CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

219407Orig1s000

OTHER REVIEW(S)

IMMUNOGENICITY ASSESSMENT

Application Type	NDA
Application Number	219407
Submit Date	08/21-2024
Received Date	08/07/2025
Division/Office	OND/ORO/DROII
Review Completion Date	08/14/2025
Proposed Proper Name[1]	ISIS721744 (Donidalorsen)
Pharmacologic Class	GalNAc-conjugated 2'-MOE modified ASO
Applicant	Ionis Pharmaceuticals, Inc
Applicant Proposed Indication(s)	Prophylaxis to prevent attacks of hereditary angioedema (HAE) in adult and pediatric patients 12 years of age and older.

Immunogenicity Assessors

Primary Assessor(s)	Ha Na Lee PhD
Secondary Assessor (s)	Daniela Verthelyi, MD, PhD

Immunogenicity Consult request

OPQR was requested to review the adequacy of method validation for quantitation of ADAs against donidalorsen in human plasma as well as the adequacy of in-study bioanalysis specifically for studies CS5 and CS7 (which will be reported in labeling).

Assessor Recommendation:

The ADA assay the applicant used is generally acceptable; however, it has several limitations, including low specificity as the ADA binding is reduced in the presence of oligonucleotides of other sequence, structure, or GalNAc moiety. The assay also shows reduced sensitivity due to on board drug, but the reduction is unlikely to result in false negative samples. Despite the shortcomings, the data stemming from the assay should be interpretable.

Review

Document Reviewed	Link to Document
Validation of an ELISA method for the Detection of Anti-ISIS721744 Antibodies in Human Plasma	\\CDSESUB1\EVSPROD\nda218614\0001\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\678354-mv09\678354-mv09-body.pdf

721744-CS05BA02 Bioanalytical Report	\\CDSESUB1\EVSPROD\nda219407\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hae\5351-stud-rep-contr\721744-cs5\721744-cs05ba02-final-report.pdf
721744-CS07BA02 Interim Bioanalytical Report 1	\\CDSESUB1\EVSPROD\nda219407\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hae\5352-stud-rep-uncontr\721744-cs7\721744-cs07ba02-interim-report.pdf

Validation of Anti-Drug Antibody Assays

The sponsor has provided validation exercises for the detection of ADA against ISI721744 but no anti-GalNAc antibody assay.

Method Principle

A brief description of each assay is given below and tables which detail the key assay parameters are given below for each assay.

Validation Exercises

Critical assay parameters are summarized below for each assay.

Validation Parameter	Validation of an ELISA Method for the Detection of Anti-ISIS678354 Antibodies in Human Plasma	Assessor Comment
Contract Research Org	(b) (4)	
Assay principle	Multi-Tiered Approach An indirect ELISA using thiol-modified ISIS721744-coated plates (0.500 µg/mL of 3'Thiol-ISIS 721744)	
Sample Pretreatment	N/A	
Positive control (PC)	Anti-ISIS721744 Affinity-purified polyclonal rabbit antibodies Antibodies diluted into the negative control pool (9 pooled drug naïve sample lots with no detectable ADA)	
Detection Ab	HRP-conjugated Protein A/G	*Acceptable. This will detect PC and all human IgG subclasses, IgA, IgE, IgM and to a lesser extent IgD in human plamsa*

		samples
PC Dose Curve and Hook Effect	No hook effect was observed up to 56,000 ng/mL	
LPC	16 ng/mL for screening and 25 ng/mL for confirmatory	
MPC	800 ng/ml	
HPC	3000 ng/ml	
Matrix and NC	Human plasma containing dipotassium EDTA	
MRD	1:25 in blocking buffer	
Screening cut- point (SCP) (non-parametric, multiplicative, 95% upper limit)	<u>*SCP for healthy plasma samples:*</u> Sixty drug-naïve matrix samples (30 male and 30 female) were analyzed n=1 in 3 independent assays by 2 analysts. Note: 4 samples were determined as biological outliers and an additional sample was eliminated due to insufficient volume. Two additional samples were removed due to >20 % CV. Evaluation was based on the natural log-transformed S/N values. The non-transformed pooled data was evaluated for statistical outliers using Tukey's Outlier Filter. Non-parametric approach was used to determine SCP. SCP using the 95th upper prediction interval of pooled cut point data was determined to be **1.37**. Floating Screening Assay Cut Point = mean NC **× 1.37** <u>*SCP for patient plasma samples:*</u> To determine disease state SCP, 23 individual drug-naïve hereditary angioedema human plasma sample lots with no detectable ADA were analyzed in 4 independent assays by 3 analysts SCP using the 95th upper prediction interval of pooled cut point data was determined to be **1.09**. Floating Screening Assay Cut Point = mean NC × **1.09**	*4 out 60 samples were positive, suggesting that the assay can yield false positive results. This is consistent with the observation that oligonucleotides with different sequences or modifications can compete the binding just as well as the drug product.* *The exclusion of the false positive results from the calculation of the cut point is acceptable.* *Use of 5% FPR for SCP determination is acceptable.*
Confirmatory cut-point (CCP) (% inhibition, Fixed, 99% upper limit)	<u>*CCP for healthy plasma samples:*</u>	*Use of 1% FPR for CCP determination is acceptable.*

	CCP was determined by analyzing 60 individual drug-naïve human plasma sample lots (30 male and 30 female) with no detectable ADA unspiked and spiked with an excess (50.0 µg/mL) of drug prior to analysis. Data were compiled from 3 independent assays by two analysts. The mean percentage signal inhibition for each sample was calculated. Non-parametric approach was applied to the CCP determination. CCP using the 99th upper prediction interval of pooled cut point data, and then transformed to a % inhibition cut point was determined to be **36.3%**. <u>*CCP for patient plasma samples:*</u> The confirmatory % inhibition cut point was determined to be **19.4%** from an upper limit of prediction interval.	
Titer Cut Point (TCP)	<u>*TCP for healthy plasma samples:*</u> TCP factor of **1.48** was determined using the same data and non-parametric approach used to establish the SCP factor but with a more stringent FPR (0.1% FPR) Floating Titer Assay Cut Point = mean NC × **1.48** <u>*TCP for patient plasma samples:*</u> TCP factor of **1.20** was determined using the same data and non-parametric approach used to establish the SCP factor but with a more stringent FPR (0.1% FPR) Floating Titer Assay Cut Point = mean NC × **1.20**	*Use of 0.1% FPR for TCP determination is acceptable.*
Assay Drug tolerance	SLPC, CLPC, 100 ng/mL, MPC and HPC concentrations were tested in the presence of 0, 0.5, 1, 2.5, 5 and 5 ug/mL of ISIS-7217443. Fortified samples will be incubated for at least one hour at 37 °C ± 2°C and frozen at -80 °C ± 10 °C prior to analysis. SLPC was not detected in the presence of ≥ 0.5 µg/mL drug; CLPC was not detected in the presence of ≥ 5 µg/mL drug; antibodies at 100,	*Information from Clin Pharm reviewer:* *For Study CS5, Cmax was reported as 2290 ng/mL at 2 hours post-dose (which is around Tmax) on Day 113 following 80 mg Q8W.* *For Study CS7, only trough donidalorsen concentrations were collected. The maximum*

	800, and 3000 ng/mL were detected in the presence of up to 10.0 µg/mL drug.	*donidalorsen trough plasma concentration based on interim CS7 study report was 153 ng/mL at Week 9 following Q4W in OLE group.* *On board interference was tested using 500 ng/mL. This concentration reduced the sensitivity of the assay resulting in negative results for the SLPC but not the CLPC. Since the CLPS corresponds to an acceptable sensitivity level, this is acceptable.*
Sensitivity (95% CI)	HPC sample was diluted 3.75-fold followed by eight 2-fold serial dilutions (3.75-, 7.50-, 15.0-, 30.0-, 60.0-, 120-, 240-, 480-, and 960-fold dilutions). Sensitivity samples were subsequently diluted 1/25 in blocking buffer in the absence or presence of excess ISIS721744. The screening assay sensitivity was calculated from 17 runs as below (one plate was excluded due to unacceptable CV): Conc above CP + ((response above CP-screening CP response) x (conc below CP-conc above CP) / (response above CP-response below CP) The confirmatory assay sensitivity was calculated as below: Mean of assay sensitivity + (t0.01, df x STD) Screening 16 ng/mL Confirmatory 25 ng/ml	
Repeatability/Intra-assay variability	Intra-assay precision was evaluated for each positive control pool and the negative control pool by multiple analyses (n=6) of each pool in selected validation runs 26RKQR2, 29RKQR2 and 30RKQR2. Acceptance criteria: - %CV ≤ 20% - At least five sample result values must be available at each level to calculate descriptive statistics. <u>*Screening Results:*</u> NC 5.9% CV	*The intra-assay precision results met the acceptance criteria.*

	SLPC (16 ng/mL) 4.6 %CV cLPC (25 ng/mL) 3.7 %CV MPC (800 ng/mL) 1.4 %CV HPC (3000 ng/mL) 5 %CV <u>*Confirmatory Results*</u>*:* NC 88.3 % CV SLPC (16 ng/mL) 11.6 %CV cLPC (25 ng/mL) 7.5 %CV MPC (800 ng/mL) 0.3 %CV HPC (3000 ng/mL) 0.2 %CV	
Intermediate Precision (IP)/inter-assay variability	Inter-assay precision was calculated from the controls in all runs used to determine the cut point and was evaluated using the negative control and the positive control pools prepared at CLPC, MPC, and HPC. *Acceptance criteria:* %CV ≤ 20% <u>Screening</u> *Results:* NC 8.2 %CV CLPC 2.5 %CV MPC 9.9 %CV (excluding 1 plate) HPC 9.5%CV <u>Confirmatory</u> *Results:* CLPC 8.1 %CV MPC 0.6 %CV (excluding 1 plate) HPC 0.3%CV (excluding 2 plates)	*The inter-assay precision results met the acceptance criteria.*
Matrix interference	For matrix interference, blank, SLPC, CLPC, HPC concentrations were spiked into at 10 individual lots of normal human plasma. <u>Screening assay</u> *Acceptance criteria:* - ≥ 8 of 10 blank sample results < cut point, - *Results from ≥ 80% of spiked matrix samples are expected to fall within 80–120% of results from the blank matrix pool prepared at the corresponding level.* *Results:* - 10 out of 10 unspiked normal plasma lots were < plate cut point - 10 out of 10 individual lots of plasma spiked at SLPC, CPLC and HPC were ≥ plate cut point <u>Confirmatory assay</u>	*Samples spiked at SLPC concentration did not meet the acceptance criteria for confirmatory assay; however, since the CLPC was detected consistently and it is an acceptable level of detection, this is acceptable*

	Acceptance criteria: - 8 of 10 spiked sample results > confirmatory cut point (CCP) - 8 of 10 blank sample results < CCP *Results:* - 10 out of 10 unspiked normal plasma lots were < CCP - 7 out of 10 (70%) individual lots of plasma spiked at SLPC were ≥ CCP - 10 out of 10 individual lots of plasma spiked at CLPC and HPC	
Specificity	Analyzed SLPC, CLPC, and HPC controls inhibited with 50.0 µg/mL ISIS 721744, 50.0 µg/mL ION-942898, or 50.0 µg/mL ION-942899. *Acceptance criteria:* - %CV ≤ 20% - A screening run is acceptable if 3 of 4 PC replicates meet S/N criteria.(SLPC OD ≥ SCP; HPC OD ≥ 1.64) - A confirmatory run is acceptable if 100% of the NC-I (<36.3%), CLPC-I, and HPC-I (≥36.3%) meet % Inhibition criteria - A titer run is acceptable if the TPC titer value is within 60–240 (exclusive of the MRD) *Results:* SLPC: 40.2% inhibition by ISIS721744 38.7% inhibition by ION-942898 38.2% inhibition by ION-942899 CLPC: 50.6% inhibition by ISIS721744 42.9% inhibition by ION-942898 46.1% inhibition by ION-942899 HPC: 97.3% inhibition by ISIS721744 78% inhibition by ION-942898 77.9% inhibition by ION-942899 Runs meet the acceptance criteria	ION-942898 (b) (4) ION-942899 (b) (4) *Both ION-942898 and 942899 inhibited the detection of anti-ISIS 721744 antibodies. This may be due to the reactivity with GalNAc; however, the applicant has not performed a competition assay using solely GalNAc. So we cannot conclude whether the lack of specificity observed is due to the GalNAc moiety. Regardless, this suggests that false positive samples could occur, and this should be considered when assessing the ADA results in the context of clinical data.*
Stability	The stability assessment was performed with the PC spiked into NC pool at SLPC, CLPC and HCP levels, compared to the freshly prepared reference controls. Freeze/thaw stability and	

	thawed matrix stability were further evaluated by preparing HCP samples undiluted and serially diluted six times in NC pool using a two-fold dilution series. Freeze-thaw stability: 6 cycles of freeze (initial freeze of at least 24 hours followed by freeze periods of at least 12 hours) and thaw at RT Control stability in thawed matrix: thawed samples at RT for 26 hours prior to analysis *Acceptance criteria:* - %CV ≤ 20% - Mean of stability sample results are expected to be within 80-120% of the mean reference control results at the corresponding level - The titered HPC stability sample must fall within one dilution of the titered fresh HPC reference control All results met the acceptance criteria.	
Lipemia	Impact of lipemia was evaluated by analyzing NC, SLPC, CLPC and HPC controls prepared in 100% lipemic matrix containing >300 mg/dL triglycerides. Reference controls prepared in non-lipemic blank matrix pool at corresponding levels were analyzed for comparison. No effect of lipemia on the detection of anti-ISIS721744 antibodies in the screening or confirmatory assays. *Acceptance criteria:* - HPC > LPC > screening cut point > blank - Fall within 80–120% of results from the blank matrix pool prepared at the corresponding level *Results:* - All met the acceptance criteria within 92.1-98.7% recovery	*The assay met the acceptance criteria. One out of five lipemic samples spiked with SLPC showed % of inhibition below confirmatory cut point (36.3) while all normal matrix spiked with SLPC showed > 36.3.* *It is acceptable*
Hemolysis	Impact of hemolysis was evaluated by analyzing NC, SLPC, CLPC and HPC controls prepared in hemolyzed matrix containing 5% fully lysed whole blood. Reference controls prepared in non-hemolyzed blank matrix pool at corresponding levels were analyzed for comparison.	*The assay met the acceptance criteria.* *All hemolyzed samples spiked with SLPC showed % of inhibition below confirmatory cut point (36.3) while all normal matrix spiked with*

	No effect of hemolysis on the detection of anti-ISIS721744 antibodies in the screening or confirmatory assays. *Acceptance criteria:* - HPC > LPC > screening cut point > blank - Fall within 80–120% of results from the blank matrix pool prepared at the corresponding level *Results:* - All met the acceptance criteria within 95.1-102% recovery	*SLPC showed > 36.3; however, since SLPC is not consistently detected in the confirmatory assay, it is acceptable.*
ADA Assay Assessment	-	*Acceptable but with several limitations 1)low specificity of the assay and 2)reduced sensitivity due to on board drug*

Analytical report review:

For the CS5 and CS7 studies, disease state cut points were applied to calculate ADA in patient plasma samples, which is acceptable. The assays met the acceptance criteria.
In the CS5 study, 106 out of 455 samples were positive in the screening assay, and 58 of these 106 screening-positive samples tested positive in the confirmatory assay. The false positive rate (FPR) among screening positives was 45.3%, and the FPR among all 455 samples was 10.8%, which is acceptable.
Sample from patient ID (b) (6) collected on day 169 showed positive in the confirmatory assay, however, due to insufficient sample volume, ADA titer was not measured. The max ADA titer is 3200.
In the CS7 study, 258 out of 655 samples were positive in the screening assay, and 179 of these 258 screening-positive samples tested positive in the confirmatory assay. The FPR among screening positives was 30.62%, and the FPR among all samples was 12.06%, which is acceptable. The max ADA titer is 204800.

Assessor's Comments:
Immunogenicity has been reported with GalNAc-conjugated ASO (Eplotersen; ADA rate: 37%), and similar to this, ADA development is observed in donidalorsen-treated patients.
Several limitations were observed from the assay the sponsor used for validation.

1) *The assay has low specificity. It is uncertain whether the assay detects anti-donidalorsen antibodies based on sequence, structure, or GalNAc moiety.*
2) *The assay also shows reduced sensitivity due to on board drug, but the reduction is unlikely to result in false negative samples.*

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/s/

HA NA LEE
08/15/2025 09:35:00 AM

DANIELA I VERTHELYI
08/19/2025 09:25:36 AM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	July 17, 2025
Requesting Office or Division:	Division of Pulmonology, Allergy, and Critical Care (DPACC)
Application Type and Number:	NDA 219407
Product Name, Dosage Form, and Strength:	Dawnzera[a] (donidalorsen) injection, 80 mg/0.8 mL (100 mg/mL)
Applicant Name:	Ionis Pharmaceuticals Inc (Ionis)
FDA Received Date:	July 15, 2025
TTT ID #:	2024-10603-2
DMEPA 1 Safety Evaluator:	Avinash Konkani, PhD, MS, BE
DMEPA 1 Associate Director for Human Factors:	Ariane O. Conrad, PharmD, BCACP, CDCES, FISMP

[a] The proposed proprietary name, Dawnzera, was found conditionally acceptable by DMEPA 1 on April 08, 2024. (PNR#2024-1044725494).

1 PURPOSE OF MEMORANDUM

Ionis Pharmaceuticals Inc submitted the revised container label received on July 15, 2025 for Dawnzera. The Division of Pulmonology, Allergy, and Critical Care (DPACC) requested that we review the revised container label for Dawnzera (Appendix A) to determine if it is acceptable from a medication error perspective. The revision is in response to a recommendation that we made during our previous review of revised label and labeling for Dawnzera.[b]

Additionally, we note that the DMEPA 1 nomenclature and labeling review team is evaluating the container label and carton labeling under separate cover.

2 CONCLUSION

Ionis Pharmaceuticals Inc implemented our recommendation to include a needle end label on the container label and we have no additional recommendations at this time.

[b] Konkani, A. Review of Revised Label and Labeling for Dawnzera (NDA 219407). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2025 JUN 30. TTT ID: 2024-10603-1.

APPENDIX A. IMAGES OF LABELS AND LABELING RECEIVED ON JULY 15, 2025

Container Label:

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/s/

AVINASH KONKANI
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ARIANE O CONRAD
07/17/2025 08:36:40 AM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	July 17, 2025
Requesting Office or Division:	Division of Pulmonology, Allergy, and Critical Care (DPACC)
Application Type and Number:	NDA 219407
Product Name, Dosage Form, and Strength:	Dawnzera (donidalorsen) injection, 80 mg/0.8 mL
Applicant Name:	Ionis Pharmaceuticals, Inc. (Ionis)
FDA Received Date:	July 15, 2025
TTT ID #:	2024-10604-2
DMEPA 1 Safety Evaluator:	Sherly Abraham, R.Ph.
DMEPA 1 Team Leader:	Damon Birkemeier, PharmD, FISMP

1 PURPOSE OF MEMORANDUM

Ionis submitted revised container label and carton labeling received on July 15, 2025 for Dawnzera. The Division of Pulmonology, Allergy, and Critical Care (DPACC) requested that we review the revised container label and carton labeling for Dawnzera (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

Ionis Pharmaceuticals implemented all of our recommendations and we have no additional recommendations at this time.

[a]Birkemeier, D. Label and Labeling Review for Dawnzera (NDA 219407). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2025 JUN 12. TTT ID: 2024-10604-1.

APPENDIX A. IMAGES OF LABELS AND LABELING RECEIVED ON JULY 15, 2025

- Ionis' response to the Agency's Information Request (IR) available from \\CDSESUB1\evsprod\NDA219407\0035\m1\us\m1-11-3-clinical-information-amendment.pdf

Container Label:

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/s/

SHERLY ABRAHAM
07/17/2025 10:20:57 AM

DAMON A BIRKEMEIER
07/17/2025 10:23:46 AM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	June 30, 2025
Requesting Office or Division:	Division of Pulmonology, Allergy, and Critical Care (DPACC)
Application Type and Number:	NDA 219407
Product Name, Dosage Form, and Strength:	Dawnzera[a] (donidalorsen) injection, 80 mg /0.8 mL (100 mg/ mL)
Applicant Name:	Ionis Pharmaceuticals Inc. (Ionis)
FDA Received Date:	June 9, 2025; June 20, 2025
TTT ID #:	2024-10603-1
DMEPA 1 Safety Evaluator:	Avinash Konkani, PhD, MS, BE
DMEPA 1 Team Leader:	Matthew Barlow, RN, BSN
DMEPA 1 Associate Director for Human Factors:	Ariane O. Conrad, PharmD, BCACP, CDCES, FISMP

[a] The proposed proprietary name, Dawnzera, was found conditionally acceptable by DMEPA 1 on April 08, 2024. (PNR#2024-1044725494).

1 PURPOSE OF MEMORANDUM

Ionis Pharmaceuticals Inc. submitted revised container label and carton labeling received on June 9, 2025 and their revised instructions for use (IFU) received on June 20, 2025 for Dawnzera. The Division of Pulmonology, Allergy, and Critical Care (DPACC) requested that we review the revised container label and carton labeling and IFU for Dawnzera (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 human factors validation study results review.[b] Additionally, we note that the DMEPA 1 nomenclature and labeling review team evaluated the container label and carton labeling under separate cover.[c]

2 DISCUSSION

We have reviewed Ionis' revised IFU and their response to recommendations. Our assessment of the revisions and their response to our container label recommendation is noted below.

- Recommendations for the IFU: Ionis implemented all of our recommendations for the IFU. Therefore, we have no additional recommendations for the IFU at this time.

- Recommendation for Container label: "We note there were issues related to incorrect orientation of the autoinjector when injecting and some participants had difficulty identifying the needle location. Per the use-related risk analysis (URRA), if user orients the autoinjector backward (i.e., needle shield against hand/finger), this may result in laceration, that may require medical attention. In addition, several use difficulties and moderator interventions occurred in the HF validation studies where participants tried to orient the needle shield against the hand/finger, because they thought that the orange shield was a button to press for activation due to their previous experience with similar devices with activation button and an inability to determine where the needle was located. We recommend including a needle end label on the container to emphasize this important injection administration information." [b]

[b] Konkani, A. Human Factors Validation Study Results Review for Dawnzera (NDA 219407). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2025 MAY 23. TTT ID: 2024-10603.

[c] Birkemeier, D. Memorandum Review of Revised Label And Labeling for Dawnzera (NDA 219407). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2025 JUN 12. TTT ID: 2024-10604-1

(b) (4)

- DMEPA review of Ionis' response: Based on our post-marketing experience with similar AI devices, we note there are known use issues related to difficulty identifying the end of the AI containing the needle. Additionally, as noted in our recommendation above, several use difficulties related to incorrect orientation of the autoinjector were observed during the HF validations studies. Therefore, to emphasize the correct orientation of the autoinjector and to minimize potential needle injury, we continue to maintain our recommendation to include a needle end label on the container.

3 CONCLUSION

Ionis Pharmaceuticals Inc. implemented all of our recommendations for the IFU, and we have no additional recommendations for the IFU at this time.

However, we disagree with Ionis's justification for not including a needle end label on the container, and we continue to maintain our previous recommendation. We have provided our recommendation for Ionis in Section 4 below.

4 RECOMMENDATIONS FOR IONIS PHARMACEUTICALS INC.

A. Container Label

We acknowledge your rationale for not implementing a needle end label on the proposed autoinjector; however, we disagree. Based on our review of the HF validation study results and use issues related to incorrect orientation of the autoinjector, we continue to recommend including a needle end label on the container label. We note that this recommendation is consistent with our recommendation for your proposed IFU.

APPENDIX A. APPLICANT'S RESPONSE TO HF ADVICE RECEIVED ON JUNE 9, 2025 AND JUNE 20, 2025

The Applicant's response dated June 9, 2025 is accessible in EDR via:
\\CDSESUB1\EVSPROD\nda219407\0033\m1\us\m1-11-3-clinical-information-amendment.pdf

The Applicant's response dated June 20, 2025 is accessible in EDR via:
\\CDSESUB1\EVSPROD\nda219407\0034\m1\us\m1-11-3-clinical-information-amendment.pdf

Updated IFU received on June 20, 2025 is accessible in EDR via:
PDF version: \\CDSESUB1\EVSPROD\nda219407\0034\m1\us\m1-14-1-3-draft-ifu.pdf
Word version: \\CDSESUB1\EVSPROD\nda219407\0034\m1\us\m1-14-1-3-draft-ifu.docx

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AVINASH KONKANI
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MATTHEW J BARLOW
06/30/2025 02:11:49 PM

ARIANE O CONRAD
06/30/2025 05:07:21 PM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	June 12, 2025
Requesting Office or Division:	Division of Pulmonology, Allergy, and Critical Care (DPACC)
Application Type and Number:	NDA 219407
Product Name, Dosage Form, and Strength:	Dawnzera (donidalorsen) injection, 80 mg/0.8 mL
Applicant Name:	Ionis Pharmaceuticals, Inc. (Ionis)
FDA Received Date:	June 9, 2025
TTT ID #:	2024-10604-1
DMEPA 1 Team Leader:	Damon Birkemeier, PharmD, FISMP
DMEPA 1 Associate Director for Nomenclature and Labeling:	Idalia E. Rychlik, PharmD

1 PURPOSE OF MEMORANDUM

Ionis Pharmaceuticals, Inc. submitted revised container label and carton labeling received on June 9, 2025 for Dawnzera. The Division of Pulmonology, Allergy, and Critical Care (DPACC) requested that we review the revised container label and carton labeling for Dawnzera (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 DISCUSSION

Ionis Pharmaceuticals, Inc. implemented most of our recommendations. However, regarding our recommendation to remove the duplicative storage information found on the principal display panel (PDP) to increase the space available for other prominent information, Ionis proposes to *"maintain the storage information on the PDP and move the room temperature/disposal statement, 'If needed, Dawnzera can be kept at room temperature (up to 30°C [86°F]) in the original carton for up to 6 weeks; If not used within the 6 weeks, discard Dawnzera.' from the back panel to the PDP."* Further, Ionis stated that *"the duplicative storage information, 'Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton and protect from direct light.' reflected on the back panel was removed."* We note that Ionis did not provide a rationale for their proposal. We disagree with Ionis' proposal and continue to recommend the storge information be moved off of the PDP to increase the space available for and the prominence of other critical information.

3 CONCLUSION

The container label and carton labeling are unacceptable from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error for Ionis Pharmaceuticals, Inc. in Section 4.

Note additional label and labeling comments may be forthcoming pending review of the updated labels and labeling by our DMEPA 1 human factors (HF) colleagues.

4 RECOMMENDATIONS FOR IONIS PHARMACEUTICALS, INC.

A. Container Label

1. The strength lacks adequate spacing between the numerical dose and unit of measure. Lack of adequate spacing may impact readability and might result in wrong strength errors. We recommend placing adequate space between the numerical dose and unit of measure (i.e., 0.8 mL instead of 0.8mL) to improve readability.

B. Carton Labeling

[a] Abraham S. Label and Labeling Review for Dawnzera (NDA 219407). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2025 FEB 19. TTT ID: 2024-10604-1.

1. We acknowledge your proposal to "*maintain the storage information on the PDP and move the room temperature/disposal statement, 'If needed, Dawnzera can be kept at room temperature (up to 30°C [86°F]) in the original carton for up to 6 weeks; If not used within the 6 weeks, discard Dawnzera.' from the back panel to the PDP."* and your statement that *"the duplicative storage information, 'Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton and protect from direct light.' reflected on the back panel was removed."* However, we disagree with your proposal and continue to recommend that you relocate the storage information off of the PDP to increase the space available for and the prominence of other critical information. See our *Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022) for additional information.

APPENDIX A. IMAGES OF LABELS AND LABELING RECEIVED ON JUNE 9, 2025

- Ionis' response to the Agency's Information Request (IR) available from \\CDSESUB1\EVSPROD\nda219407\0033\m1\us\m1-11-3-clinical-information-amendment.pdf.

Container Label:

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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:	June 6, 2025
To:	Cindy Chee Regulatory Project Manager **Division of Pulmonology, Allergy, and Critical Care (DPACC)**
Through:	Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Mary Carroll, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Meeta Patel, Pharm.D. Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG) and Instructions for Use (IFU)
Drug Name (established name):	DAWNZERA (donidalorsen)
Dosage Form and Route:	injection, for subcutaneous use
Application Type/Number:	NDA 219407
Applicant:	Ionis Pharmaceuticals Inc.

1 INTRODUCTION

On August 21, 2024, Ionis Pharmaceuticals Inc. submitted for the Agency's review an original New Drug Application (NDA) 219407 for DAWNZERA (donidalorsen) injection, for subcutaneous use. The proposed indication of use is for prophylaxis to prevent attacks of hereditary angioedema (HAE) in adults and pediatric patients 12 years of age and older under the provisions of 21 Code of Federal Regulations 314.50 and Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act.

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 Pulmonary, Allergy, and Critical Care (DPACC) on August 30, 2024 for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for DAWNZERA (donidalorsen) injection, for subcutaneous use.

2 MATERIAL REVIEWED

- Draft DAWNZERA (donidalorsen) MG and IFU received on August 21, 2024, and received by DMPP and OPDP on May 28, 2025.
- Draft DAWNZERA (donidalorsen) Prescribing Information (PI) received on August 21, 2024, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on May 28, 2025.

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. In our review of the IFU the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the MG document using the Arial font, size 10.

In our collaborative review of the MG and IFU we:

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

- ensured that the MG and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the IFU meets the criteria as specified in both the FDA Guidance for Useful Written Consumer Medication Information (published July 2006) and Instructions for Use-Patient Labeling for Human Prescription Drug and Biological Products (published July 2022).
- ensured that the MG and IFU are consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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/s/

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MARCIA B WILLIAMS
06/06/2025 08:42:01 AM

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

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

Memorandum

Date: June 5, 2025

To: Cindy Chee, Project Manager, DPACC

From: Meeta Patel, Pharm.D., Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Adewale Adeleye, Pharm.D., Team Leader, OPDP

Subject: OPDP Labeling Comments for DAWNZERA (donidalorsen) injection, for subcutaneous use

NDA: 219407

In response to DPACC's consult request dated August 27, 2024, OPDP has reviewed the proposed product labeling (PI), Medication Guide (MG), Instructions for Use (IFU), and carton/container labeling for Dawnzera.

Labeling: OPDP has two comments on section 14 of the proposed labeling based on the draft labeling received by electronic mail from DPACC on May 28, 2025.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed Medication Guide and IFU 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, and we do not have any comments.

Thank you for your consult. If you have any questions, please Meeta Patel at (301) 796-4284 or meeta.patel@fda.hhs.gov.

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/s/

MEETA N PATEL
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HUMAN FACTORS STUDY RESULTS REPORT REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
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:	May 23, 2025
Requesting Office or Division:	Division of Pulmonology, Allergy, and Critical Care (DPACC)
Application Type and Number:	NDA 219407
Product Type:	Combination Product (Drug-Device)
Product Name, Dosage Form and Strength:	Dawnzera[a] (donidalorsen) injection, 80 mg /0.8 mL (100 mg/ mL)
Device Constituent:	Autoinjector
Rx or OTC:	Rx
Applicant/Sponsor Name:	Ionis Pharmaceuticals Inc. (Ionis)
FDA Received Date:	August 21, 2024; September 27, 2024; November 25, 2024
TTT #:	2024-10603
DMEPA 1 Safety Evaluator:	Avinash Konkani, PhD, MS, BE
DMEPA 1 Team Leader:	Matthew Barlow, RN, BSN
DMEPA 1 Associate Director for Human Factors:	Ariane O. Conrad, PharmD, BCACP, CDCES, FISMP

[a] The proposed proprietary name, Dawnzera, was found conditionally acceptable by DMEPA 1 on April 08, 2024. (PNR#2024-1044725494.)

1 REASON FOR REVIEW

This review evaluates the human factors (HF) validation study results reports submitted under NDA 219407 for Dawnzera (donidalorsen) injection for the proposed 80 mg/0.8 mL autoinjector (AI).

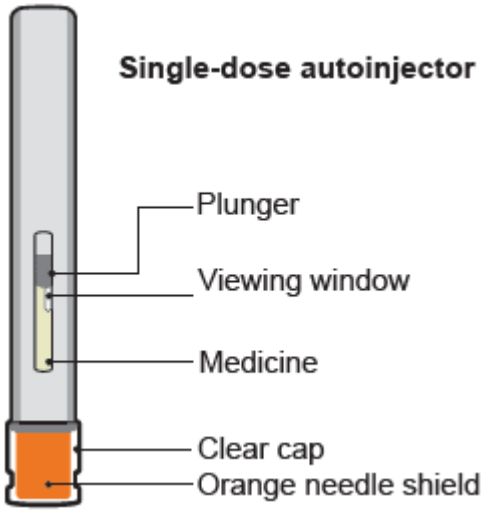
We considered the materials listed in Table 1 for this review.

Table 1. Materials Considered for this Review	
Material Reviewed	Section/Appendix
Product Information	Section 1.1
Relevant Regulatory History Related to the Proposed Product's HF Development Program	Section 1.2
Human Factors (HF) Validation Study Report and HF-Related Supporting Documents	Appendix A
Information Requests Issued During the Review	Appendix B
Labels and Labeling	Appendix C
Tasks Involving Use Errors, Use Difficulties, and Close Calls for Section 3.1	Appendix D

1.1 PRODUCT INFORMATION

Table 2 presents relevant product information for Dawnzera that Ionis Pharmaceuticals Inc. submitted on August 21, 2024.

Table 2. Relevant Product Information for Dawnzera	
Initial Approval Date	N/A
Active Ingredient	donidalorsen
Indication	prophylaxis to prevent attacks of hereditary angioedema (HAE) in adult and pediatric patients 12 years of age and older
Route of Administration	Subcutaneous
Dosage Form	Injection
Strength	80 mg/0.8 mL
Dose and Frequency	• The recommended starting dosage of Dawnzera in adult and pediatric patients 12 years of age and older is 80 mg administered subcutaneously (b) (4) • A dosing interval of 80 mg once every (b) (4) is also effective and may be considered (b) (4)

How Supplied	a sterile, preservative free, clear, colorless to yellow solution supplied in a carton containing one 80 mg/0.8 mL single dose autoinjector (AI).
Storage	• Store the AI in the refrigerator between 36°F to 46°F (2°C to 8°C) in the original carton. • The AI can be stored at room temperature up to 86°F (30°C) in the original carton for up to 6 weeks; if not used within the 6 weeks stored at room temperature, discard Dawnzera. • Do not freeze. • Do not expose to heat. • Protect from light.
Container Closure/ Device Constituent (including figure)	Autoinjector: (b) (4) 
Intended Users	Adult patients, Adolescent patients, and Caregivers
Intended Use Environment	Non-clinical (i.e., Home)

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

On September 23, 2024, we searched for previous DMEPA reviews and FDA/Ionis interactions relevant to this current review using the terms, "*IND 142564"*, "*ISIS 721744*", "Dawnzera" and "*donidalorsen*". The identified reviews and FDA/Ionis interactions are provided below.

- On May 14, 2021, Ionis submitted a Type B Meeting request, under IND 142564, to discuss the adequacy of the existing and proposed nonclinical and clinical development package to support a marketing application for ISIS 721744 for prophylaxis to prevent attacks of Hereditary Angioedema (HAE) in patients 12 years of age and older. The teleconference was held on August 30, 2021.

- In the meeting minutes dated October 18, 2021, we recommended Ionis conduct a comprehensive URRA, and based on this risk analysis, they will need to determine whether they need to submit the results of a HF validation study for the ISIS 721744 AI.[b]

- On January 20, 2023, Ionis submitted a URRA and comparative analyses (CA) under IND 142564 for ISIS 721744 injection). Additionally, Ionis conducted a separate HF validation study for the adolescent patient user group and included a summary of the HF validation study results with their URRA and CA submission.
  - On June 04, 2024, we reviewed the aforementioned URRA and CA for the proposed product ISIS 721744 AI for intended adult users' group and agreed with the Ionis' determination that they do not need to submit the results of a human factors (HF) validation study for the adult user population as part of their future marketing application. Further, we acknowledged their submission of a summary of the HF validation study results for the adolescent patient user group, and we recommended that they submit the full results report for HF validation study for the adolescent patient user group with their future marketing application for the Agency's review.[c]
- August 21, 2024, Ionis submitted NDA 219407 for Dawnzera (donidalorsen) injection 80 mg /0.8 mL autoinjector. This submission included HF validation study results for the proposed autoinjector for the adolescent patient user group, which is the subject of this review. Additionally, this submission included "*confirmatory*" HF validation study results for the proposed autoinjector that included adult HAE patients and adult HAE patient's caregivers for review ("*To confirm the comparator product analysis, adult HAE patients (and proxy participants) and adult HAE caregivers (and proxy caregivers) were evaluated in a confirmatory HF validation study*").

2 OVERALL ASSESSMENT OF HUMAN FACTORS STUDY DESIGN AND METHODOLOGY

This section provides a summary of the study design, and our evaluation of the study methodology to determine if the study has been appropriately designed to support the safe and effective use of the proposed product.

2.1 SUMMARY OF STUDY DESIGN

Table 3 presents a summary of the HF validation studies design and our discussion of methodology concerns (as applicable). See Appendix A for more details on the study design.

[b] Jackson, C. Meeting minutes for IND 142564. Silver Spring (MD): FDA, CDER, OND, OII, DPACC (US); 2021 OCT 18. Available from: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af8061ead7

[c] Konkani, A. Use-Related Risk Analysis and Comparative Analyses Review for ISIS 721744 (donidalorsen) (IND 142564). Silver Spring (MD): FDA, CDER, OSE, DMEPA1 (US); 2024 JUN 04. TTT No. 2023-3449.

Table 3. Study Methodology for Human Factors (HF) Validation Studies

<table>
<tr><th>Study Design Elements Proposed</th><th>Sponsor Provided Methodology Deviation</th><th>DMEPA Discussion of Methodology Concerns</th></tr>
<tr><td>User Group(s): <u>Adolescent study:</u>
<table>
<tr><th></th><th>Injection naive</th><th>Injection experience</th><th>Total</th></tr>
<tr><td>HAE patients</td><td>0</td><td>6</td><td>6</td></tr>
<tr><td>Proxy patients</td><td>8</td><td>7</td><td>15</td></tr>
<tr><td>Total</td><td>8</td><td>13</td><td>21</td></tr>
</table>
<u>HAE Adult and caregiver's study</u>:
<table>
<tr><th></th><th>Injection naive</th><th>Injection experience</th><th>Total</th></tr>
<tr><td>HAE patients</td><td>1</td><td>8</td><td>9</td></tr>
<tr><td>Proxy patients</td><td>3</td><td>4</td><td>7</td></tr>
<tr><td>HAE Caregivers</td><td>0</td><td>6</td><td>6</td></tr>
<tr><td>Proxy Caregivers</td><td>1</td><td>8</td><td>9</td></tr>
<tr><td>Total</td><td>5</td><td>26</td><td>31</td></tr>
</table>
</td><td>Ionis stated that, "Both studies sought to recruit as many HAE participants as possible. HAE is considered a rare disease with an estimated prevalence between 1/10,000 and 1/50,000 of the total US population, which makes recruiting the total study population within the age range unattainable. Proxy participants were used to achieve the total number of desired participants."[d] Additionally, Ionis stated that, "The HF validation test included several proxy participants who do not have HAE but whose characteristics are otherwise identical to patients with HAE. Importantly, patients with HAE and their caregivers do not have any performance-shaping factors that differ from participants without HAE. HAE does not lead to, and is not associated with, any specific dexterity, visual, or cognitive impairments in its chronic state."[e]</td><td>We sought input from the Division of Pulmonology, Allergy, and Critical Care (DPACC) clinical team regarding Ionis' approach and justification for recruiting proxy patients in both the HF studies, asserting that HAE is a rare disease and difficult to recruit for and whether the chosen proxy patients are comparable to the HAE patient population from a usability perspective. The DPACC clinical team noted that they agree with Ionis' evaluation, approach, and justification and they have no concerns. Based on the DPACC clinical team's input noted above, we find the inclusion of proxy patients and caregivers reasonable.</td></tr>
<tr><td>Training
Participants did not complete any training prior to using the autoinjector during the HF validation studies.</td><td>N/A</td><td>N/A</td></tr>
<tr><td>Test Environment & Materials
The test room represented the basic characteristics of the intended use environment (e.g., typically a room within</td><td>N/A</td><td>N/A</td></tr>
</table>

[d] NDA 219407 Response to Information Request. Carlsbad (CA): Ionis Pharmaceuticals Inc. 2024 SEP 09. Available from: \\CDSESUB1\EVSPROD\nda219407\0005\m1\us\m1-11-1-quality-information-amendment.pdf

[e] NDA 219407 Response to Information Request. Carlsbad (CA): Ionis Pharmaceuticals Inc. 2024 NOV 25. Available from: \\CDSESUB1\EVSPROD\nda219407\0013\m1\us\m1-11-1-quality-information-amendment.pdf

the home). The room was equipped with a table and any materials required to facilitate the hands-on use scenarios required of the participant (e.g., refrigerator, hand sanitizer, alcohol wipes, sharps container). The device user interface used in the study is representative of the final design. The autoinjectors utilized for testing were of commercial production equivalent quality. The IFU, carton, and autoinjector label were representative of the proposed commercial content. However, each autoinjector contained a control solution (i.e., nonsterile water) rather than active drug product.		
Sequence of Study • Simulated Use scenario 1-Storage • Simulated Use scenario 2-Administer an injection (IFU optional) • Knowledge task 1-Storage • Knowledge task 2-Inspect product packaging • Knowledge task 3-Inspect autoinjector • Knowledge task 4-Allow autoinjector to warm to room temperature • Knowledge task 5-Select injection site • Final Interview/Root Cause Analysis (RCA)	N/A	N/A

3 RESULTS AND ANALYSIS

In this section, we have carefully reviewed each reported issue (i.e., use error, close call, use difficulty), Ionis' URRA, the participants' subjective feedback, Ionis' root cause analysis (RCA), and Ionis' comments and proposed mitigations (if applicable) to determine if the results indicate that the user interface has been appropriately designed to support the safe and effective use of the proposed product. In Table 4 below, we document our points of dissent with Ionis' findings. Additionally, Appendix D provides the observed use task and knowledge ask issues where we agree with Ionis' conclusions and have no further recommendations or comments.

Table 4. Detailed Analysis of Use Related Events and DMEPA's Recommendations

Legend: **UE** = use error; **CC** = close call; **OD** = operational difficulty (Ionis' terminology); **Assist** = instances of moderator assistance (Ionis' terminology); **URRA** = use-related risk analysis; **RCA** = root cause analysis; **HFVS** = Human Factors Validation Study
Participant ID: A **=** Adolescent; P = Adult Patient, C = Caregiver

Summary of Information Supplied by Applicant	DMEPA's Identified Areas of Dissent and Recommendations
Task: Allow autoinjector to warm to room temperature Scenario: Use scenario Reported Issues: UE (n=8) Participant Type(s): A2, A3, A4, A9, A10, A13, A17, A18	

	Injection Experienced HAE adolescent (n=3) Injection Naïve Proxy adolescent (n=1) Injection Experienced proxy adolescent (n=4)
Observed error(s): Did not allow to warm to room temperature	
Relevant RCA/Subjective Feedback: In the adolescent HF validation study: Participants "*did not completely read IFU Step 1 and did not know that the device needed to be warmed to room temperature*." RCA: "*IFU Step 1's title only references one of two required actions—The title only references removal of the autoinjector from the refrigerator and participants might have overlooked the additional step indicating the need to allow the autoinjector to warm to room temperature*."	
Based on the Applicant's URRA, performing this task incorrectly or not at all may result in "Injection discomfort".	
Applicant's Comments and Proposed Post- HFVS Mitigations: None Ionis stated "*Adequate design and instruction. No additional mitigation recommended. Clear instructions are provided in the IFU and the emphasis on the removal of the autoinjector from the fridge is more important. Additionally, the removal of information from the IFU to reduce information density may have a detrimental effect on other tasks*."	Based on the subjective feedback that the participants did not read all the sub-steps in the Step 1 of the IFU ("Remove from the refrigerator") because they focused on the title only and our overall assessment, we find that the instructions in Step 1 can be improved to increase clarity and understanding of the information. We provide our recommendation in Table A to address this concern. We have determined that this change can be implemented without submitting additional HF validation testing data for Agency review.
Task: Select injection site Scenario: Use scenario	
Reported Issues: / Participant Type(s): UE (n=5) / A7, A9, A12, A16, A19, Injection Naïve Proxy adolescent (n=4) Injection Experienced proxy adolescent (n=1)	
Observed error(s): In the adolescent HF validation study: Selected inappropriate injection site	
Relevant RCA/Subjective Feedback: In the adolescent HF validation study: Participants *"focused on IFU Step 3 illustrations of acceptable injection sites but overlooked the caption "For caregivers only" above the second illustration and injected into their upper arm*." RCA: "*IFU's limited differentiation of caregiver-only injection sites – participants overlooked the caption*"	
Based on the Applicant's URRA, performing this task incorrectly or not at all may result in "Laceration /Injection site leakage, Lower C_{max}"	

<table>
<tr><td>Applicant's Comments and Proposed Post- HFVS Mitigations: None

Ionis stated "Adequate design and instruction. No additional mitigation recommended."</td><td>Based on the subjective feedback that the participants overlooked the caption in the Step 3 of the IFU and focused on the illustrations of the step 3, and our overall assessment we find that the instructions in Step 3 can be improved to increase clarity and understanding of the information.

We provide our recommendation in Table A to address this concern. We have determined that this change can be implemented without submitting additional HF validation testing data for Agency review.</td></tr>
<tr><td>Task: Orient the autoinjector (perpendicular to skin)
Scenario: Use scenario
<table><tr><th>Reported Issues:</th><th>Participant Type(s):</th></tr><tr><td>OD (n=1)</td><td>C14
Injection Naïve proxy caregiver (n=1)</td></tr><tr><td>Assist (n=1)</td><td>A15
Injection Naïve Proxy adolescent (n=1)</td></tr></table></td><td></td></tr>
<tr><td>Observed error(s):
In the adolescent HF validation study:
• Difficulty orienting autoinjector with needle shield against the skin.

In the HAE adults and caregiver HF validation study:
• Difficulty determining needle location.</td><td></td></tr>
<tr><td>Relevant RCA/Subjective Feedback:
In the adolescent HF validation study:
Participant (A15) "assumed the needle shield was a button to press because they had seen devices that looked similar but had an activation button. The participant did not read the IFU until after the moderator intervened."

RCA: "Negative transfer and concealed needle – participant expected to need to attach needle based on experience observing and/or administering other medications."

HAE adults and caregiver HF validation study:
Participant (C14) "stated that the orientation at which they held the autoinjector when examining it made it hard to identify the autoinjector's needle. The moderator handed the participant a second, unused device during the session's debriefs portion and the participant held the autoinjector at different angles until they were able to identify the needle."

RCA: "Concealed needle – participant could not readily find the needle"</td><td></td></tr>
<tr><td>Based on the Applicant's URRA, performing this task incorrectly or not at all may result in "laceration, that may require medical attention."</td><td></td></tr>
<tr><td>Applicant's Comments and Proposed Post- HFVS Mitigations: None

Ionis stated "Adequate design and instruction. No additional mitigation recommended. Clear instructions are provided in the IFU."</td><td>Based on the subjective feedback, participants had use issues identifying the correct orientation and needle end of the AI. Furthermore, based on our post-marketing experience with similar AI devices, we note there are known use issues related to difficulty identifying the end of the AI containing the needle. We determined that the current mitigations do not adequately support the identified task error based on the RCA.

We provide our recommendation in Table A to address this concern. We have determined that this change can be implemented without submitting additional HF validation testing data for Agency review.</td></tr>
</table>

<table>
<tr><td>Task: Dispose of autoinjector and cap
Scenario: Use scenario
<table><tr><td>Reported Issues:</td><td>Participant Type(s):</td></tr><tr><td>UE (n=1)</td><td>C6
Injection Experienced
HAE caregiver (n=1)</td></tr></table></td><td></td></tr>
<tr><td>Observed error(s):
In the HAE adults and caregiver HF validation study:
Recapped autoinjector after injection</td><td></td></tr>
<tr><td>Relevant RCA/Subjective Feedback:
In the HAE adults and caregiver HF validation study:
Participant “incorrectly assumed that the autoinjector was reusable due to other injection device experience and stated they would recap and put the autoinjector in the fridge”.

RCA: "Negative transfer – Experience observing and/or administering other medications"</td><td></td></tr>
<tr><td>Based on the Applicant’s URRA, performing this task incorrectly or not at all may result in “Infection, localized; Choking, laceration of airway.”</td><td></td></tr>
<tr><td>Applicant’s Comments and Proposed Post- HFVS Mitigations: None

Ionis stated that “Adequate design and instruction. No additional mitigation recommended. Clear instructions are provided in the IFU. The automatic locking needle shield also prevents needle stick injuries.”</td><td>Based on the subjective feedback that the participant incorrectly assumed that the autoinjector was reusable due to other injection device experience and stated they would recap and put the autoinjector in the fridge, the lack of a specific statement stating that the device contains a single dose in step 7 of the IFU, and our overall assessment, we find that the instructions in Step 7 can be improved to increase clarity and understanding of the information.

We provide our recommendation in Table A to address this concern. We have determined that this change can be implemented without submitting additional HF validation testing data for Agency review.</td></tr>
</table>

3.1 ANALYSIS OF THE REMAINING IDENTIFIED ISSUES

The HF validation study report showed issues with the tasks evaluated by simulated use and knowledge tasks listed in Appendix D. However, based on our review of the available assessment of these identified issues, the available participants’ subjective feedback (including when participants’ subjective feedback did not indicate any potential issue with the user interface), Ionis’ root cause analysis, our evaluation of the residual risks, and post-HF validation study changes to the user interface, we have no additional recommendations to address the identified issues with the tasks in Appendix D.

4 LABELS AND LABELING

Table A below includes the identified medication error issues with the submitted instructions for use (IFU) based on the HF study results, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Note that the DMEPA 1 nomenclature and labeling review team has evaluated the product-specific labels and labeling under separate cover[f].

Table A. Identified Issues and Recommendations for Ionis Pharmaceuticals Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Instructions for Use			
1.	The title for Step 1 in the IFU states, "Step 1 Remove from the refrigerator". However, the instruction dose not emphasize that the user needs to wait for 30 minutes for the AI to reach the room temperature after removing the AI from the refrigerator and before proceeding to the next step.	Per the use-related risk analysis (URRA), if the autoinjector is used prior to reaching room temperature, this may result in injection discomfort. Additionally, the root cause analysis of the human factors (HF) validation study results indicated that participants read the title of step 1 of the IFU's step, which does not include the instruction to wait for 30 minutes after removing the AI from the refrigerator.	We recommend emphasizing that the user needs to wait for 30 minutes after removing the AI from the refrigerator to minimize the risk for an uncomfortable injection. For example, consider revising the title of step 1 to state "Remove from the refrigerator 30 minutes before you inject".
2.	In the IFU tested during the HF validation studies, we note that there was a vertical separation line between the two images in step 3, distinguishing between injection sites for all users from sites for caregivers only. However, we note that the vertical separation line between the two images shown in step 3 of the IFU were removed	It is unclear why the vertical separation line distinguishing between injection sites for all users from sites for caregivers only was removed. This separation between the images may impact the users' ability to distinguish between the sites and understand these instructions.	We recommend reinstating the vertical separation line between the two images in the Step 3 of the IFU to improve visibility of the distinction between the sites noted. Additionally, we recommend emphasizing that back of the upper arm site is for caregivers only as shown below: "b) Only caregivers may choose the back of upper arm."

[f] Abraham, S. Label and Labeling Review for Dawnzera (NDA 219407). Silver Spring (MD): FDA, CDER, OSE, DMEPA1 (US); 2025 FEB 19. TTT No. 2024-10604.

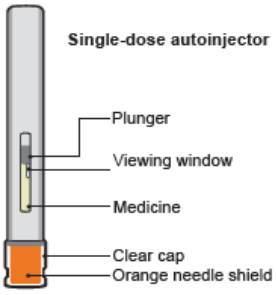
Table A. Identified Issues and Recommendations for Ionis Pharmaceuticals Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	for the version submitted under NDA 219407.		
3.	Based on our post-marketing experience with similar AI devices, we note there are known use issues related to difficulty identifying the end of the AI containing the needle. Additionally, we note that figures in the IFU (see below), which depicts the Dawnzera AI parts, do not emphasize that there is a needle inside the orange needle shield.  	As per the use-related risk analysis (URRA), if user orients the autoinjector backward (i.e., needle shield against hand/finger), this may result in laceration, that may require medical attention. Additionally, subjective feedback in the human factors (HF) validation study indicated that participants had difficulty identifying the correct orientation of the autoinjector and may not have realized that there is a needle inside the orange needle shield.	We recommend revising the figures in the IFU to further emphasize that there is a needle inside the orange needle shield. For example, the image in the "Dawnzera overview" and "Step 5 Remove and throw away the clear cap" could be revised to read "orange needle shield (contains needle)" for improved clarity.
4.	We note Step 7 of the IFU includes the statement "Do not reuse the autoinjector". However, the instruction	Per the use-related risk analysis (URRA), if the user does not properly dispose of autoinjector and cap, it may result in "*Infection,*	We recommend emphasizing that users cannot reuse the autoinjector. You may consider adding precautionary statement "the autoinjector

Table A. Identified Issues and Recommendations for Ionis Pharmaceuticals Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	does not emphasize that the proposed product is a single-dose autoinjector.	*localized; Choking, laceration of airway*". Additionally, subjective feedback from the human factors (HF) validation study indicated that some participant had difficulty understanding that the proposed product contains a single dose and should be disposed of after a single use.	contains 1 dose" before the existing statement "Do not reuse the autoinjector" in yellow box of the Step 7 of the IFU.
Container Label(s)			
1.	We note there were issues related to incorrect orientation of the autoinjector when injecting and some participants had difficulty identifying the needle location.	Per the use-related risk analysis (URRA), if user orients the autoinjector backward (i.e., needle shield against hand/finger), this may result in laceration, that may require medical attention. In addition, several use difficulties and moderator interventions occurred in the HF validation studies where participants tried to orient the needle shield against the hand/finger, because they thought that the orange shield was a button to press for activation due to their previous experience with similar devices with activation button and an inability to determine	We recommend including a needle end label on the container to emphasize this important injection administration information.

Table A. Identified Issues and Recommendations for Ionis Pharmaceuticals Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		where the needle was located.	

5 CONCLUSION AND RECOMMENDATIONS

The results of the HF validation study demonstrated several use errors, close calls, use difficulties with critical tasks that may result in harm. Based on our review of the available participants' subjective feedback, and root cause analysis, we identified additional risk controls to address the use errors with labels and labeling. Above, we have provided recommendations in Table A for Ionis. We ask that Division of Pulmonary, Allergy, and Critical Care (DPACC) convey Table A in its entirety to Ionis. These changes can be implemented without submitting additional HF validation testing data for Agency review.

5.1 RECOMMENDATIONS FOR IONIS PHARMACEUTICALS INC.

Our evaluation of the results of your human factors (HF) validation studies for your Dawnzera (donidalorsen) 80 mg /0.8 mL autoinjector indicates that there are additional risk controls that can be implemented to address use errors that occurred with critical tasks. We provide recommendations in Table A, and we recommend that you implement these recommendations and submit the revised instructions for use and labeling for our review, prior to the approval of this marketing application. We have determined that, in this instance, you may implement these revisions without submitting additional HF testing data for Agency review.

APPENDICES:

APPENDIX A. HUMAN FACTORS (HF) VALIDATION STUDY REPORT AND HF-RELATED SUPPORTING DOCUMENTS

- The HF study results report and background information can be accessed in EDR via: \\CDSESUB1\EVSPROD\nda219407\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\hae\5354-other-stud-rep\hf-validation-study\human-factor-autoinjector-report.pdf
- The HF study results report for Adolescent patient user group (page 120 to 161) and HF study results report for HAE adults and caregivers (page 162 to 208) can be accessed in EDR via: \\CDSESUB1\EVSPROD\nda219407\0001\m3\32-body-data\32r-reg-info\vv-qual-28718-human-factors.pdf
- The use-related risk analysis and comparative analyses (page 47 to 65) can be accessed in EDR via: \\CDSESUB1\EVSPROD\nda219407\0001\m3\32-body-data\32r-reg-info\vv-qual-28718-human-factors.pdf

APPENDIX B. INFORMATION REQUESTS ISSUED DURING THE REVIEW

- On September 25, 2024, we issued an Information Request (IR) to submit the followings:
  - The human factors (HF) validation study protocols for the adolescents, as well as HAE adults and caregivers' HF validation studies.
  - The moderator script for aforementioned HF validation studies.
  - The number of adolescent patient participants diagnosed with HAE in the HF validation study, and the number of adolescent proxy (surrogate) patient participants in the HF validation study.
  - The number of adult patient participants diagnosed with HAE in the "confirmatory" HF validation study, and the number of adult proxy patient participant in the "confirmatory" HF validation study.
  - The details of distinct user groups, such as number of injection experience and number of injection naïve participants in the aforementioned HF validation studies.
  - The characteristics of the proxy participants that participated in the aforementioned HF validation studies.

  On September 27, 2024, Ionis provided response to IR that can be accessed in EDR via: \\CDSESUB1\EVSPROD\nda219407\0005\m1\us\m1-11-1-quality-information-amendment.pdf

- On November 13, 2024, we issued an Information Request (IR) to submit the followings:
  - Updated HF validation study result reports including the details of all study participants' ID codes who had participated in the HF validation studies for adolescents as well as HAE adults and caregivers. For example, the participant ID codes should include

injection experience HAE patients (or proxy patients), injection naïve HAE patients (or proxy patients), injection experience caregivers, injection naïve caregivers etc. Also correctly identify each study participant in the "*Individual task performance summary*" section of both aforementioned HF validation study result reports.

- Updated HF validation study result reports including the root cause analysis (RCA) for all use issues analyzed in both of the HF validation studies (i.e., adolescents and the "*confirmatory*" study for HAE adults and caregivers).
- The number of adult patient participants diagnosed with HAE, and the number of adult proxy patient participants that were included in the "*confirmatory*" HF validation study.
- The number of adult caregiver participants, and the number of adult proxy caregiver participants included in the "*confirmatory*" HF validation study.
- The disease state(s) of the proxy patient participants that participated in the aforementioned "*confirmatory*" HF validation study.
- The disease state(s) of the proxy patient participants that participated in the HF validation study for adolescents.

On November 25, 2024, Ionis provided response to IR that can be accessed in EDR via: \\CDSESUB1\EVSPROD\nda219407\0013\m1\us\m1-11-1-quality-information-amendment.pdf

APPENDIX C. LABELS AND LABELING

C.1 List of Labels and Labeling Reviewed

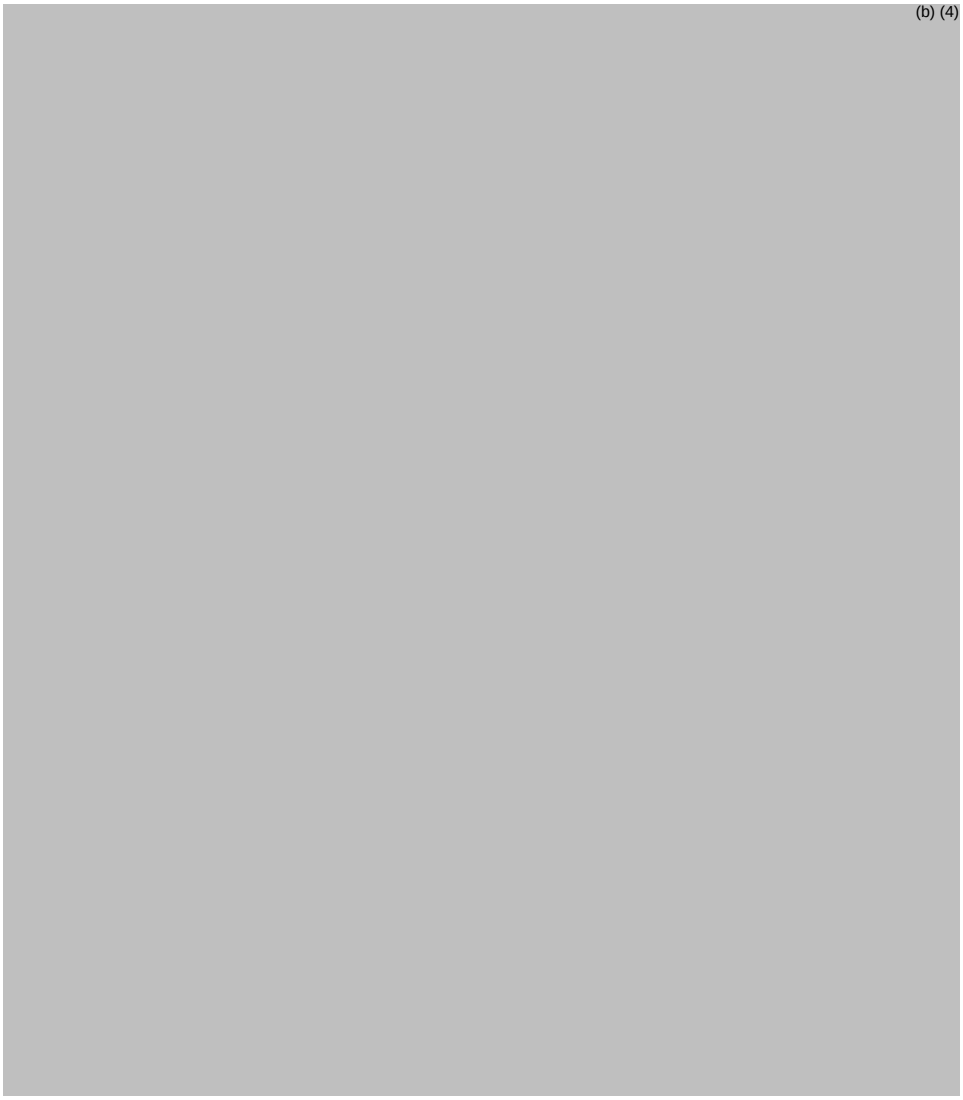
Using the principles of human factors and Failure Mode and Effects Analysis,[g] along with postmarket medication error experiences with similar products, we reviewed the following Dawnzera labels and labeling submitted by Ionis Pharmaceuticals Inc.

- Container label received on August 21, 2024
- Carton labeling received on August 21, 2024
- Instructions for Use received on August 21, 2024, available from \\CDSESUB1\EVSPROD\nda219407\0001\m1\us\114-labeling\draft\labeling\1-14-1-3-draft-ifu-text.pdf
- Prescribing Information (Image not shown) received on August 21, 2024, available from \\CDSESUB1\EVSPROD\nda219407\0001\m1\us\114-labeling\draft\labeling\1-14-1-3-draft-labeling-text.pdf

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

C.2 Label and Labeling Images

Container label



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

APPENDIX D. DETAILED LIST OF USE ERRORS, USE DIFFICULTIES, AND CLOSE CALLS FROM SECTION 3.1

Simulated use tasks (adolescents' study):

- Store carton in refrigerator.
- Wash Hands
- Clean injection site
- Remove Cap: There were five operational difficulty [use difficulty] observed for this task. The root cause analysis indicated that these use difficulties were due to "*negative transfer and concealed needle; Needle cap's open top design; Unexpected force to remove needle cap."* One Participant *"expected to attach a needle to the orange end of the autoinjector, presumably based on their experience with past injection devices where users are required to attach a needle and the needle is visible through a translucent needle shield*." Other participant "*noticed the needle cap's open top and thought the black plastic rod was an opening through which the needle would protrude. The device's overall minimalistic design gave them the impression of being easy-to-use and ready-to-go. This led the participant to assume the needle would deploy through the needle cap*." Two participants did not provide feedback. Another participant "*struggled to remove the needle cap because they twisted it rather than pulled. After inspecting the non-needle end, they pulled and removed the cap*." Based on our review of subjective feedback, root cause analysis and the user interface, we did not identify any additional mitigations to address this use error and have no recommendations at this time.
- Maintain autoinjector against injection site and monitor until delivery is completed: There were three use error observed with this task. The root cause analysis indicated that "*one participant used the medication window to determine that most of the medication was administered and assumed all the medication had been administered*" and "*two of the participants did not communicate why did they lift the AI after 1 second*". Based on our review of subjective feedback, root cause analysis and the user interface, we did not identify any additional mitigations to address this use error and have no recommendations at this time.

Knowledge assessment questions (adolescents' study):

- Knowledge task 1 – Storage: Imagine you (adolescent patient) and your parent/guardian have just come home from the pharmacy with the next dose of medication. At this moment, you do not yet have to administer an injection. Tell me what you would do with the medicine, noting that you will not be using it right now. Answers: Store this autoinjector in the refrigerator or at room temperature for up to 6 weeks; Store this autoinjector in the carton until ready to use; Store this autoinjector away from sunlight; Store this autoinjector away from reach of children.
- Knowledge task 2 – Inspect packaging for damage or tampering: Imagine you are preparing for an injection. What, if anything, would you check on or about the package to ensure the

product is appropriate for use? Answer: States to inspect if packaging is damaged or tampered.

- Knowledge task 3 – Inspect autoinjector: Imagine you are preparing for an injection. What, if anything, would you do to determine if the autoinjector is appropriate to use? Answers: Inspect or do not use if autoinjector is damaged; Check that it is the correct drug and dose; Check the expiration date is not past due; Inspect the drug for cloudy, discolored or particles.
- Knowledge task 5 – Select injection site: Imagine you are selecting an injection site. What, if anything, should you consider when selecting a site? Answer: States to Avoid injection site with inadequate condition (i.e., bruised, scars, psoriasis).

Simulated use tasks (HAE adults and caregivers – "confirmatory" HF study):

- Store carton in refrigerator.
- Wash Hands
- Clean injection site
- Remove Cap: There were two use error, one close call, eight operational difficulty [use difficulty] and one moderator assistance observed with this task. The root cause analysis indicated that these use errors were due to "*negative transfer, needle cap's open top design, mental model*". Some participants had difficulty to remove the needle cap by twisting rather than pulling, few participants had difficulty understanding to remove the cap due to the cap's open top design and "*thought that the black plastic rod was an opening through which the needle would protrude"*. Based on our review of subjective feedback, root cause analysis and the user interface, we did not identify any additional mitigations to address these use errors and have no recommendations at this time.
- Maintain autoinjector against injection site and monitor until delivery is completed: There were seven use errors observed with this task. The root cause analysis indicated that these use errors were due to "*negative transfer – experience observing and/or administering other medications*", "*test artifact – injection cushion caused autoinjector to malfunction*". Based on our review of subjective feedback, root cause analysis and the user interface, we did not identify any additional mitigations to address these use errors and have no recommendations at this time.

Knowledge assessment questions (HAE adults and caregivers – "confirmatory" HF study):

- Knowledge task 1 – Storage: Imagine you (or your child/partner/parent) have just come home from the pharmacy with the next dose of medication. You do not need to give an injection yet. Tell me what you would do with the medicine, noting that you will not be using it right now. Answers: Store this autoinjector in the refrigerator or at room temperature for up to 6 weeks; Store this autoinjector in the carton until ready to use; Store this autoinjector away from sunlight; Store this autoinjector away from reach of children.
- Knowledge task 3 – Inspect autoinjector: Imagine you are preparing for an injection. What, if anything, would you do to determine if the autoinjector is appropriate to use? Answers:

Inspect or do not use if autoinjector is damaged; Check that it is the correct drug and dose; Check the expiration date is not past due; Inspect the drug for cloudy, discolored or particles.

- Knowledge task 5 – Select injection site: Imagine you are selecting an injection site. What, if anything, should you consider when selecting a site? Answer: States to Avoid injection site with inadequate condition (i.e., bruised, scars, psoriasis).

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/

AVINASH KONKANI
05/23/2025 10:56:35 AM

MATTHEW J BARLOW
05/23/2025 12:22:42 PM

ARIANE O CONRAD
05/23/2025 01:50:35 PM

NDA219407
ICC2400821
ICCR 01013717

Date	4/11/2025		
To:	EMMA GIMOSE		
Requesting Center/Office:	CDER/OPQ	**Clinical Review Division:**	Other
From	Tiffani Chance OPEQ/OHT3/DHT3C		
Through (Team)	Rong Guo, Team Lead, Injection Team OPEQ/OHT3/DHT3C		
Through (Division) ***Optional**	Shruti Mistry, Assistant Director, Injection Team OPEQ/OHT3/DHT3C		
Subject	NDA219407 ICC2400821 ICCR 01013717		
Recommendation	**Filing Recommendation Date: 4/11/2025** ☑ CDRH did not provide a Filing Recommendation ☐ Device Constituent Parts of the Combination Product are acceptable for Filing. ☐ Device Constituents Parts of the Combination Product are Acceptable for Filing with Information requests for the 74-Day Letter, See Appendix A ☐ Device Constituents Parts of the Combination Product are Not Acceptable for Filing - See Section 5.4 for Deficiencies		
	Mid-Cycle Recommendation Date: 4/11/2025 ☑ CDRH did not provide a Mid-Cycle Recommendation ☐ CDRH has no approvability issues at this time. ☐ CDRH has additional Information Requests, See Appendix A ☐ CDRH has Major Deficiencies that may present an approvability issue, See Appendix A.		
	Final Recommendation Date: 4/11/2025 ☑ Device Constituent Parts of the Combination Product are Approvable. ☐ Device Constituent Parts of the Combination Product are Approvable with Post-Market Requirements/Commitments, See Section 2.3 ☐ Device Constituent Parts of the Combination Product are Not Approvable - See Section 2.2 for Complete Response Deficiencies		

NDA219407
ICC2400821
ICCR 01013717

Digital Signature Concurrence Table		
Reviewer	**Team Lead (TL)**	**Division (*Optional)**
Tiffani C. Chance -S Digitally signed by Tiffani C. Chance -S Date: 2025.04.11 11:14:46 -05'00'	Shruti N. Mistry -S	2025.04.11 12:22:13 -04'00'

1. SUBMISSION OVERVIEW

Submission Information	
Submission Number	NDA219407
Sponsor	Ionis Pharmaceuticals, Inc
Drug/Biologic	Donidalorsen Injection
Indications for Use	Treatment of hereditary angioedema
Device Constituent	Auto-Injector
Related Files	ICC2400819 Lead Reviewer: Tiffani Chance Purpose: Facilities Inspection Conclusion: No Inspection

Important Dates	
Discipline-Specific Review Memos Due	12/19/2024
Final Lead Device Review Memo Due	4/1/2025
Interim Due Dates	**Meeting/Due Date**
Mid-Cycle	1/09/2025

2. EXECUTIVE SUMMARY AND RECOMMENDATION

CDRH recommends the combination product is:

☑ Approvable – the device constituent of the combination product is approvable for the proposed indication.

☐ Approvable with PMC or PMR, See Section 2.3

☐ Not Acceptable – the device constituent of the combination product is not approvable for the proposed indication. We have Major Deficiencies to convey, see Section 2.2**. Specifically, CDRH has information requests to send to the sponsor.**

Section	Adequate			Reviewer Notes
	Yes	No	NA	
Device Description	X			
Labeling	X			
Design Controls	X	X		IR to be sent about lack of EPR testing and control strategies regarding the visual indicator. The sponsor has adequately addressed the IR
Risk Analysis	X	X		The donidalorsen autoinjector uses the (b) (4) ™, platform, which has been approved by FDA in other combination products, specifically (b) (4) The sponsor stated that a risk analysis was performed, but failed to provide this documentation. An IR will be sent. The sponsor has adequately addressed the IR. The sponsor has provided a sufficient risk analysis.
Design Verification	X			
Consultant Discipline Reviews			X	Not required
Clinical Validation			X	Not reviewed
Human Factors Validation			X	Deferred to DMEPA
Facilities & Quality Systems			X	Refer to ICC2400819. No facility inspection was recommended, and QS documents were complete.

2.1. Comments to the Review Team

☑ CDRH does not have any further comments to convey to the review team.
☐ CDRH has the following comments to convey to the review team:

2.2. Complete Response Deficiencies

☑ There are no outstanding unresolved information requests, therefore CDRH does not have any outstanding deficiencies.
☐ The following outstanding unresolved information requests should be communicated to the Sponsor as part of the CR Letter:
CDRH is providing the following 'letter-ready' Major Deficiencies written so they can be directly communicated to the Sponsor:
Major Deficiencies:

The sponsor has adequately addressed the following IRs.

Specifically, CDRH has the following information request to send to the sponsor.

1. In the instructions for use, the device has the following step: "(b) (4) " indicating that the device has a visual indicator that injection should be complete. Similarly, the device is stated to "click" at the beginning and end of injection. Audible and visual indicators are helpful metrics for the user to understand when the injection is over. For example, without a visual indicator, the user might remove the device prematurely, resulting in improper delivery of the therapeutic. As such, these indicators should be tested as pass/fail attributes. Additionally, please provide data supporting the reliability of these indicators through expiry of the device, and a control strategy to ensure proper attribute function. Please refer to the FDA recognized standard ISO 11608-1 Needle-based injection systems for medical use — Requirements and test methods Part 1: Needle-based injection systems for proposed sample sizes based on your system designation and the test case matrix. Alternatively, provide a rationale as to why these indicators do not require further testing.

2. You provided testing of the device needle shield displacement to a confidence and reliability of (b) (4) % respectively. However, we recommend that you evaluate your needle safety device, specifically the needle shield displacement, to the benchmark confidence and reliability (b) (4) %) for needle safety functions where the risk of failure leads to accidental needle stick. Adequate confidence and reliability testing of this feature is important to ensure that the user does not receive accidental needle sticks from the device after use. Therefore, please provide updated testing of this feature to a confidence and reliability of (b) (4) %. For further information, please refer to the agency guidance titled "Medical Devices with Sharps Injury Prevention Features (https://www.fda.gov/media/71142/download)" as well as the standard ISO 23908:2011 "Sharps injury protection - Requirements and test methods — Sharps protection features for single-use hypodermic needles, introducers for catheters and needles used for blood sampling."

3. You stated that a risk analysis was performed to address risks associated with the device design, system, use, and manufacturing. However, you did not provide this report for review. Proper identification and mitigation of device risks is important to help ensure that the device will not fail to accurately deliver treatment, or cause further harm. Therefore, please provide the following:.
   - Identify all risks that exist with the device and provide information demonstrating they have been adequately mitigated for the study.
   - Provide the scoring system used for probability and hazard, and the overall risk calculation.
   - Ensure that reports for risk mitigation are traceable.

2.3. Recommended Post-Market Commitments/Requirements

CDRH has Post-Market Commitments or Requirements	☐
CDRH does not have Post-Market Commitments or Requirements	☑

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3. PURPOSE/BACKGROUND

3.1. Scope

Ionis Pharmaceuticals, Inc is requesting approval of Donidalorsen Injection. The device constituent of the combination product is an Auto-Injector.

CDER/OPQ has requested the following consult for review of the device constituent of the combination product:

From SalesForce:

Ionis Pharmaceuticals Inc. (Ionis) hereby submits New Drug Application (NDA) 219407 for donidalorsen for prophylaxis to prevent attacks of hereditary angioedema (HAE) in adult and pediatric patients 12 years of age and older under the provisions of 21 Code of Federal Regulations 314.50 and Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. Donidalorsen is a prekallikrein-targeted N-acetyl galactosamine, GalNAc-conjugated antisense oligonucleotide indicated for prophylaxis to prevent attacks of hereditary angioedema (HAE) in adult and pediatric patients 12 years of age and older. The proposed recommended starting dosage of DAWNZERA is 80 mg administered subcutaneously (b) (4). A dosing interval of 80 mg once every (b) (4) is also effective and may be considered (b) (4)

The goal of this memo is to provide a recommendation of the approvability of the device constituent of the combination product. This review will cover the following review areas:

Device Description

Labeling

Design Controls

Design Verification

Risk Analysis

This review will not cover the following review areas:

Consultant Discipline Reviews

Clinical Validation

Human Factors Validation

Facilities & Quality Systems

The original review division will be responsible for the decision regarding the overall safety and effectiveness for approvability of the combination product.

3.2. Prior Interactions

There are no prior interactions

3.2.1. Related Files

ICC2400819
Lead Reviewer: Tiffani Chance
Purpose: Facilities Inspection
Conclusion: Pre-approval Inspection

3.3. Indications for Use

Combination Product	Indications for Use
Donidalorsen Injection	Treatment of hereditary angioedema (HAE)
Auto-Injector	Delivery of the Drug Product

3.4. Materials Reviewed

At the time of review, data was not yet available in DocuBridge. Therefore, all reviewed material came from: \\CDSESUB1\evsprod\NDA219407\0001

- \\CDSESUB1\evsprod\NDA219407\0001\m3\32-body-data\32r-reg-info
- \\CDSESUB1\evsprod\NDA219407\0001\m1\us\114-labeling\draft\labeling
- \\CDSESUB1\evsprod\NDA219407\0001\m1\us\114-labeling\draft\carton-and-container
- \\CDSESUB1\evsprod\NDA219407\0001\m3\32-body-data\32p-drug-prod\donidalorsen-injection (b) (4) \32p5-contr-drug-prod\32p53-val-analyt-proc

4. DEVICE DESCRIPTION

4.1. Device Description

The donidalorsen autoinjector is a single-use disposable device that uses the known (b) (4) platform. It is intended to administer a single fixed dose of drug into the subcutaneous tissue of the patient from an integral filled primary container that is a pre-filled syringe (PFS). The PFS consists of a barrel with a ½ inch, 27-gauge thin-wall staked needle and rigid needle shield (RNS), filled with donidalorsen solution and closed by a plunger stopper. The total volume is 1.0 mL.

The AI is indicated for treatment of HAE in adults (18+ years old) and adolescents (12–17 years old) by delivery of a single-dose, subcutaneous administration of 0.8 mL of the drug product (80 mg donidalorsen). The product will be available by prescription only through the patient's healthcare provider, and is intended for self-administration.

Figure 1: Donidalorsen Autoinjector

4.2. Steps for Using the Device

1. Visually check the autoinjector, autoinjector label, and drug product.
2. Remove and dispose of the cap.
3. Press the orange tip against the skin, which will insert the needle into the injection site.
4. Hold while the autoinjector delivers the dose and check that the orange plunger rod has filled the viewing window.

5. Lift the autoinjector straight up to remove it from the skin.
6. Dispose of the autoinjector.

Figure 3: Donidalorsen Autoinjector Device Operation Before, During, and After Injection

The AI is comprised of the following materials and has the following skin contact duration:

Per attachment G of the industry guidance “Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process," biocompatibility review is not necessary.

The AI is not intended to be delivered sterile.

4.3. Device Description Conclusion

DEVICE DESCRIPTION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☐ No ☑ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☑ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments The device description is acceptable.		
CDRH sent Device Description Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No		

5. FILING REVIEW

CDRH performed Filing Review ☐ **Finalize Filing Review Section**	☐
CDRH was not consulted prior to the Filing Date; therefore CDRH did not perform a Filing Review	☑

6. LABELING

6.1. General Labeling Review

The labeling, including the device constituent labeling, user guides, patient information, prescriber information and all other labeling materials provided for review were reviewed to meet the following general labeling guidelines as appropriate:

General Labeling Review Checklist	Adequate?		
	Yes	No	N/A
Indications for Use or Intended Use; including use environment(s); route(s) of administration for infusion, and treatment population.	X		

Drug name is visible on device constituent and packaging	X		
Device/Combination Product Name and labeling is consistent with the type of device constituent	X		
Prescriptive Statement/Symbol on device constituent	X		
Warnings	X		
Contraindications	X		
Instructions for Use	X		
Final Instructions for Use Validated through Human Factors			X
Electrical Safety Labeling/Symbols			X
EMC Labeling/Symbols			X
Software Version Labeling			X
MRI Labeling/Symbols			X
RF/Wireless Labeling/Symbols			X

Reviewer Comments

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6.2. Device Specific Labeling Review

Device Specific Labeling Review Checklist	Adequate?		
	Yes	No	N/A
Warnings not to share AI	X		
Warnings to not re-use AI	X		

6.3. Labeling Review Conclusion

LABELING REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☐ No ☑ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☑ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments The device labeling is acceptable.		
CDRH sent Labeling Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No		

7. DESIGN CONTROL SUMMARY

7.1. Summary of Design Control Activities

Risk Analysis Attributes	Yes	No	N/A
Risk analysis conducted on the combination product	**X**		
Hazards adequately identified (e.g. FMEA, FTA, post-market data, etc.)			**X**
Mitigations are adequate to reduce risk to health			**X**
Version history demonstrates risk management throughout design / development activities			**X**
Design Inputs/Outputs	**Yes**	**No**	**N/A**
Design requirements / specifications document present (essential performance requirements included)	**X**		
Design Verification / Validation Attributes	**Yes**	**No**	**N/A**

Validation of essential requirements covered by clinical and human factors testing			X
To-be-marketed device was used in the pivotal clinical trial			X
Bioequivalence Study utilized to-be-marketed device			X
Verification methods relevant to specific use conditions as described in design documents and labeling	X		
Device reliability is acceptable to support the indications for use (i.e. emergency use combination product may require separate reliability study)	X		
Traceability demonstrated for specifications to performance data	X		

Reviewer Comments

The NDA application review focuses on the final device to be marketed in the future. All testing was performed on the finished device.

7.2. Design Inputs and Outputs

Essential Performance Requirements

Design Inputs (Essential Performance Requirement)	Design Outputs (Specification)
Cap Removal Force	(b) (4)
Activation Force	
Needle Extension	
Delivered Volume	
Injection Time	
Needle Cover Lockout Displacement	

Reviewer Comments

Below is the agency combination product reference card with typical EPR specification values for an AI:

(b) (4)

In the instructions for use, the device has the following step: (b) (4)
" indicating that the device has a visual indicator that injection should be complete. The device is also stated to produce a click sound at the beginning and end of injections.

While not specifically EPRs, the audible and visual indicators are helpful for the user to understand when the injection is over, and should be tested as pass/fail attributes. This will be communicated to the sponsor as an IR.

The issue has been addressed by the sponsor.

7.3. Applicable Standards and Guidance Documents

Generally Applicable Standards and Guidance Documents:

Standard or Guidance	Conformance (Y/N/NA)
AAMI / ANSI / ISO 14971:2007/(R)2010 (Corrected 4 October 2007), medical devices - applications of risk management to medical devices	Y – Review unnecessary ((b) (4) platform)
Standard Practice for Performance Testing of Shipping Containers and Systems; ASTM D4169-09	Y – Replaced with ASTM D4169-22 Standard Practice for Performance Testing of Shipping Containers and Systems, which is FDA recognized and acceptable
IEC 60601-1-2:2014	NA
Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products (2017)	Y
Mobile Medical Applications Guidance for Industry and Food and Drug Administration Staff (2015)	NA
Guidance for Industry and FDA Staff – Medical Devices with Sharps Injury Prevention Features (2005)	Y
Use of International Standard ISO 10993-1, Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process"	Y – Review not needed.
Applying Human Factors and Usability Engineering to Medical Devices	Y – Review deferred to DMEPA

Device Specific Standards and Guidance Documents

Standard or Guidance	Recognized (Y/N/NA)	Conformance (Y/N/NA)
11608-1:2022 Needle-Based Injection Systems for Medical Use – Requirements and Test Methods – Part 1: Needle-Based Injection Systems	**Y**	**Y**
11608-5:2022 Needle-Based Injection Systems for Medical Use – Requirements and Test Methods – Part 5: Automated Functions	**Y**	**Y**

7.4. Design Control Review Conclusion

DESIGN CONTROL REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☐ No ☑ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☑ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A

Reviewer Comments

The device control review acceptable. The sponsor has adequately addressed the IR below.

The following IR should be communicated to the sponsor as a mid-cycle deficiency. Final deficiencies are not applicable at this point in review, as they depend on the sponsor's response to the information request:

In the instructions for use, the device has the following step: "(b) (4) " indicating that the device has a visual indicator that injection should be complete. Similarly, the device is stated to "click" at the beginning and end of injection. Audible and visual indicators are helpful metrics for the user to understand when the injection is over. For example, without a visual indicator, the user might remove the device prematurely, resulting in improper delivery of the therapeutic. As such, these indicators should be tested as pass/fail attributed. Additionally, please provide data supporting the reliability of these indicators through expiry of the device, and a control strategy to ensure proper attribute function. Testing should be performed using the confidence and reliability levels outlined in ISO 11608-1. Alternatively, provide a rationale as to why these indicators do not require further testing.

CDRH sent Design Control Deficiencies or Interactive Review Questions to the Sponsor: ☑ Yes ☐ No

	Date Sent: 12/23/2024	**Date/Sequence Received:** 2/28/2025
Information Request #	SN 0023: RESPONSE TO AGENCY INFORMATION REQUEST-CMC	
Sponsor Response	(b) (4)	

	(b) (4) [redacted]
Reviewer Comments	The sponsor rationale is acceptable. Per ISO 11608-1:2022, audible/ visual feedback would not need to be considered EPRs, and would not need to be tested through shelf-life for reliability. The sponsor has provided evidence as pass/fail indicating that 120 devices are capable of providing a visual and audible notification at the beginning and end of injection.
Response Adequate:	☑ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.

8. DESIGN VERIFICATION REVIEW

8.1. Performance/Engineering Verification

8.1.1. Essential Performance Requirement Evaluation

Essential Performance Requirement (Design Input)	Specification (Design Output)	Verification Method Acceptable (Y/N)	Validation (Y/N)	Aging / Stability (Y/N)	Shipping/ Transportation (Y/N)
Cap Removal Force	(b) (4)	Y	Y	Y	Y
Activation Force		Y	Y	Y	Y
Needle Extension		Y	Y	Y	Y
Delivered Volume		Y	Y	Y	Y
Injection Time		Y	Y	Y	Y

Reviewer Comment

Verification and validation methods conformed to ISO 11608-1:2022. A summary of testing is provided below, covering atmospheric testing, as well as free-fall and vibrational impact on the device. One batch of (b) (4) devices was used per test, which is acceptable as the device utilizes the (b) (4) platform, which has been tested in many other applications before. This is acceptable. The sponsor tested each specification and each condition to (b) (4) confidence and (b) (4) % reliability:

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All testing is acceptable, and no deviations were observed.

8.1.2. Verification of Design Inputs Evaluation

Design Input	Design Output	Verification Method	Results/Deviations	Adequately Verified (Y/N)	Release Testing? (Y/N)	Adequately Validated (Y/N)
Cap Removal Force	(b) (4)	Refer to 8.1.3	Refer to section 8.1	Y	N	Y
Activation Force		Refer to 8.1.3	Refer to section 8.1	Y	Y	Y
Needle Extension		Refer to 8.1.3	Refer to section 8.1	Y	Y	Y
Delivered Volume		Refer to 8.1.3	Refer to section 8.1	Y	Y	Y
Injection Time		Refer to 8.1.3	Refer to section 8.1	Y	Y	Y

Reviewer Comment

The sponsor provided the following rationale for why Cap Removal Force is not tested at release:

(b) (4)

The sponsor rationale is acceptable. Additionally, the device is not made for emergency use, so it is okay if Cap Removal Force is not tested at release.

3 GMP lots were used for stability testing (CP721744-005-AI-B, CP721744-004-AI-BA, and CP721744-006-AI-A). Detailed batch information and raw data can be found in "3.2.P.8.3 Stability Data." The sponsor states that as stability testing was adequate, further testing on batches is not needed, as the platform is the (b) (4) platform, and has undergone various testing prior. Instead, the devices will be tested at release. The lead reviewer agrees with the sponsor's rationale.

8.1.3. Evaluation of Test Methods

Title:	Cap Removal Force and Activation Force

Scope/Objective & Acceptance Criteria:	Measurement of cap removal force and activation force
Methods	(b) (4)
Results:	Refer to 8.1
Conclusions/ Reviewer Comments:	Testing was acceptable with no deviations. Refer to section 8.1 for a discussion of test results.
Acceptable:	☒Yes ☐No

Title:	Extended Needle Length
Scope/Objective & Acceptance Criteria:	*Measurement of extended needle length*
Methods	(b) (4)
Results:	Refer to 8.1
Conclusions/ Reviewer Comments:	Testing was acceptable with no deviations. Refer to section 8.1 for a discussion of test results.
Acceptable:	☒Yes ☐No

Title:	Delivered Volume
Scope/Objective & Acceptance Criteria:	Measurement of deliverable volume
Methods	(b) (4)
Results:	Refer to 8.1
Conclusions/ Reviewer Comments:	Testing was acceptable with no deviations. Refer to section 8.1 for a discussion of test results.
Acceptable:	☒Yes ☐No

Appears this way on original

8.2. Design Verification Review Conclusion

DESIGN VERIFICATION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☐ No ☑ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☑ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A

Reviewer Comments

The design verification is acceptable. The sponsor has responded adequately to the IR below.

While, in section 7, the lead reviewer noted that the device did not identify visual and audible indicators as test parameters, the lead reviewer would accept a rationale as to why these do not require further testing. For example, the device utilizes the known (b) (4) platform, and these parameters are controlled by (b) (4)

The sponsor has not provided adequate NSD C/R testing. The following deficiency is proposed:

We recommend that you evaluate your needle safety device, specifically the needle shield displacement, to the benchmark confidence and reliability (b) (4) %) for needle safety functions where the risk of failure leads to accidental needle stick. For further information, please refer to the agency guidance titled "Medical Devices with Sharps Injury Prevention Features (https://www.fda.gov/media/71142/download)" as well as the standard ISO 23908:2011 "Sharps injury protection - Requirements and test methods — Sharps protection features for single-use hypodermic needles, introducers for catheters and needles used for blood sampling."

CDRH sent Design Verification Deficiency or Interactive Review Questions to the Sponsor: ☑ Yes ☐ No

	Date Sent: 12/23/2024	**Date/Sequence Received:** 2/28/2025
Information Request #	SN 0023: RESPONSE TO AGENCY INFORMATION REQUEST-CMC	
Sponsor Response	(b) (4)	

	(b) (4)
Reviewer Comments	The sponsor has responded with appropriate testing of the device NSD.
Response Adequate:	☑ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.

9. RISK ANALYSIS

9.1. Risk Management Plan

Per the sponsor:

Risk management activities were conducted according to ISO 14971 “Medical Devices - Application of Risk Management to Medical Devices.” (b) (4)

(b) (4)

Reviewer Comments

The overall risk management plan is acceptable.

9.2. Risk Summary Report

Reviewer Comments

The sponsor has not provided a report for risk management and mitigation. The following IR should be issued:

You stated that a risk analysis was performed to address risks associated with the device design, system, use, and manufacturing. However, you did not provide this report for review. Proper identification and mitigation of device risks is important to help ensure that the device will not fail to accurately deliver treatment, or cause further harm. Therefore, please provide the following:.

- Identify all risks that exist with the device and provide information demonstrating they have been adequately mitigated for the study.
- Provide the scoring system used for probability and hazard, and the overall risk calculation.
- Ensure that reports for risk mitigation are traceable.

9.3. Risk Analysis Review Conclusion

RISK ANALYSIS REVIEW CONCLUSION

Filing Deficiencies: ☐ Yes ☐ No ☑ N/A	Mid-Cycle Deficiencies: ☐ Yes ☑ No ☐ N/A	Final Deficiencies: ☐ Yes ☑ No ☐ N/A

Reviewer Comments

The Device Risk Analysis is acceptable. The sponsor has adequately responded to the IR below.

The sponsor has not provided a report for risk management and mitigation. The following IR should be issued:

You stated that a risk analysis was performed to address risks associated with the device design, system, use, and manufacturing. However, you did not provide this report for review. Proper identification and mitigation of device risks is important to help ensure that the device will not fail to accurately deliver treatment, or cause further harm. Therefore, please provide the following:.

- Identify all risks that exist with the device and provide information demonstrating they have been adequately mitigated for the study.
- Provide the scoring system used for probability and hazard, and the overall risk calculation.
- Ensure that reports for risk mitigation are traceable.

CDRH sent Risk Analysis Deficiencies or Interactive Review Questions to the Sponsor: ☑ Yes ☐ No

	Date Sent: 12/23/2024	Date/Sequence Received: 2/28/2025
Information Request #	SN 0023: RESPONSE TO AGENCY INFORMATION REQUEST-CMC	
Sponsor Response	(b) (4)	

	 (b) (4)
Reviewer Comments	An example of the risk scores and mitigation tactics was provided in the image above. The full risk analysis can be in the following location: \\CDSESUB1\evsprod\NDA219407\0023\m1\us. The sponsor risk assessment is comple adequate. Appears this way on original
Response Adequate:	☑ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.

10. APPENDIX A (INFORMATION REQUESTS)

10.1. Mid-Cycle Information Requests

1. In the instructions for use, the device has the following step: "(b) (4) ," indicating that the device has a visual indicator that injection should be complete. Similarly, the device is stated to "click" at the beginning and end of injection. Audible and visual indicators are helpful metrics for the user to understand when the injection is over. For example, without a visual indicator, the user might remove the device prematurely, resulting in improper delivery of the therapeutic. As such, these indicators should be tested as pass/fail attributed. Additionally, please provide data supporting the reliability of these indicators through expiry of the device, and a control strategy to ensure proper attribute function. Testing should be performed to (b) (4)% confidence and (b) (4)% reliability. Alternatively, provide a rationale as to why these indicators do not require further testing.

2. You provided testing of the device needle shield displacement to a confidence and reliability of (b) (4) and (b) (4)% respectively. However, we recommend that you evaluate your needle safety device, specifically the needle shield displacement, to the benchmark confidence and reliability (b) (4)%) for needle safety functions where the risk of failure leads to accidental needle stick. Adequate confidence and reliability testing of this feature is important to ensure that the user does not receive accidental needle sticks from the device after use. Therefore, please provide updated testing of this feature to a confidence and reliability of (b) (4)%. For further information, please refer to the agency guidance titled "Medical Devices with Sharps Injury Prevention Features (https://www.fda.gov/media/71142/download)" as well as the standard ISO 23908:2011 "Sharps injury protection - Requirements and test methods — Sharps protection features for single-use hypodermic needles, introducers for catheters and needles used for blood sampling."

3. You stated that a risk analysis was performed to address risks associated with the device design, system, use, and manufacturing. However, you did not provide this report for review. Proper identification and mitigation of device risks is important to help ensure that the device will not fail to accurately deliver treatment, or cause further harm. Therefore, please provide the following:.
   - Identify all isks that exist with the device and provide information demonstrating they have been adequately mitigated for the study.
   - Provide the scoring system used for probability and hazard, and the overall risk calculation.
   - Ensure that reports for risk mitigation are traceable.

10.2. Interactive Information Requests

10.2.1. Interactive Information Requests sent on *Click or tap to enter a date.*

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/s/

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05/30/2025 11:21:47 AM

The Clinical Inspection Summary

Date	April 2, 2025
From	Suyoung Tina Chang, M.D., Medical Officer Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Rachel Bean, M.D., Clinical Reviewer, DPACC Miya Paterniti, M.D., Clinical Team Leader, DPACC Cindy Chee, Regulatory Project Manager Division of Pulmonology, Allergy, and Critical Care (DPACC)
NDA #	219407
Applicant	Ionis Pharmaceuticals Inc.
Drug	Dawnzera (donidalorsen)
NME (Yes/No)	Yes
Proposed Indication(s)	Prophylaxis to prevent attacks of hereditary angioedema (HAE) in adult and pediatric patients 12 years of age and older.
Consultation Request Date	October 9, 2024
Summary Goal Date	April 21, 2025
Action Goal Date	August 21, 2025
PDUFA Date	August 21, 2025

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Dr. Andrew Smith was inspected in support of NDA 219407, covering one study, ISIS 721744-CS5. Based on this inspection, the study appears to have been conducted adequately, and the data generated by the clinical investigator site appears acceptable in support of the respective indication.

II. BACKGROUND

According to the sponsor, donidalorsen is being developed as a long-term prophylactic treatment for hereditary angioedema (HAE) designed to selectively bind to prekallikrein messenger RNA, preventing production of the prekallikrein protein which subsequently reduces bradykinin. The sponsor has submitted NDA 219407 for prophylaxis to prevent attacks of hereditary angioedema (HAE) in adult and pediatric patients 12 years of age and older. One BIMO Review Based clinical investigator inspection was requested for clinical study ISIS 721744-CS5 because the application is for a new molecular entity (NME). However, this was a small study overall, and the review division only requested one CI to be inspected. Also, the review division did not choose to do a sponsor inspection because the sponsor had recently been inspected. The following describes the study:

Protocol ISIS 721744-CS5: "A Phase 3 Double Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of ISIS 721744 in Patients with Hereditary Angioedema (HAE)"

The study was a randomized, double-blind, placebo-controlled study to evaluate the clinical efficacy of donidalorsen in patients with HAE.

Sites: Subjects were randomized in 39 sites, including 21 sites in the European Union countries (Belgium [1 site], Bulgaria [2 sites], France [3 sites], Germany [3 sites], Italy [5 sites], Netherlands [2 sites], Poland [1 site], and Spain [4 sites]), 5 sites in the Middle East (Israel [2 sites] and Turkey [3 sites]), and 2 sites in the United Kingdom (UK), and 11 sites in North American (United States [9 sites] and Canada [2 sites]).

Subjects: A total of 91 subjects were randomized in Part A (i.e., 46 subjects who received donidalorsen every 4 weeks, 23 subjects who received donidalorsen every 8 weeks, 22 subjects who received placebo), and 83 subjects completed the Treatment Period (i.e., 44 subjects who received donidalorsen every 4 weeks, 21 subjects who received donidalorsen every 8 weeks, 18 subjects who received placebo).

Study initiation and completion dates: January 25, 2023 (first patient, first screening visit); November 9, 2023 (last patient, last visit)

Database lock date; study unblinding date: December 18, 2023; January 17, 2024

The study consisted of three periods, including an 8-week screening period, a 24-week treatment period, and a 13-week post treatment period.

During the treatment period, subjects with HAE type I (HAE-1) or type II (HAE-2) were randomly assigned in a 2:1 ratio to receive investigation drug once every 4 weeks (Cohort A) or 8 (Cohort B) weeks. Within each cohort, subjects were randomly assigned in a 3:1 ratio to receive donidalorsen or a matching volume of placebo. Data from patients receiving placebo in both Cohorts A and B were pooled for analyses. The first dose of the investigational drug was to be administered subcutaneously at the Study Center on Day 1. Subjects were instructed to report details of any HAE attack within 72 hours of the onset of the attack.

Key inclusion criteria: Male and female subjects 18 years of age and older with a documented diagnosis of HAE-1, HAE-2, or hereditary angioedema with normal C1 esterase inhibitor. The subjects must have experienced a minimum of two HAE attacks during the Screening Period and completed the angioedema activity score questionnaire at least 4 daily assessments per week for the duration of the Screening Period. Subjects must have had access to, and the ability to use, ≥1 acute medication(s) to treat angioedema attacks. Please see protocol for full details pertaining to eligibility criteria.

Primary efficacy endpoint: Time-normalized number of Investigator-confirmed HAE attacks (per 4 weeks) from Week 1 to Week 25 compared to placebo for the donidalorsen 80 mg once every 4 weeks group.

III. RESULTS (by site):

1. **Dr. Andrew Smith**
   Site #3126
   7390 S Creek Road, Suite 201
   Sandy, UT 84093-6123
   PDUFA Inspection Dates: January 13-15, 2025

For Protocol ISIS 721744-CS5, 3 subjects were screened, and 2 subjects were enrolled and randomized. All randomized subjects completed the study.

An audit of the study records was conducted for two randomized subjects. Records reviewed included, but were not limited to, protocol and amendments, Institutional Review Board submission and approvals, subject selection criteria, informed consents, investigational device controls, adverse event reporting, signed Investigator Agreements, financial disclosure statements, sponsor monitoring activities, IP accountability, subject medical records, and paper source records for verification of efficacy endpoints.

The following efficacy data were verified by comparing the data in the sponsor's data line listings with the site's paper source documents:

- Number of eligible HAE attacks
- Date, time of the first dose of investigational drug
- Date, time of symptom onset and resolution
- Location of symptoms
- Severity of symptoms
- Action taken to treat the HAE attack
- Was it was recorded as a typical attack
- Was it confirmed by the principal investigator

No discrepancies were noted. There was no evidence of underreporting of adverse events.

{See appended electronic signature page}

Suyoung Tina Chang, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

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

CONCURRENCE: {See appended electronic signature page}

Jenn Sellers, M.D., Ph.D.
Branch Chief
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Office of Scientific Investigations

CC:

Central Doc. Rm.
Review Division /Division Director/
Review Division /Medical Team Leader/
Review Division /Project Manager/
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OSI/Database PM/

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/s/

SUYOUNG T CHANG
04/02/2025 11:18:52 AM

PHILLIP D KRONSTEIN
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JENN W SELLERS
04/02/2025 11:33:34 AM

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOLOGY AND NEPHROLOGY PRODUCTS

Date: March 17, 2025

From: Interdisciplinary Review Team for Cardiac Safety Studies

Through: Christine Garnett, PharmD
Associate Director, Cardiac Safety IRT, DCN

To: Cindy Chee, RPM
DPACC

Subject: QT Consult to NDA 219407

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

This memo responds to your consult to us dated 2/19/2025 regarding the Applicant's QT labelling language for DAWNZERA. We reviewed the following materials:

- Previous IRT reviews for IND 142564 dated 08/10/2021 and 03/13/2024 in DARRTS; and
- Donidalorsen Label (link).

1 Responses for the Review Division

Question: Division has requested IRT's input on the labelling language.

IRT's response:

Below are proposed edits to the label submitted to SN 0002 (link). Our changes are highlighted (addition, ~~deletion~~). Each section is followed by a rationale for the changes made. Please note that this is a suggestion only and that we defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

(b) (4)

At the maximum recommended dose of DAWNZERA 80 mg (b) (4) clinically significant QTc interval prolongation was not observed.

Reviewer's comment: We propose to use labeling language for this product consistent with the "QTc Information in Human Prescription Drug and Biological Product Labeling Guidance for Industry" draft guidance (link).

2 BACKGROUND

Donidalorsen is a ligand-conjugated antisense oligonucleotide (LICA) drug (specifically a triantennary N-acetyl galactosamine (GalNAc)-conjugated 2′-O-(2-methoxyethyl) (2′-MOE)-modified chimeric gapmer antisense oligonucleotide (ASO) with a mixed backbone of phosphorothioate diester (PS) and phosphate diester (PO) inter-nucleotide linkages). It designed to bind to the messenger ribonucleic acid (mRNA) of plasma pre-kallikrein (PPK) which is expected to reduce the release of bradykinin. This vasodilator is known to increase vascular permeability resulting in swelling and pain associated with HAE (hereditary angioedema) attacks.

The product is formulated as sterile solution (0.8 mL vial) for injection containing donidalorsen (100 mg/mL) for subcutaneous (SC) administration. Therapeutic dose for donidalorsen is 80 mg Q4W.

The Applicant previously submitted TQT substitution request that included clinical FIH study ISIS 721744-CS1 (80 mg Q4W, SC) C-QTc analysis, as well as an integrated nonclinical risk assessment (in vitro hERG assay report 210830.JTJ (or 721744-IS08) and in vivo study. No 721744-AS03 in monkeys). Refer to previous IRT review dated 03/13/2024. The C-QTc analysis was based on day 1 data. IRT reviewed the data and the Applicant's QTc assessment report and concluded that there is low QTc prolongation risk and a substitution for a thorough QT study is reasonable for donidalorsen unless there are changes in the dosing or intrinsic or extrinsic factors. The primary factor that impacts Cmax is low body weight. Based on the Applicant's PopPK analysis, the Cmax for the lowest body weight group (37 – 68.5 kg) is 867 ng/mL (PopPK report, Table 15). The Cmax in the QTc assessment was 592 ng/mL (CV: 38%), which corresponds to ~0.7-fold the mean Cmax of the lowest body weight group. We consider this exposure coverage adequate because of the following reasons: 1) there was no C-QTc relationship; 2) large margin in in vivo QTc assessment (~62-fold) and no hERG signal; and 3) the individual observations cover approximately ~0.9 the Cmax for the low body weight group. No labelling language was provided at the time of review.

The Applicant has now submitted the label under NDA and DPACC is requesting CS-IRT review of the Applicant's proposed labeling language worded as (b) (4)

We recommend the following labeling language in section 12.2 per the FDA labeling guidance for industry: "At the maximum recommended dose of DAWNZERA 80 mg (b) (4), clinically significant QTc interval prolongation was not observed".

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

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/s/

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CHRISTINE E GARNETT
03/17/2025 01:15:25 PM

This is a corrected review that does not change the overall recommendations/conclusions of the original review dated February 19, 2025 at 9:03 AM.

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
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:	February 19, 2025
Requesting Office or Division:	Division of Pulmonology, Allergy, and Critical Care (DPACC)
Application Type and Number:	NDA 219407
Product Name, Dosage Form, and Strength:	Dawnzera (donidalorsen) injection, 80 mg/0.8 mL
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant Name:	Ionis Pharmaceuticals, Inc.
FDA Received Date:	August 21, 2024 and September 12, 2024
TTT ID #:	2024-10604
DMEPA 1 Safety Evaluator:	Sherly Abraham, R.Ph.
DMEPA 1 Team Leader:	Damon Birkemeier, PharmD, FISMP, NREMT

1 INTRODUCTION

As part of the approval process for Dawnzera (donidalorsen) 80 mg/0.8 mL autoinjector (AI), the Division of Pulmonology, Allergy, and Critical Care (DPACC) requested that we review the proposed Dawnzera Prescribing Information (PI), Patient Information, Instructions for Use (IFU), container label, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

This section lists the materials considered for our review of NDA 219407.

Table 1. Materials Considered for this Label and Labeling Review	
Materials Reviewed	Appendix Section
Relevant Product Information	A
Labels and Labeling	B

3 CONCLUSION

The Prescribing Information (PI), Patient Information, Instructions for Use (IFU), container label, and carton labeling may be improved to promote safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error for DPACC in Section 4 and for Ionis Pharmaceuticals, Inc in Section 5.

Note that DMEPA 1 is evaluating the HF validation study results under separate cover and, based on the outcome of that review, additional label and labeling comments may be forthcoming.

4 RECOMMENDATIONS FOR THE DIVISION OF PULMONOLOGY, ALLERGY, AND CRITICAL CARE (DPACC)

A. Prescribing Information

1. Highlights of Prescribing Information
    a. Recommendations to increase the readability of important product information for Highlights are noted in track changes below:

2. Section 2 Dosage and Administration
    a. Recommendations to increase the readability of important product information for Dosage and Administrations are noted in track changes below:

3. Section 16 How Supplied/Storage and Handling
    a. Recommendations to increase the readability of important product information for How Supplied/Storage and Handling are noted in track changes below:

(b) (4)

B. Patient Information

1. Recommendations to increase the readability of important product information for Patient Information is noted in track change below:

(b) (4)

C. Instructions for Use (IFU)

1. We note the expiration date on the autoinjector in the figure corresponding to Step 2a is denoted as "MM/YYYY". However, FDA recommends that, when all-numeric dates are used, they must be formatted using the year, the month, and, if applicable, the day, separated by hyphens or forward slashes in one of the following formats: YYYY-MM-DD or YYYY-MM. Thus, we recommend revising the expiration date to read "EXP: YYYY-MM".

2. Recommendations to increase the readability of important product information for IFU are noted in track changes below:

(b) (4)

5 RECOMMENDATIONS FOR IONIS PHARMACEUTICALS, INC.

Table 2. Identified Issues and Recommendations for Ionis Pharmaceuticals, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
General Comments			
1.	Note that additional label and labeling comments may be forthcoming when we have completed our evaluation of the human factors validation study results.		
Container Label and Carton Labeling			
1.	The second half of the proprietary name uses bolded font. (b) (4)	Usage of bolded font for second half of the proprietary name brings more prominence to that portion than rest of the name. The proprietary name may be misinterpreted as Zera	Remove the bolded font from the second half of the proprietary name, “ZERA”.

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		verses the intended Dawnzera. This presentation may lead to medication dispensing errors.	
2.	It appears that the established name is not at least half the size of the proprietary name.	We refer you to 21 CFR 201.10(g)(2) which states that the established name shall be printed in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features.	Revise the established name to be in accordance with 21 CFR 201.10(g)(2).
3.	The strength statement lacks prominence.	Lack of prominence of the strength statement may contribute to product selection medication errors. See 21CFR201.15(a)(6) which states a word, statement, or other information required by or under authority of the act to appear on the label may lack that prominence and conspicuousness required by section 502(c) of the act by reason, among other	Increase the prominence of the strength statement in accordance with 21 CFR 201.15(a)(6). Take into account all pertinent factors including font size, type, and color; background contrast; and statement location. If necessary, consider decreasing the prominence of other information that is not critical (e.g., net quantity statement).

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	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		reasons, of: smallness or style of type in which such word, statement, or information appears, insufficient background contrast, obscuring designs or vignettes, or crowding with other written, printed, or graphic matter.	
4.	The storage statement is not bolded.	Lack of prominence of storage statement may result in the risk of the storage information being overlooked and lead to deteriorated drug medication errors.	We recommend revising and bold the storage statement to read "Store refrigerated at 2°C to 8°C (36°F to 46°F)" or "Store refrigerated at 2°C to 8°C (36°F to 46°F)."
5.	The NDC number is found on the side panel.	The human-readable NDC is often used for product verification and identification prior to dispensing or administering a drug. It is an important safety feature that is recommended to be prominently displayed on the principal display panel of the carton labeling.	Consider relocating the NDC number from the side panel to the Principal Display Panel (PDP) above the proprietary name.
Container Label			
1.	The "Rx only" statement is bolded.	We recommend the "Rx only" statement does not compete in size or prominence with critical information on the principal display panel. See *Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize*	The "Rx only" statement should not compete in size and prominence with critical information on the principal display panel. We recommend removing the "Rx Only" statement from the container label or debolding and relocating the statement to a

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		Medication Errors (May 2022). Additionally, we note that the statement "Rx Only" is not required on small labels. Thus, in this case, since the "Rx Only" statement is present on the carton labeling, it could be removed from the container labeling to decrease clutter. We recommend removing the "Rx Only" statement from the container label or relocating the statement to a side panel on the container label.	side panel on the container label.
2.	As currently presented, the format for the expiration date is not defined.	We are unable to assess the proposed expiration date format from a medication safety perspective.	To minimize confusion and reduce the risk for deteriorated drug medication errors, we recommend identifying the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month,

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	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or forward slash to separate the portions of the expiration date. See *Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021).*
3.	As currently presented, the container label states, "Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original container". However, the carton labeling states "Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton."	Lack of consistency.	We recommend revising this sentence to read, "Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton." on the container label for consistency with the carton labeling.
Carton Labeling			
1.	The manufacturer name, Ionis, on the PDP competes in prominence with critical product information (e.g., proprietary name, established name, and strength).	Critical product information such as the proprietary name, established name, and product strength should appear as the most prominent information on the principal display panel in accordance with 21 CFR 201.15.	Relocate the manufacturer information to the side panel or decrease the prominence of the manufacturer name so it does not compete with the prominence of important product information on the principal display panel.
2.	The terminology within the statement of dosage statement is inconsistent with the terminology in	To ensure consistency with the terminology in the Prescribing Information.	We recommend revising the statement of dosage statement to read, "Recommended

Table 2. Identified Issues and Recommendations for Ionis Pharmaceuticals, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	the Prescribing Information.		Dosage: see Prescribing Information."
3.	The storage statement is duplicated on the PDP.	The proprietary name and established name along with the product strengths, route of administration, and warnings or cautionary statements should be the most prominent information on the PDP. Other less important information such as the storage statement should be on the back panel.	We recommend removing the duplicative storage information found on the PDP to increase the space available for other prominent information.
4.	The equivalency statement, "Each Dawnzera autoinjector contains 80 mg donidalosen (equivalent to 84 mg donidalosen sodium)" is found on the PDP.	The proprietary name and established name along with the product strengths, route of administration, and warnings or cautionary statements should be the most prominent information on the PDP. Other less important information such as the equivalency statement should be on the back panel.	Relocate the equivalency statement from the PDP to the back panel so it does not compete with the prominence of important product information on the PDP.
5.	As currently presented, there is no space for end-users to write the beyond-use date which is the [date] the opened product must be discarded after taking the product out of the refrigerator.	Since the product has a different expiration date after taking out of the refrigerator, the carton labeling should have a designated space and format for end-users to write the beyond-use date to minimize the risk of deteriorated drug medication errors.	We recommend including space for end-users to write the beyond-use date on the carton labeling. For example: Discard after ___/____/____

Table 2. Identified Issues and Recommendations for Ionis Pharmaceuticals, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
6.	The route of administration on the PDP and side panel are different ("for subcutaneous use" *versus* "for subcutaneous (b) (4) ").	To ensure consistency with the terminology across labeling.	Revise the statement on the side panel to read, (b) (4)
7.	The statement, "Do not expose to heat", is missing on the carton labeling.	Not including the statement, "Do not expose to heat" may result in loss of strength or potency, or destructive alteration of the product's characteristics.	Include the statement, "Do not expose to heat" on the carton labeling.
8.	It is not clear where the machine-readable product identifier is located on the label. Additionally, the format of the human-readable portion of the product identifier is not identified.	The Drug Supply Chain Security Act (DSCSA) requires, for certain prescription products, that the smallest saleable unit display a human-readable and machine-readable (2D data matrix barcode) product identifier.	The DSCSA guidance on product identifiers recommends a machine-readable (2D data matrix barcode) product identifier and a human-readable product identifier. Include the machine-readable data matrix barcode and a human readable product identifier. The guidance also recommends the format of the human-readable portion be located near the 2D data matrix barcode as the following: NDC: [insert NDC] SERIAL: [insert serial number] LOT: [insert lot number] EXP: [insert expiration date] We recommend that you review the draft guidance to

Table 2. Identified Issues and Recommendations for Ionis Pharmaceuticals, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			determine if the product identifier requirements apply to your product's labeling. The draft guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf
9.	The placeholder for the lot number is missing.	Lot number statement is required on the immediate container AND carton labeling when there is sufficient space per 21 CFR 201.10(i)(1).	Add the placeholder for the lot number in accordance 21 CFR 201.10(i)(1).
10	The placeholder for the expiration date is missing.	The label of an official drug product shall bear an expiration date per USP General Chapter <7>.	Add the placeholder for the expiration date in accordance with USP General Chapter <7>. The USP Chapter <7>Labeling requires the expiration date to appear on the immediate container and all other packaging. When all-numeric dates are used, they must be formatted using the year, the month, and, if applicable, the day, separated by hyphens or forward slashes in one of the following formats: YYYY-MM-DD or YYYY-MM. When alphanumeric dates are used, months must be displayed using at least three letters in one of the following formats: YYYY-MMM-DD or YYYY-MMM. We recommend you ensure that there are no other numbers located in close

Table 2. Identified Issues and Recommendations for Ionis Pharmaceuticals, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			proximity to the expiration date. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the expiration date format you intend to use.

APPENDICES: METHODS AND RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 3 presents relevant product information for Dawnzera received on September 12, 2024 from Ionis Pharmaceuticals, Inc.

Table 3. Relevant Product Information for Dawnzera	
Initial Approval Date	N/A
Active Ingredient	donidalorsen
Indication	Prophylaxis to prevent attacks of hereditary angioedema (HAE) in adult and pediatric patients 12 years of age and older.
Dosage Form	injection
Strength	80 mg/0.8 mL
Route of Administration	subcutaneous
Dose and Frequency	80 mg (b) (4) or 80 mg (b) (4)
How Supplied	One single-dose autoinjector per carton
Storage	Store in the refrigerator between 36°F to 46°F (2°C to 8°C) in the original carton. It can be stored at room temperature up to 86°F (30°C) in the original carton for up to 6 weeks.

APPENDIX B. LABELS AND LABELING

B.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Dawnzera labels and labeling submitted by Ionis Pharmaceuticals, Inc.

- Prescribing Information received on September 12, 2024, available from \\CDSESUB1\EVSPROD\nda219407\0002\m1\us\1-14-1-3-draft-labeling-text.docx
- Patient Information received on September 12, 2024, available from \\CDSESUB1\EVSPROD\nda219407\0002\m1\us\m1-14-1-3-draft-patient-pkg-insert.docx
- Instructions for Use received on August 21, 2024, available from \\CDSESUB1\EVSPROD\nda219407\0001\m1\us\114-labeling\draft\labeling\1-14-1-3-draft-ifu-text.docx
- Container label received on August 21, 2024
- \\CDSESUB1\EVSPROD\nda219407\0001\m1\us\114-labeling\draft\carton-and-container\1-14-1-1-draft-container-label-80mg.pdf
- Carton labeling received on August 21, 2024 \\CDSESUB1\EVSPROD\nda219407\0001\m1\us\114-labeling\draft\carton-and-container\1-14-1-1-draft-carton-label-80mg.pdf

B.2 Container Label and Carton Labeling Images

Container label

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

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

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

/s/

SHERLY ABRAHAM
02/19/2025 10:41:06 AM

DAMON A BIRKEMEIER
02/19/2025 10:42:38 AM

ICCR Facilities and Quality System Review Memo

Date:	November 6, 2024
To:	EMMA GIMOSE, FDA/OC/CDER/OPQ/OPRO/DRBPMII, Emma.Gimose@fda.hhs.gov
CC:	Office of Combination Product, Combination@fda.hhs.gov Regulatory Business Program Manager (RBPM)/Regulatory Program Manager (RPM): CINDY CHEE, CDER/OND/ORO/DROII, cindy.chee@fda.hhs.gov
Through:	Shruti Mistry, CDRH/OPEQ/OHTIII/DHTIIIC, shruti.mistry@fda.hhs.gov
From:	Tiffani Chance, CDRH/OPEQ/OHTIII/DHTIIIC, tiffani.chance@fda.hhs.gov
Applicant/Licensure:	Ionis Pharmaceuticals, Inc. 2282 Faraday Ave, Carlsbad CA, 92010 000215659
Submission (Type & Number):	NDA 219407
Combination Product Name:	Donidalorsen
Combination Product Indications for Use:	Treatment of Hereditary Angioedema
Device Constituent (Type):	Auto injector or Pen
ICCR Sharepoint Tracking Number:	ICCR01015792

ICCR CTS Tracking Number:	ICC2400819
Pre-Approval Facility Inspection:	No
Documentation Review (Status):	**Complete**
CDRH/OC Recommendation:	**Approvable**

CDRH received a consult from CDER requesting the identification of the device manufacturing sites for NDA 219407 which will require a device inspection.

PRODUCT DESCRIPTION

Donidalorsen Solution for Injection is a sterile, single-dose, ready-to-use parenteral solution of donidalorsen intended for subcutaneous (SC) administration. The formulation contains (b) (4) mg/mL donidalorsen free acid (b) (4) mg/mL donidalorsen sodium) (b) (4), at a target of pH (b) (4). (b) (4) The solution appears clear and colorless to yellow. The drug product is packaged with 0.8 mL deliverable volume in a 1 mL Long (1 mL L) staked needle glass prefilled syringe (PFS) closed with a (b) (4) rubber plunger stopper. The PFS is assembled into an autoinjector for the final drug product presentation.

Figure 1: Donidalorsen Autoinjector

REGULATORY HISTORY

The following facilities were identified as being involved in the manufacturing and/or development of the combination product, Donidalorsen, in NDA 219407.

Combination Product Applicant

Firm Name: Ionis Pharmaceuticals, Inc.

Address: 2282 Faraday Ave, Carlsbad CA, 92010

FEI: 000215659

Responsibility – The firm is responsible for drug substance quality control release and stability testing, and is thus not applicable to QS responsibilities.

Inspectional History – An analysis of the firm's inspection history showed that an inspection was conducted 9/26/2023 to 9/26/2023. The inspection covered drug CGMP and was classified NAI.

Inspection Recommendation:

An inspection is not required because The firm is not responsible for major activities related to the manufacturing and development of the final combination product or the device constituent part.

Finished Combination Product Manufacturer

Note: Per the instructions of this memo, only the firms responsible for final AI assembly was included in the inspection analysis. All other sites were either involved in drug substance control, or non-major activities related to the final combination product (secondary packaging and labeling and/ or control testing), and thus not applicable to QS responsibilities.

Firm Name: (b) (4)

Address: (b) (4)

FEI: (b) (4)

Responsibility – The firm is involved in the visual inspection of the bulk prefilled syringe, and autoinjector assembly. Additionally, the firm is responsible for drug product quality control

testing (chemical and microbial), as well as release and stability testing. As the firm is responsible for autoinjector assembly, it is applicable to QS requirements.

Inspectional History – An analysis of the firm's inspection history showed that an inspection was conducted (b) (4). The inspection covered both drug CGMPs and medical device QS and was classified VAI.

An inspection is not required because A recent medical device inspection of the firm was acceptable.

Firm Name: (b) (4)

Address: (b) (4)

FEI: (b) (4)

Responsibility – The firm is involved in autoinjector assembly. As the firm is responsible for autoinjector assembly, it is applicable to QS requirements.

Inspectional History – An analysis of the firm's inspection history showed that an inspection was conducted (b) (4). The inspection covered medical device QS and was classified VAI.

An inspection is not required because A recent medical device inspection of the firm was acceptable.

DOCUMENTATION REVIEW

Device Constituent Part Type: Auto injector or Pen

Device Constituent Part Class Class II: E.g. Prefilled Syringe, Auto Injector, Inhaler, Vaginal Ring, IUD

Combination Product NDA 219407 Proposed Indication for Use: Treatment of Hereditary Angioedema

1. Was the last inspection of the finished combination product manufacturing site, (b) (4) OAI for drug or device observations?	YES ☐	NO ☒	NA ☐
2. Is the device constituent a PMA or class III device?	YES ☐	NO ☒	UNK ☐
3. Is the final combination product meant for emergency use?	YES ☐	NO ☒	UNK ☐
4. Is the combination product meant for a vulnerable population (infants, children, elderly patients, critically ill patients, or immunocompromised patients)?	YES ☐	NO ☒	UNK ☐
5. Does the manufacturing site have a significant and known history of multiple class I device recalls, repeat class II device recalls, a significant number of MDRs/AEs, or OAI inspection outcomes?	YES ☐	NO ☒	UNK ☐
6. Is the combination product meant for users with a condition in which an adverse event will occur if the product is not delivered correctly (example insulin products for specific diabetic patients)?	YES ☐	NO ☒	UNK ☐
7. Does the manufacturing process for the combination product device constituent part use unique, complicated, or not well understood methods of manufacturing?	YES ☐	NO ☒	UNK ☐

cGMP Risk: ☒ Low or Moderate Risk of cGMP issues: If yes is not checked above, please fill out the checklist and deficiencies only. A review summary is optional.

☐ High Risk of cGMP issues: If yes is checked anywhere above, consider filling out the checklist, the deficiencies, and the review summary. If a full review is not warranted due to other factors such as device constituent classification (class I and class II devices), a low or moderate overall risk of device constituent failure, or positive compliance history, please document your rationale below for not conducting a full ICCR review.

Based on the answers to the table above, a review summary will not be provided, as the device does not introduce new technology, the indicated firms do not have a history of OAIs, the intended population is not vulnerable, and the device is not intended for emergency use.

The Quality System requirements applicable to a particular manufacturer may vary based upon the type of constituent parts being manufactured and the aspects of their manufacture that are

being performed at that site. All manufacturers are responsible for ensuring compliance with all requirements applicable to the manufacturing activities at their facilities. Where multiple facilities bear responsibility for various aspects of the manufacturing process, only the holder of the application or clearance for the product is responsible for compliance with all aspects of the Quality System requirements applicable to the entire manufacturing process and across all facilities.

Applicant:	Ionis Pharmaceuticals, Inc. 2282 Faraday Ave, Carlsbad CA, 92010 FEI: 000215659
Finished Combination Product Manufacturer:	(b) (4) (b) (4) FEI: (b) (4)
Device Constituent Part Manufacturer:	(b) (4) (b) (4) FEI: (b) (4)

Applicable Sites	Management Responsibility, 21 CFR 820.20 The firm provided a summary of how the firm's management has established responsibility to assure that the combination product is manufactured in compliance with all applicable CGMP requirements (see 21 CFR Part 4).	YES ☒	NO ☐

Ionis Pharmaceuticals, Inc.☒ (b) (4)) and ☒ (b) (4) ☒	The firm provided a description of the functions and responsibility of each facility involved in the manufacturing of the combination product and its constituent parts.	YES ☒	NO ☐
Applicable Sites Ionis Pharmaceuticals, Inc.☒ (b) (4)) and ☐ (b) (4))☐	Design Controls, General, 21 CFR 820.30 The firm explained how it utilized the design control process to develop the combination product under review and provided a description of its design control procedures.	YES ☒	NO ☐
	The firm provided a copy or a summary of the plan used to design the combination product.	YES ☒	NO ☐

Applicable Sites Ionis Pharmaceuticals, Inc.☒ (b) (4)) and ☐ (b) (4) ☐	Purchasing Controls, 21 CFR 820.50 The sponsor firm should summarize its procedure(s) for purchasing controls.	YES ☒	NO ☐
	The summary should describe the firm's supplier evaluation process and describe how it will determine type of and extent of control it will exercise over suppliers.	YES ☒	NO ☐
	The summary should define how the firm maintains records of acceptable suppliers and how it addresses the purchasing data approval process.	YES ☒	NO ☐
	The summary should explain how the firm will balance purchasing assessment and receiving acceptance to ensure that products and services are acceptable for their intended use.	YES ☒	NO ☐
	The firm should explain how it will ensure that changes made by contractors/suppliers will not affect the final combination product.	YES ☒	NO ☐
	The firm should provide a description of how it applied the purchasing controls to the suppliers/contractors used in the manufacturing of the combination product. (e.g., through supplier agreement).	YES ☒	NO ☐
Applicable Sites Ionis Pharmaceuticals, Inc.☒ (b) (4)	Corrective and Preventive Action (CAPA), 21 CFR 820.100 The sponsor firm should provide a summary of its procedure(s) for its Corrective and Preventive Action (CAPA) System.	YES ☒	NO ☐
	The CAPA system should require: a. Identification of sources of quality data and analysis of these data to identify existing and potential causes of nonconforming practices and products;	YES ☒	NO ☐
	b. Investigation of nonconformities and their causes;	YES ☒	NO ☐
	c. Identification and implementation of actions needed to correct and prevent recurrence of nonconformities; and	YES ☒	NO ☐

[redacted]) and ☐ [redacted] ☐	d. Verification or validation of the actions taken.	YES ☒	NO ☐
Applicable Sites Ionis Pharmaceuticals, Inc.☐ [redacted]) and ☐ [redacted])☐ None: ☒	Installation, 21 CFR 820.170 (check none if Installation is not required for the combination product) If applicable for the combination product, the firm should provide a summary of how it has established installation, inspection instructions, and test procedures for the installation of the combination product.	YES ☐	NO ☐
Applicable Sites Ionis Pharmaceuticals, Inc.☐	Servicing, 21 CFR 820.200 (check none if Servicing is not required for the combination product) Where servicing is a specified requirement for the combination product, the firm should provide a summary of how it has established and maintained instructions and procedures for performing and verifying that servicing of the combination product meets the specified requirements.	YES ☐	NO ☐

(b) (4)) and ☐ (b) (4) ☐ None: ☒			
Applicable Sites Ionis Pharmaceuticals, Inc.☐ (b) (4)) and ☐ (b) (4) ☐ None: ☒	Production and Process Controls The sponsor should provide a summary of the procedure(s) for environmental and contamination controls of the facility where the final manufacturing of the finished combination product, if such conditions could adversely affect the combination product. If the device constituent part is manufactured and finished at a separate medical device manufacturing facility these requirements may also apply to the finished device constituent part (see 21 CFR 4.4(c)).	YES ☐	NO ☐

Applicable Sites Ionis Pharmaceuticals, Inc.☐ (b) (4)) and ☐ (b) (4) ☐ None: ☒	The sponsor should provide a production flow diagram that identifies the steps involved in the manufacture of the finished combination product under review. This information should display the important aspects of the production process. If the device constituent part is manufactured and finished at a separate medical device manufacturing facility these requirements may also apply to the finished device constituent part (see 21 CFR 4.4(c)).	YES ☐	NO ☐
Applicable Sites Ionis Pharmaceuticals, Inc.☐ (b) (4)) and ☐	The sponsor should explain how it will control the manufacturing of the combination product through receiving or incoming, in-process, and final acceptance activities. The firm should specify which firm will perform the acceptance activities for the receiving of components/materials to be used in the combination product; for in-process testing performed during the manufacturing/assembly; and, for the final release of the combination product. The firm should also provide the acceptance/rejection criteria for the receiving components/materials, the in-process tests and the release of the finished combination product. If the device constituent part is manufactured and finished at a separate medical device manufacturing facility these requirements may also apply to the finished device constituent part (see 21 CFR 4.4(c)).	YES ☐	NO ☐

(b) (4) ☐ None: ☒	

Documentation Review Recommendation:

No Deficiencies Identified. The application was searched for documents pertaining to the manufacturing of the combination product. The documentation review of the application for compliance with the applicable quality system requirements showed no deficiencies. No additional information is required for the documentation review.

RECOMMENDATION

The documentation review of the application for compliance with the Quality System Requirements showed no deficiencies.

OC Decision: Approvable (Recommend approval to CDER)

Reviewer: Tiffani C. Chance -S Digitally signed by Tiffani C. Chance -S Date: 2024.11.06 13:47:41 -06'00'

Manager/Lead: Shruti N. Mistry -S 2024.11.06 15:07:07 -05'00'

M E M O R A N D U M

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

DATE: 10/31/2024

TO: Division of Pulmonology, Allergy, and Critical Care (DPACC)
Office of Immunology and Inflammation (OII)

FROM: Office of Study Integrity and Surveillance (OSIS)

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

RE: NDA 219407

The Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not needed for the site listed below. The rationale for this decision is noted below.

Rationale

The Office of Inspections and Investigations (OII) conducted a clinical inspection for the site in September 2024. The inspection was conducted under the following submission: NDA 218614.

The following item was discussed with the site:

- The original paper print outs from the pharmacy balances do not automatically add dates.

After review of the inspection findings, OSIS concluded that there were no human subject safety concerns and data from the reviewed study were reliable.

Site

Facility Type	Facility Name	Facility Address
Clinical	Medpace, Inc.	Clinical Pharmacology Unit, 5355 Medpace Way, Cincinnati, OH

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/s/

JAMES J LUMALCURI
10/31/2024 12:23:16 PM

M E M O R A N D U M

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

DATE: 9/20/2024

TO: Division of Pulmonology, Allergy, and Critical Care (DPACC)
Office of Immunology and Inflammation (OII)

FROM: Office of Study Integrity and Surveillance (OSIS)

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

RE: NDA 219407

The Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not needed for the site listed below. The rationale for this decision is noted below.

Rationale

OSIS conducted a Remote Regulatory Assessment (RRA) for the site in (b) (4). The RRA was conducted under the following submission: (b) (4)

OSIS concluded that data from the reviewed studies were reliable.

Site

Facility Type	Facility Name	Facility Address
Analytical	(b) (4)	

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/s/

JAMES J LUMALCURI
09/20/2024 02:46:49 PM