorough QT study 200148 cardiac safety report (NDA 217865 / SDN 003; link);
- Clinical study report Study ITF/2357/54 (NDA 217865 / SDN 003; link);
- Summary of Clinical Pharmacology Studies (NDA 217865 / SDN 003; link);
- Investigator's brochure (NDA 217865 / SDN 006; link);
- QT Evaluation report checklist (NDA 217865 / SDN 006; link); and
- Highlights of clinical pharmacology and cardiac safety (NDA 217865 / SDN 006; link).

1 SUMMARY

QTcF prolongation was detected in the thorough QT (TQT) study ITF/2357/54: "A Randomized, Partially Double-Blind, Four-Period, Four Treatment, Crossover Study Investigating the Placebo-Corrected Effects of a Therapeutic Dose (100 mg) and a Supratherapeutic Dose (300 mg) of ITF2357 (Givinostat) and Moxifloxacin on QT/QTc Interval in Healthy Male and Female Subjects." See Table 1 for overall results.

The sponsor has not determined the high clinical exposure scenario. The highest dose administered in study ITF/2357/54 (300 mg, corresponding to 3-6 mg/kg) provided 6.6-fold coverage for the therapeutic Cmax at steady state in patients with Duchenne Muscular Dystrophy (DMD) dosed 70 mg (approximately 1 mg/kg). Data analyzed using by-time analysis as the primary analysis did not suggest that a 100 mg dose

(corresponding to 1-2 mg/kg) of DUVYZA is associated with significant QTc prolonging effect. However, the by-time analysis suggests the presence of significant QTc prolonging effect for the 300 mg dose (refer to section 4.3). Integrated nonclinical risk assessment was not performed.

The sponsor performed an exposure-response analysis, which showed that increased givinostat concentration is associated with an increase in QTc response. The sponsor concluded that the results were unreliable due to significant hysteresis. The sponsor measured metabolite concentration in Study ITF/2357/54 but did not incorporate metabolite concentration into the concentration-QTc model to account for hysteresis. Tmax for parent drug was 2 hours. Tmax estimates for metabolites ITF2374, ITF2375, ITF2440, ITF2563, and ITF2955 were 5, 4, 12, 12, and 3 hours, respectively. The peak effect on QTcF was observed at approximately 5 hours post dose and is consistent with QTc prolongation by metabolites ITF2374 and/or ITF2375 (See section 3.2.3 and Figure 5). Metabolite concentration has not been measured in patients with DMD, so the coverage of metabolite concentration by the 300 mg dose in this study is not known.

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>

By-Time analysis is the primary analysis due to a delay between maximum concentration and peak QTc effect of greater than one hour (hysteresis) in both givinostat dose groups.
The sponsor has not evaluated the high clinical exposure, which is anticipated to occur in hepatic impairment.
Doses of 300 mg yielded exposures 6.6-fold the givinostat Cmax,ss observed in DMD patients receiving a therapeutic dose. Coverage of the metabolites is not known because metabolite concentrations have not been reported in DMD patients.
This study included the positive control moxifloxcin to demonstrate assay sensitivity.

<table>
<tr><th>ECG parameter</th><th>Treatment</th><th>Time (h)</th><th>ΔΔQTcF (msec)</th><th>90% CI (msec)</th></tr>
<tr><td>QTcF</td><td>Givinostat 100 mg (corresponds to 1-2 mg/kg)</td><td>5.0</td><td>5.5</td><td>2.0 to 9.0</td></tr>
<tr><td>QTcF</td><td>Givinostat 300 mg (corresponds to 3-6 mg/kg)</td><td>5.0</td><td>13.6</td><td>10.1 to 17.1</td></tr>
</table>
</td></tr>
</table>

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION

The sponsor evaluated the effect of givinostat on QT interval at exposures covering up to 6.6-fold the $C_{max,ss}$ in patients with DMD receiving a clinical dose. However, the time profile of QTc interval suggests that its metabolites could be causing QTc prolongation because the Tmax for givinostat is around 2 hours post-dose but the largest mean QTc effect occurred around 5 hours post-dose which is consistent with Tmax of metabolites ITF2374 and/or ITF2375.

The sponsor has not performed organ impairment studies to identify the high-clinical exposure scenario of parent and metabolites, so it is not known whether the exposures achieved in the Thorough QT Study (TQT) performed cover the high exposure scenario.

2 RECOMMENDATIONS

2.1 ADDITIONAL STUDIES

Not applicable.

2.2 PROPOSED LABEL

Below are proposed edits to the label submitted to NDA 217865 SDN 3 (link).

Our changes are highlighted (addition, ~~deletion~~). Please note that this is a suggestion only and that we defer final labeling decisions to the Division.

5.4 QT prolongation (b) (4) (b) (4) Avoid use of DUVYZAT in patients who are at (b) (4) (b) (4) increased risk for ventricular arrhythmias (including torsades de pointes) such as those with congenital long QT syndrome, coronary artery disease, electrolyte disturbance, concomitant use of other medicinal products known to cause QT prolongation (b) (4)
Reviewer's comment: According to the draft guidance, additional risk factors include patients with significant cardiac disease, recent myocardial infarction, heart failure, unstable angina, bradyarrhythmias, uncontrolled hypertension, high degree atrioventricular block, severe aortic stenosis, or uncontrolled hypothyroidism. *We defer to the Division which important risk factors should be highlighted for DMD patients, and whether or not the benefit-risk supports its use in patients with risk factors. The Division could also recommend ECG monitoring in patients with underlying risk factors.*
12.2 Pharmacodynamics Cardiac Electrophysiology (b) (4)

[redacted] (b) (4) The largest mean increase in QTc interval of 13.6 ms (upper confidence interval of 17.1 ms) occurred 5 hours after administration of givinostat [redacted] (b) (4) mg to healthy subjects ([redacted] (b) (4) times the [redacted] (b) (4) mg dose administered to DMD patients) [*see Warnings and Precautions (5.4)*].
Reviewer's comments: The peak effect on QTcF was observed at approximately 5 hours post dose and is consistent with Tmax of metabolites ITF2374 and/or ITF2375 (See section 3.2.3 and Figure 5). Metabolite concentration has not been measured in patients with DMD, so the coverage of metabolite concentration by the 300 mg dose in this study is not known. Furthermore, the sponsor has not performed organ impairment studies to identify the high-clinical exposure scenario of parent and metabolites.

3 SPONSOR'S SUBMISSION

3.1 OVERVIEW

Givinostat is under review as a treatment for Duchenne Muscular Dystrophy (DMD; pediatric population) and in development for the treatment of Polycytemia Vera (PV; adult population). The review division requested that the IRT review the sponsor's proposed labeling and comment on whether the effect of givinostat on QTc interval has been adequately characterized.

The IRT previously reviewed thorough QT study protocol ITF/2357/54 (DARRTS IND 126598; 11/20/2020) and provided comments regarding QT assessment in an End of Phase 3 meeting (DARRTS 8/9/2022). The sponsor has submitted the results of study ITF/2357/54 in support of the current NDA.

We agreed with caveats to protocol ITF/2357/54, specifically noting that the adequacy of dose selection would be a review issue depending on the highest therapeutic dose and whether the selected supratherapeutic dose (i.e., 300 mg) covers the high clinical exposure scenario (likely hepatic impairment; DDI and organ impairment studies were pending) for drug and any relevant metabolites. We included our standard comment regarding alternative QT methods in case the product causes significant changes in heart rate (HR) (see IRT review under IND 126598 dated 11/20/2020).

Our review of summary results of the TQT study included in the Type C EOP3 meeting materials for IND 126598 dated 08/09/2022, noted that (1) the acceptability of QTcF would be a review issue because givinostat was associated with significant HR changes, and (2) C-QTc was not adequate for parent concentrations because there was a significant time delay between peak givinostat concentration and placebo-corrected change from baseline QTc; but may be appropriate for metabolites and recommended the sponsor use suitable methods accounting for hysteresis or use by-time central tendency analysis to report study findings.

3.1.1 Clinical pharmacology

Givinostat is an inhibitor of histone deacetylase (HDAC). It is hypothesized that HDAC inhibitors delay Duchenne Muscular Dystrophy disease progression by stimulating activation of muscle satellite cells, increasing expression of muscle regeneration factors, and inhibiting fibrosis and inflammation through reduction of cytokine production and signaling. Givinostat has a weight-based dosing regimen and labeling includes instructions on dose reduction for decreased platelets, increased triglycerides, and diarrhea.

Givinostat (DUVYZAT) is formulated as an oral suspension. It has a Tmax of 2 to 3 hours and a half-life of 6 hours. It exhibits linear kinetics with an accumulation factor of 1.7 following twice daily dosing. It is extensively metabolized to ITF2374, ITF2375, ITF2440, and ITF2563 (the four major metabolites) which have steady state metabolic ratios of 3.4-, 5-, 28-, and 7-fold, respectively. A high-fat meal increases the Cmax of givinostat and ITF2375 by 20% but decreases Cmax and increases Tmax of ITF2374. The impact of food on other metabolites is not known. There are no dietary restrictions with regard to dosing.

Givinostat's major metabolic pathway is not through CYP450 enzymes but through other hepatic-mediated oxidative cleavage of the carbamic bond to generate ITF2440 and ITF2563. Givinostat is a substrate of P-glycoprotein (PgP). The strong Pgp inhibitor, clarithromycin, increased givinostat Cmax by 40% but left its AUC unchanged. The impact of organ impairment on PK of givinostat and its metabolites has not been evaluated. Hepatic and renal impairments are likely the high clinical exposure scenarios for givinostat and its metabolites, respectively, since the liver and the kidney are the major elimination routes. Steady state Cmax of givinostat capsules when 100 mg BID was dosed to healthy subjects was 181.5 ng/ml. In a phase 3 study, patients with DMD received givinostat suspension at a dose adjusted for body weight (i.e., weight-based dose bands, see Table 2).

Table 2: Givinostat Starting Dose

Weight (kg)	**≥10 and <12.5**	**≥12.5 and <20**	**≥20 and <25**	**≥25 and <30**	**≥30 and <40**	**≥40 and <50**	**≥50 and <60**	**≥60 and <70**	**≥70**
Dose (mg) (*)	20	25	30	35	40	50	55	60	70
Oral suspension volume (mL)	2.0	2.5	3.0	3.5	4.0	5.0	5.5	6.0	7.0

(*) as givinostat hydrochloride monohydrate

The population PK model predicted steady state arithmetic mean Cmax of givinostat in patients receiving the initial dosing regimen (Dose A) without dose reduction was 61.7 ng/ml. Table 3 shows that the highest dose in the TQT study (single 300 mg) provided an arithmetic mean Cmax of 409.65 ng/mL, which covers the therapeutic Cmax predicted in patients with DMD by 6.6 fold. This suggests that the highest TQT dose would cover high clinical exposure scenario if hepatic and renal impairment results in < 6.6-fold increase in steady state Cmax for givinostat. However, it's not clear whether the 300 mg dose covers the high clinical exposure for its metabolites.

Additional clinical pharmacology information on givinostat and its metabolites is summarized in the Summary of Clinical Pharmacology Studies and in the Highlights of Clinical Pharmacology and Cardiac Safety.

The sponsor did not provide estimates of metabolite concentration in DMD patients.

Table 3: Summary of dose and exposure assessment

		Mean C_{max}
Highest therapeutic or clinical trial dosing regimen	Weight-based dosing in patients (approximately 1-2 mg/kg*), see Table 2	Givinostat: 61.7 ng/mL ($C_{max,ss}$)**
Sponsor's High clinical exposure scenario	Hepatic impairment for givinostat; Renal impairment for ITF2440 and ITF2563	Not yet determined
Highest dose in QT assessment	300 mg oral tablets in TQT (corresponds to 3-6 mg/kg*)	409.65 ng/mL
C_{max} Ratio over therapeutic Cmax	Not known for metabolites 6.6 fold for givinostat	

*The weight range of participants in the TQT study was 58.7 to 96.1 kg. **Source: NDA 217865 (SDN 3; April 21, 2023) Summary of Clinical Pharmacology Studies page 36 of 82.

3.1.2 Nonclinical Safety Pharmacology Assessments

The effects of givinostat (ITF2357) (0.1, 0.3, 1, 3 and 10 µM) on K+-currents generated through the human ether-a-go-go related gene (hERG) channels were assessed (TR1725/E). The effects were measured on the maximum amplitude of the tail currents. This parameter was determined from current traces obtained from voltage-clamped CHO-K1/hERG transfected cells, using patch-clamp techniques in the whole-cell configuration. The results show that givinostat inhibits hERG K+ currents with an IC50 value of 1.4 µM corresponding to 590 ng/mL. For givinostat, the ratio between the IC50 on hERG channels with respect to the free maximum concentration (free safety margin) was >90-fold.

In addition, the inhibition of hERG K+ currents by the main metabolites ITF2374, ITF2375, ITF2440 and ITF2563 was also studied (TR2307/E; 20220028PEHPPB and 20220030PEHPPB), using the same experimental conditions used for the parent compound givinostat. ITF2374 induced a concentration-dependent inhibition of hERG tail current with an IC50 of 5.7 µM while ITF2375 showed an IC50 of 142 µM. The free safety margin evaluation for the two metabolites gave >1,000 and >10,000-fold, respectively. ITF2440 and ITF2563 did not show effect on the hERG tail current at concentration up to 10-4 M.

The effect of givinostat on the action potential duration was assessed in rabbit Purkinje fibers electrically paced at 1.0 and 0.2 Hz stimulation frequencies (TR1724/E). The action potential duration at 50% and 90% repolarization, the action potential amplitude, the maximum upstroke velocity and the resting membrane potential were measured. At 0.1, 0.3, 1, 3 and 10 µM, givinostat had no statistically significant effect on the action potential of rabbit Purkinje fibers. At 3 and 10 µM (corresponding to 1265 ng/mL and 4215 ng/mL respectively), givinostat increased the action potential duration at 50% and 90% repolarization during bradycardia although

not in a statistically significant manner. This may suggest a block of potassium channels at high concentrations.

Cardiovascular and respiratory effects were assessed in anaesthetized dogs (TR1539/E). Givinostat was administered i.v. at 0.1, 1 and 10 mg/kg to 4 male Beagle dogs, maintained under chloralose/pentobarbital anaesthesia. None of the tested doses produced any overt effect on mean arterial blood pressure or mean heart rate. Left ventricular systolic pressure remained unaffected by givinostat administration. I.V. administration of givinostat did not induce any marked changes in ECG intervals or waveform. There were no changes in the respiratory parameters.

In addition, no treatment-related changes in ECG parameters were identified in the 4-week oral toxicity study in the dog (TR1537/E) and in the 13- and 39-week oral toxicity study in the monkey (TR1618/E and TR1927/E, respectively).

The combined evidence from these in vitro and in vivo studies plus the lack of accumulation of drug in the heart as observed in tissue distribution studies, suggest that givinostat is unlikely to exert any cardiovascular side effect at therapeutic doses.

3.2 SPONSOR'S RESULTS

3.2.1 By-Time Analysis

The sponsor's intended primary analysis for givinostat was exposure-response analysis. However, due to hysteresis, the by-time analysis was determined to be more appropriate. Please see section 3.2.3 for additional details.

In the sponsor's by-time analysis, givinostat excluded the 10 msec threshold at the therapeutic dose level but failed at the supratherapeutic dose level for ΔΔQTcF.

Reviewer's comment: *The reviewer's primary analysis is by-time analysis. Our results are similar to the sponsor's results. Please see section 4.3 for more details.*

3.2.1.1 Assay Sensitivity

Assay sensitivity was established by the moxifloxacin arm. The results of the sponsor's analysis show that the study demonstrated assay sensitivity (lower bound at the geometric mean Cmax is >5 msec).

Reviewer's comment: *Results from FDA reviewer's analysis are similar to the sponsor's results. Please see section 4.3.1.1 for more details.*

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., >480 msec or >60 msec over baseline), HR (>100 beats/min and 25% over baseline), PR (>210 msec and 25% over baseline), and QRS (>120 msec and 25% over baseline).

Reviewer's comment: *Results from FDA reviewer's analysis are similar to the sponsor's results with slightly different cutoffs. Please see section 4.4 for more details.*

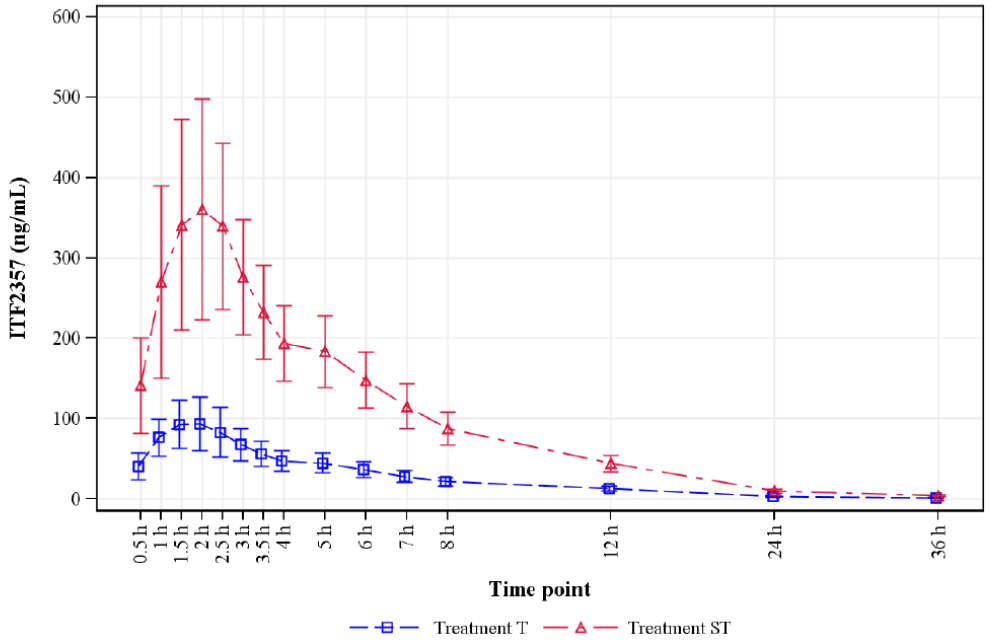
3.2.3 Exposure-Response Analysis

The sponsor used the modeling approach described in the white paper.

The relationship between givinostat plasma concentration and ΔQTcF was quantified using a linear mixed-effects modeling approach. The model included ΔQTcF as the dependent variable, plasma concentration of givinostat as the explanatory variate (0 for placebo), centered baseline QTcF (i.e., baseline QTcF for individual subject minus the population mean baseline QTcF for all subjects within the same treatment period) as an additional covariate, treatment (active = 1 or placebo = 0), time (i.e., nominal post-dose time point) as fixed effects, and random effects on intercept and slope per subject (Garnett et al). The sponsor did not include metabolite concentration in the model.

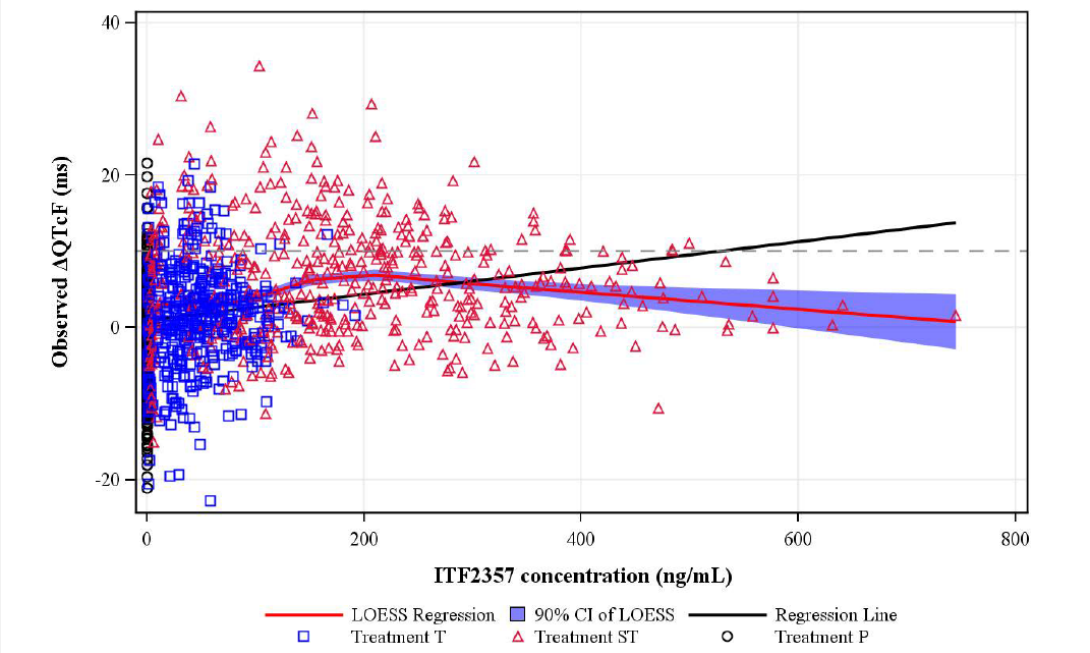
The highest mean plasma concentrations of givinostat were observed at 2 hours post-dose for both doses administered. In the by-time point analysis, mean ΔΔHR exceeded 10 bpm for 300 mg givinostat at several post-baseline time points (Figure 6), thereby demonstrating that this dose has an effect on HR.

Figure 1: Mean givinostat plasma concentrations over time (PK/QTc Population)



The LOESS regression line diverged from the linear regression line across the observed concentrations with the linear regression line also falling outside of the 90% CI of the LOESS line for both the 100 and 300 mg dose of ITF2357, indicating a linear concentration-QTc relationship does not optimally capture the data.

Figure 2: Scatter plot of observed ITF2357 plasma concentrations and ΔQTcF with simple linear regression and LOESS regression (PK/QTc Population).



A delay of 3 hours between peak concentrations of givinostat and the largest QT effects were observed for both the 100 and 300 mg dose of givinostat was observed for ΔΔQTcF.

Figure 3: Joint plot of ITF2357 plasma concentrations and ΔΔQTcF over time (100 mg) (QT/QTc Population, PK/QTc Population)

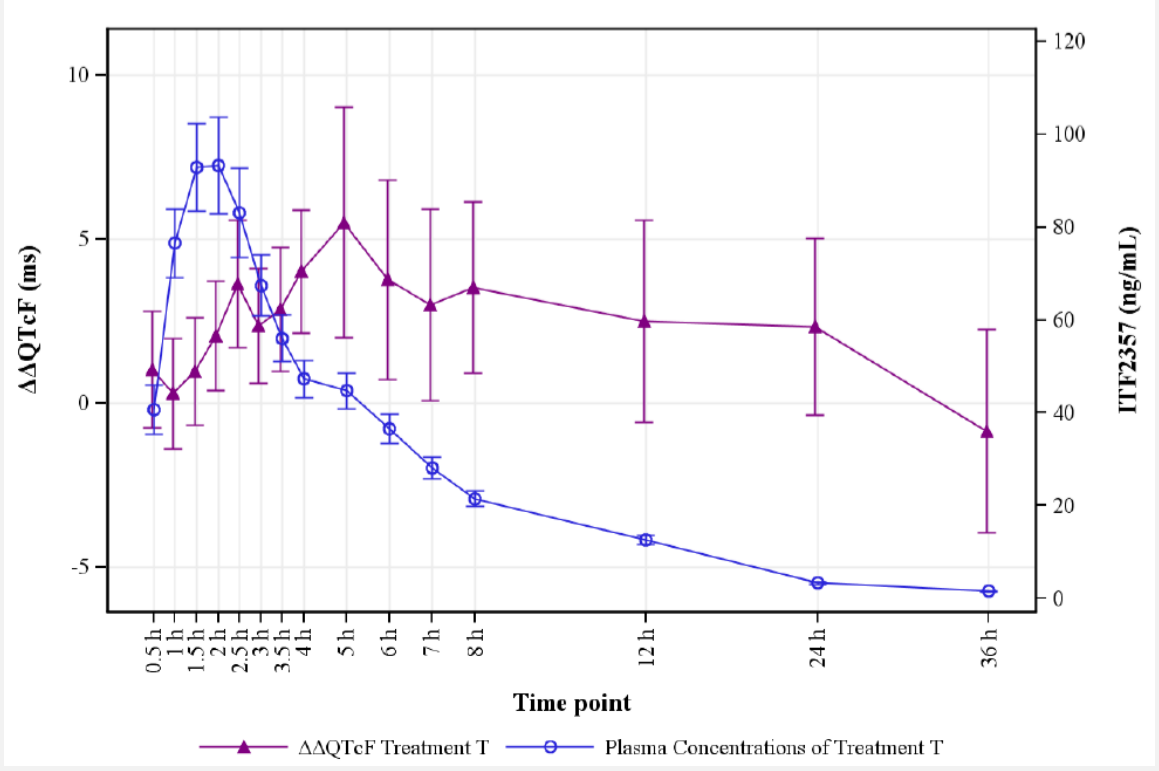
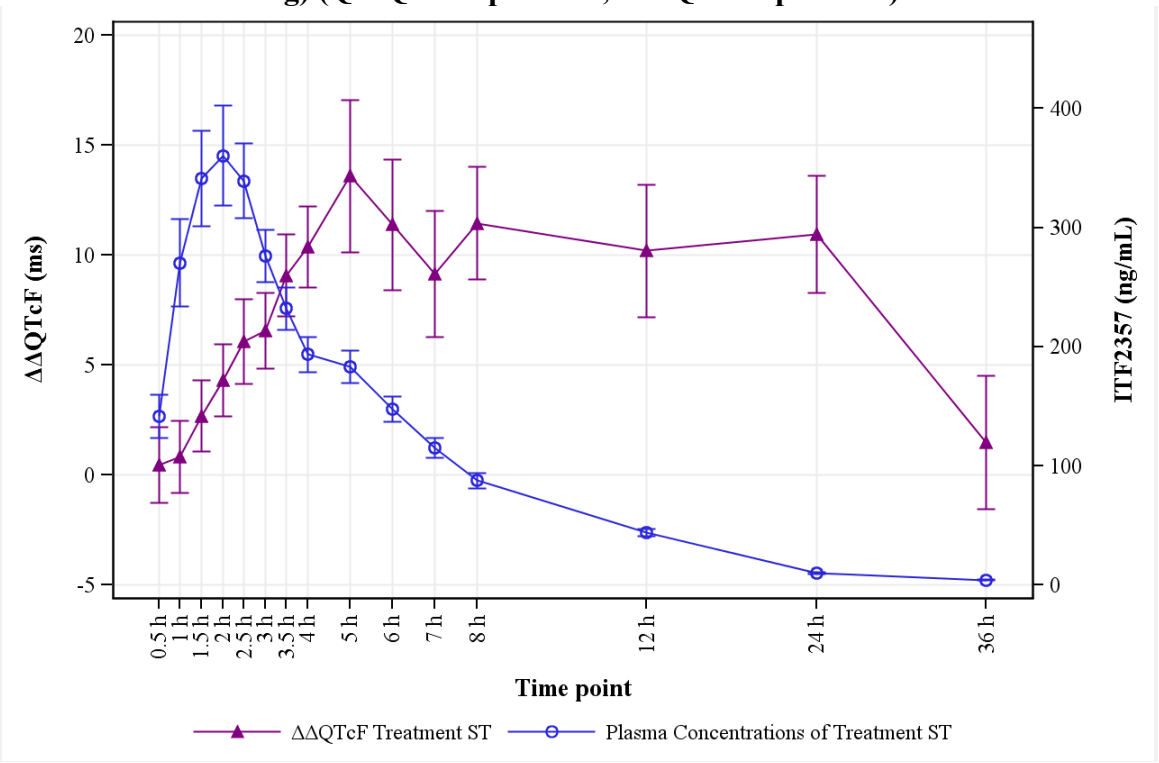


Figure 4: Joint plot of ITF2357 plasma concentrations and ΔΔQTcF over time (300 mg) (QT/QTc Population, PK/QTc Population)



The sponsor concluded:

The concentration-QTc model is however misspecified and should not be used to predict the effect of ITF2357 on the QTc interval. Interpretations of the effect of ITF2357 on the QTc interval should therefore be based on the results from time-point analysis.

Reviewer's comment: *Due to hysteresis, FDA's analysis also supports a By-Time analysis of the QTc data. The sponsor did not model metabolite concentration data to explore a potential mechanism for the hysteresis.*

3.2.4 Safety Analysis

TQT study

There were no deaths, SAEs or AEs leading to discontinuation in the TQT study. There were no AEs identified to be of clinical importance per the ICH E14 guidelines (i.e., seizure, significant ventricular arrhythmias, or sudden cardiac death) in this TQT study.

ISS

The sponsor reports there were no QTc > 500 or change from baseline > 60 msec (see Highlights of clinical pharmacology and cardiac safety table for details).

According to the Summary of TEAE by System Organ Class (SOC) and Preferred Term (PT) for the Standard MeDRA Queries Torsade de Point - QT Prolongation – Seizure only 1 (0.5%) DMD patient treated with givinostat reported 1 TEAE of Loss of

consciousness, and 2 TEAEs of syncope (see ISS, Table 14.3.1.2.2.11). Episodes of ventricular tachycardia or fibrillation: According to datasets, none.

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF for the primary analysis. This is acceptable because (1) the maximum ΔΔHR change it is borderline, i.e., the lower limit is below 10 beats/min for the largest ΔΔHR of 11.6 beats/min at 5 hours postdose with the highest dose of 300 mg BID (Table 6), and (2) the ΔΔHR is elevated but stable from 2.5 through 8 hours postdose (see section 4.3.2).

4.2 ECG ASSESSMENTS

4.2.1 Overall

Digital ECG waveforms were submitted for review. The ECGs were read semi-automatically by a central reader blinded to treatment, study period, time points and subject details. Compared to the ECG warehouse algorithm, we did not observe significant bias in QT measurements and the ECG acquisition and interpretation for this study is therefore acceptable.

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.

The statistical reviewer used a linear mixed model to analyze the drug effect by-time for each biomarker (e.g., ΔQTcF, ΔHR) independently. The default model includes treatment, sequence, period, time (as a categorical variable), and treatment-by-time interaction as fixed effects, and baseline as a covariate. The default model also includes subject as a random effect and an unstructured covariance matrix to explain the associations among repeated measures within the period.

4.3.1 QTc

Figure 5 displays the time profile of ΔΔQTcF for different treatment groups. The maximum ΔΔQTcF values by treatment are shown in Table 4.

Figure 5: Mean and 90% CI of ΔΔQTcF Time-course (unadjusted CIs).

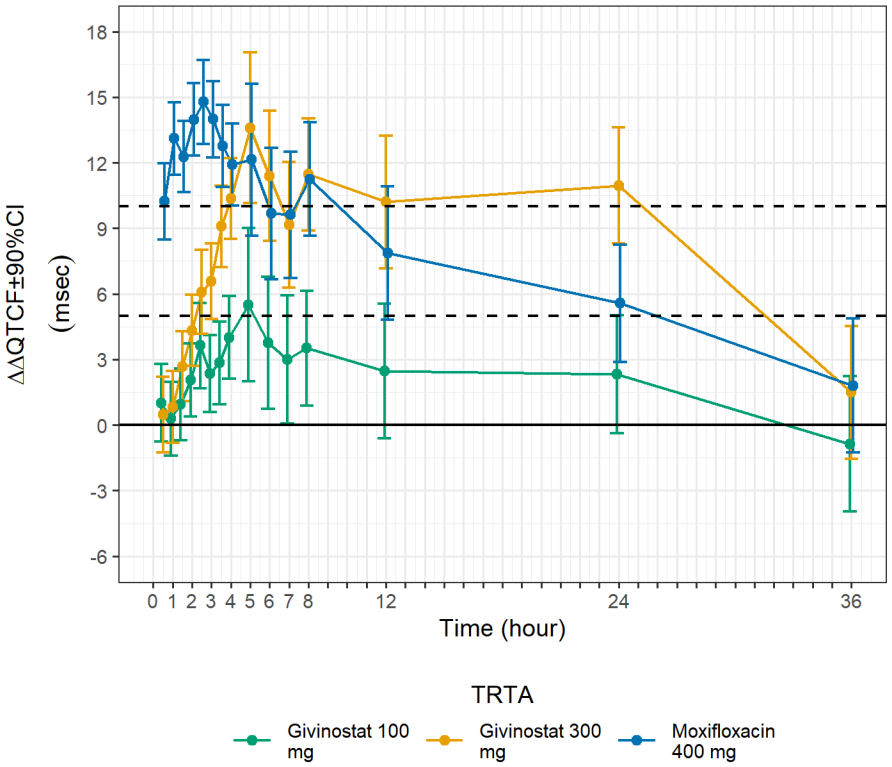


Table 4: Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for ΔΔQTcF

Actual Treatment	Nact / Npbo	Time (hour)	ΔΔQTCF (msec)	90.0% CI (msec)
Givinostat 100 mg	29 / 31	5.0	5.5	(2.0 to 9.0)
Givinostat 300 mg	31 / 31	5.0	13.6	(10.1 to 17.1)

4.3.1.1 Assay Sensitivity

The model used for assay sensitivity is the same as that used for the primary model. The time-course of changes in ΔΔQTcF is shown in Figure 5 and includes the expected time-profile with a mean effect of >5 msec after Bonferroni adjustment for 4 time points (Table 5).

Table 5: The Point Estimates and the 90% CIs Corresponding to the Largest Lower Bounds for ΔΔQTcF

Actual Treatment	Nact / Npbo	Time (hour)	ΔΔQTCF (msec)	90.0% CI (msec)	97.5% CI (msec)
Moxifloxacin 400 mg	30 / 31	2.5	14.8	(12.8 to 16.7)	(12.1 to 17.4)

4.3.2 HR

Figure 6 displays the time profile of ΔΔHR for different treatment groups. The maximum ΔΔHR values by treatment are shown in Table 6.

Figure 6: Mean and 90% CI of ΔΔHR Time-course

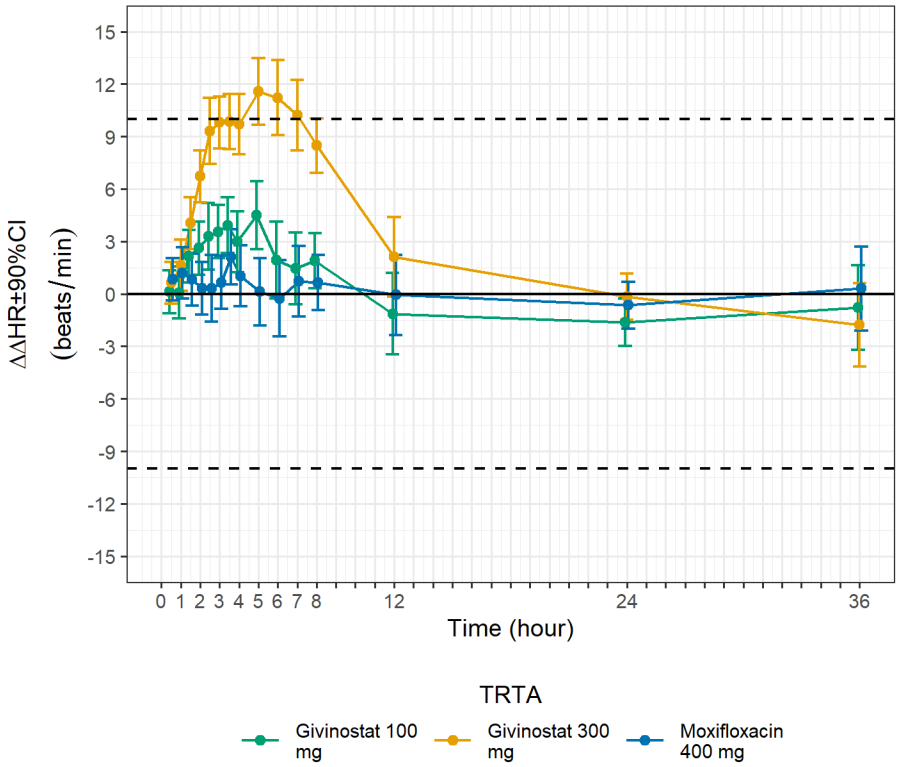


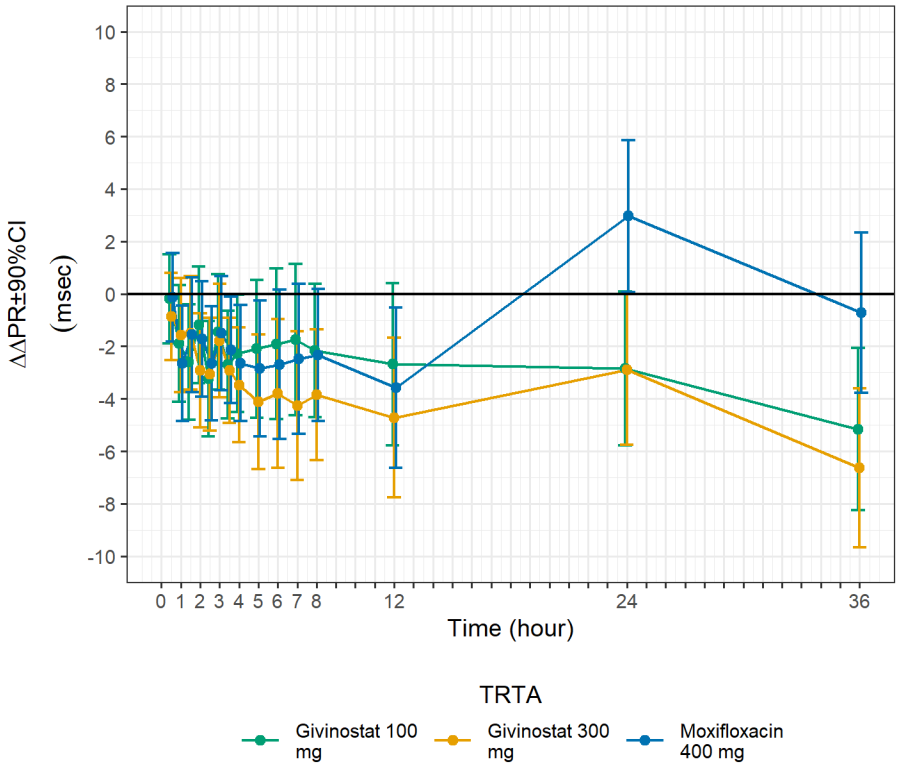
Table 6: Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for ΔΔHR

Actual Treatment	Nact / Npbo	Time (hour)	ΔΔHR (beats/min)	90.0% CI (beats/min)
Givinostat 100 mg	29 / 31	5.0	4.5	(2.6 to 6.5)
Givinostat 300 mg	31 / 31	5.0	11.6	(9.7 to 13.5)

4.3.3 PR

Figure 7 displays the time profile of ΔΔPR for different treatment groups.

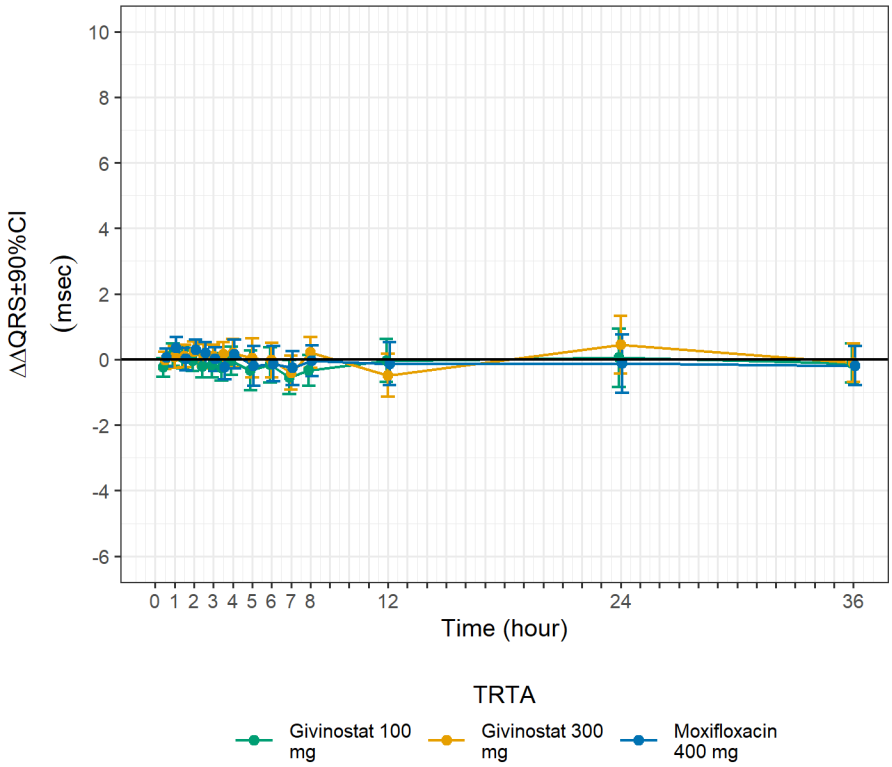
Figure 7: Mean and 90% CI of ΔΔPR Time-course



4.3.4 QRS

Figure 8 displays the time profile of ΔΔQRS for different treatment groups.

Figure 8: Mean and 90% CI of ΔΔQRS 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

There were no subjects who experienced QTcF values of >480 msec or ΔQTcF >60 msec.

4.4.2 HR

There were no subjects who experienced HR values of >100 beats/min.

4.4.3 PR

There were no subjects who experienced PR values of >220 msec.

4.4.4 QRS

There were no subjects who experienced QRS values of >120 msec and 25% increase over baseline.

4.5 EXPOSURE-RESPONSE ANALYSIS

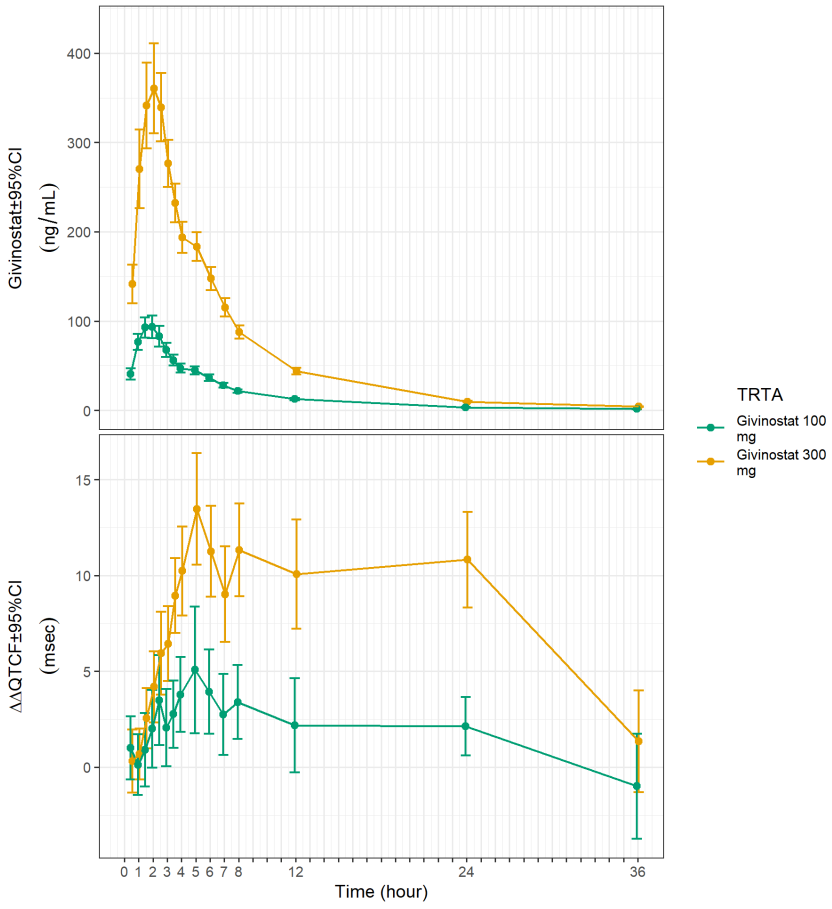
Exposure-response analysis was conducted using all subjects with baseline and at a least one post-baseline ECG, with time-matched PK.

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 need to be 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.

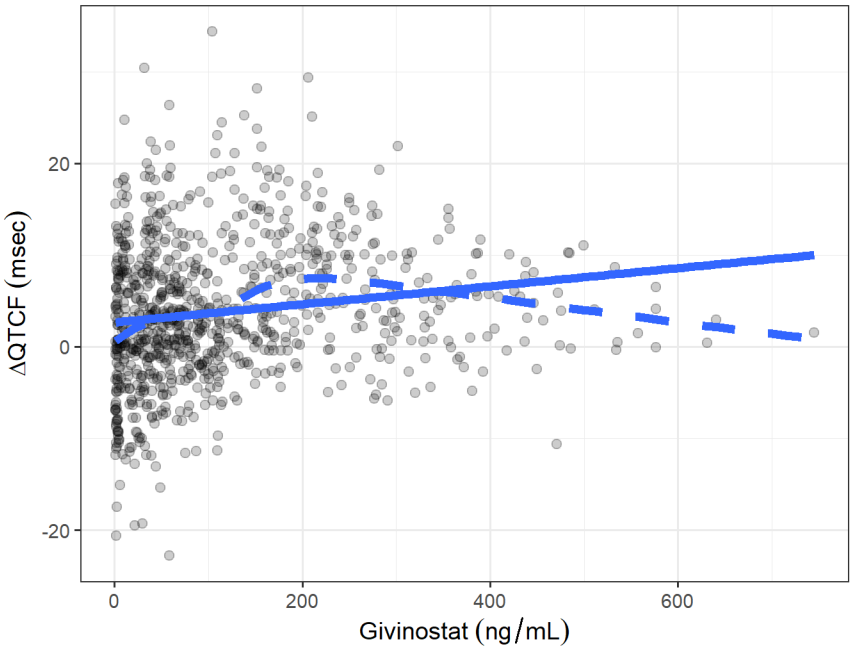
Figure 6 shows the time-course of ΔΔHR, with an absence of significant ΔΔHR changes for the therapeutic dose. However, Figure 9 offers an evaluation of the relationship between time-course of drug concentration and ΔΔQTcF, with the appearance of significant hysteresis. Figure 10 shows the relationship between drug concentration and ΔQTcF and does not support the use of a linear model.

Figure 9: Time-course of Drug Concentration (top) and ΔΔQTcF (bottom)[1]



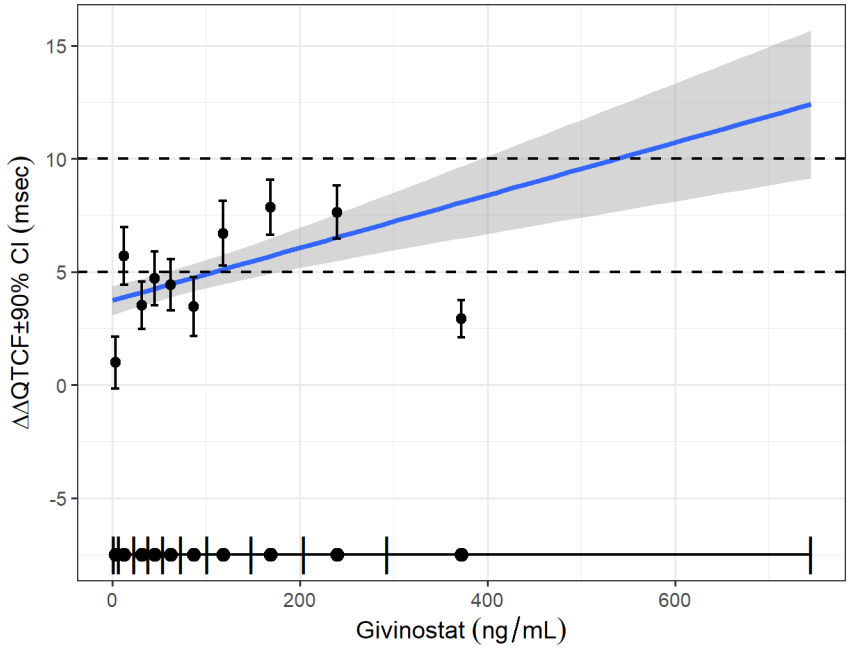
[1] ΔΔQTcF shown were obtained via descriptive statistics and might differ from Figure 1

Figure 10: Assessment of Linearity of the Concentration-ΔQTcF Relationship



Finally, the linear model was applied to the data, and the goodness-of-fit plot is shown in Figure 11. It shows that a linear model does not fit the data adequately.

Figure 11: Goodness-of-fit Plot for QTcF



Reviewer's Comment: Due to the lack of fit of the concentration-QTcF model, the concentration-QTcF estimates should not be used in decision making. A By-Time analysis is more appropriate.

4.5.1.1 Assay Sensitivity

The time course of moxifloxacin concentration and ΔΔQTcF is shown in Figure 12. Assay sensitivity was established using by-time analysis. Please see section 4.3.1.1 for additional details.

Figure 12: Time-course of Moxifloxacin Concentration (top) and QTcF (bottom)

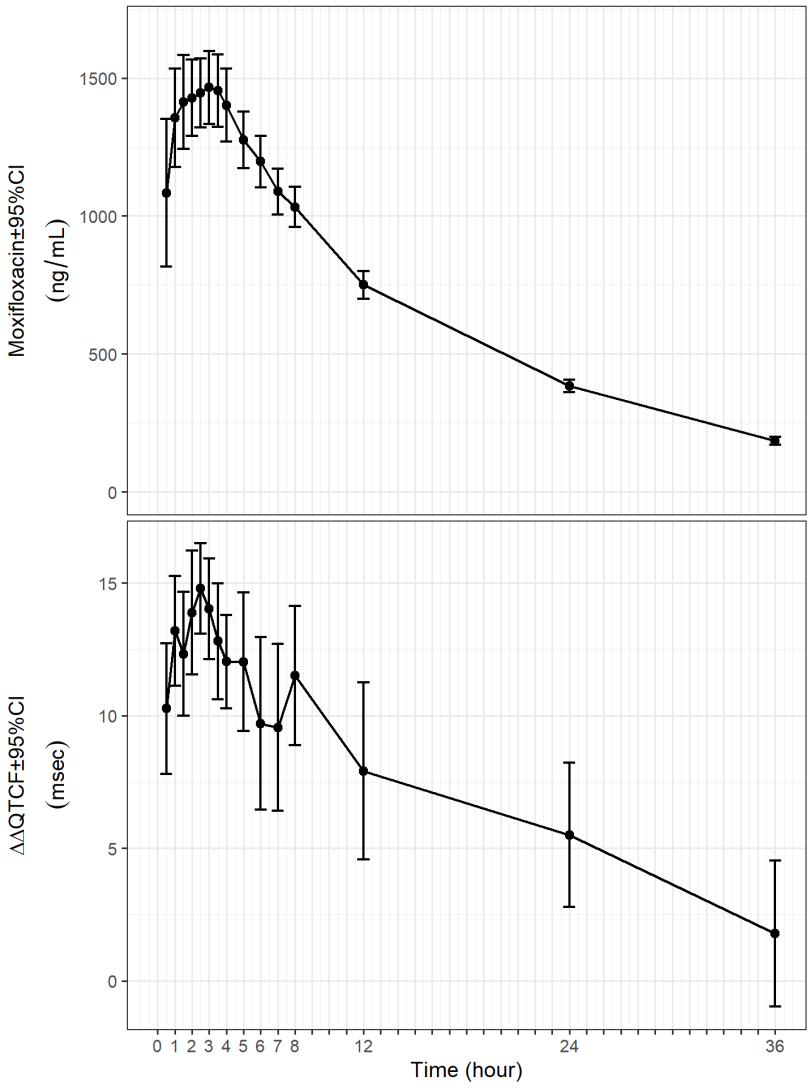


Figure 13: Goodness-of-fit plot of ΔΔQTcF for Moxifloxacin

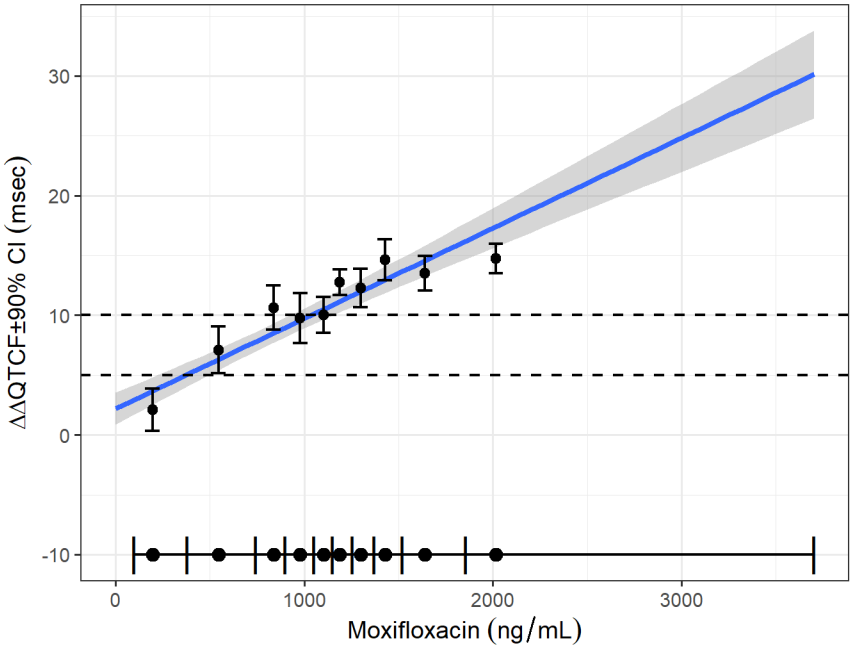


Table 7: Predictions from Concentration-QTcF Model for Moxifloxacin

Actual Treatment	Analysis Nominal Period Day (C)	Moxifloxacin (ng/mL)	ΔΔQTCF (msec)	90.0% CI (msec)
Moxifloxacin 400 mg	1	1,722.5	15.2	(13.8 to 16.6)

4.6 SAFETY ASSESSMENTS

See section 3.2.4. No additional safety analyses were conducted.

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/

LESLIE A KENNA
08/29/2023 09:02:47 AM

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YU-TING WENG
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MICHAEL Y LI
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JOSE VICENTE RUIZ
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