CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213535Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	July 21, 2020
Requesting Office or Division:	Division of Neurology 1 (DN 1)
Application Type and Number:	NDA 213535
Product Name and Strength:	Evrysdi (risdiplam) Oral Solution, 60 mg/80 mL (0.75 mg/mL)
Applicant/Sponsor Name:	Genentech, Inc.
OSE RCM #:	2019-2242-2
DMEPA Safety Evaluator:	Colleen Little, PharmD
DMEPA Team Leader:	Lolita White, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted the revised container label, carton labeling, Instructions for Use (IFU), and Instructions for Constitution (IFC), on July 14, 2020 for Evrysdi. Division of Neurology 1 (DN 1) requested that we review the revised IFU, IFC, container label, and carton labeling for Evrysdi (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

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

[a] Little, C. Label and Labeling Review Memo for Evrysdi (NDA 213535). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 JUL 01. RCM No.: 2019-2242-1.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON JULY 14, 2020

Container labels

(b) (4)

Carton labeling

Instructions for Constitution can be accessible in EDR via:
\\cdsesub1\evsprod\nda213535\0034\m1\us\instructions-for-constitution-redline.docx

Instructions for Use can be accessible in EDR via:
\\cdsesub1\evsprod\nda213535\0034\m1\us\instructions-for-use-redline.docx

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/s/

COLLEEN L LITTLE
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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: July 21, 2020

To: Rainer Paine, M.D.
Division of Neurology 1 (DN1)

Brenda Reggettz, Regulatory Project Manager, (DNP)

Tracy Peters, PharmD, Associate Director for Labeling, (DNP)

From: Sapna Shah, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

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

Subject: OPDP Labeling Comments for EVRYSDI™ (risdiplam) powder, for oral solution

NDA: 213535

In response to the DN1 consult request dated December 11, 2019, OPDP has reviewed the proposed product labeling (PI), Medication Guide, and carton and container labeling for the original NDA submission for EVRYSDI™ (risdiplam) powder, for oral solution (Evrysdi).

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DN1 (Brenda Reggettz) on July 16, 2020 and are provided below.

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

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on June 26, 2020 and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Sapna Shah at (240) 402-6068 or Sapna.Shah@fda.hhs.gov.

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SAPNA P SHAH
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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:	July 14, 2020
To:	Brenda Reggettz, PharmD Senior Regulatory Project Manager **Division of Neurology I**
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 Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
	Sapna Shah, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI), and Instructions for Use (IFU)
Drug Name (established name):	EVRYSDI (risdiplam)
Dosage Form and Route:	for oral solution
Application Type/Number:	NDA 213535
Applicant:	Genentech, Inc.

1 INTRODUCTION

On September 24, 2019, Genentech, Inc., submitted for the Agency's review an original New Drug Application (NDA)/New Molecular Entity 213535 for EVRYSDI (risdiplam), for oral solution. EVRYSDI (risdiplam) is indicated for the treatment of spinal muscular atrophy [redacted] (b) (4)

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Neurology I on December 11, 2019, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for EVRYSDI (risdiplam), for oral solution.

2 MATERIAL REVIEWED

- Draft EVRYSDI (risdiplam) PPI and IFU received on September 24, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on June 30, 2020.
- Draft EVRYSDI (risdiplam) Prescribing Information (PI) received on September 24, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on June 30, 2020.

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 PPI and IFU we:

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

4 CONCLUSIONS

The PPI and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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/s/

KELLY D JACKSON
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SAPNA P SHAH
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MARCIA B WILLIAMS
07/14/2020 12:55:55 PM

LASHAWN M GRIFFITHS
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HUMAN FACTORS STUDY REPORT AND LABELS AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	June 11, 2020
Requesting Office or Division:	Division of Neurology 1 (DN1)
Application Type and Number:	NDA 213535
Product Type:	Combination Product
Drug Constituent Name and Strength	Evrysdi (risdiplam) for Oral Solution, 60 mg/80 mL (0.75 mg/mL)
Device Constituent:	Oral Syringe
Rx or OTC:	Rx
Applicant/Sponsor Name:	Genentech, Inc. (Genentech)
Submission Date:	September 5, 2019, November 29, 2019, April 3,2020, April 24, 2020, May 8, 2020
OSE RCM #:	2019-2012-1, 2019-2242
DMEPA Safety Evaluator:	Colleen Little, PharmD
DMEPA Team Leader:	Lolita White, PharmD
DMEPA Associate/Deputy Director:	Danielle Harris, PharmD

1. REASON FOR REVIEW

This review evaluates the human factors (HF) validation study report and labels and labeling submitted under NDA 213535 for Evrysdi (risdiplam). This is a combination product with a proposed oral syringe device constituent part that is intended to treat spinal muscular atrophy (SMA).

1.1. PRODUCT DESCRIPTION

Evrysdi for oral solution will be co-packaged with one amber bottle, one bottle adapter, two 6 mL oral syringes, two 12 mL oral syringes. The proposed product is supplied as powder that must be reconstituted by a pharmacist to 0.75 mg/mL. Prior to dispensing the reconstituted oral solution, the pharmacist must select the correct oral syringe (6 mL or 12 mL) based on the prescribed daily dose volume (see Appendix A).

1.2. REGULATORY HISTORY RELATED TO THE PROPOSED PRODUCT'S HUMAN FACTORS DEVELOPMENT PROGRAM

On July 30, 2018, Genentech submitted an HF validation study protocol and draft Instructions for Use (IFU) under IND 128972. Our review determined the testing conditions and user groups were not representative of actual use and the protocol required revisions to ensure that adequate data regarding the safe and effective use of this product is collected. In addition, we identified several areas of the product user interface which could be further optimized.[a] We communicated our recommendations to Genentech in an HF Validation Study Protocol Advice letter dated November 30, 2018.

In response to our recommendations, Genentech submitted a revised HF validation study protocol, revised IFUs, and a revised use-related risk analysis on February 6, 2019 under IND 128972. Our review of the revised HF validation study protocol and draft IFUs identified additional areas of concern with the methodology as well as the proposed user interface.[b] On April 16, 2019, we issued an HF Validation Study Protocol Advice letter to Genentech[c], in which we conveyed our concern that users (i.e., patients,

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[a] Whaley, E. Human Factors Protocol Review for Risdiplam (IND 128972). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 NOV 2. RCM No.: 2018-1678.

[b] Whaley, E. Human Factors Protocol Review for Risdiplam (IND 128972). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 APR 11. RCM No.: 2018-1678-1.

[c] Chan, I. Human Factors Validation Study Protocol- Advice for IND 128972. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 APR 19.

caregivers, etc.) may have difficulty determining which syringe to use to measure and administer the intended dose. Thus, we provided a recommendation for Genentech to consider removing the co-packaged oral syringes from the proposed product and instead allow for the use of a commercial oral dosing device for the dosing and administration of the product. We also advised Genentech that if they choose not to co-package their proposed product with oral syringes, they may not need to submit the results HF validation testing data to support their marketing application.

On September 17, 2019, Genentech submitted the HF validation study report under NDA 213535. During the course of our review, we identified that Genentech did not implement our recommendation to remove the co-packaged oral syringes from the proposed product packaging. We also identified several use errors for the "select appropriate syringe size" task in the patient, caregiver, and healthcare provider (HCP) user groups in the HF validation study. We determined that Genentech did not provide sufficient data to conclude that the design of the user interface supports safe and effective use of the product by intended users for the intended use environment. Thus, on March 25, 2020, we issued an Information Request (IR), which requested Genentech to address the use errors related to the oral syringe selection and dose measurement tasks by either removing the co-packaged oral syringes or implementing additional risk mitigations and submit the results of a new HF validation study to demonstrate the effectiveness of the additional risk mitigations.[d]

In response to our March 25, 2020 IR, Genentech proposed to modify the user interface to instruct the pharmacist to select and dispense the appropriate oral syringe size instead of implementing any of the recommendations provided in the March 25, 2020 IR.[e] We determined Genentech's proposal to be acceptable. Thus, on April 6, 2020, we issued an additional IR informing Genentech that the proposed modification to the oral syringe selection task can be implemented without additional HF validation testing.[f]

On April 24, 2020, Genentech submitted revised carton labeling, Instructions for Constitution (IFC), Instructions for Use (IFU), Prescribing Information (PI) and Patient Information in response to the April 6, 2020 IR.

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[d] Little, C. Human Factors Validation Results Review Memo for Evrysdi (NDA 213535). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 MAR 25. RCM No.: 2019-2012.

[e] Human Factors Response to Information Request for Evrysdi NDA 213535. San Francisco (CA): Genentech, Inc.; 2020 MAR 30. Available from: \\cdsesub1\evsprod\nda213535\0025\m1\us\response.pdf.

[f] Reggettz, B. NDA 213535: Human Factors Information Request. Silver Spring (MD): FDA, CDER, ORO, DRON, DN1 (US); 2020 APR 06.

2. MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide our findings and evaluation of each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	**Appendix Section (for Methods and Results)**
Product Information/Prescribing Information	A
Background Information Previous HF Reviews (DMEPA and CDRH)	B
Background Information on Human Factors Engineering (HFE) Process	C
Human Factors Validation Study Report	D
Information Requests Issued During the Review	E
Labels and Labeling	F

3. OVERALL ASSESSMENT OF MATERIALS REVIEWED

The sections below provide a summary of the study design, errors/close calls/use difficulties observed (Table 2), and our analysis to determine if the results support the safe and effective use of the proposed product.

3.1 SUMMARY OF STUDY DESIGN

The HF validation study included 15 pharmacists, 15 caregivers, 15 SMA patients, and 15 healthcare providers (HCP). Genentech clarified that adolescent patients who self-administer were not included as part of the intended user population for their HF validation study because adolescent SMA patients are expected to present with severe symptoms and thus are not expected to self-administer. We agreed with Genentech and found the exclusion of SMA adolescent patients from the HF validation study acceptable. The participants in the pharmacist user group completed a knowledge-based task assessment (no simulated-use) to evaluate the constitution process. Study participants in the caregiver, patient, and HCP user groups completed a simulated-use scenario to assess the oral administration process and a knowledge-based task assessment to evaluate the enteral administration process and to further evaluate the oral administration process.

We acknowledge that Genentech evaluated two different product strengths (0.75 mg/mL and 0.25 mg/mL) in the submitted HF validation study but only currently seeks approval for

the 0.75 mg/mL strength. Genentech states that the HF performance data for the 0.25 mg/mL strength can be leveraged to support the 0.75 mg/mL strength because the reconstitution and administration tasks for both strengths are identical. For example, participants must choose between an oral syringe with 0.1 mL incremental markings or an oral syringe with 0.2 mL incremental markings for either strengths. While we acknowledge that all participants did not interact with the intend to market product (i.e., 0.75 mg strength); we agree with Genentech's assessment and determined that this methodology is acceptable in this instance because the use tasks evaluated are identical across both strengths. Thus, we considered the HF performance data for both strengths in our analyses below.

We note that the HF validation study defines successful user performance for measuring the correct dose volume as "user is able to align the plunger to a graduation mark within +/- 20% tolerance". Genentech provided the following justification to support this success criteria: "Acceptable dose tolerance of +/- 20% was defined by clinical science representative. Based on the actual PK data observed in SMA patients at the therapeutic dose, a dose tolerance of +/-20% for oral dosing is deemed acceptable."

We sought input from the clinical team to help determine the acceptability of Genentech's justification regarding the +/- 20% dose tolerance range. The clinical team stated that Genentech's justification for the dose tolerance range was acceptable. Thus, we align with Genentech's success criteria, "User is able to align the plunger to a graduation mark within +/- 20% tolerance" in the HF validation study as acceptable user performance.

We acknowledge that the HF validation study tested the oral syringe selection task in the simulated-use scenario in the caregiver, patient, and HCP user groups and that subsequently, the proposed user interface was modified to instruct the pharmacist to select and dispense the appropriate oral syringe size. Based on other currently marketed products, we expect that pharmacists are likely to be familiar with selecting and dispensing the appropriate oral syringe based on the prescribed dose. We find that this syringe selection task does not introduce any new or unique risk in the intended user group (i.e., pharmacists). Thus, we determined that this modification could be implemented without additional HF testing.

3.2 RESULTS AND ANALYSES

Table 2 describes the study results, Applicant's analyses of the results, and DMEPA's analyses and recommendations.

Table 2: Discussion of Identified Issues and Recommendations		
	Discussion of Identified Issue	**DMEPA's Analysis and Recommendations**
1.	For the pharmacist only knowledge assessment questions to assess tasks associated with calculating the "discard after" date, there were 10 use errors (6 failures, 1 close call, and 3 use difficulties). For example, three participants were completely unable to locate the warning statement, "do not (b) (4) the (b) (4) constituted solution (b) (4) exceeds the original powder (b) (4) date" in the IFC. (b) (4) The subjective data and Genentech's root cause analysis indicated that: • The location and wording of the warning statement, "do not (b) (4) the (b) (4) constituted solution (b) (4) exceeds the original powder (b) (4) date" was unclear and lacks prominence. Genentech has revised the aforementioned warning statement in the IFC to "Do not dispense the constituted solution if the solution's Discard After date exceeds the original powder expiration date" as an additional mitigation to address these use issues. However, we find this mitigation does not address the use errors related to participants being unable to locate the warning statement.	Based on the URRA, if this task is omitted or not performed correctly there is risk of toxicity inducing significant harm (e.g., drug-induced liver injury, cancer, anaphylaxis). Thus, we are concerned with the residual risks for errors associated with calculating the "discard after" date. We sought input from the Office of Pharmaceutical Quality (OPQ) regarding Genentech's assertion that the use of the reconstituted oral solution within 64 days after the powder expiration date does not pose a risk to patients. OPQ informed us that the reconstituted oral solution has been shown to remain stable for 64 days when stored under refrigerated conditions and any unused portion should be discarded after 64 days. Therefore, we disagree with Genentech's assertion (b) (4) We agree with Genentech's root cause analysis that the location of the warning statement regarding the "discard after" date may be unclear and could be more prominently displayed. Our review of the study results identified subjective feedback that indicated the presentation of the instructions related to the discard after date could be improved for clarity. One participant suggested that the discard after date warning statement should be relocated to step 7 for relevancy. Our review of the IFC finds the presentation of the instructions regarding the discard date can be improved. For example, the

Table 2: Discussion of Identified Issues and Recommendations		
	Discussion of Identified Issue	**DMEPA's Analysis and Recommendations**
		instructions for how to calculate the "discard after" date are provided in step 7 on page 13; however, the warning statement regarding the "discard after date" is located on page 4 of the IFC. Based on our overall assessment, we find the user interface can be improved. **We provide recommendation #7 in Table 4 to address this concern**. We have determined that this change can be implemented without additional HF validation testing to be submitted for review.
2.	For the pharmacist only knowledge assessment question, "Now that you have calculated the expiry date, what would you do with this information", there were 15 use errors (2 failures, 7 close calls, and 6 use difficulties). For example, two participants were completely unable to locate the instruction to remove the detachable portion of the container label that includes the powder expiration date in the IFC. The subjective data and Genentech's root cause analysis indicated that: • The location of the instruction to remove the detachable portion of the container label in the IFU and on the container label was unclear. • Figure H in the IFC does not accurately represent the product. • The adhesive on the container label does not allow for easy removal of the detachable portion.	Based on Genentech's URRA, if this task is omitted or not performed correctly there is risk of toxicity inducing significant harm (e.g., drug-induced liver injury, cancer, anaphylaxis). Thus, we are concerned with the residual risks for this error. We agree with Genentech's root cause analysis that the IFC and detachable portion of the container label may be unclear in terms of instructing users to write the calculated "discard after date" and lot number before removing the detachable portion of the container label. Our review of the labels and labeling finds that the instructions related to the detachable portion of the container label in the IFC and on the container label can be further improved to mitigate errors. **We provide recommendations #8, 9, and 16 in Table 4 to address this concern.** We have determined that these changes can be implemented without additional validation testing to be submitted for review. Our review of the study results identified subjective feedback

Table 2: Discussion of Identified Issues and Recommendations		
	Discussion of Identified Issue	**DMEPA's Analysis and Recommendations**
	Genentech has revised the container label to include the statement , "Write the Discard After Date and lot number on the bottle label" as an additional mitigation to address these use issues. However, we find this mitigation does not adequately address the use errors related to the location of the instructions to write the calculated "discard after" date and lot number and the removal of the detachable portion of the container label.	that indicated participants had difficulty removing the detachable portion of the container label. However, our heuristic review of the intend-to-market product samples submitted under this NDA determined that the user interface has been modified to allow for easier removal of the detachable portion of the container label. Thus, we do not have recommendations related to the physical removal of the detachable portion of the container label.
3.	For the pharmacist only knowledge assessment question to assess the "place the carton in the appropriate storage conditions" task, there were 2 use errors (1 close call and 1 use difficulty). For example, one participant had difficulty locating the post-reconstitution storage information. For the non-pharmacist knowledge assessment question to assess comprehension of the storage statement, there were 9 use errors (6 close calls, and 3 use difficulties). For example, one participant (n=1 nurse) was initially unable to locate the storage conditions. The subjective data and Genentech's root cause analysis indicated that: • The storage information provided throughout labels and labeling is inconsistent. Genentech has revised the container label to include the statement , "Write the Discard After Date and lot number on the bottle label" as an additional mitigation to address these use issues. However, we find this mitigation does not	Based on Genentech's URRA, if the proposed product is not stored correctly there is risk of toxicity inducing significant harm (e.g., drug-induced liver injury, cancer, anaphylaxis). Thus, we are concerned with the residual risks for this error. We agree with Genentech's root cause analysis that the storage information provided on the container label, carton labeling, IFC, and IFU is inconsistent. Our heuristic review of the user interface identified that the storage statement for the reconstituted oral solution in the IFC instructs pharmacists to store the "carton upright"; whereas, the carton labeling does not state that the constituted oral solution should be stored in the carton. Thus, we find that the user interface can be further improved to mitigate storage errors and **we provide recommendations #1 and 14 in table 4 to address this concern**. We have determined that these changes can be implemented without additional validation testing to be submitted for review.

Table 2: Discussion of Identified Issues and Recommendations		
	Discussion of Identified Issue	**DMEPA's Analysis and Recommendations**
	adequately address the use errors regarding confusion related to the presentation of the storage information.	
4.	For the "check the in-use date on the bottle label" task, there were 112 use errors (72 failures, 21 close calls, 19 use difficulties). For example, nine participants (n = 1 experienced caregiver, n=3 naïve caregivers, n=4 patients, n=1 nurse) were completely unable to locate the statement, "do not use (b) (4) in the IFU. The subjective data and Genentech's root cause analysis indicated that: • The instruction to check the "discard after" date is not included in the step-by-step instructions. • The user interface does not explain the difference between the powder and "discard after" date which caused confusion. • The location of the discard information within the IFU was unclear. • The handwritten "discard after" date was illegible. • The term "(b) (4)" is not commonly used in the US. • The statement "discard any unused portion 64 days after (b) (4) constitution" on carton labeling was unclear. • Elements of study artifact attributed to 8 errors. For example, one participant was given a bottle without a handwritten "discard after" date.	Based on Genentech's URRA, if this task is omitted or not performed correctly there is risk of toxicity inducing significant harm (e.g., drug-induced liver injury, cancer, anaphylaxis). Thus, we are concerned with the residual risks for this error. We disagree with Genentech's root cause analysis that the "discard any unused portion…" statement attributed to 3 failures, 3 close calls and 1 use difficulty. Our review of the subjective data did not identify any participant feedback indicating the "discard any unused portion…" statement on carton labeling caused confusion or led to use errors in the HF study. Our review of the study results identified subjective feedback that indicated all information related to the expiration date should be included on carton labeling. We also identified subjective feedback that indicated participants had difficulty understanding the difference between the "discard after" date on the container label and the powder expiration date on carton labeling. For example, one participant attributed the different expiration dates ("discard after" date vs. powder expiration date) to "doctor error" or use of an "incorrect box." Additionally, several participants indicated that they expected to find information regarding the "discard after" date in the "How to store…" section on page 8 in the IFU. Our review of the user interface finds that the proposed carton labeling does not inform users when to discard the oral solution. Additionally, the proposed container label provides the "discard

Table 2: Discussion of Identified Issues and Recommendations		
	Discussion of Identified Issue	**DMEPA's Analysis and Recommendations**
	Genentech has revised the format of the "discard after" date on the container label as an additional mitigation to address these use issues. However, we find this mitigation does not address the use errors related to users not being able to locate information related to the "discard after" date.	after date" but does not inform users to discard any unused portion 64 days after constitution. Our review of the IFU finds that the warning statement, "Do not use…after the discard after date written on the bottle" is located on page 5 under the "Important Information" section; whereas, other storage information is located on page 8. Based on our overall assessment, we find that the user interface can be further improved to mitigate errors and **we provide recommendations #1, 15, and 17 in Table 4 to address this concern**. We have determined that these changes can be implemented without additional validation testing to be submitted for review.

3.4 ANALYSIS OF OTHER CRITICAL AND ESSENTIAL TASK ERRORS

The HF validation study showed use errors, (e.g. failures, difficulties, and close calls) with the eight critical tasks listed below, however our assessment of these use errors finds the residual risk is acceptable and thus are not the focus of this review. We reviewed the available participants' subjective feedback, the Applicant's root cause analysis, and Applicant's proposed risk mitigation strategy to determine acceptability. In addition, we compared the use tasks of the proposed product with the same use tasks in an already marketed product with same or similar user groups to determine if there are any current concerns of vulnerability to use error. Subsequently, our assessment of the aforementioned considerations in totality finds the residual risk is acceptable for the use tasks below; thus, we find no mitigations are necessary at this time to address the use errors related to the following use tasks:

- Check correct drug product/strength
- Measure the required volume of purified water
- Select the appropriate oral syringe
- Press the plunger down completely towards the tip of the syringe
- Close the child resistant cap
- Ensure patient is upright
- Aim the dispenser at the cheek

3.4. LABELS AND LABELING

Tables 3 and 4 below include the identified medication error issues with the submitted packaging, label and labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 3: Identified Issues and Recommendations for Division of Neurology 1			
	Identified Issue	**Rationale for Concern**	**Recommendation**
Full Prescribing Information- Section 2 Dosage and Administration			
1.	Table 1 and Table 2 includes trailing zeros.	Trailing zeros have led to ten-fold overdoses.	Remove the trailing zeros in these tables (e.g. change 1.0 mL to 1 mL).
2.	Table 1 includes the error prone symbols "<" and "≥".[g]	These error prone symbols have been misinterpreted and used as opposite of intended.	Consider replacing the symbols "<" and "≥" with their intended meanings to prevent misinterpretation and confusion.
3.	Table 2 includes (b) (4) in the dose strength column; however, section (b) (4) states the net quantity is 80 mL.	We are concerned that misinterpretation of (b) (4) as the net quantity statement may lead to confusion.	Remove (b) (4) from the "Dose Strength" column in Table 2.
Full Prescribing Information- Section 16 How Supplied/Storage and Handling			
1.	The Instructions for Constitution (IFC) includes the number and size (mL) of the co-packaged oral syringes provided in each carton; however, Section 16.1 How Supplied does not include this information.	We are concerned that inconsistent descriptions of the user interface may lead to confusion and may result in wrong dose errors if the pharmacist dispenses the wrong size oral syringe due to	Consider listing number and size in mL of the co-packaged oral syringes provided in each carton.

[g] ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2015 [cited 2019 FEB 13]. Available from: http://www.ismp.org/tools/errorproneabbreviations.pdf.

Table 3: Identified Issues and Recommendations for Division of Neurology 1			
	Identified Issue	**Rationale for Concern**	**Recommendation**
		lack of clarity regarding the number and size of oral syringes that are provided in each carton.	

Table 4: Identified Issues and Recommendations for Genentech, Inc. (entire table to be conveyed to Applicant)			
	Identified Issue	**Rationale for Concern**	**Recommendation**
General (Instructions for Constitution (IFC), Instructions for Use (IFU), Carton Labeling, Prescribing Information)			
1.	The subjective feedback and your root cause analysis indicated that the storage information could be improved to provide the same storage information throughout labels and labeling. For example, the presentation of storage information in (b) (4) however, this information is not present on the carton labeling or in the "How to store…" section of the IFC and IFU.	1. We are concerned that the storage information as presented throughout labels and labeling may lead to confusion and degraded drug medication error. 2. We note that your root cause analysis indicates the "discard any unused portion…" statement attributed to 3 failures, 3 close calls and 1 use difficulty. However, our independent review of the subjective data did not identify any participant feedback indicating the	1. Revise the storage information on the container label, carton labeling, IFC (including storage information provided in the "Selecting the Oral Syringe..." section), IFU, and PI (section 2 and section 16) to include all aspects storage for your proposed product (e.g., protect from light, do not freeze, store in carton, etc.). 2. Revise the storage statement for the reconstituted oral solution to include the statement, "Discard any unused portion 64 days after reconstitution." on the carton label, container labeling, IFC, IFU, (b) (4)

Table 4: Identified Issues and Recommendations for Genentech, Inc. (entire table to be conveyed to Applicant)			
	Identified Issue	**Rationale for Concern**	**Recommendation**
		"discard any unused portion…" statement on carton labeling caused confusion or led to use errors in the HF study.	
3.	Your user interface contains inconsistent terminology throughout labels and labeling. For example (note the examples provided are not all inclusive): • Section 2.1 of the PI includes the term "re-usable oral syringe"; whereas, carton labeling includes the term "oral syringe" and the IFC includes the term. • Carton labeling states (b) (4) (b) (4) hereas, the IFC states, (b) (4)	We are concerned that inconsistent terminology may contribute to confusion which may lead to medication error. Additionally, in this instance, use of the term (b) (4) in the storage statements is ambiguous and may contribute to confusion because the term (b) (4)" can be interpreted to mean (b) (4)	1. Ensure all terminology is consistent throughout labels and labeling. 2. Remove the word (b) (4) from the storage statements in labels and labeling.
Instructions for Constitution (IFC)			
4.	The important warning statement, (b) (4) is in section 2.3 in the PI; however, this	We are concerned that this important warning statement may be overlooked and result in wrong technique error, which may lead to user harm.	Include the statement, (b) (4) in the "Important Information" section within the IFC.

Table 4: Identified Issues and Recommendations for Genentech, Inc. (entire table to be conveyed to Applicant)			
	Identified Issue	**Rationale for Concern**	**Recommendation**
	important warning statement is not included in the IFC.		
5.	Your proposed IFC and PI provide inconsistent information regarding the equipment that is required to reconstitute your proposed product. For example, you propose to remove the following statement from the PI, (b) (4) [redacted] However, you propose to include the following statement in the IFC, (b) (4) [redacted]	We are concerned that this statement may cause confusion and lead to wrong technique errors. The meaning of the ter (b) (4) [redacted]	Clarify the (b) (4) [redacted] that is required to reconstitute your proposed product.
6.	In your HF validation study, we identified subjective feedback demonstrating that some participants had difficulty locating important preparation precautions (e.g., use gloves) within the IFC. Our review of the IFC and subjective feedback finds that the broad header "Important Information…" may not convey that the section includes information regarding how users should prepare for constitution.	We are concerned users may overlook the precautionary statements regarding the preparation process, which may lead to wrong technique error.	Revise the IFC to include an additional section that includes important preparation precautionary statements. Ensure that the title of this new section is prominent and clear and specific to inform the reader this section includes information regarding how users should prepare for constitution.
7.	In your HF validation study, some	We are concerned that the location of	Relocate or repeat the warning statement,

Table 4: Identified Issues and Recommendations for Genentech, Inc. (entire table to be conveyed to Applicant)			
	Identified Issue	**Rationale for Concern**	**Recommendation**
	participants had difficulty comprehending and locating the warning statement, "Do not dispense the constituted solution if the solution's Discard After date exceeds the original powder expiration date" in the "Important Information" section of the IFC. For example, one participant suggested that the warning statement should be relocated to step 7 for relevancy. We acknowledge that you have revised the aforementioned warning statement in the IFC to "Do not dispense the constituted solution if the solution's Discard After date exceeds the original powder expiration date" to minimize confusion. However, this mitigation does not address the use errors related to participants being unable to locate the warning statement.	the warning statement regarding the "discard after" date may not be obvious to intended users.	"Do not dispense the constituted solution if the solution's Discard After date exceeds the original powder expiration date." to appear with step 7 in the IFC.
8.	Figure H does not accurately depict your proposed product. Specifically, Figure H does not clearly represent the location of the discard date information because it gives the impression that the "discard after"	We are concerned this graphic as presented suggests there may be additional information beneath the detachable portion of the container label which may cause confusion and lead to deteriorated drug error.	Revise Figure H to be representative of the intend-to-market product. Additionally, ensure that Figure H depicts the location of the handwritten "discard after" date.

Table 4: Identified Issues and Recommendations for Genentech, Inc. (entire table to be conveyed to Applicant)			
	Identified Issue	**Rationale for Concern**	**Recommendation**
	date is written beneath the detachable portion of the container label.		
9.	Based on our review of the subjective feedback and root cause analysis, the order of use steps in your IFC may lead to confusion. Specifically, it is unclear how users will be able to transcribe the lot number found on the detachable portion of the container label (step 7) because the previous step (step 6) instructs users to discard the detachable portion of the container label.	We are concerned that users will not be able to document this important product information as intended.	Revise the IFC to ensure that users are instructed to discard the detachable portion of the container label after they are instructed to write the "discard after date" and the lot number on remaining portion of the container label.
10.	Your PI and IFC contain inconsistent information regarding direct contact with your proposed product. For example, Section 2.3 in the PI states, (b) (4) ; whereas, the IFC states, "Avoid getting (b) (4) on (b) (4) your skin.	We are concerned that providing inconsistent information regarding direct contact with your proposed product may result in accidental exposure which may lead to user harm.	Revise the IFU to state, (b) (4)

Table 4: Identified Issues and Recommendations for Genentech, Inc. (entire table to be conveyed to Applicant)			
	Identified Issue	**Rationale for Concern**	**Recommendation**
	skin, wash the area with soap and water."		
11.	The table in the "Selecting the Oral Syringe for the Prescribed Dose…" section can be improved to decrease risk of overdose medication errors and wrong technique dispensing errors.	1. This table includes trailing zeros. Trailing zeros have led to ten-fold overdoses. 2. We are concerned that the statement, (b) (4) in the dose strength column may be misinterpreted as the net quantity (80 mL), which may lead to a delay in therapy if the day supply calculation is based on (b) (4)	1. Remove the trailing zeros (e.g. change 1.0 mL to 1 mL and 6.0 mL to 6 mL). 2. Remove the statement, (b) (4) from the "Dose Strength" column.
12.	The dosing volumes provided for oral syringe selection are not consistent within the IFU. For example, the IFU instructs users to use the 12 mL oral syringe for daily doses 6.2 mL or higher; however, the oral syringe selection table states "6.2 mL to 6.6 mL." Additionally, we note the PI states that the maximum daily dose is 6.6 mL.	We are concerned that the lack of clarity in the oral syringe selection instructions may lead to wrong dose errors if the wrong oral syringe is dispensed with your proposed product.	Revise the IFU to a statement similar to, "Select the 12 mL oral syringe if the dosing volume is between 6.2 mL and 6.6 mL."
Instructions for Use (IFU)			
13.	The description and location of the components of the user interface can be improved. For example, the "Important Information…" section	We are concerned that unidentified components of the user interface may lead to confusion.	1. Revise the IFU to relocate the description of the components of the user interface to appear before the "Important Information…" section.

Table 4: Identified Issues and Recommendations for Genentech, Inc. (entire table to be conveyed to Applicant)			
	Identified Issue	**Rationale for Concern**	**Recommendation**
	refers to the bottle adapter, which precedes the description of the user interface in the "Each...carton contains" section. Additionally, step A3 states "...insert the syringe tip into the bottle adapter"; however, Figure A does not identify the bottle adapter as a component of the user interface.		2. Ensure Figure A identifies and labels all components of the user interface that are mentioned in the IFU.
14.	The subjective data and your root cause analysis indicated that the location of the storage information in the IFU lacks prominence. For example, one participant suggested revising the header "Storage" to appear similar to the header on page 4.	We are concerned that the storage information may be easily overlooked which may lead to deteriorated drug error.	Increase the prominence of the "How to Store" header to a format similar to the other headers in the IFU (e.g. "Important information about...").
15.	In you HF validation study, some participants had difficulty locating the discard after date warning statements.	We are concerned that as presented the storage information may be easily overlooked which may lead to deteriorated drug medication error.	1. Relocate the "discard after" date warning statements (i.e., (b) (4) sk your pharmacist for the **Discard After** date if it is not written on the bottle label") to the "How to Store..." section in IFU. 2. Include a figure in the IFU that accurately depicts the location of the "discard after" date on the container label.

Table 4: Identified Issues and Recommendations for Genentech, Inc. (entire table to be conveyed to Applicant)			
	Identified Issue	**Rationale for Concern**	**Recommendation**
			3. Increase the prominence of the "Ask your pharmacist…" warning statement (e.g. bullet list format).
Container Labels			
16.	The subjective data and your root cause analysis indicates that the container label as presented was not clear regarding removal of the detachable portion.	We are concerned that if the reconstituted oral solution is dispensed with both the powder expiration date and the handwritten post-reconstitution expiration date on the container label, patients may be confused which may lead to deteriorated drug errors.	Add a statement similar to "Pharmacist: peel here" in the upper right hand corner of the detachable container label either within or above the arrow.
17.	The container label does not inform users to discard any unused portion after 64 days after reconstitution. Our review of the study results identified subjective feedback that indicated participants had difficulty understanding the difference between the "discard after" date on the container label and the powder expiration date on carton labeling. For example, one participant attributed the different expiration dates ("discard after" date vs. powder expiration date)	We are concerned that as presented, the purpose of the discard after date may be unclear, which may cause confusion and lead to a delay in therapy or deteriorated drug medication error.	Revise your container label to include a statement that informs users to discard any unused portion 64 days after reconstitution. Ensure this statement is in close proximity to your "Discard After: __/__/__" statement.

Table 4: Identified Issues and Recommendations for Genentech, Inc. (entire table to be conveyed to Applicant)			
	Identified Issue	**Rationale for Concern**	**Recommendation**
	to "doctor error" or use of an "incorrect box."		
18.	As currently presented, there are two barcodes on the container label.	Since the drug barcode is often used as an additional verification before drug administration, the presence of multiple barcodes is confusing to the healthcare providers.[h]	Ensure the barcode that includes the NDC number is on the static portion of the PDP of the container label (i.e., not the detachable portion of the container label).
Carton Labeling			
19.	The "carton contains" section on the back panel describes the co-packaged syringes as , (b) (4) however, the IFU states each carton contains 2 oral syringes.	We are concerned that inconsistent descriptions of the user interface maybe confusing to the end user (i.e., patient, caregiver) since the reconstituted oral solution is dispensed with 2 oral syringes (b) (4)	Revise the (b) (4) statement in the "carton contains" section to "oral syringes".
20.	The usual dosage statement incorrectly refers users to the IFU.	The dosage statement should meet 21 CFR 201.55 and maintain consistency with Prescribing Information.	Revise the dosage statement to "Usual dosage: See prescribing information."
21.	As currently presented, the format for the expiration date is not defined.	Lack of clarity regarding the expiration date might contribute to confusion and deteriorated drug medication errors.	Identify the format for the expiration date you intend to use. We recommend that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical

[h] Institute for Safe Medication Practices. Safety briefs: More barcodes than needed. ISMP Med Saf Alert Acute Care. 2014;19(2):1-3.

Table 4: Identified Issues and Recommendations for Genentech, Inc. (entire table to be conveyed to Applicant)			
	Identified Issue	**Rationale for Concern**	**Recommendation**
			characters are or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.[i]
22.	(b) (4)	We are concerned that th (b) (4) as presented clutters the PDP and detracts from the warning statement, "Attention pharmacists...".	1. Remove (b) (4) 2. Consider increasing the prominence of the warning statement, "Attention pharmacists..." and consider the use of different font color or surrounding this information in a box (see example below) to achieve increased prominence. **Attention pharmacist: Evrysdi must be reconstituted with water prior to dispensing.**

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

4. CONCLUSION AND RECOMMENDATIONS

The human factors (HF) validation study results identified use errors, close calls, and use difficulties with critical and non-critical tasks. Upon review of the human factors (HF) validation study results, we identified several use errors for the "select appropriate syringe size" task in the patient, caregiver, and healthcare provider (HCP) user groups. Subsequently, Genentech modified the user interface to instruct the pharmacist to select and dispense the appropriate oral syringe size. We determined that this modification to the syringe selection task did not introduce any new or unique risk in the intended user group based on our review of similar currently marketed products. Thus, we determined that this modification could be implemented without additional HF testing.

Based on our review of the subjective feedback and root cause analysis of the use-related issues for the remaining tasks evaluated in the HF validation study as well as our expert review of the proposed product user interface, we identified some recommendations to improve prominence, clarity, and understanding of important information. We find these revisions can be implemented without submission of additional HF validation testing data for Agency's review.

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

4.1 RECOMMENDATIONS FOR GENENTECH, INC.

Based on our evaluation of the HF validation study reports and proposed label and labeling, we identified areas of vulnerability that may lead to medication errors. We have provided recommendations in Table 4 and we recommend that you implement these recommendations and submit the revisions to the NDA for our review.

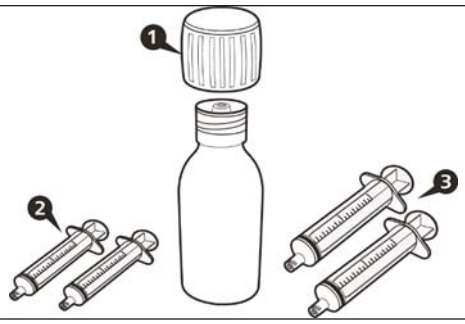
APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. DRUG PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 5 presents relevant product information for Evrysdi that Genentech submitted on May 8, 2020.

Table 5. Relevant Product Information

Initial Approval Date	N/A
Therapeutic Drug Class or New Drug Class	survival of motor neuron 2 (SMN2) splicing modifier
Active Ingredient (Drug or Biologic)	risdiplam
Indication	for the treatment of spinal muscular atrophy (SMA) in (b) (4) patients
Route of Administration	oral, enteral (gastrostomy tube, nasogastric tube)
Dosage Form	powder for oral solution
Strength	60 mg/80 mL (0.75 mg/mL)
Dose and Frequency	**Age** / **Recommended Daily Dose**: 2 months to < 2 years of age — 0.2 mg/kg; ≥ 2 years of age (< 20 kg) — 0.25 mg/kg; ≥ 2 years of age (≥ 20 kg) — 5 mg Taken orally once daily, at approximately the same time each day, using the re-usable oral syringe provided.
How Supplied	carton containing one amber glass bottle (containing 60 mg risdiplam powder for solution), one bottle adapter, two 6 mL and two 12 mL oral syringes, one Instructions for Constitution, one Instructions for Use
Storage	Prior to constitution, store the dry powder at room temperature, at 20°C to 25°C (68°F to 77°F) [see USP controlled room temperature] and keep in the original carton. After constitution, store the oral solution in a refrigerator between 2°C to 8°C (36°F to 46°F) for up to 64 days. Do not freeze. Keep the oral solution bottle always in an upright position with the cap tightly closed [see INSTRUCTIONS FOR USE]. Store in the original amber bottle to protect from light

Container Closure/Device Constituent	
Intended Users	pharmacists, healthcare providers, non-professional caregivers, patients with SMA
Intended Use Environment	pharmacy, clinical environment, home

APPENDIX B. BACKGROUND INFORMATION

B.1 PREVIOUS HF REVIEWS

B.1.1 Methods

On January 6, 2020, we searched the L:drive and AIMS using the term, risdiplam to identify reviews previously performed by DMEPA or CDRH.

B.1.2 Results

Our search identified 1 previous review[b] since the date of our last search[j], and we confirmed that our previous recommendations were implemented or considered.

APPENDIX C. BACKGROUND INFORMATION ON HUMAN FACTORS ENGINEERING PROCESS

The background information can be accessible in EDR via:
\\cdsesub1\evsprod\nda213535\0002\m5\53-clin-stud-rep\535-rep-effic-safety-stud\sma\5354-other-stud-rep\human-factors-summary-report\human-factor-report.pdf

APPENDIX D. HUMAN FACTORS VALIDATION STUDY RESULTS REPORT

The HF study results report submitted on September 17, 2019 can be accessible in EDR via:
\\cdsesub1\evsprod\nda213535\0002\m5\53-clin-stud-rep\535-rep-effic-safety-stud\sma\5354-other-stud-rep\human-factors-summary-report\human-factor-report.pdf

The Amendment submitted on November 29, 2019 can be accessible in EDR via:
\\cdsesub1\evsprod\nda213535\0012\m5\53-clin-stud-rep\535-rep-effic-safety-stud\sma\5354-other-stud-rep\risdiplam-hfe-information-update\risdiplam-hfe-information-update.pdf

[j] Date of last search on February 17, 2019 in Whaley, E. Human Factors Protocol Review for Risdiplam (IND 128972). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 APR 11. RCM No.: 2018-1678-1.

APPENDIX E. INFORMATION REQUESTS ISSUED DURING THE REVIEW

On November 15, 2019, we issued an Information Request (IR) to request:

- discussion of whether additional risk mitigation measures are necessary to address the identified use errors
- plans to validate your proposed mitigations or provide your justification to support that no additional validation data is required
- participant subjective feedback for all use errors, close calls, and use difficulties observed in the study
- Identify close calls and use difficulties observed in your HF study within your study report

Our IR and the Applicant's response can be accessible in EDR via:
\\cdsesub1\evsprod\nda213535\0012\m1\us\clinical-resp-fda-req-info20191129.pdf

APPENDIX F. LABELS AND LABELING

E.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[k] along with postmarket medication error data, we reviewed the following Evrysdi labels and labeling submitted by Genentech.

- Container label received on September 17, 2019
- Carton labeling received on April 24, 2020
- 6 mL oral syringe pouch labeling received on September 17, 2019
- 12 mL oral syringe pouch labeling received on September 17, 2019
- Instructions for Constitution received on May 8, 2020 can be accessible in EDR via: \\cdsesub1\evsprod\nda213535\0030\m1\us\instructions-for-constitution-redline.docx
- Instructions for Use received on April 24, 2020 can be accessible in EDR via: \\cdsesub1\evsprod\nda213535\0029\m1\us\instructions-for-use-redline.docx
- Prescribing Information (Image not shown) received on May 8, 2020 can be accessible in EDR via: \\cdsesub1\evsprod\nda213535\0030\m1\us\redlined-label-text.docx

3 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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

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/s/

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Memo To File

Date	6/2/2020
From	Cara Alfaro, Pharm.D., Clinical Analyst Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Brenda Reggettz, Regulatory Project Manager Rainer Paine, M.D., Medical Officer and Team Leader Division of Neurology 1 Office of Neuroscience
NDA #	213535
Applicant	Genentech, Inc.
Drug	Risdiplam powder for oral solution
NME	Yes
Proposed Indication	Treatment of spinal muscular atrophy in (b) (4) patients
Consultation Request Date	1/9/2020
Summary Goal Date	3/24/2020
Priority/Standard Review	Priority
Action Goal Date	7/1/2020
PDUFA Date	5/24/2020, extended to 8/24/2020

OSI received a consult from the Division of Neurology 1 (DN1) on 1/9/2020 that identified the following clinical investigators for Good Clinical Practice (GCP) inspections:

- Dr. Mazurkiewicz-Beldzinska (Site 306699, Poland)
- Dr. Steinborn (Site 306698, Poland)
- Dr. Masson (Site 297883, Italy)
- Dr. Boespflug-Tanguy (Site 297474, France)

An inspection assignment for these four sites was issued on 1/29/2020, and the Office of Regulatory Affairs (ORA) scheduled these inspections. However, at the current time, the COVID-19 global pandemic has significantly limited our ability to conduct on-site GCP inspections. As a result, and in an effort to protect the health, safety, and welfare of FDA employees and study staff, the need for planned inspections in support of NDA 213535 was reevaluated. Following discussions between OSI and DN1, a decision was made that assessment of the application could proceed without GCP inspections. Therefore, at this time, OSI will be unable to determine if Protocols BP39055 (SUNFISH) and BP39056 (FIREFISH) were conducted adequately and whether the study data are reliable in support of the proposed indication.

{See appended electronic signature page}

Cara Alfaro, Pharm.D.
Clinical Analyst
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

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cc:

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OSI/DCCE/GCPAB/Branch Chief/Kassa Ayalew
OSI/DCCE/GCPAB/Team Leader/Phillip Kronstein
OSI/DCCE/GCPAB/Reviewer/Cara Alfaro
OSI/GCPAB Program Analyst/Yolanda Patague

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/s/

CARA L ALFARO
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Ophthalmology Consult Review of NDA 213535

Consult Request Date: September 26, 2019
Review completed: May 8, 2020

Product name: Risdiplam

Applicant: Genentech, Inc.

Division Request: Review of Ophthalmic Assessments in Original NDA submission (receipt date 9/24/19). Risdiplam is a new molecular entity that has been submitted for the treatment of spinal muscular atrophy in (b) (4) patients. Dr. Chambers has provided previous consult reviews on the sponsor's ophthalmologic safety monitoring program for potential retinal toxicity: PIND/WRO (2/24/16), type C F2F meeting (1/11/18), amended protocol for Study BP39056 (6/12/18), type C F2F meeting (12/11/18), preNDA meeting (6/10/19).
Medical Officer: Rainer Painer, MD, PhD

Submission is accessible in DARRTS or at: \\CDSESUB1\evsprod\NDA213535\213535.enx
Please note that ophthalmology scans from each study are included in the NDA (as agreed at the 6/10/19 preNDA meeting).

Background
In a 39-week study in cynomolgus monkeys, retinal toxicity was observed in all animals at exposures above the no-observed-adverse-effect level (NOAEL) i.e., at approximately 2-fold of the average exposure observed at the pivotal dose selected for patients with SMA. These consisted of peripheral photoreceptor loss and hyper-reflective retinal pigment epithelium which was not fully reversible as well as, at higher exposures, reversible microcystic macular degeneration in the macula. The expected initial clinical symptoms of such structural changes in the peripheral retina would be impaired night vision or loss of peripheral vision. Blindness was not observed in any of the monkeys even at high doses (approximately 4 times the exposures achieved at the pivotal dose in patients with SMA) after 9 months of daily administration of risdiplam. These findings were not observed in albino or pigmented rats when dosed chronically with risdiplam at exposures exceeding those administered to monkeys.

Due to this nonclinical finding, a panel of ophthalmological assessments was performed in all clinical studies in SMA patients, including imaging to detect structural changes of the retina, and visual function testing to detect potential functional impairment in central or peripheral vision.

NDA Submission: December 2019 Safety Update report
The 90-day Safety Update Report (90DSU) provides updated cumulative safety data from the two ongoing pivotal studies in treatment naïve patients, one in infantile-onset spinal muscular atrophy (SMA) (Study BP39056; also known as FIREFISH); and another in children, adolescents, and young adults with later-onset SMA (Study BP39055; also known as SUNFISH). Data from these pivotal studies are supported by safety data from the ongoing open-label safety study BP39054 (also known as JEWELFISH), involving SMA patients who have previously received an SMA treatment. The clinical cutoff date for this 90DSU is 28 June 2019.

Ophthalmological assessments	BP39056 (FIREFISH)	BP39055 (SUNFISH)	BP39054 (JEWELFISH)
Spectral domain optical coherence tomography	X	X	X
Fundus photography	X	X	X
Fundus autofluorescence	-	X	X
Visual field threshold perimetry	-	X	X
Fundus examination	X	X	X
Slit lamp	X	X	X
Intraocular pressure	X	X	X
Best Corrected Visual Acuity	-	X	X
Fix and follow	X	X	X
Sloan low contrast	-	X	X
Simple visual field test	-	X	X
Visual Testing (Ocular Examination)	X	X	X

X = assessment/examination in the study schedule of assessments;
–= assessment/examination not in the study schedule of assessments for this study.

Adverse Events in 'Eye Disorders' System Organ Class, by SMA Type, Safety-Evaluable Patients
Protocol: Risdiplam Pooled Safety 3 Month Safety Update

MedDRA System Organ Class MedDRA Preferred Term	Type 1 (N=64)	Type 2/3 (N=94)	All Patients (N=158)
Eye disorders			
Number of patients with at least one adverse event	3 (5%)	6 (6%)	9 (6%)
Total number of events	4	7	11
Conjunctival hyperaemia	2 (3%)	0	2 (1.3%)
Blepharitis	0	1 (1%)	1 (0.6%)
Dry eye	0	1 (1%)	1 (0.6%)
Eczema eyelids	0	1 (1%)	1 (0.6%)
Eye allergy	0	1 (1%)	1 (0.6%)
Macular cyst	1 (2%)	0	1 (0.6%)
Ocular hyperaemia	0	1 (1%)	1 (0.6%)
Photopsia	0	1 (1%)	1 (0.6%)
Retinal exudates	1 (2%)	0	1 (0.6%)
Vision blurred	0	1 (1%)	1 (0.6%)

Investigator text for AEs is coded using MedDRA version 22.0. Percentages are based on N in the column headings. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately. Includes AEs with onset from first dose of risdiplam up to the clinical cutoff date.

Over 90% of the 158 patients successfully completed their SD-OCT assessments as scheduled, except at Week 70 and 87 (89.7% and 86.2%) while 100% of patients completed their Week 78, 117 and 130 assessments, respectively. The longest duration of follow-up was 30 months (130 weeks). Most patients completed 8 weeks' follow-up (127 out of 158), 115 out of 158 patients completed at least 6 months of follow-up, and 91 out of 158 patients completed 12 months of follow-up. Fifty-two out of 158 patients completed at least 2 years of follow-up.

Reviewer's Comments: *In the absence of direct trauma or vascular injury, retinal changes are often slow to develop. Adverse retinal findings, if they were to occur, would not be expected to be observed on OCT until at least month 6.*

STUDY BP39056 (FIREFISH) – PART 1

Fundus Photography
All 20 patients had at least one post-baseline assessment and 19 patients were followed up until at least 12 months; the longest follow-up time was 27 months, which was achieved by 3 patients.

Reviewer's Comments: *Acceptable, but this is a low number of individuals.*

SD-OCT
All 20 patients had at least one post-baseline OCT assessment and 19 patients were followed up until at least 12 months; the longest follow-up was 27 months, which was achieved by 3 patients.

Reviewer's Comments: *Acceptable, but this is a low number of individuals.*

Fundus Examination
All 20 patients had at least one post-baseline assessment and 19 patients were followed up until at least 12 months; the longest follow-up was 27 months, which was achieved by 3 patients.

Reviewer's Comments: *Acceptable, but this is a low number of individuals.*

Intraocular Pressure
All 20 patients had at least one post-baseline assessment and 19 patients were followed up until at least 12 months; the longest follow-up was 27 months, which was achieved by 3 patients.

Reviewer's Comments: *Acceptable, but this is a low number of individuals.*

Ocular Examination (Slit Lamp)
All 20 patients had at least one post-baseline assessment and 19 patients were followed up until at least 12 months; the longest follow-up was 27 months, which was achieved by 3 patients.

Visual Function- Fix and Follow
All 20 patients had at least one post-baseline assessment and 19 were followed up until at least 12 months; the longest follow-up was 27 months, which was achieved by 3 patients.

Reviewer's Comments: *Acceptable, but this is a low number of individuals.*

STUDY BP39056 (FIREFISH) – PART 2

Fundus Photography
Thirty-eight patients had at least one post-baseline assessment. Thirty-seven patients were followed up until at least 6 months and the longest follow-up was 14 months, which was achieved by 2 patients.

Reviewer's Comments: *Acceptable.*

SD-OCT and Fundus Examination
Thirty-eight patients had at least one post-baseline assessment who were all followed up until at least 6 months; the longest follow-up was 14 months, which was achieved by 4 patients.

Reviewer's Comments: *Acceptable.*

Intraocular Pressure
Thirty-seven patients had at least one post-baseline assessment who were all followed up until at least 6 months; the longest follow-up was 14 months, which was achieved by 4 patients.

Reviewer's Comments: *Acceptable.*

Ocular Examination (Slit Lamp)
Thirty-eight patients had at least one post-baseline assessment who were all followed up until at least 6 months; the longest follow-up was 14 months, which was achieved by 4 patients.

Reviewer's Comments: *Acceptable.*

Ocular Examination (Visual Testing)
Thirty-eight patients had at least one post-baseline assessment who were all followed up until at least 6 months; the longest follow-up was 14 months, which was achieved by 4 patients. Three patients had 6 findings consistent with strabismus in both eyes at their last assessment:

- One patient showed esotropia unchanged to baseline.
- A second patient showed esotropia which had improved compared to baseline in a clinically significant manner.

- A third patient showed poor fixation of the gaze (deviation convergens alternans) that had worsened compared to baseline in a clinically significant manner. This finding was reported, after the CCOD of this report, as adverse event of heterophoria in both eyes which resolved with sequelae after patient received glasses for correction.

Reviewer's Comments: *Acceptable.*

Visual Function- Fix and Follow
Thirty-eight patients had at least one post-baseline assessment who were all followed up until at least 6 months; the longest follow-up was 14 months, which was achieved by 4 patients.

Reviewer's Comments: *Acceptable.*

STUDY BP39055 (SUNFISH) – PART 1

Fundus Autofluorescence (FAF)
Twenty-four patients (47.1%) had at least one post-baseline assessment and 17 were followed up until at least Week 52; the longest follow-up time was 117 weeks which was achieved by 1 patient.

Reviewer's Comments: *The percentage of patients evaluated is too low to be reliable.*

Fundus Photography
All 51 patients had at least one post-baseline assessment and the majority of patients (43 patients) were followed up until at least Week 104; the longest follow-up time was 130 weeks which was achieved by 15 patients.

Reviewer's Comments: *Acceptable.*

SD-OCT
All 51 patients performed at least one post-baseline assessment, 50 patients were followed up until at least Week 78 and the majority of patients (47 patients [94.0%]) were followed up until at least Week 104; the longest follow-up time was up to Week 130 which was achieved by 15 patients. The proportion of patients with missing SD-OCT by visit varied from 0 to 15.7% up to Week 130 while no patient missed their Week 117 and Week 130 assessment.

Reviewer's Comments: *Acceptable.*

Fundus Examination
All 51 patients completed at least one post-baseline assessment and 50 patients were followed up until at least until Week 78; the longest follow-up time was 130 weeks which was achieved by 15 patients.

Reviewer's Comments: *Acceptable.*

Intraocular Pressure
All 51 patients completed at least one post-baseline assessment; the majority of patients (36 patients) were followed up until at least Week 104; the shortest follow-up time was 17 weeks and the longest was 130 weeks which was achieved by 15 patients.

Reviewer's Comments: *Acceptable.*

Ocular Examination (Slit Lamp)
All 51 patients completed at least one post-baseline assessment and the majority of patients (47 patients) were followed up until at least Week 104; 15 patients achieved a follow-up until Week 130.

Reviewer's Comments: *Acceptable.*

Best Corrected Visual Acuity
All 51 patients performed at least one post-baseline assessment, the majority of patients (47 patients) were assessed until at least Week 104 and 15 patients achieved a follow-up until Week 130.

Reviewer's Comments: *Acceptable.*

Low Contrast Visual Acuity
Low contrast visual acuity was required only in patients above 10 years of age. As such a total of 23 patients (45.1% overall and 100% of patients in the 12-25 year cohort performed at least one post-baseline assessment); the majority (20 patients) were followed up until at least Week 52 and the longest follow-up time was 117 weeks which was achieved by 1 patient.

Reviewer's Comments: *Acceptable, but this is a low number of individuals.*

Visual Field Threshold Perimetry
Visual Field Threshold Perimetry was required only in patients above 10 years of age. As such 22 patients (43.1%) overall and 90% of patients in the 12-25 year cohort performed at least one post-baseline assessment; the majority of all patients (17) were followed up at least until Week 104 and the longest follow-up time was 130 weeks which was achieved by 11 patients.

Reviewer's Comments: *Too few patients to be meaningful.*

STUDY BP39055 (SUNFISH) – PART 2

Fundus Autofluorescence (FAF)
A total of 34 patients (18.9%) performed at least one post-baseline assessment and 19 patients were followed up until at least Week 26; the longest follow-up time was 52 weeks which was achieved by 4 patients.

Reviewer's Comments: *Too few patients to be meaningful.*

Fundus Photography
All 180 patients performed at least one post-baseline assessment; the majority of patients (176 patients) were followed up until at least Week 26 and the longest follow-up time was 87 weeks which was achieved by 1 patient.

Reviewer's Comments: *Acceptable.*

SD-OCT
All 180 patients performed at least one post-baseline assessment. The majority of patients (171 patients [97.7%]) were followed up until at least Week 43 and the longest follow-up was up to Week 87, which was achieved by 2 patients. The proportion of patients with missing SD-OCT assessments by visit varied from 0 to 14.3% with a total of 16 missed assessments out of a total number of 1216 scheduled SD-OCT assessments including baseline.

Reviewer's Comments: *Acceptable.*

Fundus Examination
All 180 patients completed at least one post-baseline assessment; the majority of patients (173 patients) were followed up until at least Week 43 and the longest follow-up was until Week 87 which was achieved by 2 patients.

Reviewer's Comments: *Acceptable.*

Intraocular Pressure
A total of 177 patients (98.3%) completed at least one post-baseline assessment; the majority of patients (143 patients) were followed up until at least Week 35 and the longest follow-up was until Week 87 which was achieved by 2 patients.
Overall, 27 patients (15.0%) had 35 findings at the last assessment visit (Table 6). All findings were assessed as not clinically significant changes compared to baseline.

Reviewer's Comments: *Acceptable*

Ocular Examination (Slit Lamp)
All 180 patients completed at least one post-baseline assessment; the majority of patients (173 patients) were followed up until at least until Week 43 and the longest follow-up was up to Week 87 which was achieved by 2 patients.

Reviewer's Comments: *Acceptable.*

Best Corrected Visual Acuity
A total of 174 patients (96.7%) performed at least one post-baseline assessment; the majority of patients (167 patients) were followed up until at least Week 43 and the longest follow-up was until Week 87 which was achieved by 2 patients.

Reviewer's Comments: *Acceptable.*

Low Contrast Visual Acuity
Ten patients (5.6%) performed at least one post-baseline assessment; the majority of these patients (8 patients) were followed up until at least Week 8 and the longest follow up was until Week 52 which was achieved by 1 patient.

Reviewer's Comments: *Too few patients to be meaningful.*

Visual Field Threshold Perimetry
A total of 97 patients (53.9%) performed at least one post-baseline assessment; the majority of these patients (88 patients) were followed up until at least Week 26 and the longest follow-up was until Week 87 which was achieved by 1 patient.

Reviewer's Comments: *Between the percentage and duration of follow-up, the visual field monitoring is not sufficient to evaluate safety.*

STUDY BP39054 (JEWELFISH)

Fundus Autofluorescence (FAF)
Eleven of the 45 patients (24.4%) performed at least one post-baseline FAF assessment and one of the patients showed 2 abnormal findings, drusen changes outside of the macula, at the last visit.

Reviewer's Comments: *Too few patients to be meaningful.*

Fundus Photography
Fourteen of the 45 patients (31.1%) performed at least one post-baseline fundus photography assessment and two of the patients (4.4%) showed 3 findings at the last visit.

Reviewer's Comments: *Too few patients to be meaningful.*

SD-OCT
Twenty-one of the 45 patients (46.7%) performed at least one post-baseline SD-OCT assessment. The shortest follow-up was Week 8 and longest follow-up was Week 117 which was achieved by 1 patient.

Reviewer's Comments: *Too few patients to be meaningful.*

Best Corrected Visual Acuity (BCVA)
Eighteen of the 45 patients (40%) performed at least one post-baseline BCVA assessment, were assessed until at least Week 8 and one patient completed the Week 117 BCVA assessment.

Reviewer's Comments: *Too few patients to be meaningful.*

Low Contrast Visual Acuity
Twelve of 45 patients (26.7%) performed at least one post-baseline Low Contrast Visual Acuity assessment, were assessed until at least Week 17 and one patient completed the Week 104 ophthalmology visit with a valid Low Contrast Visual Acuity result.

Reviewer's Comments: *Too few patients to be meaningful.*

Visual Field Threshold Perimetry
Thirteen of 45 patients (28.9%) performed at least one post-baseline Visual Field Threshold Perimetry assessment; 12 patients were assessed until at least Week 52 and 2 patients were followed up until Week 104.

Reviewer's Comments: *Too few patients to be meaningful.*

Summary Comments:

1) The company was unable to have a sufficient number of reliable visual field tests performed to be able to rule out retinal injuries. Visual fields are not the best way to monitor potential retinal cell loss, but since they measure visual function, it would have been reassuring if they had been able to widely get reliable visual fields. This is not a fatal flaw; visual fields might have served as an alternative to the OCTs.

2) With current technologies, retinal thinning seen on Optical Coherence Tomography is the most likely method to detect retinal injury. The company included unhelpful categorizations (e.g., 15% thickening, 15% thinning, >25% thinning, >25% thickening, 15% thinning and thickening, >15% thickening and 25% thinning, etc.) The company reported a very large number of "OCT changes in thickness due to different angle of scans" or "changes in OCT measurements most consistent with variable angles of scans." The central retinal thickness is most critical and is not affected by angle. Since the actual values are present on the scans, these values were requested and subsequently submitted. After review, there were no significant findings from the OCT scans.

3) The company's summaries of findings were not helpful. Events should not have been dismissed as adverse events for reasons such as not having been seen on the last exam or "One patient with a small dot opacity on the posterior line capsule of the lens first seen at Week 8 through Week 78, however, not seen at Week 26, thus suggesting that due to the small size it could also have been present at screening and not considered as AE." However, the roughly 4000 pages of listings in this submission have been reviewed in this consult, and there are no more than a few findings that could potentially be attributed to risdiplam. The vast majority of abnormalities were either present at baseline or common events for the age group being studied.

4) There were no issues with intraocular pressure. There are no issues with anterior segment of the eye findings. There are no issues with cataracts (although the company did a poor job with reporting cataracts).

Conclusions:

The study population for whom this product would be indicated presents challenges when performing ophthalmic monitoring. Visual function monitoring was poor throughout the studies. In those patients with ocular functional examinations, no significant pattern of abnormal findings were observed.

Ocular monitoring of anatomic ocular structures was acceptable and monitoring of retinal anatomical findings by optical coherence tomography was significantly more complete than the functional monitoring. Ocular monitoring of anatomic ocular structures did not reveal any significant pattern of abnormal findings. From an ophthalmological perspective, there is no objection the approval of this drug product.

Wiley A. Chambers, M.D.,
Supervisory Medical Officer, Ophthalmology

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/

WILEY A CHAMBERS
05/08/2020 08:08:27 AM

Interdisciplinary Review Team for QT Studies Consultation Review

Submission	NDA 213535
Submission Number	003
Submission Date	9/17/2019
Date Consult Received	10/2/2019
Drug Name	Risdiplam
Indication	Spinal Muscular Atrophy
Therapeutic dose (Proposed)	0.20 mg/kg for 2 months to < 2 years 0.25 mg/kg for ≥ 2 years of age (< 20 kg) 5 mg for ≥ 2 years of age (≥ 20 kg)
Clinical Division	DNP

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

This review responds to your consult dated 10/02/2019 regarding the sponsor's QT evaluation. The QT-IRT reviewed the following materials:

- Previous QT-IRT review under IND-128972 in DARRTs (Dt: 01/16/2018; link);
- Previous QT-IRT review under IND-128972 in DARRTs (Dt: 02/07/2018; link);
- Sponsor's clinical study report # BP29840 (SN0002; link);
- Sponsor's clinical study report # NP39625 (SN0002; link);
- Sponsor's PK/PD report # 1096622 (Page # 218, SN0002; link);
- Sponsor's propose product label (SN0002; link); and
- Highlights of clinical pharmacology and cardiac safety (SN0002; link).

1 SUMMARY

The submitted data are not adequate to characterize the risk of QTc prolongation associated with the oral administration of risdiplam. The PK/ECG data available from these clinical studies are at considerably lower exposures (Cmax) of risdiplam than those expected with therapeutic doses at the steady-state. The QT-IRT recommends that the sponsor characterizes the effect of risdiplam on the QTc interval in a dedicated study at a clinically relevant exposure.

Considering the quality of available ECG data (see Section 4.5), the exposure-response analysis focused on the data available from studies # BP29840 (excluding drug interaction and food effect arms) and # NP39625 performed in healthy subjects. Study # BP29840 was a randomized, adaptive single ascending dose (SAD: 0.6, 2, 6, and 18 mg), placebo-controlled, parallel group study investigating the safety, tolerability, pharmacokinetics and pharmacodynamics of risdiplam following oral administration in healthy subjects. Study # NP39625 was a randomized, placebo-controlled study evaluating the safety, tolerability, pharmacokinetics and pharmacodynamics of single oral doses of RO7034067 (2, 6, and 12 mg) in healthy Japanese subjects. The data from studies # BP29840 and # NP39625 were

analyzed using by exposure-response analysis as the primary analysis to characterize the effect of risdiplam on the QTc interval (see Section 4.5).

None of the submitted clinical studies included separate positive control (e.g, moxifloxacin) to demonstrate assay sensitivity. Moreover, no QT bias assessment was conducted by the sponsor. The highest dose evaluated was 18 mg (as single dose), which offers lower exposures (Cmax ~92 ng/mL; observed) than those observed with the therapeutic doses in pediatric population (Cmax 184 ng/mL; Table 1). Table 1 describes the peak concetrations of risdiplam with different age groups based on the proposed dose by the sponsor and its comparison with the highest observed exposures of risdiplam (Cmax 92 ng/mL) in the above described studies.

Table 1: The Exposures of Risdiplam at Proposed Doses

Proposed Dose	Concentration* (ng/mL)	Fold Higher	Study Number
5 mg once daily for patients with age ≥ 2 years (≥ 20 kg)	123 (58 to 242)	1.35	BP39055 (SUNFISH)
0.25 mg/kg once daily for patients with age ≥ 2 years (< 20 kg)	159 (78 to 214)	1.73	BP39055 (SUNFISH)
0.2 mg/kg once daily for patients with age 2 months to < 2 years	184 (38 to 364)	2.00	BP39056 (FIREFISH)

**Presented as observed mean peak concentrations based on sparse PK sampling.*

Thus, the PK/ECG data available from these clinical studies are at considerably lower exposures (Cmax) of risdiplam than those associated with therapeutic doses in pediatric population at steady-state (see Section 3.1). Although the sponsor claims that it is less-likely to observe increased exposure of risdiplam in a worst-case clinical scenario (e.g., drug interactions), clinical pharmacology study (likely, hepatic impairment) confirming this expectation is pending.

Moreover, the available nonclinical data (see Section 3.1.2) and by time analysis (see Section 4.3) are also not adequate for the QT assessment of risdiplam.

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION

- The sponsor submitted exposure-response analysis using 5 clinical studies conducted in healthy subjects (Studies # BP29840; n=26, # NP39625; n=18) and SMA patients (Studies # BP39054; n=12, Part 1 of # BP39055; n=51, and Part 1 of # BP39056; n=21). The exposures of risdiplam observed in studies with SMA patients (Part 1 of # BP39055, and Part 1 of # BP39056) were slightly higher than those observed in studies with healthy subjects. However, studies # BP39056 and # BP39054 with SMA patients were open label without a placebo control. The exposures of risdiplam observed in study # BP39054 with SMA patients were considerably lower than those observed in studies with healthy subjects. For study # BP39055 with SMA patients, there was a limited data available with matched ECG/PK at higher exposures.

- Considering the quality of available ECG data, the exposure-response analysis was conducted with data from studies # BP29840 (excluding drug interaction and food effect arms) and # NP39625 performed in healthy subjects (see Section 4.5). The submitted data are not adequate to characterize the risk of QTc prolongation associated with the oral administration of risdiplam. The PK/ECG data available from these clinical studies are at considerably lower exposures (Cmax) of risdiplam than those expected with therapeutic doses at the steady-state.
- We recommend that the sponsor characterizes the effect of risdiplam on the QTc interval in a dedicated study at a clinically relevant exposure. If the Division believes the benefit-risk supports excluding small mean QTc effects (10 ms) for this product, we recommend that the sponsor conducts a 2-parts thorough QT study with part-1) exploring the safety of a higher single dose in healthy subjects that can achieve higher or at least similar Cmax as the steady state Cmax in patient population and part-2) thorough QT study using the identified highest safe dose from part 1.

2 RECOMMENDATIONS

2.1 ADDITIONAL STUDIES

The submitted data is not adequate to characterize the QT effects of risdiplam. It is recommended that the sponsor conducts a dedicated QT study to characterize the risk of QTc prolongation associated with the oral administration of risdiplam. As described in the previous QT-IRT review (Dt: 02/07/2018) that sponsor may conduct a 2-parts clinical study exploring the safety (part-1) of a higher single dose in healthy subjects (that can achieve higher or at least similar Cmax as the steady state Cmax in patient population) followed by thorough QT study (part-2) at highest safe dose identified in part 1.

2.2 PROPOSED LABEL

We do not agree with the proposed labeling language (under Section 12.2) by the sponsor (SN0002; link). The submitted data are not adequate (b) (4)

12.2 Pharmacodynamics
(b) (4)

3 SPONSOR'S SUBMISSION

3.1 OVERVIEW

3.1.1 Clinical

Genentech Inc. is developing risdiplam (RO7034067, MW: 401.46 g/mol) for the treatment of spinal muscular atrophy (SMA) in (b) (4) patients. Risdiplam is a survival of motor neuron 2 (SMN2) per-mRNA splicing modifier. It is believed that risdiplam increases the expression of functional SMN protein in the SMN2 gene. The proposed therapeutic dose is 5 mg once daily for patients with age ≥ 2 years (≥ 20 kg), 0.25 mg/kg

once daily for patients with age ≥ 2 years (< 20 kg), and 0.2 mg/kg once daily for patients with age 2 months to < 2 years. The highest studied dose is 18 mg (Cmax: 93 ng/mL; as single dose) in healthy subjects. The proposed therapeutic doses are highest studied doses in patients. The peak concentrations of 184 ng/mL (Tmax ~2 h; half-life ~50 h; Racc ~2) are expected with 0.2 mg/kg once daily dosing in patients (age 2 months to 2 years; body weight and age are main significant covariates; Table 1). No data is available in infants below 2 months of age.

These dose levels were selected in order to target an at least 2-fold increase in SMN protein at an exposure of ≤2000 ng.h/mL. The product is formulated as powder for oral solution (60 mg in a bottle; with a bottle adapter and oral syringes) which is to be constituted with purified water to form an oral solution (60 mg/80 mL; 0.75 mg/mL).

Risdiplam is believed to be metabolized by flavin monooxygenase 1 and 3 (FMO1 and FMO3), and with some contribution by CYP1A1, CYP 2J2, CYP 3A4 and CYP 3A7 enzymes. Risdiplam appears to be the major component (83% of drug related material) in plasma with M1 as the major circulating metabolite. The sponsor claims that risdiplam has a low drug interaction potential as a victim drug with no drug-drug interactions expected via the FMO1 and FMO3 pathways. Following a dose of 18 mg, ~53% of the dose (14% unchanged risdiplam) is excreted in the feces and 28% in urine (8% unchanged risdiplam). Renal impairment is not expected to impact the pharmacokinetics of risdiplam. However, the hepatic impairment study (Study # BP40995) currently ongoing.

Previously, the QT-IRT reviewed the sponsor's thorough QT study substitution request. The sponsor indicated that risdiplam has a low potential of QTc prolongation using non-clinical data, concentration-QT from their phase-1 study (# BP29840) conducted in healthy subjects, and ECG monitoring conducted in their clinical studies (# BP39055 & # BP39056). However, the QT-IRT (Dt: 01/16/2018) indicated that the submitted data is not adequate to exclude small mean QTc effects (10 ms; per the ICH E14). The study did not cover high exposure margin over the worst-case scenario to satisfy the requirement for waiving the positive control for assay sensitivity (ICH E14 Q&A (R3), Section 5.1). Previously, the QT-IRT suggested that the data may be adequate to exclude the large mean QTc effects (i.e., >20 ms) of risdiplam, if there exists adequate exposure margin at the final therapeutic dose and the Division considers it is acceptable for this indication. It was suggested by the QT-IRT (Dt: 02/07/2018) that sponsor may conduct a 2-parts thorough QT study with part-1) exploring the safety of a higher single dose in healthy subjects that can achieve higher or at least similar Cmax as the steady state Cmax in patient population and part-2) thorough QT study using the identified highest safe dose from part 1.

Now, the sponsor submitted concentration-QT analysis using ECG/PK data from 5 clinical studies (Studies # BP29840; n=26, # NP39625; n=18, # BP39054; n=12, Part 1 of # BP39055; n=51, and Part 1 of # BP39056; n=21). Studies # BP29840 and # NP39625 were performed in healthy subjects. Studies # BP39054, # BP39055 and # BP39056 are conducted in SMA patients.

POP-PK analysis was performed using data from Study BP39054 (JEWELFISH; n=12 patients), study BP39055 (SUNFISH P-1; n=51 patients) Part 1, Study BP39056 (FIREFISH P-1 & -2; n=62 patients), and Study BP29840 (n=26 healthy subjects).

Study BP29840 was designed as a three-part study: Part 1 was an adaptive single ascending dose, placebo-controlled, parallel study; Part 2 was designed as an open-label, randomized, two-period crossover, single dose investigation of the effect of food on the PK of risdiplam, and Part 3 investigated the PK interaction between itraconazole and risdiplam, using an open-label, one-sequence, two-period crossover design. Based on an exploratory investigation of the effect of food on the PK of risdiplam conducted during Part 1, Part 2 of the study was omitted. In Part 1, subjects received a single dose of 0.6 - 18 mg, with each dose level being given to 3 to 6 subjects. In Part 3, 8 subjects received a single dose of 6 mg risdiplam alone and in combination with itraconazole.

Study NP39625 was a placebo-controlled study to assess the safety, tolerability and pharmacokinetics of risdiplam in healthy Japanese subjects. Six subjects per dose level received a single dose of 2, 6 or 12 mg of risdiplam.

BP39054 is an open label study in infants, children and adults with SMA previously enrolled in study BP29420 (Moonfish) or previously treated with Nusinersen, AVXS-101 or olesoxime (Protocol version 3). Initially a dose of 3 mg risdiplam was administered to all patients. After the iDMC (Independent Data Monitoring Committee) confirmed and selected the Part 2 dose level (5 mg o.d. for patients with a body weight ≥ 20 kg, and 0.25 mg/kg o.d. for patients with body weight < 20kg) for study BP39055, all patients in BP39054 were switched to the same dose level.

Part 1 of # BP39055 is placebo-controlled study in adult and pediatric Type 2 and Type 3 SMA patients of age 2-25 years. Patients were randomized to risdiplam or placebo in a 2:1 ratio. Patients aged 2-11 years who were randomized to risdiplam received 0.02, 0.05, 0.15 or 0.25 mg/kg, and those aged 12-25 years received 3 or 5 mg. All patients initially randomized to placebo were switched to risdiplam treatment at the dose level of their cohort after at least 12 weeks of treatment with placebo, and after selection of the dose level for Part 2 of the study all patients received risdiplam at the Part 2 dose level.

Part 1 of # BP39056 is an open label study where Type 1 SMA patients of age 1-7 months were enrolled. Patients received risdiplam at various dose levels until selection of the dose level for Part 2 of the study, i.e. 0.2 mg/kg, and thereafter they received risdiplam at the Part 2 dose level until 2 years of age.

3.1.2 Nonclinical Safety Pharmacology Assessments

Refer to highlights of clinical pharmacology and cardiac safety and previous QT-IRT review under IND-128972 in DARRTs (Dt: 01/16/2018; link).

3.2 SPONSOR'S RESULTS

3.2.1 By-Time Analysis

The sponsor's primary analysis is based on concentrations-QTc analyses. Please see section 3.2.3 for additional details.

Reviewer's Comments: *The sponsor presented figures by-time analysis for mean changes from baseline for studies BP29840 and NP39625. However, due to the small sample size, the by-time analysis is not interpretable. The FDA statistical reviewer used non-parametric*

method in by-time point analysis to explore the time trend of data. Please see section 4.3 for additional details.

3.2.1.1 Assay Sensitivity

Not applicable.

3.2.1.1.1 QT Bias Assessment

No QT bias assessment was conducted by the sponsor.

Reviewer's comment: The available data was not suitable for conducting bias assessment.

3.2.2 Categorical Analysis

In reviewer's categorical analysis, 1 subject on placebo had QTcF between 480 and 500 msec from study BP39055, and 2 subjects from studies BP39055 and 4 subjects from BP39056 had ΔQTcF > 60 msec.

In sponsor's categorical analysis, 1 subject had QTcF between 480 and 500 msec from study BP39055 and 4 subjects had ΔQTcF > 60 msec from studies BP39056. FDA reviewer could not locate ΔQTcF > 60 msec summary table from sponsor's BP39055 report. Please see section 4.4 for reviewer's additional details.

3.2.3 Exposure-Response Analysis

The sponsor conducted concentration-QT analysis using data from studies # BP29840, # NP39625, # BP39054, Part 1 of # BP39055, and Part 1 of # BP39056. The sponsor used following model -

$$Y_{ijk} = (\alpha + \alpha_{ij}) + (\beta + \beta_{ij}) \cdot conc_{ijk} + \tau_j + \gamma \cdot age_i + (\tau\beta)_j \cdot c_{ijk}$$
$$+\beta\gamma \cdot age_i \times c_{ijk} + \delta_l + \epsilon_{ijk}$$

Y_{ijk} - is the change from baseline in QTcF (ΔQTcF) for subject i in study j (subject within a study) with repetition k; α - is an overall mean effect; α_{ij} - are subject specific random intercepts (with mean zero and constant variance); β - is an overall slope; β_{ij} - are subject specific random slopes (with mean zero and constant variance); $conc_{ijk}$ - are the concentrations observed in subject i in study j with repetition k; τ_j - is the effect of the categorical variable 'study'; γ - is the coefficient for age; age_i - age at screening (in months); interaction terms; δ_l - is the effect of the two-level categorical variable 'sex'; and eta_{ijk}- are random error terms. The sponsor's analysis claims no evidence for a prolongation in QTcF with the upper limit of the two-sided 90%-CI of ΔQTcF not exceeding 10 msec.

Reviewer's comment: Please see section 4.5 for the reviewer's analysis. The reviewer's analysis included clinical studies (# BP29840, # NP39625) conducted in healthy subjects.

3.2.4 Cardiac Safety Analysis

The sponsor summarized the results of their cardiac safety assessment in 2.7.4 Summary of Clinical Safety section 4.2.

A review of AEs coding to the MedDRA SMQ Torsade de pointes/QT prolongation including the PT Seizure did not show any events suspected to be due to risdiplam-induced QT prolongation. Three AEs in 3 patients were retrieved:

One patient had Grade 2 loss of consciousness on Study Day 442, while on 0.2 mg/kg risdiplam, which resolved the same day without treatment and without change to risdiplam therapy. No ECG during the AE was available, the patient's ECG did not show any clinically significant abnormal finding at baseline.

One patient died on Study Day 68, 1 day after receiving the last dose of study drug, at 0.2mg/kg, due to fatal acute respiratory failure. Grade 4 cardiac arrest was reported on Day 59 which resolved the same day and occurred in the course of acute respiratory failure due to unspecified respiratory infection. No clinically significant abnormal findings were observed on ECGs at baseline and on the day before AE onset. Further details are provided in the CSR BP39056 (FIREFISH) patient narratives.

One patient died on Study Day 236, 1 day after receiving the last dose of study drug, at 0.25mg/kg, due to fatal cardiac arrest and respiratory failure, both with onset on Study Day236. ECG at baseline was normal, and no ECG was reported during the course of the event. Further details are provided in the CSR BP39056 (FIREFISH) patient narratives.

Reviewer's comment: The percentage of patients with QTc >480 ms or change from baseline >60 ms are shown in the IRT analysis in section 4.4.1. None of the patients taking risdiplam had QTcF > 480 msec. Six subjects had ΔQTcF > 60 msec from pooled studies BP39055 and BP39056.

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF for the primary analysis, which is acceptable as no large increases or decreases in heart rate (i.e. |mean| < 10 bpm) were observed (see Section 4.3.2).

4.2 ECG ASSESSMENTS

4.2.1 Overall

Waveforms of three studies were submitted, but only those in study BP39054 have annotations, while those in studies BP39055 and BP39056 haven't any. Waveforms from other two studies BP29840 and NP39625 haven't been submitted. Overall ECG acquisition and interpretation in this study can't be determined.

4.2.2 QT Bias Assessment

Not applicable.

4.3 BY TIME ANALYSIS

The sample sizes for study BP29840 doses at 0.6 mg (n=3), 2 mg (n=3), 6 mg (n=3), 18 mg (n=6), and placebo (n=7); for study NP39625 doses at 2 mg (n=6), 6 mg (n=6), 12 mg (n=6), and placebo (n=6). Given the smaller sample size within each of the 7 dose cohorts (n=3 to 6 on treatment, and n= 6 to 7 on placebo) and the potential unbalanced carry-over effects, the statistics reviewer applied non-parametric statistics (e.g. Hodges-Lehman

Estimate, median) and its 90% CI interval of ΔΔQTcF for studies BP29840 and NP39625 by time. No positive control group included in both studies.

All figures present the time points up to 24 hours. The time points 48 up to 264 hours are too distant for plotting purpose. All time-points were considered in the summary table of the largest upper bound for ECG parameters.

4.3.1 QTc

Figure 1 displays the time profile of ΔΔQTc for different treatment groups up to 24 hours. The largest median and 2-sided 90% CI for ΔΔQTc by dose cohort and study are shown in Table 3.

Figure 1: Median and 90% CI of ΔΔQTcF Timecourse (unadjusted CIs)

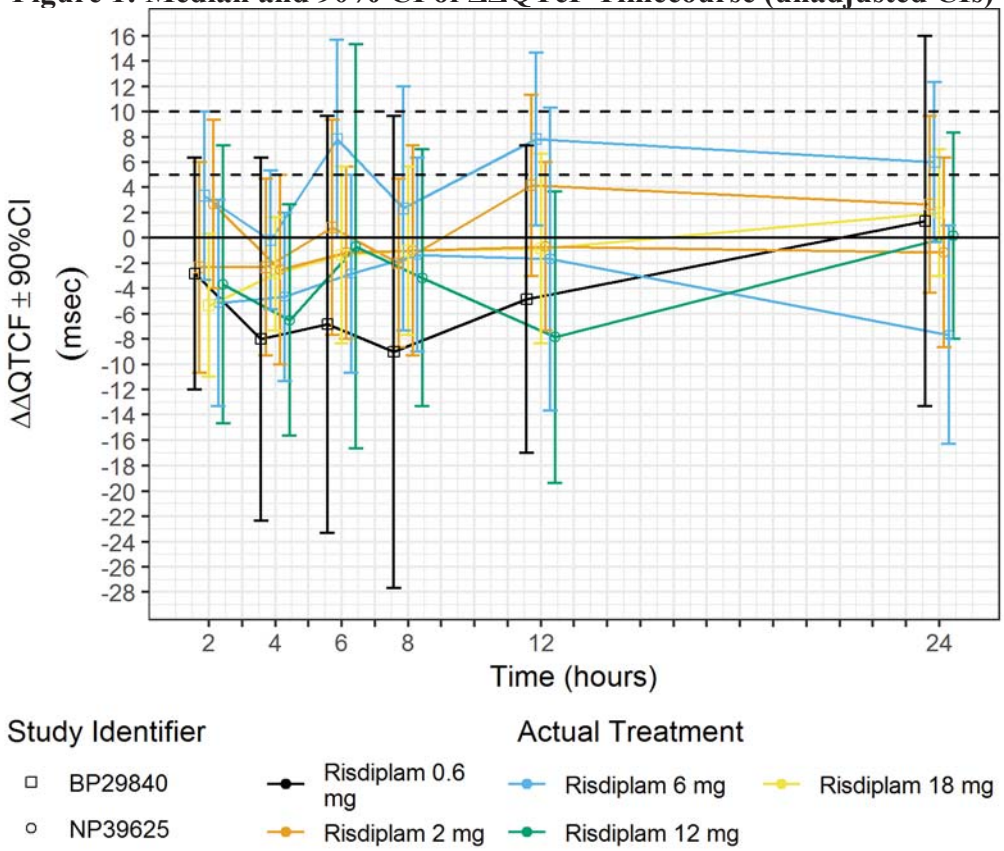


Table 2: Median and the 90% CIs Corresponding to the Largest Upper Bounds for ΔΔQTc

Study Identifier	Actual Treatment	Time (hours)	ΔΔQTCF (msec)	90.0% CI (msec)
BP29840	Risdiplam 0.6 mg	48.000	6.0	(-6.3 to 18.3)
BP29840	Risdiplam 2 mg	216.000	6.5	(-10.7 to 23.7)
BP29840	Risdiplam 6 mg	216.000	4.3	(-8.7 to 17.3)
BP29840	Risdiplam 18 mg	72.000	0.5	(-9.0 to 10.0)

Study Identifier	Actual Treatment	Time (hours)	ΔΔQTCF (msec)	90.0% CI (msec)
NP39625	Risdiplam 2 mg	120.000	-0.8	(-11.7 to 10.0)
NP39625	Risdiplam 6 mg	120.000	-4.0	(-19.7 to 11.7)
NP39625	Risdiplam 12 mg	120.000	3.2	(-10.0 to 16.3)

Given the small sample size in these studies, the non-parametric analysis results (which was not powered as primary analysis in the original study design) may not be interpretable for the multiple dose part in particular.

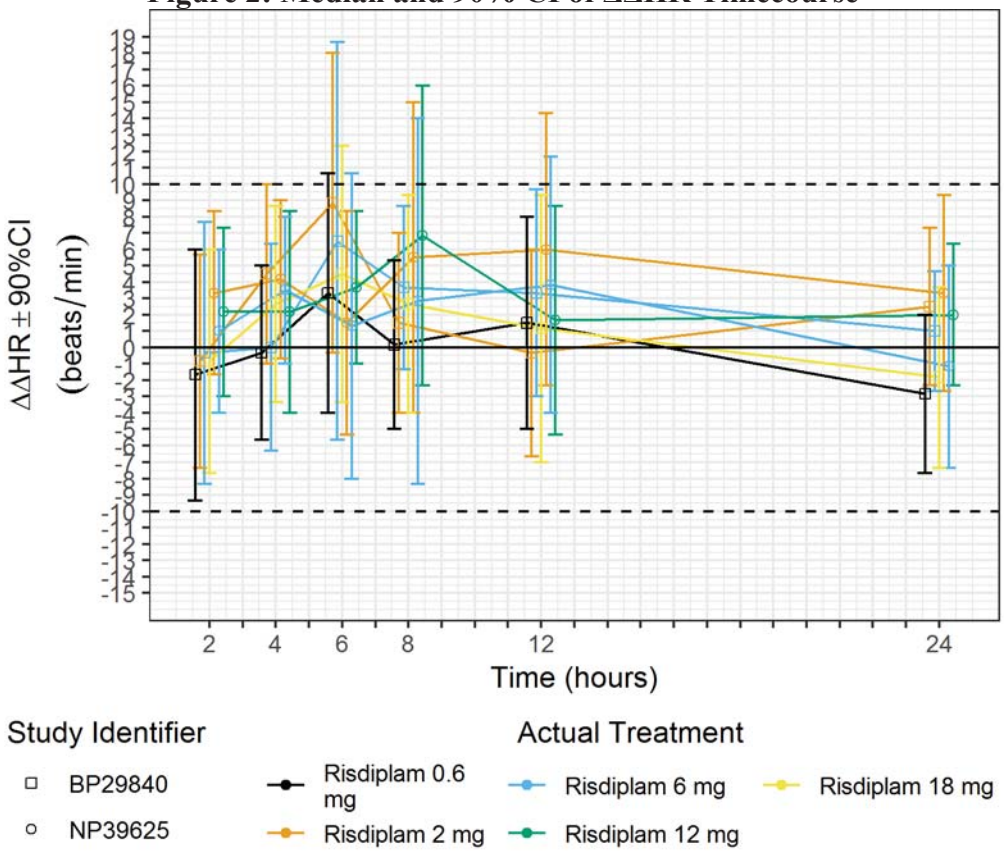
4.3.1.1 Assay sensitivity

Not applicable.

4.3.2 HR

Figure 2 displays the time profile of ΔΔHR for different doses groups.

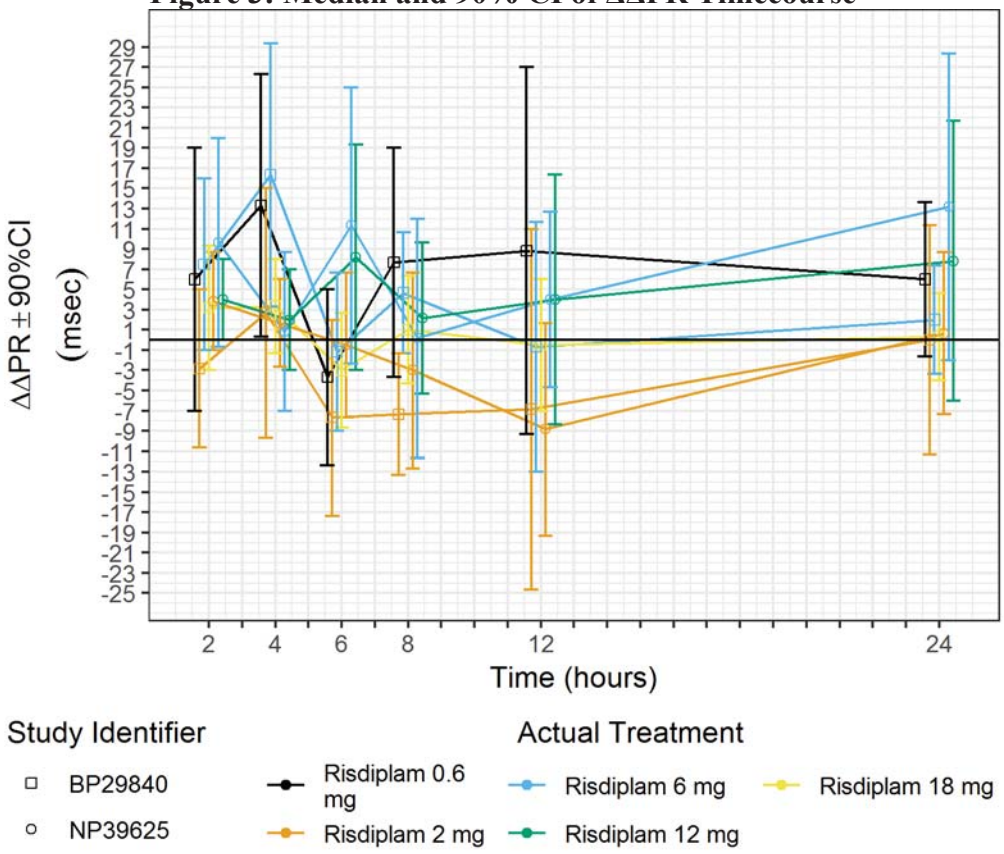
Figure 2: Median and 90% CI of ΔΔHR Timecourse



4.3.3 PR

Figure 3 displays the time profile of ΔΔPR for different doses groups.

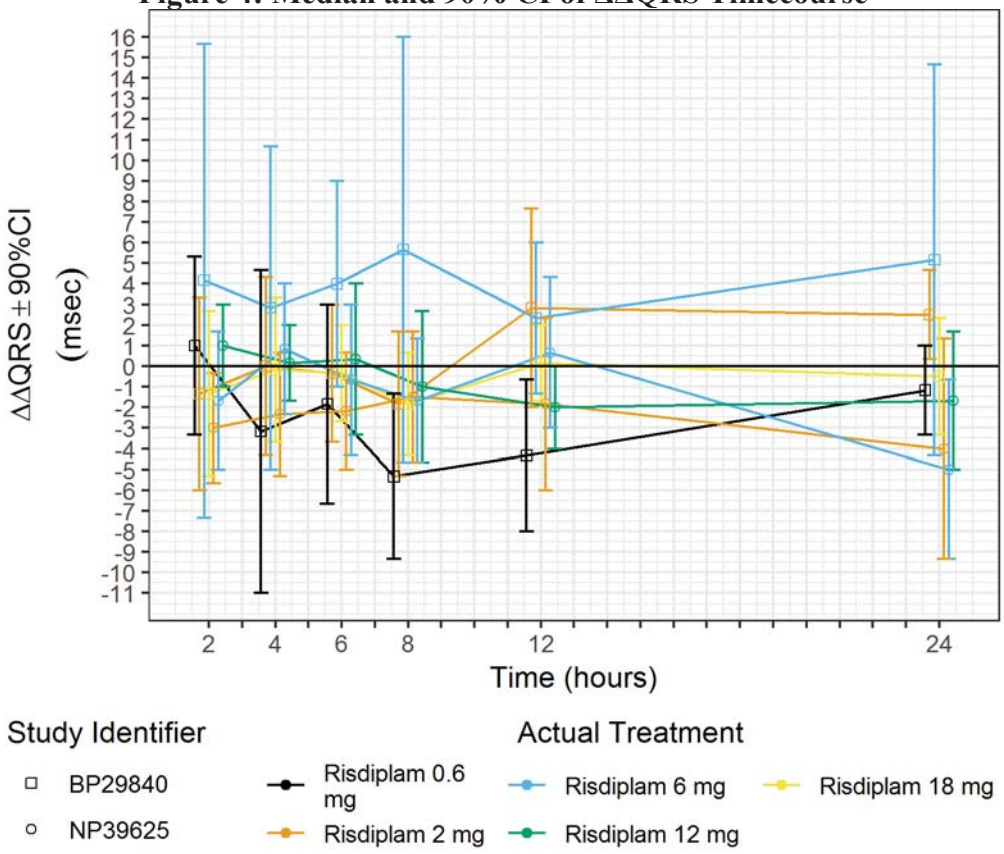
Figure 3: Median and 90% CI of ΔΔPR Timecourse



4.3.4 QRS

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

Figure 4: Median and 90% CI of ΔΔQRS Timecourse



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 and includes both scheduled and unscheduled ECGs.

The categorical analysis pooled all doses for studies BP39054, BP39055 and BP39056, and combined doses for Studies BP29840 and NP39625

4.4.1 QTc

Table 3 lists the categorical analysis results for QTcF (≤ 450 msec, between 450 and 480, between 480 and 500 msec). One subject on placebo had QTcF > 480 msec (483.3) and ΔQTcF > 60 msec (73.3 msec) from study BP39055.

Table 3: Categorical Analysis for QTc

Study Identifier	Actual Treatment	Total (N)		Value <= 450 msec		450 msec < Value <= 480 msec		480 msec < Value <= 500 msec	
		# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
BP29840, NP39625	All doses	44	506	43 (97.7%)	502 (99.2%)	1 (2.3%)	4 (0.8%)	0 (0%)	0 (0%)
	Placebo	13	143	13 (100.0%)	143 (100.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Study Identifier	Actual Treatment	Total (N)		Value <= 450 msec		450 msec < Value <= 480 msec		480 msec < Value <= 500 msec	
		# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
BP39054	All doses	11	178	11 (100.0%)	178 (100.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
BP39055	All doses	51	755	49 (96.1%)	753 (99.7%)	2 (3.9%)	2 (0.3%)	0 (0%)	0 (0%)
	Placebo	16	140	14 (87.5%)	138 (98.6%)	1 (6.2%)	1 (0.7%)	1 (6.2%)	1 (0.7%)
BP39056	All doses	21	245	18 (85.7%)	240 (98.0%)	3 (14.3%)	5 (2.0%)	0 (0%)	0 (0%)

Table 4 lists the categorical analysis results for ΔQTc (≤ 30 msec, between 30 and 60 and > 60 msec). Two subjects (1 on risdiplam 0.02 mg/kg, the other on risdiplam 0.05 mg/kg) from study BP39055 and four subjects (2 subjects on Cohort 1 and 2 subjects on Cohorts 2 when the outliers occurred) from study BP39056 had ΔQTcF > 60 msec.

Table 4: Categorical Analysis for ΔQTcF

Study Identifier	Actual Treatment	Total (N)		Value <= 30 msec		30 msec < Value <= 60 msec		Value > 60 msec	
Study Identifier	Actual Treatment	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
BP29840, NP39625	All doses	44	506	44 (100.0%)	506 (100.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
BP29840, NP39625	Placebo	13	143	13 (100.0%)	143 (100.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
BP39054	All doses	11	178	10 (90.9%)	177 (99.4%)	1 (9.1%)	1 (0.6%)	0 (0%)	0 (0%)
BP39055	All doses	51	755	45 (88.2%)	743 (98.4%)	4 (7.8%)	10 (1.5%)	2 (3.9%)	2 (0.07%)
BP39055	Placebo	16	140	7 (43.7%)	131 (93.6%)	6 (37.5%)	6 (4.3%)	3 (18.8%)	3 (2.1%)
BP39056	All doses	21	245	6 (28.6%)	217 (88.5%)	11 (52.3%)	20 (8.2%)	4 (19.0%)	8 (3.3%)

4.4.2 HR

Table 5 lists the categorical analysis results for maximum HR (≤ 100 bpm and > 100 bpm). Sixth-two subjects had HR > 100 bpm. Five subjects experienced HR > 100 bpm with a 25% increase from the baseline.

Table 5: Categorical Analysis for HR

Study Identifier	Actual Treatment	Total (N)		Value <= 100 beats/min		Value > 100 beats/min	
		# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
BP29840, NP39625	All doses	44	506	44 (100.0%)	506 (100.0%)	0 (0%)	0 (0%)
	Placebo	13	143	13 (100.0%)	143 (100.0%)	0 (0%)	0 (0%)

Study Identifier	Actual Treatment	Total (N)		Value <= 100 beats/min		Value > 100 beats/min	
		# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
BP39054	All doses	12	196	9 (75.0%)	182 (92.9%)	3 (25.0%)	14 (7.1%)
BP39055	All doses	51	755	13 (25.5%)	535 (70.9%)	38 (74.5%)	220 (29.1%)
	Placebo	16	140	3 (18.8%)	84 (60.0%)	13 (81.2%)	56 (40.0%)
BP39056	All doses	21	245	0 (0%)	1 (0.4%)	21 (100.0%)	244 (99.6%)

4.4.3 PR

Table 6 lists the categorical analysis results for PR (≤ 200 msec and > 220 msec with and without 25% increase over baseline). One subject on risdiplam 0.25 mg/kg from study BP39055 experienced PR > 220 msec with a 25% increase from the baseline.

Table 6: Categorical Analysis for PR

Study Identifier	Actual Treatment	Total (N)		Value <= 220 msec		Value > 220 msec & < 25%		Value > 220 msec & >= 25%	
		# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
BP29840, NP39625	All doses	44	506	43 (97.7%)	497 (98.2%)	1 (2.3%)	9 (1.8%)	0 (0%)	0 (0%)
	Placebo	13	143	12 (92.3%)	141 (98.6%)	1 (7.7%)	2 (1.4%)	0 (0%)	0 (0%)
BP39054	All doses	11	181	10 (90.9%)	166 (91.7%)	1 (9.1%)	15 (8.3%)	0 (0%)	0 (0%)
BP39055	All doses	51	755	50 (98.0%)	754 (99.9%)	0 (0%)	0 (0%)	1 (2.0%)	1 (0.1%)
	Placebo	16	140	15 (93.8%)	139 (99.3%)	0 (0%)	0 (0%)	1 (6.2%)	1 (0.7%)
BP39056	All doses	21	241	21 (100.0%)	241 (100.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

4.4.4 QRS

Table 7 lists the categorical analysis results for QRS (≤ 120 msec and > 120 msec with and without 25% increase over baseline). No treated subject experienced QRS > 120 msec with a 25% increase from the baseline.

Table 7: Categorical Analysis for QRS

Study Identifier	Actual Treatment	Total (N)		Value <= 120 msec		Value > 120 msec & < 25%		Value > 120 msec & >= 25%	
		# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
BP29840, NP39625	All doses	44	506	43 (97.7%)	505 (99.8%)	1 (2.3%)	1 (0.2%)	0 (0%)	0 (0%)
	Placebo	13	143	13 (100.0%)	143 (100.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Study Identifier	Actual Treatment	Total (N)		Value <= 120 msec		Value > 120 msec & < 25%		Value > 120 msec & >= 25%	
		# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
BP39054	All doses	11	181	11 (100.0%)	181 (100.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
BP39055	All doses	51	755	51 (100.0%)	755 (100.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Placebo	16	140	15 (93.8%)	135 (96.4%)	0 (0%)	4 (2.9%)	1 (6.2%)	1 (0.7%)
BP39056	All doses	21	245	21 (100.0%)	245 (100.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

4.5 EXPOSURE-RESPONSE ANALYSIS

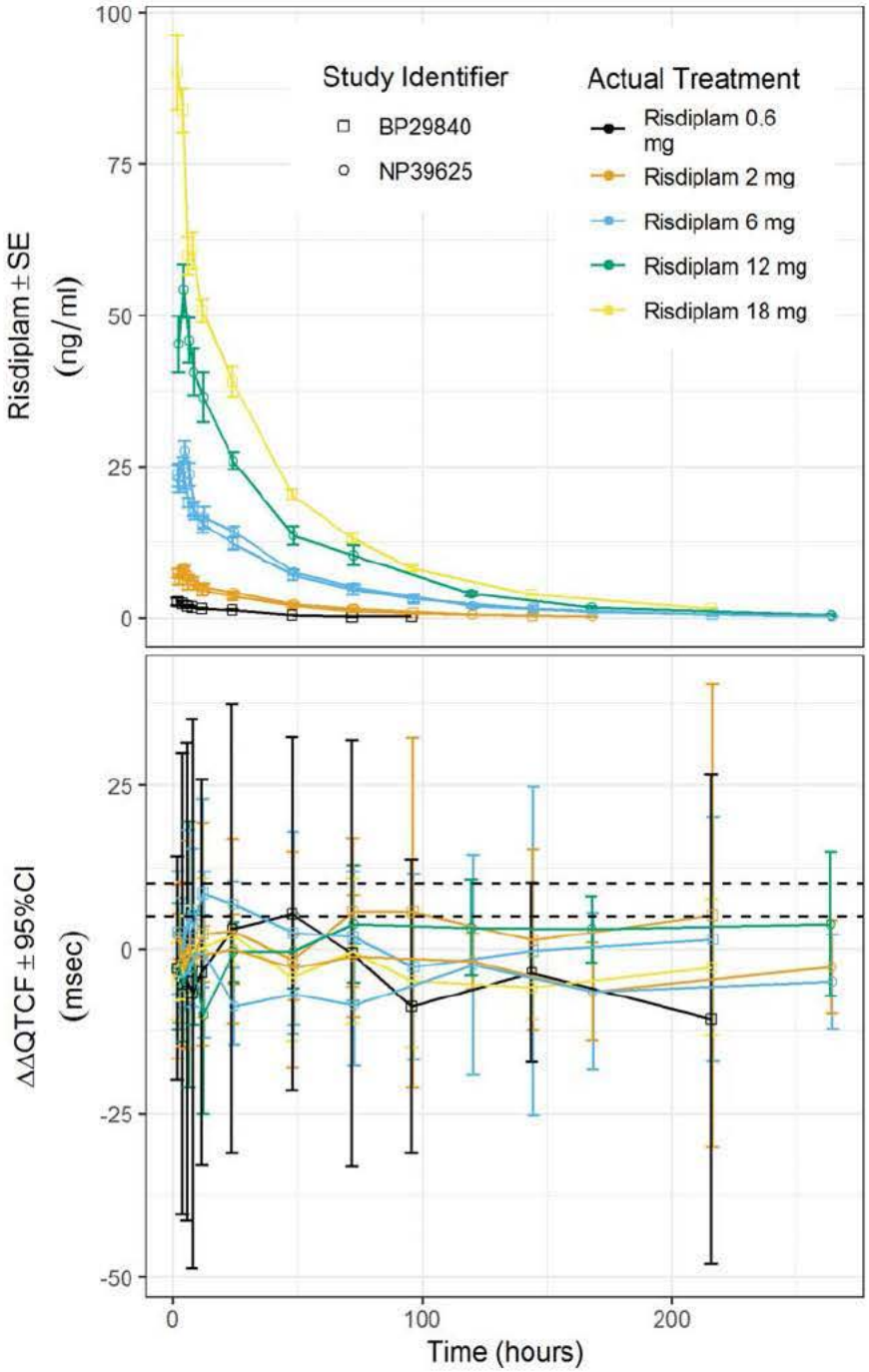
The objective of the clinical pharmacology analysis is to assess the relationship between concentration of risdiplam and ΔQTcF. The exposure-response analysis was conducted with data from studies # BP29840 (excluding drug interaction and food effect arms) and # NP39625 using all subjects with baseline and at a least one post-baseline ECG with time-matched PK.

The exposures of risdiplam observed in studies with SMA patients (Part 1 of # BP39055, and Part 1 of # BP39056) were slightly higher than those observed in studies with healthy subjects. However, studies # BP39056 and # BP39056 with SMA patients were open label without a placebo control. The exposures of risdiplam observed in study # BP39054 with SMA patients were considerably lower than those observed in studies with healthy subjects. For study # BP39055 with SMA patients, there was a limited data available with matched ECG/PK at higher exposures. Considering the overall quality of available ECG data, clinical studies conducted in healthy subjects were utilized for the exposure-response analysis.

Prior to evaluating the relationship using a linear model, the three key assumptions of the model were evaluated using exploratory analysis: 1) absence of significant changes in heart rate (more than a 10 bpm increase or decrease in mean HR); 2) delay between plasma concentration of risdiplam and ΔQTcF; and 3) presence of non-linear relationship.

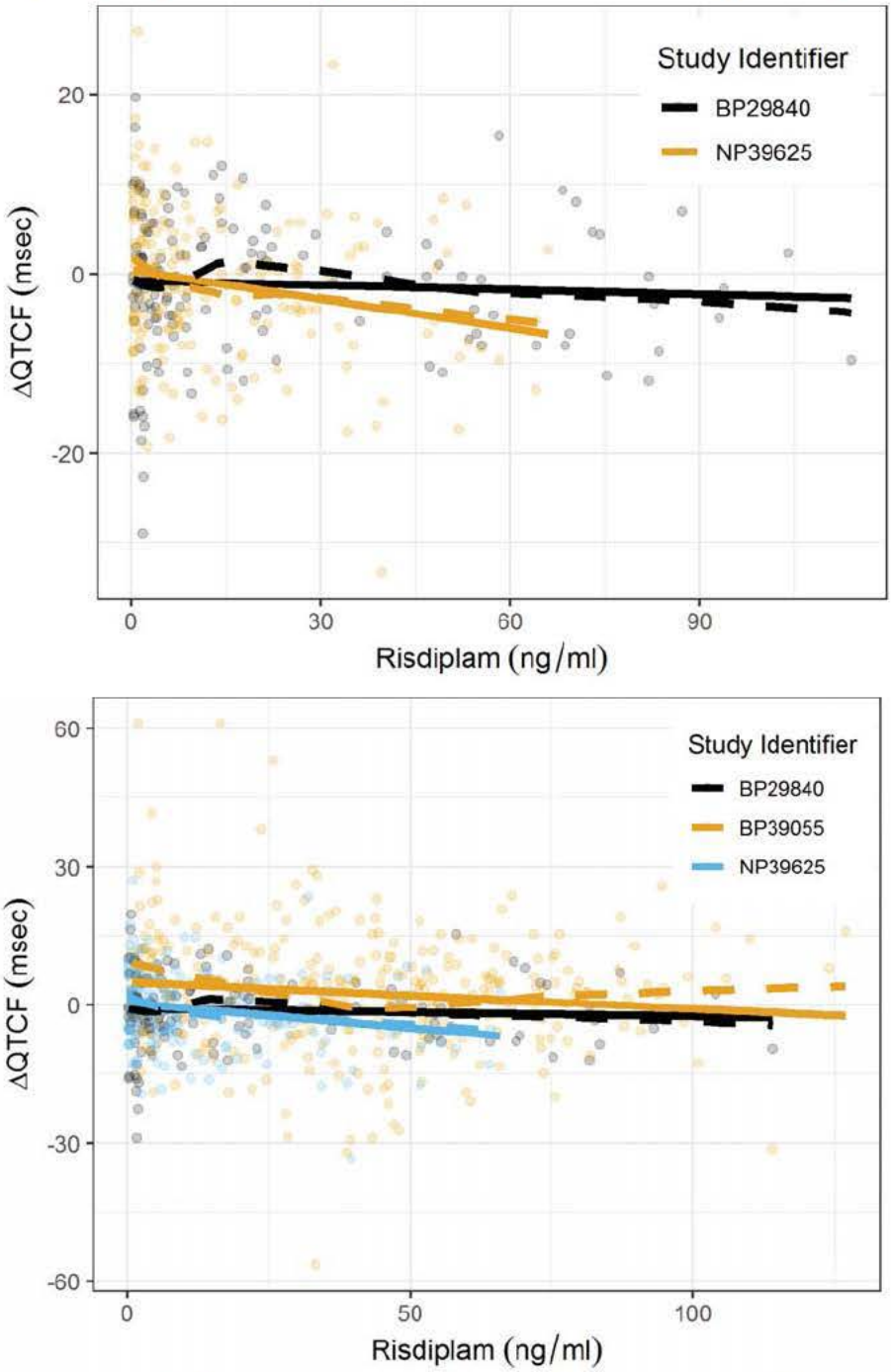
An evaluation of the time-course of risdiplam concentration and changes in ΔΔQTcF is shown in Figure 5. There is no apparent correlation between the time at maximum effect on ΔΔQTcF and peak concentrations of risdiplam indicating no significant hysteresis. Figure 2 shows the time-course of ΔΔHR, which suggests an absence of significant ΔΔHR changes (see Sections 4.3.2 and 4.4.2).

Figure 5: Time course of risdiplam concentration (top) and QTc (bottom)



After confirming the absence of significant heart rate changes or delayed QTc changes, the relationship between risdiplam concentration and ΔQTcF was evaluated to determine if a linear model would be appropriate. Figure 6 shows the relationship between risdiplam concentration and ΔQTc using studies in healthy subjects (Studies # BP29840, # NP39625) and available data from study in SMA patients (Part 1 of # BP39055) which support the use of a linear model.

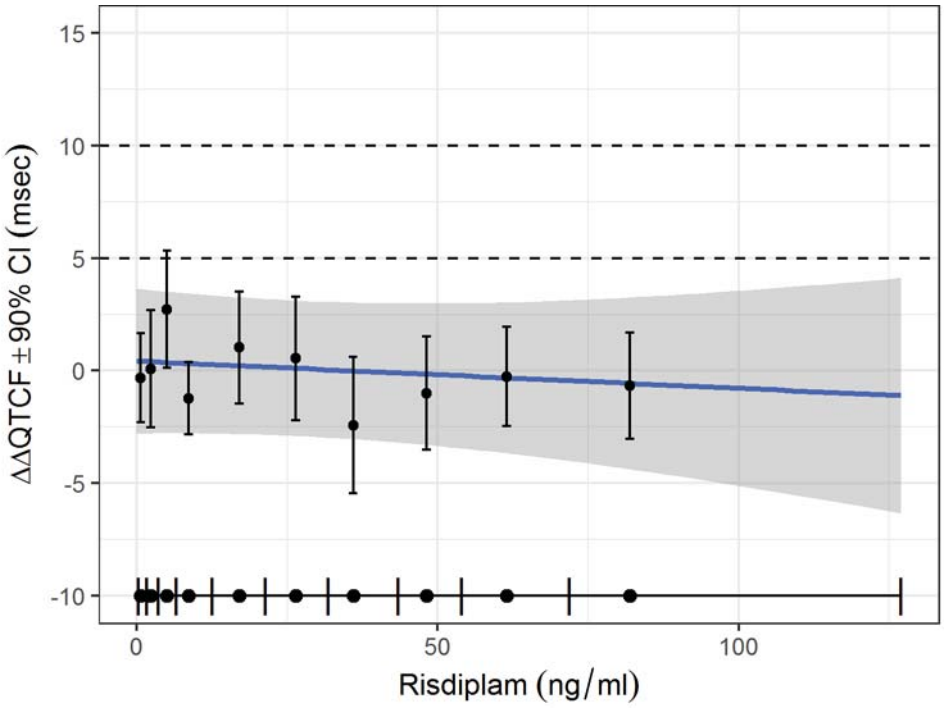
Figure 6: Assessment of linearity of risdiplam concentration-QTc relationship (top: all studies with healthy subjects, bottom: all studies with placebo control)



Finally, the linear model was applied to the data and the goodness-of-fit plot is shown in Figure 7. Although the concentration-response analysis of risdiplam data did not indicate a positive slope in the relationship between ΔQTcF and the plasma concentration for these studies, the exposures (Cmax: 92 ng/mL) covered in these studies are considerably (~2-fold) lower that those associated with therapeutic doses (Cmax: 184 ng/mL) in pediatric population (see Sections 1 and 3.1). In absence of mechanistic understanding of the effects

of risdiplam, the available data do not support extrapolation of the concentration-QTc relationship to affirm the cardiac safety at the therapeutic doses in SMA patients.

Figure 7: Goodness-of-fit plot for QTc



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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: January 7, 2020

To: Eric Bastings, MD, Acting Director
Division of Neurology 1

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

From: Jovita Randall-Thompson, PhD, Pharmacologist
Controlled Substance Staff

Subject: NDA 213535 (IND 128972), Risdiplam (RO7034067)
Indication: Treatment of spinal muscular atrophy (SMA) (b) (4)
Dosages: 0.2 mg/kg in patients aged 2 months to 2 years, and 0.25 mg/kg or a maximum of 5 mg, in patients aged 2 years and over, given once daily
Formulation: A powder for oral solution, 60 mg of risdiplam mixed in water (79 mL), presented in a 0.75 mg/mL strength
Sponsor: Genentech

Materials Reviewed: NDA 213535, for filing purposes
NDA 213535, Model 1.11.4 Drug Abuse Liability Assessment: Risdiplam, September 17, 2019
IND 128972, CSS Review, J. Randall-Thompson, DARRTS, January 30, 2018

I. Background

This memorandum is in response to a consult request dated September 26, 2019, from the Division of Neurology Products (DN1) pertaining to the fileability of NDA 213535, risdiplam, and is being submitted in lieu of a filing checklist.

Pursuant to Section 505(b)(l) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314, Genentech (the Sponsor) submitted NDA 213535 for risdiplam oral solution (0.2 mg/kg, 0.25 mg/kg or the maximum dose of 5 mg) proposed for (b) (4) spinal muscular atrophy (SMA).

Risdiplam is a small molecule (401.46 g/mL) and is a splicing modifier of Survival of Motor Neuron 2 gene (SMN2). The drug restores SMN protein levels in SMA patients through the modulation of

SMN2 pre-mRNA splicing by including an exon 7 into the mRNA transcript. It crosses the blood brain barrier (BBB), and is activein the central nervous system (CNS). The drug is formulated as a powder for oral solution and rapidly absorbed at therapeutic doses 0.25 and 5 mg/kg (C_{max} between 79 and 184 ng/mL; T_{max} range of 1 to 4 hours; Drug Abuse Liability Assessment: Risdiplam, pages 17 - 18). One major metabolite (M1, 30% of the plasma concentration of risdiplam) was identified (Drug Abuse Liability Assessment: Risdiplam, page 18).

Risdiplam has a similar pharmacological effect to the approved drug nusinersen (Spinraza, NDA 209531). Nusinersen is an antisense oligonucleotide with an inclusion of exon 7 in SMN2 pre-mRNA, and is not scheduled under the Controlled Substance Act (CSA).

Under IND (128972), the Sponsor proposed to conduct an in vitro binding assessment of the drug. In response, CSS recommended that the Sponsor conduct the binding assessment to support the position that risdiplam does not show a signal of abuse and additional abuse-related studies are not needed.

The following sections provide conclusions and recommendations.

II. Conclusions*

1. There is no need to further evaluate the abuse potential of risdiplam, based on the following:

    a. Risdiplam is not chemically or pharmacologically similar to any known drug of abuse that is scheduled. The main action of Risdiplam, the molecular mechanism of splicing modification of the SMN2 gene and secondary slice targets are not associated with abuse-related effects.

    b. Radioligand binding and enzymatic functional assays performed by the Sponsor revealed that risdiplam (only) significantly binds to the histamine 3 and muscarinic M1 receptors and both risdiplam and its metabolite (M1) inhibit several cyclooxygenase receptor subtypes (1 and 2) and acetylcholinesterase (Drug Abuse Liability Assessment: Risdiplam, page 14). However, these receptors and enzymes when activated or inhibited do not result in any meaningful abuse-related effects .

    c. When administered orally to healthy volunteers in phase 1 studies, centrally-mediated adverse events (AEs) associated with risdiplam were limited and included somnolence and dizziness.

    d. In summary, the mechanism of action, general nonclinical responses, and associated CNS-related adverse events (AEs)) shown with risdiplam did not present a signal of abuse potential (IND 128972, CSS Review, DAARTS J. Randall-Thompson, January 30, 2018).

* To be conveyed to Sponsor, if appropriate

III. Recommendations (to the Division)

Based on the lack of an abuse signal found with risdiplam, we believe that CSS need not be involved in the review of this NDA. Consequently, CSS will not submit a filing checklist or further review for NDA 213535.

Additionally, the label for Spinraza, a similar drug with the same indication as risdiplam does not include a Section 9, Drug Abuse and Dependence. Therefore, as is the case with Spinraza, Section 9 should not be included in the label for risdiplam tablets.

CSS recommends that the Division contact CSS if the DN1 review team identifies any abuse-related concerns associated with the drug during the course of their review of this NDA.

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/s/

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