

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761177Orig1s000

OTHER REVIEW(S)

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)

Date of This Memorandum: August 20, 2021
Requesting Office or Division: Division of General Endocrinology (DGE)
Application Type and Number: BLA 761177
Product Name and Strength: Skytrofa (lonapegsomatropin) for injection, 3 mg, 3.6 mg, 4.3 mg, 5.2 mg, 6.3 mg, 7.6 mg, 9.1 mg, 11 mg, and 13.3 mg
Applicant/Sponsor Name: Ascendis Pharma
OSE RCM #: 2020-1429-2
DMEPA 1 Safety Evaluator: Jason Flint, MBA, PMP
DMEPA Team Leader (Acting): Ebony Whaley, PharmD, BCPPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on August 17, 2021 for Skytrofa. The Division of General Endocrinology (DGE) requested that we review the revised instructions for use, quick reference guide, container labels and carton labeling for Skytrofa (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

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

^a Flint, J. Human Factors Validation Study and Label and Labeling Review for Skytrofa (BLA 761177). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2021JUL13. RCM No.: 2020-1492-1.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON AUGUST 17, 2021

Carton and Container labels

<\\CDSESUB1\evsprod\bla761177\0052\m1\us\114-labeling\draft\carton-and-container>

Instructions for Use

<\\CDSESUB1\evsprod\bla761177\0052\m1\us\114-labeling\draft\labeling\gh-au-ifu.pdf>

<\\CDSESUB1\evsprod\bla761177\0052\m1\us\114-labeling\draft\labeling\gh-au-ifu-cover.pdf>

Quick Reference Guide

<\\CDSESUB1\evsprod\bla761177\0052\m1\us\114-labeling\draft\labeling\gh-ai-qrg.pdf>

Prescribing Information

<\\CDSESUB1\evsprod\bla761177\0052\m1\us\114-labeling\draft\labeling\draft-labeling-text.pdf>

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/

JASON A FLINT
08/20/2021 09:31:12 AM

EBONY A WHALEY
08/20/2021 10:23:57 AM

HUMAN FACTORS STUDY REPORT AND LABELS AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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

Date of This Review:	July 13, 2021
Requesting Office or Division:	Division of General Endocrinology (DGE)
Application Type and Number:	BLA 761177
Product Type:	Combination Product
Drug Constituent Name and Strength	Skytrofa (lonapegsomatropin) for Injection, 3 mg, 3.6 mg, 4.3 mg, 5.2 mg, 6.3 mg, 7.6 mg, 9.1 mg, 11 mg, and 13.3 mg
Device Constituent:	Autoinjector
Rx or OTC:	Rx
Applicant/Sponsor Name:	Ascendis Pharma
Submission Date:	May 11, 2021; June 15, 2021
OSE RCM #:	2020-1429 2020-1499
DMEPA Safety Evaluator:	Jason Flint, MBA, PMP
DMEPA Team Leader (Acting):	Ebony Whaley, PharmD, BCPPS
DMEPA Associate Director for Human Factors (Acting):	Lolita White, PharmD
DMEPA Deputy Director:	Irene Z. Chan, PharmD, BCPS

1. REASON FOR REVIEW

This review evaluates human factors (HF) validation study results submitted under BLA 761177 for Skytrofa (lonapegsomatropin).

1.1. PRODUCT DESCRIPTION

This is a combination product with a proposed autoinjector device constituent part that is

(b) (4)

The GH Autoinjector is an electronic device that uses two mixing steps to reconstitute the medication. The first step is accomplished by the device itself, while the second step is performed by the user. The device uses status icons to indicate the current state to the user. The GH autoinjector uses two disposable components: (1) a needle and (2) a cartridge containing the medication and sterile water for injection.

(b) (4)

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

We reviewed an HF validation study report submitted under BLA 761177 on July 13, 2020. Our review identified deficiencies with the study methodology that precluded a reliance on

the HF validation study results to support the marketing application. We provided HF recommendations¹ to the Applicant on January 13, 2021. We held a teleconference with the Applicant on January 19, 2021 to discuss the HF validation study methodology issues and the possible need for additional HF validation study data. The Applicant provided written responses to our HF recommendations on January 22, 2021, and we reviewed and provided feedback to the Applicant on January 27, 2021² that additional HF validation study data would be required to support their application. Subsequent to our most recent communication, the Applicant submitted an HF validation study protocol for our review on February 11, 2021, which we reviewed and provided recommendations for on March 30, 2021³. We note that the Applicant incorporated all of our recommendations from the HF validation study protocol review.

2. MATERIALS REVIEWED

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

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

¹ Whaley, E. Human Factors Results Review Memorandum for Skytrofa (lonapegsomatropin) BLA 761177. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 20210113. RCM No.: 2020-1429; 2020-1499.

² Whaley, E. Review of Responses to Human Factors Recommendations for Skytrofa (lonapegsomatropin) BLA 761177. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 20210127. RCM No.: 2020-1499-1.

³ Flint, J. Human Factors Validation Study Protocol Review for Skytrofa (lonapegsomatropin) BLA 761177. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 20210330. RCM No.: 2020-1429, 2020-1499.

3. OVERALL ASSESSMENT OF MATERIALS REVIEWED

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

3.1. SUMMARY OF STUDY DESIGN

Table 2 presents a summary of the HF validation study design. See Appendix C for more details on the study design.

Table 2. Study Methodology for Human Factors (HF) Validation Study					
Study Design Elements	Details				
Participants				Study Participants*	Total
			Patients	Caregivers	
	Stratification Groups	Injection-naïve	7	9	16
		Injection-experienced	8	7	15
Total		15	16	31	
16 of the 31 participants were given a two-cartridge use scenario					
Training	No training was offered				
Test Environment	Simulated home environment				
Sequence of Study	<pre> graph TD A[1 Participant Enrollment] --- B[2 Introduction and Background Interview] B --- C[3 Study Introduction] C --- D[4 Simulated Use Scenarios] D --- E[5 Simulated Use Deviation Probing] A --- F[6 Knowledge Tasks] F --- G[7 Knowledge Task Deviation Probing] G --- H[8 Post Study Interview] H --- I[9 Wrap Up and Compensation] A --- F </pre>				

3.2. RESULTS RELATED TO CRITICAL TASKS

Table 3 below describes the critical task use errors, use difficulties and close -calls that were identified in the HF validation study, and DMEPA's analyses and recommendations.

Table 3. Identified Issues and DMEPA's Findings

	Identified Issue and Rationale for Concern	DMEPA's Analysis and Findings
1.	For the task Turn up and down until 2 beeps, there were 2 use errors. One participant aborted the injection process by pressing and holding the power button and did not receive a dose. The other participant performed this manual mixing step prematurely during the automated mixing that the device completes. The subjective data and the Applicant's root cause analysis stated: (b) (4) Information Oversight - The information in the IFU was overlooked. The Applicant has not proposed mitigations to address these use errors.	Based on the URRRA, if this task is omitted or not performed correctly there is risk of no dose received - User cannot perform injection sequence, single incident. We disagree with the Applicant's root cause analysis (b) (4) (b) (4) After considering the subjective feedback, our review of the labels and labeling (user interface, etc.) finds that step 5 (b) (4) (b) (4) Based on our overall assessment, we find the user interface can be improved. We provide a recommendation in Table 4 to address this concern. We have determined that this change can be implemented without additional HF validation testing to be submitted for review.

⁴ We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/regulatory-information/search-fdaguidance-documents>.

2.	For the task Mount needle on new cartridge, there were 2 use errors. For example, participants did not add the needle onto the cartridge before inserting the cartridge into the device. Another user attempted to insert the needle into the AI without the cartridge. The subjective data and the Applicant’s root cause analysis stated: Negative Transfer from a device where only the needle is changed. Information oversight – information in the IFU was overlooked. The Applicant has not proposed mitigations to address this use error.	Based on the URRRA, if this task is omitted or not performed correctly there is risk of delayed medication administration. Our review of the study results identified subjective feedback that indicated one participant was used to adding the needle to an insulin pen injector and tried to perform the same action with this device. The Applicant confirmed in an information request response that the GH Autoinjector is designed to only deliver the medication with the needle attached. If a user attempts to deliver an injection without the needle attached, the device cancels the injection process, and notifies the user that an error has occurred. Our review of the labels and labeling (user interface, etc.) finds that the IFU contains adequate instructions to support this step. We find that the residual risk is acceptable and do not have any additional recommendations at this time.
3.	For the task Troubleshoot three red flashing icons. There was 1 use error that the Applicant categorized as a Close Call that occurred when the participant encountered a malfunction with the device shortly after powering on the device. Despite seeing three red flashing icons and beeping, the user attempted to give their injection. The subjective data and the Applicant’s root cause analysis stated: Experimental Artifact - The participant thought the device would be a nonfunctional study prototype. The Applicant has not proposed mitigations to address this use error.	Based on the URRRA, if this task is omitted or not performed correctly there is risk of no dose received - User does not perform injection sequence, single incident With this error, the participant pressed the green button to turn on the device (with the cartridge inserted), but the device displayed three red icons and beeped (indicating a self-test error) and powered off, at which time the participant continued without addressing the malfunction since the participant thought the device was a nonfunctional study prototype. Our review of the labels and labeling (user interface, etc.) finds that the labeling has instructions regarding how to turn the device on, and the troubleshooting section of the IFU provides detail regarding how to respond to the device malfunction experienced by this participant. We did not identify any further risk mitigation measures to address this use error, and find that the residual risk is acceptable.
4.	For the task Select Injection site, there was 1 use error – the participant indicated they would inject into their arm or shoulder.	Based on the URRRA, if this task is omitted or not performed correctly there is risk of compromised medical care.

	The subjective data and the Applicant's root cause analysis stated: Negative Transfer – transferred their knowledge of other medical needle applications to use of the product.	Our review of the study results identified subjective feedback from the participant indicating that the forearm or shoulder was “where needles mostly go and where the blood runs.” Our review of the labels and labeling (user interface, etc.) finds that the QRG and IFU contain instructions and images regarding where to administer the injection. We have not identified any further risk mitigation measures to address this use error, and find that the residual risk is acceptable.
5.	For the task Identify second cartridge needed (only for two-cartridge dose participants) there were 2 use errors. The subjective data and the Applicant's root cause analysis stated: Test artifact: the participants were given a confusing prescription  The applicant has not proposed risk mitigations to address this use error.	Based on the URRRA, if this task is omitted or not performed correctly there is risk of underdose. We agree with the Applicant's root cause analysis that participants that experienced this use error were confused by the prescription that was provided as a test prompt. Our review of the study results identified subjective feedback that indicated the language used on the prescription was confusing. Our review of the labels and labeling (user interface, etc.) finds that the IFU contains a user prompt asking if the patient requires two cartridges for their weekly dose, and provides instructions on what to do if two cartridges are required for a full dose. We have not identified any further risk mitigation measures to address this use error, and find that the residual risk is acceptable.
6.	For the task Insert DCC into device until click there were 2 use errors, and 1 use difficulty: The subjective data and the Applicant's root cause analysis stated: Device feedback – the cartridge was not fully seated	Based on the URRRA, if this task is omitted or not performed correctly there is risk of delayed medication administration. We agree with the Applicant's root cause analyses that the device feedback may have contributed to one of the use errors. Our review of the study results identified subjective feedback that indicated the participant heard a click that indicated the cartridge was fully seated

	User pressed cartridge more than once – pressing the cartridge once inserts the cartridge, and the second releases the cartridge The applicant has not proposed risk mitigations to address these use errors.	when it was not. Subsequently, the cartridge fell out of the device prior to the injection. step(Note, the applicant reported this as a use error for the critical task of holding the device on the skin, but our analysis determined that the error was with insertion of the cartridge, which led to the cartridge falling out when the participant went to deliver the injection). In an information request response, the Applicant indicated that for this particular use error, the medication in the cartridge was mixed, and the user was able to re-insert the cartridge and deliver the medication – the device is designed to not deliver an injection if the mixing steps are incomplete. Further, the Applicant confirms that this use difficulty was only seen “in one case throughout device development, verification, usability validation and clinical trials with 750 devices produced and applied in testing (200 devices), PQ (300 devices), clinical trials (250 devices).” Our review of the labels and labeling (user interface, etc.) finds that the IFU and QRG contain instructions and images supporting this use task. We have not identified any further risk mitigation measures to address this use error, and find that the residual risk is acceptable.

3.3. ANALYSIS OF NON-CRITICAL TASK ERRORS

We note that the results of the HF validation study showed use errors, (e.g. failures, difficulties, and close calls) with non-critical tasks (including use tasks and knowledge tasks). We determined that the residual risk is acceptable without further need for risk mitigation strategies for the following non-critical tasks:

- Wash hands
- Identify needle expiration date
- Can you share your auto-injector with another person?
- If you have small children in your house, is there anything special you need to do with your injection materials?
- Should you clean the device while it is charging?
- Can other chargers, such as your phone charger, be used to charge this device?

3.4. LABELS AND LABELING

Tables 4 below includes the identified medication error issues with the submitted product samples, packaging, label and labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error that we already conveyed to the Applicant. However, we have since identified another are of concern regarding the statements related to training on the container label and carton labeling. Our evaluation of the proposed prescribing information submitted under BLA 761177 did not identify areas of vulnerability that may lead to medication errors.

Table 4: Identified Issues and Recommendations for Applicant (already conveyed to Applicant)			
	Identified Issue	Rationale for Concern	Recommendation
Instructions for Use (IFU)			
1.	Step 5 of the IFU and QRG lacks clarity (b) (4)	In the HF validation study, we note that one user inadvertently aborted their injection during the manual mixing phase by pressing and holding the power button. Adding clarifying information to step 5 of the IFU warning users to avoid the power button during this step may help to alleviate this use error. We acknowledge this information about pressing and holding the power button to abort the injection process does appear later in the IFU, however, we find the risk of medication error resulting in no dose administered warrants redundancy and including this information earlier.	We recommend you add a statement to step 5 of the IFU and QRG to warn users to avoid the power button during this step. We have determined that this change can be implemented without additional HF validation testing to be submitted for review.
Carton, Container and Blister Labeling			
1.	The proposed strengths are not clearly differentiated. Specifically, we note you use the color (b) (4) to highlight the strength statements on all of your proposed carton,	Lack of adequate strength differentiation may contribute to selection errors.	The following recommendation was issued to the Applicant prior to the finalization of this review: To minimize the potential risk of dispensing errors, we recommend

blister, and container labels. We do not find that this approach provides adequate strength differentiation. In addition, the (b) (4) color (b) (4) and decreases the prominence of the strength statement.		revision of the colors to provide adequate differentiation between strengths. We recommend that the colors used to denote the statement of strength (b) (4) (b) (4) Consider the use of different colors, boxing, or some other means to provide adequate differentiation between the strengths on your carton, container, and blister labels.
2. After addressing recommendation #1 above, the Applicant provided edited carton, container, and blister labeling, to which we provided the following response: We note that the color scheme utilized for some of the proposed strengths have similar color hues: (b) (4)		

Additionally, we note that the color scheme for the proposed 5.2 mg strength [REDACTED] (b) (4)

The use of similar color hues minimizes the difference between the strengths, which may lead to strength selection errors. Revise the labeling to include unique, well differentiated colors that do not overlap with the color hues used for other strength presentations [REDACTED] (b) (4).

We also note that the strength presentations lack prominence, which may contribute to strength selection errors. Consider enlarging the font size for the proposed strengths or other risk mitigation measures to minimize the risk of wrong strength errors.

Our evaluation of the labels and labeling identified two additional concerns that were not yet conveyed to the Applicant. The concerns are as follows:

1. For your cartridge labels, which appear to be clear, ensure there is adequate contrast between the background and text to allow for readability/legibility of important information.
2. We note the statement under the stop sign graphic that states "[REDACTED] (b) (4). Do not use the SKYTROFA cartridges for the first time [REDACTED] (b) (4) training from a healthcare provider." While we encourage and agree that being trained is an important best practice, especially at the initiation of therapy, we note that the development and validation of the user interface for this product did not include specific required training. As such, we ask that you revise the statement in all applicable areas of labeling to remove the [REDACTED] (b) (4) statement. The remainder of the statement can remain as proposed.

4. CONCLUSION AND RECOMMENDATIONS

Based on our review of the HF validation study results and labels and labeling, we determined that certain changes should be implemented in the design of the user interface to further support safe and effective use of the product and minimize the risk for medication errors. The recommendations in Table 4 were already communicated to the Applicant prior to this review being finalized, and labeling negotiations between the Applicant and the Agency are ongoing. Section 3.1 below includes additional recommendations that should be conveyed to Ascendis Pharma and implemented prior to approval of the BLA.

4.1. RECOMMENDATIONS FOR ASCENDIS PHARMA

Since our previous communications, we have identified additional labeling recommendations that we advise are implemented prior to approval of your BLA. These changes can be implemented without additional HF validation testing. Our recommendations are as follows:

1. For your cartridge labels, which appear to be clear, ensure there is adequate contrast between the background and text to allow for readability/legibility of important information.
2. We note the statement under the stop sign graphic that states “ (b) (4) . Do not use the SKYTROFA cartridges for the first time (b) (4) training from a healthcare provider.” While we encourage and agree that being trained is an important best practice, especially at the initiation of therapy, we note that the development and validation of the user interface for this product did not include specific required training. As such, we ask that you revise the statement in all applicable areas of labeling to remove the (b) (4) statement. The remainder of the statement can remain as proposed.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. DRUG PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 5 presents relevant product information for Skytrofa (lonapegsomatropin) that Ascendis Pharma submitted on May 11, 2021.

Table 5. Relevant Product Information	
Initial Approval Date	N/A
Therapeutic Drug Class or New Drug Class	Human growth hormone
Active Ingredient (Drug or Biologic)	Lonapegsomatropin – tcgd
Indication	(b) (4)
Route of Administration	Subcutaneous injection
Dosage Form	Injection
Strength	3.0, 3.6, 4.3, 5.2, 6.3, 7.6, 9.1, 11.0 and 13.3 mg
Dose and Frequency	0.24 mg hGH/kg body weight once weekly
How Supplied	carton containing 4 cartridges and 6 single-use needles
Storage	Can be stored at room temperature [not to exceed 86°F(30°C)] for up to 6 months. Alternatively, can be stored under refrigeration at 36°F to 46°F (2°C to 8°C) until the expiration date.
Container Closure/Device Constituent	Box with 4 cartridges and 6 needles for use with Skytrofa Autoinjector
Intended Users	Patients and Caregivers
Intended Use Environment	Home Environment

APPENDIX B. BACKGROUND INFORMATION

B.1 PREVIOUS HF REVIEWS

B.1.1 Methods

On June 8, 2021, we searched the L:drive and AIMS using the terms, “Skytrofa” and “lonapegsomatropin” to identify reviews previously performed by DMEPA or CDRH.

B.1.2 Results

Our search identified three previous reviews⁵⁶⁷, and we confirmed that our previous recommendations were implemented.

APPENDIX C. BACKGROUND INFORMATION ON HUMAN FACTORS ENGINEERING PROCESS

The background information can be accessible in the HF results report. See Appendix D.

APPENDIX D. HUMAN FACTORS VALIDATION STUDY RESULTS REPORT

The HF study results report can be accessible in EDR via:

<\\CDSESUB1\evsprod\bla761177\0041\m5\53-clin-stud-rep\535-rep-effic-safety-stud\growth-hormone-deficiency-ghd\5354-other-stud-rep\gh-auto-injector-hf\gh-auto-inject-hf-supp-sus-protocol.pdf>

APPENDIX E. INFORMATION REQUESTS ISSUED DURING THE REVIEW

We issued one information request, and the response is below:

<\\CDSESUB1\evsprod\bla761177\0048\m1\us\12-cover-letters\cover-letter.pdf>

APPENDIX F. LABELS AND LABELING

E.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,⁸ along with postmarket medication error data, we reviewed the following Skytrofa (lonapegsomatropin) labels and labeling submitted by Ascendis Pharma on May 11, 2021.

⁵ Whaley, E. Human Factors Results Review Memorandum for Skytrofa (lonapegsomatropin) BLA 761177. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 20210113. RCM No.: 2020-1429; 2020-1499.

⁶ Whaley, E. Review of Responses to Human Factors Recommendations for Skytrofa (lonapegsomatropin) BLA 761177. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 20210127. RCM No.: 2020-1499-1.

⁷ Flint, J. Human Factors Validation Study Protocol Review for Skytrofa (lonapegsomatropin) BLA 761177. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 20210330. RCM No.: 2020-1429, 2020-1499.

⁸ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

Instructions for Use	\\CDSESUB1\evsprod\bla761177\0041\m1\us\114-labeling\draft\labeling\gh-ai-ifu.pdf
Quick Reference Guide	\\CDSESUB1\evsprod\bla761177\0041\m1\us\114-labeling\draft\labeling\gh-ai-grg.pdf
IFU Cover	\\CDSESUB1\evsprod\bla761177\0041\m1\us\114-labeling\draft\labeling\gh-ai-ifu-cover.pdf
Blister 3.6	\\CDSESUB1\evsprod\bla761177\0029\m1\us\114-labeling\draft\carton-and-container\dcc-blister-pack-carton-3-6-mg.pdf
Blister 3.0	\\CDSESUB1\evsprod\bla761177\0029\m1\us\114-labeling\draft\carton-and-container\dcc-blister-pack-carton-3-mg.pdf
Blister 4.3	\\CDSESUB1\evsprod\bla761177\0029\m1\us\114-labeling\draft\carton-and-container\dcc-blister-pack-carton-4-3-mg.pdf
Blister 5.2	\\CDSESUB1\evsprod\bla761177\0029\m1\us\114-labeling\draft\carton-and-container\dcc-blister-pack-carton-5-2-mg.pdf
Blister 6.3	\\CDSESUB1\evsprod\bla761177\0029\m1\us\114-labeling\draft\carton-and-container\dcc-blister-pack-carton-6-3-mg.pdf
Blister 7.6	\\CDSESUB1\evsprod\bla761177\0029\m1\us\114-labeling\draft\carton-and-container\dcc-blister-pack-carton-7-6-mg.pdf
Blister 9.1	\\CDSESUB1\evsprod\bla761177\0029\m1\us\114-labeling\draft\carton-and-container\dcc-blister-pack-carton-9-1-mg.pdf
Blister 11	\\CDSESUB1\evsprod\bla761177\0029\m1\us\114-labeling\draft\carton-and-container\dcc-blister-pack-carton-11-mg.pdf
Blister 13.3	\\CDSESUB1\evsprod\bla761177\0029\m1\us\114-labeling\draft\carton-and-container\dcc-blister-pack-carton-13-3-mg.pdf
Inner 3	\\CDSESUB1\evsprod\bla761177\0029\m1\us\114-labeling\draft\carton-and-container\dcc-inner-carton-3-mg.pdf
Inner 3.6	\\CDSESUB1\evsprod\bla761177\0029\m1\us\114-labeling\draft\carton-and-container\dcc-inner-carton-3-6-mg.pdf
Inner 4.3	\\CDSESUB1\evsprod\bla761177\0029\m1\us\114-labeling\draft\carton-and-container\dcc-inner-carton-4-3-mg.pdf
Inner 5.2	\\CDSESUB1\evsprod\bla761177\0029\m1\us\114-labeling\draft\carton-and-container\dcc-inner-carton-5-2-mg.pdf
Inner 6.3	\\CDSESUB1\evsprod\bla761177\0029\m1\us\114-labeling\draft\carton-and-container\dcc-inner-carton-6-3-mg.pdf
Inner 7.6	\\CDSESUB1\evsprod\bla761177\0029\m1\us\114-labeling\draft\carton-and-container\dcc-inner-carton-7-6-mg.pdf

Inner 9.1	\\CDSESUB1\evsprod\bla761177\0029\m1\us\114-labeling\draft\carton-and-container\dcc-inner-carton-9-1-mg.pdf
Inner 11	\\CDSESUB1\evsprod\bla761177\0029\m1\us\114-labeling\draft\carton-and-container\dcc-inner-carton-11-mg.pdf
Inner 13.3	\\CDSESUB1\evsprod\bla761177\0029\m1\us\114-labeling\draft\carton-and-container\dcc-inner-carton-13-3-mg.pdf
Outer Carton 3	\\CDSESUB1\evsprod\bla761177\0029\m1\us\114-labeling\draft\carton-and-container\dcc-outer-carton-3-mg.pdf
Outer Carton 3.6	\\CDSESUB1\evsprod\bla761177\0029\m1\us\114-labeling\draft\carton-and-container\dcc-outer-carton-3-6-mg.pdf
Outer Carton 4.3	\\CDSESUB1\evsprod\bla761177\0029\m1\us\114-labeling\draft\carton-and-container\dcc-outer-carton-4-3-mg.pdf
Outer Carton 5.2	\\CDSESUB1\evsprod\bla761177\0029\m1\us\114-labeling\draft\carton-and-container\dcc-outer-carton-5-2-mg.pdf
Outer Carton 6.3	\\CDSESUB1\evsprod\bla761177\0029\m1\us\114-labeling\draft\carton-and-container\dcc-outer-carton-6-3-mg.pdf
Outer Carton 7.6	\\CDSESUB1\evsprod\bla761177\0029\m1\us\114-labeling\draft\carton-and-container\dcc-outer-carton-7-6-mg.pdf
Outer Carton 9.1	\\CDSESUB1\evsprod\bla761177\0029\m1\us\114-labeling\draft\carton-and-container\dcc-outer-carton-9-1-mg.pdf
Outer Carton 11	\\CDSESUB1\evsprod\bla761177\0029\m1\us\114-labeling\draft\carton-and-container\dcc-outer-carton-11-mg.pdf
Outer Carton 13.3	\\CDSESUB1\evsprod\bla761177\0029\m1\us\114-labeling\draft\carton-and-container\dcc-outer-carton-13-3-mg.pdf
Sharp Label 3	\\CDSESUB1\evsprod\bla761177\0029\m1\us\114-labeling\draft\carton-and-container\dcc-label-3-mg.pdf
Sharp Label 3.6	\\CDSESUB1\evsprod\bla761177\0029\m1\us\114-labeling\draft\carton-and-container\dcc-label-3-6-mg.pdf
Sharp Label 4.3	\\CDSESUB1\evsprod\bla761177\0029\m1\us\114-labeling\draft\carton-and-container\dcc-label-4-3-mg.pdf
Sharp Label 5.2	\\CDSESUB1\evsprod\bla761177\0029\m1\us\114-labeling\draft\carton-and-container\dcc-label-5-2-mg.pdf
Sharp Label 6.3	\\CDSESUB1\evsprod\bla761177\0029\m1\us\114-labeling\draft\carton-and-container\dcc-label-6-3-mg.pdf
Sharp Label 7.6	\\CDSESUB1\evsprod\bla761177\0029\m1\us\114-labeling\draft\carton-and-container\dcc-label-7-6-mg.pdf

Sharp Label 9.1	\\CDSESUB1\evsprod\bla761177\0029\m1\us\114-labeling\draft\carton-and-container\dcc-label-9-1-mg.pdf
Sharp Label 11	\\CDSESUB1\evsprod\bla761177\0029\m1\us\114-labeling\draft\carton-and-container\dcc-label-11-mg.pdf
Sharp Label 13.3	\\CDSESUB1\evsprod\bla761177\0029\m1\us\114-labeling\draft\carton-and-container\dcc-label-13-3-mg.pdf

E.2 Label and Labeling Images



Labeling.pdf

3 mg Outer Carton

(b) (4)



3 mg Inner Carton

(b) (4)

3 mg Cartridge Label

(b) (4)

3 mg Blister Lid

(b) (4)

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/

JASON A FLINT
07/13/2021 04:37:27 PM

EBONY A WHALEY
07/13/2021 09:28:07 PM

LOLITA G WHITE
07/13/2021 09:41:07 PM

IRENE Z CHAN
07/14/2021 08:50:56 AM



DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS
INTERCENTER CONSULT MEMORANDUM

Date	8/18/2020		
To:	Melinda Bauerlien		
Requesting Center/Office:	CDER/OPQ	Clinical Review Division:	N/A-OPQ/OSE led
From	Shanly Chen, PharmD OPEQ/OHT3/DHT3C		
Through (Team)	Rumi Young, MS, Team Lead, Injection Team OPEQ/OHT3/DHT3C		
Through (Division) *Optional	CPT Alan Stevens, Assistant Director OPEQ/OHT3/DHT3C		
Subject	ICCR 00023092 ICC 2000610 BLA 761177 Sponsor: Ascendis Pharma Durg Product: ACP-011 lonapegsomatropin Indication: Treatment of pediatric growth hormone deficiency		
Recommendation	Filing Recommendation Date: 8/18/2020 ☐ 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: 12/11/2020 ☐ 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: 6/17/2021 ☐ 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		

Digital Signature Concurrence Table

Reviewer	Team Lead (TL)	Division (*Optional)
Shanly M. Chen -S Digitally signed by Shanly M. Chen -S Date: 2021.06.22 09:45:18 -04'00'		Rumi Young -S Digitally signed by Rumi Young -S Date: 2021.06.22 14:22:31 -04'00'

1. SUBMISSION OVERVIEW

Submission Information	
Submission Number	BLA 761177
Sponsor	Ascendis Pharma
Drug/Biologic	ACP-011 lonapegsomatropin
Indications for Use	Treatment of pediatric growth hormone deficiency
Device Constituent	Auto-Injector
Related Files	MAF3239

Review Team		
Lead Device Reviewer	Shanly Chen, PharmD	
Discipline Specific Consults	Reviewer Name (Center/Office/Division/Branch)	CON #
Electrical Safety	Sandy Weininger	CON2023796
Electromagnetic compatibility	John Baxley	CON2022343
MR compatibility	Sunder Rajan – consulted, but determined MR comp not needed for this file	CON2022305

Important Dates	
Discipline-Specific Review Memos Due	12/11/20
Final Lead Device Review Memo Due	3/18/21
Interim Due Dates	Meeting/Due Date
Filing	8/24/20
74-Day Letter	9/7/20
Mid-Cycle	11/20/20
Primary Review	2/25/21
Sponsor Meeting(s)	4/12/21
PDUFA goal	6/25/21

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](#).

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:

Comment #1: Below is a summary of interaction history. Full list of deficiencies are in Appendix A.

IRs to Sponsor	Date Issued	Status
Round 1	8/26/2020	Sponsor Responded 9/14/2020
Round 2	12/30/2020	Sponsor Responded 1/11/2021
Round 3	4/6/2021	Sponsor Responded 4/19/21
IRs to MAF Holder	Date Issued	Status
Round 1	9/8/2020	MAF holder responded 9/21/2020
Round 2	10/21/2020	MAF holder responded 11/20/2020
Round 3	12/29/2020	MAF holder responded 1/19; 4/12
Round 4	2/23/2021	MAF holder responded 4/12/21 (Amend 05)
Round 5	4/6/2021	MAF holder responded 4/22/2021 (Amend 06) 5/06/2021 (Amend 07) 05/24/2021 (Amend 08) 6/2/21 (Amend 09)
Round 6	5/28/2021	6/4/21 (Amend 10, not uploaded to IMAGE yet. See Shared Folder) 6/7/21 (Amend 11, not uploaded to IMAGE yet. See Shared Folder)
Round 7	6/8/21	6/9/21 (Amend 12, not uploaded to IMAGE yet. See Shared Folder)

Comment #2 (communicated 4/2/2021): The sponsor has confirmed there have been 2 changes to the IFU and device in the trial vs the finished final product. These changes were implemented based on feedback from users during the CT301EXT study.

(b) (4)

(b) (4)

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:

2.3. Recommended Post-Market Commitments/Requirements

CDRH has Post-Market <u>Commitments or Requirements</u>	■
CDRH does not have Post-Market Commitments or Requirements	■

Post-Market Commitment or Requirement:

1. In your 4/22/21 response (b) (4)

Consistent

underdosing/mis-dosing due to alarm failures can result in delayed harm to the patient. For example, once the epiphyseal plates in the bone closes, as a child transitions through puberty and reaches adulthood, an adult patient cannot grow taller with GH supplementation. While the short term consequences of underdose/mis-dose are minor, the long term consequences are permanent. IEC 60601-1-8 table 1 includes determination for alarm conditions that can result in delayed potential harm. Your device implements audio/visual cues that alert the operator to situations where potential or actual harm can occur, thus your device includes alarm conditions as defined by IEC 60601-1-8. (b) (4)

and your response is incomplete. Address the following:

Your alarms should be complaint and be validated to be complaint to IEC 60601-1-8:2006 and A1:2012. Provide the following information:

- a. List all alarms that your device contains
- b. Determine the alarm conditions and assignment of priorities.
- c. Describe the characteristics of your visual and auditory alarms
- d. Discuss how your alarms are complaint to IEC 60601-1-8:2006 and A1:2012
- e. Provide visual and auditory volume testing for your alarms relevant to IEC 60601-1-8:2006 and A1:2012.

Provide the following information for each test performed:

- i. Provide the title of your performance test.
- ii. Describe the objective or scope of this test method. Include the specific (ISO, ASTM, IEC, etc.) standard the protocol is based on.
- iii. Include the acceptance criteria and sample size.
- iv. State if the data you obtain are attribute or variable data.
- v. Then discuss one-side or two-sided tolerance limit, sample size, k values, upper/lower limits and any other relevant statistic you selected achieve confidence/reliability of 95%/95%. If you have an alternative confidence/reliability target, provide a risk based justification.
- vi. Describe your method and protocol.
- vii. Provide a summary of your results including relevant summary statistics such as but not limited to mean, standard deviation, median, percent error, etc. Your results summary should demonstrate your testing performed achieves your acceptance criteria to confidence/reliability of 95%/95% or alternative confidence/reliability.
- viii. Describe how your results support the scope/objective tested.

- f. Additionally, include reported test values and protocol.
2. In your 6/4/21 response you state you will test 119 devices to validate the CAPA changes you implement are effective at preventing the (b) (4) assembly problem. However, you have not provided the validation testing. Provide the following information for each test performed:
- Provide the title of your performance test.
 - Describe the objective or scope of this test method. Include the specific (ISO, ASTM, IEC, etc.) standard the protocol is based on.
 - Include the acceptance criteria and sample size.
 - State if the data you obtain are attribute or variable data.
 - Then discuss one-side or two-sided tolerance limit, sample size, k values, upper/lower limits and any other relevant statistic you selected achieve confidence/reliability of 95%/95%. If you have an alternative confidence/reliability target, provide a risk based justification.
 - Describe your method and protocol.
 - Provide a summary of your results including relevant summary statistics such as but not limited to mean, standard deviation, median, percent error, etc. Your results summary should demonstrate your testing performed achieves your acceptance criteria to confidence/reliability of 95%/95% or alternative confidence/reliability.
 - Describe how your results support the scope/objective tested.

This information should be provided to confirm the CAPA actions per (b) (4) Deviation report #3 are effective (b) (4)

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3. PURPOSE/BACKGROUND

3.1.Scope

Ascendis Pharma is requesting approval of lonapegsomatropin, a dual cartridge chamber and auto injector. The device constituent of the combination product is a Auto-Injector.

CDER/OPQ has requested the following [consult](#) for review of the device constituent of the combination product:

After discussion with the RPM on 8/14/2020 the CDRH consult is of:

- The autoinjector that is not included in the kit but sold separately. The autoinjector is to be used only with this DP.
- Sterility assurance of the injection needles included in the kit but not assembled in the cartridge. The injection needles are to be assembled by the healthcare provider.

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](#):

Facilities review and refuse to file checklist for the auto injector only

This review will not cover the following review areas:

Components that are part of primary or secondary packaging

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

3.2.1. Related Files

3.3.Indications for Use

Combination Product	Indications for Use
Auto-Injector	MAF3239 / Vol 002 / 001: The primary target indication for the GH Auto-Injector is pediatric growth hormone deficiency (GHD); the majority of patients are between (b) (4) years of age.

3.4.Materials Reviewed

Materials Reviewed	
Sequence	Module(s)
Seq 001	3.2.P.7 GH
Image: MAF3239	

4. DEVICE DESCRIPTION

4.1.Device Description

Seq 001 / 2.3.P.2 / pg 3

Lonapegsomatropin for injection is presented in a dual-chamber cartridge (DCC) containing a lyophilized powder in chamber 1 and a diluent for reconstitution in chamber 2. Lonapegsomatropin drug product is provided in 9 different strengths. Succinic acid is added as a (b) (4), trehalose dihydrate is provided as a (b) (4), tromethamine is used for pH adjustments, and water for injection is used as a diluent. (b) (4)

Seq 001 / 2.3.P.2 / pg 8

As mentioned in Section 1.2.3, it was decided to develop a delivery system for the combination product. A DCC was chosen for the lyophilized drug product. Thin and short injection needles (G31 x 4 mm) were chosen for the delivery system based on the intended pediatric use and subcutaneous delivery route.

The viscosity of reconstituted TransCon hGH (ACP-001) drug product solution (31 mPa·s at 23°C) implies that a high pressure is required for delivery through a thin needle. Therefore, it was decided to develop an auto-injector for the injection procedure to eliminate the need to apply high forces by hand and to minimize the time needed for completing an injection. However, even with a powerful auto-injector, the maximum force permitted for use with a DCC ((b) (4)N) would not permit delivery of typical TransCon hGH (ACP-001) volumes (b) (4) within a reasonably short time (b) (4)

Reviewer comments:

A02 / Vol 02 / JNC2037a 5.15.2

To reduce the maximum force permitted the injection time was extended to total injection of time of (b) (4) Verification was captured by defining and testing EPRs for total injection of (b) (4) The usability was validated through human factors testing. To prevent the patient from removing the auto injector from the skin too early various auditory and light cues was added to the device. To prevent the motor from exceeding (b) (4)N, sponsor defined the acceptance criteria at (b) (4)N and (b) (4)N per PR:03.23.

For the purpose of use with the GH Auto-injector, the DCC (b) (4)

Seq 001 / 2.3.A.1

Lonapegsomatropin drug product in dual-chamber cartridge (DCC) is manufactured under contract by Vetter Pharmafertigung GmbH & Co. KG, Germany (hereafter referred to as Vetter). (b) (4)

Seq 001 / 3.2.P.2.2 CCS – Dose accuracy

The GH Auto-Injector and DCC combination product is designed to deliver (b) (4)% of the labeled dose (mg hGH) covering all variations of delivered volume regardless of whether they are related to the DCC, the needle or the GH Auto-Injector. (b) (4)

For that reason, the dose accuracy evaluation is focused on delivering at least (b) (4)% of the labelled dose (in mg hGH) in concordance with the ISO 11608-1 requirements for a type B1 needle-based injection system (NIS). (b) (4)

(b) (4)

Reviewer comments:

While the DCC is not part of this review, based on the dose accuracy testing. Based on the manufacturing of the DCC, it is not possible for the system to deliver more than (b) (4)% of the labeled dose. The dose accuracy testing was focused on delivering more than (b) (4)% of the expelled volume (b) (4). To ensure the device can deliver the full dose at highest expelled volume (b) (4)sec, we can look at the worst case scenario which is the DCC intended to deliver 13.3mg of lonapegsomatropin.

The sponsor the target volume for the highest labeled dose (13.3mg) is 0.605. Sponsor was able to verify the DCC with the AI will expel mean volume of 0.615mL with standard deviation of 0.004mL.

Steps in manufacturing

(b) (4)

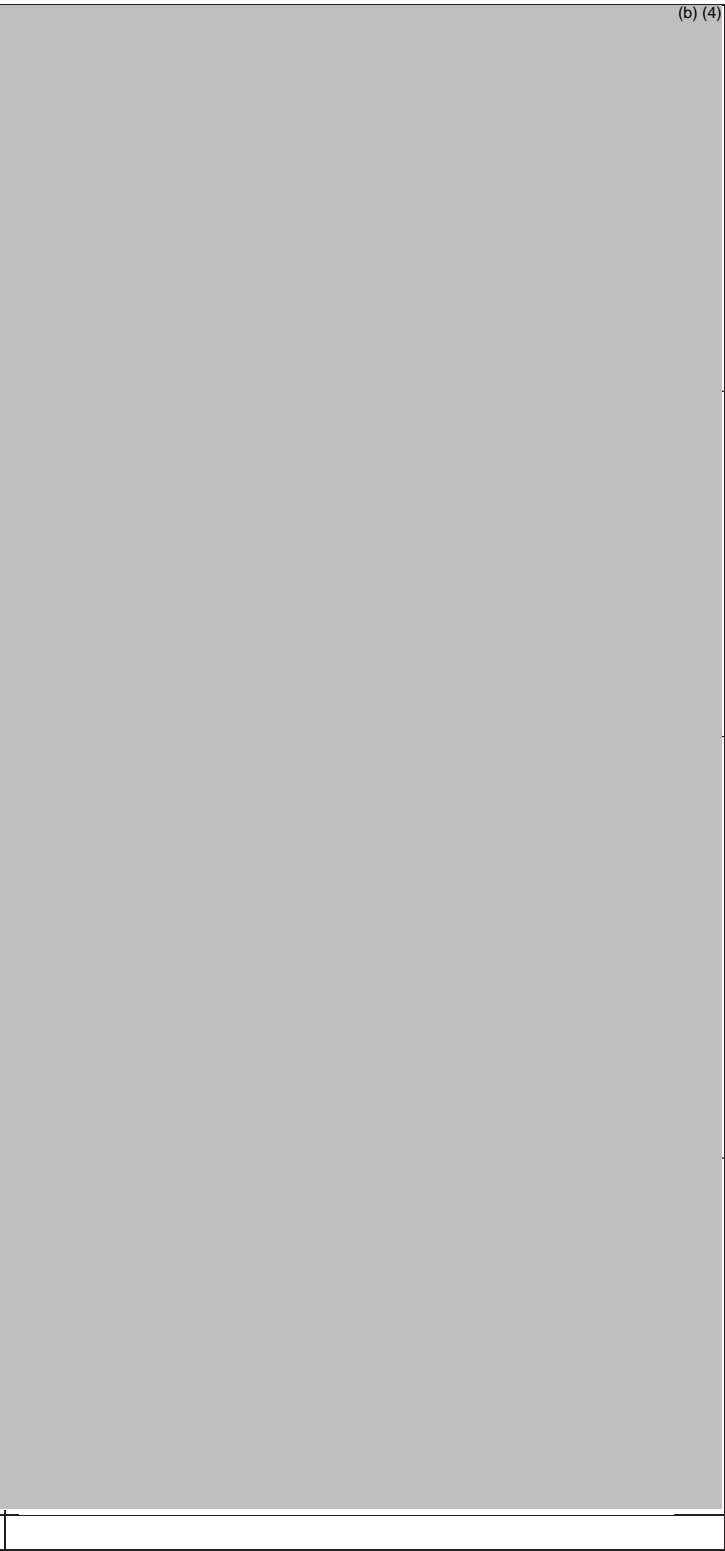
4.2.Steps for Using the Device

Seq 001 / 1.14.1.3 / GH Auto Injector IFU Word

These instructions are only a brief summary of the more in depth step by step, see file for complete details.

- Remove the auto-injector from the package.
- Connect the USB (large end) of the cable to the charger (only use the provided charger).

(b) (4)

• Fully charge the auto-injector before using it the first time. This will take 2 hours and 30 minutes. • Gather your supplies and place these on a flat, hard and clean surface. • Turn on GH Auto-Injector • Insert cartridge	
• Wait while mixing • Turn GH Auto-Injector up and down	
• Keep the auto-injector upright for automatic air removal • Pull off the needle cover • Press and hold green top against injection site for 10 to 15 seconds until you hear 2 loud beeps.	
• The injection is finished when you hear 2 loud beeps and the green top flashes 2 times. • Press needle cover down to release cartridge. • Remove the used cartridge by pulling straight up	

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
<u>Reviewer Comments</u>		
See IR below		
CDRH sent Device Description Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☐ No		

	Date Sent: Round#1 9/8/2020	Date/Sequence Received: 9/21/2020
Information Request #1 to MAF holder	Provide drawings of the internal components and interactions of your device. Discuss the internal/external components used for your device and how they related to your EPRs.	
Sponsor Response	MAF3239 / A02 / Vol 01 / 001 FDA Cover Letter See Image for full details. Sponsor provided the internal components and how they relate to the EPRs	
Reviewer Comments	Their response was adequate, however there are issues with the data for EPR testing. The deficiencies related to EPRs are in section 9.1 that address this.	
Response Adequate:	☐ Yes ☐ No, See IR # Sent on	

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	☐

5.1. Filing Review Checklist

Filing Review Checklist Description	Present		
	Yes	No	N/A
Description of Device Constituent / Seq 1 / 2.3.P.2 / pg 3	X		
Device Constituent Labeling / seq 1 / 1.14.1.3	X		
Letters of Authorization / seq 1 / 1.4.2	X		
Essential Performance Requirements defined by the application Sponsor / seq 1 / 3.2.P.7 GH / pg 19	X		
Design Requirements Specifications included in the NDA / BLA by the application Sponsor / seq 1 / 3.2.P.7 GH / pg 7	X		
Design Verification Data included in the NDA / BLA or adequately cross-referenced to a master file. / seq 1 / 3.2.P.2.4 CCS Dose / pg 19	X		

Risk Analysis supplied in the NDA / BLA by the application Sponsor / seq 1 / 3.2.P.7 GH / pg 25		X		
Traceability between Design Requirements, Risk Control Measures and V&V Activities / MAF3239 / Vol 007 / 003 and 004		X		
Verification/ Validation Check	Full Test Reports for Verification and Validation Testing		X	
	Engineering Performance (must include Safety Assurance Case for Infusion Pumps)			X
	Reliability			X
	Biocompatibility / MAF3239 / Vol 004	X		
	Sterility			X
	Software / MAF3239 / Vol 006	X		
	Cybersecurity		X	
	Electrical Safety / MAF3239 / Vol 007 / 005 and 006	X		
	EMC/RF Wireless / MAF3239 / Vol 007 / 007 and 008	X		
	MR Compatibility			X
	Human Factors			X
	Shelf Life, Aging and Transportation / MAF3239 / Vol 009	X		
	Clinical Validation / seq 1 / 5.3.1.2 / 102 clinical study	X		
Human Factors Validation			X	
Quality Systems/ Manufacturing Controls Check	Description of Device Manufacturing Process / seq 1 / 3.2.P.7 / 25	X		
	Description of Quality Systems (Drug cGMP-based, Device QSR-based, Both) / seq 1 / 3.2.R.QMS GH Auto-injector	X		
	CAPA Procedure / seq 1 / 3.2.R.QMS GH Auto-injector / pg 6	X		
	Control Strategy provided for EPRs / MAF3239 / Vol 05 / 002	X		

Reviewer Comment

Full Test Reports for Verification and Validation Testing

Full test reports are not provided.

EPRs spot checked in MAF3239 / Vol 005 / 002

8 Dose setting, no summary, no test data

12 Air removal, no summary, no test data

13 Dose accuracy, summary and data in 3.2.P.2.4

14 Actuation function by user, no summary, no test data

15 force required for assembly and actuation, no summary, no test data

18 depth of needle insertion, no summary, no test data

19-20 Injection, no summary, no test data

Sterility

Seq 1 / 3.2.R.QMS Auto Injector / pg 2, (b) (4). The auto injector is provided non-sterile to the user and need to be reprocessed between each use. While the sponsor does include cleaning in the human factor study. Reprocessing is composed of cleaning, disinfecting and sterilization, from the sponsor's HF it is unclear which steps relate to which process. Also they do not evaluate the cleaning steps from a reprocessing perspective per FDA guidance "*Reprocessing Medical Devices in Health Care Settings: Validation Methods and Labeling*" <https://www.fda.gov/media/80265/download>.

Shelf Life, Aging and Transportation

MAF3239 / Vol 007

The sponsor has provided summaries on shelf-life and aging. However they did not provide testing on simulated shipping and transportation.

Clinical Validation

Seq 1 / 5.3.1.2 / 102 clinical study

The clinical study is evaluating the effectiveness of the biologic administered using syringe vs autoinjector.

Control Strategy provided for EPRs

See IR in full test reports

5.2.Facilities Information

Firm Name:	Ascendis Pharma
Address:	Tuborg Boulevard 12, DK-2900 Hellerup Denmark
FEI:	3014573847
Responsibilities:	Per 2.3.P.3, page 3 QA release. Per sponsor response to IR on 8/17/20: “With regards to the final finished product, Ascendis Pharma is (b) (4) through Sharp Corporation, 7451 Keebler Way, Allentown, PA 18106, USA on the labeled and packed product.” Ascendis Pharma is the sponsor on this file and has a central role in coordinating all parts of this combo product.

Inspectional History

An analysis of the firm’s inspection history over the past 2 years:

- Inspection was conducted [Click or tap to enter a date.](#) to [Click or tap to enter a date.](#). The inspection covered [Choose an item.](#) and was classified [Choose an item.](#).
- An analysis of the firm’s inspection history over the past 2 years showed that it has never been inspected.
- N/A - the manufacturing site does not require an inspection at this time given the risk of the combination product

Inspection Recommendation:

- A pre-approval inspection is required because:
The firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part; and,
A recent medical device inspection of the firm has not been performed.
- An inspection is not required because the manufacturing site does not require an inspection at this time given the responsibilities of the firm and adequacy can instead be captured through the **QS review in this memo (Section 12)**.

Firm Name:	Phillips-Medisize A/S
Address:	Gimsinglundvej 20, 7600 Struer, Denmark
FEI:	3003346138
Responsibilities:	Per 3.2.P.7, page 25, this company does the entire manufacturing to release of the auto-injector. Manufacturing and packaging of GH Auto-Injector. The GH Auto-Injector was developed and is manufactured by Phillips-Medisize A/S, Struer, Denmark.

(b) (4)

Analysis:

(b) (4)

(b) (4)

There are 3 major components (drug, DCC, auto-injector) to this combo product and Phillips-Medisize A/S will be handling most of the work involved in the auto-injector. All three components must work in concert for the combo product to work safely and effectively. Therefore, it is recommended that this firm be inspected again.

Inspectional History

An analysis of the firm's inspection history over the past 2 years:

■ Inspection was conducted (b) (4) The inspection covered (b) (4)

*A recent MDSAP was conducted in 2020. See Section 12 for review of MDSAP inspection report and firm responses.

■ An analysis of the firm's inspection history over the past 2 years showed that it has never been inspected.

■ N/A - the manufacturing site does not require an inspection at this time given the risk of the combination product

Inspection Recommendation:

Surveillance inspection is recommended.

See Section 12 for review of MDSAP inspection report and firm responses.

Firm Name:	Sharp Corporation
Address:	7451 Keebler Way Allentown, PA 18106 USA

FEI:	3004161147
Responsibilities:	Packaging (b) (4) (b) (4) Labeling Analysis: (b) (4) (b) (4) (b) (4) (b) (4) Per sponsor response to IR on 8/17/20: “With regards to the final finished product, Ascendis Pharma (b) (4) through Sharp Corporation, 7451 Keebler Way, Allentown, PA 18106, USA on the labeled and packed product.”

Inspection History

An analysis of the firm’s inspection history over the past 2 years:

- Inspection was conducted [Click or tap to enter a date.](#) to . The inspection covered [drug CGMP](#) and was classified VAI.
- An analysis of the firm’s inspection history over the past 2 years showed that it has never been inspected.
- N/A - the manufacturing site does not require an inspection at this time given the risk of the combination product

Inspection Recommendation:

- A pre-approval inspection is required because:
 The firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part; and,
 However, a recent medical device inspection of the firm [revealed major deficiencies](#).
- 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 and a recent medical device inspection of the firm was acceptable.



(b) (4)

5.3.Filing Review Conclusion

FILING REVIEW CONCLUSION	
Acceptable for Filing: ☐ Yes ☐ No (Convert to a RTF Memo) ☐ N/A	
Facilities Inspection Recommendation: ☐ (PAI) Pre-Approval Inspection ☐ Post-Approval Inspection ☐ Routine Surveillance ☐ No Inspection ☐ N/A	
Site(s) needing Routine Surveillance inspection: Phillips-Medisize A/S located Denmark *this recommendation was revised after MDSAP was provided.	
Site not requiring inspection: Ascendis Pharma located Denmark Sharp Corporation located USA	
<u>Reviewer Comments</u> Based on discussions with Mekonnen LemmaDechassa (CDER), they are recommending an inspection of Phillips-Medisize A/S only.	

(b) (4) since Phillips-Medisize A/S was last inspected and they will be handling most of the work involved in the auto-injector.

See Section 12 for review of MDSAP inspection report and firm responses.

Sharp Corporation has been recently inspected and another pending inspection.

See sections above for more details regarding the mentioned and other firms related to this file.

Refuse to File Deficiencies: Yes No N/A

74-Day Letter Deficiencies: Yes No N/A

	Date Sent: Round#1 9/8/2020	Date/Sequence Received: 9/21/2020
Information Request #2 to MAF holder	In your MAF3239 device description you have only stated what test was done for each essential performance requirement (EPR). Please provide a summary and full test report for each relevant item in your EPR table.	
Sponsor Response	Reviewed in Design Verification Section 9.1.1	

	Date Sent: Round#1 8/26/2020	Date/Sequence Received: 9/14/2020
Information Request #1 to Sponsor	You state that the auto injector is not provided sterile, however it is intended to be used multiple times, up to four years or 210 injections, whichever comes first. You have also provided cleaning steps for your device. However you have not evaluated your cleaning steps from the context of reprocessing. Since your device is intended to be reused, the user should reprocess your device after each use to ensure it is fit for use again. Otherwise there is risk of injection site reactions or infection due to containments remaining on your device after use. Please provide test reports and discussions on evaluating reprocessing steps for your device per FDA guidance “ <i>Reprocessing Medical Devices in Health Care Settings: Validation Methods and Labeling</i> ” https://www.fda.gov/media/80265/download .	
Sponsor Response	Reviewed in Labeling Section 6.2	

	Date Sent: Round#1 8/26/2020	Date/Sequence Received: 9/14/2020
Information Request #2 to Sponsor	Provide documentation for your final finished product to demonstrate that the device EPRs (list of the EPRS) are met after shipping or transportation.	
Sponsor Response	Reviewed in Design Verification Section 9.1.1	

	Date Sent: Round#1 8/26/2020	Date/Sequence Received: 9/14/2020

Information Request #3 to sponsor	Confirm that the auto-injector used in the clinical study is the same design and manufacture as the test article used in design verification testing and final commercial device. If there are differences in design and manufacture, identify these differences and explain why the differences do not impact the clinical study outcomes.
Sponsor Response	Reviewed in Clinical Validation Section 10.1

	Date Sent: Round#1 8/26/2020	Date/Sequence Received: 9/14/2020
Information Request #4 to sponsor	Confirm if the needle (K173083) will be included in primary or secondary packaging. Also describe how you will ensure the sterility of the needle into the final finished product.	
Sponsor Response	Reviewed in Section Filing 5.2 above	

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:

Seq 01 / 1.14.1.3 / Draft Labeling Text - Word

-----INDICATIONS AND USAGE----- TRADENAME (b) (4)

-----DOSAGE AND ADMINISTRATION----- TRADENAME should be administered subcutaneously into the abdomen, buttock, or thigh with regular rotation of the injection sites (2.4)

The recommended (b) (4) dose is 0.24 mg (b) (4) kg body weight once weekly. (b) (4)

Seq 01 / 1.14.1.3 GH Auto-Injector Instructions for Use

Below is an abbreviated version of the instructions for Use, see docubridge for full instructions

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. [MAF3239 / Vol 003 / 004 IFU]	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	
<u>MRI</u> Labeling/Symbols			X
RF/Wireless Labeling/Symbols			X

Reviewer Comments

MAF3239 / Vol 003 / 004 IFU

MAF3239 / Vol 007 / 005 GOM...(IEC 60601-1 checklist)

The sponsor has provided necessary labeling for most items of the above checklist.

Regarding EMC and ES labeling, they have provided the labeling per IEC 60601-1 checklist.

MRI labeling is not needed since it will not be used in an MRI environment.

The device is not intended to use RF or wireless technologies.

IR to sponsor Round #2: See **Label#01** and **Label#02**

6.2.Device Specific Labeling Review

Device Specific Labeling Review Checklist	Adequate?		
	Yes	No	N/A
Reprocessing	X		

	Date Sent: Round#1 8/26/2020	Date/Sequence Received: 9/14/2020
Information Request #1 to Sponsor	You state that the auto injector is not provided sterile, however it is intended to be used multiple times, up to four years or 210 injections, whichever comes first. You have also provided cleaning steps for your device. However you have not evaluated your cleaning steps from the context of reprocessing. Since your device is intended to be reused, the user should reprocess your device after each use to ensure it is fit for use again. Otherwise there is risk of injection site reactions or infection due to containments remaining on your device after use. Please provide test reports and discussions on evaluating reprocessing steps for your device per FDA guidance “ <i>Reprocessing Medical Devices in Health Care Settings: Validation Methods and Labeling</i> ” https://www.fda.gov/media/80265/download .	

Sponsor Response	Seq 0009 / 1.11.1 Quality Info Amendment The GH Auto-Injector was evaluated per FDA guidance “Reprocessing Medical Devices in Health Care Settings: Validation Methods and Labeling”. It is assessed that Chapter IX is not applicable for the GH Auto-Injector as the device is for single patient use only. The GH Auto-Injector is a Non-Critical Device in the sense of the guidance Chapter VI, because its surface contacts only intact skin and does not penetrate it. The skin is only penetrated by the sterile single use needle (K173803) attached to the single use dual-chamber cartridge loaded into the GH Auto-Injector. (b) (4) The comprehension of the injection site cleaning step in the 1.14.1.3 GH Auto-Injector Instructions for Use, page 29 was confirmed in the summative HFE study (see “CHWV1908a HFE Report v1.0” submitted with MAF3239 by Phillips Medisize). This use step is intended to reduce the risk of injection site reactions or infection and to avoid soiling the Green Top. 1.14.1.3 GH Auto-Injector Instructions for Use, page 36 explains that if the GH Auto-Injector is dirty or if medicine has been spilled onto it, the user should clean the device with a damp cloth (b) (4). The device must then be stored with its cover on to avoid contamination between use. These use steps were also included in the summative HFE study.
Reviewer Comments	The sponsor has tested cleaning instructions in CHWV1908a HFE Report v1.0. There was 1 participant that forgot to clean device after use, however this failure does not indicate problems with the reprocessing instructions. Other participants was able to clean the device successfully based on the instructions in the IFU. The injector is only for 1 patient not to be shared, reusable with a 5 year lifespan (4 in use + 1 storage) and intended to deliver injections 1x weekly. Their instructions say to clean with damp cloth (b) (4) if dirty and must be store with its cover. The sponsor is arguing their device is considered non-critical per the FDA guidance on reprocessing. Spoke with David Wolloscheck, microbiologist, states assessing sterility on reprocessing instructions are not routinely done for pen injectors. While this devices is an auto injector the level of risk vs a pen injector is lower in the sterility context. Specifically, no part of the auto injector is in the fluid path vs there are parts of the pen injector that can be in the fluid path. Instructions states to check if the auto injector is dirty after every injection. In NAC1602c IDA0067 for PR:08.03 standard cleaning, sponsor did do durability testing on their device. The user will only wipe the green tip of the auto injector since that is the only part that risk contamination in the durability test.
Response Adequate:	☐ Yes ☐ No, See

6.3.Clinical Labeling Review

The following Clinical Labeling Review was completed by Insert Consultant Name ; The full memo is located in [Appendix B.](#)

☐ The Lead Reviewer Below is a summary of the review & recommendation : Adequate, see above comments

6.4. 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		
CDRH sent Labeling Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☐ No		

	Date Sent: Round#2 12/30/2020	Date/Sequence Received: 1/19/21
Information Request to sponsor Label#01	Your labeling should indicate your device is intended to be prescription use only. Update your packaging and labeling to include the phrase “Rx only” or similar phrase.	
Sponsor Response	Ascendis Pharma acknowledges to update the packaging and labeling of the GH Auto-Injector to include the phrase “Rx only” in accordance with 21 CFR 801.109. The “Rx only” will be applied on the device packaging box and in the Instructions for Use (IFU) for the GH Auto-Injector. (b) (4)	
Reviewer Comments	Acceptable	
Response Adequate:	☐ Yes ☐ No, See IR # Sent on	

	Date Sent: Round#2 12/30/2020	Date/Sequence Received: 1/19/21
Information Request to sponsor Label#02	You labeling should indicate the software version in your auto-injector. Update your labeling to include the version of software shipped with your auto-injector.	
Sponsor Response	Ascendis Pharma acknowledges that the GH Auto-Injector should indicate the software version embedded in the device, as this could be important in relation to e.g. post market surveillance.	

	Each GH Auto-Injector and its packaging has been marked with a unique device serial number (SN). This unique device SN unambiguously identifies the software version embedded in the device.
Reviewer Comments	Acceptable
Response Adequate:	☒ Yes ☐ No, See IR # Sent on

■ No Additional Information Requests – Finalize Labeling Review Section

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

Risk Analysis

See section 8.1

Hazards Identified

See section 8.2

Version history

All documents includes a complete version.

Design Input/Output

See section 7.2 below

Design V/V

MAF3239 / Vol 007 / 009 HFE Report

Sponsor provided a summary of HF trials performed used to validate the device design.

Seq 01 / 5.3.5.2 / TransCon hGH CT-301EXT – Clinical Study Report

Clinical trial to assess the comfort, ease of use and safety of the auto-injector

Below is a summary of the summary of results regarding the ease of use for the auto-injector. The patients was transition from injecting with manual needle/drug to the auto-injector at week 6 of the study:

At Transition Week 6, the majority of subjects strongly or somewhat agreed with the following statements about the GH Auto-Injector: it did not cause a lot of pain or discomfort (95.5%), the medicine could be injected without difficulty or making a mistake (100.0%), in a short amount of time (95.6%), without touching blood (97.8%), and left little to no marks on the skin (95.6%); subjects could see that it had been properly injected (95.5%) and were easily notified by sound and lights that the medicine was received or if there was a problem (95.6%); and it did not cause an injury that required seeing a doctor for help (100.0%). Responses at Transition Week 13 were similar to responses seen at Transition Week 6.

Sponsor concluded the device was safe and easy to use based on patient feedback.

(b) (4)

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 – MAF3239 / Vol 02 / 02
Standard Practice for Performance Testing of Shipping Containers and Systems; ASTM D4169-16	Y – Seq 9 / 3.2.R
IEC 60601-1-2:2014	Y – MAF3239 / Vol 02 / 02
Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products (2017)	Y – MAF3239 / Vol 02 / 02
Mobile Medical Applications Guidance for Industry and Food and Drug Administration Staff (2015)	N/A – no mobile app
Guidance for Industry and FDA Staff – Medical Devices with Sharps Injury Prevention Features (2005)	N/A – not claiming sharps injury prevention
Use of International Standard ISO 10993-1, Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process"	Y – MAF3239 / Vol 02 / 02
Applying Human Factors and Usability Engineering to Medical Devices	Y – MAF3239 / Vol 02 / 02

Device Specific Standards and Guidance Documents

Standard or Guidance	Recognized (Y/N/NA)	Conformance (Y/N/NA)
EN 62304: 2006 / AC: 2008 Medical device software - Software life-cycle processes	Y	Y
ISO 11608-4: 2006 Needle-based injection systems for medical use - Requirements and test methods - Part 4: Requirements and test methods or electronic and electromechanical pen-injectors	Y	Y
IEC 60601-1-8:2006 and A1:2012 Medical Electrical Equipment -Part 1-8: General requirements for basic safety and essential performance - Collateral Standard: General requirements, tests and guidance for alarm systems in medical electrical equipment and medical electrical systems	Y	N
<i>IEC 60601-1-11: 2015:</i> Medical electrical equipment - Part 1-11: General requirements for basic safety and essential performance - Collateral standard: Requirements for medical electrical equipment and medical electrical systems used in the home healthcare environment	Y	Y
IEC 62133-2: 2017 Secondary cells and batteries containing alkaline or other non-acid electrolytes - Safety requirements for portable sealed secondary cells, and for batteries made from them, for use in portable applications – Part 2: Lithium systems available and is FDA recognised consensus standard.	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		
CDRH sent Design Control Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☐ No		

	Date Sent: Round 5 4/6/2021	Date/Sequence Received: 4/22/21

Information Request to MAF holder Design1	In <u>MAF3239 / Original / Vol 02 / 02 List of applied standards / page 10</u> you state your product does not contain any alarms so your device does not need to be compliant to <u>IEC 60601-1-8:2006 and A1:2012</u> Medical Electrical Equipment -Part 1-8: General requirements for basic safety and essential performance - Collateral Standard: General requirements, tests and guidance for alarm systems in medical electrical equipment and medical electrical systems. Your device has electronic lights/sound cues that prompt the user to move to next steps while using your device. However, your device also contains electronic alarms that signal unsatisfactory functional states to warn the operator. Therefore, you alarms should be complaint and be validated to be complaint to <u>IEC 60601-1-8:2006 and A1:2012</u>. Provide the following information: 1. List all alarms that your device contains 2. Determine the alarm conditions and assignment of priorities. 3. Describe the characteristics of your visual and auditory alarms 4. Discuss how your alarms are complaint to <u>IEC 60601-1-8:2006 and A1:2012</u> 5. Provide visual and auditory volume testing for your alarms relevant to <u>IEC 60601-1-8:2006 and A1:2012</u>. Provide the following information for each test performed: a. Provide the title of your performance test. b. Describe the objective or scope of this test method. Include the specific (ISO, ASTM, IEC, etc.) standard the protocol is based on. c. Include the acceptance criteria and sample size. d. Then discuss one-side or two-sided tolerance limit, sample size, k values, upper/lower limits and any other relevant statistic you selected achieve confidence/reliability of 95%/95%. If you have an alternative confidence/reliability target, provide a risk based justification. e. Describe your method and protocol. f. Provide a summary of your results including relevant summary statistics such as but not limited to mean, standard deviation, median, percent error, etc. Your results summary should demonstrate your testing performed achieves your acceptance criteria to confidence/reliability of 95%/95% or alternative confidence/reliability. g. Describe how your results support the scope/objective tested. 6. Additionally, include reported test values and protocol.
Sponsor Response	Amed 06 / Vol 01 / 02 Response (b) (4)

Reviewer Comments	IEC 60601-1-8 defines alarm condition as “state of the ALARM SYSTEM when it has determined that a potential or actual HAZARDOUS SITUATION exists for which OPERATOR awareness or response is required.” It is true that the hazards for underdosing lonapegsomatropin includes a patient not reaching normal height and thus the hazard is relatively minor compared to other more serious disease conditions. The sponsor is seeking approval for this ICC product, the clinical purpose is to treat childhood growth hormone deficiency (GHD). Per sponsor Seq 01 / 5.3.1.2 / Clinical Study Report / pg 20 the consequences of GHD “in children and adults, GHD is characterized by abnormal body composition and altered glucose metabolism; in children, additional salient features include slow growth rate and short stature.” And so the risk of constant missed doses or underdosing the patient, will lead to long term consequences that may not be curable once the child reach adulthood. For example, once the epiphyseal plates in the bone closes as a child transitions through puberty and reaches adulthood, an adult patient cannot grow any taller with GH supplementation. While the short term consequences of missed doses and underdose are minor, the long term consequences are permanent. The sponsor has demonstrated that their device is safe to confidence/reliability 95%/95% through other EPR testing. Per Clinical (Marina Zemskova) email sent 6/3/21 they believe the risk for underdose is extremely low. Per DMEPA (Jason Flint) in phone conversation 6/3/21, a PMC would be reasonable. Therefore, we are asking for a PMC for the company to be complaint to IEC 60601-1-8.
Response Adequate:	☐ Yes ☐ No, See IR # Sent on

Follow-On Deficiency	Date Sent:	Date/Sequence Received:
Information Request #		
Sponsor Response		
Reviewer Comments		
Response Adequate:	☐ Yes ☐ No, See IR # Sent on	

8. RISK ANALYSIS

8.1. Risk Management Plan



8.2. Hazard Analysis and Risk Summary Report



8.3. 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
<u>Reviewer Comments</u>		
CDRH sent Risk Analysis Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☐ No		



9. DESIGN VERIFICATION REVIEW

9.1. Performance/Engineering Verification

9.1.1. Essential Performance Requirement Evaluation

Essential Performance Requirement (Design Input)	Specification (Design Output)	Verification Method <u>Acceptable</u> (Y/N)	<u>Validation</u> (Y/N)	Aging / Stability (Y/N)	Shipping/ Transportation (Y/N)
Compatible cartridges	Fits Dual-Chamber Cartridge (DCC) developed by Vetter VLK for lonapegsomatropin drug product	Y - MKS1803d IDA0067 Design Verification Report Feature	Y- See IR to MAF Holder, Round #3, Design#4 MKS1803e and CHWV1908a	N - MAPD1925b GH Auto-injector Lifetime testing summary IR to MAF holder, Round 5, IR design 2	Y –MAPD2035e IDA0067 and MKS2013c
Compatible needles	Needles from B.Braun Omnican fine 31G x 5/32” K173803	Y - MKS1803d IDA0067 Design Verification Report Feature	Y- Phase 1 and 3 clinical trials, see section 10	N - MAPD1925b GH Auto-injector Lifetime testing summary IR to MAF holder, Round 5, IR design 2	Y –MAPD2035e IDA0067 and MKS2013c
Injector lifetime	5 years or 210 successful injections	N – see 9.1.2 below	Y - Accelerated aging testing	N - MAPD1925b GH Auto-injector Lifetime testing summary IR to MAF holder, Round 5, IR design 2	N/A
Dose accuracy	Minimum ^(b) ₍₄₎ % of labeled mg hGH dose (single-dose empty-all)	N – see 9.1.2 below	Y- Phase 1 and 3 clinical trials, see section 10	N - MAPD1925b GH Auto-	Y –MAPD2035e IDA0067 and MKS2013c

				injector Lifetime testing summary IR to MAF holder, Round 5, IR design 2	
Actuation function	On/off button Cartridge insertion Skin-contact activation	N- MKS1803e IDA0067 Design Verification Report – Performance	Y- MAF3239 / Vol 07 / 09 HFE report	N - MAPD1925b GH Auto-injector Lifetime testing summary IR to MAF holder, Round 5, IR design 2	Y –MAPD2035e IDA0067 and MKS2013c
Force required for assembly and actuation	On/off button: (b) (4) N Cartridge insertion: (b) (4) N Skin-contact activation force: (b) (4) N	N – see 9.1.2 below	Y - Phase 1 and 3 clinical trials MAF3239 / Vol 07 / 09 HFE report	N - MAPD1925b GH Auto-injector Lifetime testing summary IR to MAF holder, Round 5, IR design 2	Y –MAPD2035e IDA0067 and MKS2013c
Depth of needle insertion	4 mm (needle length), (b) (4) mm when in auto injector see IR to MAF holder, Round #3, Design#5	N – see 9.1.2 below	Y- Phase 1 and 3 clinical trials, see section 10	N - MAPD1925b GH Auto-injector Lifetime testing summary IR to MAF holder, Round 5, IR design 2	Y –MAPD2035e IDA0067 and MKS2013c
Total Injection time	Maximum (b) (4) Seconds	Y – see IR to MAF holder, Round #3, Design#1	Y- Phase 1 and 3 clinical trials, see section 10	N - MAPD1925b GH Auto-injector Lifetime testing summary	Y –MAPD2035e IDA0067 and MKS2013c

				IR to MAF holder, Round 5, IR design 2	

Reviewer Comment

The sponsor has only provided summaries of test reports and are missing the full report to do a complete evaluation of the EPRs. The V/V activities are address in section 9.1.2 below. Luer connection testing is not needed since the needle connects to the dual chamber cartridge. The autoinjector does not have a luer lock connection.

	Date Sent: Round#1 8/26/2020	Date/Sequence Received: 9/14/2020
Information Request #2 to Sponsor	Provide documentation for your final finished product to demonstrate that the device EPRs are met after shipping or transportation.	
Sponsor Response	Seq 9 / 1.11.1 Quality Info Amendment Seq 9 / 3.2.R GH Auto-injector testing <i>3.2.P.7 GH Auto-Injector, section 3.4 presents an overview of EPRs tested and successfully verified after simulated shipping of the GH Auto-Injector in column 7 of Table 5. GH Auto-Injectors were exposed to simulated shipping according to ASTM D4169-16. All applicable EPRs for the device were successfully verified following preconditioning according to ASTM D4169-16 – distribution cycle 13. A summary of the transportation testing performed including traceability to the device EPRs can be found in 3.2.R MAPD2035e IDA0067 GH Auto-Injector Transportation Testing Summary Report.</i>	
Reviewer Comments	They only provided a brief summary. The MAF holder has the full data, will address deficiency to MAF holder.	
Response Adequate:	☐ Yes ☐ No, See Round #3 IR to MAF holder, Design #2	

9.2.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		
CDRH sent Design Verification Deficiency or Interactive Review Questions to the Sponsor: ☐ Yes ☐ No		

	Date Sent: Round#3 12/29/2020	Date/Sequence Received: 1/19/21
Information Request to MAF holder Design#1	(b) (4)	
Sponsor Response		
Reviewer Comments	The total injection time varies due to the different doses in the cartridge, the instructions is intended to cover all dosage strengths and so the EPR was formulated with a max total injection time of (b) (4)sec. The max time does not exceed (b) (4). The sponsor has also validated the beeps used to tell patients that they can remove the injector is effective through HF testing. This ensures the patient will not remove the auto injector prematurely.	

	Furthermore, the patient has the option to restart the injection if they pause the injection early.
Response Adequate:	☐ Yes ☐ No, See IR # Sent on

	Date Sent: Round#3 12/29/2020	Date/Sequence Received: 1/19/21
Information Request to MAF holder Design#2	(b) (4)	
Sponsor Response		
Reviewer Comments	The MAF holder provided reports and are reviewed in section 9.1.3 for adequacy.	
Response Adequate:	☐ Yes ☐ No, See IR # Sent on	

	Date Sent: Round#3 12/29/2020 Click or tap to enter a date.	Date/Sequence Received: 1/19/2021
Information Request to MAF holder Design#3	(b) (4)	

	(b) (4)
Sponsor Response	See test summaries 9.1.3
Reviewer Comments	Not acceptable – see comments in 9.1.3
Response Adequate:	☐ Yes ☒ No, See Round #5 IR to MAF holder, Design #2-8

Follow-On Deficiency	Date Sent: 4/6/21 Round #5	Date/Sequence Received: 4/22/21
Information Request to MAF holder design#2	(b) (4)	
Sponsor Response		





Reviewer Comments	a)/b) analysis is appropriate for all except PR 03.27 (See Round 5, IR to MAF holder Design #5) since they are still analyzing an attribute acceptable criteria as variable. Additionally, they were missing Dose accuracy after cool, warm testing reanalysis. Review of reference report shows re-analysis adequate otherwise. c) Acceptable response assuming PR 02.11 verification was adequate. A review of the referenced report (MKS1803d IDA0067 Design Verification Report – Feature (1.00)) it states 1 sample was tested and it passed. The single autoinjector sample was manually changed to different situations (1 day after end of life, 211 injections, no injections). The testing and therefore response was acceptable. d) The approach is acceptable Amend 08 / Vol 03 / 03_Shelf Life Test Sponsor only tested 19 devices. Devices underwent 1 year of accelerated aging (2018-03-06 till 2018-04-03), then 3 years real time (2018-04-03 till 2021-04-12), then 1 year of accelerated aging (2021-04-14 till 2021-05-06) for a total of 5 years of aging. Table shows data after 5 years of aging on same devices for PR:03.27 full needle insertion. (b) (4) See Round 6, Design#1 – resolved

Amend 07 / Vol 02 / 01_Dose Accuracy / pg 6

Sponsor did testing on correct temps per the standard (5C, 23C, 40C). However this is a time=0 aging. They still need to do testing after 5 year aging.

Amend 08 / Vol 03 / 05 Life Cycle Test

(b) (4)

It is unclear which temperature the sponsor tested dose accuracy at and they have not tested dose accuracy at all relevant temps (5C, 23C, 40C).

See Round #6, IR Design#2 - resolved

Amend 06 / Vol 02 / 01_Re-analysis / pg10

		Free Fall Testing	Cold Storage	Dry Heat Storage	Damp Heat Storage	Cyclical	Vibration and Shock
		PR:08.20	PR:09.01	PR:09.02	PR:09.03	PR:08.23	PR:08.07 PR:08.08
		Dose Accuracy	Dose Accuracy	Dose Accuracy	Dose Accuracy	Dose Accuracy	Dose Accuracy
		[ml]	[ml]	[ml]	[ml]	[ml]	[ml]
Measurements							
	Avr. (x)	0.613	0.619	0.618	(b) (4)	0.614	0.617
	Std. dev. (s)	0.008	0.003	0.005		0.003	0.006
	Number of devices (n)	20	15	15		15	5
Acceptance limits							
USL		(b) (4)					
LSL		(b) (4)					
Statistical Evaluation (95%/95% confidence/probability)							
	Probability content (p)	0.95	0.975	0.975	(b) (4)	0.95	0.95
	Tolerance limit factor (k_{target})	(b) (4)					
	Actual Tolerance limit factor (k_{act})	6.60	17.63	11.46	5.67	18.53	9.92
	Statistical tolerance interval	Max. (b) (4)					
		Min. (b) (4)					
Normality test (Shapiro-Wilk)							
	Normality control p-value	(b) (4)					
	Normal/not-normal	Normal	Normal	Normal	Not-Normal	Normal	Normal
Acceptance criteria							
	Conclusion	Pass	Pass	Pass	Pass	Pass	Pass

¹For PR:09.03 normality cannot be confirmed due to a single outlier which is confirmed with a Grubb's test. Outlier is within specification. When removing the outlier from the statistical evaluation the normality assumption is confirmed. The remaining sample size of 14 gives a k_{target} of (b) (4) and the re-analyzed data gives a (b) (4)

	Outlier shows data is not normal, need to apply attribute approach See Round #6, IR Design#3
Response Adequate:	☐ Yes ☐ No, See Round #6 IR to MAF Holder Design 1

Follow-On Deficiency	Date Sent: 5/28/21 Round #6	Date/Sequence Received: 6/4/21
Information Request to MAF holder design#1	(b) (4)	
Sponsor Response		

Reviewer Comments	Sponsor's new test proposal measures variable data on the depth of needle insertion after aging and can be used to supplement the EPR regarding needle insertion. Shapiro-Wilk test confirms normality of the data and the k(target) ^{(b) (4)} supports confidence/reliability of 95%/95%
Response Adequate:	☐ Yes ☐ No, See IR # Sent on
Follow-On Deficiency	Date Sent: 5/28/21 Round #6 Date/Sequence Received: 6/4/21

**Information Request
to MAF holder
design#2**

(b) (4)

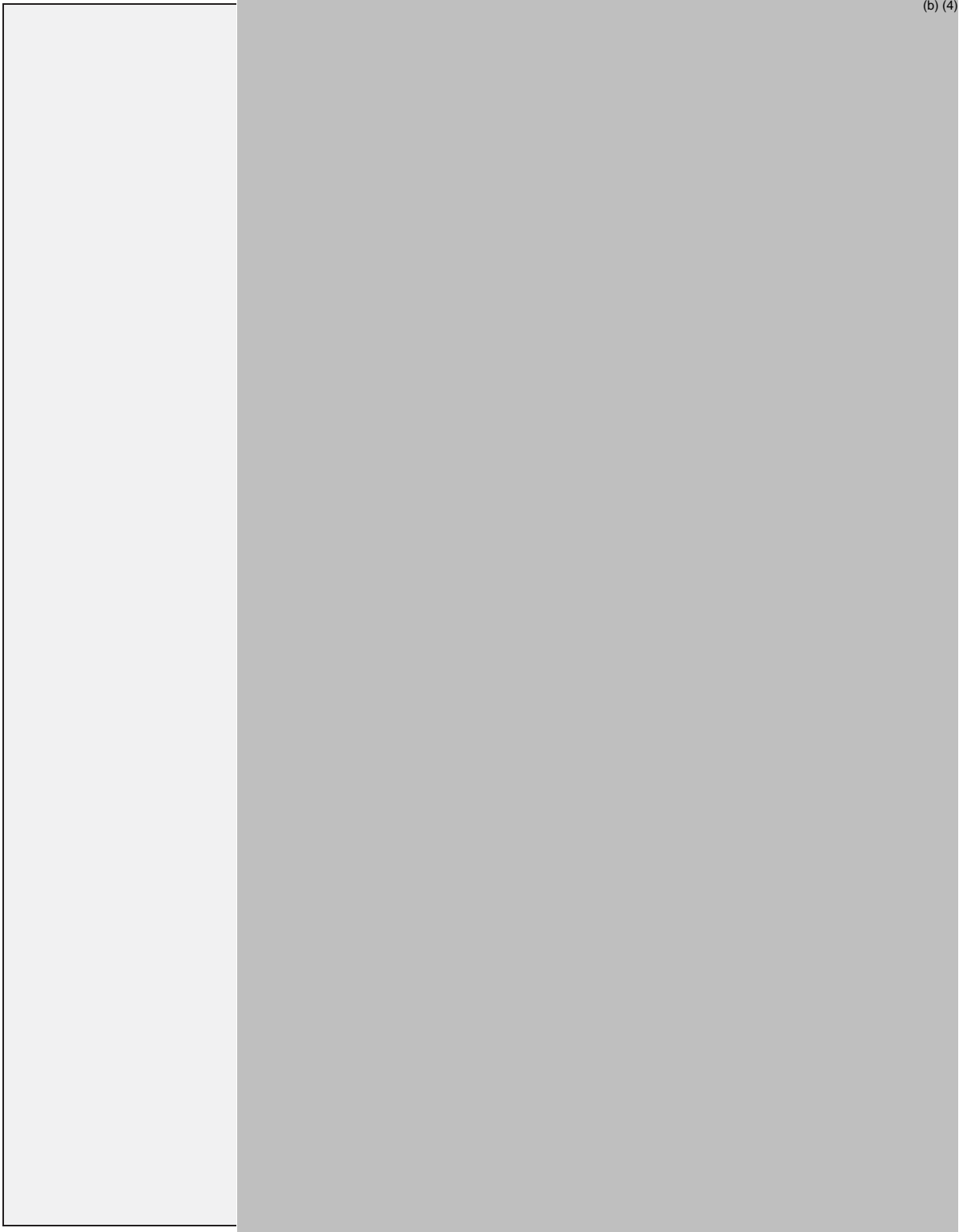
Sponsor Response

(b) (4)

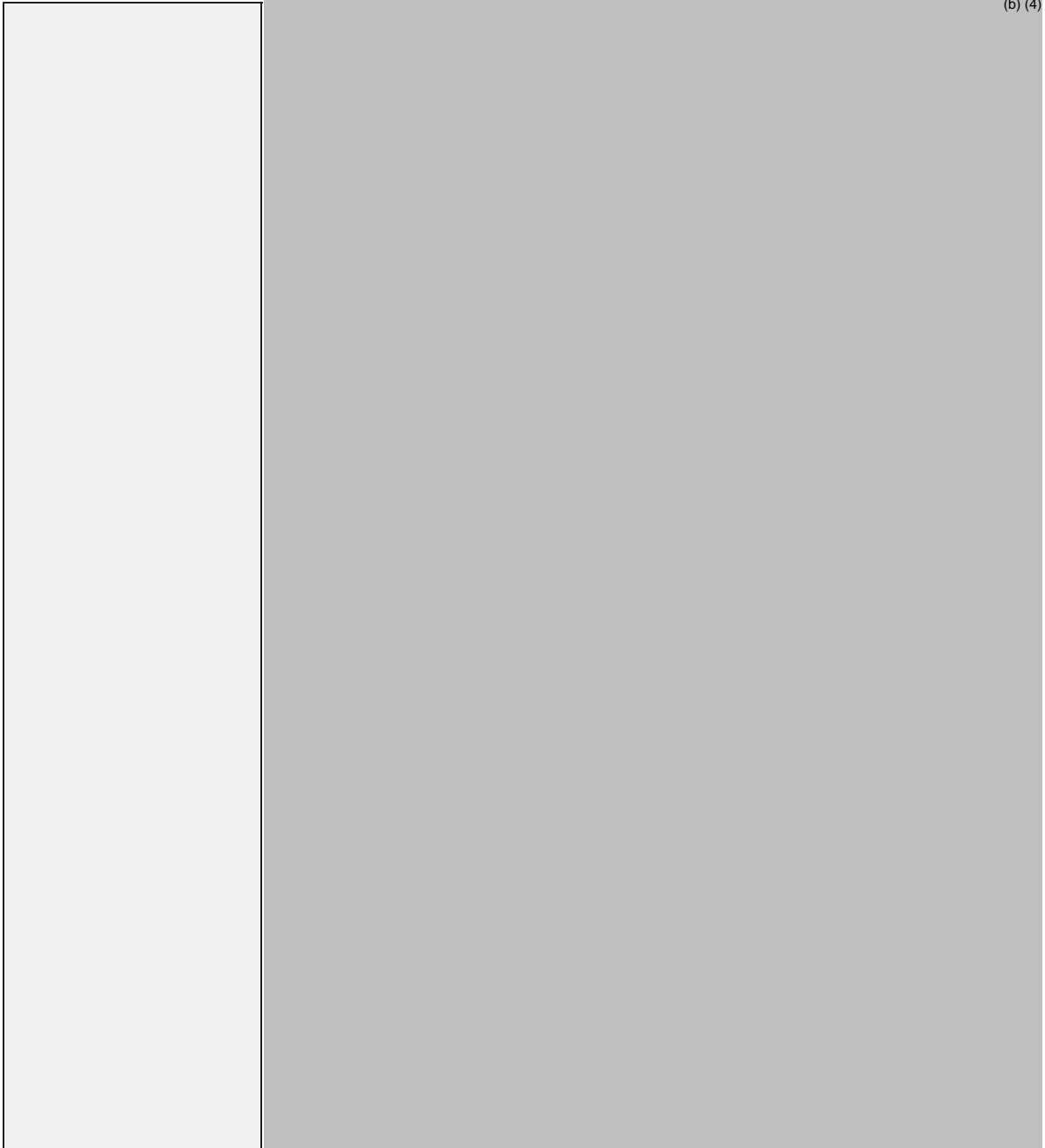
Reviewer Comments	Sponsor has performed dose accuracy testing after Cool (5C), Standard (23C) and Warm (40C) after aging of 5 years and 420 injection cycles which is beyond what is required per ISO 11608. Variable data is normal per Shapiro-Wilk and the k(target) ^{(b) (4)} achieves confidence/reliability of 95%/95%.
Response Adequate:	☐ Yes ☐ No, See IR # Sent on

Follow-On Deficiency	Date Sent: 5/28/21 Round #6	Date/Sequence Received: 6/4/21
Information Request to MAF holder design#3		
Sponsor Response		

(b) (4)



(b) (4)



Reviewer Comments	Sponsor has completed damp heat testing per the ISO 11608 protocol. This time the data is normal per Shapiro-Wilk, sponsor has applied variable data analysis with n=19 and k(target) ^{(b) (4)} to achieve confidence/reliability 97.5%/95%. Sponsor damp heat testing data is acceptable, however they have not provided an adequate response to the root cause. Mean or standard deviations cannot be applied to Cauchy distributions, only median or mode are applicable to these data distributions. Also the variance of data for Cauchy distributions are infinite. Data that typically fit Cauchy are things like the distribution of an electron cloud or the location of a point on a rock rolling downhill. However, for dose

	accuracy after damp heat storage, Cauchy is not an appropriate statistical approach to assess normality. If the data above fits a Cauchy distribution then the mean and standard deviation have no meaning. Furthermore, for all other data on dose accuracy the sponsor has applied Shapiro-Wilk to assess normality, except for this one specific data set in which an outlier was found. Therefore, the sponsor has not demonstrated their data is normal nor provided a complete response to the previous IR.
Response Adequate:	☐ Yes ☐ No, See IR # Sent on

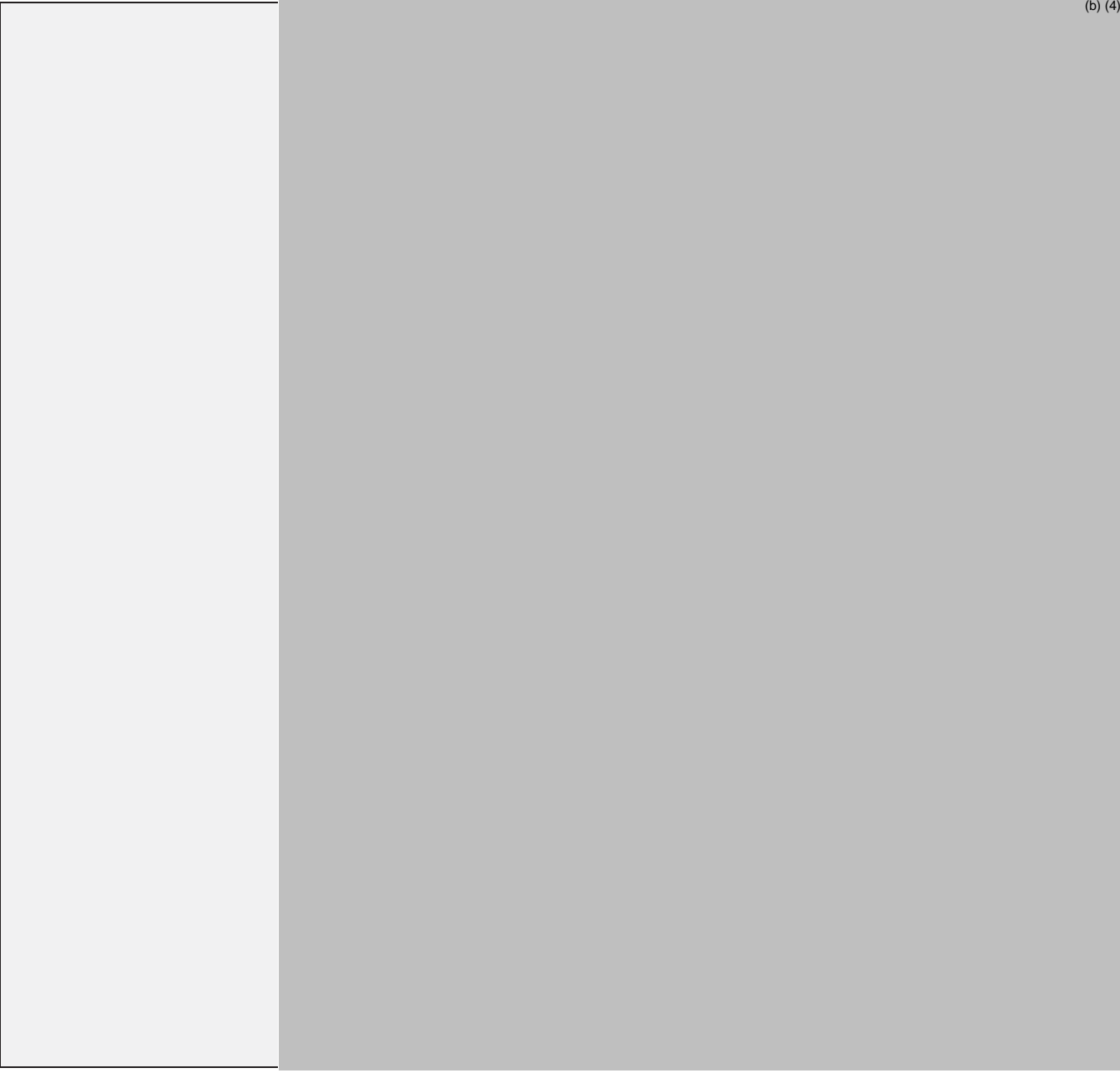
Follow-On Deficiency	Date Sent: 6/8/21 Round #7	Date/Sequence Received: 6/9/21
Information Request to MAF holder design#1	(b) (4)	
Sponsor Response		

	(b) (4)
Reviewer Comments	(b) (4) Based on the response and the teleconference, the root cause was due to the testing protocol. (b) (4) (b) (4) Residue left on the AI will give lower dose accuracy measurements, thus resulting in the outlier. Sponsor response adequate.
Response Adequate:	☐ Yes ☐ No, See IR # Sent on

Follow-On Deficiency	Date Sent: 5/28/21 Round #6	Date/Sequence Received: 6/4/21
Information Request to MAF holder design#4	(b) (4)	
Sponsor Response	(b) (4)	

		(b) (4)
Reviewer Comments	Sponsor has adequate complete the root cause analysis, however per (b) (4) the CAPA is incomplete since to confirm the manufacturing changes are effective to confidence/reliability of 95%/95% the verification testing should be done on 119 samples since it's attribute data. The sponsor did not specific a k(target). Final verification of the effectiveness of the CAPA can be a part of the PMC: Sponsor will test 119 devices to confirm the CAPA actions per (b) (4) Deviation Report #3 are effective at ensuring the (b) (4)	
Response Adequate:	☐ Yes ☐ No, See IR # Sent on	

Follow-On Deficiency	Date Sent: 4/6/21 Round #5	Date/Sequence Received: 4/12/21	(b) (4)
Information Request to MAF holder design#3			
Sponsor Response			



	(b) (4)
Reviewer Comments	Their test approach is appropriate, and their results show they pass. However, this was done on un-aged devices. See review of Round #5 IR to MAF holder Design 2 for additional review. This led to Round #6 IR to MAF holder Design 2.
Response Adequate:	☐ Yes, ☐ No, See IR # Sent on

Follow-On Deficiency	Date Sent: 4/6/21 Round #5	Date/Sequence Received:4/22/21
Information Request to MAF holder design#4	(b) (4)	
Sponsor Response		

		(b) (4)
Reviewer Comments	Reanalysis is acceptable since k-values (both one sided and two sided) are appropriate for sample size and data was normal. The shelf-life/lifecycle testing performance for these attributes are addressed in Round #5, IR to MAF holder Design #2	
Response Adequate:	☐ Yes ☐ No, See IR # Sent on	

Follow-On Deficiency	Date Sent: 4/6/21 Round #5	Date/Sequence Received: 4/22/21
Information Request to MAF holder design#5		
Sponsor Response		
Reviewer Comments	While the sponsor provided the n=59 testing, they did not provide it after aging and cycling. Therefore, this deficiency is resolved but they still need to address	

	Round 5 IR to MAF holder design #2. This led to Round 6 IR to MAF holder design #1.
Response Adequate:	☐ Yes ☐ No, See IR # Sent on

Follow-On Deficiency	Date Sent: 4/6/21 Round #5	Date/Sequence Received: 4/22/21
Information Request to MAF holder design#6	(b) (4)	
Sponsor Response		
Reviewer Comments		
Response Adequate:	☐ Yes ☐ No, See IR # Sent on	

Follow-On Deficiency	Date Sent: 4/6/21 Round #5	Date/Sequence Received: 4/22/21
Information Request to MAF holder design#7	(b) (4)	

	(b) (4)
Sponsor Response	
Reviewer Comments	Adequate except for PR:07.02 damp heat testing which is addressed by Round 7, IR Design#1
Response Adequate:	☐ Yes ☐ No, See IR # Sent on

Follow-On Deficiency	Date Sent: 4/6/21 Round #5	Date/Sequence Received: 4/22/21
Information Request to MAF holder design#8	(b) (4)	
Sponsor Response		

Reviewer Comments	Sponsor has provided traceability matrix that adequately identifies the test requirement and the various protocols, results, summary.
Response Adequate:	☐ Yes ☐ No, See IR # Sent on

	Date Sent: Round#3 12/29/2020	Date/Sequence Received: 1/19/21
Information Request to MAF holder Design#4	(b) (4)	
Sponsor Response		

	(b) (4)
Reviewer Comments	Sponsor has validated tactile/audio feedback for the user steps required for the auto injector
Response Adequate:	☐ Yes ☐ No, See IR # Sent on

	Date Sent: Round#3 12/29/2020	Date/Sequence Received: 1/19/21
Information Request to MAF holder Design#5	(b) (4)	
Sponsor Response		
Reviewer Comments	Acceptable, in addition needle length is part of the EPR and release testing.	
Response Adequate:	☐ Yes ☐ No, See IR # Sent on	

9.3.Discipline Specific Sub-Consulted Review Summary

- No Additional Discipline Specific Sub-Consults were requested
- The following additional Discipline Specific Sub-Consults were requested:

<u>Discipline</u> -Specific Design Verification / Validation adequately addressed				
Discipline	Consult needed	Consultant	Section	

	Yes	No	N/A			Adequately Addressed (Y/N/NA)
Engineering (Materials, Mechanical, General)			X			N/A
Biocompatibility		X		Gang peng curb side on sensitivity testing only	14.1	Y
Sterility			X	Auto injector is not manufactured sterile		N/A
Software / Cybersecurity	X			Lead reviewer, with input from Tali	14.2	Y
Electrical Safety	X			Sandy Weinenger	14.3	Y
EMC	X			John Baxley	14.4	Y
MR Compatibility			X	MR not needed per Rajan Sunder		N/A
Human Factors			X	Human factors was determined to be part of DMEPA's review		N/A
Clinical			X	Covered by clinical validation review	10	N/A

CDRH sent [Deficiencies or Interactive Review Questions](#) to the Sponsor Yes No

See appendix B for specific deficiencies sent for each specialty. See Appendix A for full deficiency history.

9.3.1. Biocompatibility Review

The following Software and Cybersecurity review was completed by Shanly Chen. The full memo is located in **Appendix B**. Below is a summary of the [recommendation](#):

Adequate, see section 14.1

There is 2 skin contacting components the (b) (4)

Both are considered intact skin contacting for less than 24 hours and so only require CSI testing.

9.3.2. Software and Cybersecurity Review

The following Software and Cybersecurity review was completed by Shanly Chen. The full memo is located in **Appendix B**. Below is a summary of the [recommendation](#):

Adequate, See section 14.3

9.3.3. Electrical Safety Review

The following Software and Cybersecurity review was completed by Sandy Weininger. The full memo is located in **Appendix B**. Below is a summary of the [recommendation](#):

Adequate, see section 14.2. Sponsor appropriately designed their device to lock out operation when charging to mitigate the risk of shock due to mains. Sponsor tested relevant basic safety criteria to verify conformance with IEC 60601-1. Sponsor asserts that the device has no essential performance, meaning that if it fails, the patient will not be put at unacceptable risk. This affects the type of testing done. Note that basic safety (for

physical hazards, e.g. surface temperatures, electric shock) are adequately addressed. The device uses a 3.7 V, 270 mAh Li ion rechargeable battery that conforms to IEC 62133-2. The safety of the charging system is assessed under IEC 60601-1. Device is constructed and tested for ingress of fluids at an IPX2 level.

9.3.4. EMC Review

The following Software and Cybersecurity review was completed by John Baxley. The full memo is located in **Appendix B**. Below is a summary of the [recommendation](#):

Adequate, See section 14.4

Consultant has issued an midcycle IR the sponsor response was appropriate.

9.3.5. MR Compatibility Review

The following Software and Cybersecurity review was completed by Sunder Rajan.

Adequate CON2022305

I contacted the MR compatibility consultant Sunder Rajan regarding MR compatibility. He stated the device is not intended and not likely to be used in the MRI suite or for contrast injections, therefore there is no need for MR related labeling.

10. CLINICAL VALIDATION REVIEW

10.1. Review of Clinical Studies Clinical Studies

- There is no device related clinical studies for review
- There are clinical studies for review

This information was obtained from the following [documents](#):

Study Name	Seq 01 / 5.3.1.2 A Single Center, Phase 1, Randomized, Open-Label Bioequivalence Trial in Healthy Volunteers Comparing TransCon hGH Administered as a Single Dose via Syringe and Needle vs. Auto-Injector
Study Type	Phase 1 open label
Objectives/Endpoints	The primary objective was: To establish pharmacokinetic (PK) bioequivalence between TransCon hGH administered by syringe/needle and auto-injector, measured as human growth hormone (hGH) maximum concentration (C _{max}) and area under the concentration-time curve (AUC).
Drug/Device Studied	Syringe/needle vs auto-injector
Number and Type of Subjects	N=27 Male (100%) Mean ages in years (27.6) Age range in years (18-61)
Brief description of protocol	Two treatments modalities were to be available: TransCon hGH administered by syringe and needle (termed 'A') and TransCon hGH administered by auto-injector (termed 'B'). Approximately 26 healthy male subjects were to be randomly assigned to receive 1 of the 2 treatment modality sequences, AB or BA, in a 1:1 ratio. A (or B, depending on sequence)

	was to be given during Period 1, followed by B (or A, depending on sequence) in Period 2 with an interval washout of at least 14 days.
Results	This single center, Phase 1, randomized, open-label, single dose, crossover study successfully demonstrated that a single fixed nominal dose of TransCon hGH 13.3 mg SC administered by an auto-injector was bioequivalent to TransCon hGH 13.3 mg SC administered by syringe and needle. When comparing TransCon hGH dosing by auto-injector to syringe and needle, geometric LS mean ratios (expressed as percentages) of hGH Cmax, AUC0-168, AUC0-t, and AUC0-inf were all approximately 100%. Associated 90% CIs were all within the standard bioequivalence range of 80-125%. No significant difference in overall absolute (and baseline-corrected) serum exposure to hGH were observed between the two treatment modalities.
Device Related Comments	Sponsor used the final version for the auto-injector.
Reviewer Comments	The trial was to include only male volunteers because females generally secrete more growth hormone (GH) than males and generate lower IGF-1 responses per dose of GH. Since males are more sensitive to doses of GH and produce more IGF-1, detecting variation between test groups can be more easily achieved.
Reviewer Conclusion	Trial show there is no significant difference in PK/PD when using syringe/needle vs auto-injector.

Study Name	Seq 01 / 5.3.5.2 TransCon hGH CT-301EXT enliGHten: A Multicenter, Phase 3, Long-Term, Open-Label Trial Investigating Safety and Efficacy of Lonapegsomatropin Administered Once-Weekly in Children With Growth Hormone Deficiency Who Have Completed a Prior Lonapegsomatropin Clinical Trial
Study Type	Phase 3 open label
Objectives/Endpoints	Primary: To assess the long-term safety of weekly lonapegsomatropin in children with growth hormone deficiency (GHD) previously treated in a phase 3 lonapegsomatropin trial. Secondary: In subjects using the GH Auto-Injector: to assess comfort, ease-of-use, and safety
Drug/Device Studied	Lonapegsomatropin and GH Auto-injector
Number and Type of Subjects	N=296 Male (233) / Female (63) Mean Years of Age (10.28) Range of age in years (3.6 – 16.4)
Brief description of protocol	This is a multicenter, phase 3, long-term, open-label extension trial of weekly lonapegsomatropin in children who previously participated in a phase 3 lonapegsomatropin trial (ie, CT-301 or CT-302). The final visit of the prior trial may have served as the first visit of the extension trial, and data collected in the prior trial should have served as baseline data for the extension trial. Lonapegsomatropin was provided in single-use glass vials and administered with syringe and needle, initially at a strength of 12.1 mg hGH/vial and subsequently at either 12.1 mg hGH/vial or 24.2 mg hGH/vial. After becoming available, lonapegsomatropin was supplied in dual-chamber cartridges (DCCs) for administration using a GH Auto-Injector (in the United States only).
Results	Based on the Device Usability Questionnaire, as assessed by subjects who switched to the GH Auto-Injector, the majority of subjects strongly agreed that the device was

	comfortable, easy to use, and safe. No subject experienced an injury caused by the GH Auto-Injector that required seeing a doctor for help. Treatment compliance during the trial was high, with a mean compliance of 98.70%. The majority of subjects (90.5%) had compliance rates >95%.
Device Related Comments	A subgroup of patient were transition from syringe/needle to using the auto-injector. These patients were transition to the auto-injector on week 6. The patient were surveyed on the ease of use of the device on week 6 and week 13.
Reviewer Comments	A result of 100% signifies that all patient strongly agree with all question on the survey about device usability. The overall satisfaction between week 6 (87.198%) vs week 13 (91.460%) were similar.
Reviewer Conclusion	This study secondary endpoints show that the device was safety and effective for patient use after training.

	Date Sent: Round#1 8/26/2020	Date/Sequence Received: 9/14/2020
Information Request #3 to sponsor	(b) (4)	
Sponsor Response		
Reviewer Comments	MAF3239 / Vol 003 / 007 IFU changes The sponsor has confirmed there have been 2 changes to the IFU and device in the trial vs the finished final product. These changes was implemented based on feedback from users during the CT301EXT study. (b) (4)	

	(b) (4) . I agree with the sponsor this change is minor does not require validation.
Response Adequate:	☒ Yes ☐ No – Comment to CDER regarding clinical to commercial timeout difference.

Reviewer Comment
While the IR to sponsor, Round #1, IR#3 was resolved. CDRH defers to CDER for clinical adequacy

10.2. Clinical Validation Review Conclusion

CLINICAL VALIDATION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☒ No ☐ N/A	Mid-Cycle Deficiencies: ☐ Yes ☒ No ☐ N/A	Final Deficiencies: ☐ Yes ☒ No ☐ N/A
Reviewer Comments None		
CDRH sent Clinical Validation Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☐ No		

11. HUMAN FACTORS VALIDATION REVIEW

CDRH Human Factors Review conducted	☐
Human Factors deferred to DMEPA	☒

12. FACILITIES & QUALITY SYSTEMS

12.1. Facility Inspection Report Review

CDRH Facilities Inspection Review conducted - MDSAP	☒
CDRH Facilities Inspection Review was not conducted	☐

Background:

Due to the Covid 19 pandemic, routine pre approval inspections are delayed or not conducted due to travel restrictions and ORA's prioritization of critical products. Therefore, an ORA pre-approval inspection of this site is pending. Furthermore, we are unable to request documents through 704(a)(4) process due to the fact that that regulation only applies to drug or device and drug manufacturers. Even though Phillip-Medisize device is intended to be used with the drug, the manufacturing site itself is only manufacturing the device and therefore not covered under 704(a)(4). We are currently reviewing the MDSAP report performed by (b) (4) (third party) issued on 10/2/2020.

See DocMan for complete document, from MDSAP report NCR-1651297-A-00409358-RR-NC-Nonconformance Report-ENG_2020-10-02 (002):

(b) (4)

Based on a review of the MDSAP and FDA inspection history (13 years ago), Phillips Medisize should still be inspected but it is not necessary prior to approval of this BLA. We have post approval inspection comments to communicate to the team, see section 2.3 above.

We recommend surveillance inspection for Phillips.

12.2. Quality Systems Documentation Review

CDRH Quality Systems Documentation Review conducted	☒
CDRH Quality Systems Documentation Review was not conducted	☐

12.2.1. Description of the Device Manufacturing Process

12.4. Facilities & Quality Systems Review Conclusion

FACILITIES & QUALITY SYSTEMS REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☐ No ☐ N/A	Mid-Cycle Deficiencies: ☐ Yes ☐ No ☐ N/A	Final Deficiencies: ☐ Yes ☐ No ☐ N/A
Reviewer Comments		
CDRH sent Facilities & QS Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☐ No		

14.APPENDIX B (CONSULTANT MEMOS)

14.1. Biocompatibility Review Memo – Shanly Chen

(b) (4)





14.2. Software and Cybersecurity Review Memo – Shanly Chen

Software
Level of Concern
v05.02.2019

’

Need to have plan

Per FDA guidance “Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices” <https://www.fda.gov/media/73065/download> page 6, question 2. The software would be consider major level of concern due it being used in conjunction with a biologic.

(b) (4)

14.3. Electrical Safety Memo – Sandy Weininger

eConsult Cover Sheet

Consult Number: CON2023796

Document Number: ICC2000610

Applicant:

Trade Name:

Consult Type: Electrical Safety Standards

Requestor: Shanly Chen [SHANLY.CHEN]
shanly.chen@fda.hhs.gov

Requestor Home: CDRH\ OHT3\ DHT3C\ THT3C3

Requested Consultant: Sandy Weininger [SXW]
sandy.weininger@fda.hhs.gov ; 301-796-2582

Gatekeeper / Consultant: Sandy Weininger [SXW]
sandy.weininger@fda.hhs.gov ; 301-796-2582

Consultant Home: CDRH\ OSEL\ DBP

Date Requested: September 21, 2020

Due Date: December 11, 2020

Instructions: This deadline is for midcycle IRs. I have an combo product BLA 761177 (MAF3239) that consists of the drug substance, dual cartridge container, and auto injector. (b) (4)

Please provide a review of the auto injector for electrical safety.

Scope of review:

You have requested an electrical safety review of an auto injector system that is part of a combination product. The device is low power.

Recommendation and deficiencies (if any):

Sponsor has performed a risk analysis to identify any hazardous situations that have unacceptable risk, proposed risk control measures for these risks, and tested the device to verify that it performs safely. Sponsor has identified relevant safety standards and demonstrated compliance.

I recommend the device be found reasonably safe from an electrical safety perspective.

Device description and safety discussion:

The IDA0067 GH Auto-Injector is a reusable electronic auto injector designed to be used with a dual-chamber cartridge containing TransCon hGH (ACP-011). (b) (4)

(b) (4)

Sponsor tested relevant basic safety criteria to verify conformance with IEC 60601-1. Sponsor asserts that the device has no essential performance, meaning that if it fails, the patient will not be put at unacceptable risk. This affects the type of testing done. Note that basic safety (for physical hazards, e.g. surface temperatures, electric shock) are adequately addressed. The device uses a 3.7 V, 270 mAh Li ion rechargeable battery that conforms to IEC 62133-2. The safety of the charging system is assessed under IEC 60601-1. Device is constructed and tested for ingress of fluids at an IPX2 level.

14.4. EMC Memo – John Baxley CON2022343

Date: December 9, 2020
From: John Baxley, Biomedical Engineer
Urological Devices Team (CDRH\OHT3\DHT3B\THT3B3)
Subject: BLA 761177: ACP-011 Ionapegsomatropin (Ascendis Pharma)
and MAF3239: GH Auto-Injector (Philips-Medisize)
To: LT. Shanly Chen, Pharm. D., Regulatory Review Officer
General Hospital Devices Team (CDRH\OHT3\DHT3C\THT3C3)
Recommendation: No EMC concerns

REVIEW

Device Description:

The GH Auto-Injector is a battery-powered device intended for subcutaneous injection of Ionapegsomatropin (a growth hormone). It is a reusable, single-patient use, full single dose delivery device. The auto-injector is sold with the following accessory components:

- Protective cover
- Charger with micro USB cable

The pre-filled, dual-chamber cartridge (containing the drug in powdered form and water for injection) and cartridge needle are packaged separately. Prior to use, the user screws the needle (in its cover) onto the cartridge, and inserts the cartridge/needle assembly into the auto-

[REDACTED] (b) (4)

[REDACTED] After injecting the entire contents of the cartridge, the used cartridge/needle assembly is removed from the auto-injector and thrown away in a sharps disposal container.

The auto-injector has the following electronic functions:

[REDACTED] (b) (4)

Additionally, the device [REDACTED] (b) (4) and will disable further use after reaching either 5 years or 210 injections. Typical use is one injection per week.

All users (including experienced and inexperienced patients and/or caregivers) will receive training by registered (or similarly qualified) nurses at e.g. endocrinology centers before using the GH Auto-Injector.

The following device description characteristics are relevant to this EMC evaluation:

System:

- GH Auto-Injector
 - Note: This is a standalone device; there are no required electrical companion/accessory devices.

Operational state(s):

- ON/Prepare
- Mixing
- Injection
- Charging
 - Note: The ON/Prepare, Mixing, and Injection functions are disabled during Charging

Power source(s):

- Clinical use: Battery (rechargeable Lithium ion)
- Charging: AC mains

Electrical connections/peripherals:

- Micro USB port (labeled/designed for Charging only)

Wireless communication:

- None

Use environment/conditions:

- Home healthcare environment

EMC-related risks:

- Insufficient mixing → risk of drug-related injury (not likely, due to instructions for a confirmatory visual check of cartridge through the auto-injector's window prior to injection)
- Under injection → negligible risk (reduces efficacy of treatment, but does not pose a significant health risk)
- Over injection → not possible, assuming the cartridge is labeled with the correct dose (entire cartridge contents is intended to be delivered)

Reviewer comments: The device description is complete from an EMC review perspective. Based on the potential EMI risks to the patient regarding drug delivery devices in general, this is a Tier II EMC review.

Electromagnetic Compatibility (EMC):

Amendment 001 of the submission contains the Version 2 (V02) EMC test report, conducted per the FDA-recognized standards IEC 60601-1-2:2014 (4th edition).

These test reports are summarized in Section 17, and highlighted below:

- Equipment Under Test (EUT): The testing was conducted on the final version of the GH Auto-Injector.
- Essential Performance: None
- Operational Mode(s) Tested: The device was in one or more of the following operational modes (as applicable for each individual test; see table below):
 - Continues mode: Modified* device powered via AC mains (using the charger), with a dummy cartridge inserted and the plunger rod motor continuously operating.
(*Since AC mains connection is needed for continuous motor operation, and AC mains connection is

physically disabled during the normal device mode, a modified device was created to permit this continuous motor operation. Simulates a worst-case for EM emissions.)

- Charging mode: Device powered via AC mains (using the charger), with the battery icon flashing.
- Normal mode: Device operating under battery power, running its internal self-test followed by flashing of the “Green Top” LED.
- Tests: All applicable radiated emissions and immunity tests specified in IEC 60601-1-2:2014 were performed (see table below, summarizing the test strategy from the V02 EMC test report).
- Test Levels (Immunity): For each immunity test, all test levels are stated and justified.
- Acceptance Criteria/Results: For the emissions tests, the CISPR 11 acceptance criteria were applied and successfully met. During the immunity tests, acceptance criteria derived from the critical device functions (see table below) were passed with only the following observed degradations:

Applying ESD to the USB port (+15 kV air discharge) during the Charging mode, the EUT temporarily stopped charging and gave an acoustic signal; applying ESD over the USB port (+15 kV air discharge) during the Normal mode, the EUT shut down.

All device functions were confirmed to be operational after each EMC test, including after the above noted ESD degradations. To assess the immunity test acceptance criteria, the device was monitored with video (to detect changes in the LED display and cartridge movement) and microphone (to detect alarms and changes in motor operation).



- Adaptations/deviations: None.
- Environment of Use: Consistent with the labeling, the subject device is intended for use in the home healthcare environment. The test conditions reflect this usage (Class B).
- Device Modifications: None required.

Amendment 001 of the device master file contains the labeling (Instructions for Use manual content) for the GH Auto-Injector, which I reviewed from an EMC perspective. This manual contains:

- routine warnings/cautions to minimize the risks associated with electromagnetic interference (i.e., warnings on recognizing nearby RF communications equipment and other common household emitters (i.e., microwave ovens) and maintaining separation distances, and advising not to use accessories/cables other than those provided by the manufacturer),
- a statement that the Micro USB port can only be used for Charging (i.e., physically blocked during clinical use),
- a statement of the device's intended use environment and information to convey the key device functions (as there is no essential performance), and
- tables summarizing the EMC testing to IEC 60601-1-2.

Reviewer comments:

- EMC testing per the FDA-recognized version of the IEC 60601-1-2 standard was performed on the final, proposed version of the subject device, operating under both battery and AC mains power. Additionally, a modified version of the subject device was created to enable testing while the device's plunger motor was continuously operating.
- I agree that the device does not have essential performance, due to the inability of the device to inject more than the prescribed dose, and the low risks associated with incomplete mixing and under-injection. Additionally, I concur with the sponsor's specified acceptance criteria for the immunity tests, which assess the key device functions associated with each operation mode (i.e., plunger motor function for the continuous mode, charging status display for the charging mode, and cartridge insertion ready status for the normal mode). These functions were appropriately monitored during the tests.
- Regarding the selection of tests for each operation mode:
 - The continuous mode is the worst case for EM emissions (b) (4) so is the correct mode for these tests. Additionally, the continuous mode enables the device to remain functioning for the extended period of time required for RF / proximity field immunity testing.
 - The charging mode is the only applicable mode for the immunity tests that are unique to AC mains power (i.e., EFT/burst, surge, conducted RF, and voltage dips/interruptions), and, therefore, is appropriate for these tests. Additionally, ESD tests were successfully performed for this mode. (Note: Since clinical use of the device is disabled during charging, there are minimal EMC-related risks associated with this mode.)
 - The normal mode is battery-powered, so only the following tests are applicable: radiated emissions, radiated RF / proximity field immunity, power frequency magnetic field immunity, and ESD immunity

tests. ESD immunity testing was performed in the normal mode. The other applicable tests are addressed as follows:

- Radiated emissions and radiated RF / proximity field immunity tests were appropriately performed in the continuous mode (see above for rationale).
- Power frequency magnetic field immunity testing was performed in the charging mode. **Since the charging mode is disabled during clinical use, and, thus, is not associated with any clinical functions of the device, the relevance of this test to demonstrating device EMC is unclear. The sponsor should repeat this test while the device is in one of the clinical use modes (i.e., either the continuous or normal mode).**
- Based on this concern (in bold), on September 30, 2020 I recommended that Dr. Chen issue the following interactive review request:

Round#2 10/19/2020

(b) (4)

Based on this response and my review of the photograph of the EUT taken during the power frequency magnetic field immunity test, I agree that the device actually was tested in the continues mode rather than the charging mode. Therefore, it is evident that that the device was originally tested in a clinical use mode as requested in my deficiency, and that the V02 EMC report was in error in this regard. Therefore, my concern is resolved. Below is a revised table, summarizing the test strategy from the corrected V03 EMC test report:

Operation Modes	Tests Performed	Immunity Acceptance Criteria
Continues	Conducted emissions Radiated emissions Radiated RF / proximity field immunity Power frequency magnetic field immunity	Continuous drive of motor and display update. Transient pauses in drive/display are allowed. Must be able to function as intended after exposure.
Charging	ESD immunity EFT/burst immunity Surge immunity Conducted immunity Voltage dips / interruptions immunity	Battery icon flashes until battery charged, after which it remains constantly ON. Flicker in display is accepted. Must be able to function as intended after exposure.
Normal	ESD immunity	“Green Top” LED flashes as indication of waiting for cartridge insertion. Flicker in display accepted. Must be able to function as intended after exposure.

- All emissions and immunity tests were properly carried out per IEC 60601-1-2.
- The device met CISPR 11 Class B (home healthcare environment) requirements for emissions. The device passed all immunity tests with either no observed response or, in the case of ESD, acceptable degradations (since restarting the device would not increase the risk of patient harm). All key device functions were verified to operate as intended after these tests.
- No device modifications were required to pass these tests.
- The labeling contains routine warnings to aid the user in recognizing and mitigating problems related to EMI from RF communications equipment and surrounding electrical equipment. Of note, the labeling specifically warns the user not to use the device near microwave ovens (a common emitter in the home healthcare

environment). In light of the observed degradation noted during ESD testing during clinical use (i.e., normal mode), the troubleshooting section of the labeling includes complete instructions on what to do if the device turns OFF (i.e., press the ON button to re-power the device). The labeling summarizes the key clinical functions of the device (in the absence of essential performance), and summarizes the compliance with the EMC test standard.

- Given the expected use conditions for auto-injectors, specific warnings for other common emitters (e.g., MRI, electrosurgery, diathermy, RF identification, electronic article surveillance, wireless power transfer, etc.) are not necessary.
- Conclusion: I have no EMC concerns.

RECOMMENDATION

Based on the information provided in MAF3239 and in response to my interactive review request, I have no EMC concerns regarding the device constituent of this combination product.

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/s/

SEJAL KIANI
06/23/2021 11:10:45 AM
Signing on behalf of Shanly Chen, PharmD, OPEQ/OHT3/DHT3C

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

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

Memorandum

Date: June 2, 2021

To: Shivangi Vachhani R., M.D., Medical Officer
Division of General Endocrinology (DGE)

Sejal Kiani, Project Manager, (DGE)

Monika Houstoun, Associate Director for Labeling, (DMEP)

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

Through: Melinda McLawhorn, Team Leader, OPDP

Subject: OPDP Labeling Comments for SKYTROFA® (lonapegsomatropin-tcgd) for injection, for subcutaneous use

BLA: 761177

In response to DGE's consult request dated July 15, 2021, OPDP has reviewed the proposed product labeling (PI) and Instructions for Use (IFU) for SKYTROFA® (lonapegsomatropin-tcgd) for injection, for subcutaneous use. This is a new supplemental NDA.

PI, IFU: OPDP's comments on the proposed PI are based on the draft materials sent by DGE on May 14, 2021 and are provided below. We have no comments on the proposed labeling at this time.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed PPI will be sent under separate cover.

Thank you for your consult. If you have any questions, please contact Charuni Shah at (240) 402-4997 or charuni.shah@fda.hhs.gov.

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/s/

CHARUNI P SHAH
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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: May 25, 2021

To: Sejal Kiani
Regulatory Project Manager
Division of General Endocrinology (DGE)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Nyedra W. Booker, PharmD, MPH
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Charuni Shah, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Instructions for Use (IFU) and
Quick Reference Guide (QRG)

Drug Name (established name): SKYTROFA (lonapegsomatropin-tcgd)

Dosage Form and Route: for injection, for subcutaneous use

Application Type/Number: BLA 761177

Applicant: Ascendis Pharma Endocrinology Division A/S

1 INTRODUCTION

On June 25, 2020 Ascendis Pharma Endocrinology Division A/S submitted for the Agency's review an Original Biologics License Application (BLA) 761177 for SKYTROFA (lonapegsomatropin-tcgd) for injection, for subcutaneous use. The proposed indication for SKYTROFA (lonapegsomatropin-tcgd) for injection, for subcutaneous use is for the treatment of pediatric patients 1 year and older who have growth failure due to inadequate secretion of endogenous growth hormone (GH).

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 General Endocrinology (DGE) on July 15, 2020, for DMPP and OPDP to review the Applicant's proposed Instructions for Use (IFU) and Quick Reference Guide (QRG) for SKYTROFA (lonapegsomatropin-tcgd) for injection, for subcutaneous use.

2 MATERIAL REVIEWED

- Draft SKYTROFA (lonapegsomatropin-tcgd) for injection, for subcutaneous use IFU and QRG received on June 25, 2020 and received by DMPP and OPDP on May 14, 2021.
- Draft SKYTROFA (lonapegsomatropin-tcgd) for injection, for subcutaneous use Prescribing Information (PI) received on June 25, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on May 14, 2021.

3 REVIEW METHODS

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

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

In our collaborative review of the IFU and QRG we have:

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

4 CONCLUSIONS

The IFU and QRG 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 IFU and QRG 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 IFU and QRG.

Please let us know if you have any questions.

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/s/

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CHARUNI P SHAH
05/26/2021 09:04:15 AM

LASHAWN M GRIFFITHS
05/26/2021 11:01:17 AM

Clinical Inspection Summary

Date	5/4/2021
From	Cynthia F. Kleppinger, M.D., Senior Medical Officer Min Lu, M.D., M.P.H., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Shivangi Vachhani, M.D., Clinical Reviewer Marina Zemskova, M.D., Medical Team Leader Division of General Endocrinology (DGE) Sejal Kiani, MS, Regulatory Project Manager Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, and Nephrology
BLA	761177
Applicant	Ascendis Pharma A/S
Drug	Lonapegsomatropin
NME	Yes
Therapeutic Classification	Growth hormone
Proposed Indication	Treatment of pediatric growth hormone deficiency
Consultation Request Date	8/14/2020
Summary Goal Date	5/4/2021 (extended from initial due date of 3/4/2021)
Action Goal Date	6/25/2021
PDUFA Date	6/25/2021

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The inspection for this biologics license application (BLA) consisted of one domestic site in addition to the sponsor.

An inspection assignment was issued to the Office of Regulatory Affairs (ORA) on 8/20/2020 to conduct good clinical practice (GCP) inspections of three sites, the sponsor, and the contract research organization.

The ongoing COVID-19 global pandemic has significantly limited ORA's ability to conduct onsite GCP inspections. Following discussions between the Office of Scientific Investigations (OSI) and the Division of General Endocrinology (DGE), a decision was made that assessment of the application could proceed without GCP inspections if they were not possible before the action due date. Abiding by guidelines to protect the health, safety, and welfare of FDA employees and study staff, and with repeated evaluations of the current situation and mission-critical priorities, the planned inspections of Dr. Paul S. Thornton (Site 741), Dr. Naomi D. Neufeld (Site 748) and

(b) (4) were not able to be conducted.

In general, based on the inspections of the one clinical site and the sponsor, the inspectional findings support validity of data as reported by the sponsor under this BLA.

II. BACKGROUND

Ascendis Pharma has submitted a new biologics license application (BLA) for lonapegsomatropin, a long-acting prodrug of human growth hormone (hGH), which has been developed as a once-weekly treatment administered as a subcutaneous (SC) injection for growth failure in children due to inadequate secretion of endogenous growth hormone (GH).

Lonapegsomatropin (TransCon hGH/ACP-011) is designed to release hGH with the same mode of action and distribution as daily somatotropin (hGH), but with a once-weekly injection.

Five clinical studies were conducted with lonapegsomatropin in the clinical development: two phase 1 (healthy adult volunteers) and three phase 3 studies (children with growth hormone deficiency). Inspections were requested for the following two studies:

TransCon hGH CT-301 *A Multicenter, Phase 3, Randomized, Open-Label, Active-Controlled, Parallel-Group Trial Investigating the Safety, Tolerability, and Efficacy of Lonapegsomatropin Administered Once a Week Versus Standard Daily hGH Replacement Therapy Over 52 Weeks in Prepubertal Children with Growth Hormone Deficiency*

This was a phase 3, randomized, open-label, active-controlled trial of lonapegsomatropin as compared to standard daily GH over 52 weeks. All centers were specialized treatment centers in the management of pediatric growth hormone deficiency (GHD). Subjects were pre-pubertal children with GHD (either isolated or as part of a multiple pituitary hormone deficiency) in Tanner stage 1 aged 3 -12 years for boys and 3 -11 years for girls.

The study began November 15, 2016 and completed January 17, 2019. It was conducted at 73 sites in 15 countries. There were 358 subjects screened and 162 subjects randomized with 161 subjects dosed; 159 subjects completed the trial.

Subjects were randomized 2:1 ratio to lonapegsomatropin/Genotropin®

- Lonapegsomatropin 0.24 mg hGH/kg/week (administered once weekly), or
- Genotropin® 0.034 mg hGH/kg/day, a dose equivalent to 0.24 mg hGH/kg/week (administered daily)

The primary endpoint is annualized height velocity (AHV) at 52 weeks for weekly lonapegsomatropin and daily hGH treatment groups.

TransCon hGH CT-301EXT *A Multicenter, Phase 3, Long-Term, Open-Label Trial Investigating Safety and Efficacy of Lonapegsomatropin Administered Once-Weekly in Children with Growth*

Hormone Deficiency Who Have Completed a Prior Lonapegsomatropin Clinical Trial

This is a multicenter, phase 3, long-term, open-label extension trial of weekly lonapegsomatropin in children with GHD who previously participated in a phase 3 lonapegsomatropin trial (i.e., CT-301 or CT-302). All subjects completing the prior phase 3 lonapegsomatropin trial who did not permanently discontinue trial medication, were without evidence of closed epiphyses, and met all other entry criteria were invited to participate. Subjects entered the extension trial and began or continued lonapegsomatropin (depending on trial medication from the parent trial).

The efficacy endpoints of long-term weekly lonapegsomatropin treatment include the following:

- Annualized height velocity (AHV)
- Change in height standard deviation score
- Proportion of subjects with insulin-like growth factor-1 (IGF-1) standard deviation score (SDS) of 0 to +2.0
- IGF-1 SDS
- insulin-like growth factor binding protein-3 (IGFBP-3) SDS

The safety endpoints as measured throughout the long-term dosing of weekly lonapegsomatropin treatment include the following:

- Incidence of adverse events (AEs)
- Incidence of antibodies against human growth hormone (hGH), including neutralizing antibodies
- Incidence of antibodies against polyethylene glycol (PEG)
- Incidence of antibodies against TransCon hGH
- Incidence of insulin-like growth factor-1 (IGF-1) standard deviation score (SDS) > 2.0, > 3.0
- Parameters of HbA1c and lipids
- Hormone levels, including thyroid status and morning cortisol
- All other hematology and chemistry parameters
- Vital sign measurements

This trial is ongoing. The trial began December 19, 2017 and data cut-off for the study report is September 30, 2019. The trial is being conducted at 63 clinical sites in 15 countries. As of the data cut-off date, 296 subjects had entered this extension trial. Overall, ten subjects have prematurely withdrawn from the trial.

III. RESULTS (by Site)

NOTE: Site inspections focused on review of informed consent documents (ICDs), institutional review board (IRB)/ ethics committee (EC) correspondences, 1572s/investigator agreements, financial disclosures, training records, (CVs and licenses, delegation of duties, monitoring logs and reports, inclusion/exclusion criteria, enrollment logs, subject source documents including medical history records, drug accountability, concomitant medication records, and adverse event reports. Source records were compared to the sponsor's data line listings.

1. Aristides K. Maniatis, M.D.
Rocky Mountain Pediatric Endocrinology
7336 South Yosemite Street, Suite 200
Centennial, Colorado 80112-2340

Site: 731

Dates of inspection: February 22 – March 2, 2021

For Study CT-301, there were 10 subjects screened and 6 subjects enrolled into the study; 6 subjects completed the study. There were 10 subject records reviewed.

For Study CT-301EXT, there were 35 subjects screened and 35 subjects enrolled into the study. The trial is still ongoing. There were 17 subject records reviewed.

The institutional review board of record was (b) (4)
(b) (4).

Dr. Maniatis is the owner, President, and CEO of Rocky Mountain Pediatric Endocrinology. He has been conducting research as an investigator for approximately 8 years. All study subjects were seen for their study visits onsite.

Source records were organized and available. Some of the corrections in the paper source records were illegible. The study coordinator transcribed the information from the source documents/electronic medical records to electronic case reporting forms (eCRFs). In reviewing the records, it was noted that Dr. Maniatis was reviewing source documentation months after the study visit. The electronic medical record (EMR) system does not keep an audit trail of changes made after the chart or note is signed off. The EMRs are backed up by a 3rd party vender, (b) (4).

Source records were compared to the sponsor data line listings. There were no discrepancies except for a few missing adverse events (as noted below). The efficacy endpoints were verifiable.

At the conclusion of the inspection, it was discussed with Dr. Maniatis that he needed to do a timelier review of the study coordinator's notes regarding subjects' visits and ensure errors in the paper records were corrected in a legible way.

In addition, a Form FDA-483, Inspectional Observations, was issued for the following deficiencies:

1. Investigational drug disposition records are not adequate with respect to dates. Specifically, for the CT-301 study, five subjects were missing a total of 43 vials of used investigational product (IP).

- Subject (b) (6) had 13 missing vials
- Subject (b) (6) had 7 missing vials
- Subject (b) (6) had 15 missing vials
- Subject (b) (6) had 4 missing vials
- Subject (b) (6) had 4 missing vials

OSI Reviewer Comment: The initial vials had been accounted for during a monitoring visit 5/24/2017. The monitor from (b) (4) became aware of the missing vials during a monitoring visit on 09/27/2017. The vials had been stored in an unlabeled location and were inadvertently discarded by site staff. The site correctly notified the sponsor and the IRB of the missing vials. Due to the number of missing vials, a corrective and preventive action (CAPA) plan was put in place. The site added a lock on the refrigerator door to limit the number of people who can access it. A separate labelled bin was dedicated for returned used IP vials. The site also received additional training.

2. An investigation was not conducted in accordance with the signed statement of the investigator and investigational plan. Specially, not all adverse events (AEs) were reported.
 - Subject (b) (6) had reported headaches at Visit 2 on (b) (6) Visit 3 on (b) (6), Visit 5 on (b) (6), and Visit 6 on (b) (6) that were not captured on the AE case report form (CRF). The subject took ibuprofen and acetaminophen to treat. The headaches were added to the medical history on (b) (6) after the subject had been in the study for almost a year.
 - The same subject had reported upper respiratory infections (URIs) in their diary on (b) (6) that were also not captured on the AE CRF. The URIs were added to the medical history on (b) (6) after the subject had been in the study for one year.
 - Subject (b) (6) had a bloody nose that was not reported at Visit 2 on (b) (6). Epistaxis was not part of the medical history for this subject.

OSI Reviewer Comment: Dr. Maniatis responded to the Form FDA 483 on 03/09/2021 and his response was deemed acceptable. He clarified that he added the intermittent headaches and URIs to Subject (b) (6)'s medical history instead of creating an adverse event because, upon questioning the subject, they reported that their symptoms had begun before the screening phase, although nothing had been mentioned. He acknowledged that he inadvertently missed the epistaxis reported in the diary by the subject.

Although regulatory violations were noted as described above, they are not significant and should not impact primary safety and efficacy analyses.

2. Sponsor:
Ascendis Pharma A/S
500 Emerson Street
Palo Alto, CA 94301

Dates of inspection: April 27 – May 4, 2021 (*Full report pending*)

The inspection consisted of reviewing the organizational structure and responsibilities, transfer of obligations, contractual agreements, selection of sites, training, investigational product accountability, the evaluation of the adequacy of monitoring and corrective actions taken by the sponsor/monitor/contract research organization (CRO), deviations related to key safety and efficacy endpoints, quality assurance and audits, adverse events evaluation and reporting, 1572s and investigator agreements, the interactive voice/web response system, financial disclosures, standard operating procedures (SOPs), trial master file review, record retention, selection criteria for all committee members, oversight of committees, data management, escalation of issues, and clinical trial oversight.

For Study CT-301, not all Form FDA 1572s “Statement of Investigator” were properly signed in a timely manner:

- For Site 762, the 1572 was signed on July 5, 2017; however, the first subject was screened on January 5, 2017 and the first subject was treated on [REDACTED] (b) (6).
- For Site 768, the 1572 was signed on June 28, 2017; however, the first subject was screened on October 17, 2017 and the first subject was treated on [REDACTED] (b) (6).
- For Site 772, the 1572 was signed on June 6, 2019; however, the first subject was rolled over into the extension study on [REDACTED] (b) (6).

OSI Reviewer Comment: Monitoring and the collection of the Form FDA 1572 had been transferred to the contract research organization. Although not properly obtained, these deviations should have no impact on safety or efficacy analyses.

For Study CT-301 (ClinicalTrials.gov ID: NCT02781727), although completed January 17, 2019, ClinicalTrials.gov has not been updated. Ascendis Pharma requested a delay, which was granted December 17, 2019 and confirmed by the FDA ORA inspector during the inspection.

OSI Reviewer Comment: The process for the requested delay was confirmed by OSI staff that provide oversight for ClinicalTrials.gov. The request was properly executed, and the reviewed documents were appropriate.

Although both studies were open-label, the sponsor had stated in the clinical study report for Protocol CT-301 that there were procedures in place to keep selected sponsor staff (medical monitors/medical experts and statisticians) blinded to treatment assignment. This was assessed during the inspection. The blinded individuals for the CT-301 study remained blinded until after the database lock date. There are no individuals that are still blinded for the CT-301 study and no one was blinded in the CT-301 EXT study. Those that were blinded had restricted access to certain areas of the case report forms. The sponsor staff had

internal work instructions that guided how they would maintain the blind for blinded individuals.

In addition, for Study CT-301, the persons performing the height measurements (auxologists) at the sites were intended to be blinded. The Site Qualification Visit Reports (SQVRs) state under Section 2.0 Protocol/CIP and Trial-Specific Requirements, Question #1, Part H, “Is the site able to perform auxology measurements by the same blinded auxologist throughout the trial period?” All SQVRs were reviewed and the answer to this question was “yes” for all. However, based on the delegation logs, the same sites delegated the task to unblinded personnel, such as the investigator, sub-investigator, or the study coordinator. Per Section 7.1.2 of the original protocol “The trial auxologists will be trained and kept blinded to treatment allocation as far as possible at each site” and per Section 10.1.2 “Auxology measurements (actual height and body weight), to be performed by the same, trained, blinded auxologist at approximately the same time of day (morning) at each visit if possible.”

Sponsor staff acknowledged that sometimes the site investigators, sub-investigators, study coordinators or a nurse who was unblinded would perform the measurements if a blinded trained auxologist or other blinded staff were unavailable at the site. The sponsor and CRO lacked procedures that addressed blinded personnel at the sites.

OSI Reviewer Comment: Although a blinded auxologist would have been ideal, it was not a strict requirement in the protocol.

Subject (b) (6) was enrolled into the study despite meeting exclusion criteria #1; specifically, weight was 11.4 kg (below the 12 kg requirement as needed for blood drawn). The issue was recognized prior to the subject being dosed. The Ascendis Pharma medical monitor approved the subject to be included in the study on December 13, 2017. This was reported as a protocol deviation.

OSI Reviewer Comment: The sponsor was reminded that, although not a regulatory violation, protocol waivers are discouraged.

The inspection revealed adequate adherence to the regulations and the investigational plan. There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, issued.

Data from this sponsor appear acceptable.

{See appended electronic signature page}

Cynthia F. Kleppinger, M.D.
Senior Medical Officer
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Min Lu, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:

Central Doc. Rm./ BLA 761177
DGE/Division Director/ Theresa Kehoe
DGE /Team Lead/Marina Zemskova
DGE /Clinical Reviewer/ Shivangi Vachhani
DRO /Regulatory Project Manager/Sejal Kiani
OSI/DCCE/Acting Division Director/ Kassa Ayalew
OSI/DCCE/GCPAB/Branch Chief/Kassa Ayalew
OSI/DCCE/GCPAB/Team Leader/Min Lu
OSI/DCCE/GCPAB Reviewer/Cynthia Kleppinger
OSI/DCCE/GCPAB/Program Analyst/Yolanda Patague
OSI/DCCE/Database Project Manager/Dana Walters

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Division of Pediatric and Maternal Health
Office of Rare Diseases, Pediatrics, Urologic
and Reproductive Medicine
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
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PLLR Labeling Memorandum

Date: 3/31/2021

Date consulted: 2/9/2020

From: Wenjie Sun, MD, Medical Officer, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Through: Miriam Dinatale, DO, Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, OND, Division Director
Division of Pediatric and Maternal Health

To: Division of General Endocrinology (DGE)

Drug: Lonapegsomatropin-tcgd for injection, for subcutaneous use

BLA: 761177

Applicant: Ascendis Pharma Endocrinology Division A/S

Subject: Pregnancy and Lactation Labeling

Proposed

Indication: for treatment of pediatric patients 1 year and older who have growth failure due to inadequate secretion of endogenous growth hormone (GH)

Materials Reviewed:

- Applicant's submitted background package and proposed labeling for BLA 761177
- DGE consult form for DPMH, DARRTS Reference ID 4744097

- DPMH review of Norditropin (somatropin) injection, NDA 21148, by Catherine Roca, MD, on February 6, 2018, DAARTS Reference ID 4217578¹

Consult Question:

DGE is seeking assistance from DPMH in developing Sections 8.1, 8.2 and 8.3 of the product's labeling.

BACKGROUND

On June 25, 2020, the applicant (Ascendis Pharma Endocrinology Division A/S) submitted a new BLA 761177 for lonapegsomatropin for injection, a long-acting prodrug of somatropin, for approval. FDA granted the product Orphan Drug Designation on April 14, 2020, based on the plausible hypothesis that lonapegsomatropin is clinically superior than the same drug(s) already approved. The applicant also seeks Priority Review Designation with their submission on June 25, 2020. On January 21, 2021, FDA find the nonproprietary name, lonapegsomatropin-tcgd, conditionally acceptable.

The Division of General Endocrinology (DGE) consulted the Division of Pediatric and Maternal Health (DPMH) on February 9, 2021, to assist with the Pregnancy and Lactation subsections of labeling.

DATA REVIEW

Lonapegsomatropin is a long-acting prodrug of human growth hormone consisting of a parent drug somatropin which is transiently conjugated to a methoxypolyethylene glycol (mPEG) carrier, (b) (4)

Following subcutaneously injection, lonapegsomatropin releases fully active somatropin (191 amino acids) via autocleavage of the TransCon linker in a controlled manner. Lonapegsomatropin is dosed as a once-weekly subcutaneous injection.

The nonclinical toxicology finding are as follows:

In animal reproduction studies, there was no evidence of embryo-fetal or neonatal harm when pregnant rats were administered subcutaneous lonapegsomatropin at doses up to 13-fold the clinical dose of 0.24 mg hGH/kg/week.

There is no information on whether lonapegsomatropin is present in animal milk.

Carcinogenicity studies have not been conducted with lonapegsomatropin. Lonapegsomatropin was not mutagenic in the Ames test, in the human chromosomal aberration assay or in the rat bone marrow micronucleus test.

In an animal fertility study, lonapegsomatropin was administered via subcutaneous injection to male and female rats before cohabitation, through mating to implantation. Lonapegsomatropin did not affect fertility or early

¹ The somatropin injection review was part of the materials reviewed to avoid duplicating background information and literature relevant to the underlying medical condition but was not a source relied upon for the labeling recommendations below.

embryo-fetal development at doses up to 20-fold the clinical dose of 0.24 mg hGH/kg/week

In discussion with the DGN Pharmacology Toxicology Team, the DGN Pharmacology Toxicology Team agrees with the applicant that “maternal GH and IGF-1 do not appear to cross the placenta in humans, rabbits or rats.^{2,3,4,5,6,7} mPEG is not expected to cross the placenta (humans/animals) due to the high molecular weight (40 kDa) of this moiety.⁸”

There were no pregnant or lactating patients exposed to lonapegsomatropin during the clinical trials. There is no information within the published literature on the effect of lonapegsomatropin in pregnancy, lactation, and fertility.

There are published reports on the use of somatropin during pregnancy, lactation, and use in male and females of reproductive potential. In a DPMH review of somatropin in 2018⁹, Catherine Roca, MD, concluded that in pregnancy, “data from the published literature do not indicate a clear risk for adverse pregnancy outcomes with somatropin.” Limited available data with somatropin use in pregnant patients are insufficient to determine a drug-associated risk of adverse developmental outcomes.

Regarding lactation, DPMH concluded the following in their 2018 review of somatropin⁹:
“Limited data from the literature and the pharmacological properties of somatropin indicate that it is unlikely that somatropin will transfer into breastmilk. No adverse effects have been reported in breastfeeding infants when somatropin is used by nursing mothers. Small studies in breastfeeding mothers indicate that somatropin may increase milk production.”

Regarding fertility, DPMH concluded the following in their 2018 review of somatropin⁹:
“Data from the literature do not describe any safety concerns related to somatropin and fertility or any effects on hormonal contraception; therefore, subsection 8.3 will not be included in the labeling.”

² Laron Z, Pertzalan A, Mannheimer S, et al. Lack of placental transfer of human growth hormone. *Acta Endocrinol (Copenh)*. 1966a;53(4):687-692.

³ Laron Z, Pertzalan A, Mannheimer S, et al. Lack of Placental Transplacental Passage of Growth Hormone in Rabbits. 1966b; *Experientia*, 22: 831-2

⁴ King KC, Adam PA, Schwartz R, et al. Human placental transfer of human growth hormone-I 125. *Pediatrics*. 1971;48(4):534-539.

⁵ Davenport ML, Clemmons DR, Miles MV, et al. Regulation of serum insulin-like growth factor-I (IGF-I) and IGF binding proteins during rat pregnancy. *Endocrinology*. 1990;127(3):1278-1286.

⁶ Fhølenhag KI, Sandström IM, Malmlöf K, et al. Human growth hormone does not cross the placenta of the pregnant rat. *Growth Regul*. 1994;4(4):181-187

⁷ Verhaeghe J. Does the physiological acromegaly of pregnancy benefit the fetus? *Gynecol Obstet Invest*. 2008;66(4):217-226.

⁸ Martin PL, Breslin W, Rocca M, et al. Considerations in assessing the developmental and reproductive toxicity potential of biopharmaceuticals. *Birth Defects Res B Dev Reprod Toxicol*. 2009;86(3):176-203.

⁹ DPMH review of Norditropin (somatropin) injection, NDA 21148, by Catherine Roca, MD, on February 6, 2018, DAARTS Reference ID 4217578

DPMH conducted an updated review of the published literature since 2018 using Embase, Pubmed, Micromedex,¹⁰ ReproTox,¹¹ TERIS,¹² Shepard's,¹³ LactMed,¹⁴ Hale,¹⁵ and Briggs.¹⁶ No new information was noted by these reference sites and no additional articles were found on use of somatropin or lonapegsomatropin during pregnancy and lactation.

Publications on off label use of somatropin during in vitro fertilization cycles (IVF) to assist with ovarian response were identified:

- A recent study with 92 females with poor ovarian reserve randomly assigned to three regimens: gonadotrophin and GH from the eighth day of the cycle for about 5 days (n=34); gonadotrophin and GH from the third day of the previous cycle for about 20 days (n=32); and gonadotrophin and a placebo from the eighth days of the cycle for about 5 days (n=26). The authors found that oocyte quality and pregnancy rates were higher in the GH group than the placebo group. The authors concluded GH may play an important role in recruitment of dominant follicles and enhance follicular survival and cell proliferation leading to high- quality embryo.¹⁷
- In a study, 445 follicles were collected from 62 females undergoing standard infertility treatment. The women were randomized to receive standard treatment with or without GH co-treatment. In women who had GH co-treatment, there were increases in the receptor density for granulosa follicle stimulating hormone receptors (FSHR), bone morphogenetic hormone receptors (BMPRII), luteinizing hormone receptors (LHR), and growth hormone receptors (GHR) compared with the non-GH-treated patients of the same age and ovarian reserve. The authors concluded that growth hormone co-treatment increased GHR density, which may increase GHR activity. The GH co-treatment was associated with a significant increase in pregnancy rate.¹⁸
- In a randomized controlled trial, 158 patients with poor embryo development were randomly assigned to the GH treatment group (n=107) versus GH untreated group (n=51). The authors found that the GH treated group had a significantly

¹⁰ Truven Health Analytics information, <http://www.micromedexsolutions.com/>. Accessed 2/9/2021.

¹¹ Reprotox Website: www.Reprotox.org. REPROTOX dydtem was developed as an adjunct information source for clinicians, scientists, and government agencies. Accessed 2/10/2021.

¹² Teris database, Truven Health Analytics, Micromedex Solutions. Accessed 2/10/2021.

¹³ 2020 Shepard's: A Catalog of Teratogenic Agent. Accessed 2/10/2021.

¹⁴ <http://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm>. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The lactMed data base provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfeeding infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility. Access 2/10/21

¹⁵ Hale, Thomas. Hale's Medications and Mother's Milk 2019. Springer Publishing Company, New York, NY.

¹⁶ Briggs GG, Freeman RK. Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk. 10th Ed. 2015. Online, accessed 2/10/21

¹⁷ Safdarian L, et al. Growth Hormone (GH) Improvement of Ovarian Responses and Pregnancy Outcome in Poor Ovarian Responders: A Randomized Study. Asian Pac J Cancer Prev. 2019 Jul 1;20(7):2033-2037.

¹⁸ Regan SLP, et al. Growth hormone during in vitro fertilization in older women modulates the density of receptors in granulosa cells, with improved pregnancy outcomes. Fertil Steril. 2018 Dec; 110(7):1298-1310.

- higher number of retrieved oocytes (10.29 ± 5.92 versus 8.16 ± 4.17 , $P = 0.023$), cleaved embryos (6.73 ± 4.25 versus 5.29 ± 3.23 , $P = 0.036$), implantation rate (36.00% versus 17.86%, $P = 0.005$), clinical pregnancy rates per cycle (43.93% versus 19.61%, $P = 0.005$), and live birth rate per cycle (41.12% versus 17.65%, $P = 0.006$).¹⁹
- In a randomized open-label parallel study of 127 infertile females who satisfied the Bologna criteria for poor responders, females treated with GH (three times with sustained-release GH 20mg during mid-luteal, late luteal, and menstrual cycle day 2) were compared to those who were not treated with GH. The authors found that the number of follicles on the human chorionic gonadotropin triggering day (3.1 ± 2.3 vs. 2.4 ± 1.6 , $P = 0.043$) and the proportion of metaphase II oocytes (67.5 vs. 52.3%, $P = 0.030$) were higher in the GH group than in controls. The percentage of clinical and ongoing pregnancies and miscarriage was not different between the two groups.²⁰

The approved somatropin labeling notes that oral estrogen may reduce the serum IGF-1 response to somatropin; the labeling recommends patients on oral estrogen replacement may require greater dose of somatropin to achieve the defined treatment goal.²¹

DISCUSSION/CONCLUSIONS

There are no data on use of lonapegsomatropin during pregnancy and lactation or its effects on fertility. Lonapegsomatropin is a prodrug of somatropin. mPEG is not expected to cross the placenta (humans/animals) due to the high molecular weight (40 kDa) of this moiety and there are no new safety signal identified with use of somatropin identified in this review.

Pregnancy

There are no new safety signals identified with the use of somatotropin, the active ingredient of lonapegsomatropin. Although the data available on the use of somatotropin during pregnancy are limited to case reports and one study of 201 pregnancies, somatropin has been approved for several decades. Therefore, DPMH does not recommend any postmarketing pregnancy studies at the current time.

Lactation

An updated search of the published literature did not identify any new data since 2018 on use of somatotropin during lactation. In the 2018 DPMH review of somatotropin, the reviewer concluded “there is no information regarding the presence of somatropin in human milk. Limited published data indicate that exogenous somatropin does not increase normal breastmilk concentrations of growth hormone. No adverse effects on the breastfed infant have been reported with somatropin.” Based on its physical

¹⁹ Li J, et al. Does growth hormone supplementation improve oocyte competence and IVF outcomes in patients with poor embryonic development? A randomized controlled trial. BMC Pregnancy Childbirth. 2020 May 20;20(1):310.

²⁰ Choe SA, et al. Increased proportion of mature oocytes with sustained-release growth hormone treatment in poor responders: a prospective randomized controlled study. Arch Gynecol Obstet. 2018 Mar;297(3):791-796.

²¹ Approved labeling for Norditropin. DailyMed. Accessed 2/9/2021.

characteristic, somatropin is a peptide of 191 amino acids with a large molecular weight, and its transfer into milk is very unlikely. Oral absorption after infant ingestion is likely to be minimal. Therefore, based on the drug's physical properties and lack of safety signals observed with its prodrug, somatropin, DPMH does not recommend any postmarketing lactation studies at the current time.

Females and Males of Reproductive Potential

Data from the literature do not describe any safety concerns related to somatropin and fertility or any effects on hormonal contraception. Therefore, subsection 8.3 should be omitted.

RECOMMENDATIONS

DPMH revised subsections 8.1 and 8.2 in lonapegsomatropin-tcgd labeling for compliance with the PLLR (see below). DPMH refers to the final BLA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on lonapegsomatropin-tcgd use in pregnant patients to evaluate for a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Available published data over several decades for somatropin, the active (b) (4), have not identified a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. (b) (4) administered subcutaneous lonapegsomatropin at doses up to 13-fold the clinical dose of 0.24 mg (b) (4)/kg/week (*see Data*).

The estimated background risk of (b) (4) birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

No embryonic or fetal development toxicities occurred in rats administered subcutaneous lonapegsomatropin at doses up to 13-fold the clinical dose of 0.24 mg (b) (4)/kg/week.

In a peri- and post-natal developmental study in rats, there were no adverse effects on the pregnant/lactating female or on development of the conceptus and the offspring following exposure of the female from implantation through weaning to doses of a structurally related pegylated somatropin up to 13-fold the clinical dose of 0.24 mg (b) (4)/kg/week.

8.2 Lactation

Risk Summary

There are no data on the presence of lonapegsomatropin in human milk, effect on the breastfed infant, or effects on milk production. High molecular weight therapeutic proteins, including lonapegsomatropin, are expected to have low passage into human milk and limited systemic exposure in the breastfed infant. Additionally, published data indicate that exogenous somatropin does not increase normal ^{(b) (4)} concentrations of growth hormone. No adverse effects on the breastfed infant have been reported with somatropin. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TRADENAME and any potential adverse effects on the breastfed infant from TRADENAME or from the underlying maternal condition.

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HUMAN FACTORS VALIDATION STUDY PROTOCOL REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	March 30, 2021
Requesting Office or Division:	Division of General Endocrinology (DGE)
Application Type and Number:	BLA 761177
Product Type:	Combination Product
Drug Constituent Name and Strength:	Skytrofa (lonapegsomatropin) for Injection, 3 mg, 3.6 mg, 4.3 mg, 5.2 mg, 6.3 mg, 7.6 mg, 9.1 mg, 11 mg and 13.3 mg
Device Constituent:	Autoinjector
Rx or OTC:	Rx
Applicant/Sponsor Name:	Ascendis Pharma
FDA Received Date:	2/11/2021
OSE RCM #:	2020-1429 2020-1499
DMEPA Safety Evaluator:	Jason Flint, MBA, PMP
DMEPA Team Leader:	Whaley, Ebony. PharmD, BCPPS
DMEPA Associate Director for Human Factors (Acting):	Lolita White, PharmD
DMEPA Associate Director for Nomenclature and Labeling:	Mishale Mistry, PharmD, MPH

1 REASON FOR REVIEW

This review evaluates a human factors (HF) validation study protocol submitted under BLA 761177 for Skytrofa (lonapegsomatropin). This is a combination product with a proposed Autoinjector device constituent part that is intended (b) (4)

1.1 REGULATORY HISTORY

We reviewed an HF validation study submitted under BLA 761177 on July 13, 2020. Our review identified deficiencies with the study methodology that precluded our ability to review the HF validation study results. We provided HF recommendations^a to the applicant on January 13, 2021. We held a teleconference with the applicant on January 19, 2021 to discuss the study methodology issues regarding the human factors (HF) validation study and the possible need for additional HF validation study data. The applicant provided written responses to our HF recommendations on January 22, 2021; we reviewed those responses and provided feedback to the applicant on January 27, 2021^b that additional HF validation study data would be required to support their application. Subsequent to our most recent communication, the applicant submitted an HF validation study protocol for our review on February 11, 2021, which is the focus of this review.

2 MATERIALS REVIEWED

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

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Background Information Previous HF Reviews (DMEPA and CDRH) and FDA/Sponsor Interactions	B
Human Factors Validation Study Protocol	C
Information Requests Issued During the Review	D - N/A
CDRH Human Factors Consult Review	E – N/A
Product Sample, Label and Labeling, Packaging	F – N/A

^a Whaley, E. Human Factors Results Review Memorandum for Skytrofa (lonapegsomatropin) BLA 761177. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 20210113. RCM No.: 2020-1429; 2020-1499.

^b Whaley, E. Review of Responses to Human Factors Recommendations for Skytrofa (lonapegsomatropin) BLA 761177. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 20210127. RCM No.: 2020-1499-1.

3 REVIEW SUMMARY AND DISCUSSION

Our overall assessment of the HF validation study protocol contained in the submission indicated that the protocol requires revisions to ensure that adequate data regarding the safe and effective use of this product is collected.

Please see table below in section 5.1 for our evaluation and recommendations.

4 COMMUNICATION OF DMEPA'S ANALYSIS TO OFFICE OF NEW DRUGS

DMEPA communicated our findings to the Division of General Endocrinology (DGE) via e-mail on March 30, 2021. At that time we also requested concerns that could inform our review. Per e-mail correspondence from DGE on March 30, 2021, they stated no additional concerns and did not have additional feedback regarding DMEPA's recommendations.

5 CONCLUSION & RECOMMENDATIONS

We find that the HF validation study protocol is Not Acceptable. Please see section 5.1 for our recommendations. We advise that the Applicant implement our recommendations prior to commencing their HF validation study.

5.1 RECOMMENDATIONS FOR ASCENDIS PHARMA

Our review of the human factors validation study protocol identified several areas of concern. Please see the Identified Issues and Recommendations table. We recommend that you implement all recommendations before commencing your human factors validation study.

Identified Issues and Recommendations for Sponsor			
	Identified Issue	Rationale for Concern	Recommendation
HF Validation Study Methodology			
1.	You define “Critical tasks” as “user tasks that, if performed incorrectly or not performed at all, would or could cause (b) (4) harm to the patient or user, where harm is defined to include compromised medical care.”	We note that you reference the CDHR guidance “Applying Human Factors and Usability Engineering to Medical Devices 2016” for this definition. However, your product is a combination product; as such, we refer you to the draft guidance “Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development.” ^d	Revise your definition of Critical Tasks to “Critical tasks are user tasks that, if performed incorrectly or not performed at all, would or could cause harm to the patient or user, where harm is defined to include compromised medical care” per the draft guidance. ^b Additionally, ensure all critical tasks (based on the above definition) are evaluated in your HF validation study.
2.	We note that the moderator’s script indicates that a participant could (b) (4) to familiarize themselves with the product.	We are concerned that this statement may not be representative of actual use, and may indicate to the participant that they should take more time than they would normally.	Revise your moderator’s script to state the participant can take as much time as they usually would to familiarize themselves with the product (i.e. proceed as they normally would at home).
3.	The moderator’s script includes the statement (b) (4) prior to you being able to use it at home on your own. However, for this	We are concerned that including this statement may lead participants to be more vigilant as compared to real-world use which would and will bias the participants’ performance (e.g. observer-expectancy effect).	Remove (b) (4) from your moderator’s script.

	study, it is important that we understand how users that haven't been trained interact with the device."		
4.	We note that the prescriptions given to the participants (b) (4) For example "Inject contents of 1 cartridge subcutaneously (b) (4) once weekly.	In the real world, prescriptions may (b) (4) and including this information may bias the participants knowledge of the critical task "Choose injection site".	Remove (b) (4) from the prescriptions.
5.	We note that you intend to assess participant understanding of the need to perform a second injection if 2 cartridges constitute a full dose as a knowledge task.	Knowledge tasks are designed to evaluate tasks that cannot be observed under simulated use.	Revise your HF validation study protocol to assess this as a simulated use task. For example, instead of asking "What would you do to deliver this dose?", you may have the participant collect the materials needed to deliver the dose.
6.	The moderator script (b) (4)	Open-ended questions provide an opportunity to collect more robust subjective feedback from study participants.	Where possible, consider using open-ended questions. For example, the question (b) (4) "What, if anything, was confusing about the tasks?"
7.	We note that your HF validation study protocol does not include	We are concerned that a user will be unable to troubleshoot and correct device issues they may	Ensure that you evaluate the user's ability to troubleshoot device issues in your HF validation study, either through simulated

	assessment of a user's ability to troubleshoot any issues they may encounter with the device.	encounter, which may lead to a missed dose.	use scenarios or knowledge-based tasks as appropriate.
8.	Your 3/19/2021 email communication inquired regarding the acceptability of assessing the critical warnings in the IFU using knowledge tasks.	We acknowledge that assessing the critical warnings in the IFU by observing user behavior (for example by simulated use) may be difficult because it involves users' understanding of information, rather than their actions..	It is acceptable to assess the critical warnings in the IFU through knowledge task assessment.
9.	Your 3/19/2021 email communication inquired regarding (b) (4). However, your protocol states "GHD patients and caregivers may be either experienced or naïve with injections, but as the GH Auto-Injector is not yet available on the market, all users will be naïve to the GH Auto-Injector".	The participants in your HF validation study should be representative of the intended users of your proposed product, which may include both injection naïve and injection experienced users. Note that we generally consider injection naïve and injection experienced users as separate and distinct user groups.	We do not agree (b) (4). Your HF validation study should include at least 15 injection naïve and 15 injection experienced users as separate and distinct user groups.
Instructions for Use (IFU)			
1.	We note that the IFU indicates that the mixed medication should appear	We are concerned that laypersons may not understand the term (b) (4).	We recommend you select a different descriptor to aid laypersons' understanding of what the mixed medication should look like.

	"colorless and clear or (b) (4)		
General Recommendations			
1. Additionally, please note that when you conduct the study and if you observe use related errors and failures, the Agency expects that you apply the human factors engineering process to implement necessary changes to the product user interface. Depending on the nature of changes and the risk, you may need to perform additional human factors validation study to demonstrate the effectiveness of the changes. 2. Furthermore, to ensure that you provide the complete content of your HF validation study report, we recommend that you refer to our draft guidance <i>Contents of a Complete Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications</i>^c. In addition, Appendix D, within the draft guidance, provides a hypothetical example of the results and associated analysis of human factors validation study data in a tabular format that can facilitate an efficient Agency review. Guidance on human factors procedures to follow can be found in the following guidance documents^d: <i>Applying Human Factors and Usability Engineering to Medical Devices</i> <i>Guidance on Safety Considerations for Product Design to Minimize Medication Errors</i> Note that we recently published three draft guidance documents that, while not yet finalized, might also be useful in understanding our current thinking and our approach to human factors for combination products, product design, and labeling^d: <i>Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development</i> <i>Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors</i>			

^c When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>

^d We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

Contents of a Complete Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. DRUG PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 3 presents relevant product information for Skytrofa (lonapegsomatropin) for Injection, received on 2/11/2021 from Ascendis Pharma.

Table 3. Relevant Product Information	
Initial Approval Date	N/A
Therapeutic Drug Class or New Drug Class	Human growth hormone
Active Ingredient (Drug or Biologic)	Lonapegsomatropin
Indication	(b) (4)
Route of Administration	Subcutaneous injection
Dosage Form	Injection
Strength	3 mg, 3.6 mg, 4.3 mg, 5.2 mg, 6.3 mg, 7.6 mg, 9.1 mg, 11 mg and 13.3 mg
Dose and Frequency	0.24 mg hGH/kg body weight once weekly
How Supplied	carton containing 4 cartridges and 6 single-use needles
Storage	can be stored at room temperature [not to exceed 86°F(30°C)] for up to 6 months. Alternatively, TRADENAME can be stored under refrigeration at 36°F to 46°F (2°C to 8°C) until the expiration date.
Container Closure/Device Constituent	GH Autoinjector

	(b) (4)
Intended Users	include pediatric patients, caregivers, and healthcare providers (HCPs)
Intended Use Environment	Home and Clinic Environments

APPENDIX B. BACKGROUND INFORMATION

B.1 PREVIOUS HF REVIEWS

B.1.1 Methods

On 2/22/2021, we searched FDA previous reviews using the terms, "126053", "lonapegsomatropin" and "761177" to identify reviews previously performed by DMEPA or CDRH.

B.1.2 Results

Our search identified three previous reviews, but we note that the HF protocol used to execute the HF validation study reviewed in January 2021^e was different than those that were reviewed in 2017^f and 2018^g.

APPENDIX C. HUMAN FACTORS VALIDATION STUDY PROTOCOL

The HF study protocol can be accessible in EDR via:

<\\CDSESUB1\evsprod\bla761177\0026\m5\53-clin-stud-rep\535-rep-effic-safety-stud\growth-hormone-deficiency-ghd\5354-other-stud-rep\gh-auto-injector-hf\gh-auto-inject-hf-supp-protocol.pdf>

APPENDIX D. INFORMATION REQUESTS ISSUED DURING THE REVIEW

N/A

APPENDIX E: CDRH HUMAN FACTORS CONSULT REVIEW

N/A

APPENDIX F. PRODUCT SAMPLE, LABELS AND LABELING, PACKAGING

N/A

^e Whaley, E. Human Factors Memo for Skytrofa (lonapegsomatropin) BLA 761177. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 20210113. RCM No.: 2020-1429; 2020-1499.

^f Vee, S. Human Factors Protocol Review for TransCon Human Growth Hormone IND 126053. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 20170303. RCM No.: 2017-79.

^g Ogonna, C. Human Factors Protocol Addendum for Transcon Human Growth Hormone IND 126053. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 20180423. RCM No.: 2018-533.

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration

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MEMORANDUM TO FILE

Version Date: March 3, 2021

From: Ethan D. Hausman, MD, Medical Officer
Division of Pediatric and Maternal Health (DPMH)

Through: Shetarra Walker, MD, MSCR, Clinical Team
Leader, DPMH
John J. Alexander, MD, MPH, Deputy Director
DPMH

BLA Number: 761,177

Applicant: Ascendis Pharma Endocrinology Division A/S

Drug: ACP-011 (lonapegsomatropin)

Indication: Pediatric growth hormone deficiency (GHD)

**Dosage Form and
Route of Administration:** Injection for subcutaneous (SC) administration

Proposed Pediatric Regimen: Recommended starting dose: 0.24 mg hGH/kg body weight once weekly (QW). The starting dose should be individualized based on etiology of GHD, treatment goals, and expected sensitivity to therapy.

Division Consult Request: The Division of General Endocrinology (DGE) requests DPMH assistance for labeling the candidate product as well as to assess risk of a cleavage moiety (methoxypolyethylene glycol, mPEG) of the prodrug.

Background

The candidate drug, ACP-011 (lonapegsomatropin), is under development for treatment of pediatric growth hormone deficiency (GHD). The product received orphan designation for the proposed indication on April 13, 2020.

Pediatric GHD has numerous etiologies including primary pituitary and or hypothalamic hypofunction (malformation or genetic disorders), secondary issues such as destructive lesions (infarct or tumor), and tertiary issues such as GH receptor insensitivity.¹ Exogenous GH is used to treat primary and secondary causes of GHD but is not effective for receptor insensitivity. Untreated GHD causes loss of final adult height, which can be extreme and associated with serious and severe psychiatric co-morbidity, decreased bone mineral density, increased cardiovascular risk, and lassitude.²

Loss of growth hormone in adults is associated with other morbidities including increased central obesity, decreased lean body mass, anxiety and depression, impaired sexual desire and function, fatigue with decreased exercise tolerance, and increased sensitivity to both heat and cold.³ The Applicant is not currently seeking an indication for treatment of adults and this topic is not discussed further.

The agreed initial pediatric study plan (iPSP; March 24, 2017) describes two pediatric studies, one study in treatment-naïve children with GHD (CT-301) and a second study in children with prior exposure to GH replacement therapy. Per discussion with DGE on February 5, 2021, only study CT-301 will be described in labeling.

DGE requests input on the neuro-toxicological risk of methoxypolyethylene glycol, (mPEG); however, the Division of Neurology (DN), and Pharmacotoxicology are the primary consultants for the mPEG issue. From the consult request, during the nonclinical program, mPEG accumulation in the brain was noted in the 26-Week studies in rats and monkeys and in 52-week studies in monkeys. All animals were asymptomatic.

DGE also requests DPMH assistance with labeling this product. A discussion of the mPEG issue is presented first followed by the labeling review.

Methoxypolyethylene glycol (mPEG)

The pivotal phase 3 trial CT-301 included patients ≥ 3 years old and supportive trial CT-302 included patients ≥ 1 -year-old with no neurologic adverse events in the human trials (including Phase 1 and 2 studies). During the clinical development program, no pregnant or lactating women were exposed to lonapegsomatropin. Clinical pharmacology modeling predicts a median steady state level of mPEG in the choroid plexus of children administered lonapegsomatropin at 0.24 mg hGH/kg/week (the proposed dose) as 2-fold lower than the predicted steady state levels in the choroid plexus of monkeys at the no observed effect level (NOEL, 0.4 mg hGH/kg/week) for the test article-related microscopic findings in the brain (vacuolation of epithelial cells and/or macrophages within the choroid plexus) observed in male and females dosed at ≥ 1.6 mg hGH/kg/week

¹ Marcante KJ, Kliegman RM. Nelson Essentials of Pediatrics 8th Ed., 2019. Elsevier. Phila, PA, USA; pp: 653-656.

² Ibid.

³ Diez JJ, Sangiao-Alvarellos S, Cordido F. Treatment with growth hormone for adults with growth hormone deficiency syndrome: benefits and risks. Int J Mol Sci. 2018 Mar 17;19(3):893

for 52 weeks. However, it remains unknown whether there will be accumulation of mPEG in brain with long-term treatment.

(b) (4)

A literature search using various terms including methoxypolyethylene glycol, mPEG, adverse, harm, toxic, toxicity, brain, and nervous system failed to produce any relevant clinical data. Therefore, DPMH is unable to comment on the safety or toxicity of mPEG in treated patients. Per a February 25, 2021 team meeting and related email communications with the pharmacotoxicology reviewer, the pharmacotoxicology review stated that the nonclinical data contains no findings supporting a relevant clinical safety issue due to mPEG exposure, and there no need to address the preclinical mPEG data regarding in labeling. Additional details may be found in the DN review.

Labeling Review

Because the product is intended for pediatric use, pediatric information is distributed throughout labeling. DPMH's labeling review and recommendations focus on sections 1 (Indications and Usage), 5 (Warnings and Precautions) and 8.4 (Pediatric Use). Text of sections 2.1, 2.2. and 2.3 of Dosage and Administration are presented for illustrative purposes and are acceptable, pending revision by other disciplines. Review of the remaining sections [e.g., 6 (Adverse Reactions), and 14 (Clinical Studies)] is deferred to DGE and other consultant disciplines (e.g., Clinical Pharmacology).

For this review, text which DPMH recommends deleting is noted by ~~strike-out~~, text added by other reviewers is noted in **bold blue**, and any text which DPMH recommends adding is noted in **bold red**. The comments below were provided to DGE on February 18, 2021. The reader is directed to final approved labeling, which may include revised language not addressed in this review.

1 Indication

TRADENAME (lonapegsomatropin) is indicated for the treatment of pediatric **patients 1 year and older** (b) (4)

Reviewer comment: At the February 18, 2021 internal meeting, DGE clarified that in addition to the single study patients 3.2 to 13.1 years currently described in section 14 of labeling, additional supportive information in pediatric patients 1 year and older was received in the BLA. At a follow-up meeting on February 25, 2021, the review team informed DPMH that previously approved human GH-like products do not have age limits in the indication statement but are not generally used for the proposed indication (b) (4) until children are diagnosed around 2 years of age. The consensus at the meeting was that the product could be labeled for patients as young as 1 year of age based on the conditions of study.

DPMH notes that another GH product, Norditropin Flexpro (BLA 21148, somatropin) is indicated for use in pediatric patients with GH deficiency and for "short stature

associated with Noonan syndrome, short stature associated with Turner syndrome, short stature born small for gestational age (SGA) with no catch-up growth by age 2 to 4 years, Idiopathic Short Stature (ISS), and growth failure due to Prader-Willi Syndrome (1.1).” At the February 18, 2021 internal meeting, DGE stated that indicating the drug for those additional conditions should not be done at this time, since labeling the drugs for those other conditions would require clinical studies to establish safety and effectiveness.

2 Dosage and Administration

2.1 General Dosing Information

For subcutaneous injection, once-weekly.

Therapy with TRADENAME should be supervised by a physician who is experienced in the diagnosis and management of pediatric patients with growth failure due to growth hormone deficiency (GHD).

Fundoscopy examination should be performed routinely before initiating treatment with TRADENAME to exclude preexisting papilledema, and periodically thereafter [see Warnings and Precautions (5.5)]

Individualize and titrate the dosage of TRADENAME based on response.

Assess compliance and evaluate other causes of poor growth such as hypothyroidism, under nutrition, advanced bone age and antibodies to human growth hormone (hGH) if patients experience failure to increase height velocity, particularly during the first year of treatment.

Discontinue TRADENAME for stimulation of linear growth once epiphyseal fusion has occurred.

2.2 (b) (4)

The recommended (b) (4) dose of TRADENAME for treatment-naïve patients and patients (b) (4) daily somatropin therapy is 0.24 mg (b) (4)/kg body weight, given once-weekly.

(b) (4) changing from daily somatropin therapy to once-weekly TRADENAME, wait at least 8 hours between the final dose of the daily somatropin and the first dose of once-weekly TRADENAME

2.3 (b) (4)

TRADENAME (b) (4) is available in 9 cartridges (b) (4). Selection of the appropriate cartridge is based on the prescribed dose (mg (b) (4)/kg) and the patient's body weight (kg).

- If prescribing a dose of 0.24 mg (b) (4)/kg/week, (b) (4)
- If prescribing a dose other than 0.24 mg (b) (4)/kg/week, calculate the total weekly dose (in mg (b) (4)) and select the appropriate cartridge as follows:
 - Total weekly dose (mg (b) (4)) = prescribed weekly dose (mg (b) (4)/kg) x patient's body weight (kg)
 - Round the total weekly dose (mg (b) (4)) to the closest cartridge dose while also considering treatment goals and clinical response

Table 1: Recommended Cartridge(s) for Patients Prescribed Doses of 0.24 mg (b) (4) kg/week

Weight (kg)	Cartridge(s) (mg hGH)
11.5 – 13.9	3.0
14.0 – 16.4	3.6
16.5 – 19.9	4.3
20.0 – 23.9	5.2
24.0 – 28.9	6.3
29.0 – 34.9	7.6
35.0 – 41.9	9.1
42.0 – 50.9	11.0
51.0 – 60.4	13.3
60.5 – 69.9	(b) (4)
70.0 – 84.9	(b) (4)
85.0 – 100.0	(b) (4)

Reviewer comment: At the February 25, 2021 meeting, the review team discussed the potential need for development of additional cartridge (presentations) to support lower dosing in patients as young as 1 year of age with growth failure. This rationale is inferred from CDC growth charts that show the lowest 5th percentile of weight for unaffected males and females at 2 years is 11kg and 10kg, respectively.⁴ However, if the drug is indicated for children as young as 1 year of age, the lowest 5th percentiles for unaffected males and females are approximately 8.6 kg and 8 kg, respectively. It may be inferred, therefore, that children with growth failure due to inadequate GH secretion at 1 year of age will be smaller/lighter, requiring smaller doses and unique presentations.

4 Contraindications

- **Acute critical illness after open heart surgery, abdominal surgery or multiple accidental trauma, or those with acute respiratory failure due to the risk of increased mortality with use of pharmacologic doses of somatropin [see Warnings and Precautions (Error! Reference source not found.)]**
- (b) (4) Systemic hypersensitivity reactions have been reported with post-marketing use of somatropin products [see Warnings and Precautions (Error! Reference source not found.)].

(b) (4)

⁴ https://www.cdc.gov/growthcharts/clinical_charts.htm; website accessed February 26, 2021.

- (b) (4) Prader-Willi syndrome who are severely obese, have a history of upper airway obstruction or sleep apnea or have severe respiratory impairment due to the risk of sudden death [*see Warnings and Precautions (Error! Reference source not found.)*].

- **Active proliferative or severe non-proliferative diabetic retinopathy**

Reviewer comment: The Contraindications as modified by other reviewers are consistent with labeling for other GH products. At the February 18, 2021 meeting DPMH and DGE discussed whether diabetic retinopathy should also be described in Warnings and Precautions. DGE stated that no cases of retinopathy were noted in the clinical development plan. DGE stated that this is a class issue described in Contraindications across GH labeling, that clinicians would not use the drug in patients with pre-existing diabetic retinopathy, and clinicians would discontinue the drug in patients who develop diabetic retinopathy. Therefore, DGE concluded that additional descriptions of diabetic retinopathy in Warnings and Precautions is not warranted.

5 Warnings and Precautions

Reviewer comment: The Warnings and Precautions as modified by other reviewers are consistent with labeling for other GH products. The categories in Warnings and Precautions are listed below with short explanations of the risk and are relevant to all GH replacement products.

5.1 Acute Critical Illness. Increased mortality has been reported with GH replacement therapy in patients after heart surgery, trauma, and respiratory failure.

5.2 Severe Hypersensitivity. This includes anaphylaxis and angioedema.

5.3 Increased Risk of Neoplasms. This includes progression of **current/pre-existing malignancies**, risk of recurrence of prior malignancies after oncologic treatment, and risk of new tumor types during treatment.

5.4 Sudden Death in Pediatric Patients with Prader-Willie Syndrome

5.5 Glucose Intolerance and Diabetes Mellitus

5.6 Intracranial Hypertension

5.7 Fluid retention

5.8 Hypoadrenalism

5.9 Hypothyroidism

5.10 Slipped Capital Femoral Epiphysis

5.11 Progression of Preexisting Scoliosis

5.12 Pancreatitis

5.13 Lipoatrophy

5.14 Laboratory Tests. This should include monitoring of (b) (4), alkaline phosphatase, and parathyroid hormone all of which may increase during treatment.

8.4 Pediatric Use

Safety and effectiveness of TRADENAME have been established in pediatric patients **1 year and older. Pediatric use was established in a controlled study of 161 treatment-naïve pediatric patients ages 3 to 13 years, and supportive data in pediatric patients 1 year and older** [see *Adverse Reactions (6)* *Clinical Studies (14)*].

The safety and effectiveness of TRADENAME in children less than **1 year** of age have not been established.

Reviewer comment: The revisions reflect how safety and efficacy were established in the single study described in section 14, as well as additional supportive data received in the application describing a pediatric study of 146 pediatric patients 1 to 17 years. At the February 18, 2021 meeting DGE stated their review will additionally describe the study design and data collected in the supportive study.

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/s/

ETHAN D HAUSMAN
03/03/2021 05:26:54 AM

SHETARRA E WALKER
03/03/2021 09:01:17 AM

JOHN J ALEXANDER
03/03/2021 02:11:16 PM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: February 14, 2021
Requesting Office or Division: Division of General Endocrinology (DGE)
Application Type and Number: BLA 761177
Product Name and Strength: Skytrofa (lonapegsomatropin-tcgd) for injection,
3 mg, 3.6 mg, 4.3 mg, 5.2 mg, 6.3 mg, 7.6 mg, 9.1 mg, 11
mg, 13.3 mg
Applicant/Sponsor Name: Ascendis Pharma Endocrinology Division A/S
OSE RCM #: 2020-1429-1
DMEPA Safety Evaluator: Ebony Whaley, PharmD, BCPPS
DMEPA Team Leader: Millie Shah, PharmD, BCPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted draft Prescribing Information (PI) received on June 25, 2020 for Skytrofa. The Division of General Endocrinology (DGE) requested that we review the draft PI for Skytrofa (Appendix A) to determine if it is acceptable from a medication error perspective.

2 CONCLUSION

The PI is unacceptable from a medication error perspective. In the PI, the product strengths and dosing table are described using trailing zeroes. Additionally, each product strength is not followed by a unit of measure (e.g. "mg").

3 RECOMMENDATIONS FOR THE DIVISION OF GENERAL ENDOCRINOLOGY (DGE)

We recommend the following be implemented prior to approval of this BLA 761177:

Table 1: Identified Issues and Recommendations for Division of Endocrinology (DGE)			
	Identified Issue	Rationale for Concern	Recommendation
Highlights of Prescribing Information			
1.	The Dosage Forms and Strengths section contains trailing zeroes.	To avoid ten-fold misinterpretation, trailing zeros should be eliminated from dose expressions. ^a	Remove all instances of trailing zeroes in the Dosage Forms and Strengths section of the PI.
2.	Each numerical value in the Dosage Forms and Strengths section is not followed by units of measure.	Lack of units of measure may contribute to confusion and wrong dose errors.	Consider revising the Dosage Forms and Strengths section to ensure that each instance of product strength is followed by the unit of measure (e.g. "mg") to mitigate the risk of wrong strength errors.
Full Prescribing Information			
1.	See Highlights of Prescribing Information recommendations #1-2 and revise Section 3 Dosage Forms and Strengths, Table 1 in Section 2 Dosage and Administration, and Section 16.1 How Supplied accordingly.		
2.	Table 1 in Section 2 Dosage and Administration can be improved to clarify doses that require administration of two cartridges to complete a dose.	Confusion regarding dosing and the number of cartridges required for each dose might result in wrong dose errors.	Consider revising the statements ^{(b) (4)} to "XX mg using two XX mg cartridges". For example, revise ^{(b) (4)} to "15.2 mg using two 7.6 mg cartridges".

^a ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2015 [cited 2021 FEB 11]. Available from: <http://www.ismp.org/tools/errorproneabbreviations.pdf>.

APPENDIX A. LABEL RECEIVED ON JUNE 25, 2020

See link:

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/s/

EBONY A WHALEY
02/14/2021 12:53:53 PM

MILLIE B SHAH
02/16/2021 08:48:45 AM

MEMORANDUM

REVIEW OF RESPONSES TO HUMAN FACTORS RECOMMENDATIONS

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

Date of This Memorandum: January 27, 2021

Requesting Office or Division: Division of General Endocrinology (DGE)

Application Type and Number: BLA 761177

Product Name and Strength: Skytrofa^a (lonapegsomatropin-tcgd)^b for injection,
(b) (4)

Submission Date: January 22, 2021

Applicant/Sponsor Name: Ascendis Pharma Endocrinology Division

Panorama #: 2020-1499-1

DMEPA Safety Evaluator: Ebony Whaley, PharmD, BCPPS

DMEPA Team Leader: Millie Shah, PharmD, BCPS

DMEPA Associate Director for Human Factors (Acting): Lolita White, PharmD

DMEPA Associate Director for Nomenclature and Labeling: Mishale Mistry, PharmD, MPH

1 PURPOSE OF MEMO

On January 22, 2021, the Applicant submitted responses and clarifications to the Agency's recommendations regarding their human factors (HF) validation study methodology for Skytrofa (lonapegsomatropin) for injection BLA 761177 (See Appendix A). The responses and clarifications are in response to study methodology concerns that we identified in a previous HF memorandum.^{c,d} This memorandum provides our response to the Applicant.

^a The pending proprietary name Skytrofa was found acceptable on December 11, 2020.

^b The nonproprietary name suffix "-tcgd" was found conditionally acceptable on January 15, 2021.

^c Whaley E. Human Factors Memo for Skytrofa (BLA 761177). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 JAN 13. RCM No.: 2020-1429 2020-1499.

^d Kehoe, T. Information Request for Skytrofa (BLA 761177). Silver Spring (MD): FDA, CDER, OND, DGE (US); 2021 JAN 14.

2 CONCLUSION

We have provided responses to the Applicant's responses and clarifications in Section 3 below.

3 RECOMMENDATIONS FOR ASCENDIS PHARMA

We reviewed your responses and clarifications regarding our recommendations for your human factors (HF) validation study protocol methodology for Skytrofa (lonapegsomatropin) for injection BLA 761177. Please see the table below for our responses to your January 22, 2021 submission.

Original FDA Recommendation – Information Request dated January 14, 2021	Applicant’s Submission dated January 22, 2021	FDA Response to Applicant
Our review of your human factors (HF) validation study results report identified several deficiencies in your study methodology which preclude our ability to assess whether the HF validation study demonstrated that the proposed combination product user interface supports safe and effective use by the intended users, for the product’s intended uses and under the expected use conditions. We recommend you address the deficiencies listed below and conduct another HF validation study. We strongly encourage you to submit your revised HF validation study protocol for our review prior to commencing your study. We will review and provide comments within 60 days after receipt of your revised HF validation study protocol.	Do our explanations and/or description of our planned training program sufficiently address the concerns raised by the FDA about the methodology and applicability of the HF study for the commercial use? Do the HF study results in conjunction with clinical data from CT-301EXT provide sufficient reassurance that the product may be commercialized safely for patients without conducting a revised HF study prior to approval?	No. We continue to find that a new HF validation study is necessary to address the HF validation study methodology concerns we identified. As previously noted, we strongly encourage you to submit your revised HF validation study protocol for our review prior to commencing your study. We will review and provide comments within 60 days after receipt of your revised HF validation study protocol. See our additional responses below to specific deficiencies.
(b) (4)		We disagree with your rationale and continue to find (b) (4) is not reflective of real-world interaction with the user interface. For your new HF validation study, revise your study methodology to remove the (b) (4)

Original FDA Recommendation – Information Request dated January 14, 2021	Applicant’s Submission dated January 22, 2021	FDA Response to Applicant
represent real-world interaction with the user interface and may have impacted user performance. Revise your study methodology to remove the (b) (4)		
<i>Moderator script – training and leading language</i> The moderator script used in your study included leading language, which is not reflective of actual use. We note that untrained participants were given detail about the product (e.g., mixing time, how supplied) in the Device Description portion of the study that could be considered training. Additionally, in the Familiarization Period, participants were instructed to ensure they knew how to use the product before proceeding with testing and were also informed that the product is expensive and should not be wasted. Use of training and leading language might impact participant performance and bias the study results. Revise your study methodology to remove all instances of details in the use of the proposed product and leading language.	Training • Ascendis acknowledges the concerns regarding the untrained arm. • 06 Mar 2017, FDA wrote: "In the absence of data to support your assertion that all patients who receive growth hormone therapy receives training, there may be instances where some patients may not receive training prior to attempting to use the product for the first time" • However, Ascendis is implementing a thorough training program to train all patients and caregivers before use of the auto-injector with access to retraining as needed ○ The auto-injector is only available through our patient support program pharmacy, and the patient must be referred to us to receive the device ○ Patients will receive required training in-person or live virtual training (due to COVID-19) with a certified nurse educator. Training will be documented. ○ Prescribing healthcare providers will be notified if recipients have not completed training within one week Training procedure • Upon commercialization, the auto-injector will ONLY be available through our patient support program pharmacy. All patients prescribed lonapegsomatropin will need a valid prescription to receive the auto-injector and that prescription must be received by our patient support program pharmacy. This is handled via an enrollment form or statement of medical necessity which includes patient demographic info, prescriber	We acknowledge your plan to utilize a training program for your commercial product. However, in the absence of a regulatory mandate (e.g. REMS), it is not guaranteed that training will routinely and consistently occur for each user. As such, we continue to recommend that you revise your study methodology to remove all instances of details in the use of the proposed product and leading language.

Original FDA Recommendation – Information Request dated January 14, 2021	Applicant’s Submission dated January 22, 2021	FDA Response to Applicant
	details, and the prescription. Therefore, no patients will receive the auto-injector without being offered injection training support • The patient support program nurse will contact the patient to coordinate shipment of the auto-injector and schedule injection training. Included in the shipment will be the IFU and a QR Code to the auto-injector/ injection training video • Field-based nurses, certified by our internal team, will conduct training at the patient’s home/or other location. Others may choose virtual training (due to COVID-19) which will be handled by the same team of field-based nurses via videoconferencing • The program will also offer auto-injector support via a 24-7 hotline • Specialty pharmacy partners will also be trained on the device and certify their training staff • Training will be documented by the certified nurse educator and the family member	
<i>Injection attempt methodology</i> We note that your study allowed for participants to complete a second injection attempt if they failed or believed they failed the first injection attempt; however, the methodology of analyzing the use errors/difficulties/close calls can be improved. Specifically, we note that if participants failed the first injection attempt, the root cause analysis (RCA) for the first injection attempt was not performed until after the second injection attempt. This methodology may have caused participants to be biased by the second injection attempt and/or not	• As this is a repeated use product, it was necessary to evaluate whether a use deviation negatively affected the dose the patient received (in the first trial) was a single event or would become a chronic event • Use issues related to repeated use may not be seen or may be biased by the act of RCA if performed prematurely (i.e. after the first trial) ○ Thus, we would not be able to draw conclusions regarding the 4 participants that had to perform a second trial ▪ All 4 participants completed the Trial 2 successfully. A premature RCA after Trial 1 could alter their behavior on the Trial 2.	We note that the purpose of the second attempt is to evaluate whether the user repeated the error or learned from their first attempt, given that the product is a chronic use medication. Therefore, we acknowledge your concern regarding the timing of RCA and the potential impact to user performance for second injection attempts. If the purpose of the second attempt is to demonstrate learning, then the study should be appropriately designed to be representative of real-world use. For example, you should incorporate a decay period between the first and

Original FDA Recommendation – Information Request dated January 14, 2021	Applicant’s Submission dated January 22, 2021	FDA Response to Applicant
be able to recall clearly why the use errors/difficulties/close calls occurred during their first injection attempt. Revise your study methodology such that RCA is performed after each injection attempt for every use error, close call, and use difficulty.		second injection attempts as the proposed product is administered once weekly. Alternatively, if the focus of this use scenario is not designed to demonstrate learning over time, we continue to recommend that RCA should be performed after each injection attempt for every use error, close call, and use difficulty.
<i>Two-cartridge use scenario</i> We find that your study protocol is not comprehensive because it does not assess the use scenario where a user needs to administer two injections to administer a full dose. For example, patients weighing greater than or equal to 60.5 kg must administer two cartridges (two injections) to complete a full dose. We expect your study to assess all potential use scenarios for your proposed product. As such, revise your protocol to include assessment of the two-cartridge dosing scenario.	• 125/135 participants successfully administered the dose on the first attempt, and the remaining 10 by the second attempt • Our assumption is that if a successful administration was observed during the first attempt, then participant would be successful in completing subsequent administrations • A physician’s prescription would indicate whether 2 cartridges/week is required ○ Similar to a physician’s prescription to take 2 tablets of a medication • In CT-301EXT, 11/160 US subjects are currently using 2 cartridges/week ○ 9/11 subjects were using 2 cartridges/week at the time of the 01 JUN 2020 data cut for the Day 120 Safety Update ○ There have been no helpline calls about two-cartridge use issues in the CT-301EXT trial	Please note that our concern is that your HF study methodology did not assess users’ understanding of the scenario in which consecutive administration of two injections is required to complete a dose. As such, your study results did not provide data to support that users understand that there are dosing regimens that require two consecutive injections to complete a dose. We continue to recommend that you revise your study protocol to include an assessment of the two-cartridge (two injection) dosing scenario.
<i>Training video</i> We identified subjective feedback from participants in your HF validation study	• Ascendis conducted several formative studies to develop the training video ○ 2 internal formative usability studies (N=9 and N=6) were conducted to test the effectiveness of the video in training users	We continue to recommend that you ensure the training video is optimized and aligns with the labeling. If your new HF validation study identifies

Original FDA Recommendation – Information Request dated January 14, 2021	Applicant’s Submission dated January 22, 2021	FDA Response to Applicant
results report which indicated that some participants were confused by the training video. Specifically, we note participants indicated confusion with the following portions of the training video: inspecting the autoinjector and the timing of the mixing process. Confusion regarding the training video might impact participant performance and study results. As such, based on the subjective feedback, ensure that the training video is optimized to mitigate the risk of user confusion.	how to use the product (in the HFE report in BLA Module 5.3.5.4) ○ Positive feedback from study participants on the helpfulness of the video ● 3 validation study participants expressed confusion about different aspects of the video ▪ (b) (6): Believed he would be able to start the manual mixing quickly because the video made it seem like the automatic mixing was completed quickly, but he also recalled that the progress bar was supposed to be complete before moving on (which prevented him from going too quickly) ▪ (b) (6): Device sounds from the video, which were playing simultaneous to when she was performing the task, caused difficulty for her in detecting the sounds expected from her device ▪ (b) (6): The zoomed-in views led to the belief that emphasis was on plunger movement, not drug inspection ○ The subjective feedback did not reveal any consistent patterns of confusion regarding the video ○ All 3 participants were untrained; any confusion caused by the video will be clarified during training ○ For commercial use, video will be introduced in the supervised training by a certified nurse educator	subjective feedback indicating confusion with the training video, we expect the feedback is addressed and you consider whether the training video can be further improved.
<i>Post-validation revisions to user interface</i> We note you implemented revisions to components of the user interface (i.e., instructions for use [IFU] and quick reference guide [QRG]) following the completion of the HF validation study.	● The revisions to components of the user interface and IFU were summarized in MAPD2012a IDA0067 Summary of IFU Changes 2.00 submitted with MAF3239 Amendment 1 (per the Agency’s request, the Applicant submitted the Summary of IFU Changes document to the eCTD in 5.3.5.4).	A critical task is a user task which, if performed incorrectly or not performed at all, would or could cause harm to the patient or user, where harm is defined to include

Original FDA Recommendation – Information Request dated January 14, 2021	Applicant’s Submission dated January 22, 2021	FDA Response to Applicant
The revisions impact critical tasks. We note that these revisions to the user interface were not evaluated in a subsequent HF validation study to ensure that they mitigate the errors observed and do not introduce new risks. As such, the revised, to-be-marketed user interface should be validated in the new HF validation study.	• The summary lists all changes mentioned in Table 1 in the HFE-report (BLA Module 5.3.5.4). It includes a justification for each change, a rationale for the changes, and whether the critical task performance of the completed usability validation would be impacted • None of the changes are impacting critical tasks to an extent that requires re-evaluation of the usability validation • Applicant question: Could the Agency clarify what changes to the user interfaces (ie., IFU and QRG) would impact critical tasks?	compromised medical care.^e For example, your use-related risk analysis indicates that failure to correctly manually mix the autoinjector by inverting it 5-10 times might result in underdose due to poor reconstitution of drug. As such, we consider the manual mixing task to be a critical task. If after conducting your new HF validation study, you implement additional revisions to components of the user interface that impact critical tasks, provide information or data to support that the proposed revisions are effective and do not introduce new risks.

^e Draft Guidance for Industry and FDA Staff: Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development. Food and Drug Administration. 2016. Available from <https://www.fda.gov/media/96018/download>.

APPENDIX A.

See EDR links:

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

Date of This Memorandum: January 13, 2021
Requesting Office or Division: Division of General Endocrinology (DGE)
Application Type and Number: BLA 761177
Product Name and Strength: Skytrofa^a (lonapegsomatropin) for injection,
(b) (4)
Submission Date: July 13, 2020
Applicant/Sponsor Name: Ascendis Pharma Endocrinology Division
Panorama #: 2020-1429; 2020-1499
DMEPA Safety Evaluator: Ebony Whaley, PharmD, BCPPS
DMEPA Team Leader: Millie Shah, PharmD, BCPS
DMEPA Associate Director for Human Factors (Acting): Lolita White, PharmD
DMEPA Associate Director for Nomenclature and Labeling: Mishale Mistry, PharmD, MPH

1 PURPOSE OF MEMO

This memorandum provides our preliminary evaluation of the human factors (HF) validation study results report for Skytrofa (lonapegsomatropin), BLA 761177 submitted on July 13, 2020. This is a combination product with a proposed autoinjector device constituent part that is

(b) (4)
Skytrofa is administered as a once weekly subcutaneous injection and is supplied with a (1) single dose, dual-chamber glass cartridge containing lyophilized lonapegsomatropin powder and the diluent and (2) a reusable

^a The pending proprietary name Skytrofa was found acceptable on December 11, 2020.

autoinjector. The intended users of Skytrofa include pediatric patients, caregivers, and healthcare providers (HCPs).

2 DISCUSSION AND CONCLUSION

We evaluated the HF validation study results report for Skytrofa and identified concerns with the study methodology. There are multiple study methodology deficiencies that preclude our ability to assess whether the HF validation study demonstrates that the proposed combination product user interface supports safe and effective use by the intended users, for the product's intended uses and under the expected use conditions. We note that we reviewed the HF validation study protocol for the proposed product under IND 126053.^{bc} However, additional revisions were made to the study methodology that were not included as part of our previous reviews of the HF validation study protocol. Thus, based on the identified deficiencies, we recommend that the Applicant revise and submit their HF validation study protocol for Agency review, and conduct another HF validation study. We have provided letter ready comments for the division to incorporate as part of their communication to the Applicant (see *Section 3*).

3 RECOMMENDATIONS FOR ASCENDIS PHARMA

Our review of your human factors (HF) validation study results report for your BLA 761177 lonapegsomatropin for injection identified several deficiencies in your study methodology which preclude the Agency's ability to assess whether the HF validation study demonstrated that the proposed combination product user interface supports safe and effective use by the intended users, for the product's intended uses and under the expected use conditions. We recommend you address the deficiencies listed below and conduct another HF validation study. We strongly encourage you to submit your revised HF validation study protocol for Agency review prior to commencing your study. We will review and provide comments within 60 days after receipt of your revised HF validation study protocol.

HF validation study methodology deficiencies

- (b) (4)
1. Your study protocol allowed for participants (b) (4)
(b) (4)
This study methodology does not represent real-world interaction with the user interface

^b Vee, S. Human Factors Protocol Review for TransCon Human Growth Hormone IND 126053. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 MAR 3. RCM No.: 2017-79.

^c Ogbonna, C. Human Factors Protocol Review for TransCon Human Growth Hormone IND 126053. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 MAY 1. RCM No.: 2018-533.

and may have impacted user performance. Revise your study methodology to remove (b) (4).

B. Moderator script – training and leading language

1. The moderator script used in your study included leading language, which is not reflective of actual use. We note that untrained participants were given detail about the product (e.g., mixing time, how supplied) in the Device Description portion of the study that could be considered training. Additionally, in the Familiarization Period, participants were instructed to ensure they knew how to use the product before proceeding with testing and were also informed that the product is expensive and should not be wasted. Use of training and leading language might impact participant performance and bias the study results. Revise your study methodology to remove all instances of details in the use of the proposed product and leading language.

C. Injection attempt methodology

1. We note that your study allowed for participants to complete a second injection attempt if they failed or believed they failed the first injection attempt; however, the methodology of analyzing the use errors/difficulties/close calls can be improved. Specifically, we note that if participants failed the first injection attempt, the root cause analysis (RCA) for the first injection attempt was not performed until after the second injection attempt. This methodology may have caused participants to be biased by the second injection attempt and/or not be able to recall clearly why the use errors/difficulties/close calls occurred during their first injection attempt. Revise your study methodology such that RCA is performed after each injection attempt for every use error, close call, and use difficulty.

D. Two cartridge use scenario

1. We find that your study protocol is not comprehensive because it does not assess the use scenario where a user needs to administer two injections to administer a full dose. For example, patients weighing greater than or equal to 60.5 kg must administer two cartridges (two injections) to complete a full dose. We expect your study to assess all potential use scenarios for your proposed product. As such, revise your protocol to include assessment of the two cartridge dosing scenario.

E. Training video

1. We identified subjective feedback from participants in your HF validation study results report which indicated that some participants were confused by the training video. Specifically, we note participants indicated confusion with the following portions of the training video: inspecting the autoinjector and the timing of the mixing process. Confusion regarding the training video might impact participant performance and study results. As such, based on the subjective feedback, ensure that the training video is optimized to mitigate the risk of user confusion.

F. Post-validation revisions to user interface

1. We note you implemented revisions to components of the user interface (i.e., instructions for use [IFU] and quick reference guide [QRG]) following the completion of the HF validation study. The revisions impact critical tasks. We note that these revisions to the user interface were not evaluated in a subsequent HF validation study to ensure that they mitigate the errors observed and do not introduce new risks. As such, the revised, to-be-marketed user interface should be validated in the new HF validation study.

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MEMORANDUM

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

Date: 12 January 2021

To: Marina Zemskova MD, Clinical Team Leader
Division of General Endocrinology (DGE) / Office of Cardiology, Hematology,
and Endocrinology (OCHEN) / CDER

Sejal Kiani, Regulatory Healthy Project Manager
DGE / OCHEN / CDER

Through: Teresa Buracchio MD, Deputy Director
Division of Neurology 1 (DN1) / Office of Neuroscience (ON) / CDER

From: David A Hosford MD PhD, Medical Reviewer
DN1 / ON / CDER

Subject: Consult to DN1 for BLA 761,177 (lonapegsomatropin [REDACTED]) (b) (4)
[REDACTED]

Sponsor: Ascendis Pharma AS (Copenhagen, Denmark)

Materials Reviewed:
DGE Consult to DN1
Applicant's Clinical Overview
Applicant's Summary of Clinical Safety
Applicant's Integrated Summary of Safety (relevant tables and listings)
DGE Nonclinical Filing Review
DGE Clinical Pharmacology Filing Review
DGE Biometrics Filing Review
DGE Clinical Filing Review

DGE Clinical Review of Applicant's Priority Request
 DGE Mid-Cycle Review
 IRT Consult from DGE
 FDA Reviews and Documents Regarding BLA 125,611 (Rebinyn)
 Relevant Biomedical Literature (see reference list)

I. Background on ACP-011 and its Clinical Development

Ascendis Pharma AS is developing ACP-011 (lonapegsomatropin), a long-acting pro-drug of recombinant human growth hormone (rhGH; or somatropin), (b) (4)

Lonapegsomatropin consists of somatropin that is conjugated to 4 X 10kDa methoxypolyethyleneglycol (mPEG) (i.e., 4 strands of mPEG, each of 10kDa, for a total mPEG molecular weight of 40kDa) via a proprietary TransCon linker. After ACP-011 is administered, mPEG and the linker are cleaved from somatropin. The applicant intends for the product to be administered in the marketplace using an auto-injector to deliver a once-weekly SC injection.

The applicant has submitted data from four completed trials, two in healthy adults and three in children with Growth Hormone Deficiency (GHD). The two largest completed trials in the target population are: CT-301, a 52-week randomized, active-controlled study of ACP-011 delivered SC once-weekly (n = 105) vs. genotropin (somatotropin) delivered SC once-daily (n = 56); and CT-302, a 26 week open-label, uncontrolled study of ACP-011 (n = 146). A fifth study, CT-301EXT, is an open-label, uncontrolled extension study of ACL-011 for children who have completed CT-301 or CT-302. There were 296 children enrolled in this trial as of the cut-off date of 9/30/19. At the time of this cut-off date, 378 subjects (305 children with GHD and 73 healthy adults) had been exposed to ACL-011, with 252 children exposed for at least one year.

II. Regulatory Background on ACP-011

The following list shows FDA interactions with the applicant and/or milestones reached during the development of ACL-011 for this indication.

- a. PIND meeting with DGE in June 2015
- b. IND 126,053 opened in September 2015
- c. End of Phase 2 meeting in July 2016
- d. Fast Track Designation Request denied on 9/3/19
- e. Pre-BLA meeting in December 2019
- f. Orphan Drug Designation on 4/14/20
- g. BLA 761,177 submitted on 6/25/20 and filed on 8/24/20; Priority Review denied
- h. Proprietary Name Granted on 12/11/20 (Skytrofa)
- i. Action Goal Date in June 2021

III. Reason for Consult to DN1

In nonclinical repeat-dose toxicology studies of ACL-011 in the rat (26-week once-weekly SC

dosing and 26-week recovery period) and in the juvenile monkey (26-week and 52-week once-weekly SC dosing and 26-week recovery periods), intracellular vacuoles that stained positively for mPEG were identified in choroid plexus epithelial cells and in choroid plexus interstitial macrophages. Immunostaining was also identified in the cytoplasm of ependymal cells and specialized glial cells in the median eminence and infundibulum, and in ependymal cells lining the third and sometimes the fourth ventricle. All animals with these findings were asymptomatic during the studies. Per FDA's clinical pharmacology staff, the NOELs for these studies, which were defined as the highest tested dose that did not produce choroid plexus findings, is predicted to have a safety margin of approximately two-fold the highest clinical doses used in the trials of ACL-011.

DGE has requested that DN1 evaluate the following:

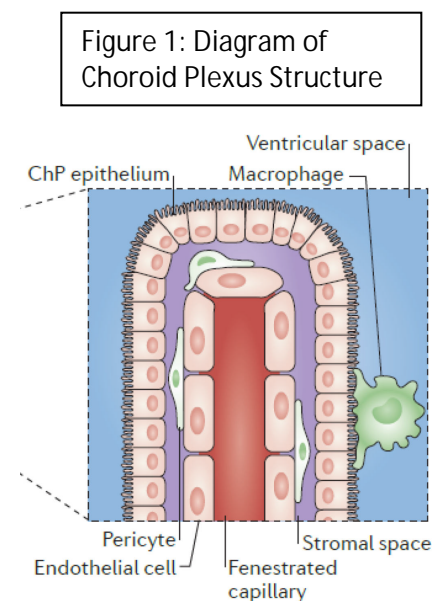
1. the potential risk associated with accumulation of mPEG in the brain including the type of known and/or expected adverse events associated with vacuolation of epithelial cells within the choroid plexus and/or mPEG accumulation in the brain;
2. and whether the pediatric population is at increased risk for the neurologic deficits, etc.

IV. Review of Choroid Plexus Function and Choroid Plexus Vacuolation Observed after Treatment with Other Pegylated Compounds

A. Structure and Function of the Choroid Plexus

The choroid plexus (ChP) is a brain structure that is highly conserved from some chordate invertebrates (e.g., the lancelet) through all vertebrates (Bill and Korzh, 2014; Lun et al., 2015). The ChP lines each of the cerebral ventricles, and it is comprised of cuboidal epithelial cells that are joined by tight junctions. The basement membranes of the ChP epithelial cells surround a matrix of fenestrated capillaries, and hence the ChP forms a barrier between the cerebrospinal fluid (CSF) and the intrastromal capillaries. The ChP is sometimes termed the blood-CSF barrier (Lun et al., 2015, including the figure to the right), and it can be likened to a semipermeable membrane that separates the blood from the CSF.

There are at least four principal functions of the ChP. First, the fenestrations between the capillary endothelial cells facilitate the delivery of water, ions, proteins, and other vascular constituents to the epithelial cells of the ChP, and the epithelial cells take up and use these constituents to form the majority of CSF that is secreted into the intraventricular space (Lun et al., 2015). Second, ChP epithelial cells also express and secrete proteins such as transthyretin, which transports thyroxin into the CSF, and these cells also regulate the transport of ferritin-bound iron and free iron from the vasculature into the CSF (Lun et al., 2015; Deane et al., 2004). Third, the



ChP facilitates brain signaling by producing and secreting Insulin-like Growth Factor 2 (IGF2), myo-inositol, fibroblast growth factors, retinoic acid, and other growth signaling factors (Lun et al., 2015). A fourth and recently identified function of the ChP is to regulate adult neurogenesis by releasing external factors that cause the differentiation of neural stem cells within the subventricular zone of the ventricles into neuroblasts (Lun et al., 2015). This fourth function may turn out to be critically important in helping the adult brain to recover following neuronal injury.

B. Choroid Plexus Vacuolation Observed in Nonclinical Studies after Administration of Pegylated Compounds

Although the ChP is essentially intact at birth, the functions that are described above undergo changes during the lifecycle of the nonclinical vertebrates that have been studied. It is therefore possible that injury to the ChP epithelial cells at any time during the lifecycle of a vertebrate may alter brain function, even in a fully developed organism. In this context, the recognition of vacuolation in ChP epithelial cells following the administration of pegylated compounds in nonclinical studies is of potential concern as regards the administration of these compounds to patients.

Vacuolation in renal tubular cells after the administration of pegylated compounds in nonclinical studies has been described for several decades (e.g., Bendele, 1998). Rudmann and colleagues (2013) studied a variety of pegylated compounds in a nonclinical study in rats, and they found that as the mPEG molecular weight of these compounds increased, that vacuolation was also found in other tissues including the ChP. Indeed, ChP vacuolation and the presence of positive PEG-staining in ChP epithelial cells were observed in nonclinical toxicology studies that were conducted during the development program for 5 out of 12 FDA-approved pegylated compounds (reviewed by Turecek et al, 2016). It was reported that there were no apparent clinical signs of ChP vacuolation or mPEG accumulation in these nonclinical studies, and it has been suggested that vacuolation in ChP epithelial cells and in cells of other tissues may be a biological phenomenon that accompanies the clearance of PEG from these tissues (Turecek et al., 2016).

Please note that DN1's nonclinical reviewer, Dr. David B. Hawver, will review these nonclinical findings in much greater detail in a separate consult review.

C. Summary of Clinical Findings in Clinical Trials of Approved Pegylated Compounds

In order to study the possible clinical consequences of ChP vacuolation in patients, one must first identify a list of FDA-approved pegylated compounds. This reviewer found it difficult to identify all FDA-approved pegylated products. Combining results obtained via the search engines developed by FDA, PubMed, and Google, it appears that at least two dozen pegylated drug products have been approved for use in a variety of indications and age groups. Each of these products is pegylated with one or more (up to 40) strands of mPEG, with a total mPEG molecular weight ranging from approximately 400 daltons (Da) to approximately 400kDa.

At least six of these approved products were noted to have ChP vacuolation that was observed in the nonclinical toxicology studies that were submitted in their marketing applications. Five of these products were cited and described by Stidl and colleagues (2018), and a newer product (Rebinyn) was identified in the FDA database. Because Stidl and co-authors were all employees in the biopharmaceutical industry, this reviewer verified the nonclinical findings of ChP vacuolation per label of each product, and then examined the CNS adverse events that were described in the clinical studies submitted in the approval packages. Table 1, below, briefly lists pertinent details of this evaluation. Unless otherwise indicated, all products are approved for adults only, and the products are administered SC.

Table 1. Six FDA-Approved Pegylated Drug Products

Product Brand, Name and Year Approved, Age group	Product mechanism and indication(s)	Total mPEG molecular weight	CNS findings
Somavert 2003 Adult	Growth hormone antagonist Approved for acromegaly	24 – 30 kDa	No CNS TEAEs occurred in a greater proportion of active vs. placebo group
Macugen 2004 [NOTE: administered intravitreally]	Aptinib, an aptamer Approved for age-related macular degeneration	40kDa	Only eye-associated TEAEs reported
Cimzia 2008 Adults	TNF-alpha blocker Approved for rheumatoid arthritis, Crohn's, psoriasis	40kDa	Class warning for demyelinating disease (includes signs of seizures, Anxiety, bipolar disorder, suicide attempt in 1 placebo-controlled Crohn's study (no details provided). Headache in 3.4% CIMZIA vs. 2.5% placebo. "Rare seizures, optic neuritis, peripheral neuropathy" (no details provided in label)
Krystexxa 2010 Adults [NOTE: administered IV]	Recombinant uricase protein Approved for gout	Approximately 400kDa	No common CNS AEs more frequent with active drug vs. placebo

Omontys 2012 Adults [NOTE: can be given SC or IV]	Erythropoiesis stimulating agent Approved for anemia due to chronic kidney disease in dialysis patients	40kDa	No common CNS AEs Rare seizures reported in patients undergoing dialysis
Rebinyn 2017 Adults and Children Children 1 – 12 years: n = 25 Adolescents 13-17 years: n = 18 Adults: n = 62 Total: n = 105	Recombination coagulation factor IX Approved for hemophilia B NOTE: only on demand for bleeding episodes, or treatment of perioperative bleeding	40kD	Per label, no CNS AEs reported at $\geq 1\%$. Because there were only 105 subjects studied, this indicates that there were no CNS AEs; a single event would be a proportion of 1%.

In the six approved pegylated products that had findings of ChP vacuolation in nonclinical toxicology studies, the only common (i.e., > 1%) CNS events (neurologic or psychiatric) that were reported in a greater proportion of subjects treated with the product than with the comparator were headache, dizziness, tic, and enuresis. Rare seizures were reported in Omontys-treated subjects with CKD while they were undergoing dialysis, but seizures are relatively common in patients with CKD during dialysis (e.g., reported as 8% by Glenn et al., 1992). Rare seizures were also reported in subjects treated with Cimzia, a TNF-alpha blocker. The occurrence of seizures in Cimzia-treated subjects is not clearly associated with the pegylation of this product because seizures have been reported as adverse events during treatment with other TNF-alpha blockers, none of which are pegylated except for Cimzia (Bechtel et al., 2009). The other CNS AEs reported in the Cimzia label included rare optic neuritis, bipolar disorder, anxiety, and a suicide attempt. No details for any of these events were provided.

In considering the occurrence of CNS TEAEs in children, only the studies of Rebinyn in hemophilia B in children and in adults are informative, because no other approved pegylated product caused ChP vacuolation in the nonclinical package of studies for products that are approved for use in children. There were no CNS events (neurologic or psychiatric) in these studies of Rebinyn. However, a caveat is that there were only 43 subjects in the age range of 1 – 18 years, and only 25 of these subjects were in the age range of 1 – 12 years.

D. Is the Pediatric Population at Greater Risk for ChP Vacuolation after Administration of

Pegylated Compounds?

In 2012, The CHMP Safety Working Group of the EMA considered this question by reviewing EU-marketed pegylated drugs that were accompanied by nonclinical toxicological findings of ChP vacuolation (EMA, 2012). The authors noted that ChP vacuolation was observed only if four criteria were met:

1. the study was conducted in Cynomolgus monkeys;
2. a PEG moiety size of at least 40 kDa was applied;
3. the study was at least of 6 weeks duration;
4. the administered dose gave rise to at least a monthly PEG exposure of 0.4 $\mu\text{mol/kg/month}$ (PEGylated human growth hormone).

Based upon these observations, the CHMP Safety Working group (EMA, 2012):

“recommended that before conducting clinical trials of more than 4 weeks duration with a PEGylated drug product, the applicant should address:

- whether ependymal cell vacuolation has been observed in the non-clinical studies;
- whether the PEGylated drug product may undergo active transport across the blood-CSF barrier e.g. via a literature review elucidating to what extent there is a physiological role for active transport of the pegylated protein into the CSF;
- the biodistribution of the PEGylated drug product via applying a method enabling detection of the PEG moiety unless the monthly PEG exposure is significantly lower than the cases where ependymal cell vacuolation has been observed ($\geq 0.4 \mu\text{mol/kg/month}$).”

The Safety Working Group concluded with the following recommendation (EMA, 2012).

“In case ependymal vacuolation is observed in the non-clinical studies for a drug product intended for long-term treatment, paediatric development should only be initiated in case a sufficiently large safety margin can be established in a long-term toxicity study applying animals representative for the paediatric population in question and the finding can be demonstrated to be reversible. If feasible, ex vivo/in vitro data evaluating the effect of PEG vacuolation on the viability and function of choroid plexus ependymal cells could contribute to the risk assessment process.”

E. Application of These Principles to the FDA Review of Rebinyn (BLA 125,611)

Rebinyn was developed for use in patients (adults or children) with hemophilia B. After the BLA for Rebinyn (Coagulation Factor IX (Recombinant), GlycoPEGylated) was submitted to FDA on 5/16/16, the potential safety concern about ChP vacuolation that was observed in cynomolgus monkeys and in rat during the product's nonclinical studies was discussed in great detail. Special consideration was given to the potential safety risk of ChP vacuolation in the pediatric age group, if the product were to be approved for that group.

The following images were included in the review by the FDA's consultant neuropathologist in then-DPP, Dr. Deepa Rao (Rao, 2017). The images show the immunohistochemical (IHC) staining of PEG in ChP epithelial cells (Fig. 2 [green staining]), and the presence of ChP epithelial cell vacuolation as imaged by electron microscopy (Fig. 3 [vacuoles labeled "3" on right side]).

Figure 2. Light microscopic images with green-IHC staining in ChP Epithelial Cells

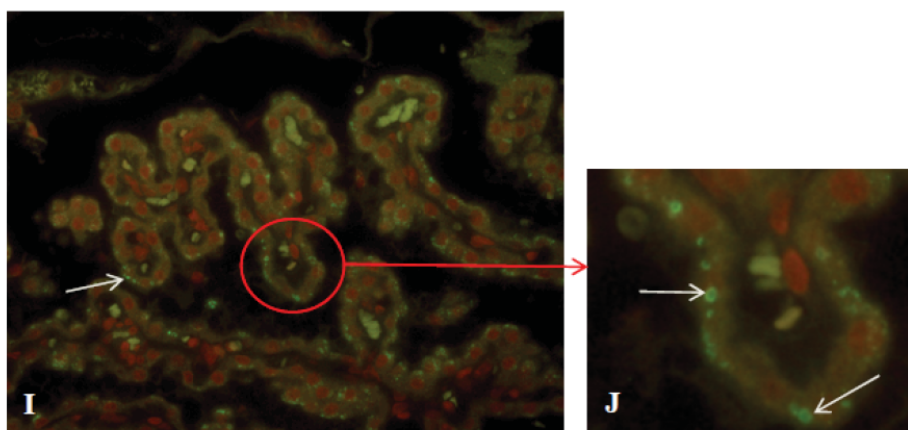


Figure 3 Detection of PEG in nude rat choroid plexus epithelial cells, 26 weeks dosing of NNC156-0009/kg/5th day and 26 weeks off treatment

Immunohistochemical staining of PEG (white arrow) in the cytoplasm of the epithelial cells in choroid plexus, 1200 IU (I) NNC0156-0009/kg/5th day followed by 26 week off treatment. J is digital enlargements of the area of interest in figs I (Images I was taken with a 60x objective) (green = PEG and red = nuclei staining)

Figure 3. Electron micrographic images showing ChP epithelial cell vacuolation (labeled "3" on right side)

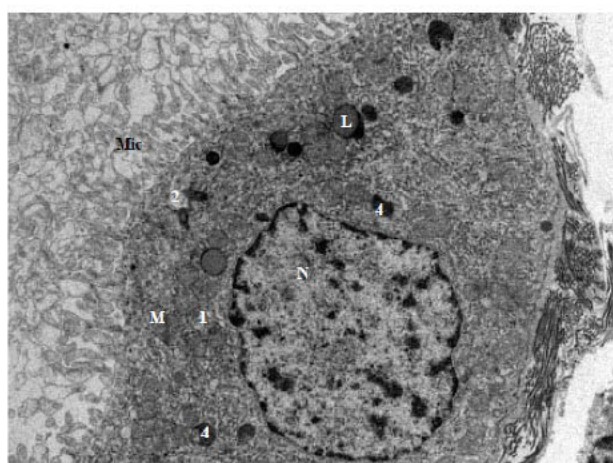


Figure 3 CP epithelial cell from a nude control rat treated with vehicle for 26 weeks
A choroid plexus epithelial cell from a Rowett Nude rat in the vehicle control group.
N = nucleus, M = mitochondria, L = lipid droplet, Mic = microvilli
Type 1 = rER, Golgi vesicles, mucinous content
Type 2 = undefined. Probably mucin droplets
Type 4 = "dense body" lysosome and lysosome related lipofuscin

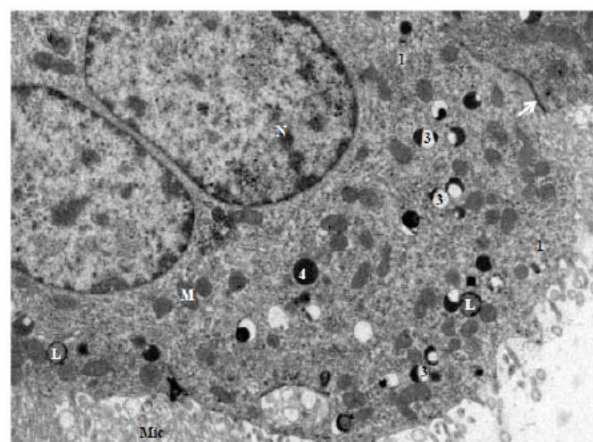


Figure 4 Choroid plexus epithelial cell from a nude rat treated with 1200IU nonacog beta pegol for 26 weeks
A choroid plexus epithelial cell from a Rowett nude rat treated with 1200IU nonacog beta pegol/kg/fifth day.
N = nucleus, M = mitochondria, L = lipid droplet, Mic = microvilli
Type 1 = rER, Golgi vesicles, mucinous content
Type 3 = PEG vesicles (verified by immunohistochemistry)
Type 4 = "dense body" lysosome and lysosome related lipofuscin

There were reportedly no signs that could be attributed to ChP epithelial cell vacuolation in these nonclinical studies. These studies will be reviewed in greater detail in the consult review from my FDA colleague in DN1's nonclinical staff, Dr. David B. Hawver.

As cited in Table 1, there were no CNS AEs that were reported in the submitted studies of Rebinyn, with the caveat that only 43 of the total exposed population of 105 were in the pediatric age range (1-18 years), and only 25 were in the age group of 1 – 12 years.

The clinical reviewer, Dr. Megha Kaushal, summarized these data and made the following recommendations (Kaushal, 2017).

“No clear safety signal that could be attributed to the accumulation of PEG was observed in the clinical trials. Upon review of the data, it is unclear whether monitoring of neurologic function in the clinical studies was adequate to detect all clinically important neurologic signs or symptoms. In addition, it is unclear whether the size of the safety database (i.e., number of adult and/or pediatric subjects exposed to the product; duration of follow-up of those subjects) was sufficient to assess the safety of the product.

“Due to these uncertainties, a Blood Product Advisory Committee (BPAC) was held on April 4th, 2017. Based on their discussion, the majority of the AC members suggested a post-marketing study to be conducted which would assess neurologic and neurocognitive parameters in a standardized approach. The particular metrics in these assessments were not discussed by the committee or by the applicant. Some of the committee members recommended restricting the routine prophylaxis indication to only pediatric subjects above 2 years of age, while others stated that an arbitrary age cut offs should not be used. All of the committee members agreed that short-term use (on demand treatment and perioperative use) of the study drug was not concerning. The committee members agreed that premarketing approval studies would be useful; however, post-marketing studies may be sufficient to collect more safety data with respect to neurocognitive function in patients.

“Based on the review of the submitted clinical data, discussion at the BPAC, discussion with the entire review team, and with CBER upper management, the recommendation for this original biologic application is to approve the following indications for all age groups:

- a) on-demand treatment and control of bleeding [episodes];
- b) perioperative management” (Kaushal, 2017, Executive Summary).”

Rebinyn was approved for adults and children with these indication restrictions on 5/31/17. A post-marketing requirement (PMR) for a dedicated clinical trial to assess the potential risk related to mPEG accumulation was considered. However, no PMR was issued for numerous reasons, including the difficulty of obtaining baseline data collection from subjects before

they are already using Rebinyon for one of the two indicated reasons.

V. Review of Adverse Events Reported in Clinical Trials of ACP-011 (lonapegsomatropin)

A. Description of Clinical Trials in this BLA and any Reported CNS TEAEs

ACP-011 produced ChP epithelial cell vacuolation in nonclinical studies. My FDA colleague, Dr. David B. Hawver, will review these findings in greater detail in his consult review.

Of the studies submitted in BLA 761,177 for ACP-011, five clinical trials were completed or ongoing as of the cut-off date of 9/30/19. In these studies, 378 individuals were exposed to ACP-011 (305 children with growth hormone deficiency (GHD) and 73 healthy adults). In the two clinical trials that had been completed (CT-301 and CT-302) and the third clinical trial that was ongoing (CT-301EXT), 252 children with GHD were exposed to ACP-011 for at least 52 weeks.

CT-301 was a 52-week randomized, unblinded, comparator-controlled trial in which 105 children with GHD were treated with ACP-011 SC once weekly, and 56 children with GHD were treated with the active comparator, Genotropin (somatotropin) SC once daily. This is a particularly informative study, because ACP-011 is pegylated, whereas Genotropin is not pegylated. This reviewer examined ISS table 4.2.2 to identify CNS TEAEs (neurologic or psychiatric) that were reported in at least two subjects and at a greater rate in the ACP-011 group than the Genotropin group in study CT-301, or in its open-label extension study, CT-301EXT (see description below). Four CNS events met these criteria (preferred terms shown):

1. headache (13% ACP-011 vs. 4% Genotropin);
2. dizziness (3% ACP-011 vs. 2% Genotropin);
3. tic (2% ACP-011 vs. 0% Genotropin);
4. enuresis (2% ACP-011 vs. 0% Genotropin).

There were two neurologic SAEs that occurred in a single subject who completed this study and enrolled into CT-301EXT. These events are described further below.

CT-302 was an open-label uncontrolled trial in which 146 children with GHD were treated with ACP-011 for 26 weeks. Per ISS table 4.2.2, CNS TEAEs (neurologic or psychiatric) that were observed in at least two subjects (i.e., > 1% of the group) in CT-302 or while these subjects continued in ongoing CT-301EXT included six events (preferred terms shown):

1. headache (12%)
2. dizziness (2%)
3. migraine (2%)
4. insomnia (3%)
5. anger (1%)
6. anxiety (1%)

CT-301EXT is the ongoing open-label extension study that is available for enrollment of any subject who completed studies CT-301 or CT-302. As of the cut-off date, 296 children with GHD were enrolled. All CNS TEAEs that occurred in at least two subjects in CT-301EXT are reported above under their parent studies, CT-301 or CT-302.

There was an additional subject (b) (6) in CT-301EXT who had two neurologic SAEs that occurred: generalized tonic-clonic seizure (preferred term) after 930 days of treatment; and epilepsy (preferred term) after 973 days of treatment. This subject's past medical history included GHD, orchidopexy, asthma, oral surgery, and a functional cardiac murmur. The concomitant medications included Combivent (for asthma) and multivitamins. The subject was treated with a single dose of lorazepam (0.5mg IV) after the first event of generalized tonic-clonic seizure. ACP-011 was not discontinued. A treatment for the second event of epilepsy is shown to have been administered, but the treatment is not listed. ACP-011 was not discontinued. The details presented were sourced from ISS Listings 4.2, 3.1, and 3.2.

B. Reviewer's Interpretation of Reported CNS Events in this BLA

Only headache occurred in a clearly greater proportion in the group treated with ACP-011. In the randomized, comparator-controlled study CT-301 or in CT-301EXT, it occurred in 13% of the ACP-011 group and in 4% of the Genotropin group. Headache occurred in approximately the same proportion of subjects (12%) in the open-label study CT-301 or in CT-301EXT. Causes of headache are legion. However, there is a potential even if unlikely association between headache and altered function of the choroid plexus. If ChP epithelial cell vacuolation leads to an underproduction of CSF, that would cause low CSF pressure. Headaches have been reported as a symptom of low CSF pressure (Mokri, 2004). Alternatively, if ChP epithelial vacuolation leads to an overproduction of CSF, this would cause high CSF pressure, which is termed intracranial hypertension. This condition typically presents with headaches and is associated with other signs such as papilledema (Graff-Radford and Schievink, 2014).

The only other clinically noteworthy CNS TEAEs that were reported in these studies of ACP-011 were two SAEs in the same subject: generalized tonic-clonic seizure and epilepsy. Because seizures have also been reported after treatment of adults with two other pegylated products, Omontys and Cimzia (see Table 1 and ensuing discussion), one can speculate that ChP vacuolation can be associated with seizures. However, several facts may suggest otherwise. First and as regards the rare seizures reported with use of the TNF-alpha blocker, Cimzia, seizures may occur during treatment with any TNF-alpha blocker (Bechtel et al., 2009). Second and as regards the rare seizures reported with use of Omontys in adults with CKD during dialysis, seizures are relatively common in patients with CKD during dialysis sessions (Glenn et al., 1992). Third and as regards the subject with events of seizure/epilepsy after treatment with ACP-011, recall that both events occurred more than 900 days after the subject began treatment with ACP-011. But these events in this single subject bear further scrutiny, as discussed next.

Camfield and Camfield (2015) have published incidence rates of epilepsy in children, and the rate ranges from 33 – 82 per 100,000 per year in developed countries. Using these data to calculate a mean incidence rate of 58 per 100,000 patient-years, one can compare that rate to the rate of epilepsy in the studies of ACP-011. The total exposure to ACP-011 was 406 patient-years (ISS Table 3.99.1.4: derived from 301 patients with a mean exposure of 70.2 weeks). If one applies the incidence rate for epilepsy of 58 per 100,000 patient-years to the 406 patient-years of exposure to ACP-011, then 0.24 patients exposed to ACP-011 could be predicted to develop epilepsy during these studies. Of course there is a wide confidence interval around these data, and only one proband. Nevertheless, given that these calculations are in the range of 0 to 1 person developing epilepsy during the studies, this reviewer believes that it is conceivable that the subject of interest could have developed epilepsy for reasons other than exposure to ACP-011.

VI. Reviewer's Discussion about Potential Safety Risks of mPEG Accumulation in the Choroid Plexus in Children or Adults, and Their Detection

There are insufficient clinical data to determine the safety risk of pegylated products that might produce ChP vacuolation and mPEG accumulation in adults, much less in children. The many years of availability of six marketed pegylated products that could have the potential to produce CNS risks due to this phenomenon, together with at best a tenuous CNS risk as determined by evaluation of known CNS adverse events in the patients who have received them, is somewhat reassuring.

Using the data available for all of the pegylated compounds that potentially cause CNS mPEG accumulation and ChP vacuolation, one might assume that headaches are a hallmark of this risk. This reviewer suggests that headaches are typically not clinically significant, with some exceptions such as high-CSF pressure or low-CSF pressure headaches. High-CSF pressures are associated with papilledema, and hence an ophthalmoscopic exam could be used as a non-invasive method to detect this possibility. However, low-CSF pressure headaches would only be detectable by a measurement of CSF pressure, which would be obtainable only with an invasive lumbar puncture.

Generalized tonic-clonic seizures may also be a rare event associated with the use of pegylated compounds that produce ChP vacuolation, but that association is tenuous at best. These seizures are easily observed if they occur, and hence their presence can be ascertained through routine adverse event assessments.

VII. DN1 Responses to DGE Consult

Question 1

1. What is the potential risk associated with accumulation of mPEG in the brain including the type of known and/or expected adverse events associated with vacuolation of epithelial cells within the choroid plexus and/or mPEG accumulation in the brain?

DN1 Response

There is no clear safety risk associated with mPEG accumulation in the brain during treatment with the marketed pegylated products that are known to cause mPEG accumulation and ChP epithelial cell vacuolation in nonclinical studies. Based on the sparse clinical data and the discussions above, the only clinical events that have even a low likelihood of association with these phenomena are headaches. Although speculative, if these headaches are caused by the under-production or over-production of CSF due to dysfunctional ChP epithelial cells, there are methods that could be used to detect these potential causes in patients who develop severe or chronic headache during treatment. These methods include ophthalmoscopic exam for papilledema to detect high CSF pressure, or measurement of CSF pressure via a lumbar puncture to detect low or high CSF pressure.

There is a much lower possibility that tonic-clonic seizures are caused by pegylated compounds. Because this type of seizure is easily observable, the occurrence of seizures is easily ascertainable by routine adverse event assessments.

Question 2

2. Is the pediatric population at increased risk for neurologic deficits?

DN1 Response

Data are very limited for children who have been administered pegylated compounds known to produce ChP vacuolation in nonclinical studies. The 3-year history of marketed Rebinyn without known CNS consequences in the children to whom it has been administered may be somewhat reassuring. Note that review of the nonclinical data by the DN1 nonclinical review team is still underway; however, if there remain concerns for potential adverse CNS effects related to ChP epithelial cell vacuolation and mPEG accumulation once this review is completed, a dedicated clinical trial could be considered for the detection of potential CNS risks in children. Such a trial should include assessments of cognition with sensitive neuropsychological tests, assessments of behavior using parent-rated or clinician-rated scales that are fit for purpose, and rigorous neurologic exams, as suggested by the BPAC meeting for Rebinyn in 2017. This trial should also be controlled and would need to be of sufficient duration to detect changes in neurocognitive function in order to be interpretable.

VIII. References (in order of citation in text)

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/s/

DAVID HOSFORD
01/13/2021 05:27:26 PM

TERESA J BURACCHIO
01/14/2021 03:23:39 PM



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

Date: November 25, 2020

From: Interdisciplinary Review Team for Cardiac Safety Studies

Through: Christine Garnett, Pharm.D.
Clinical Analyst, DCN

To: Sejal Kiani, RPM
DGE

Subject: IRT Consult to BLA-761177 (SDN001)

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

This memo responds to your consult to us dated 7/15/2020 regarding your question on product labeling QT assessment. We reviewed the following materials:

- Sponsor's clinical study protocol # CT-101 (SN0001; [link](#));
- Sponsor's clinical study report # CT-101 (SN0001; [link](#));
- Sponsor's proposed product label (SN0001; [link](#)); and
- Highlights of clinical pharmacology and cardiac safety (SN0001; [link](#)).

1 IRT Responses

The applicant did not propose QT labeling language in Section 12.2 (Cardiac Electrophysiology, [link](#)). We agree with the applicant's proposal because it is consistent with our labeling practices for large molecules for which a dedicated QT study is generally not needed and when one has not been conducted.

The submitted ECG data do not indicate any unexpected or important effects of lonapegsomatropin on the QTc interval at the proposed therapeutic dose.

2 Internal Comments to the Division

None.

3 Background

Ascendis Pharma (Endocrinology Division) is developing lonapegsomatropin

(b) (4)

(b) (4) Lonapegsomatropin (TransCon hGH, ACP-011; MW: ~63.2 kDa) is a long-acting prodrug of human growth hormone (somatropin; MW: ~22 kDa). Lonapegsomatropin consists of a parent drug, somatropin, that is transiently conjugated to a methoxypolyethylene glycol carrier (4×10 kDa mPEG) via a proprietary TransCon linker (also named (b) (4)). Lonapegsomatropin is expected to release unmodified and fully active somatropin via autocleavage of the TransCon linker in a controlled manner (first-order kinetics). The sponsor describes that the carrier has a shielding effect that minimizes renal excretion and receptor-mediated clearance of lonapegsomatropin.

The product is formulated as sterile lyophilized powder for reconstitution (a dual-chamber glass cartridge, with diluent; Auto-Injector) containing 3.0, 3.6, 4.3, 5.2, 6.3, 7.6, 9.1, 11.0, 13.3 mg lonapegsomatropin (as hGH) for subcutaneous administration. During the early development, the sponsor utilized (b) (4) kDa mPEG carrier (ACP-001) (b) (4).

The maximum proposed therapeutic dose for the present indication is 0.24 mg hGH/kg once weekly (Studies # CT-301 and CT-302). The peak concentrations of 15.2 ng/mL (T_{max} : ~12 h; Half-life: ~16.2 h) for somatropin are expected at steady-state with the anticipated therapeutic dose (corrected for cross-reactivity with hGH). The sponsor expects minimal accumulation at steady-state with the proposed maximum therapeutic dose (Based on Studies # CT-101 and CT-102). Steady state concentrations of mPEG were approximately 15,000 ng/mL (Study # CT-301). The apparent half-life of the residual mPEG was estimated to be 435 h and predicted to reach systemic steady state after approximately 3 months. Studies do not describe the concentration of free TransCon linker (b) (4).

The sponsor claims that somatropin undergoes protein catabolism in both the liver and kidneys and highlights that it has a low drug interaction potential as a victim drug resulting in increased exposures. No clinical studies have been conducted by the sponsor to evaluate the pharmacokinetics in organ impairment.

The sponsor did not conduct a dedicated QT study for lonapegsomatropin. The sponsor states that subcutaneous administration of lonapegsomatropin in clinical studies was not associated with clinically relevant QT prolongation.

The sponsor conducted a phase 1, randomized, open-label study in healthy subjects (n=46; 28 + 18) evaluating the safety and tolerability of a single dose of ACP-011 at three different dose levels (i.e., 0.24, 0.30, and 0.42 mg hGH/kg) and comparing exposures of a single dose of ACP-011 (40 kDa mPEG carrier; 0.24 mg/kg, Treatment B) to ACP-001 (b) (4) kDa mPEG carrier; 0.24 mg/kg, Treatment A) in a cross-over (2 period, 2 sequence) design (Group 1; n=24). In group 2, subjects received single doses of 0.30 mg/kg (Treatment C) and 0.42 mg/kg (Treatment D) (n=9/cohort) in a single period. Each dose was followed by PD sampling through Day 15 and PK sampling through Day 57 (outpatient visits on Days 9, 11, 15, 22, 29, 36, 43, and 57).

PK samples were planned at the following time points (nominal) at screening, at pre-dose (-2, -1, and 0 h), and at 2, 4, 8, 12, 16, 24, 36, 48, 72, 96, 120, 144, 168, 192, 240, 336 h post-dose. Group 2 included additional samples at 504, 672, 840, 1008, and 1344 h post-dose. Single 12-lead ECGs were planned at screening, at pre-dose (-2 h), and at 2, 4, 12, 24, 36, 48, 72, 96, 168, 336 h post-dose. Group 2 included additional samples at 672 and 1344 h post-dose.

Overall, intensive ECG sampling in healthy adults found mean values for ECG parameters that were similar at each time point assessed, and there were no apparent dose- or treatment-related trends in changes from baseline (Study # CT-101).

Even at lonapegsomatropin doses considered suprathapeutic for adults (0.30 and 0.42 mg hGH/kg), the mean change in QTcF at any time point was minimal and never exceeded 1.4 msec, suggesting that lonapegsomatropin does not have a clinically meaningful effect on QTcF prolongation. No individual 12-lead ECG abnormality was considered clinically significant by the Investigator or reported as a TEAE (Study # CT-101).

The peak concentration (C_{max}: 2480 ng/mL; lonapegsomatropin) observed with highest dose studied (i.e., 0.42 mg/kg; single dose) is expected to offer only ~2-fold margin over the therapeutic exposures (C_{max}: 1230 ng/mL) associated with the maximum proposed dose at the steady-state. The submitted ECG data do not indicate any unexpected or important effects of lonapegsomatropin on the QTc interval at the proposed therapeutic dose.

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 cderrcpqt@fda.hhs.gov.

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/s/

GIRISH K BENDE
11/25/2020 12:58:19 PM

CHRISTINE E GARNETT
11/25/2020 12:59:48 PM

MEMORANDUM

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

DATE: 10/20/2020
TO: Division of General Endocrinology (DGE)
Office of Cardiology, Hematology, Endocrinology and Nephrology (OCHEN)
FROM: Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)
SUBJECT: **Decline to conduct an on-site inspection**
RE: BLA 761177

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

Rationale

The Office of Regulatory Affairs (ORA) inspected the clinical site in December 2017, which falls within the surveillance interval. The inspection was conducted under the following submission: (b) (4)

OSIS inspected the analytical site in January 2019, which falls within the surveillance interval. The inspection was conducted under the following submission: (b) (4).

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

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

Inspection Sites

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

James J.

Lumalcuri -S

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