CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761184Orig1s000

OTHER REVIEW(S)

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

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

Memorandum

Date: May 8, 2023

To: Dana Smith, Regulatory Project Manager,
Division of General Endocrinology (DGE)

Geanina Roman-Popoveniuc, Medical Officer, DGE

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

CC: Susannah O'Donnell, Team Leader, OPDP

Subject: OPDP Labeling Comments for NGENLA (somatrogon-ghla) injection, for subcutaneous use

BLA: 761184

Background:
In response to DGE's consult request dated January 11, 2023, OPDP has reviewed the proposed Prescribing Information (PI), for the original BLA submission for NGENLA (somatrogon-ghla) injection, for subcutaneous use.

PI/PPI/IFU:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on April 24, 2023, and our comments are provided below.

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

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
05/08/2023 10:11:29 AM

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 3, 2023
To:	Sejal Kiani Senior 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)**
	Marcia Williams, PhD, LCSW-C, BCD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon Williams, MSN, BSN, RN 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: Patient Package Insert (PPI) and Instructions for Use (IFU)
Drug Names (established names):	NGENLA (somatrogon-ghla)
Dosage Form and Route:	injection, for subcutaneous use
Application Type/Number:	BLA 761184
Applicant:	Pfizer Ireland Pharmaceuticals

1 INTRODUCTION

On October 22, 2020 Pfizer Ireland Pharmaceuticals (Pfizer) submiteed an original BLA for somatrogon (MOD-4023) [C-terminal peptide (CTP)-modified hGH] injection, for subcutaneous use. Somatrogon is a modified recombinant human growth hormone (rhGH) that has been developed (b) (4) On January 21, 2022, the Agency issued a Complete Response Letter (CPL) to the application. After a Type A Guidance Meeting on March 29, 2022, Type C Written Responses provided by the Agency on 1 July 2022, responses by Pfizer provided on July 26, 2022, and the General Advice letter provided by the Agency on August 26, 2022, Pfizer resubmitted the BLA application on November 22, 2022 for the Agency's review.

This is a collaborative review from DMPP and OPDP. This review is written by the Division of Medical Policy Programs (DMPP) and OPDP in response to a request by on January 11, 2023 by DGE to review the Applicant's proposed PPI and IFUs for somatrogon (MOD-4023).

2 MATERIAL REVIEWED

- Draft NGENLA somatrogon PPI and IFUs received on November 22, 2023, and received by DMPP and OPDP on April 24, 2023.
- Draft NGENLA somatrogon Prescribing Information (PI) received on November 22, 2023, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 24, 2023.
- Comparator labeling NORDITROPIN (somatropin) dated March 29, 2020.

3 REVIEW METHODS

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

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

In our collaborative review of the PPI and IFUs we:

- simplified wording and clarified concepts where possible

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

4 CONCLUSIONS

The PPI and IFUs are acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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/s/

SHARON W WILLIAMS
05/03/2023 10:48:04 AM

CHARUNI P SHAH
05/03/2023 10:57:53 AM

MARCIA B WILLIAMS
05/03/2023 11:04:37 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine
Division of Pediatrics and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9855

MEMORANDUM TO FILE

Date of Consult Request:	December 5, 2022
From:	Division of Pediatrics and Maternal Health (DPMH) Kerri-Ann Jennings, MS, BSN, RN Senior Regulatory Project Manager
To:	Division of General Endocrinology (DGE)
IND Number:	BLA 761184
Drug:	Ngenla (somatrogon-ghla)
Applicant:	Pfizer Ireland Pharmaceuticals
Indication:	(b) (4)

The Division of General Endocrinology (DGE) submitted a consult request to the Division of Pediatrics and Maternal Health (DPMH) on December 6, 2022, requesting assistance with PLLR labeling recommendations and attendance at internal meetings.

DPMH participated in applicable internal meetings with DGE from December 15, 2022 through April 18, 2023 to discuss this application. DPMH Maternal Health has not added any new information to the labeling and no new data has been reviewed.

DPMH – Maternal Health has no further comments at this time, thus, this memorandum will close out the consult request.

DPMH Maternal Health MO Reviewer- Christos Mastroyannis, MD
DPMH Maternal Health Team Leader- Tamara Johnson, MD, MS
DPMH Division Director- Lynne Yao, MD
DPMH RPM- Kerri-Ann Jennings, MS, BSN, RN

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/s/

KERRI-ANN JENNINGS
04/20/2023 02:01:50 PM

OFFICE OF PRODUCT EVALUATION AND QUALITY
OFFICE OF HEALTH TECHNOLOGY 3

DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS

INTERCENTER CONSULT MEMORANDUM

Date	4/4/2023		
To:	Melinda Bauerlin		
Requesting Center/Office:	CDER/OPQ	**Clinical Review Division:**	Choose an item.
From	Elvira.Castro OPEQ/OHT3/DHT3C		
Through (Team)	Courtney Evan , Team Lead, Injection Team OPEQ/OHT3/DHT3C		
Through (Division) *Optional	CPT Alan Stevens, Division Director, Injection Team OPEQ/OHT3/DHT3C		
Subject	BLA 761184 Review of Somatrogon (MOD-4023) [C – Terminal peptide (CTP)- modified hGH] injection. ICC2201052 ICCR 00885164		
Recommendation	**Filing Recommendation Date: 4/4/2023** ☐ 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: Click or tap to enter a date. ☑ 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: Click or tap to enter a date. ☑ 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)
Elvira E. Castro -S Digitally signed by Elvira E. Castro -S Date: 2023.04.04 10:26:40 -04'00'	Courtney Evans -S Digitally signed by Courtney Evans -S Date: 2023.04.05 08:25:08 -04'00'	

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1. SUBMISSION OVERVIEW

Submission Information	
Submission Number	BLA 761184
Sponsor	Pfizer Ireland Pharmaceutical
Drug/Biologic	Somatrogon (MOD-4023)/
Indications for Use	(b) (4)
Device Constituent	Pen-Injector
Related Files	IND 79745

Review Team		
Lead Device Reviewer	*Elvira Castro*	
Discipline Specific **Consults**		

Important Dates	
Discipline-Specific Review Memos Due	
Final Lead Device Review Memo Due	
Interim Due Dates	**Meeting/Due Date**
Filing	NA
74-Day Letter	NA
Mid-Cycle	2/24/2023
Primary Review	4/10/2023
Internal Meeting(s)	
Sponsor Meeting(s)	

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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.

Section	Adequate			Reviewer Notes
	Yes	No	NA	
Device Description	X			
Labeling	X			
Design Controls	X			
Risk Analysis	X			
Design Verification	X			
Consultant Discipline Reviews			X	
Clinical Validation			X	
Human Factors Validation			X	
Facilities & Quality Systems			X	

2.1. Comments to the Review Team

☑ CDRH does not have any further comments to convey to the review team.

☐ CDRH has the following comments to convey to the review team:

2.2. Complete Response Deficiencies

☑ There are no outstanding unresolved information requests, therefore CDRH does not have any outstanding deficiencies.

☐ The following outstanding unresolved information requests should be communicated to the Sponsor as part of the CR Letter:

2.3. Recommended Post-Market Commitments/Requirements

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

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3. PURPOSE/BACKGROUND

3.1. Scope

CDER is requesting to conduct assessment on the device functionality of the device constituent part of the combination product pen-injector in a Somatrogon 24mg and 60mg pen. This file is the resubmission of the file BLA 761184 originally submitted 22 October 2020 and Complete Response Letter (CRL) dated 21 January 2022. Further reference is made to the 29 March 2022 Type A Guidance Meeting, the purpose of which was to discuss Pfizer's proposal to address the clinical deficiencies described in the CRL. Further reference is made about the Type C Written Responses provided by the Agency on 01 July 2022, Pfizer's responses provided on 26 July 2022 (Sequence 0076), and the General Advice letter provided by the Agency on 26 August 2022 concerning the safety data to be included in the BLA resubmission.

CDRH/OHT3 provided consult on the original review under ICC2100073 (ICCR 00055001). The final recommendation for the review was "Device Constituent Part of the Combination Product are Approvable." CDRH/OHT3 did not communicate any comments or deficiencies in the Complete response letter or subsequent meetings. This review will assess:

1) New device information/data as provided in the resubmission
2) Whether product changes in the post-CR resubmission of the combination product affects the ability to leverage any information/data provided under the original submission.

This medication Somatrogon (also referred to as MOD-4023) is a C-terminal peptide (CTP)-modified recombinant human growth hormone (rhGH) that has been developed (b) (4) Somatrogon is intended to be administered as a once weekly subcutaneous (SC) injection using a disposable, prefilled pen that has the capability for setting and delivering the desired dose, which is individualized based on the patient body weight.

There are 2 mechanically identical Somatrogon prefilled pen presentations; 24 mg-containing a volume of 1.2 mL Somatrogon at 20 mg/mL (lilac pen, dose button, and label) and 60 mg-containing a volume of 1.2 mL Somatrogon at 50 mg/mL (blue pen cap, dose button, and label). Needles are not included in the carton containing the pen.

Each pen presentation contains multiple doses of Somatrogon drug product solution. The doses variable, set within the range of 10 to 600 µL, which is selected using a manual dial dose setting mechanism and injected by a manually driven piston. The healthcare provider will decide which strength is most appropriate for the patient from the 2 available presentations, based on the dose required defined by pediatric patient body weight.

Both pen presentations are mechanically identical. The pens vary in the color of the pen cap, dose button, and label. The pens also vary in the printing on the dose sleeve of the dosing mechanism and the printing on the cartridge holder.

The final assembled Somatrogon prefilled pen consists of a cartridge containing drug product solution, printed cartridge holder. The dosing mechanism, and a pen cap. The label is wrapped around the body of the prefilled pen.

The sponsor has recommended pen needles compatible for use with the pen injector. The needles are manufactured by Becton Dickinson and Company BD Micro-Fine™ (or Ultra-Fine™) (31gauge), Novo Nordisk NovoFine® (31 gauge) and Novo Fine® Plus (32gauge) and are up to a length of 8mm and all suitable for subcutaneous injection. Both needles are 510K cleared NovoFine K173479 and BD Ultrafine K024109.

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Table 3.2.P.2.4-4. Needles Compatible for use with the Somatrogon 24 mg and 60 mg Prefilled Pen

Manufacturer	Trade Name	Needle Type
Becton Dickinson and Company	BD Micro-Fine™ (or BD Ultra-Fine™)	31 gauge x 5 mm 31 gauge x 8 mm
Novo Nordisk	NovoFine®	31 gauge x 6 mm
	NovoFine® Plus	32 gauge x 4 mm

Choose an item. has requested the following consult for review of the device constituent of the combination product:

Please review the updated batch analyses in in SN 0007 Section 3.2.P.5.4, stability data in 3.2.P.8.1 of the proposed device Pen injector.

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:

- Pen Injector information and device performance

This review will not cover the following review areas:

Drug product, drug contacting device constituent parts, human factors

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

BLA 761184, ICC2100073, ICCR 00055001

3.2.1. Related Files

3.3. Indications for Use

Combination Product	Indications for Use
Pen-Injector	Delivery of the Drug Product
Somatrogon	(b) (4)

3.4. Materials Reviewed

Materials Reviewed	
Sequence	**Module(s)**
SN 0077	1.14.1 Draft Labeling 1.16. Risk Management
SN0077	3.2.P Product Development 3.2.P.2. Pharmaceutical Development
SN0077	1.11.11 Quality Information Amended 1.14 Labeling 3.2.P.5Control of Drug 3.2.P.5 Batch Analysis
SN0077	3.2.P. 5.6 Justification of Specification

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SN0077	3.2.S.4 Control of Drug Substance
SN0077	3.2.P.8 Stability Data 3.2.P.8.1 Stability Summary and Conclusion
SN0001	3.2.P.3.5.Process Validation -Simulated Shipping 3.2.P.2 Risk Management.

4. DEVICE DESCRIPTION

4.1. Device Description

Information can be found in SN 0077 [3.2.P.2.4. Product Development]

The sponsor Pfizer develop a Somatrogon Prefilled Pen a single use, disposable, prefilled pen. The proposed method of giving the medication is by subcutaneous injection once a week in the front top of the thigh, abdomen area, upper buttocks, or rear of the upper arms. The disposable delivery device which is designed to accommodate a 3mL glass cartridge to deliver multiple doses of Somatrogon drug product solution subcutaneously.

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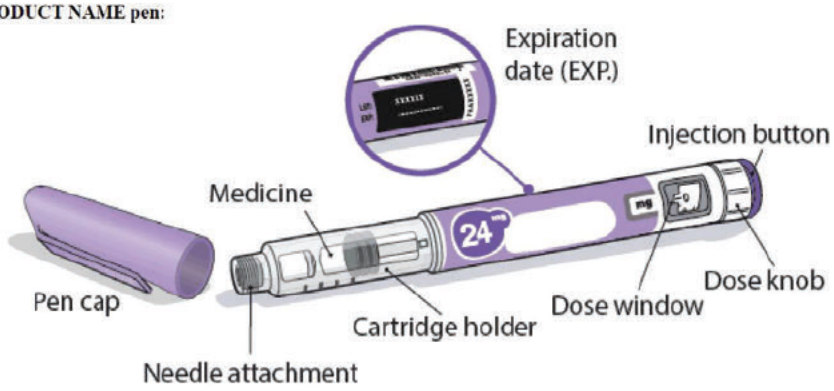
24 mg PRODUCT NAME pen:



The sponsor stated that the Pen needles are not included in the box. The user will see a prescription from their healthcare provider to get pen needles up to a length of 8mm from the user's pharmacy.

Table 3.2.P.2.4-1. Functional Description of the Somatrogon Prefilled Pen Components

Component Name	Component Image (illustrations only and not to scale)	Description
Dosing Mechanism		
24 mg dose button (injection button)[a]		The dose button is pushed outwards by the dose selection spring and retained by the dose sleeve. It can rotate freely. When pressed down by the user after dose selection, it couples the click ring and clutch to initiate delivery of the selected dose.
60 mg dose button (injection button)[a]		

(b) (4)

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(b) (4)

24 mg cartridge holder[a]		The cartridge holder encloses and holds the cartridge in position and is attached to the housing. The tip is threaded to enable attachment of a new needle prior to each use of the pen. Features on the cartridge holder locate and retain the pen cap when the pen is not in use. The cartridge holder allows full visibility of the somatrogon drug product solution and cartridge plunger stopper. It is printed with a scale in milligram (mg) units to indicate approximate available injectable content in the cartridge.
60 mg cartridge holder[a]		
24 mg pen cap[a]		The pen cap fits over the cartridge holder when the pen is not in use. It is designed to prevent the pen from rolling away on a horizontal surface.

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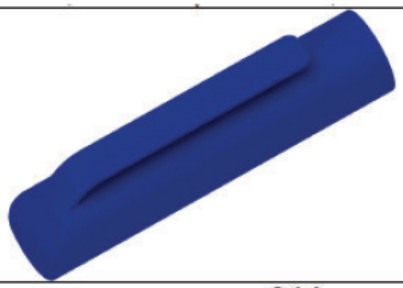
60 mg pen cap[a]		See description above for the 24 mg pen cap.
	Label	
24 mg label[a]	(b) (4)	The label provides the outer "skin" to the housing of the pen and conceals (b) (4) other features used to aid manufacture. The label contains specific information about the drug product presentation such as strength information and expiration date. The label also provides a space for recording the date of first use of the pen.
60 mg label[a]		

4.2. Steps for Using the Device

A. preparing for your injection

Step 1 - Getting ready

- Wash and dry your hands.
- You can use your pen straight from the refrigerator. For a more comfortable injection, leave your pen at room temperature for up to 30 minutes.
- Check the name, strength, and label of your pen to make sure it is the medicine your healthcare provider has prescribed for you.
- Check the expiration date on the pen label. **Do not** use if the expiration date has passed.
- **Do not** use your pen if:
  o it has been frozen or exposed to heat
  o it has been dropped
  o it looks broken or damaged
  o it has been more than 28 days after first use of the pen.
- **Do not** remove the pen cap from your pen - until you are ready to inject.

Step 2 - Choose and clean your injection site

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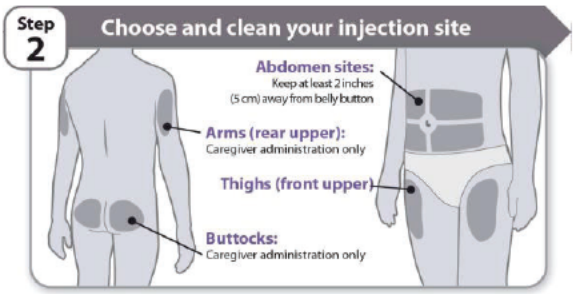
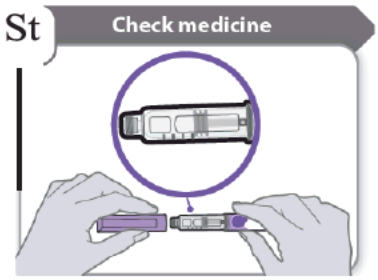


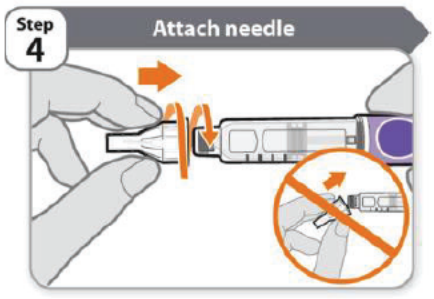
- PRODUCT NAME can be given in the abdomen, thighs, buttocks, or upper arms.
- Choose the best place to inject, as recommended by your healthcare provider.
- If more than 1 injection is needed to complete your full dose, each injection should be given in a different injection site.
- **Do not** inject into bony areas, areas that are bruised, red, sore or hard, and areas that have scars or skin conditions.
- Clean the injection site with an alcohol swab.
- Allow the injection site to dry.
- **Do not** touch injection site after cleaning.

Step 3 - Check medicine



- Pull off the pen cap and keep it for after your injection.
- Check the medicine inside the cartridge holder.
- Make sure the medicine is colorless to slightly light yellow. **Do not** inject the medicine if it is cloudy or dark yellow.
- Make sure the medicine is free of flakes or particles. **Do not** inject the medicine if it has flakes or particles.
- Note: it is normal to see one or more bubbles in the medicine

Step 4 - Attach needle



- Take a new needle and pull off the protective paper.
- Line the needle up with your pen keeping them both straight.
- Gently push and then screw the needle onto your pen.

Do not over tighten.
Note: Be careful not to attach the needle at an angle. This may cause the pen to leak.
Caution: Needles have sharp tips at both ends. Handle with care to make sure you do not prick yourself (or anyone else) with the needle.

Step 5 - Pull off outer needle cover

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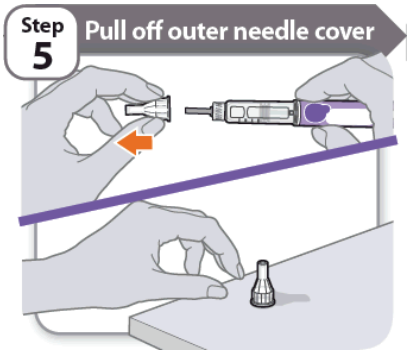
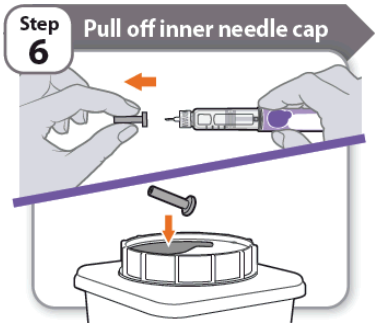


- Pull off the outer needle cover.
- Make sure you keep the outer needle cover. You will need it later to remove the needle.

Note: You should see an inner needle cap after you have removed the outer cover. If you do not see this, try to attach the needle again.

Step 6 - Pull off inner needle cap

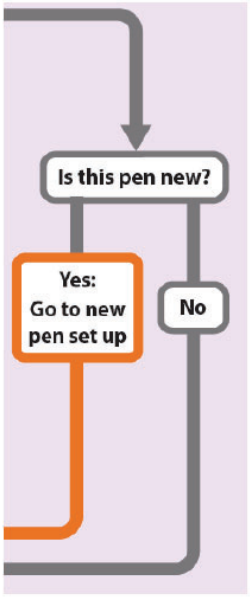


- Pull off the inner needle cap carefully to show the needle.
- Throw away the inner needle cap (b) (4) a sharp container. It is not needed again.

Is this pen new?

Yes: Go to new pen set-up

No



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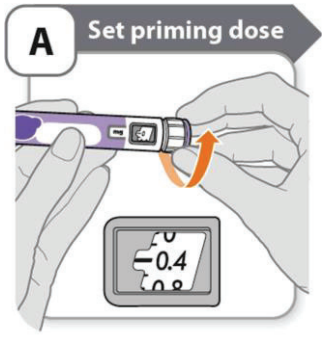
New pen set up (priming) – for the first use of a new pen only

You must set up each new pen (priming) before using it for the first time

- New pen set up is done before each new pen is used for the first time.
- The purpose of setting up a new pen is to remove air bubbles and make sure you get the correct dose.
  Important: Skip Step-A through to Step-C if you have already set up your pen.

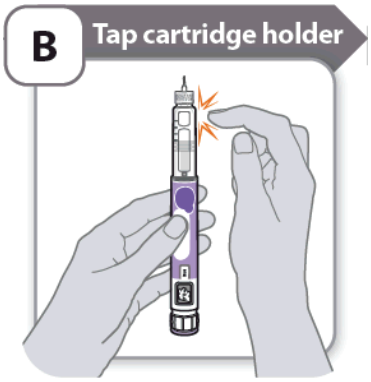
A - Set priming dose



- Turn the dose knob to **0.4**.
  - This is the amount to prime the pen.

Note: If you turn the dose knob too far, you can turn it back.

B - Tap cartridge holder



- Hold the pen with the needle pointing up so that the air bubbles can rise.
- Tap the cartridge holder gently to float any air bubbles to the top
  Important: **Follow Step-B even if you do not see air bubbles.**

C - Press button and check for liquid

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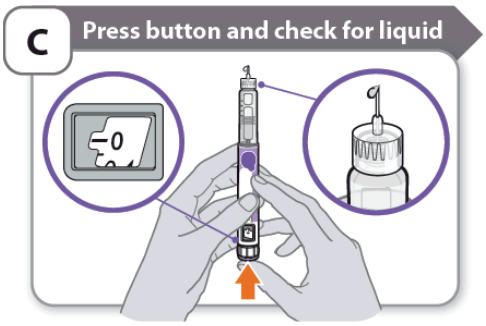


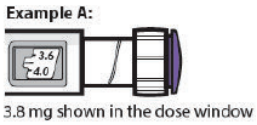
Press the injection button until it cannot go any further and **"0"** is shown in the dose window.

- **Check** for liquid at the needle tip. If liquid appears, your pen is set up.
- Always make sure that a drop of liquid appears before you inject. If liquid has not appeared, repeat Step-A through to Step-C.
  o If liquid does not appear after you have repeated Step-A through Step-C five (5) times, attach a new needle and try 1more time. **Do not** use the pen if a drop of liquid still does not appear. Contact your healthcare provider or pharmacist and use a new pen.

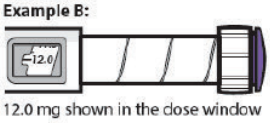
Setting your prescribed dose

Step 7 – Set your dose

Example A:
3.8 mg shown in the dose window



Example B:
12.0 mg shown in the dose window



• Turn the dose knob to set your dose.
o The dose can be increased or decreased by turning the dose knob in either direction.
o The dose knob turns 0.2 mg at a time.
o Your pen contains 24 mg of medicine, but you can only set a dose of up to 12 mg for a single injection.
o The dose window shows the dose in mg. See **Examples A and B**.
• **Always check the dose window to make sure you have set the correct dose.**

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Important: Do not press the injection button while setting your dose.

What should I do if I cannot set the dose I need?

- If your dose is more than 12 mg you will need to split your dose into more than 1 injection.
- You can give from 0.2 mg to 12 mg in a single injection.
  - o Use a new needle for each injection **(See Step 4: Attach needle).**
  - o If you normally need to give 2 injections for your full dose, be sure to give your second dose.

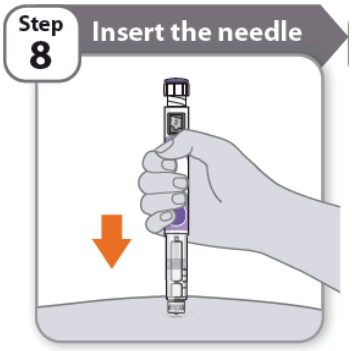
What should I do if I do not have enough medicine left in my pen?

- If your pen contains less than 12 mg of medicine, the dose knob will stop with the remaining amount of medicine shown in the dose window.
- If there is not enough medicine left in your pen for your full dose, you may either:
  - o Inject the amount left in your pen, then prepare a new pen to complete your dose in full. Remember to subtract the dose you have already received. For example, if the dose is 3.8 mg and you can only set the dose knob to 1.8 mg, you should inject another 2.0 mg with a new pen.
  - o Or get a new pen and inject the full dose.

Only split your dose if you have been trained or advised by your healthcare provider on how to do this.

Injecting your dose

Step 8 - Insert the needle



- Hold your pen so you can see the numbers in the dose window.
- Insert the needle straight into your skin.

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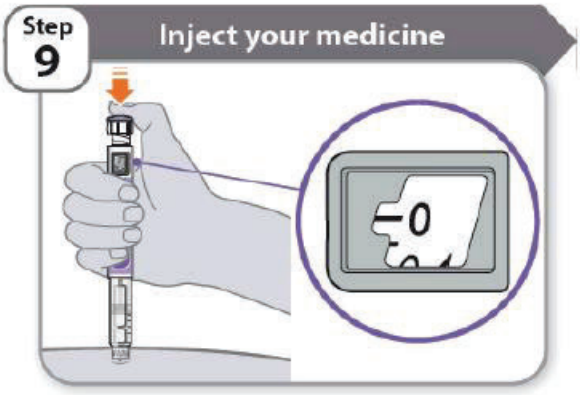
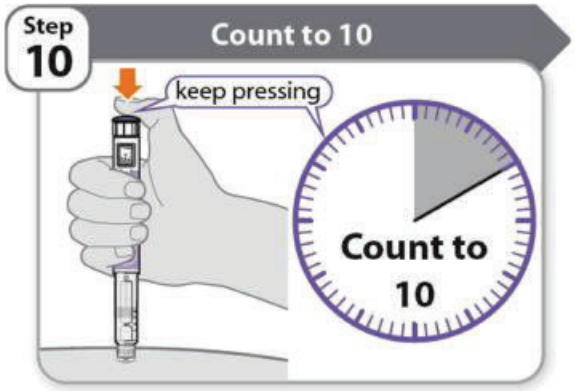
Step 9 - Inject your medicine



- Keep holding the needle in the same position in your skin.
- **Press the injection button** until it cannot go any further and **"0"** is shown in the dose window.

Step 10 - Count to 10



- **Continue to press the injection button while counting to 10**. Counting to 10 will allow the full dose of medicine to be given.
- After counting to 10, let go of the injection button and slowly remove the pen from the injection site by pulling the needle **straight out.**
  Note: You may see a drop of medicine at the needle tip. This is normal and does not affect the dose you just received.

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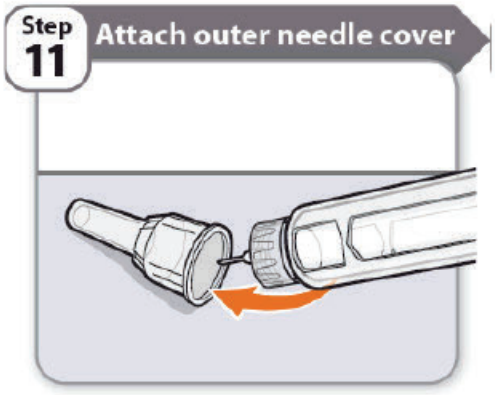
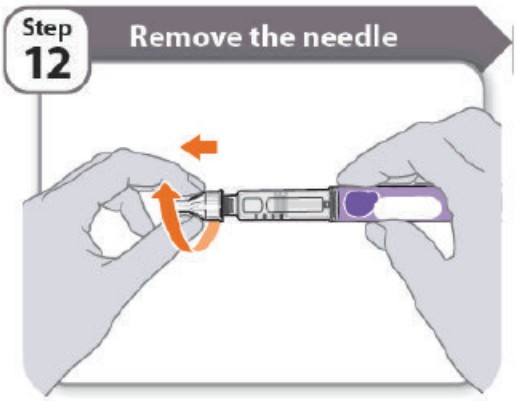
Step 11 - Attach outer needle cover



- Carefully place the outer needle cover back on the needle.
- Press on the outer needle cover until it is secure.
  Caution: Never try to put the inner needle cap back on the needle. You may prick yourself with the needle.

Step 12 - Remove the needle



- Unscrew the capped needle from the pen.
- Gently pull until the capped needle comes off.
  Note: If the needle is still on, replace the outer needle cover and try again. Be sure to apply pressure when unscrewing the needle.
- Throw away the needle in the sharps container (**See How do I dispose of the pen needles and pens?**). **Important:** Always remove and throw away used needles. **Do not** reuse needles.

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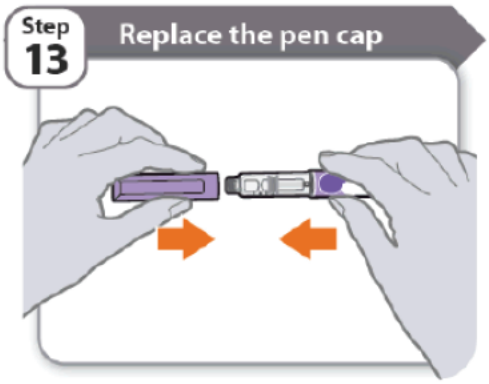
Step 13 - Replace the pen cap



- Replace the pen cap back onto your pen.
- **Do not** recap the pen with a needle attached.
- If there is any medicine left in your pen, store in the refrigerator between uses (**See How should I store my pen?**).

Step 14 - After your injection

- Press lightly on the injection site with a clean cotton ball or gauze pad, and hold for a few seconds.
- **Do not** rub the injection site. You may have slight bleeding. This is normal.
- You may cover the injection site with a small adhesive bandage, if needed.
- If your pen is empty or it has been **more than 28 days** after first use, throw it away even if it contains unused medicine. Refer to **"Storage and disposal"** on the right side of this leaflet.

Storage and disposal:

How should I store my pen?

(b) (4)

- **Do not** freeze your pen or expose it to heat.
- **Do not** use your pen if it has been frozen or stored in direct sunlight.

(b) (4)

Before first use (unused pens):

- Store your pens in the refrigerator between 36°F to 46°F (2°C to 8°C).
- Unused pens may be used until the expiration date printed on the label, only if the pen has been kept in the refrigerator.

After first use (up to 28 days of use):

- Store your pen in the refrigerator at 36°F to 46°F (2°C to 8°C) and away from direct sunlight.
- Keep the pen cap on your pen when it is not in use.
- **Do not** store the pen with a needle attached.
- If your pen is empty or it has been **more than 28 days** after first use, throw it away even if it contains unused medicine.
- To help you remember when to dispose of your pen you can write the date of first use on the pen label and below:

Date of first use _____ / _____ / _____

(b) (4)

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How should I dispose of the pen needles and pens?

- Throw away your pen, and pen needles into a FDA-cleared sharps disposal container or puncture resistant container.
- If you do not have a FDA-cleared sharps disposal container, you may use a household container that:
  - is made of heavy-duty plastic
  - can be closed with a tight-fitting, puncture resistant lid, without sharps being able to come out
  - is upright and stable during use
  - is leak-resistant, and properly labeled to warn of hazardous waste inside the container.
- When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles, syringes, and prefilled syringes.
- For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: https://www.fda.gov/safesharpsdisposal
- Do not throw away your used sharps disposal container in your household trash unless your community guidelines permit this.
- Keep the sharps container out of the reach of children.

4.3. Device Description Conclusion

DEVICE DESCRIPTION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☑ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☐ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☐ No ☐ N/A
Reviewer Comments The sponsor has provided an adequate device description and method of operation.		
CDRH sent Device Description Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No		

5. FILING REVIEW

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

LABELING

5.1. 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:

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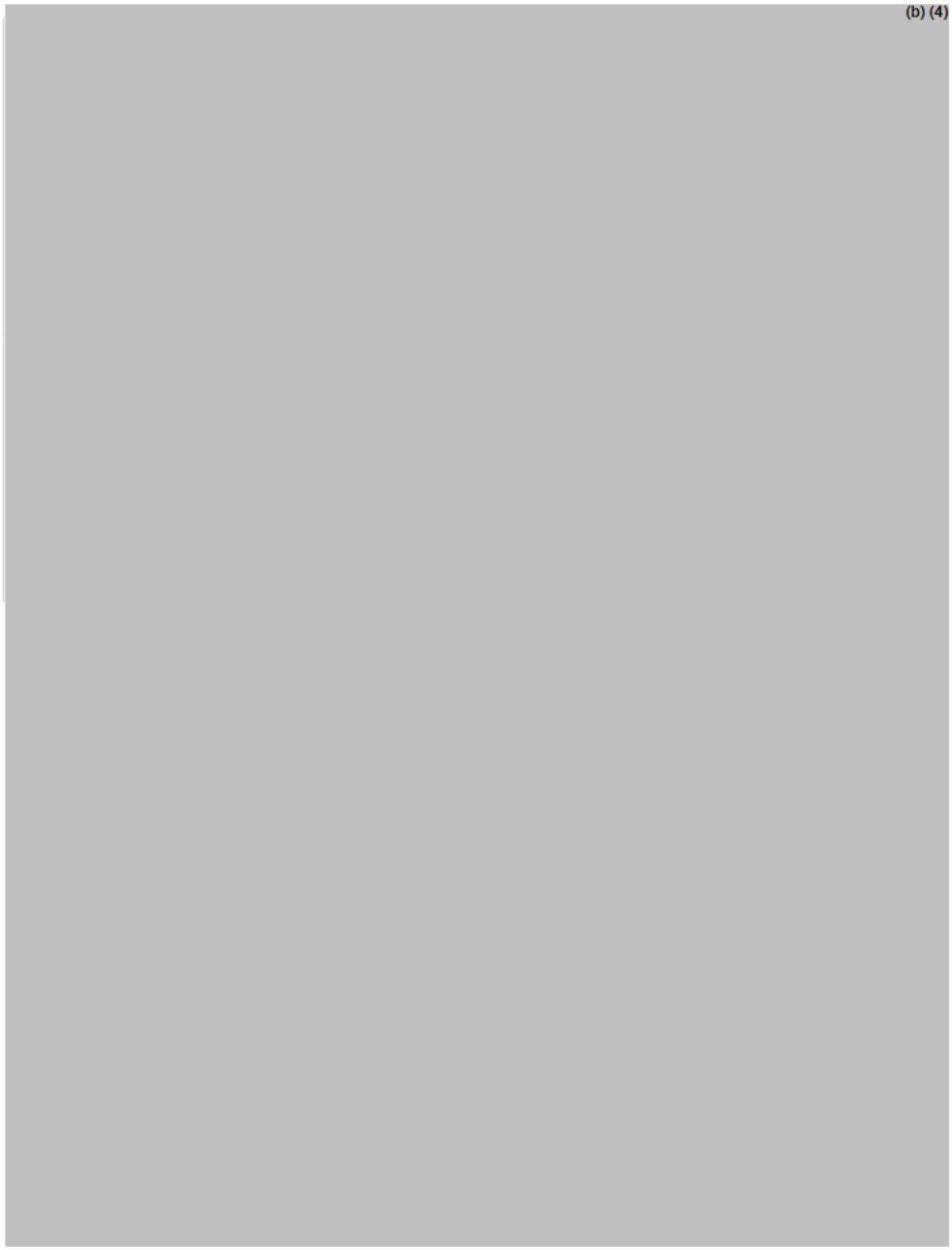

General Labeling Review Checklist	Adequate?		
	Yes	No	N/A
Indications for Use or Intended Use; including use environment(s); route(s) of administration for infusion, and treatment population.	X		
Drug name is visible on device constituent and packaging	X		
Device/Combination Product Name and labeling is consistent with the type of device constituent	X		

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Prescriptive Statement/Symbol on device constituent	X		
Warnings	X		
Contraindications	X		
Instructions for Use	X		
Final Instructions for Use Validated through Human Factors			X
Electrical Safety Labeling/Symbols			X
EMC Labeling/Symbols			X
Software Version Labeling			X
MRI Labeling/Symbols			X
RF/Wireless Labeling/Symbols			X

Reviewer Comments
In SN 0077 1.14.1 Draft labeling: The firm provided proposed labeling that includes package insert. Included in the package insert is the step by step on how to use the devices.

5.2. Labeling Review Conclusion

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

☑

6. DESIGN CONTROL SUMMARY

6.1. 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		

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Verification methods relevant to specific use conditions as described in design documents and labeling	X		
Device reliability is acceptable to support the indications for use (i.e. emergency use combination product may require separate reliability study)	X		
Traceability demonstrated for specifications to performance data	X		

Reviewer Comments
The Firm provided clarification how they were able develop a risk management plan since the proposed device-drug combination is not commercially available.

6.2. Design Inputs and Outputs

Essential Performance Requirements

(b) (4)

(b) (4)

6.3. 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
Standard Practice for Performance Testing of Shipping Containers and Systems; ASTM D4169-09	Y
IEC 60601-1-2:2014	NA
Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products (2017)	Y
Mobile Medical Applications Guidance for Industry and Food and Drug Administration Staff (2015)	NA
Guidance for Industry and FDA Staff – Medical Devices with Sharps Injury Prevention Features (2005)	NA
Use of International Standard ISO 10993-1, Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process"	Y

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Applying Human Factors and Usability Engineering to Medical Devices	Y

Device Specific Standards and Guidance Documents

Standard or Guidance	Recognized (Y/N/NA)	Conformance (Y/N/NA)
ISO 11608-1:2014 Needle -based injection system for medical use Requirements and Test methods -Part1: Needle -based injection system.	**Y**	**Y**

6.4. Design Control Review Conclusion

DESIGN CONTROL REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☐ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☐ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☐ No ☐ N/A
Reviewer Comments The Sponsor provided an adequate design control and followed appropriate standards for pen injectors/combination product.		
CDRH sent Design Control Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☐ No		

7. RISK ANALYSIS

7.1. Risk Management Plan

Table 14. Comprehensive risk analysis of critical and essential tasks

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7.2. Risk Analysis Review Conclusion

RISK ANALYSIS REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☐ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☑ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☐ No ☐ N/A
Reviewer Comments- The full test report can be found in SN 0001 3.2.P.2.4 Risk Management. The Firm uses to identify the potential used related risks for the Somatrogon single-patient use disposable prefilled pen, a reviewer of known use problems with similar devices was conducted, including other devices requiring dialup dosing. The Risk assessment of the combination product is adequate.		
CDRH sent Risk Analysis Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No		

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8. DESIGN VERIFICATION REVIEW

8.1. Performance/Engineering Verification

8.1.1. Essential Performance Requirement Evaluation

(b) (4)

Reviewer Comment:
The FIRM stated in SN 0077 Container Closure System the analysis of the design and functional attributes of the pen was performed to determine which functional characteristics are considered essential to dosing and could therefore be required to be routinely tested as part of release or stability. Since there is a high level of confidence in the understanding of specific functional attributes or existing established levels of control and/or consistency observed acceptable results, so the Firm based on the result that no additional testing of their attributes is required on a routine basis. (b) (4)

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8.1.2. Verification of Design Inputs Evaluation

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8.2. Design Verification Review Conclusion

DESIGN VERIFICATION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☐ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☑ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☐ No ☐ N/A
Reviewer Comments The design Verification that the sponsor provided is adequate.		
CDRH sent Design Verification Deficiency or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No		

<<END OF REVIEW>>

8.3. APPENDIX A.

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10.APPENDIX B (CONSULTANT MEMOS)

10.1. Human Factors Review Memo – Insert Consultant Name

10.2. Clinical Review Memo – Insert Consultant Name

10.3. Insert Discipline Review Memo – Insert Consultant Name

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/s/

SEJAL KIANI
04/05/2023 04:13:53 PM
Signing on behalf of Elvira Castro OPEQ/OHT3/DHT3C

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

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

Date of This Review:	March 28, 2023
Requesting Office or Division:	Division of General Endocrinology (DGE)
Application Type and Number:	BLA 761184
Product Name, Dosage Form, and Strength:	Ngenla (somatrogon-ghla)[a] Injection, 24 mg/1.2 mL (20 mg/mL); 60 mg/1.2 mL (50 mg/mL)
Product Type:	Combination Product (Biologic-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Pfizer Ireland Pharmaceuticals (Pfizer)
FDA Received Date:	November 22, 2022
TTT ID #:	2022-2873
DMEPA 1 Safety Evaluator:	Peggy Rahbani, PharmD, BCPS
DMEPA 1 Acting Team Leader:	Madhuri R. Patel, PharmD

[a] The nonproprietary name, somatrogon-ghla, was found conditionally acceptable on July 16, 2021.

1 REASON FOR REVIEW

As part of the approval process for Ngenla (somatrogon-ghla) injection, 24 mg/1.2 mL; 60 mg/1.2 mL, the Division of General Endocrinology (DGE) requested that we review the proposed Ngenla Prescribing Information (PI), Patient Prescribing Information (PPI), Instructions for Use (IFU), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 REGULATORY HISTORY

We previously reviewed the HF validation study protocol, and the proposed instruction for use (IFU), container and carton labeling under BLA 761184 and provided recommendations to Pfizer on January 21, 2022. The Applicant also received a Complete Response Letter from the Agency on January 21, 2022. On November 22, 2022, the Applicant resubmitted their BLA with a revised PI, PPI, IFU, container labels, and carton labeling addressing recommendations we made during a previous review[b].

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E – N/A
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We previously recommended revising the IFU storage and disposal section to clearly differentiate between expiration date and in-use date. The revised IFU includes the additional statement of "Do not use after the expiration date printed on the label has passed." However,

[b] Bhalodia A. Human Factors Protocol Review for Ngenla (BLA 761184). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 DEC 22. RCM No.: 2020-2249.

this does not address the in-use date. Hence, we continue to recommend revising the IFU storage and disposal section.

4 CONCLUSION & RECOMMENDATIONS

The proposed Instruction for Use (IFU) may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issue, our rationale for concern, and our proposed recommendation to minimize the risk for medication error in Section 4 for the Division.

Table 1. Identified Issues and Recommendations for Division of General Endocrinology (DGE)

IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Instructions for Use (IFU)		
The statement "Do not use after the expiration date printed on the label has passed." does not account for the in-use (28 days after first use) date.	Lack of clarity on the expiration date and in-use date may lead to deteriorated drug errors.	We recommend revising the statement to read "Do not use after the expiration date printed on the label has passed or if it has been more than 28 days after first use."

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Ngenla (somatrogon-ghla) injection, 24 mg/1.2 mL; 60 mg/1.2 mL received on November 22, 2022 from Pfizer Ireland Pharmaceuticals (Pfizer).

Table 3. Relevant Product Information for Ngenla (somatrogon-ghla) injection, 24 mg/1.2 mL; 60 mg/1.2 mL	
Initial Approval Date	N/A
Active Ingredient	somatrogon
Indication	(b) (4)
Route of Administration	Subcutaneous
Dosage Form	Injection
Strength	24 mg/1.2 mL (20 mg/mL) and 60 mg/1.2 mL (50 mg/mL)
Dose and Frequency	0.66 mg/kg body weight administered once weekly, on the same day each week, at any time of day
How Supplied	Single-patient-use, disposable prefilled pen containing 24 mg/1.2 mL that delivers a dose in 0.2 mg increments Single-patient-use, disposable prefilled pen containing 60 mg/1.2 mL that delivers a dose in 0.5 mg increments
Storage	Refrigerator at 36°F to 46°F (2°C to 8°C)
Container Closure	Single-patient use, multidose, disposable prefilled pen (b) (4) (b) (4)

APPENDIX B. PREVIOUS DMEPA REVIEWS

On March 1, 2023, we searched for previous DMEPA reviews relevant to this current review using the term, 'Ngenla'. Our search identified one previous review[c] and we confirmed that our previous recommendations were implemented.

[c] Bhalodia A. Human Factors Protocol Review for Ngenla (BLA 761184). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 DEC 22. RCM No.: 2020-2249.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[d] along with postmarket medication error data, we reviewed the following Ngenla (somatrogon-ghla) Injection, Patient Prescribing Information (PPI), Prescribing Information (PI), Instruction for Use (IFU), and labels and labeling submitted by Pfizer Ireland Pharmaceuticals (Pfizer).

- Container label received on November 22, 2022
- Carton labeling received on November 22, 2022
- Instructions for Use, Patient Prescribing Information (PPI), and Prescribing Information received on November 22, 2022, available from \\CDSESUB1\EVSPROD\bla761184\0077\m1\us\lab143302-lab144902-lab145202-lab145402-annotated.pdf

F.2 Label and Labeling Images

Container Labels:

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

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/s/

PEGGY M RAHBANI
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MADHURI R PATEL
03/31/2023 10:26:48 AM

HUMAN FACTORS STUDY REPORT REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

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

Date of This Review:	December 22, 2021
Requesting Office or Division:	Division of General Endocrinology (DGE)
Application Type and Number:	BLA 761184
Drug Constituent Name and Strength	Ngenla [MOD-4023][a] (somatrogon-ghla)[b] Injection, 24 mg/1.2 mL; 60 mg/1.2 mL
Product Type:	Combination Product (Biologic-Device)
Device Constituent:	Prefilled Pen
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Pfizer Ireland Pharmaceuticals (Pfizer)
FDA Received Date:	October 22, 2020, May 14, 2021, December 1, 2021, and December 10, 2021
OSE RCM #:	2020-2249
DMEPA 1 Human Factors Evaluator:	Avani Bhalodia, PharmD, BCPS
DMEPA 1 Team Leader (Acting):	Murewa Oguntimein, PhD, MHS, CPH, MCHES
DMEPA 1 Associate Director for Human Factors:	Jason Flint, MBA, PMP

[a] "MOD-4023" is Pfizer's identifier for their growth hormone product which has been developed as a proposed biologic-device combination product in a prefilled pen configuration. During the writing of this review, the proposed proprietary name Ngenla was found conditionally acceptable by DMEPA. For the purposes of this review, MOD-4023 is used throughout the review to refer to this product.

[b] The nonproprietary name, somatrogon-ghla, was found conditionally acceptable on July 16, 2021.

1 REASON FOR REVIEW

The Division of General Endocrinology (DGE) requested a consultative review of a human factors (HF) validation study report submitted under BLA 761184 for MOD-4023 (somatrogon) Injection.

1.1 PRODUCT DESCRIPTION

This is combination product with a proposed multidose prefilled pen (PFP) device constituent part that is intended (b) (4) See Appendix A for additional information.

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

- On October 16, 2018, the Applicant submitted an HF validation study protocol for the proposed PFP presentation for our review. We evaluated the proposed protocol and provided recommendations to the Applicant. We recommended that the Applicant implement all recommendations before commencing the HF validation study.[c] The Applicant implemented our recommendations.

- On February 7, 2019, the Applicant submitted responses to the Agency's HF validation study protocol recommendations submitted under IND 132494 for MOD-4023 Injection.[d] We completed our review of the responses and provided further recommendations.[e] The Applicant implemented our recommendations.

- On April 4, 2019, the Applicant submitted responses to the Agency's additional recommendations.[f] We completed our review of the responses and advised that the Applicant implement all recommendations before commencing their HF validation study.[g] The Applicant implemented our recommendations.

[c] Schlick J. Human Factors Protocol Review for MOD-4023 (IND 132494). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 DEC 6. RCM No.: 2018-2241.

[d] Schlick J. Human Factors Protocol Review for MOD-4023 (IND 132494). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 DEC 6. RCM No.: 2018-2241.

[e] Schlick J. Human Factors Protocol Review Memorandum for MOD-4023 (IND 132494). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 MAR 5. RCM No.: 2018-2241-1.

[f] Schlick J. Human Factors Protocol Review Memorandum for MOD-4023 (IND 132494). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 MAR 5. RCM No.: 2018-2241-1.

[g] Schlick J. Human Factors Protocol Review Memorandum for MOD-4023 (IND 132494). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 JUN 19. RCM No.: 2018-2241-2.

- On October 22, 2020, the Applicant submitted BLA 761184 to seek approval for MOD-4023. As such, the BLA submission included the results of their HF validation study to support their marketing application, which is the subject of this review.

1.3 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)	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

2 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 indicate that the user interface has been optimized to support the safe and effective use of the proposed product.

2.1 SUMMARY OF HF VALIDATION STUDY DESIGN

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

Table 2. Study Methodology for Human Factors (HF) Validation Study

Study Design Elements	Details
Participants	See nested table below
Training	Half of the participants in each user group including three out of the 6 younger Pediatrics (ages 10-12) were trained by a registered nurse prior to simulating use. The nurse trainer took the participant through the information in the IFU and simulated an injection into an injection pad. Training typically lasted 15 minutes and was followed by a one-hour decay period.
Study Environment	The study took place in rooms with normal office lighting, temperature, humidity, and background noise.
Sequence of Study	Training (for trained participants) Post-training break (1 hour) Carton differentiation task to assess if participants are able to differentiate the carton that is consistent with their prescription (i.e., 24 mg or 60 mg) Dose scenario 1 [(normal dose with a new pen (priming required)]

	Pediatric Patients (ages 10-17)	Parents/Caregivers (ages 18-70)	HCPs (ages 22-70)
Trained	N=16	N=16	N=16
Injection Naïve	8	8	n/a
Injection Experienced	8	8	16
Untrained	N=16	N=16	N=16
Injection Naïve	8	8	n/a
Injection Experienced	8	8	16
Total per User Group	N=32	N=32	N=32
Grand Total	N=96		

	Distractor break (5-10 minutes) Dose scenario 2 [normal dose with pen from scenario 1 (priming not required)] Dose scenario 3 [(split dose with existing pen (priming not required) and new pen (priming required)] Post-test interview – knowledge-based questions Post-test interview – root cause analysis

2.1.1 TASK CATEGORIZATION

We note the Applicant categorized the following tasks as essential:

- Store pen
- Cap and store the pen in the refrigerator until next use

However, per our guidance[h], we categorize tasks as critical or non-critical and include a critical task definition; "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". Therefore, based on the use-related risk analysis (URRA) and the definition of critical tasks as stated in the guidance, we considered the above listed tasks as non-critical.

3 RESULTS AND ANALYSES

Table 3 describes the study results, the Applicant's analyses of the results, and DMEPA 1's analyses and recommendations. Over the course of the review, we sent several information requests asking the Applicant to update their URRA, provide information regarding injection hold times and the incidence of wet injections experienced during the HF validation study (Appendix E).

[h] Draft Guidance for Industry and FDA Staff, Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development and can be found online at: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM484345.pdf

Table 3: Identified Issues and DMEPA's Findings		
	Identified Issue and Rationale for Concern	**DMEPA's Analysis and Findings**
1.	For the differentiation and simulated task to "check pen contents and expiry date – choose correct pen", the following use events were observed: Scenario 1 [(normal dose with a new pen (priming required)] • 1 use difficulty (untrained) • 1 close call (untrained) The subjective data and the Applicant's root cause analysis indicated: • Test artifact – participants were not aware that an alternative pen would be in the refrigerator which confused the participants when choosing the correct pen. The Applicant has not proposed mitigation strategies for the use difficulty and close call.	Based on the URRA, if this task is omitted or not performed correctly there is risk of losing therapeutic effect. Our review of the study results identified subjective feedback that indicated that the use difficulty and close call in choosing the correct pen were due to participants being confused by seeing both the 24 mg and 60 mg pens in the refrigerator. Our review of the labels and labeling (user interface, etc.) indicate that both strengths are differentiated by different colors. We have not identified additional changes to the user interface to further reduce the risks associated with these use difficulty and close call. We find that the residual risk in this case is acceptable.
2.	For the task to "attach needle", the following use events were observed: Scenario 1 [(normal dose with a new pen (priming required)] • 3 use difficulties (untrained) Scenario 2 [normal dose with pen from scenario 1 (priming not required)] • 2 use difficulties (untrained) • 1 close call (trained) Scenario 3 [(split dose with existing pen (priming not required) and new pen (priming required)] • 2 use difficulties (1 trained, 1 untrained) The subjective data and the Applicant's root cause analysis indicated:	Based on the URRA, if this task is omitted or not performed correctly there is risk of intradermal or intramuscular injection, reversible injuries, transection of dermis, bleeding from injury, or loss of therapeutic effect. Our review of the study results identified subjective feedback that indicated that these use difficulties and close call were due to relying on the "click" to confirm the needle attachment. Additionally, one participant stated that it was not clear from the IFU that he needed to push while twisting on the needle. Our review of the labels and labeling (user interface, etc.) finds that the image in Step 4 of the IFU can be improved. **We provide a recommendation in the Identified Issues and Recommendations for Pfizer Table to address this concern.** We have determined that this

	• Participant relied on the "click" to confirm the attachment. • Participants reported to experience learning curve with respect to attaching the needle the first time whereby they had some use difficulty during the first scenario but no issues in the following scenarios. • For one participant, it was not clear from the instructions for use (IFU) or needle itself that he needed to push while twisting on the needle. The Applicant has not proposed mitigation strategies for these use difficulties and close call.	change can be implemented without submitting additional validation testing for Agency review.
3.	For the task to "remove the outer needle cover", the following use events were observed: Scenario 1 [(normal dose with a new pen (priming required)] • 1 use error (untrained) • 1 close call (untrained) Scenario 2 [normal dose with pen from scenario 1 (priming not required)] • 2 use errors (untrained) • 1 use difficulty (trained) Scenario 3 [(split dose with existing pen (priming not required) and new pen (priming required)] • 1 use error (untrained) The subjective data and the Applicant's root cause analysis indicated: • Participant did not firmly attach the needle resulting in removing the entire needle from the pen while removing the needle cover.	Based on the URRA, if this task is omitted or not performed correctly there is risk of losing therapeutic effect. Our review of the study results indicates that the root cause analysis was incomplete because the Applicant did not identify why some participants were tightening and untightening the needle, others did not firmly attach the needle, and another bent the needle. We note that use errors with the previous task to attach the needle and not attaching the needle correctly resulted in use issues with this task. Additionally, we note that some participants did not refer to the IFU. Our review of the labels and labeling (user interface, etc.) finds that the IFU Step 5, "Pull of outer needle cover" contains text and illustration on pulling off the outer needle cover. Additionally, the carton labeling states to read enclosed instructions before use. Because this task is related to the previous task, it is possible that the recommendation above will also address the use errors seen with this task. We have not identified additional changes to the user interface to further reduce the risks associated with these use errors, use difficulty and close call. We find that the residual risk in this case is acceptable.

	• Participants did not review the IFU likely assuming they could figure out how to use the product or recall from the first simulation. • Participant was observed tightening and untightening the needle when he intended to remove the cap from the needle. In the root cause analysis, the Applicant stated that the needle label not providing information regarding the appropriate way to remove it and human nature of twisting "on" and twisting "off" were the most likely contributing factors. The Applicant has not proposed mitigation strategies for these use errors, use difficulty and close call.	
4.	For the task to "remove the needle cap", the following use events were observed: Scenario 1 [(normal dose with a new pen (priming required)] • 1 use error (untrained) • 2 use difficulties (1 trained, 1 untrained) Scenario 2 [normal dose with pen from scenario 1 (priming not required)] • 1 use error (untrained) Scenario 3 [(split dose with existing pen (priming not required) and new pen (priming required)] • 1 use error (untrained) • 1 use difficulty (trained) • 1 close call (untrained) The subjective data and the Applicant's root cause analysis indicated: • Participant removed the inner needle cap at a slight angle and realized she had bent the needle which suggests there may be learning curve when interacting with the product the first time.	Based on the URRA, if this task is omitted or not performed correctly there is risk of losing therapeutic effect. Our review of the study results identified subjective feedback that indicated that some of the use errors and close calls were due to negative transfer – that is, they relied on previous experience with other injection devices that do not require the user to remove an inner needle cap. However, we note that for the use difficulties, the root cause analysis was incomplete because the Applicant did not identify why some participants bent the needle and others did not remove the inner needle cap. Our review of the labels and labeling (user interface, etc.) finds that the IFU Step 6, "Pull off inner needle cap" contains text and illustration on pulling off the inner needle cap. We have not identified additional changes to the user interface to further reduce the risks associated with these use errors, use difficulties and close call. We find that the residual risk in this case is acceptable.

	• Negative transfer – participants relied on experience with other injection devices which do not require the removal of an inner needle cap. • Participant did not remove the inner needle cap due to having not removed the outer needle cover in prior task. • Participant removed the entire needle inadvertently when attempting to remove the inner needle cap. The needle had not been tightened enough when attaching to the pen and the participant retightened the needle to the pen and had no further issues. • Participant bent the needle slightly while removing the inner needle cap. Participant realized it was bent and replaced the needle. The Applicant has not proposed mitigation strategies for these use errors, use difficulties and close call.	
5.	For the task to "prime a new pen – set prime dose", the following use events were observed: Scenario 1 [(normal dose with a new pen (priming required)] • 16 use errors (4 trained, 12 untrained) Scenario 3 [(split dose with existing pen (priming not required) and new pen (priming required)] • 17 use errors (5 trained, 12 untrained) The subjective data and the Applicant's root cause analysis indicated: • Negative Transfer - participants did not prime the pen as they do not prime their existing pens. • Participants claimed to be confused by the "prime" dose described in the IFU whereby they thought it was just an example. Thus, a number of participants dialed	Based on the URRA, if this task is omitted or not performed correctly there is risk of inconvenience to patient, subcutaneous emphysema, injection of small amount of air, or no harm expected. We reached out to the clinical review team and they agree with the Applicant that one decrease in dose will not affect the overall efficacy and they do not find underdose due to not priming a new pen, to be clinically significant. Our review of the study results identified subjective feedback that indicated that some of the use errors were due to negative transfer and confusing priming information. The majority of the participants were confused and thought the prime number was just an example of how to dial the pen rather than the instructed priming dose. Our review of the labels and labeling (user interface, etc.) finds that the IFU can be improved. **We provide a recommendation in the Identified**

	to the prescribed dose and bypassed the initial "prime" dose. • Participants noted they did not see the priming section at all and some only noticed one section in the priming sequence such as "tap". The Applicant stated that because this product is multi-use, this error with intended use would happen only once with a new pen and based on the risk analysis and regularity of dosing with such medication, this error would not be clinically significant. The Applicant has not proposed mitigation strategies for these use errors.	**Issues and Recommendations for Pfizer Table to address this concern.** We have determined that this change can be implemented without submitting additional validation testing for Agency review.
6.	For the task to "prime – tap cartridge", the following use events were observed: Scenario 1 [(normal dose with a new pen (priming required)] • 16 use errors (5 trained, 11 untrained) Scenario 3 [(split dose with existing pen (priming not required) and new pen (priming required)] • 19 use errors (8 trained, 11 untrained) The subjective data and the Applicant's root cause analysis indicated: • Participants did not tap the pen because they did not see bubbles in the syringe. • Participant overlooked the instruction to tap the syringe. • Negative Transfer - participants did not prime the pen as they do not prime their existing pens. The Applicant stated that because this product is multi-use, this error with intended use would happen only once with a new pen and based on the risk analysis and regularity of dosing with such medication, this error would not be clinically significant.	Based on the URRA, if this task is omitted or not performed correctly there is risk of inconvenience to patient, subcutaneous emphysema, injection of small amount of air, or no harm expected. We reached out to the clinical review team and they agree with the Applicant that one decrease in dose will not affect the overall efficacy and they did not find underdose due to not priming a new pen, to be clinically significant. Our review of the study results identified subjective feedback that indicated that the use errors was due to negative transfer and the fact that the majority of the participants did not tap the cartridge because they did not see the bubbles in the syringe. Our review of the labels and labeling (user interface, etc.) finds that the IFU contains text and illustration on tapping the cartridge under "New pen set up (priming) – for the first use of a new pen only" section. We have not identified additional changes to the user interface to further reduce the risks associated with these use errors. We find that the residual risk in this case is acceptable.

	The Applicant has not proposed mitigation strategies for these use errors.	
7.	For the task to "prime – press the button", the following use events were observed: Scenario 1 [(normal dose with a new pen (priming required)] • 14 use errors (2 trained, 12 untrained) Scenario 3 [(split dose with existing pen (priming not required) and new pen (priming required)] • 17 use errors (6 trained, 11 untrained) The subjective data and the Applicant's root cause analysis indicated: • Participants did not press or fully press the button as they saw the medication expel from the pen. • Negative Transfer - participants did not prime the pen as they do not prime their existing pens. The Applicant stated that because this product is multi-use, this error with intended use would happen only once with a new pen and based on the risk analysis and regularity of dosing with such medication, this error would not be clinically significant. The Applicant has not proposed mitigation strategies for these use errors.	Based on the URRA, if this task is omitted or not performed correctly there is risk of losing therapeutic effect, inconvenience to patient, subcutaneous emphysema, injection of small amount of air, or no harm expected. We reached out to the clinical review team and they agree with the Applicant that one decrease in dose will not affect the overall efficacy and they do not find underdose due to not priming a new pen, to be clinically significant. Our review of the study results identified subjective feedback that indicated that the majority of the use errors were due to negative transfer. However, we note that for a few of the use errors, the root cause analysis was incomplete because the Applicant did not identify why participants did not press or fully press the button. Our review of the labels and labeling (user interface, etc.) finds that the IFU contains text and illustration on pressing the button under "New pen set up (priming) – for the first use of a new pen only" section. We have not identified additional changes to the user interface to further reduce the risks associated with these use errors. We find that the residual risk in this case is acceptable.
8.	For the task to "prime – check for liquid at the tip of needle", the following use events were observed: Scenario 1 [(normal dose with a new pen (priming required)] • 14 use errors (3 trained, 11 untrained) Scenario 3 • 20 use errors (6 trained, 14 untrained) The subjective data and the Applicant's root cause analysis indicated:	Based on the URRA, if this task is omitted or not performed correctly there is risk of inconvenience to patient, subcutaneous emphysema, injection of small amount of air, or no harm expected. We reached out to the clinical review team and they agree with the Applicant that one decrease in dose will not affect the overall efficacy and they don't find underdose due to not priming a new pen, to be clinically significant.

	• Participant reported seeing liquid although not observed by the moderator. In the root cause analysis, the Applicant stated that the needles are small, and a small amount of liquid could be difficult to see. • Test artifact – participant did not have needle attached due to a safety concern by the study moderator. • Participant did not see liquid as the needle cover had not been removed in prior step. • Negative Transfer - participants did not prime the pen as they do not prime their existing pens. The Applicant stated that because this product is multi-use, this error with intended use would happen only once with a new pen and based on the risk analysis and regularity of dosing with such medication, this error would not be clinically significant. The Applicant has not proposed mitigation strategies for these use errors.	Our review of the study results identified subjective feedback that indicated that majority of the use errors were due to negative transfer. Our review of the labels and labeling (user interface, etc.) finds that the IFU contains text and illustration on checking for liquid at the tip of needle under "New pen set up (priming) – for the first use of a new pen only" section. We have not identified additional changes to the user interface to further reduce the risks associated with these use errors. We find that the residual risk in this case is acceptable.
9.	For the task to "dial up the dose you need to inject", the following use events were observed: Scenario 1 [(normal dose with a new pen (priming required)] • 5 use errors (untrained) • 2 close calls (1 trained, 1 untrained) Scenario 2 [normal dose with pen from scenario 1 (priming not required)] • 5 use errors (untrained) Scenario 3 [(split dose with existing pen (priming not required) and new pen (priming required)] • 8 use errors (3 trained, 5 untrained) • 3 use difficulties (untrained) • 2 close calls (1 trained, 1 untrained) The subjective data and the Applicant's root cause analysis indicated:	Based on the URRA, if this task is omitted or not performed correctly there is risk of losing therapeutic effect, inconvenience to patient, possible local reaction, headache, possible initial hypoglycemia followed by reactive hyperglycemia, unconsciousness, seizure, edema and fluid retention possible, possible resulting hypothyreosis, reversible injuries (e.g., superficial scratches), or no harm expected. Our review of the study results identified subjective feedback that indicated that majority of the use errors were due to negative transfer as two participants who normally administer injections in mL assumed that the dose on this pen would be similar to what they are currently using did inappropriate conversions from mg to mL. Another root cause for scenario 3 specifically included cognitive load issues requiring users to remember how much was delivered from the first pen prior to delivering the remaining from the second pen in addition to doing the math as there were more use issues observed in

	• Negative transfer – participants transferred their knowledge of currently used devices that administer in mL. For example, one participant injected 1.2 mg instead of 10 mg because she works with mL dosing exclusively in the emergency department. • Participant misinterpreted the value (e.g., 2.5 mg rather than 25 mg). • One participant incorrectly aligned the position of the indicator in the dose window. • Participants had difficulty due to cognitive load required to remember how much was delivered (in addition to math required) from the first pen prior to delivering the balance from the second pen. • Test artifact – use issue is attributable to a study artifact due to memory from the prior scenarios in the session. For example, one participant dialed 25 mg with the second pen instead of subtracting the dose already given from the first pen (16 mg) because the dose in the previous scenarios were 25 mg. • Participants were confused by the overfill in the pen. The Applicant has not proposed mitigation strategies for these use errors, use difficulties and close calls.	scenario 3. Additionally, some participants did not split the dose in attempt to avoid the potential risks associated with administering two injections to a child. Another participant used one pen because he doesn't normally split doses with his current pen. However, we note the root cause analysis was incomplete for a few use errors. One participant dialed 2.5 mg rather than 25 mg and repeated this error for all three scenarios. It is not clear from the root cause analysis why this participant continued to make this use error; however, we note that the decimal points on the prefilled pen dial are prominent. One participant set the dose knob an extra 0.5 mg because she was looking at the top of the window and not the value that aligned with the indicator in the middle of the window. However, we note that this design is common for other marketed prefilled pens, and we find the residual risk acceptable in this particular instance. Our review of the labels and labeling (user interface, etc.) finds that the information regarding splitting the dose in the IFU can be improved to inform users to only split the dose if they have been trained. This language is included in label and labeling (user interface, etc.) of currently marketed products with the same or similar user interface and use environments. **We provide a recommendation in the Identified Issues and Recommendations for Pfizer Table to address this concern.** We have determined that this change can be implemented without submitting additional validation testing for Agency review.
10.	For the task to "insert the needle", the following use events were observed: Scenario 1 [(normal dose with a new pen (priming required)] • 2 use errors (1 trained, 1 untrained) Scenario 2 [normal dose with pen from scenario 1 (priming not required)] • 1 use error (untrained) Scenario 3 [(split dose with existing pen (priming not required) and new pen (priming required)]	Based on the URRA, if this task is omitted or not performed correctly there is risk of intradermal injection, reversible injuries (e.g., superficial scratches), loss of therapeutic effect, inconvenience to patient or no harm expected. Our review of the study results identified subjective feedback that indicated that the use errors were due to assumption that needle cover and cap were part of the needle and participants were focused on getting the dosage right. For those participants who re-inserted the

	• 2 use errors (1 trained, 1 untrained) The subjective data and the Applicant's root cause analysis indicated: • Participants re-inserted the same needle when they removed it to set the dose. In the root cause analysis, the Applicant states that one participant assumed that re-inserting the same needle is acceptable as reinserting for the same needle/same injection is not mentioned in the IFU. Participant described being focused on getting the dosage right. • Participant did not insert the needle into injection site because she did not remove the needle cover and cap. She assumed that the needle cover and cap were part of the needle. The Applicant has not proposed mitigation strategies for these use errors.	needle, they understood to attach a new needle, and mentioned they would never re-insert a needle at home. Our review of the labels and labeling (user interface, etc.) finds that the IFU labels components of the pen and needle and the important information section includes an instruction to always use a new sterile needle for each injection. We have not identified additional changes to the user interface to further reduce the risks associated with these use errors. We find that the residual risk in this case is acceptable.
11.	For the task to "press the injection button", the following use events were observed: Scenario 2 [normal dose with pen from scenario 1 (priming not required)] • 1 use error (untrained) • 1 close call (trained) Scenario 3 [(split dose with existing pen (priming not required) and new pen (priming required)] • 1 use error (untrained) The subjective data and the Applicant's root cause analysis indicated: • Participant was unable to fully depress the dialer because he did not attach the needle fully to the pen. In the root cause analysis, the Applicant states that this inability to press down is a device mitigation whereby	Based on the URRA, if this task is omitted or not performed correctly there is risk of losing therapeutic effect, inconvenience to patient, or no harm expected. Our review of the study results identified subjective feedback that indicated the graphic in Step 10 may be confusing. One participant began counting to 10 while injecting because she had interpreted the graphic as counting as you push not counting after you had pushed. She suggested the IFU say, "hold down the device" and then "push and hold for 10 seconds". Our review of the labels and labeling (user interface, etc.) finds that the IFU Step 9, "Inject your medicine" instructs the user to keep holding the needle in the same position in your skin and then press the injection button until it cannot go any further and "0" is shown in the dose window. IFU Step 10, "Count to 10" instruct users to continue to press

	the dialer cannot be depressed if the needle is not correctly attached, which is a signal to the user that something is wrong. • Participant noted that she counted to 10 while she was pressing down on the button (not after the button had been fully depressed) because she reported that she had interpreted the graphic as counting as you push not counting after you had pushed. The Applicant has not proposed mitigation strategies for these use errors and close call.	the injection button while counting to 10. However, the image in Step 10 can be improved. **We provide a recommendation in the Identified Issues and Recommendations for Pfizer Table to address this concern.** We have determined that this change can be implemented without submitting additional validation testing for Agency review.
12.	For the task to "wait for the instructed hold period while holding the injection button down and then release the injection button before removing the pen from the injection site", the following use events were observed: Scenario 1 [(normal dose with a new pen (priming required)] • 22 use errors (4 trained, 18 untrained) • 4 use difficulties (1 trained, 3 untrained) Scenario 2 [normal dose with pen from scenario 1 (priming not required)] • 23 use errors (5 trained, 18 untrained) • 5 use difficulties (untrained) Scenario 3 [(split dose with existing pen (priming not required) and new pen (priming required)] • 24 use errors (7 trained, 17 untrained) • 11 use difficulties (3 trained, 8 untrained) The subjective data and the Applicant's root cause analysis indicated: • Negative transfer - relied on experience with other injection devices • Participants misinterpreted the information in the IFU and thought the counting started once one started to	Based on the URRA, if this task is omitted or not performed correctly there is risk of losing therapeutic effect, inconvenience to patient, or no harm expected. Our review of the study results identified subjective feedback that indicated that the majority of the use errors were due to negative transfer and IFU misinterpretation. Most of the participants misinterpreted the IFU information and thought the counting started once they started to press the button rather than after the button had been fully depressed. We sent an information request (IR) to the Applicant to clarify whether there were instances of wet injection or underdose during the HF validation study. The Applicant responded on May 14, 2021, that dose accuracy for a complete dose is achievable within a set timeframe limit (2 seconds once the dose window reads zero). The Applicant also stated that the IFU instructs the user to hold for a count of 10, to increase the chance of the user holding for the required 2 seconds and as a mitigation for users pulling up prematurely. Based on this information, for the 20 use difficulties, participants actually received the full dose as they held the pen for 2 seconds. Additionally, the IR response indicated that immediate removal of the pen from the injection site would likely be within a margin of (b) (4) % of the set dose, and that there were no

	press the button rather than after the button had been fully depressed • Participants did not realize from reviewing the IFU, that the injection button had to be depressed the entire time while counting to 10. • Participants did not see the information in the IFU The Applicant has not proposed mitigation strategies for these use errors and use difficulties.	observations of wet injections during the HF validation test related to those participants that did not hold for the minimum hold time of 2 seconds. Thus, we find the residual risk acceptable in this particular case. Our review of the labels and labeling (user interface, etc.) finds that the IFU Step 10, "Count to 10" instructs users to hold the button down while counting to 10 following fully depressing the dialer as a mitigation for users pulling up prematurely. However, the image in Step 10 can be improved. **We provide a recommendation in the Identified Issues and Recommendations for Pfizer Table to address this concern.** We have determined that this change can be implemented without submitting additional validation testing for Agency review.
13.	For the task to "remove the needle from the pen", the following use events were observed: Scenario 1 [(normal dose with a new pen (priming required)] • 1 use error (untrained) • 9 use difficulties (2 trained, 7 untrained) Scenario 2 [normal dose with pen from scenario 1 (priming not required)] • 1 use error (untrained) • 8 use difficulties (2 trained, 6 untrained) Scenario 3 [(split dose with existing pen (priming not required) and new pen (priming required)] • 1 use error (untrained) • 12 use difficulties (6 trained, 6 untrained) The subjective data and the Applicant's root cause analysis indicated: • Participants had difficulty removing the needle as the approach to hold the outer cover firmly while untwisting was not intuitive and initial discovery of how needles need to be removed. Some participants did not read the IFU.	Based on the URRA, if this task is omitted or not performed correctly there is risk of localized inflammation, allergic skin reaction, contact dermatitis, minor skin cut, or inconvenience. Our review of the study results indicates that the root cause analysis was incomplete because it did not identify why the participants could not remove the needle from the pen correctly. The Applicant states that this is a required technique which is not unique to this pen and the needle used during these simulations is an on-market needle which is screwed onto the pen. Our review of the labels and labeling (user interface, etc.) finds that the IFU Step 12, "Remove the needle" contains text and illustration on how to remove the needle from the pen. We have not identified additional changes to the user interface to further reduce the risks associated with these use errors and use difficulties. We find that the residual risk in this case is acceptable.

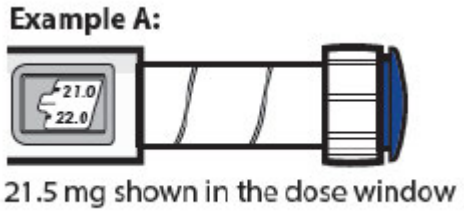
	• Participant did not remove the needle due to misunderstanding that the device was a single-use rather than multi-use device. Although not reported by the participant, the Applicant's root cause analysis stated that the terminology "Single patient" may have been confused with the concept of "single use" which for a pediatric patient, is not unexpected. • Negative transfer – participant used past experience with another pen The Applicant has not proposed mitigation strategies for these use errors and use difficulties.	
	The Knowledge Task Assessments: The knowledge task answers were categorized as correct, incorrect, and partially correct. Partially correct answers for these knowledge task questions indicates that the participant provided some, but not all the information necessary to demonstrate a complete and accurate understanding of the information provided by the IFU and product labeling, as well as any implications for the use of the product and patient safety.	
14.	For the knowledge task question, "What are you supposed to do if this pen has been frozen or stored in direct sunlight?", there were 2 partially correct (untrained) and 1 incorrect (untrained) answer. The subjective data and the Applicant's root cause analysis indicated: • Participant stated they would call the pharmacy and expected this information to be located in storage section in the IFU. • Abnormal use- participant responded to place the product back in the refrigerator but when the moderator asked the participant if that is what the IFU instructs to do, then participant replied no. • Participant did not look for the information in the IFU.	Based on the URRA, if this task is omitted or not performed correctly there is risk of losing therapeutic effect, local infection, or inflammation. Our review of the study results identified subjective feedback that indicated that the participants expected to find the answer under the storage section in IFU. Our review of the labels and labeling (user interface, etc.) finds that the IFU contains information on what to do if this pen has been frozen or stored in direct sunlight in Step 1, Getting ready. However, one participant expected to find this information under the storage section in IFU. Additionally, our review of the label and labeling (user interface, etc.) of currently marketed products with a similar user interface and use environments include this information in the storage section of the IFU. Based on our overall assessment and review of other similar products, we find that the IFU can be improved. **We provide a recommendation in the Identified Issues and Recommendations for Pfizer Table to address this concern.** We have determined that this

	The Applicant has not proposed mitigation strategies for these use errors.	change can be implemented without submitting additional validation testing for Agency review.
15.	For the knowledge task question, "How should the pen appear prior to use (What if it appeared to be damaged or broken)?", there were 3 partially correct answers (1 trained, 2 untrained). The subjective data and the Applicant's root cause analysis indicated: • Participants mentioned checking for the amount of medicine, color, integrity of medicine, appearance and that the medication should not have any bubbles, but participants did not mention inspecting for damage. In the root cause analysis, the Applicant stated that users may not find or may have overlooked this information due to the amount of content provided. The Applicant has not proposed mitigation strategies for these use errors.	Based on the URRA, if this task is omitted or not performed correctly there is risk of losing therapeutic effect, or reversible injuries (e.g., superficial scratches). Our review of the study results indicates that the root cause analysis was incomplete because the Applicant did not identify why participants in the study did not mention inspecting for damage. Our review of the labels and labeling (user interface, etc.) finds that the IFU Step 1, "Getting ready" contains information to not use the pen if it has been broken or damaged. We have not identified additional changes to the user interface to further reduce the risks associated with these use errors. We find that the residual risk in this case is acceptable.
16.	For the knowledge task question, "How should the medication appear prior to use?", there was 1 incorrect answer (untrained). The subjective data and the Applicant's root cause analysis indicated: • Negative transfer - participant assumed the color of the medication as white given that her current HGH medication is reported to be white. The Applicant has not proposed mitigation strategies for this use error.	Based on the URRA, if this task is omitted or not performed correctly there is risk of losing therapeutic effect. Our review of the study results identified subjective feedback that indicated that the use error was due to negative transfer. However, the participant was able to look in the instructions document and correctly answer clear and free from particles; when asked how the instructions document describes the appearance of the medication. Our review of the labels and labeling (user interface, etc.) finds that the IFU Step 3, "Check medicine" contains information on how the medication should appear prior to use and the participant was able to answer correctly after looking in the IFU.

		We have not identified additional changes to the user interface to further reduce the risks associated with this use error. We find that the residual risk in this case is acceptable.
17.	For the knowledge task question, "What should you look for to ensure that medication in the pen has not expired?", there were 6 incorrect answers (3 trained, 3 untrained). The subjective data and the Applicant's root cause analysis indicated: • All errors occurred with pediatric participants. Pediatric users may not be accustomed to checking for expiry dates on devices and instead may rely on a caregiver or other person to assist with this task. The Applicant has not proposed mitigation strategies for these use errors.	Based on the URRA, if this task is omitted or not performed correctly there is risk of losing therapeutic effect. Our review of the study results indicated that this error occurred in all pediatric participants and none of the adults. As indicated in root cause analysis, children may not be accustomed to checking for expiry dates on devices and instead may rely on a caregiver or other person to assist with this task. Also, we note that the use errors occurred in both trained and untrained arm equally. Our review of the labels and labeling (user interface, etc.) finds that the IFU Step 1, "Getting ready" contains information to check the expiration date on the pen label and to not use if the expiration date has passed. Additionally, pen label and carton labeling include the expiration date. We have not identified additional changes to the user interface to further reduce the risks associated with these use errors. We find that the residual risk in this case is acceptable.
18.	For the knowledge task question, "How long can the medication in this pen be used after its first use?", there were 2 incorrect answers (1 trained, 1 untrained). The subjective data and the Applicant's root cause analysis indicated: • Participants responded that the medication could be used until the expiration date as it appears that these users confused the expiration date with the in-use date (28 days after first use) due to these topics being similar in nature suggesting the IFU is not immediately clear on the difference.	Based on the URRA, if this task is omitted or not performed correctly there is risk of losing therapeutic effect. Our review of the study results identified subjective feedback that indicated that the participants confused the expiration date with the in-use date. Our review of the labels and labeling (user interface, etc.) finds that the information on how long the medication in this pen can be used after its first use in the IFU can be improved. **We provide a recommendation in the Identified Issues and Recommendations for Pfizer Table to address this concern.** We have determined that this change can be implemented without submitting additional validation testing for Agency review.

	The Applicant has not proposed mitigation strategies for these use errors.	
19.	For the knowledge task question, "How do you know what type of needle you are supposed to use?", there were 2 partially correct (1 trained, 1 untrained) and 5 incorrect (1 trained, 4 untrained) answers. The subjective data and the Applicant's root cause analysis indicated: • Participants could not find or had difficulty finding this information. In the root cause analysis, the Applicant stated that it is due to information not found with Step 4 where needle attachment is described. The Applicant has not proposed mitigation strategies for these use errors.	Based on the URRA, if this task is omitted or not performed correctly there is risk of intradermal or intramuscular injection, reversible injuries, transection of dermis, or bleeding from injury. Our review of the study results identified subjective feedback that indicated the majority of participants noted this information would be available from the pharmacist in case they needed to find out (citing that the needles would be co-prescribed). Our review of the labels and labeling (user interface, etc.) finds that the IFU contains information on what type of needle to use on the bottom, left panel. Additionally, this information is also included on the carton labeling. We have not identified additional changes to the user interface to further reduce the risks associated with these use errors. We find that the residual risk in this case is acceptable.
20.	For the knowledge task question, "What is the maximum dose that can be given as a single injection from this pen?", there were 7 incorrect answers (2 trained, 5 untrained). The subjective data and the Applicant's root cause analysis indicated: • Negative Transfer - participants assumed that all medication can be delivered from one injection as the pen is labeled with the total mgs of medication. The Applicant has not proposed mitigation strategies for these use errors.	Based on the URRA, if this task is omitted or not performed correctly there is risk of reversible injuries (e.g., superficial scratches), losing therapeutic effect, inconvenience to patient or no harm expected. Our review of the study results identified subjective feedback that indicated that these errors were due to negative transfer. Additionally, after moderator prompting the participants to look in the IFU, some participants were unable to find the information in the IFU. However, some participants found the information explaining the maximum dialable dose after reviewing the IFU. The Applicant has engineered in safety to prevent users from administering full amount of medication in the pen, for example the maximum dose that can be dialed is 30 mg in the 60 mg pen and 12 mg in the 24 mg pen.

		However, our review of the labels and labeling (user interface, etc.) finds that the strength presentation on carton labeling and container label can be improved. **We provide a recommendation in the Identified Issues and Recommendations for Pfizer Table to address this concern.** We have determined that this change can be implemented without submitting additional validation testing for Agency review.
21.	For the knowledge task question, "With a 60 mg pen, if the dose was 36 mg, what would you do?" or "With a 24 mg pen, if the dose was 14 mg, what would you do?", there were 1 partially correct (untrained) and 8 incorrect (3 trained, 5 untrained) answers. The subjective data and the Applicant's root cause analysis indicated: • The Applicant stated that the root cause analysis for the use errors were that the information in this section of the IFU is dense and could be considered to be complex if a user has not seen this done but is rather trying to understand it based on a written description. Participants reported that they would need two pens as the maximum dialable dose is 30 mg for 60 mg pen and 12 mg for 24 mg pen. Some participants did not realize they could dial the remaining of the dose from the same pen. The Applicant has not proposed mitigation strategies for these use errors.	Based on the URRA, if this task is omitted or not performed correctly there is risk of losing therapeutic effect, inconvenience to patient, possible local reaction, headache, possible initial hypoglycemia followed by reactive hyperglycemia, unconsciousness, seizure, edema and fluid retention possible, possible resulting hypothyreosis, reversible injuries (e.g., superficial scratches), or no harm expected. Our review of the study results indicates that the root cause analysis was incomplete because the Applicant did not identify why participants in the study reported that two pens would be needed. Our review of the labels and labeling (user interface, etc.) finds that the IFU explains how to split a dose from the same pen in the event that the prescribed dose is larger than the maximum dialable dose. We have not identified additional changes to the user interface to further reduce the risks associated with these use errors. We find that the residual risk in this case is acceptable.
22.	For the knowledge task question, "If the prescribed dose was 3.8 mg (24 mg pen) or 21.5 mg (60 mg pen), how would you set the dose knob? Can you show me?" there were 4 incorrect answers (1 trained, 3 untrained). The subjective data and the Applicant's root cause analysis indicated:	Based on the URRA, if this task is omitted or not performed correctly there is risk of losing therapeutic effect, inconvenience to patient, possible local reaction, headache, possible initial hypoglycemia followed by reactive hyperglycemia, unconsciousness, seizure, edema and fluid retention possible, possible resulting hypothyreosis, reversible injuries (e.g., superficial scratches), or no harm expected.

	• Participants appeared to have an issue aligning the dose dial to the correct dose due to the fact that correct dose was unlabeled. The Applicant has not proposed mitigation strategies for these use errors.	Our review of the study results identified subjective feedback that indicated that the participants had issues aligning the dose dial to the correct value due to the fact that the correct dose was not labeled. Our review of the labels and labeling (user interface, etc.) finds that the IFU contains illustration on setting the dose for injection for an unlabeled dose.  We have not identified additional changes to the user interface to further reduce the risks associated with these use errors. We find that the residual risk in this case is acceptable.
23.	For the knowledge task question, "How do you know that the dose has been delivered?", there were 2 partially correct answers (untrained). The subjective data and the Applicant's root cause analysis indicated: • Study artifact – participants may not have provided correct response due to not performing the injections correctly. • Participant may have overlooked the information in the IFU. The Applicant has not proposed mitigation strategies for these use errors.	Based on the URRA, if this task is omitted or not performed correctly there is risk of losing therapeutic effect. Our review of the study results identified subjective feedback that indicated that the participant had not seen the dose dialer go down all the way because of not fully pressing the dialer all the way down during simulated use scenario. This knowledge task question response may have been affected by performance during the simulated use injection scenario. Our review of the labels and labeling (user interface, etc.) finds that the IFU Step 9, "Inject your medicine" contains image and text to support completion of this task. We have not identified additional changes to the user interface to further reduce the risks associated with these use errors. We find that the residual risk in this case is acceptable.

3.1 ANALYSIS OF NON-CRITICAL TASKS

The HF validation study showed use errors, (e.g., failures, difficulties, and close calls) with the following non-critical tasks. Based on our review of the available participants' subjective feedback, and the Applicant's root cause analysis, we determined that the residual risk is acceptable without further need for risk mitigation strategies at this time to address the use errors related to the following non-critical use tasks:

- Store pen
- Cap and store the pen in the refrigerator until next use

3.2 LABELS AND LABELING

Tables A below includes the identified medication error issues with the submitted label and labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table A: Identified Issues and Recommendations for Pfizer (entire table to be conveyed to Applicant)			
	Identified Issue	**Rationale for Concern**	**Recommendation**
Instructions for Use (IFU)			
1.	Image in Step 4 does not clearly instruct the user to push and then twist on the needle.	We are concerned if the user does not attach the needle correctly, there is risk of intradermal or intramuscular injection, reversible injuries, transection of dermis, bleeding from injury, or loss of therapeutic effect. The human factors (HF) validation study results identified subjective feedback that indicated that one participant stated that it was not clear from the IFU that he needed to push while twisting on the needle.	We recommend revising the image in Step 4 to clearly show to push and then twist on the needle.
2.	The IFU does not clearly emphasize the dose required to prime the pen.	We are concerned if the user does not set a prime dose, there is risk of inconvenience to the patient, subcutaneous emphysema, or injection of small amount of air. The HF validation study results indicated that participants dialed to the prescribed dose and bypassed the initial "prime" dose as a number of	We recommend revising the IFU priming steps to clearly emphasize the dose stated in the IFU is the prime dose.

		participants thought the prime number was just an example of how to dial the pen rather than the instructed priming dose.	
3.	The IFU does not include information on only splitting the dose if trained or advised by healthcare provider on how to do it.	We are concerned if the user does not split the dose, there is risk of losing therapeutic effect, inconvenience to patient, possible local reaction, headache, possible initial hypoglycemia followed by reactive hyperglycemia, unconsciousness, seizure, edema, and fluid retention possible, or possible resulting hypothyreosis. The HF validation study results identified subjective feedback that indicated that the participants had difficulty splitting the dose.	We recommend revising the IFU to include information on only splitting the dose if trained or advised by healthcare provider on how to do it. For example, "Only split your dose if you have been trained or advised by your healthcare provider on how to do this."
4.	The image in Step 10 does not clearly instruct the user to count to 10 after pressing the injection button and to keep holding the injection button	We are concerned if the user does not continue to press the injection button while counting to 10, there is risk of losing therapeutic effect, or inconvenience to patient. The HF validation study results identified subjective feedback	We recommend revising the image in Step 10 to make it more clear to the user to start counting after fully pressing the injection button and to keep holding the injection button while counting to 10.

	while counting to 10.	that indicated that the graphic in Step 10 may be confusing.	
5.	We note the information on what to do if this pen has been frozen or stored in direct sunlight is found in Step 1, getting ready. However, this information is not included in the storage section of the IFU.	We are concerned if the user uses the pen that has been frozen or stored in direct sunlight, there is a risk of losing therapeutic effect, local infection, or inflammation. The HF validation study results identified subjective feedback that indicated that the participant expected to find the information in the storage section in IFU.	We recommend revising the IFU to add the information on what to do if this pen has been frozen or stored in direct sunlight in storage section of the IFU.
6.	The difference between expiration date and in-use (28 days after first use) date is not clearly stated in the IFU.	Lack of clarity on the difference between expiration date and in-use date may lead to loss of therapeutic effect. The HF Validation study results identified subjective feedback that indicated that the participants confused the expiration date with the in-use date.	We recommend revising the IFU storage and disposal section to clearly differentiate between expiration date and in-use date.
Container labels and Carton labeling			
1.	The strength is expressed as (b) (4)	The HF Validation study results identified subjective feedback that indicated that participants	For consistency with the PI, revise the strength presentation (b) (4) to "24 mg/1.2 mL

	(b) (4)	assumed that all medication can be delivered from one injection as the pen is labeled (b) (4) Additionally, this format is inconsistent with the presentation of strength in the Dosage Forms and Strengths section of the prescribing information (PI). The strength should be expressed as total quantity per total volume, followed by the quantity per mL enclosed in parentheses.	(20 mg/mL)" and (b) (4) to "60 mg/1.2 mL (50 mg/mL)".

4 CONCLUSION AND RECOMMENDATIONS

The results of the HF validation study demonstrated several use errors/close calls/use difficulties with critical tasks that may result in harm to the patient. However, based on our review of the available participants' subjective feedback, and root cause analysis, we identified additional risk mitigations to address the use errors. Additionally, our evaluation of the proposed packaging, label and labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table A for Pfizer. We ask that the Division of General Endocrinology (DGE) convey Table A in its entirety to Pfizer so that recommendations are implemented prior to approval of this BLA. In this particular instance, we have determined that that these changes can be implemented without additional HF validation testing to be submitted for review.

4.1 RECOMMENDATIONS FOR PFIZER

Our evaluation of the proposed label and labeling identified areas of vulnerability that may lead to medication errors. We have provided recommendations in Table A and we recommend that you implement these recommendations prior to approval of this BLA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. DRUG PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 5 presents relevant product information for MOD-4023 that Pfizer submitted on October 22, 2020.

Table 5. Relevant Product Information	
Initial Approval Date	N/A
Therapeutic Drug Class or New Drug Class	A long-acting recombinant growth hormone analog
Active Ingredient (Drug or Biologic)	somatrogon
Indication	(b) (4) [redacted]
Route of Administration	Subcutaneous
Dosage Form	Injection
Strength	24 mg/1.2 mL 60 mg/1.2 mL
Dose and Frequency	0.66 mg/kg body weight administered once weekly, on the same day each week, at any time of day
How Supplied	• Single-patient-use, disposable prefilled pen containing 24 mg/1.2 mL that delivers a dose in 0.2 mg increments • Single-patient-use, disposable prefilled pen containing 60 mg/1.2 mL that delivers a dose in 0.5 mg increments
Storage	Refrigerator at 36°F to 46°F (2°C to 8°C)
Container Closure/Device Constituent	Single-patient use, multidose, disposable prefilled pen (b) (4) [redacted]
Intended Users	• Pediatric patients • Adult caregivers • Healthcare professionals
Intended Use Environment	Home or medical setting

APPENDIX B. BACKGROUND INFORMATION

B.1 PREVIOUS HF REVIEWS

B.1.1 Methods

On March 21, 2021, we searched the L:drive and AIMS using the terms, MOD-4023, 761184 and 132494 to identify reviews previously performed by DMEPA or CDRH.

B.1.2 Results

Our search identified three previous reviews[i,j,k], and we confirmed that our previous recommendations were implemented.

[i] Schlick J. Human Factors Protocol Review for MOD-4023 (IND 132494). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 DEC 6. RCM No.: 2018-2241.

[j] Schlick J. Human Factors Protocol Review Memorandum for MOD-4023 (IND 132494). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 MAR 5. RCM No.: 2018-2241-1.

[k] Schlick J. Human Factors Protocol Review Memorandum for MOD-4023 (IND 132494). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 JUN 19. RCM No.: 2018-2241-2.

APPENDIX C. BACKGROUND INFORMATION ON HUMAN FACTORS ENGINEERING PROCESS

The background information can be accessible in EDR via:
\\CDSESUB1\evsprod\bla761184\0001\m3\32-body-data\32r-reg-info\hf-engineering-report-somatrogon-prefilled-pen.pdf

APPENDIX D. HUMAN FACTORS VALIDATION STUDY RESULTS REPORT

The HF study results report can be accessible in EDR via:
\\CDSESUB1\evsprod\bla761184\0001\m3\32-body-data\32r-reg-info\hf-engineering-report-appendix-1.pdf

APPENDIX E. INFORMATION REQUESTS ISSUED DURING THE REVIEW

On May 13, 2021, we issued an Information Request (IR) to:

- obtain information on whether there were instances of wet injection or underdose for study participants who did not hold the injection button down for the required hold time.
- obtain Applicant's rationale to support including the algorithm to determine when to prime the pen in the proposed IFU.

The Applicant provided an acceptable response on May 14, 2021 that can be accessible in EDR via:

\\CDSESUB1\evsprod\bla761184\0034\m5\53-clin-stud-rep\535-rep-effic-safety-stud\pediatric-ghd\5354-other-stud-rep\response-hf-info-request\response-13may21-qqr13-1.pdf

\\CDSESUB1\evsprod\bla761184\0034\m5\53-clin-stud-rep\535-rep-effic-safety-stud\pediatric-ghd\5354-other-stud-rep\response-hf-info-request\response-13may21-qqr13-2.pdf

On November 29, 2021, we issued an IR to:

- obtain information on which, if any, IFU changes were made based on the use errors, use difficulties and close calls seen in the HF validation study results and include them in table 24 Use Issue Descriptions and Root Cause Analysis.
- obtain clinical impact of potential use errors with the following tasks: remove the needle from the pen and replace cap on pen.
- obtain the time each participant held the injection button down after the dose window read zero for the 22 use errors and 4 use difficulties during scenario 1, 23 use errors and 5 use difficulties during scenario 2, and 24 use errors and 11 use difficulties during scenario 3.

The Applicant provided an acceptable response on December 1, 2021 that can be accessible in EDR via:

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\\CDSESUB1\evsprod\bla761184\0068\m5\53-clin-stud-rep\535-rep-effic-safety-stud\pediatric-ghd\5354-other-stud-rep\response-hf-info-request\qqr19-1-response-29nov2021.pdf

\\CDSESUB1\evsprod\bla761184\0068\m5\53-clin-stud-rep\535-rep-effic-safety-stud\pediatric-ghd\5354-other-stud-rep\response-hf-info-request\qqr19-2-response-29nov2021.pdf

\\CDSESUB1\evsprod\bla761184\0068\m5\53-clin-stud-rep\535-rep-effic-safety-stud\pediatric-ghd\5354-other-stud-rep\response-hf-info-request\qqr19-3-response-29nov2021.pdf

On December 8, 2021, we issued an IR to further request the information regarding the time each participant held the injection button down after the dose window read zero for the 22 use errors and 4 use difficulties during scenario 1, 23 use errors and 5 use difficulties during scenario 2, and 24 use errors and 11 use difficulties during scenario 3.

The Applicant provided an acceptable response on December 10, 2021 that can be accessible in EDR via:

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\\CDSESUB1\evsprod\bla761184\0069\m1\us\response-ir-8-dec-2021.pdf

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[l] along with postmarket medication error data, we reviewed the following MOD-4023 labels and labeling submitted by Pfizer.

- Container labels received on October 22, 2020
- Carton labeling received on October 22, 2020
- Instructions for Use (Image not shown) received on October 22, 2020, available from \\CDSESUB1\evsprod\bla761184\0001\m1\us\lab143301-lab144901-lab145201-lab145401-annotated.doc

F.2 Labels and Labeling Images

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

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

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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/

AVANI BHALODIA
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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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Division of Pediatrics and Maternal Health Memorandum

Date: November 4, 2021 **Date Consulted:** February 16, 2021

From: Christos Mastroyannis, M.D., Medical Officer, Maternal Health
Division of Pediatrics and Maternal Health (DPMH)

Through: Tamara Johnson, MD, MS, Team Leader, Maternal Health, DPMH

Lynne Yao, MD, Director, DPMH

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

BLA: 761184

Drug: Somatrogon injection, for subcutaneous use

Proposed Indication: (b) (4)

Applicant: Pfizer Ireland Pharmaceuticals

Subject: Evaluation of possible safety signal and pregnancy labeling

Materials Reviewed:

- BLA 761184 submitted on October 22, 2020.
- Center for Devices and Radiological Health (CDRH) Consult Memo for ICCR case number 00070937 (Somatrogon), by Joey Kotarek, PhD, dated 4/22/21.
- Division of Urology, Obstetrics and Gynecology (DUOG) Consult Review by Deputy Director Audrey Gassman, MD, dated 5/11/21. DARRTS Reference ID: 4796171.

- DPMH PLLR Review for Sogroya (somapacitan) BLA 761156 by Jeanine Best, MSN, RN, PNP, dated April 17, 2020. DARRTS Reference ID: 4594104.[1]
- DPMH PLLR Review for Norditropin (somatropin) NDA 21448/S037 and 038, by Catherine Roca, MD, dated February 7, 2018. DARRTS Reference ID: 4217578.[1]
- Applicant's response to information request (IR) submitted on March 2, 2021.
- Applicant's response to IR submitted on March 12, 2021.

Consult Question: "DGE requests DPMH input regarding possible clinical consequences of interference of antibodies specific to HCG with diagnostic assays or with pregnancies."

INTRODUCTION

On October 22, 2020, the applicant, Pfizer Ireland Pharmaceuticals, submitted an original BLA for somatrogon injection (b) (4) On February 16, 2021, Division of General Endocrinology (DGE) consulted the Division of Pediatric and Maternal Health (DPMH) to assist in the evaluation of a possible safety signal and labeling review for the *Pregnancy, Lactation,* and *Females and Males of Reproductive Potential.* The consult request includes the following information:

> In the phase 2 study (CP-4-004) long-term phase, of 48 patients, 18 (37.5%) developed anti-drug antibody (ADA) and in 3 patients, the antibodies showed specificity for CTP. In the phase 3 study (CP-4-006) main study (1 year), of 109 patients, 84 (77%) tested positive for ADA, and 4 of them had antibodies with specificity to CTP. In the extension phase, 26 (68.4%) of 38 subjects were positive for ADA and 5 of the patients had antibodies with specificity for CTP. The applicant has conducted in vitro studies to demonstrate that somatrogon spiked into human serum and urine samples do not interfere with the results of pregnancy tests based on detection of hCG. However, we are concerned with potential interference of CTP-specific antibodies in diagnostic assays that rely on detection of beta subunit hCG (e.g., pregnancy test, ovarian cancer, choriocarcinoma of the uterus). DGE requests DPMH input regarding possible clinical consequences of interference of antibodies specific to hCG with diagnostic assays or with pregnancies.

DPMH recommended the DGE Review Team consult the Center for Devices and Radiological Health (CDRH) to provide an assessment of the potential impact anti-CTP antibodies on diagnostic assays.[2] The reader is referred to the CDRH Consult Memo by Joey Kotarek, PhD for details.[3] DGE also consulted the Division of Urology, Obstetrics and Gynecology (DUOG) to provide a clinical perspective on the presence of anti-CTP antibodies and whether these

[1] The Sogroya and Norditropin NDA reviews were part of the materials reviewed but were not a source relied upon for the labeling recommendations below. Rather the cross-reference is included to avoid duplicating background information relevant to this class of products.
[2] Personal Communication between Tamara Johnson, MD, MS, and Marina Zemskova, MD, dated 2/18/21.
[3] CDRH Consult Memo for ICCR case number 00070937 by Joey Kotarek, PhD, dated 4/22/21.

antibodies are of clinical concern in terms of interfering with pregnancy. The reader is referred to the DUOG Consult Review by Audrey Gassman, MD for details.[4]

The focus of this DPMH consult will be on the potential impact of anti-CTP antibodies on pregnancy, as well as Pregnancy and Lactation Labeling Rule (PLLR) labeling recommendations for somatrogon.

BACKGROUND

Regulatory History

- On October 22, 2020, the applicant submitted an original BLA for somatrogon injection (b) (4)
- On February 19, 2021, DGE sent the applicant an information request (IR) as follows:

  To evaluate the impact of immunogenicity of your product on the efficacy and safety in the intended population we request that you provide the following information:
  1. Information on all patients with positive antibodies at any time points during the study in Study CP-4-004 and Study CP-4-006 (including extension periods).
  2. Information on 2 patients with positive neutralizing antibodies in study CP-4-006.
  3. We also noted that some samples positive for anti-somatrogon antibodies showed specificity for the carboxi-terminal peptide (CTP) of beta chain of human chorionic gonadotropin (hCG) that is fused to the growth hormone molecule:
     a. 3 (16.7%) of 18 subjects of Study CP-4-004 open-label extension (OLE) phase
     b. 4 (4.8%) of 84 subjects in Study CP-4-006, main period; and
     c. 5 (19.2%) of 26 subjects of CP-4-006 OLE phase.

     Assess the risk of anti-CTP antibodies in terms of interfering with hCG positive results in the diagnostic testing (e.g., pregnancy, test for ovarian cancers, etc.) or pregnancy outcomes (e.g., spontaneous abortions) or provide data if available."

- On March 2, 2021, the applicant submitted their response to question 3 discussed below.
- On March 12, 2021, the applicant submitted their response to questions 1 and 2 which is deferred to DGE Review Team.

Drug Characteristics[5]

- *Description:* somatrogon is a recombinant human growth hormone (rhGH) comprised of the amino acid sequence of human growth hormone (hGH) (b) (4) with one copy of the C-terminal peptide (CTP) from the beta chain of human chorionic gonadotropin (hCG) at the N-terminus and 2 copies of CTP (in tandem) at the C-terminus (b) (4)
- *Mechanism of action:* binds to the growth hormone (GH) receptor and initiates a signal transduction cascade culminating in changes in growth and metabolism. Consistent with

[4] DUOG Consult Review by Audrey Gassman, MD, dated 5/11/21. DARRTS Reference ID: 4796171.
[5] Somatrogon (BLA 761194), proposed package insert.

GH signaling, somatrogon binding leads to activation of the STAT5b signaling pathway and increases the serum concentration of Insulin-like Growth Factor (IGF-1). IGF-1 was found to increase in a dose-dependent manner during treatment with somatrogon, partially mediating the clinical effect. As a result, GH and IGF-1 stimulate metabolic changes, linear growth, and enhance growth velocity in pediatric patients with growth hormone deficiency (GHD).

- *Dosage and administration:* 0.66 mg/kg body weight administered once weekly by subcutaneous injection.
- *Contraindications:* (b) (4)
- *Warnings and Precautions:* (b) (4)
- *Mean population PK estimated effective half-life:* (b) (4)

Growth Hormone Deficiency (GHD) and Pregnancy

- The prevalence of GHD is estimated to be approximately 1:4000 to 1:10,000.[6]
- Women with GHD may have reduced fertility.[7,8]
- No practice guidelines from the American College of Obstetricians and Gynecologists (ACOG) or the Endocrine Society were found regarding specific treatment of pregnant women with GHD.
- One study in the literature suggests maintaining replacement therapy in women with GHD until placental GH levels are sufficient. (This regimen maintains pregestational GH replacement during the first trimester and tapering off GH replacement during the second trimester).[9] However, other regimens include discontinuing therapy once pregnancy starts, or continuing throughout gestation.[10]

Reviewer's Comment
Placental growth hormone (PGH) is a pregnancy-specific protein that is produced by syncytiotrophoblast and extra villous cytotrophoblast layers of the human placenta. PGH differs from pituitary growth hormone by 13 amino acids and possesses one glycosylation site.[11] From 12 to 20 weeks' gestation, PGH gradually replaces the pituitary growth hormone, which becomes undetectable by the third trimester. PGH is secreted only in the maternal circulation and has not been detected in the fetal blood. After the placenta is removed with the birth of an infant, there is a decrease in PGH concentration.[12]Dysregulation of PGH in pathologic

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[6] Stanley T. Diagnosis of growth hormone deficiency in childhood. Curr Opin Endocrinol Diabetes Obes. 2012;19(1):47-52.
[7] De Boer JAM, Schoemaker J, and van der Veen EA. Impaired reproductive function in women treated for growth hormone deficiency during childhood. Clin Endocrinol. 1997;46:681-689.
[8] Vila G, et al. Pregnancy outcomes in women with growth hormone deficiency. Fertil and Steril. 2015;104(5):1210-1217.
[9] Wiren L, Boguszewski CL and Johannsson G. Growth hormone (GH) replacement therapy in GH-deficient women during pregnancy. Clin Endocrinol. 2002;57:235-239.
[10] Vila G, et al. Pregnancy outcomes in women with growth-hormone deficiency. Fertil Steril. 2015;104:1210-1217.
[11] Lacroix M, et al. Human placental growth hormone-a review. Placenta. 2002 Apr; 23 SupplA:S87-94.
[12] Frankenne F, et al. The physiology of growth hormones (GHs) in pregnant women and partial characterization of the placental GH variant. JCEM. 1988;66(6):1170-1180.

conditions of pregnancy may adversely impact fetal growth.[13] However, it is unknown if somatrogon anti-drug antibodies (ADA) could have any cross reactivity with PGH given the similarities between PGH and pituitary growth hormone.

REVIEW

PREGNANCY

Nonclinical Experience[5]

In an embryo-fetal development study in rats (b) (4) (b) (4) at doses up to 30 mg/kg* (45 times the maximum recommended human dose based on exposure), (b) (4)

In a pre- and postnatal development study in rats, somatrogon was administered via subcutaneous injection to pregnant rats at doses up to 30 mg/kg**. There was no evidence of maternal toxicity and no adverse effects on the first generation (F1) offspring. Somatrogon elicited an increase in F1 mean body weights (b) (4)

For additional details, refer to the Nonclinical Review by Elena Braithwaite, PhD.

Clinical Experience

Somatrogon is not currently approved in any country and has only been used in the applicant's clinical trials. The applicant's submitted Clinical Summary of Safety states that there have been no studies of somatrogon in pregnant women. Pregnant women were excluded from clinical trials with somatrogon and the applicant stated only 1 adult pregnancy case (no pediatric pregnancy cases) was reported during the clinical development program.

The subject (b) (6) was a 36-year-old female who was administered the last dose of somatrogon 5 days prior to the estimated date of conception, thus exposure did not occur during pregnancy. The pregnancy was complicated by gestational diabetes (prior maternal history of impaired glucose tolerance) and the pregnancy outcome was a healthy baby boy (gestational age at birth unknown, weight 2550 grams, Apgar score of 9). The patient did not develop anti-CTP antibodies during treatment with somatrogon.

Reviewer's Comment

There are no available clinical experience data with somatrogon use during pregnancy in the indicated pediatric population. The single case reported above occurred in an adult and exposure occurred preconception rather than during pregnancy. DPMH discussed with the Clinical Team the anticipated age of pediatric patients exposed to somatrogon. The Clinical Review Team stated that pediatric patients aged 3 years and older with growth failure due to GHD could be exposed to somatrogon until an age that they still have opened epiphysis (which may be up 15 to 16 years old).[14] Thus, it is possible that adolescents treated with somatrogon

[13] Newbern D, et al. Placental hormones and the control of maternal metabolism and fetal growth. Curr Opin Endocrinol Diabetes Obes. 2011 Dec; 18(6):409-16.

[14] DPMH Personal Communication with Marina Zemskova, MD, Clinical Team Lead, dated 3/23/21.

could be exposed during pregnancy. The applicant is not currently seeking approval of somatrogon in adults as efficacy was not demonstrated in this population during the clinical development program.

Review of Published Literature
The applicant did not submit a literature review related to somatrogon use during pregnancy.

This Reviewer performed a search in PubMed, Embase, Micromedex[15], TERIS[16], Reprotox[17], and Briggs[18] to find relevant articles related to the use of somatrogon during pregnancy. Search terms included "somatrogon" AND "pregnancy," "birth defects," "congenital malformations," "stillbirth," "spontaneous abortion," OR "miscarriage." No relevant articles were identified.

DPMH's Review of the Applicant's Response to IR
On March 2, 2021, the applicant submitted their response to DGE information request to assess the risk of anti-CTP antibodies observed in subjects enrolled in the Phase 2 (CP-4-004 open label extension) and Phase 3 trials (CP-4-006 and CP-4-006 open label extension) with somatrogon in terms of interfering with hCG positive results in diagnostic testing or pregnancy outcomes (e.g., spontaneous abortions).

The applicant stated that another way of presenting the incidence of anti-CTP antibodies is to use the number of tests performed as the denominator instead of the number of subjects. The applicant asserted that in the totality of the program there were only 12/426 (2.9%) anti-drug antibodies (ADA) samples tested that showed specificity towards CTP. The applicant noted that this low incidence of CTP specificity detection (2.9%) is near the rate of false positive detection,[19] and also that the detections were weak transient responses that did not correlate with antibody titers. The applicant further stated that the CTP specificity results had values that were for the most part very close to the detection cut point implying a low level of putative response. The applicant concluded that the CTP specificity observed amongst somatrogon positive samples was sporadic and of low incidence and magnitude, which reduces the risk of interfering in the diagnostic testing or pregnancy outcomes and supports the use of total number of tests performed to assess incidence rather than the number of subjects who tested positive at some point in time.

Reviewer's Comment:
DPMH discussed the applicant's above response with the Immunogenicity Review Team.[20] The Immunogenicity Team responded that the risk assessment the applicant provided is acceptable. Even though it appears that the risk is low for anti-CTP antibodies, developed

[15] Truven Health Analytics information, http://www.micromedexsolutions.com/. Accessed 7/29/21.
[16] TERIS database, Truven Health Analytics, Micromedex Solutions, Accessed 7/29/21.
[17] Reprotox® Website: www.Reprotox.org. REPROTOX® system was developed as an adjunct information source for clinicians, scientists, and government agencies. Accessed 7/29/21.
[18] Briggs, GG. Freeman, RK. & Yaffe, SJ. (2017). Drugs in pregnancy and lactation: A reference guide to fetal and neonatal risk. Philadelphia, Pa, Lippincott Williams & Wilkins.
[19] Tan CY, et al. Criteria to Reevaluate Anti-drug antibody Assay Cut Point Suitability in the Target Population. The AAPS Journal 2020;22:19.
[20] Personal Communication with Montserrat Puig, PhD, Immunogenicity Reviewer, dated 3/23/21.

due to treatment, to interfere with diagnostic tests and possible pregnancy, in reality we do not know what the right answer is. The Immunogenicity Review Team confirmed anti-CTP antibodies were transient (most subjects had one positive time point only) and mostly of low titer compared to somatrogon ADAs. Refer to Table 1 Appendix B for details. The Immunogenicity Team also confirmed that there is no available data on the affinity of the anti-CTP antibodies to hCG. DPMH agrees the low titer and transient nature of the anti-CTP antibodies suggest the risk to pregnancy is likely low. However, as noted by the Immunogenicity Review Team, the binding affinity and ability to neutralize hCG activity remains an important unknown. The Immunogenicity Review Team further noted that the applicant changed the formulation from vial to pen at the end of Phase 2 and anti-CTP antibodies were only observed in pediatric patients treated with the pen, although the cause is unclear at this time.

DPMH requested the Immunogenicity Review Team also provide input on whether there was a potential concern for possible B cell memory with future endogenous hCG exposure that could impact pregnancy or fertility in patients previously treated with somatrogon who developed anti-CTP antibodies.[21] DPMH provided a review article by Kara et al. 2019,[22] which notes immune responses against hCG may impair fertility of women and induce pregnancy loss within the 1st trimester. The development of an hCG vaccine for contraception is also described, which aims to induce the secretion of antibodies that will bind hCG and block its activity, thus impeding pregnancy. Trial participants' antibody titers declined over time though, indicating the hCG vaccine is reversible, and additional published literature describe successful future pregnancy in hCG vaccine trial participants.[23] The Immunogenicity Review Team reasoned if patients were at risk to develop B cell memory to the CTP epitope of somatrogon, then it would likely have been noticed during the clinical trials by observing longevity of the anti-CTP antibodies in a patient's serum with repeated dosing of the antigen (somatrogon). However, instead what was observed for anti-CTP antibodies was a weak titer and transient response (only 1 timepoint for most patients). While acknowledging that there are limited long-term data on anti-CTP antibodies to evaluate the potential risks to pregnancy, the Immunogenicity Review Team expressed low concern for anti-CTP antibody neutralization or interference with hCG with long-term chronic administration.

The reader is referred to the below section of this DPMH review document titled "FEMALES AND MALES OF REPRODUCTIVE POTENTIAL" and to the CDRH Memo by Joey Kotarek, PhD, for the assessment of the potential impact of anti-CTP antibodies on hCG diagnostic assays such as pregnancy tests.[3]

Summary of DUOG Consult

DGE also consulted DUOG to provide a clinical perspective on the presence of anti-CTP antibodies and whether these antibodies were of concern in terms of interfering with pregnancy or fertility based on DUOG's experience with development of gonadotropin products, specifically corifollitropin alfa. Refer to the DUOG consult review for details.[4]

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[21] DPMH Personal Communication with Montserrat Puig, PhD, Immunogenicity Review Team, dated 3/26/21.
[22] Kara E, et al. Modulation of Gonadotropins Activity by Antibodies. Frontiers in Endocrinology, 2019, Vol 10.
[23] Talwar G, et al. Current status of a unique vaccine preventing pregnancy. Front Biosci 2017 June 1;9:321-332.

Briefly, corifollitropin alfa is a fusion protein of recombinant FSH link to CTP of human hCG. The NDA application for corifollitropin alfa only has information on single dose administration and the product was not approved in the U.S. for reasons unrelated to immunogenicity. The only information on chronic use of corifollitropin alfa is from literature and the EMA as follows: of the 2,511 women treated with corifollitropin who were evaluated for the formation of post-treatment antibodies, only 4 (0.16%) had evidence of antibody formation. In each case, these antibodies were non-neutralizing and did not interference with response to stimulation. Two of these four women become pregnant during the same treatment cycle in which antibodies were detected, suggesting that the presence of non-neutralizing antibodies after stimulation with corifollitropin is not clinically relevant. DUOG concluded this is relatively reassuring and recommended based on limited this information that all patients treated with somatrogon who develop anti-CTP antibodies have follow-up titers to determine if the anti-CTP antibodies resolve over time as well as testing for neutralizing antibodies specific for CTP to confirm specificity of the anti-CTP result. DUOG also noted there was a recent report of a false positive pregnancy test during corifollitropin administration and EMA added this information to the Elonva product label.[24,25]

The DUOG consult review states that patients who have positive anti-CTP antibody results could theoretically have unintended reproductive consequences if the antibodies increase, persist, and/or if neutralizing antibodies develop and block hCG. There is very limited long-term data to assess whether the anti-CTP antibodies resolve after somatrogon discontinuation as was seen with corifollitropin alfa. hCG is not normally made by any organ of the healthy non-pregnant female. hCG plays a crucial role in the implantation of the embryo onto the endometrium. DUOG noted the most likely result of neutralizing hCG would be that implantation of the embryo on the endometrium would be blocked and the onset of pregnancy prevented. No autoimmune reactivity against any other organ would be expected and this makes it difficult to develop a predictive and feasible nonclinical*** or clinical study.
[***Dr. Braithwaite commented that “from a nonclinical perspective, studies in animals don’t always predict immune responses in humans (another reason why it would be difficult to design a nonclinical study to investigate the impact of neutralizing hCG antibodies on reproduction)].
The DUOG consult review also discusses leveraging the available data from the hCG vaccine. A 2017 review article is cited,[23] which states hCG vaccine development has been extremely difficult because the CTP region of beta hCG is a poor immunogen and necessitates the use of strong adjuvants to evoke the production of antibodies. The authors state “the ability of the anti-hCG titers above 50 ng/mL to prevent pregnancy in sexually active women without derangement of ovulation and menstrual regularity was clearly demonstrated.” DUOG noted that although the assays used to develop the hCG vaccine are likely different from those used for somatrogon, it would appear that low levels of anti-CTP antibodies are unlikely to interfere with fertility. Overall, the DUOG review team concluded there is insufficient data to conclude that chronic somatrogon use results in development of

[24] Gersh, R. False positive blood hCG test following corifollitropin alfa injection. Human Reproduction, 33(5),(2018),978.
[25] Current Elonva product information (https://www.ema.europa.eu/en/documents/product-information/elonva-epar-product-information_en.pdf)

anti-CTP antibodies that could neutralize the effects of hCG. In addition, it is unclear that there are additional nonclinical or clinical studies or trials that could be developed to further assess this risk.

LACTATION

Nonclinical Experience

Animal lactation studies have not been conducted with somatrogon.

Clinical Trials

The applicant's submitted Clinical Summary of Safety states lactation studies have not been conducted with somatrogon; thus, it is not known whether somatrogon is present in human milk. Lactating women were excluded from clinical trials during the clinical development program for somatrogon and no lactation exposure cases have been reported.

Review of Published Literature

The applicant did not submit a literature review related to somatrogon use during lactation.

This Reviewer performed a search in *Medications and Mother's Milk*[26], LactMed[27], Micromedex[15], Reprotox[17], Briggs[18], PubMed, and Embase to find relevant articles related to the use of somatrogon during lactation. Search terms included "somatrogon" AND "lactation" OR "breastfeeding." No relevant articles were identified.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience[5]

(b) (4) Somatrogon elicited an increase in estrous cycle length, copulatory interval, and number of corpora lutea at (b) (4)

For additional details, the reader is referred to the Nonclinical Review by Elena Braithwaite, PhD.

Review of Published Literature

The applicant did not submit a literature review related to somatrogon effects on fertility.

This Reviewer performed a search in PubMed, Embase, and Reprotox[8] to find relevant articles related to the use of somatrogon and effects on fertility. Search terms included "somatrogon" AND "fertility," "contraception," "oral contraceptives," OR "infertility." No relevant articles were identified.

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[26] Hale, Thomas (2020) Medication's and Mother's Milk. https://www.halesmeds.com Accessed 7/29/21.

[27] http://toxnet nlm nih.gov/cgi-bin/sis/htmlgen?LACT. 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 database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding. Accessed 7/29/21.

Summary of CDRH Consult

As noted by the CDRH Review Team,[3] the sponsor provided evidence that somatrogon (and its incorporated CTP subunit) did not interfere with 4 home-use (urine) hCG pregnancy tests and one (serum) quantitative hCG pregnancy test. For the large majority of the hCG/pregnancy tests marketed in the US, we do not know what epitope they are targeting. Many pregnancy tests target up to 5 epitopes of hCG (rather than just the 2 epitopes-b-8 and b-9-for anti-CTP antibodies provided by the applicant). The immunology reviewer finds this reassuring because if the test has other epitopes beyond b-8 and b-9, then in theory could still detect hCG. However, the sponsor has not provided evidence that these results are representative of how somatrogon or any anti-CTP antibodies generated due to somatrogon treatment may impact results from all hCG pregnancy tests marketed in the U.S. The risks associated with the interference of somatrogon (or any associated anti-CTP antibodies) with pregnancy tests constitute false positive and false negative results. CDRH concluded drug labeling may be adequate to mitigate these risks.

DISCUSSION and CONCLUSIONS

Pregnancy

Pregnant women were excluded from clinical trials with somatrogon. Only 1 adult pregnancy case (no pediatric cases) was reported during the clinical development program and exposure to somatrogon occurred preconception rather than during pregnancy. Therefore, there are no available data on somatrogon use in pregnant women to evaluate for a drug associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Similarly, there are no available data to evaluate the potential impact of anti-CTP antibodies that develop during treatment with somatrogon on pregnancy.

Overall, DPMH agrees with the DUOG Review Team's conclusions[4] that neither clinical trials nor nonclinical studies can be leveraged to determine if the anti-CTP antibodies reported during clinical trials for somatrogon are clinically relevant and/or would affect fertility and/or pregnancy loss with chronic somatrogon use for the reasons stated in the consult review as follows: 1) there is unlikely to be value in repeating the embryofetal developmental study in another species as monkeys or rabbits as the immunological response in these species is not predictive of the immunological response in humans and 2) there is unlikely to be a value in conducting a large postmarketing database or study to directly assess fertility and/or early pregnancy loss given the age of the population treated [pediatrics], the fact that not all somatrogon-treated patients will attempt to become pregnant, the relatively high background rate of pregnancy loss in the general population (20% of clinically recognized pregnancies), as well as the presence of other risk factors for infertility (such as male factor infertility, polycystic ovarian disease, etc.).

DPMH further acknowledges that the use of somatrogon is anticipated to be rare in females of reproductive potential considering it is intended to be given primarily prepubertal patients; however, if in the future the indication were to be expanded to adults, then the considerations around further study in pregnant women should be revisited.

Lactation
Lactating women were excluded during the clinical development program for somatrogon and no lactation exposures were reported. Overall, there are no available data on the presence of somatrogon in human or animal milk, the effects on the breastfed infant, or the effects on milk production. DPMH recommends subsection 8.2 of labeling include the following risk/benefit statement which is a PLLR requirement: "the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TRADENAME and any adverse effects from TRADENAME or from the underlying maternal condition."

Females and Males of Reproductive Potential
There are no available human data on the effects of somatrogon on fertility. Animal reproduction studies in rats do not suggest somatrogon adversely affects fertility. The effect of anti-CTP antibodies generated during treatment with somatrogon on fertility also remains unknown.

Based on the CDRH conclusion that the risks associated with the interference of somatrogon (or any associated anti-CTP antibodies) with pregnancy tests may constitute false positive and false negative results, DPMH recommends subsection 8.3 of labeling include a pregnancy testing heading which states that somatrogon or treatment-associated anti-CTP antibodies may interfere with blood or urine pregnancy tests.

RECOMMENDATIONS
DPMH updated subsections 8.1, 8.2, and 8.3 of labeling for compliance with the PLLR (see below). The labeling recommendations below reflect input from the Nonclinical Review Team. DPMH refers to the final BLA action for final labeling.

DPMH Proposed Somatrogon Pregnancy and Lactation Labeling
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
There are no available data on TRADENAME use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. In reproduction studies in pregnant rats, there was no evidence of embryo-fetal toxicity following administration of somatrogon subcutaneously during organogenesis at doses up to 45 times the maximum recommended human dose based on exposure data *(see Data).*

The estimated background risk of major birth defects and miscarriage is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data
Animal Data
In an embryo-fetal development study in rats administered somatrogon via subcutaneous injection every 2 days from Gestation Day (GD) 6 to 18, during the period of organogenesis, at doses up to 30 mg/kg (45 times the maximum recommended human dose based on exposure), there were no adverse maternal or embryo-fetal effects.

In a pre- and postnatal development study in rats, somatrogon was administered via SC injection to pregnant rats every 2 days from GD 6 to Lactation Day 20 at doses up to 30 mg/kg. There was no evidence of maternal toxicity and no adverse effects on the first generation (F1) offspring. Somatrogon elicited an increase in F1 mean body weights (both sexes) as well as an increase in the mean copulatory interval in F1 females at the highest dose (30 mg/kg), which was consistent with a longer estrous cycle length; however, there were no associated effects on mating indices.

8.2 Lactation

Risk Summary

There are no data on the presence of somatrogon in human or animal milk, the effects on the breastfed infant, or the effects on milk production. 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.

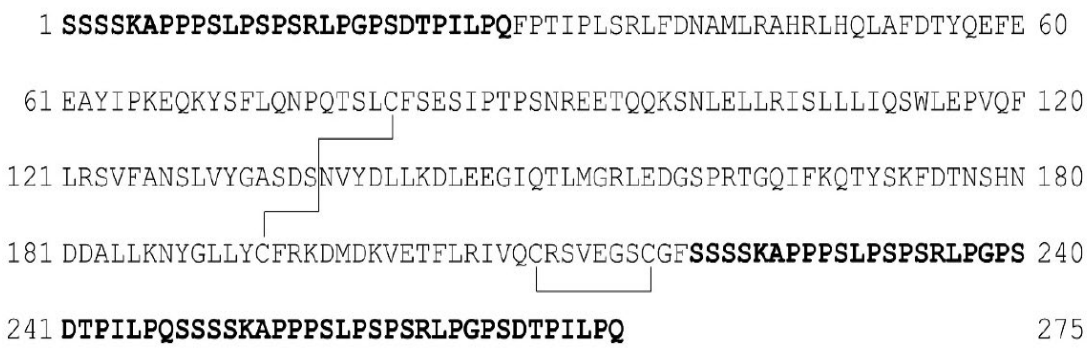
8.3 FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Interference with Diagnostic Assays of hCG

The presence of anti-somatrogon antibodies with specificity for the carboxi-terminal peptide (CTP) of beta chain of human chorionic gonadotropin (hCG) may potentially interfere with blood or urine pregnancy tests leading to either false positive or false negative results. Based on the clinical concern and the rationale for testing, consider alternative methods to determine pregnancy status or assess choriocarcinoma.

APPENDIX A[28]

Figure 1. Somatrogon Primary Structure (Amino Acid Sequence)



Somatrogon amino acid sequence; residues are numbered sequentially starting with the N terminus. The confirmed disulfide bonds are illustrated with connecting lines. The function, intact molecule is composed of recombinant human growth hormone (rhGH) and 1 copy of C-terminal peptide (CTP) form the beta chain of human chorionic gonadotropin (hCG) at the N-terminus (bold amino acids [1-28]) and 2 copies of CTP (in tandem) at the C-terminus (bold amino acids [220-247], and [248-275]).

APPENDIX B

Table 1: Data for Anti-CTP Antibody Patients[29]

Study	Months	presentation	participants	ADA+ (somatrogon)	Anti-hGH Ab	Anti-CTP Ab Patient ID_Visit(month)
CP-4-006 (Ph3, main)	12	Pen injector	109 (somatrogon) 115 (Genotropin)	77.1% (1.8% NAb+) 15.7%	77.1%	3.7% (4 individuals) • 025-207_V7(m9); neg at m12 [somatrogon pos m6,9,12, titer: 250/50/250] • 064-308_V8(m12); neg at m12 baseline OLE [somatrogon pos m6,9,12, titer: 50/50/250] • 215-079_V6(m6), neg at m12 [somatrogon pos m6, 12, titer: 250/250] • 227-145_V8(m12) [somatrogon pos m6, 12, titer: 10/250]
CP-4-006 (Ph3, open label extension (OLE))	12 (the majority of data is available till 6 months)	Pen injector	79	43.03%	41.8%	6.3% (5 individuals) • 040-024(S)_OLE(m12); no further data [somatrogon pos baseline,m6,m12; titer: 250] • 064-308(S)_OLE(baseline) was neg; pos at m12 of main (see above); no further data [somatrogon pos baseline, titer: 250] • 202-136(S)_OLE(6m); no further data [somatrogon pos baseline and m6, titer:1250] • 227-145(S)_OLE (baseline); neg at OLE(m6)

[28] Figure 1 copied from the applicant's submitted Clinical Overview for Somatrogon (BLA 761184), page 11 of 60.
[29] Table provided by the Immunogenicity Review Team during DPMH Personal Communication with Montserrat Puig, PhD, dated 4/5/21.

						[somatrogon pos baseline, titer:50/250] • 021-013(G)_OLE(12m); no further data [somatrogon pos m6&12; titer: 250/1250]
CP-4-004 (Ph2, main)	12	vial	14 (somatrogon 0.66 mg/kg/wk) 11 (Genotropin)	35.7% (No NAb+) 18.2%	35.7%	No Ab+
CP-4-004 (Ph2 OLE), VIAL	4 years	vial	43	25.6% (at year 3)	23.3%	No Ab+
CP-4-004 (Ph2 OLE)_PEN	Up to 12 months	pen	40	37.5%	32.5%	7.5% (3 individuals) • 10013_V1(baseline); neg m1,3,6,9,12; also neg through main, OLE-vial. • [somatrogon ADA+ during OLE-vial (>Y2) and OLE-PEN; titers:50 to 250] • 11008_V4(m6); neg m9,12; also negative before V4 • [somatrogon ADA+ during OLE-vial and OLE-PEN; titers:50 to 1250] • 17006_V5(m9), neg at m12, also neg during OLE-vial • [somatrogon ADA+ during OLE-vial (>Y4) and OLE-PEN; titers:50 to 250]

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/

CHRISTOS MASTROYANNIS
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TAMARA N JOHNSON
11/05/2021 07:05:33 AM

LYNNE P YAO
11/05/2021 10:15:52 AM

Clinical Inspection Summary

Date	6/11/2021
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	Sonia Doi, M.D., Ph.D., Clinical Analyst 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	761184
Applicant	Pfizer Ireland Pharmaceuticals
Drug	Somatrogon (MOD-4023)
NME	Yes
Therapeutic Classification	Recombinant human growth hormone
Proposed Indication	Treatment of pediatric patients with growth failure due to inadequate secretion of endogenous growth hormone
Consultation Request Date	12/10/2020
Summary Goal Date	06/22/2021 (*moved up from original due date of 8/6/2021*)
Action Goal Date	10/22/2021
PDUFA Date	10/22/2021

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The inspection for this biologics license application (BLA) consisted of two domestic clinical sites and the co-sponsor (OPKO Health, Inc.) of Study CP-4-006.

The ongoing COVID-19 global pandemic has significantly limited the ability of the Office of Regulatory Affairs (ORA) to conduct onsite foreign good clinical practice (GCP) inspections. As a result, the planned inspection of the sponsor Pfizer Ireland Pharmaceuticals was not conducted. Remote data investigation of source records by ORA was not feasible due to local restriction to obtain remote access of source records.

In general, based on the inspections of the two clinical sites and the co-sponsor, the inspectional findings support validity of data as reported by the sponsor under this BLA.

II. BACKGROUND

Pfizer Ireland Pharmaceuticals has submitted a biologics license application (BLA) for somatrogon, a long acting recombinant human growth hormone (rhGH) that has been developed for use in the treatment of pediatric patients who have growth failure due to an inadequate secretion of endogenous growth hormone (pediatric growth hormone deficiency [GHD]).

Pfizer Ireland Pharmaceuticals appointed Pfizer Inc. to serve as its authorized representative in connection with BLA 761184. Somatrogon has been granted Orphan Drug Designation (ODD) by the Office of Orphan Drug Products for the treatment of GHD. On September 3, 2020, Pfizer Inc. transferred the ownership and all rights to the ODD to Pfizer Ireland Pharmaceuticals.

The safety and efficacy of somatrogon for the proposed indication is supported by the results of a single pediatric Phase 3 study, a supportive pediatric Phase 2 study, and data from the ongoing open-label extensions (OLEs) of both studies.

The Phase 3 study was managed by OPKO Biologics Ltd. (OBL), a subsidiary of OPKO Health, Inc. (OPKO), the initial sponsor, and conducted by investigators contracted by and under the direction of OPKO. After database lock, OPKO transferred the complete set of data from the database to Pfizer. The data in the clinical study report (CSR) reflect and include the data reported in both the OPKO database (transferred to Pfizer) and the safety database (Pfizer Global Safety database for serious adverse events [SAEs]).

Inspections were requested for the Phase 3 study CP-4-006 entitled "*A Phase 3, Open-label, Randomized, Multicenter, 12 months, Efficacy and Safety Study of Weekly MOD-4023 Compared to Daily Genotropin® Therapy in Pre-Pubertal Children with Growth Hormone Deficiency*".

This 12-month, open-label, multicenter, randomized, active controlled, parallel group study compared the efficacy and safety of weekly somatrogon to daily growth hormone (GH) in prepubertal children with growth hormone disorder (GHD). Prepubertal children (boys 3-11 years, girls 3-10 years) diagnosed with GHD who had no prior exposure to any recombinant human growth hormone (rhGH) therapy, had impaired height and height velocity (HV), and with a baseline insulin-like growth factor-1 (IGF-1) level of at least 1 standard deviation (SD) below the mean IGF-1 level standardized for age and sex were enrolled into the study.

After a screening period of up to 12 weeks, eligible subjects were randomized (stratified by region, GH peak levels at screening, and chronological age) in a 1:1 ratio to weekly subcutaneous (SC) doses of somatrogon or daily SC administration of Genotropin® for 12 months (main study). Somatrogon was provided as a solution for injection containing 20 or 50 mg/mL of somatrogon in a single subject use, multi-dose disposable prefilled pen. Genotropin® was provided in prefilled cartridges for administration with the Genotropin® pen delivery device.

The primary endpoint was annual height velocity (HV) in cm/year after 12 months of treatment. Subjects who successfully completed the 12-month main study could participate in a single-arm long-term open-label extension (LT-OLE) treatment period with somatrogon.

The study began April 19, 2017 and completed August 23, 2019. A total of 84 study sites screened 536 subjects and randomized 228 subjects in this study. Of the 228 subjects who were randomized, 4 subjects (3 in the somatrogon group; 1 in the Genotropin® group) did not receive study drug (3 withdrawn by parent/guardian, 1 lost to follow-up during the screening phase). Therefore, 224 subjects were randomized and received at least 1 dose of study drug; 2 of these subjects discontinued during the main study. There were 212 subjects that went into the LT-OLE study and 10 subjects did not.

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. **David P. Flynn, M.D.**
   St. Luke's Children's Endocrinology
   305 E. Jefferson Street
   Boise, ID 83712-6273
   Site: 007

Dates of inspection: March 1– 3, 2021

There were 5 subjects screened and 4 subjects enrolled into the study; 3 subjects completed the study. There were 5 subject records reviewed.

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

Dr. Flynn is medical director of St. Luke's Children's Endocrinology.

The source documents were organized and the records for each subject were maintained in a separate file. Source documents were attributable, legible, contemporaneous, original, and accurate. Both paper case report forms (CRFs) and electronic CRFs were used for the study. All subject information was initially entered into paper CRFs. The required information was transposed from each subject's paper CRF to the eCRF by the delegated study staff. All data for the subjects recruited for the trial was entered into the eCRFs via an Electronic Data Capture (EDC) system provided by the sponsor.

Source records were compared to the sponsor data line listings. There were no discrepancies. There was no under-reporting of adverse events. The primary efficacy endpoint was verifiable.

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.

2. **Joel W. Steelman, M.D.**
   Cook Children's Medical Center
   1500 Cooper Street, 2nd Floor
   Fort Worth, TX 76104-2710
   Site: 021

Dates of inspection: January 25 – 27, 2021

There were 7 subjects screened and 5 subjects enrolled into the study; 5 subjects completed the study (all rolled into the open-label extension study). There were 7 subject records reviewed.

The IRB of record was Cook Children's Health Care System IRB. Subjects were recruited from patients of Cook Children's Medical Center Endocrinology Dodson Specialty Clinic.

Source records were organized, legible, and available. Paper documents, including the subject diary, for each subject were maintained in a binder; electronic medical records for medical histories were printed and provided within each subject's binder. All records were complete, and deviations were reported as appropriate to the sponsor and IRB. The site initially utilized Inform for the study EDC system, and transitioned to Medidata Rave on approximately 09/24/2018. The site did not receive a formal copy of the eCRFs at the time of inspection. A USB flash drive with the site's data was sent during the inspection.

Source records were compared to the sponsor data line listings. There were no discrepancies. There was no under-reporting of adverse events. The primary efficacy endpoint was verifiable.

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.

3. **OPKO Health, Inc. (with focus on subsidiary OPKO Biologics Ltd.)**
   4400 Biscayne Blvd.
   Miami, FL 33137-3212

**In trying to announce the inspection of the CRO* [redacted] (b) (4) *it was discovered that* [redacted] (b) (4) *The study was managed by OPKO Biologics Ltd. (OBL) and they had hired* (b) (4) *for monitoring and regulatory work. OBL informed FDA that* (b) (4) *was not responsible for housing the electronic records or the electronic Trial Master File. Rather, the CP-4-006 study used a cloud-based controlled platform*

(Veeva) which is accessible under OBL's control/oversight.

Dates of inspection: February 23 – March 1, 2021

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/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.

OPKO Health, Inc. (OPKO) was established in 2007. In 2008, company officials made a private investment in a company named Prolor Biotech based in Israel, which was working on technologies that allowed for therapeutic half-life extension. In 2012, OPKO acquired Prolor as a wholly owned subsidiary, which became OPKO Biologics (OBL). Then in 2014, OPKO partnered with Pfizer for the development and marketing of somatrogon. A Joint Development Committee was established. During the study preparation phase, OBL played a larger role but this transitioned to OPKO and Transition Therapeutics (based in Toronto, Canada) around June 2017. (OPKO acquired Transition Therapeutics, which became a subsidiary of OPKO).

A Joint Risk Management Team with OPKO and Pfizer staff met on a quarterly basis to review and discuss safety data with the goal of monitoring the safety risk profile and determining the safety strategy for the study. After completion of the main study and database lock, OPKO transferred the complete set of data from the database to Pfizer according to the OPKO-Pfizer Data Transfer Plan. The database was unlocked and re-locked twice after the initial database lock, and the files were transferred from OPKO to Pfizer a total of three times. In each instance, OPKO's Standard Operating Procedure (SOP) for Database Freeze Lock and Unlock and all necessary processes appeared to be followed.

(b) (4) was involved in the site qualification visits for clinical investigator sites. During the lead up to study initiation in October 2016, OPKO discovered that (b) (4) was also providing monitoring services to a competitor and decided to terminate the contract with (b) (4) and switch to (b) (4) (b) (4) for the US, Canada and Spain monitoring. The responsibility for monitoring in Spain was subcontracted (b) (4) In January 2020, OPKO received notification from a financial entity to make all future payments to them (b) (4) (b) (4) In March 2020, OPKO made the decision to take over management of monitoring of sites that were monitored by (b) (4)

(b) (4) did not possess any study related files as they were all part of the electronic Trial Master File (eTMF) hosted on the cloud based Veeva platform. The sites in the US and

Canada transitioned monitoring responsibility to OPKO and OPKO contracted monitoring responsibility directly to (b) (4) This occurred after the completion of the main study, during the LT-OLE, and there was never a lapse in monitoring during the transition from (b) (4) to OPKO monitoring.

No major issues of clinical investigator noncompliance with the investigational plan or FDA regulations were identified that warranted special action by OPKO. No clinical investigators were terminated from the protocol. Monitoring of the sites by the CROs and sponsor oversight appeared to be adequate. After completion of the main study, subject case report forms were provided as PDF zip files to the sites on password protected USBs.

During the main study there were three levels of blinding: fully unblinded personnel (Level 1), fully blinded personnel (Level 3), and partially blinded personnel (Level 2) who had access to all pages and data available except for raw and derived primary endpoint auxology data and secondary endpoint bone maturation data. After the completion of the main study and during the ongoing Long-term Open Label Extension of the protocol, all personnel have been unblinded. The inspection did not reveal any accidental unblinding prior to full unblinding of the trial.

As specified in the protocol, sample collection to measure IGF-1 was to be performed on Day 4 (-1). However, it was noted that there were samples collected out-of-window throughout the weekly dosing interval. This issue was discussed in depth during the inspection and there was documentation that OPKO staff made attempts to keep the sites in compliance. When these out of window IGF-1 samples were obtained, the sites were to input a minor protocol deviation according to the Protocol Deviations Plan so that they could be tracked. Monitoring report follow-up letters specifically noted IGF-1 was collected out-of-window and newsletters were sent to clinical investigators during the main study and extension study highlighting the importance of obtaining the IGF-1 levels three to four days post dose as per protocol. The sponsor took steps to correct the deviations from the approved protocol both through the monitor and directly through emails to the site and updates in the monthly study newsletter.

There was not a finalized Protocol Deviation Plan (PDP) in effect prior to the initiation of the study. Version 1 of the PDP was finalized on 9/8/17. The study start date was 12/2016 and the first subject visit and screening for the study took place on 4/19/2017. OPKO representatives present during the inspection were unable to account for why the PDP was not finalized prior to the initiation of the study.

(b) (4) was assigned the responsibilities for pharmacovigilance and SAE management, periodic report generation, and reporting of SAEs to the sponsor and CROs. (b) (4) assumed these obligations beginning 12/15/2016 but this was not reported to the FDA as part of an FDA 1571 submission until 9/11/2020. Moreover, the information did not include the actual effective date for the transfer of regulatory obligations. Prior to the closeout of the inspection on 3/1/2021, OPKO voluntarily resubmitted a Form FDA 1571 to the FDA listing the transfer of obligations to (b) (4) and the effective date for the transfer of obligations as 12/15/2016.

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.

{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}*

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cc:

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DGE /Acting Deputy Director/ Patrick Archdeacon
DGE /Team Lead/Marina Zemskova
DGE /Clinical Reviewer/ Sonia Doi
DRO /Regulatory Project Manager/Sejal Kiani
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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/s/

CYNTHIA F KLEPPINGER
06/11/2021 03:45:24 PM

MIN LU
06/11/2021 04:27:58 PM

KASSA AYALEW
06/11/2021 05:02:04 PM

MEMORANDUM

To:	Melinda Bauerlien, Senior Regulatory Health Project Manager CDER/OPQ/OPRO/DRBPMI/RBPMB2
From:	Joey Kotarek, Ph.D., CDRH/OPEQ/OHT7/DCTD
Date:	April 23, 2021
Re:	ICCR case number 00070937 (Somatrogon)

Background

CDER is reviewing BLA 761184 for somatrogon, a synthetic long-acting analog of human growth hormone. The drug is indicated for use in the treatment of pediatric patients, who have growth failure due to an inadequate secretion of endogenous growth hormone (pediatric growth hormone deficiency).

The drug includes the carboxy-terminal peptide (CTP) present in the beta chain of the human chorionic gonadotropin (hCG). CDER has requested help in evaluation the risk of anti-CTP antibodies (and potential anti-hCG antibodies) with pregnancy test interference.

Per the description provided by Dr. Puig in email correspondence sent 03/26/2021, 3 subjects (out of 40 subjects in the sponsor's phase 2 trial who received pen injections of somatrogon) tested positive for anti-CTP antibodies. Also, 4 subjects (out of 109 subjects who received pen injections of somatrogon) tested positive anti-CTP antibodies in the sponsor's phase 3 pivotal trial, and 5 subjects (out of 79 subjects who received pen injections of somatrogon) in the sponsor's phase 3 open label extension trial also tested positive for anti-CTP antibodies.

In previous correspondence with the Agency, the sponsor additionally provided results from testing intended to demonstrate that the CTP labeled drug itself did not interfere with hCG pregnancy testing. The sponsor assessed the potential for drug interference with one blood (serum) hCG assay (run on a Roche cobas E170 Analyzer) and four (home use) urine pregnancy tests ("Clearblue easy", "e.p.t. Pregnancy Test", "1First Response Pregnancy", and "One-Step Pregnancy Test"). Results from this testing indicated that at concentrations significantly higher than what were expected *in vivo*, the presence of somatrogon did not lead to false positive or false negative results, and that results from samples with hCG concentrations near the cutoff (25 mIU/mL) were not impacted by the presence of somatrogon. In their response to Information Requested dated 19 February, 2021, sponsor concludes (based on this evidence) that somatrogon does not interfere with hCG quantitation in blood pregnancy tests. The sponsor has also indicated that anti-CTP antibodies observed in their study population were rare and transient.

Discussion:

<u>Lack of representative hCG assays</u>

The sponsor has provided evidence that the somatrogon (and its incorporated CTP subunit) did not interfere with four home use (urine) hCG pregnancy tests and one (serum) quantitative hCG pregnancy test. However, the sponsor has not provided evidence that these results are representative of how somatrogon may impact results from all hCG pregnancy tests marketed in the United States. While 510k cleared hCG assays typically utilize an immunoassay targeting a portion of the beta

subunit of hCG, sponsors typically do not disclose information describing the specific epitope bound by anti-hCG antibodies utilized in these immunoassays to the Agency. As CDRH does not have information to confirm what region of hCG is recognized by hCG pregnancy assays (and it is expected to vary across different hCG assays), it is not expected that any testing intended to rule out the potential for somatrogon to interfere with hCG assays could be considered representative of the impact somatrogon may have on the large number of hCG assays used to detect pregnancy in the United States.

Therefore, the results provided by the sponsor are not adequate to demonstrate that somatrogon would not lead to false positive or false negative results in hCG assays as used by somatrogon patients. For the same reason (lack of information regarding the specific epitope targeted by pregnancy assays marketed in the United States), it is not anticipated that the sponsor would be able to provide testing that was adequate to demonstrate that any anti-CTP antibodies generated due to somatrogon treatment would not lead to false positive or false negative results in hCG assays used by somatrogon patients.

Risks

The risks associated with the interference of somatrogon (and any associated anti-CTP antibodies) with pregnancy tests constitute false positive and false negative results. The risk of false negative results include delayed prenatal care, or initiation of treatment that was contraindicated for pregnancy that could lead to harm to the fetus and in some cases, a later decision to terminate pregnancy. The risks of false positive results include delay of treatment that was contraindicated for pregnancy, leading to harm to the patient.

Mitigations

As described above, given the lack of information regarding the epitopes utilized by pregnancy assays marketed in the United States, it is not anticipated that the sponsor would be able to provide testing that is adequate to mitigate the risk of interference. However, drug labeling mitigations may be adequate to mitigate these risks. It should be noted that labeling for many prescription *in vitro* diagnostic immunoassays include limitations alerting users to the risk of interference from human anti-mouse (HAMA) antibodies, as such antibodies are ubiquitous and in many cases the ability of such antibodies to interfere with device results is not ruled out. If patients administered somatrogon were adequately cautioned by their HCPs that pregnancy tests may be unreliable due to somatrogon therapy, the risks associated with false positives and false negatives may be adequately mitigated. Additionally, while the sponsor's approach to testing a subset of hCG assays would not be adequate to demonstrate a lack of interference in all hCG assays, testing may be adequate to demonstrate that somatrogon therapy did not interfere with any specific hCG assays the sponsor chose to validate for use in patients on somatrogon therapy.

While the risks associated with somatrogon interference in hCG assays are expected to correlate with somatrogon therapy, it is not clear whether anti-CTP antibodies may persist after termination of somatrogon therapy (and if so, for how long anti-CTP antibodies may persist). While drug labeling may still be adequate to address the risks of anti-CTP antibody interference with hCG assays, we defer to CDER as to the time course that should be described in any such labeling mitigations.

If CDER determines that labeling may be adequate to mitigate the risks of erroneous hCG assay results in somatrogon patients, CDRH can also provide feedback any for such drug labeling.

Summary and Recommendation

The information provided by the sponsor is not adequate to demonstrate that either somatrogon or anti-CTP antibodies in patients taking somatrogon would not lead to false positive or false negative results in hCG pregnancy assays marketed in the United States. Drug labeling mitigations may be adequate to address this risk of false positive and false negative results.

Joseph A. Kotarek -S
Digitally signed by Joseph A. Kotarek -S
Date: 2021.04.23 16:15:07 -04'00'

Joey Kotarek, Ph.D.
FDA/CDRH/OPEQ/OHT7/DCTD

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/

SEJAL KIANI
05/20/2021 04:10:45 PM
Signing on behalf of Joey Kotarek, Ph.D., CDRH/OPEQ/OHT7/DCTD

OFFICE OF PRODUCT EVALUATION AND QUALITY
OFFICE OF HEALTH TECHNOLOGY 3

DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS

INTERCENTER CONSULT MEMORANDUM

Date	4/2/2021		
To:	Melinda Bauerlien		
Requesting Center/Office:	CDER/OPQ	**Clinical Review Division:**	N/A-OPQ/OSE led
From	Rob Nakielny OPEQ/OHT3/DHT3C		
Through (Team)	Courtney Evans, Team Lead, Injection Team OPEQ/OHT3/DHT3C		
Through (Division) *Optional	Rumi Young, Assistant Director, Injection Team OPEQ/OHT3/DHT3C		
Subject	BLA761184 , Somatrogon (mod-4023) [c-terminal peptide (ctp)-modified ICC2001105 Case #00047455		
Recommendation	**Filing Recommendation Date:** Click or tap to enter a date. ☑ 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: 3/17/2021** ☑ CDRH did not provide a Mid-Cycle Recommendation (requested Pre-Approval Inspection) ☐ 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: 5/5/2021** ☐ 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 **Recommendation: A pre-approval inspection was recommended but has not occurred. The approvability of the device constituent performance is deferred to CDRH consulted reviewer, Janice Ferguson (ICC2100073).**		

Digital Signature Concurrence Table

Reviewer	Team Lead (TL)	Division (*Optional)
Robert Nakielny -S Digitally signed by Robert Nakielny -S Date: 2021.05.06 11:02:34 -04'00'		Rumi Young -S Digitally signed by Rumi Young -S Date: 2021.05.06 14:48:11 -04'00'

1. SUBMISSION OVERVIEW

Submission Information	
Submission Number	BLA761184
Sponsor	Pfizer Ireland Pharmaceuticals
Drug/Biologic	Somatrogon (mod-4023) [c-terminal peptide (ctp)-modified hGH] injection
Indications for Use	For use in the treatment of pediatric patients, who have growth failure due to an inadequate secretion of endogenous growth hormone (pediatric growth hormone deficiency [GHD])
Device Constituent	Pen-Injector
Related Files	Pfizer Belgium, Puurs, Belgium, FEI 1000654629 • There is a CDRH 02/01/2019 memo on CMS regarding an informant complaint, where CDRH identified "warning letter level" Quality deficiencies of device assembly and recommended consideration of a for-cause inspection (the for-cause inspection has not happened).

Review Team	
Lead Device Reviewer	*Rob Nakielny*

Interim Due Dates	Meeting/Due Date
Mid-Cycle	Internal meeting 3/17/21, Sponsor meeting 4/7/2021
Primary Review	4/23/2021
Internal Meeting(s)	6/22/21 late cycle
Sponsor Meeting(s)	7/19/21 late cycle

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.

Section	Adequate			Reviewer Notes
	Yes	No	NA	
Device Description	x			N/A
Facilities & Quality Systems		x		(Facility Inspection has not been Performed)

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 #:
A pre-approval inspection was recommended but has not been performed (Refer to section 5.1 Facilities Information).

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

Post-Market Commitment or Requirement:

TABLE OF CONTENTS

3. PURPOSE/BACKGROUND

3.1. Scope

Pfizer Ireland Pharmaceuticals is requesting approval of Somatrogon (mod-4023) [c-terminal peptide (ctp)-modified hGH] injection. The device constituent of the combination product is a Pen-Injector.

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

Facilities inspection consult.

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 and Quality Systems review only.

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

Existing Previous for-cause inspection request (2019)

• There is a CDRH 02/01/2019 memo on CMS regarding an informant complaint, where CDRH identified "warning letter level" Quality deficiencies of device assembly and recommended consideration of a for-cause inspection

- The for-cause inspection has not been completed as of 5/5/2021.
- Facility: Pfizer Belgium, Puurs, Belgium, FEI 1000654629
- 2/1/2019 Washout N (investigation into informant complaint)
  - Result, "Recommend an inspection be created to follow-up at the manufacturer. Refer to Dorothy Lee and CDRH"
  - Details into the investigation:

    The purpose of this investigation is to report information received from a confidential informant that may indicate the need to initiate a for-cause inspection.

    Background on the investigation:

    Pfizer did an internal inspection. The mock inspection found deficiencies in all US regulation medical device and combination product subsystems review including:

(b) (4)

(b) (4)

(b) (4)

Table 3.2.P.3.1-1. Sites and Responsibilities for Manufacture, Testing and 21 CFR Part 4 Requirements of Somatrogon Drug Product

Name and Address		FEI Number	Responsibility and Quality System Provision	
Pfizer Manufacturing Belgium NV	Rijksweg 12 Puurs 2870 Belgium	1000654629	Assembly of prefilled pen Labeling Release and stability testing Secondary packaging	21 CFR Part 210 21 CFR Part 211 21 CFR Part 4.4 (b)(1) 21 CFR Part 820.20 Management Responsibility 21 CFR Part 820.30 Design Controls 21 CFR Part 820.50 Purchasing Controls 21 CFR Part 820.100 Corrective and Preventive Action

Historical Information:

8 Inspections, 0 recalls, 2 NAI, 5 VAI, 1 OAI

- 4/28/2000 OAI (official action indicated)
- 6/26/2003 VAI (voluntary action indicated)
- 7/113/2007 VAI
- 9/23/2011 VAI
- 3/18/2014 NAI (no action indicated)
- 6/30/2015 VAI
- 6/21/2017 VAI
- 11/16/2017 NAI (no action indicated) (it has been 3+ years since the last inspection)

4/7/21 – Midcycle meeting communications to sponsor

Communicated the need for a pre-approval inspection based on the 3+ years prior to the last inspection and based on the existing for-cause pending inspection. This was presented to the sponsor who acknowledged the PAI of both facilities (drug and device mfg.) in the external midcycle meeting.

3.3. Indications for Use

Combination Product	Indications for Use
Somatrogon (mod-4023) [c-terminal peptide (ctp)-modified	For use in the treatment of pediatric patients, who have growth failure due to an inadequate secretion of endogenous growth hormone (pediatric growth hormone deficiency [GHD])
Pen-Injector	Delivery of the Drug Product

3.4. Materials Reviewed

Materials Reviewed	
Sequence	**Module(s)**
0001	3.2.P Drug Product (prefilled pen) 3.2.A.1 Facilities and Equipment [Puurs] [somatrogon]

4. DEVICE DESCRIPTION

4.1. Device Description

The somatrogon drug product is a single-patient-use, disposable prefilled pen designed for subcutaneous injection. The pen encloses a 3 mL (b) (4) clear glass cartridge containing the somatrogon drug product solution and together they form a single integral product, intended exclusively for use in the given combination.
There are 2 mechanically identical somatrogon prefilled pen presentations; 24 mg-containing a volume of 1.2 mL somatrogon at 20 mg/mL (lilac pen cap, dose button, and label) and 60 mg – containing a volume of 1.2 mL somatrogon at 50 mg/mL (blue pen cap, dose button, and label). Needles are not included in the carton containing the pen. Both pen presentations are mechanically identical.

Each pen presentation contains multiple doses of somatrogon drug product solution. The dose is variable, set within the range of 10 to 600 µL, which is selected using a manual dial dose setting mechanism and injected by a manually driven piston. The healthcare provider will decide which strength is most appropriate for the patient from the 2 available presentations based on the dose required which is defined by a patient's body-weight.

Figure 3.2.P.1-1. Somatrogon Prefilled Pen

24 mg Prefilled Pen

60 mg Prefilled Pen

Note: Information contained within the labels is not finalized and is representative.

Table 3.2.P.1-1. Description of the Somatrogon 24 mg and 60 mg Prefilled Pen

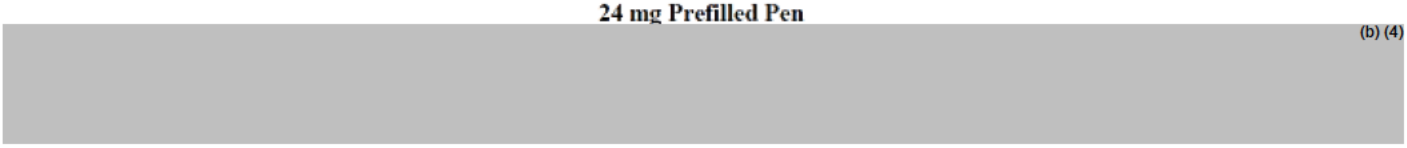
Feature	24 mg Prefilled Pen	60 mg Prefilled Pen
Somatrogon solution concentration	20 mg/mL	50 mg/mL
Nominal volume	1.2 mL	1.2 mL
Color scheme	Lilac pen cap, dose button, and label	Blue pen cap, dose button, and label
Dose increments	0.2 mg / 10 µL	0.5 mg / 10 µL
Maximum dose	12 mg (600 µL)	30 mg (600 µL)

Figure 3.2.P.1-2. Exploded View of the Somatrogon 24 mg Prefilled Pen

(b) (4)

Figure 3.2.P.1-4. Representation of the Components of the Somatrogon Prefilled Pen 24 mg Prefilled Pen

(b) (4)



4.2. Steps for Using the Device

The principles and features of operation of the somatrogon prefilled pen include:

- Removal of the pen cap and needle attachment;
- User-priming and dose setting, with visual, audible and tactile feedback during dose setting;
- Dose delivery, with audible and tactile feedback, at a speed and force controlled by the user;
- Visual feedback that dose delivery has completed;

4.3. Device Description Conclusion

DEVICE DESCRIPTION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☑ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☑ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments The device description is acceptable		

CDRH sent Device Description Deficiencies or Interactive Review Questions to the Sponsor: ☐ **Yes** ☑ **No**

5. FILING REVIEW

5.1. Facilities Information

Firm Name:	Pfizer Manufacturing Belgium NV
Address:	Rijksweg 12, Puurs 2870, Belgium
FEI:	1000654629
Responsibilities:	Assembly of prefilled pen. Labeling. Release and stability testing. Secondary packaging

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 3 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 in over three years.
In addition, there is a pending For-Cause Inspection request based on an investigation into information presented by a confidential informant alleging Quality Systems deficiencies (refer to section 3.2 Prior Interactions for details into the investigation)

On 3/18/21 during the Internal Midcycle meeting the need for a pre-approval inspection was communicated to the review team.

☐ An inspection is not required because Choose an item.

5.2. Quality System Documentation Triage Checklist

Device Type Table

Was the last inspection of the finished combination product manufacturing site, or other site, OAI for drug or device observations?	☐ Yes ☑ No ☐ UNK
Is the device constituent a PMA or class III device?	☐ Yes ☑ No ☐ UNK
Is the final combination product meant for emergency use?	☐ Yes ☑ No ☐ UNK
Is the combination product meant for a vulnerable population (infants, children, elderly patients, critically ill patients, or immunocompromised patients)?	☑ Yes ☐ No ☐ UNK

Does the manufacturing site have a significant and known history of multiple class I device recalls, repeat class II device recalls, a significant number of MDRs/AEs, or OAI inspection outcomes?	☐ Yes ☑ No ☐ UNK
Is the combination product meant for users with a condition in which an adverse event will occur if the product is not delivered correctly (example insulin products for specific diabetic patients)?	☐ Yes ☑ No ☐ UNK
Does the manufacturing process for the combination product device constituent part use unique, complicated, or not well understood methods of manufacturing?	☐ Yes ☑ No ☐ UNK
cGMP Risk:	
☐ Low or Moderate Risk of cGMP issues: If yes is not checked above, please fill out the checklist and deficiencies only. A review summary is optional.	
☑ High Risk of cGMP issues: If yes is checked anywhere above, consider filling out the checklist, the deficiencies, and the review summary. If a full review is not warranted due to other factors such as device constituent classification (class I and class II devices), a low or moderate overall risk of device constituent failure, or positive compliance history, please document your rationale below for not conducting a full ICCR review.	

Reviewer Comment the combination product is meant for a vulnerable population - infants, children. In addition, the facility has a pending for-cause inspection. This is justification for a facilities and QS systems review.

6. FACILITIES & QUALITY SYSTEMS

6.1. Facility Inspection Report Review

CDRH Facilities Inspection Review conducted	☐
CDRH Facilities Inspection Review was not conducted	☑

6.2. Quality Systems Documentation Review

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

6.2.1. Description of the Device Manufacturing Process

Summary of Manufacturing Process / Production Flow

The Sponsor provided the following summary of the manufacturing process of the combination product, including the drug product/biologic and device constituent parts:

(b) (4)

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(b) (4)

Device Manufacturing Process Conclusion		
The Sponsor provided adequate information for the summary of the manufacturing process / production flow.	☒Yes	☐No

6.2.2. cGMP Review

Does Sponsor have all elements of their GMP compliance approach included in submission:

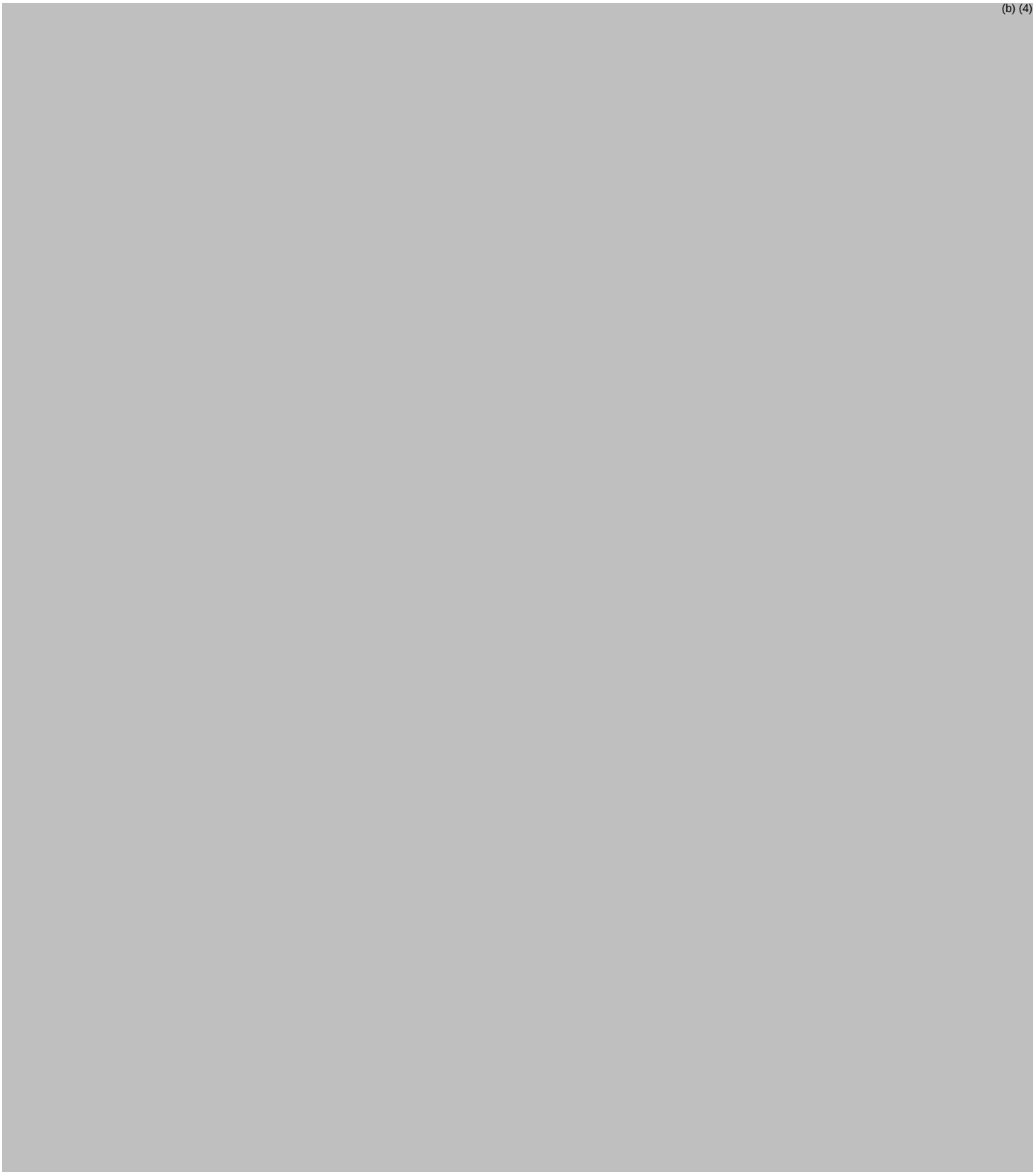
What Quality System did the Sponsor choose:

☐ Device QSR-based

☑ Drug cGMP-Based Streamline –

☐ Stream-line Both (**no streamlined approach**)

(b) (4)



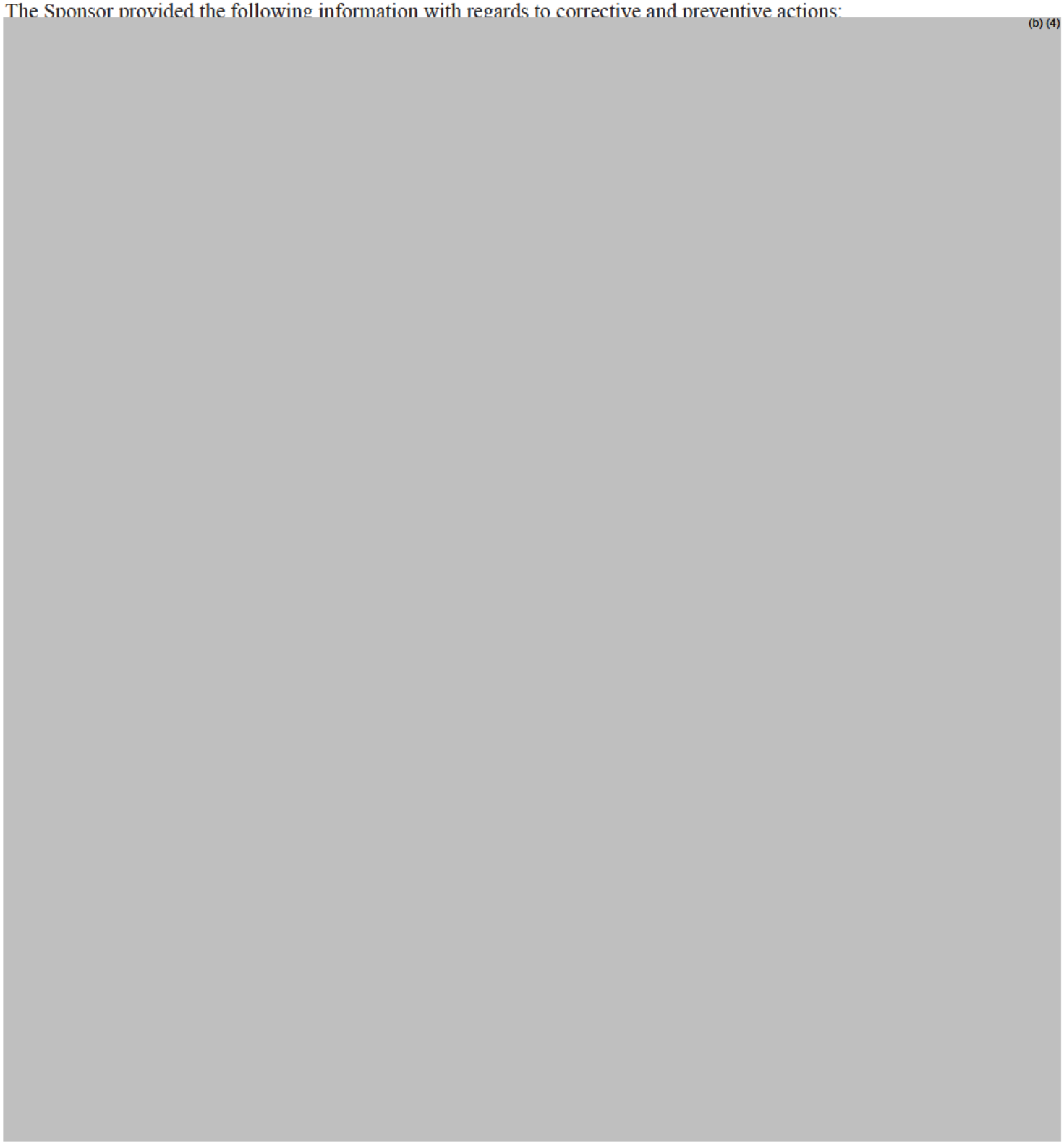
(b) (4)

The Sponsor provided adequate summary information about the GMP compliance activities	☑ Yes	☐ No

6.2.3. Corrective and Preventive Action Review

The Sponsor provided the following information with regards to corrective and preventive actions:

(b) (4)



(b) (4)

CAPA Conclusion		
The Sponsor provided adequate information for corrective and preventive actions.	☐Yes	☒No

6.3. Control Strategy Review

The Sponsor provided the following control strategy information regarding the EPRs of the device constituents:

Note: The Control Strategy Review was presented as the responsibility of the Main CDHR reviewer (Janice Ferguson). The below concerns related to the EPR's (b) (4) was similar to the concerns held by the main reviewer; therefore, this section was not pursued further.

(b) (4)

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6.4. 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 The EPRs and Control Strategy were reviewed and concerns presented to the main CDRH reviewer. The Interactive Request posed by the main reviewer sufficed to address my CAPA related deficiencies.		
CDRH sent Facilities & QS Deficiencies or Interactive Review Questions to the Sponsor: ☑ Yes ☐ No		

	Date Sent:	**Date/Sequence Received:**
Information Request #1 **Sent by Janice Ferguson (main CDRH reviewer)**	(b) (4)	
Sponsor Response		

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Reviewer Comments	Sponsor response was adequate in presenting evidence of process installation and operational qualification performed for automated assembly and labeling processes for this device.
Response Adequate:	☑ **Yes** ☐ **No, See IR # Sent on** Click or tap to enter a date.

<<END OF REVIEW>>

7. APPENDIX A (INFORMATION REQUESTS)

7.1. Interactive Information Requests

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

(Note: See above sections for specific responses and requests made)

- IR#2 Response 04/27/2021
- IR#2 Request 04/23/2021– requesting evidence that the IQ and OQ were performed on the automated equipment used for assembly and labeling.

- IR#1 Response 04/16/2021
- IR#1 Request 04/09/2021 (from Janice Ferguson, main CDRH reviewer)– requesting more information specific to certain elements of the CAPA process

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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/

SEJAL KIANI
05/20/2021 04:15:47 PM
Signing on behalf of Rob Nakielny OPEQ/OHT3/DHT3C

OFFICE OF PRODUCT EVALUATION AND QUALITY
OFFICE OF HEALTH TECHNOLOGY 3

DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS

INTERCENTER CONSULT MEMORANDUM

Date	5/10/2021		
To:	Melinda Bauerlien		
Requesting Center/Office:	CDER/OPQ	**Clinical Review Division:**	DGE
From	Janice Ferguson, RN, BSN, CRNI OPEQ/OHT3/DHT3C		
Through (Team)	Courtney Evans , Team Lead, Injection Team OPEQ/OHT3/DHT3C		
Through (Division) *Optional	Rumi Young, Assistant Director, Injection Team OPEQ/OHT3/DHT3C		
Subject	BLA 761184, Somatrogon (MOD-4023) [CTP-modified hGH] Injection ICC2100073 ICCR 00055001		
Recommendation	**Filing Recommendation Date: NA** ☐ 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: 3/17/2021 ☐ 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: Click or tap to enter a date. ☐ 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)
Janice L. Ferguson -S Digitally signed by Janice L. Ferguson -S Date: 2021.05.10 17:25:18 -04'00'	Courtney Evans -S Digitally signed by Courtney Evans -S Date: 2021.05.14 15:36:08 -04'00'	

1. SUBMISSION OVERVIEW

Submission Information	
Submission Number	BLA 761184
Sponsor	Pfizer Ireland Pharmaceuticals
Drug/Biologic	Somatrogon CTP-modified hGH Injection
Indications for Use	for use in the treatment of pediatric patients, who have growth failure due to an inadequate secretion of endogenous growth hormone (pediatric growth hormone deficiency [GHD]).
Device Constituent	Pen-Injector
Related Files	IND 79745

Review Team		
Lead Device Reviewer	*Janice Ferguson, RN, BSN, CRNI*	
Discipline Specific Consults	**Reviewer Name (Center/Office/Division/Branch)**	**CON #**

Important Dates	
Discipline-Specific Review Memos Due	
Final Lead Device Review Memo Due	
Interim Due Dates	**Meeting/Due Date**
Filing	NA
74-Day Letter	NA
Mid-Cycle	3/17/2021
Primary Review	5/14/2021
Internal Meeting(s)	3/17/2021 Mid Cycle CMC 3/24/2021 Mid Cycle
Sponsor Meeting(s)	4/7/2021 Mid Cycle

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.

Section	Adequate			Reviewer Notes
	Yes	No	NA	
Device Description	X			
Labeling	X			
Design Controls	X			
Risk Analysis	X			
Design Verification	X			
Consultant Discipline Reviews			X	
Clinical Validation			X	
Human Factors Validation			X	
Facilities & Quality Systems			X	Being done under separate ICCR

2.1 Comments to the Review Team

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

2.2 Complete Response Deficiencies

- There are no outstanding unresolved information requests, therefore CDRH does not have any outstanding deficiencies.
- The following outstanding unresolved information requests should be communicated to the Sponsor as part of the CR Letter:

2.3 Recommended Post-Market Commitments/Requirements

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

TABLE OF CONTENTS

3. PURPOSE/BACKGROUND

3.1 Scope

Pfizer Ireland Pharmaceuticals is requesting approval of Somatrogon CTP-modified hGH Injection. The device constituent of the combination product is a Pen-Injector. Somatrogon is a long-acting recombinant human growth hormone (rhGH) that has been developed to use in the treatment of pediatric patients, who have growth failure due to an inadequate secretion of endogenous growth hormone. Somatrogon is intended to be administered as a once weekly subcutaneous (SC) injection using a disposable, prefilled pen that has the capability for setting and delivering the desired dose, which is individualized and determined based on patient body weight.

There are no pen needles being supplied with the pen injector device. The drug carton has a list of the compatible needles recommended by the sponsor.

Choose an item. has requested the following consult for review of the device constituent of the combination product:

Assessment of design controls, performance, stability and suitability of Somatrogon drug product pre-filled pen for its intended use.

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:

Assessment of design controls Essential performance requirements PFP Stability Suitability of the device for its intended use.

This review will **not** cover the following review areas:

Review of Drug product in container -cartridge Sterility of Drug product Biocompatibility of drug product Facilities Review Human Factors

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

No prior interactions

3.2.1 Related Files

NA

3.3 Indications for Use

Combination Product	Indications for Use
Somatrogon CTP-modified hGH Injection	for use in the treatment of pediatric patients, who have growth failure due to an inadequate secretion of endogenous growth hormone (pediatric growth hormone deficiency [GHD]).
Pen-Injector	Delivery of the Drug Product

3.4 Materials Reviewed

Materials Reviewed	
Sequence	**Module(s)**
0001	1.2 Cover letter
0001	1.14.1.1 Draft Labeling
0001	1.6.3 Correspondence regarding meetings IND79745 Question #6 Additional information 1-4
0001	3.2.P.2 Pharmaceutical Development-Intro
0001	3.2.P.2.4 Product Development Product Verification Product Validation Manufacturing Process Development Risk Management
0001	3.2.P.3.4 Control of Critical Steps and Intermediates In-Process Monitoring and Control (PFP)
0001	3.2.P.7 Container Closure System
0001	3.2.P.8 Stability
0008	1.11.1 Information not Covered Q 7 & Q 8
0022	1.11.1 Quality Information Amendment 3.2.R Somatrogon Formative Study-Axial Force User Study
0028	1.11.1 Quality Information Amendment Q1-3
0030	1.11.1 Quality Information Amendment Q1-2 3.2.P.3.3 Description of Manufacturing Process and Process Controls (Prefilled pen) 3.2.P.5.1 Specifications (Prefilled Pen) 3.2.P.5.2 Analytic Overview (Prefilled Pen) Analytic Procedures-Axial Force (PFP) 3.2.P.5.3 Validation of Analytical Procedures -Axial Force (PFP) 3.2.P.5.6 Justification of Specifications (PFP) 3.2.P.8.1 Stability Summary and Conclusion (PFP) 3.2.P.8.3 Stability Data-Stability Only- Analytic Method and Validation
0032	1.11.1 Quality Information Amendment 3.2.P.5.1 Specifications 3.2.P.5.6 Justification of Specifications 3.2.P.8.2 Post-Approval Stability Protocol and Stability Commitment

4 DEVICE DESCRIPTION

4.1 Device Description

Information found in Seq. 0001 [Pharmaceutical Development 3.2.P.2.4.1 Product Development]

The Somatrogon drug product is a single-patient-use, disposable prefilled pen designed for subcutaneous injection. The pen encloses a 3 mL (b) (4) clear glass cartridge containing the Somatrogon drug product solution.

There are 2 mechanically identical Somatrogon prefilled pen presentations; 24 mg-containing a volume of 1.2 mL Somatrogon at 20 mg/mL (lilac pen, dose button, and label) and 60 mg-containing a volume of 1.2 mL Somatrogon at 50 mg/mL (blue pen cap, dose button, and label). Needles are not included in the carton containing the pen.

Each pen presentation contains multiple doses of Somatrogon drug product solution. The dose s variable, set within the range of 10 to 600 µL, which is selected using a manual dial dose setting mechanism and injected by a manually driven piston. The healthcare provider will decide which strength is most appropriate for the patient from the 2 available presentations, based on the dose required defined by pediatric patient body weight.

Both pen presentations are mechanically identical. The pens vary in the color of the pen cap, dose button, and label. The pens also vary in the printing on the dose sleeve of the dosing mechanism and the printing on the cartridge holder.

The final assembled Somatrogon prefilled pen consists of a cartridge containing drug product solution, printed cartridge holder. The dosing mechanism, and a pen cap. The label is wrapped around the body of the prefilled pen.

The sponsor has recommended pen needles for use with the pen injector. The needles recommended are 510k cleared devices. Compatibility testing with the pen injector was provided.

Photographic Representation of the Final Finished device with Cartridge

(b) (4)

Table 3.2.P.1-1. Description of the Somatrogon 24 mg and 60 mg Prefilled Pen

Feature	24 mg Prefilled Pen	60 mg Prefilled Pen
Somatrogon solution concentration	20 mg/mL	50 mg/mL
Nominal volume	1.2 mL	1.2 mL
Color scheme	Lilac pen cap, dose button, and label	Blue pen cap, dose button, and label
Dose increments	0.2 mg / 10 µL	0.5 mg / 10 µL
Maximum dose	12 mg (600 µL)	30 mg (600 µL)

Figure 3.2.P.1-2. Exploded View of the Somatrogon 24 mg Prefilled Pen

(b) (4)

(b) (4)

Materials of Construction

Information found in Seq. 0001 [3.2.P.1 Description and Composition of the Drug Product Table 3.2.P.1-2]

Table 3.2.P.1-2. Composition of the Somatrogon 24 mg and 60 mg Prefilled Pen

Component Name	Material of Construction
Dosing Mechanism Components	
24 mg or 60 mg dose button (b) (4)	(b) (4)
Other Components	
24 mg or 60 mg cartridge holder	
24 mg or 60 mg pen cap	
24 mg or 60 mg cartridge (3 mL)	
Label	
24 mg or 60 mg label	

Needle Compatibility

Information found in Seq. 0001 [Pharmaceutical Development 3.2.P.2.6.1 Compatibility]

Four needles from two manufacturers are identified for use with the pen as indicated in the Instructions for Use:

Table 3.2.P.2.4-4. Needles Compatible for use with the Somatrogon 24 mg and 60 mg Prefilled Pen

Manufacturer	Trade Name	Needle Type
Becton Dickinson and Company	BD Micro-Fine™ (or BD Ultra-Fine™)	31 gauge x 5 mm
		31 gauge x 8 mm
Novo Nordisk	NovoFine®	31 gauge x 6 mm
	NovoFine® Plus	32 gauge x 4 mm

Table 3.2.P.2.6-1. Somatrogon Lots Used in Needle Compatibility Studies

Presentation	PFP Lot Number	DPS Lot Number	Date of DPS Manufacture	Date of Analytical Testing	Approximate Age of DPS
24 mg PFP	3ET1900074	AH8136	Nov. 2018	Jan. 2020	14 months
60 mg PFP	3ET1900075	AK7464	Dec. 2018	Jan. 2020	13 months
24 mg PFP (post-expiry)	R40666	N67404	Apr 2016	Jan. 2020	45 months
60 mg PFP (post-expiry)	R40667	N94621	May 2016	Jan. 2020	44 months

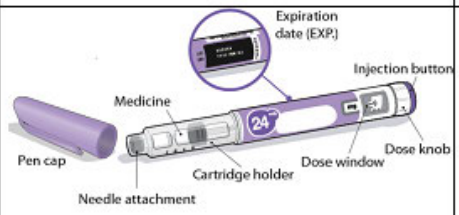
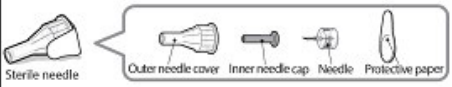
DPS = drug product solution; PFP = prefilled pen

Reviewer Comment:
The sponsor has identified 4 needles for use with the pen injector device. The needles were tested under conditions which the patient is expected to use the product. (Room temperature x 30 minutes) Testing was done at different stages of shelf-life and at post expiry.
The recommended compatible needles are clearly listed on the outside carton label.
Needle compatibility verification testing found in Section 9 Design verification.

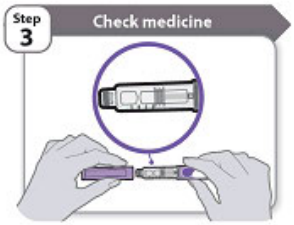
4.2 Steps for Using the Device

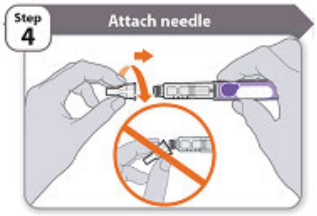
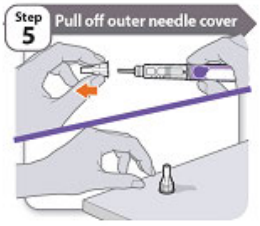
Information found in Seq. 0001 [Pharmaceutical Development Product Development 3.2.P.2.4.4]

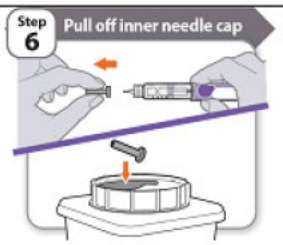
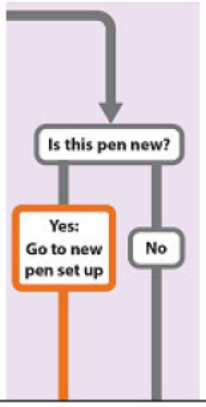
Table 3.2.P.2.4-2. Representative Operating Principles for the Somatrogon Prefilled Pen Relative to the IFU

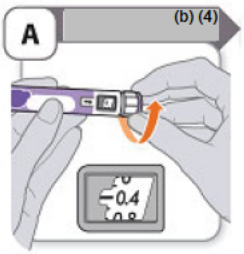
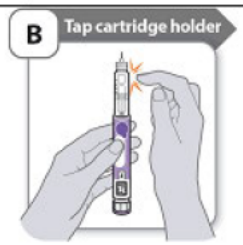
IFU Step	Operation	User Handling Step	Associated Image from the IFU[a]	Operational Sequence and Expected User Interaction
N/A (product orientation only)	Supplies you will need each time you inject	**Included in the carton:** - 1 PRODUCT NAME prefilled pen. **Not included in the carton:** - 1 new sterile needle for each injection. - Alcohol swabs. - Cotton balls or gauze pads. - Adhesive bandage. - 1 FDA-cleared sharps disposal container for disposal of pen needles and pens **(See How should I dispose of the pen needles and pens?).**		This step identifies the supplies required for each injection and orients the user to the pen.
N/A (product orientation only)	Needles to use	Pen needles are **not included** with your PRODUCT NAME pen. You will need a prescription from your healthcare provider to get pen needles up to a length of 8 mm from your pharmacy. - Needles to use with your PRODUCT NAME pen: 32G (Novo Nordisk®, NovoFine® Plus) 31G (Novo Nordisk®, NovoFine®) 31G (Becton Dickinson and Company, BD Ultra-Fine™ or BD Micro-Fine™) - Talk with your healthcare provider about the right needle for you. **Caution**: Never use a bent or damaged needle. Always handle pen needles with care to make sure you do not prick yourself (or anyone else) with the needle. **Do not** attach a new needle to your pen until you are ready to take your injection.	**Sterile needle (example) not supplied:** 	This step identifies the compatible needles for use with the pen and provides an example of the components of a needle and how it is packaged.

IFU Step	Operation	User Handling Step	Associated Image from the IFU[a]	Operational Sequence and Expected User Interaction
1	Getting ready	- Wash and dry your hands. - You can use your pen straight from the refrigerator. For a more comfortable injection, leave your pen at room temperature for up to 30 minutes. - Check the name, strength, and label of your pen to make sure it is the medicine your healthcare provider has prescribed for you. - Check the expiration date on the pen label. **Do not** use if the expiration date has passed. - **Do not** use your pen if: it has been frozen or exposed to heat it has been dropped it looks broken or damaged it has been more than 28 days after first use of the pen. **Do not** remove the pen cap from your pen – until you are ready to inject.	There is no image associated with this IFU step.	This step guides preparation for use of the pen.

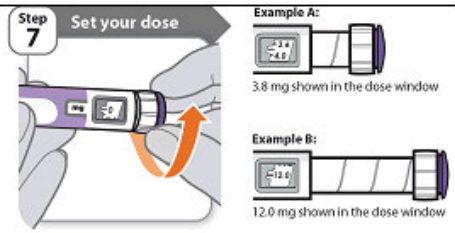
IFU Step	Operation	User Handling Step	Associated Image from the IFU[a]	Operational Sequence and Expected User Interaction
2	Choose and clean your injection site	- PRODUCT NAME can be given in the abdomen, thighs, buttocks, or upper arms. - Choose the best place to inject, as recommended by your healthcare provider. - If more than 1 injection is needed to complete your full dose, each injection should be given in a different injection site. - **Do not** inject into bony areas, areas that are bruised, red, sore or hard, and areas that have scars or skin conditions. - Clean the injection site with an alcohol swab. - Allow the injection site to dry. - **Do not** touch injection site after cleaning.		This step identifies all possible injection sites and provides instructions on how to choose and clean the site prior to injection.
3	Check medicine	- Pull off the pen cap and keep it for after your injection. - Check the medicine inside the cartridge holder. - Make sure the medicine is colorless to slightly yellow. **Do not** inject the medicine if it is cloudy or dark yellow. - Make sure the medicine is free of flakes or particles. **Do not** inject the medicine if it has flakes or particles. **Note:** It is normal to see one or more bubbles in the medicine.		This step first instructs how to remove the pen cap with the advice to keep it for after the injection has been performed. It then instructs to check medicine to ensure that it appears as expected. The expected appearance of the medicine within the cartridge is provided.

IFU Step	Operation	User Handling Step	Associated Image from the IFU[a]	Operational Sequence and Expected User Interaction
4	Attach needle	- Take a new needle and pull off the protective paper. - Line the needle up with your pen keeping them both straight. - Gently push and then screw the needle onto your pen. **Do not** over tighten. **Note:** Be careful not to attach the needle at an angle. This may cause the pen to leak. **Caution:** Needles have sharp tips at both ends. Handle with care to make sure you do not prick yourself (or anyone else) with the needle.		This step instructs on how to correctly attach the needle to the pen and provides guidance, as to handling, to minimize the possibility of needle injury.
5	Pull off outer needle cover	- Pull off the outer needle cover. - Make sure you keep the outer needle cover. You will need it later to remove the needle. **Note:** You should see an inner needle cap after you have removed the outer cover. If you do not see this, try to attach the needle again.		This step instructs how to pull off the outer needle cover and to retain it for removal of the needle following injection. This step also describes how the pen should appear once the needle is screwed-on. Further instruction is given should the pen not appear as expected.

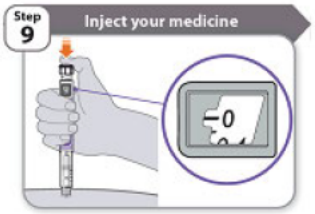
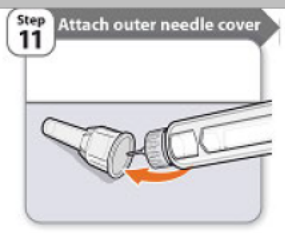
IFU Step	Operation	User Handling Step	Associated Image from the IFU[a]	Operational Sequence and Expected User Interaction
6	Pull off inner needle cap	- Pull off the inner needle cap carefully to show the needle. - Throw away the inner needle cap in a sharps container. It is not needed again.		This step instructs that removal of the inner needle cap will reveal the needle and advises that it should be disposed of as it is no longer required, and to minimize the possibility of the user recapping the used needle, which could result in a needle injury.
N/A (user decision only)	User decision	**Is this pen new?** **Yes: Go to New pen set up** **No**		The user must decide whether to follow the subsequent steps that cover new pen set up (priming) for the first use of a new pen (steps A, B and C, below), or whether to go straight to step 7 because the pen has previously been used (no user-priming required).

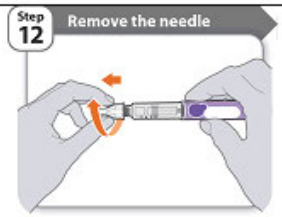
IFU Step	Operation	User Handling Step	Associated Image from the IFU[a]	Operational Sequence and Expected User Interaction
New pen set up (priming) – for the first use of a new pen only **You must set up each new pen (priming) before using it for the first time** - New pen set up is done before each new pen is used for the first time. - The purpose of setting up a new pen is to remove air bubbles and make sure you get the correct dose. **Important:** Skip Step-A through to Step-C if you have already set up your pen.				
A	(b) (4)	- Turn the dose knob to **0.4**. **Note:** If you turn the dose knob too far, you can turn it back.		This step instructs how to set the dose to prime the pen ready for first use.
B	Tap cartridge holder	- Hold the pen with the needle pointing up so that the air bubbles can rise. - **Tap** the cartridge holder gently to float any air bubbles to the top. **Important:** Follow Step-B even if you do not see air bubbles.		This step advises on how to float any air bubbles to the top of the pen when the pen is held so that the needle is pointing upwards. Advice is given to perform this even if no bubbles are visible.

IFU Step	Operation	User Handling Step	Associated Image from the IFU[a]	Operational Sequence and Expected User Interaction
C	Press button and check for liquid	- **Press the injection button** until it cannot go any further and "**0**" is shown in the dose window. - **Check** for liquid at the needle tip. If liquid appears, your pen is set up. - Always make sure that a drop of liquid appears before you inject. If liquid has not appeared, repeat Step-A through to Step-C. If liquid does not appear after you have repeated Step-A through Step-C five (5) times, attach a new needle and try 1 more time. **Do not** use the pen if a drop of liquid still does not appear. Contact your healthcare provider or pharmacist, and use a new pen.		This step instructs how to ensure that the pen is prepared ready for first injection including pressing the injection button and checking for liquid. It also provides instructions for repeated priming attempts if liquid does not appear at the needle tip (unsuccessful user-priming).

IFU Step	Operation	User Handling Step	Associated Image from the IFU[a]	Operational Sequence and Expected User Interaction
Setting your prescribed dose				
7	Set your dose	- Turn the dose knob to set your dose. The dose can be increased or decreased by turning the dose knob in either direction. The dose knob turns 0.2 mg at a time. Your pen contains 24 mg of medicine but you can only set a dose of up to 12 mg for a single injection. The dose window shows the dose in mg. See **Examples A and B**. - **Always check the dose window to make sure you have set the correct dose.** **Important: Do not** press the injection button while setting your dose. **What should I do if I cannot set the dose I need?** - If your dose is more than 12 mg you will need more than 1 injection. - You can give from 0.2 mg to 12 mg in a single injection. If you need help dividing up your dose the right way, ask your Healthcare provider. Use a new needle for each injection **(See Step 4: Attach needle)**. If you normally need to give 2 injections for your full dose, be sure to give your second dose.		This step instructs on setting the dose for injection and provides example images and advice on what to do if there is not enough medicine to enable injection of the complete dose. This step also defines the limit of a single dose (eg 12 mg for the 24 mg pen).

IFU Step	Operation	User Handling Step	Associated Image from the IFU[a]	Operational Sequence and Expected User Interaction
7 continued		**What should I do if I do not have enough medicine left in my pen?** - If your pen contains less than 12 mg of medicine, the dose knob will stop with the remaining amount of medicine shown in the dose window. - If there is not enough medicine left in your pen for your full dose, you may either: inject the amount left in your pen, then prepare a new pen to complete your dose in full. Remember to subtract the dose you have already received. For example, if the dose is 3.8 mg and you can only set the dose knob to 1.8 mg, you should inject another 2.0 mg with a new pen. Or get a new pen and inject the full dose.		
Injecting your dose				
8	Insert the needle	- Hold your pen so you can see the numbers in the dose window. - Insert the needle straight into your skin.		This step instructs how to correctly insert the needle into the skin to begin the injection.

IFU Step	Operation	User Handling Step	Associated Image from the IFU[a]	Operational Sequence and Expected User Interaction
9	Inject your medicine	- Keep holding the needle in the same position in your skin. - **Press the injection button** until it cannot go any further and "**0**" is shown in the dose window.		This step advises how to correctly perform the injection and describes the change in appearance of the dose window following the injection.
10	Count to 10	- **Continue to press the injection button while counting to 10.** Counting to 10 will allow the full dose of medicine to be given. - After counting to 10, let go of the injection button and slowly remove the pen from the injection site by pulling the needle **straight out**. **Note:** You may see a drop of medicine at the needle tip. This is normal and does not affect the dose you just received.	(b) (4)	This step instructs a count to 10 while continuing to press on the injection button to ensure the entire dose is injected. Removal of the pen from the injection site is described and reassures the user that a drop of medicine at the injection site is normal.
11	Attach outer needle cover	- Carefully place the outer needle cover back on the needle. - Press on the outer needle cover until it is secure. **Caution:** Never try to put the inner needle cap back on the needle. You may prick yourself with the needle.		This step describes how to securely attach the outer needle cover retained from Step 5 in preparation for safe removal of the needle from the pen. This step also provides a caution that replacing the inner needle cap should never be tried.

IFU Step	Operation	User Handling Step	Associated Image from the IFU[a]	Operational Sequence and Expected User Interaction
12	Remove the needle	- Unscrew the capped needle from the pen. - Gently pull until the capped needle comes off. **Note:** If the needle is still on, replace the outer needle cover and try again. Be sure to apply pressure when unscrewing the needle. - Throw away the needle in the sharps container **(See How do I dispose of the pen needles and pens?)**. **Important:** Always remove and throw away used needles. **Do not** reuse needles.		This step instructs safe removal of the needle from the pen and how to safely dispose of the needle.
13	Replace the pen cap	- Replace the pen cap back onto your pen. - **Do not** recap the pen with a needle attached. - If there is any medicine left in your pen, store in the refrigerator between uses **(See How should I store my pen?)**.		This step provides an instruction to replace the pen cap, which includes an instruction not to do so with a needle attached. It also advises that if there is medicine remaining in the pen, it should be stored in the refrigerator until the next injection is required.
14	After your injection	- Press lightly on the injection site with a clean cotton ball or gauze pad, and hold for a few seconds. - **Do not** rub the injection site. You may have slight bleeding. This is normal. - You may cover the injection site with a small adhesive bandage, if needed. - If your pen is empty or it has been **more than 28 days** after first use, throw it away even if it contains unused medicine. Refer to **"Storage and disposal"** on the right side of this leaflet.	There is no image associated with this IFU step.	This step instructs on how to care for the injection site following injection, and also when to store or dispose of the pen after use.

a. The images presented are representative of the 24 mg pen IFU.
IFU = Instructions for Use; N/A = not applicable

Information found in Seq. 0001 [Pharmaceutical Development Product Development 3.2.P.2.4.2]

Somatrogon Prefilled Pen Operation and Feedback

The principles and features of operation of the somatrogon prefilled pen include:

- Removal of the pen cap and needle attachment;
- User-priming and dose setting, with visual, audible and tactile feedback during dose setting;
- Dose delivery, with audible and tactile feedback, at a speed and force controlled by the user;
- Visual feedback that dose delivery has completed
- Removal and disposal of the needle and replacement of the pen cap for future use, or safe disposal of the needle and pen to avoid injury

The somatrogon pen is provided pre-assembled containing the somatrogon drug product solution cartridge and ready to use following attachment of a recommended needle. Needles are not included in the carton with the pen.

On first use of a new pen, the user is required to attach a needle to the tip of the cartridge holder and "user-prime" the pen ahead of dose setting. The desired dose is then dialed by turning the dose knob until the correct dose in milligrams (mg) is displayed in the dose window on the pen. The injection is performed by the user inserting the needle at the

injection site and then pressing down on the injection button until it cannot go any further. The pressure of the user pushing the injection button advances the dosing mechanism flange and plunger stopper within the cartridge, dispensing the required dose into the subcutaneous tissue. The user continues to press the injection button until a hard stop is felt and the number "0" is visible in the dose window. This is followed by a hold time where the user counts to 10 before removing the needle from the injection site. The user is then instructed on how to safely remove and dispose of the needle, and to re-cap and store the pen in a refrigerator for future use. At the point when the cartridge is empty, or if more than 28 days after first use is reached, or after the printed expiration date has passed, whichever is sooner, the entire pen is disposed of as defined in the IFU.

Descriptions of the key operating features of the pen and feedback to the user is provided in greater detail below.

User-Priming of the Prefilled Pen

Before a pen can be used for the first time, the pen must be prepared by the user- "user-primed". User-priming brings the dosing mechanism flange into full contact with the cartridge plunger stopper, overcomes the break loose force of the stopper, and expels air from the cartridge. This is to ensure that the pen will deliver the full selected dose of somatrogon drug product solution from first use of the pen.

Defined steps are followed to user-prime the pen. The cartridge content is available from the pen in dose increments (units) of 10 µL, which are displayed in milligrams "mg" in the dose window; the unused pen displays "0" in the dose window prior to user-priming. To start the user-priming steps, a needle is attached, and the dose knob is turned two increments (20 µL), which corresponds to 0.4 mg for the 24 mg pen, and 1.0 mg for the 60 mg pen.

Figure 3.2.P.2.4-2 depicts the dose window of the unused pen and after selection of the user-priming dose.

Dose Selection of User-Priming Figure 3.2.P.2.4-2

The pen is then held in an upright position so that the needle is pointing up and air bubbles can rise. The cartridge holder should be gently tapped so that any air bubbles will float to the top. The injection button is then pressed, and the dosing mechanism flange moves forward according to the selected priming dose until it cannot travel any further and "0" is again displayed in the dose window. If liquid is present at the needle tip, the user-priming step is complete, and the pen is ready for dose setting and first use. If no liquid is ejected after 5 attempts of user-priming, the user is advised to change the needle before 1 further attempt totaling a maximum of 6 user-priming attempts. If still no liquid is ejected from the needle, a new pen should be used. The user-priming steps relative to the IFU are presented in Table 3.2.P.2.4-2.

Dose Setting of the Prefilled Pen

Following user-priming, the user selects the dose of somatrogon drug product solution to be injected by turning the dose knob. The selection can be corrected by turning the dose knob in either direction to increase or decrease the selected dose.

The dosing mechanism gives visible, audible and tactile feedback to the user during dose setting with the set dose displayed in the dose window of the pen. One “click” sounds, which is also perceived by touch, for each dose unit (increment or decrement) as the dose knob is turned. Figure 3.2.P.2.4-3 shows examples of the dose window display during dose setting.

The pen mechanism has a means to prevent selecting a dose which exceeds the residual deliverable volume in the cartridge, and thus users cannot turn the dose knob to a greater amount than that left in the cartridge – “Stop last dose”. Dose volumes within a range of 10 µL to 600 µL (0.01 mL to 0.6 mL) can be selected, so long as there is enough drug product solution remaining in the cartridge.

Examples of the Somatrogon Prefilled Pen Dose Window Display Figure 3.2.P.2.4.3

Dose Delivery

The somatrogon drug product solution is delivered by pushing down on the injection button at a speed and force controlled by the user. The dosing mechanism of the pen pushes forward the cartridge plunger stopper with travel according to the selected dose. The dosing mechanism gives audible and tactile feedback to the user during the injection with the figure in the dose window returning to the "0" position at the end of travel. The scale printed on the transparent cartridge holder enables the patient to estimate the residual volume in the cartridge and allows full visual inspection of the drug product solution. The progression of the cartridge plunger stopper gives evidence for the delivery of the drug product solution.

Figure 3.2.P.2.4-4 demonstrates the visibility of the cartridge plunger stopper in the pen. The user can inject more than 1 dose with 1 pen.

Visibility of the Cartridge Plunger Stopper in the Prefilled Pen Figure 3.2.P.2.4-4

(b) (4)

Somatrogon Prefilled Pen Components 3.2.P.2.4.3

Table 3.2.P.2.4-1 provides details of the somatrogon pen components, each with a representative image (not to scale) and an overview of the function of the component within the pen. The components are grouped according to assembly, and those that come into skin contact are footnoted.

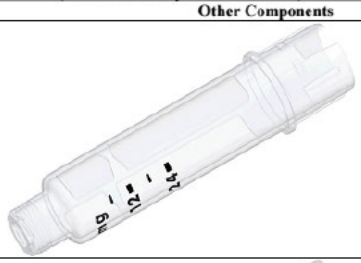
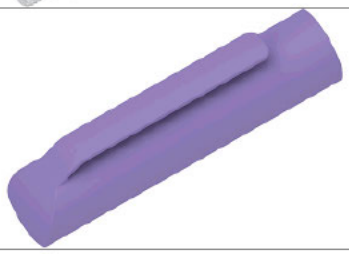
Information found in Seq. 0001 [Pharmaceutical Development Product Development 3.2.P.2.4.3]

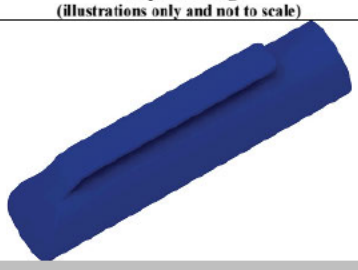
Functional Description of the Somatrogon Prefilled Pen Components Table 3.2.P.2.4-1

Component Name	Component Image (illustrations only and not to scale)	Description
Dosing Mechanism		
24 mg dose button (injection button)[a]		The dose button is pushed outwards by the dose selection spring and retained by the dose sleeve. It can rotate freely. When pressed down by the user after dose selection, it couples the click ring and clutch to initiate delivery of the selected dose.
60 mg dose button (injection button)[a]		

(b) (4)

2 Pages have been Withheld in Full as B4 (CCI/TS) immediately following this page

Component Name	Component Image (illustrations only and not to scale)	Description
Other Components		
24 mg cartridge holder[a]		The cartridge holder encloses and holds the cartridge in position and is attached to the housing. The tip is threaded to enable attachment of a new needle prior to each use of the pen. Features on the cartridge holder locate and retain the pen cap when the pen is not in use. The cartridge holder allows full visibility of the somatrogon drug product solution and cartridge plunger stopper. It is printed with a scale in milligram (mg) units to indicate approximate available injectable content in the cartridge.
60 mg cartridge holder[a]		
24 mg pen cap[a]		The pen cap fits over the cartridge holder when the pen is not in use. It is designed to prevent the pen from rolling away on a horizontal surface.

Component Name	Component Image (illustrations only and not to scale)	Description
60 mg pen cap[a]		See description above for the 24 mg pen cap.

(b) (4)

4.3 Device Description Conclusion

DEVICE DESCRIPTION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☐ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☐ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☐ No ☐ N/A
Reviewer Comments Sponsor has adequately provided a description of the device. **No deficiencies.**		
CDRH sent Device Description Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☐ No		

5 FILING REVIEW

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

5.1 Filing Review Checklist

Filing Review Checklist				
Description		**Present**		
		Yes	**No**	**N/A**
Description of Device Constituent				X
Device Constituent Labeling				X
Letters of Authorization				X
Essential Performance Requirements defined by the application Sponsor				X
Design Requirements Specifications included in the NDA / BLA by the application Sponsor				X
Design Verification Data included in the NDA / BLA or adequately cross-referenced to a master file.				X
Risk Analysis supplied in the NDA / BLA by the application Sponsor				X
Traceability between Design Requirements, Risk Control Measures and V&V Activities				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			X
	Sterility			X
	Software			X
	Cybersecurity			X
	Electrical Safety			X
	EMC/RF Wireless			X
	MR Compatibility			X
	Human Factors			X
	Shelf Life, Aging and Transportation			X
	Clinical Validation			X
	Human Factors Validation			X
	Description of Device Manufacturing Process			X
	Description of Quality Systems (Drug cGMP-based, Device QSR-based, Both)			X

Quality Systems/ Manufacturing Controls Check	CAPA Procedure			X
	Control Strategy provided for EPRs			X

Reviewer Comment
CDRH was not consulted for the filing review

5.2 Facilities Information

Firm Name:	Pfizer Belgium, Purrs, Belgium
Address:	Rijksweg 12 Purrs 2870 Belgium
FEI:	1000654629
Responsibilities:	**See comment below**

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 choose an item 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 Choose an item.

☐ An inspection is not required because Choose an item.

☐ **Facilities Review will be conducted under ICC2001105 By Robert Nakielny (CDRH)**

Add Additional Facility

5.3 Quality System Documentation Triage Checklist

Device Type Table

Was the last inspection of the finished combination product manufacturing site, or other site, OAI for drug or device observations?	☐ Yes ☐ No ☐ UNK
Is the device constituent a PMA or class III device?	☐ Yes ☐ No ☐ UNK
Is the final combination product meant for emergency use?	☐ Yes ☐ No ☐ UNK
Is the combination product meant for a vulnerable population (infants, children, elderly patients, critically ill patients, or immunocompromised patients)?	☐ Yes ☐ No ☐ UNK

Does the manufacturing site have a significant and known history of multiple class I device recalls, repeat class II device recalls, a significant number of MDRs/AEs, or OAI inspection outcomes?	☐ Yes ☐ No ☐ UNK
Is the combination product meant for users with a condition in which an adverse event will occur if the product is not delivered correctly (example insulin products for specific diabetic patients)?	☐ Yes ☐ No ☐ UNK
Does the manufacturing process for the combination product device constituent part use unique, complicated, or not well understood methods of manufacturing?	☐ Yes ☐ No ☐ UNK
cGMP Risk:	
☐ Low or Moderate Risk of cGMP issues: If yes is not checked above, please fill out the checklist and deficiencies only. A review summary is optional.	
☐ High Risk of cGMP issues: If yes is checked anywhere above, consider filling out the checklist, the deficiencies, and the review summary. If a full review is not warranted due to other factors such as device constituent classification (class I and class II devices), a low or moderate overall risk of device constituent failure, or positive compliance history, please document your rationale below for not conducting a full ICCR review.	

Reviewer Comment:
CDRH was issued a consult under a separate ICC (ICC 2001105) to perform a facilities inspection review. All issues will be addressed in that review.

5.4 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 inspection:**
Reviewer Comments **CDRH was not consulted during filing** **The Facilities review will be on ICC2001105**
Refuse to File Deficiencies: ☐ Yes ☐ No ☐ N/A **74-Day Letter Deficiencies:** ☐ Yes ☐ No ☐ N/A

Add Additional Information Request

6 LABELING

6.1 General Labeling Review

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

General Labeling Review Checklist	Adequate?		
	Yes	No	N/A
Indications for Use or Intended Use; including use environment(s); route(s) of administration for infusion, and treatment population.	X		
Drug name is visible on device constituent and packaging	X		
Device/Combination Product Name and labeling is consistent with the type of device constituent	X		
Prescriptive Statement/Symbol on device constituent	X		
Warnings	X		
Contraindications	X		
Instructions for Use	X		
Final Instructions for Use Validated through Human Factors			X
Electrical Safety Labeling/Symbols			X
EMC Labeling/Symbols			X
Software Version Labeling			X
MRI Labeling/Symbols			X
RF/Wireless Labeling/Symbols			X

(b) (4)

[redacted]

(b) (4)

Reviewer Comments:
The steps for use of the device is contained within the package insert.
Steps for Using Device found in Section 4.2

6.2 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:

6.3 Labeling Review Conclusion

LABELING REVIEW CONCLUSION		
Filing Deficiencies: Yes No N/A	**Mid-Cycle Deficiencies:** Yes No N/A	**Final Deficiencies:** Yes No N/A
Reviewer Comments: The labeling adequately covers the device requirements for labeling. Recommended pen needles listed on the device carton. ***No deficiencies.***		
CDRH sent Labeling Deficiencies or Interactive Review Questions to the Sponsor: Yes No		

7 DESIGN CONTROL SUMMARY

7.1 Summary of Design Control Activities

Risk Analysis Attributes	Yes	No	N/A
Risk analysis conducted on the combination product	X		
Hazards adequately identified (e.g. FMEA, FTA, post-market data, etc.)	X		

Mitigations are adequate to reduce risk to health	X		
Version history demonstrates risk management throughout design / development activities		X	
Design Inputs/Outputs	**Yes**	**No**	**N/A**
Design requirements / specifications document present (essential performance requirements included)	X		
Design Verification / Validation Attributes	**Yes**	**No**	**N/A**
Validation of essential requirements covered by clinical and human factors testing	X		
To-be-marketed device was used in the pivotal clinical trial	X		
Bioequivalence Study utilized to-be-marketed device			X
Verification methods relevant to specific use conditions as described in design documents and labeling	X		
Device reliability is acceptable to support the indications for use (i.e. emergency use combination product may require separate reliability study)	X		
Traceability demonstrated for specifications to performance data	X		

Reviewer Comments
This is acceptable

7.2 Design Inputs and Outputs

Essential Performance Requirements

(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
ISO 11608-Needle Based Injection Systems for Medical Use-Requirements and Tests Methods, Part 1: 2014-Needle-Based Injection Systems and Part 2:2012-Needles	Y
Standard Practice for Performance Testing of Shipping Containers and Systems; ASTM D4169-09	Y
IEC 60601-1-2:2014	NA
Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products (2017)	NA

Mobile Medical Applications Guidance for Industry and Food and Drug Administration Staff (2015)	**NA**
Guidance for Industry and FDA Staff – Medical Devices with Sharps Injury Prevention Features (2005)	**NA**
Use of International Standard ISO 10993-1, Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process"	**Y**
Applying Human Factors and Usability Engineering to Medical Devices IEC 62366:2015 Medical Devices-Application of Usability Engineering to Medical Devices ANSI/AAMI HE75:2009-Human Factors Engineering-Design of Medical Devices Guidance	**Y**

Device Specific Standards and Guidance Documents

Standard or Guidance	Recognized (Y/N/NA)	Conformance (Y/N/NA)
FDA Guidance Applying Human Factors and Usability Engineering to Medical Devices – issued February 2016;	**Y**	

7.4 Design Control Review Conclusion

DESIGN CONTROL REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☐ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☐ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☐ No ☐ N/A
Reviewer Comments The sponsor provided a risk analysis, Design inputs/outputs and provided applicable standards and guidance's for which they utilized for this submission.		
CDRH sent Design Control Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☐ No		

8 RISK ANALYSIS

8.1 Risk Management Plan

Information found in Seq. 0001 [3.2.P.2.4 Risk Management]

8.2 Hazard Analysis and Risk Summary Report

(b) (4)

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(b) (4)

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
Reviewer Comments The pen is not novel and is like other pens currently on the market. The instructions for use are thorough and explicit with regards to attaching the needle and dose setting. It is recommended that all users receive training on the correct way to inject and use all aspects of the pen injector prior to beginning therapy. This drug is not used in emergency situations.		
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

(b) (4)

Reviewer Comment:

Verification: Design verification testing was done (b) (4)

Validation: The sponsor provided (b) (4)

Stability: Stability testing provided in Seq. 0001 3.2.P.8.3. Prefilled pen data to the end of shelf life, including in use testing, are provided by the primary lot study (clinical pen presentation). Data was also provided for the commercial presentation (additional lot studies) to three months for both long term and accelerated storage study lots. The comparability of the results from the primary and addition study lots tested indicate that the results from testing of the clinical presentation are applicable to the commercial presentation. The design differences between the presentations relate to color and print layout on the dose sleeve, which are confirmed during design verification testing to have no impact on the pen functions. Pfizer considers the primary studies to be fully representative of those intended

for commercialization. (b) (4)

Shipping: Per ISTA 3A test standard is also an FDA recognized consensus standard and meets the same intent as ASTM D4169 Performance Testing of Shipping Containers and Systems. Functional characteristics tested. The testing demonstrated that the EPRs of the combination product were not impacted or compromised following simulated shipping of the device.

Information found in Seq. 0022 [1.11.1 Quality Information Amendment]

(b) (4)

9.1.2 Verification of Design Inputs Evaluation

(b) (4)

9.1.3 Evaluation of Test Methods

(b) (4)

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Conclusions/ Reviewer Comments:	**All test results met their acceptance criteria**
Acceptable:	**☒Yes ☐No**

Biocompatibility

Per ISO 10993-1 the device is skin contacting limited duration

Table 3.2.P.2.4-13. Somatrogon 24 mg and 60 mg Prefilled Pen Components Biocompatibility Test Results

Test	Test System	Evaluation Criteria	Result
Cytotoxicity ISO 10993-5 2009	Cytotoxicity – MEM elution test Name: Fibroblast cell Organism: Mouse Cell Line: L-929 (ECACC Catalogue 85103115 or equivalent source) Source: European Collection of Authenticated Cell Cultures (ECACC)	(b) (4)	Pass Cells treated with the test articles extract exhibited a response of grade 0 (no reactivity) at 48 hours.
Irritation ISO 10993-10 2010	Animal irritation test Species: Rabbit Strain: New Zealand White Source: (b) (4) Number used: 6 Initial Weight: 2.3 to 2.5 kg Age: Young adult Sex: Female Identification: Ear tag or marking		Pass There was no erythema and no edema observed on the skin of the animals treated with the (b) (4) test article extract. The primary irritation index for the (b) (4) test article extract was calculated to be 0.0. The irritation response of the (b) (4) (b) (4) test article extract was categorized as negligible. There was no erythema and no edema observed on the skin of the animals treated with the (b) (4) test article extract. The primary irritation index for the (b) (4) test article extract was calculated to be 0.0. The irritation response of the (b) (4) test article extract was categorized as negligible.
Sensitization ISO 10993-10 2010	Guinea pig maximization test Species: Guinea pig Strain: Hartley, Albino Source: (b) (4) Number used: 30 Sex: Female Age: Young adult Initial Weight: 300 to 405 g Identification: Ear tag		Pass All animals were clinically normal throughout the study and no evidence of sensitization was observed. The test article extracts showed no evidence of causing delayed dermal contact sensitization in the guinea pig. The test article was not considered a sensitizer in the guinea pig maximization test.

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 The sponsor was asked to provide the following: (b) (4)		
CDRH sent Design Verification Deficiency or Interactive Review Questions to the Sponsor: ☐ Yes ☐ No		

	Date Sent:	**Date/Sequence Received:**
Information Request #1	(b) (4)	
Sponsor Response		

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Reviewer Comments	(b) (4) (b) (4) This information is acceptable.
Response Adequate:	**Yes** **No, See IR # Sent on** Click or tap to enter a date.

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:

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

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	
CDRH Facilities Inspection Review was not conducted	

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

Summary of Manufacturing Process / Production Flow

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(b) (4)

Device Manufacturing Process Conclusion		
The Sponsor provided adequate information for the summary of the manufacturing process / production flow.	☒Yes	☐No

12.2.2 cGMP Review

(b) (4)

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(b) (4)

GMP Compliance Summary Conclusion		
The Sponsor provided adequate summary information about the GMP compliance activities	Yes	No

12.2.3 Corrective and Preventive Action Review

(b) (4)

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(b) (4)

CAPA Conclusion		
The Sponsor provided adequate information for corrective and preventive actions.	☒Yes	☐No

12.3 Control Strategy Review

The Sponsor provided the following control strategy information regarding the EPRs of the device constituents:

(b) (4)

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(b) (4)

Control Strategy Conclusion		
The Sponsor provided adequate information to support the manufacturing control activities for the essential performance requirements of the combination product. The sponsor will provide (b) (4)	☒Yes	☒No

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 The sponsor was asked (b) (4)		

(b) (4)

CDRH sent Facilities & QS Deficiencies or Interactive Review Questions to the Sponsor: Yes No

(b) (4)

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	(b) (4)
Reviewer Comments	The sponsor has provided a description of Pfizer's CAPA process.
Response Adequate:	☐ **Yes** ☐ **No, See IR #** **Sent on** Click or tap to enter a date.

<<END OF REVIEW>>

13 APPENDIX A (INFORMATION REQUESTS)

13.1 Filing/74-Day Information Requests

13.2 Mid-Cycle Information Requests (sent 3/8/2021 received 3/19/2021) See body of memo for sponsor responses.

(b) (4)

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14. APPENDIX B (CONSULTANT MEMOS)

14.1 Human Factors Review Memo – Insert Consultant Name

14.2 Clinical Review Memo – Insert Consultant Name

14.3 Insert Discipline Review Memo – Insert Consultant Name

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/s/

SEJAL KIANI
05/20/2021 04:21:20 PM
Signing on behalf of: Janice Ferguson, RN, BSN, CRNI OPEQ/OHT3/DHT3C

Food and Drug Administration (FDA)
Center for Drug Evaluation and Research (CDER)
Office of New Drugs (OND)
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine
Division of Urology, Obstetrics and Gynecology (DUOG)

Consult Review

Requesting Organization:	Center of Drug Evaluation and Research (CDER) Division of General Endocrinology
Review Date:	May 11, 2021
To:	Marina Zemskova, clinical team lead - Division of General Endocrinology (DGE) Montserrat Puig Sonia Doi
From:	Audrey Gassman, M.D. – Deputy Division Director, DUOG
BLA	761184
Drug:	Somatrogon (MOD-4023 injection)
Proposed Indication:	(b) (4)
Sponsor:	Pfizer Ireland Pharmaceuticals Inc.

Introduction:

This a consult response on a biologic product (MOD-4023, hereafter referred to as somatrogon). The BLA for this product was received by the DGE on October 22, 2020, with the PDUFA goal date of October 22, 2021. The product is a long-acting growth hormone analog that is intended for chronic use via subcutaneous administration.

During the review, the clinical and OBP reviewers identified antibody formation in some treated subjects. Given DUOG's experience with development of gonadotropin products, specifically corifollitropin alfa, the Division was asked to provide a clinical perspective on the presence of anti-CTP antibodies (CTP is the carboxyterminal peptide of human chorionic gonadotropin) and whether these antibodies were of clinical concern in terms of interfering with pregnancy. In addition, DGE asked if the Division had any other comments or recommendations regarding this BLA.

Brief Background:

NOTE: This consult review is based on the reviewer's knowledge of available information from development of other Chinese hamster ovary (CHO)-derived gonadotropins including corifollitropin alfa. As corifollitropin alfa was not approved in the US for reasons unrelated to antibody formation, publications and information from the EMA are also included for reference where applicable. Also important is that the corifollitropin alfa NDA application only has information on single dose

administration of the product. The only information on chronic use of corifollitropin alfa, which is the proposed use for the BLA subject to this consult, is from the literature and the EMA.

Somatrogon is a fusion glycoprotein produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology. The fusion protein contains the amino acid sequence of human growth hormone (hGH) and one copy of the C-terminal peptide from the beta chain of the human chorionic gonadotropin (hCG) at the N-terminus and 2 copies (in tandem) at the C-terminus. The glycosylation and CTP domains allow the product to have a half-life that allows weekly dosing.

Nonclinical studies for somatrogon demonstrated no adverse effects on fertility or development in any of the developmental and reproductive toxicology studies conducted in rats. Anti-drug antibodies (ADAs) were not measured in these nonclinical studies. As animal adaptive immune responses are not predictive of human responses, the risk of infertility or other adverse events in humans due to antibody formation could not be adequately addressed in the submitted nonclinical studies.

The clinical safety database for somatrogon is obtained from 2 randomized, open-label, controlled clinical studies in pediatric patients with growth hormone deficiency (GHD). These studies included an initial safety and dose finding study (Study CP-4-004) that evaluated 53 pediatric patients (13 using 0.25 mg/kg/week, 15 using 0.48 mg/kg/wk and 14 using 0.66 mg/kg/wk) compared to 11 using genotropin (an approved r-GH comparator]). CP-4-004 was conducted using the product in a multi-dose vial presentation. The 0.66 mg/kg/wk dose was then assessed in 109 patients with GHD (Study CP-4-006) using a pen-injector (which is expected to be the commercial product). The clinical trial database did not identify any cases of systemic allergic reactions or anaphylaxis, although injection site reactions were reported. Both Studies CP-4-004 and CP-4-006 have open-label extension studies with patients in CP-4-004 eventually switching to the pen-injector during the extension. In the extension database, no cases of systemic allergic reaction or anaphylaxis were reported.

In the some of the clinical studies, Somatrogon was compared to Genotropin. Genotropin is somatropin analog [rDNA origin]. Genotropin is a polypeptide hormone of recombinant Escherichia coli DNA origin. It has 191 amino acid residues and a molecular weight of 22,124 daltons. The amino acid sequence of the product is identical to that of human growth hormone of pituitary origin (somatropin). Genotropin is synthesized in a strain of Escherichia coli that has been modified by the addition of the gene for human growth hormone (r-hGH).

In the clinical study program for genotropin, antibodies to growth hormone (anti-hGH antibodies) were present in six subjects who were previously treated patients with genotropin at baseline. Three of the six became negative for anti-hGH antibodies during 6 to 12 months of treatment with Genotropin. Of the remaining 413 patients, eight (1.9%) developed detectable anti-hGH antibodies during treatment with Genotropin; none had an antibody binding capacity > 2 mg/L. Genotropin is not synthesized using the same CHO cell bank but is derived from Escherichia coli. During drug manufacturing, preparations of Genotropin contain a small amount of periplasmic Escherichia coli peptides (PECP). Anti-PECP antibodies are found in a small number of patients treated with Genotropin, but the clinical significance of this is unknown.

The detection of anti-drug antibodies (ADAs) defines the immunogenicity of the drug product, in this case, somatrogon. As a result of ADAs, reduction of efficacy and in some cases, neutralization of the drug can interfere with the treatment. More severe and dangerous for the patient are life-threatening immune reactions, hypersensitivity or cross-reactions with endogenous proteins, which could lead to deficiency syndromes or result in infertility if interfering with hCG signaling from the embryo. Important factors to be considered when assessing a product for immunogenicity include (but are not limited to):

glycosylation patterns, concealment or removal of MHC epitopes, and impurities and contaminants in the production steps.

The following table is an overview provided by email (dated 5/11/2021) from the OBP/DBRRIII review team (Sonia Doi and Montserrat Pugh) outlining results from antibody testing in the BLA program from both somatrogon and genotropin treated patients

Study	Months	Presentation	Subjects	ADA+ (somatrogon)	Anti-hGH Ab	Anti-CTP Ab Patient ID_Visit(month)
CP-4-006 (Phase 3, main)	12	Pen injector	109 (somatrogon) 115 (genotropin)	77.1% (1.8% NAb+) 15.7%	77.1%	3.7% (4 individuals) • 025-207_V7(m9); neg at m12 [somatrogon pos m6,9,12, titer: 250/50/250] • 064-308_V8(m12); neg at m12 baseline OLE [somatrogon pos m6,9,12, titer: 50/50/250] • 215-079_V6(m6), neg at m12 [somatrogon pos m6, 12, titer: 250/250] • 227-145_V8(m12) [somatrogon pos m6, 12, titer: 10/250]
CP-4-006 (Phase 3, open label extension (OLE))	12 (majority of data is from 6 months after the phase 3 trial at the 18 month timepoint)	Pen injector	79	43.03%	41.8%	6.3% (5 individuals) • 040-024(S)_OLE(m12); no further data [somatrogon pos baseline,m6,m12; titer: 250] • 064-308(S)_OLE(baseline) was neg; pos at m12 of main (see above); no further data [somatrogon pos baseline, titer: 250] • 202-136(S)_OLE(6m); no further data [somatrogon pos baseline and m6, titer:1250]

						• 227-145(S)_OLE (baseline); neg at OLE(m6) [somatrogon pos baseline, titer:50/250] • 021-013(G)_OLE(12m); no further data [somatrogon pos m6&12; titer: 250/1250]
CP-4-004 (Phase 2, main)	12	Vial	14 (somatrogon 0.66 mg/kg/wk) 11 (Genotropin)	35.7% (No NAb+) 18.2%	35.7%	No Ab+
CP-4-004 (Phase 2 OLE), VIAL	4 years	Vial	43	25.6% (at year 3)	23.3%	No Ab+
CP-4-004 (Phase 2 OLE)_PEN	Up to 12 months	Pen	40	37.5%	32.5%	7.5% (3 individuals) • 10013_V1(baseline); neg m1,3,6,9,12; also neg through main, OLE-vial. [somatrogon ADA+ during OLE-vial (>Y2) and OLE-PEN; titers:50 to 250] • 11008_V4(m6); neg m9,12; also negative before V4 [somatrogon ADA+ during OLE-vial and OLE-PEN; titers:50 to 1250] • 17006_V5(m9), neg at m12, also neg during OLE-vial [somatrogon ADA+ during OLE-vial (>Y4) and OLE-PEN; titers:50 to 250]

NOTE: The DUOG reviewer evaluated the information from Somatrogon primarily from internal knowledge obtained from review of corifollitropin alfa (EMA tradename ELONVA) as well as other gonadotropins that are manufactured using CHO cell bank technology. Corifollitropin alfa is a

somewhat similar fusion protein to Somatrogon (which is a recombinant fusion protein that has a recombinant human growth hormone [rhGH] attached to CTP proteins), but instead of rhGH it is human follicle stimulating hormone (rhFSH) linked to the carboxyterminal peptide (CTP) of human chorionic gonadotropin. This allowed corifollitropin alfa to have twice the half-life of recombinant FSH. (b) (4) *.[1] [2]The human immune system can produce antibodies* (b) (4) *that could contribute to immunogenicity/neutralization of the corresponding biotherapeutics.[3][4]*

Consult Response:

This consult will solely focus on patients who have CTP positive antibody results. These are the patients that could theoretically have unintended reproductive consequences if the antibodies increase, persist and/or develop neutralizing antibodies and block human chorionic gonadotropin (hCG).

HCG is not normally made by any organ of the healthy non-pregnant female, that is why its detection in blood or urine is the basis of the pregnancy diagnostic test. Eggs fertilized in vitro and cultivated till blastocyst stage produce hCG. hCG also plays a crucial role in the implantation of the embryo onto the endometrium. In nonclinical primate studies (which are very similar in gestation to that in humans), marmoset embryos exposed to anti-hCG antibodies fail to implant, whereas the same embryos exposed to normal globulins implant perfectly leading to the onset of pregnancy.[5] Thus the most likely result of neutralizing hCG would be that implantation of the embryo on the endometrium would be blocked and the onset of pregnancy prevented. No autoimmune reactivity against any other organ would be expected and this makes it difficult to develop a predictive and feasible nonclinical or clinical study.

Of note, clinical assessment of this program from a reproductive standpoint is further complicated because of an observed higher ADA response in patients treated with the pen-injector presentation

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1 (b) (4)

2 (b) (4)

3 (b) (4)

4 (b) (4)

[5] JP Hearn, AA Gidley-Baird, JK Hodges, PM Summers, GE Webley: Embryonic signals during the peri-implantation period in primates. J Reprod Fertil Suppl 36, 49-58 (1988).

compared to those treated in a phase 2 trial with the vial presentation. Additional investigation needs to occur into the manufacturing changes when the formulation/presentation was changed. It is important to note that no anti-CTP antibodies were seen with the vial presentation and were only identified with the pen-injector. Of importance, there is very limited long-term data to assess whether the anti-CTP antibodies resolve after product discontinuation as was seen with corifollitropin alfa. Given the antibody and clinical database limitations, this reviewer summarizes her perspective below:

1. Clinical Safety Database: It is reassuring that the safety database for corifollitropin alfa program is similar to that of Somatrogon in terms of no significant case reports of either systemic hypersensitivity or allergy in the clinical trials. The corifollitropin database did not identify any clinically relevant immunogenic or drug-related hypersensitivity reactions in patients receiving up to three injections (in three cycles) of corifollitropin alfa. This is very clinically consistent with the lack of systemic immune response or antibody response (as seen in extension studies for phase 2 and 3) reported for Somatrogon. However, given the limited long-term data for Somatrogon, continued monitoring for systemic reactions and anaphylaxis in patients on chronic dosing will be necessary.
2. Nonclinical safety database: Somatrogon had no adverse effects on fertility or development in any of the developmental and reproductive toxicology studies conducted in rats. ADAs were not measured in these studies. As animal adaptive immune responses are not predictive of human responses, the issue of whether anti-CTP antibodies are clinically relevant cannot be addressed in the available nonclinical studies.

In conclusion, neither clinical trials nor nonclinical studies can be leveraged to determine if the anti-CTP antibodies reported in the phase 3 clinical trial are clinically relevant and/or would affect fertility and/or pregnancy loss with chronic Somatrogon use. It is my understanding that:

- There is unlikely to be a value in repeating the embryofetal developmental study in another species such as monkeys or rabbits as the immunological response in these species is not predictive of the immunological response in humans.
- There is unlikely to be a value in conducting a large postmarketing database or study to directly assess fertility and/or early pregnancy loss given the age of the population treated, the fact that not all somatropin-treated patients will attempt to become pregnant, the relatively high background rates of pregnancy loss in the general population (20% of clinically recognized pregnancies and most likely higher in chemically-diagnosed pregnancies) as well as the presence of other risk factors for infertility (such as male factor infertility, polycystic ovarian disease, etc.).

3. Antibody database: It is critical to leverage the available antibody data to inform the clinical risk(s). The clinical trial database for somatrogon demonstrates an increased ADA incidence from 36-37% in subjects who were treated in the phase 2 dose finding study somatrogon-vial as compared to 77% of subjects treated with the phase 3 somatrogon-pen injector. Along with the increase in ADA in phase 3, there was also an increase in the presence of anti-CTP antibodies (Ab) from 0 in phase 2 to 4% [4 subjects out of 109]. Of note, all subjects with anti-CTP Ab that also had anti-hGH Ab. In the neutralizing Ab assay for somatrogon ((b) (6) (12 month) and (b) (6) (b) (6) (6 and 12 month)) did not have anti-CTP Ab. In the two patients who developed neutralizing antibodies during somatrogon treatment (Subject (b) (6) at 12 months and Subject (b) (6) at 6 and 12 months) did not have anti-CTP Ab.

The reviewer's comments are as follows:

- Anti-CTP testing: It is unclear to the reviewer that the Applicant's anti-ADA and anti-CTP testing was sufficiently specific or sensitive. It is very concerning to the reviewer that both anti-CTP and anti-rhGH were reported in the same patients. This leads to questions about whether development of a more accurate assay needs to be developed to detect anti-CTP.
- Leveraging data from corifollitropin alfa: Of the 2,511 women treated with corifollitropin who were evaluated for the formation of post-treatment antibodies, only four (0.16%) had evidence of antibody formation. In each case, these antibodies were non-neutralizing and did not interfere with the response to stimulation or the normal physiologic responses of the Hypothalamic-Pituitary-Ovarian (HPO) axis. Two of these four women became pregnant during the same treatment cycle in which antibodies were detected, suggesting that the presence of non-neutralizing antibodies after stimulation with corifollitropin is not clinically relevant. This is somewhat reassuring. Based on this limited information, all patients who develop a positive anti-CTP should have: 1) follow-up titers to determine if their anti-CTP antibodies resolve over time and 2) testing for neutralizing antibodies specific for CTP to confirm specificity of the anti-CTP result.
- Leveraging data from the hCG vaccine: A recent published review[6] noted that there is a long history of attempting to develop an hCG vaccine to prevent pregnancy. This 2017 article noted that hCG vaccine development has been extremely difficult because the CTP region of hCG β was a poor immunogen and necessitated the use of strong adjuvants to evoke the production of antibodies. This review article states that, "The ability of the anti-hCG titers above 50 ng/ml to prevent pregnancy in sexually active women without derangement of ovulation and menstrual regularity was clearly demonstrated".[7] Although the assays used to develop the hCG vaccine are likely different from those used for Somatrogon, it would appear that low levels of anti-CTP antibodies are unlikely to interfere with fertility.

4. From a pregnancy testing standpoint: The only issue regarding pregnancy testing that was identified with corifollitropin alfa during the postmarketing period was not the presence of anti-CTP antibodies interfering with testing, but rather the occurrence of false positive pregnancy testing if performed after product administration (See Additional Comment #1).

In summary, there is insufficient data to conclude that chronic Somatrogon use results in development of anti-CTP antibodies that could neutralize the effects of hCG. It's unclear that there are any additional nonclinical or clinical studies or trials that could be developed to further assess this risk. Given the limited data from the Somatrogon program, the corifollitropin alfa experience, and published hCG vaccine data, this reviewer has the following summary recommendations:

1) Evaluation of the sensitivity and specificity of the anti-CTP assay to ensure that it is only detecting anti-CTP. It was concerning that the patients who were anti-CTP positive also had anti-hGH antibodies. This raises concerns about the sensitivity and specificity of the anti-CTP assay.

[6] Gursaran P Talwar, Kripa N Nand, Jagdish C Gupta, Atmaram H Bandivdekar, Radhey S Sharma, Nirmal Kumar Lohiya. Current status of a unique vaccine preventing pregnancy. Front Biosci (Elite Ed) 2017 Jun 1;9:321-332.

[7] Ibid.

2) Development of a specific and sensitive antibody assays for anti-CTP antibodies, including a neutralizing antibody assay. If neutralizing antibodies are identified, then titers should be measured and the patient(s) followed to ensure resolution. Based on the limited published experience from the hCG vaccine trials, resolution to titers lower than 50 mg/mL may be a clinically important threshold to consider and additional literature on the hCG vaccine might be useful in further refining cutoff points.

3) Continued assessment of anti-CTP antibodies in patients to determine the cause of the increase in ADA antibodies with the pen-injector. It is possible that there will be resolution of these antibodies over time. Based on the experience with gonadotropin, patients that develop anti-CTP products and/or allergic reactions should be switched to another rhGH product. This will likely allow the antibodies to resolve as long as neutralizing antibodies have not developed. It would be helpful to know if those antibodies are also interfering with other antibody assays for this product. Different methodologies might be useful to address sensitivity and specificity assay issues.

4) Assessment of the development of anti-CHO antibodies. As previously mentioned, CHO cells product non-native glycosylation that may cause ADA and other antibodies. It would be worthwhile to evaluate other drug and biologic products that are manufactured using CHO technology to see if there are significant differences or assay recommendations that would further improve quality. Based on my understanding of gonadotropin products, I would suspect that the high rate of ADA with the pen injector could be a result of either increased delivery of the product with the pen as opposed to the vial (less dead space in the vial) resulting in an increased antibody response or other changes that resulted in increased aggregation or oxidation (such as increased dimer production) that have a significant impact on antibody formation.

5) Assessment of cross-reactivity between Somatrogon and other recombinant hGH products (genotropin). Although these products are produced using different technologies, it is worth assessing whether sensitivity to a recombinant product results in accelerated antibody response to administration of a second similar product. It may be worthwhile to further assess patients who were treated with genotropin and then were placed on Somatrogon to see if the development of antibodies resulted in a more prominent response.

Please feel free to contact me if there are any further issues or questions.

Additional comment:

1. There was a recent report of a false positive pregnancy test that was reported during corifollitropin alfa administration.[8] After receiving this report, the EMA added this to the corifollitropin product label, "Elonva may cause a false positive hCG pregnancy test if the test is administered during the ovarian stimulation portion of the ART cycle. This may be due to cross-reactivity of hCG pregnancy tests with the carboxy-terminal peptide of the beta subunit of Elonva."[9] Although the pregnancy testing interference studies were negative, given the known

[8] R. Gersh. Reply: False positive blood hCG test following Corifollitropin alfa injection. Human Reproduction., 33(5), (2018), 978.

[9] Current ELONVA product information (https://www.ema.europa.eu/en/documents/product-information/elonva-epar-product-information_en.pdf)

cross-reactivity with corifollitropin, it would be reasonable to advise providers to repeat all positive pregnancy tests to determine whether the test was a false positive. Of note, the false positive level identified with Elonva was a very small quantitative result, but it is important for physicians to be aware of this potential cross-reactivity from the CTP protein.

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/s/

AUDREY L GASSMAN
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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: March 18, 2021

From: Interdisciplinary Review Team for Cardiac Safety Studies

Through: Christine Garnett, PharmD
Clinical Analyst, DCN

To: Sejal Kiani, RPM
DGE

Subject: IRT Consult to BLA-761184 (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 11/19/2020 regarding the sponsor's QT related language in the proposed label. We reviewed the following materials:

- Sponsor's clinical study protocol # CP-4-004 (SN0001; link);
- Sponsor's clinical study report # CP-4-004 (SN0001; link);
- Sponsor's clinical study protocol # CP-4-006 (SN0001; link);
- Sponsor's clinical study report # CP-4-006 (SN0001; link); and
- Sponsor's proposed product label (SN0001; link);

1 IRT Responses to the Division

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 molecular weight proteins for which a dedicated QT study is generally not needed and when one has not been conducted (ICH E14 Q&A 6.3 (R3)).

The submitted safety ECG data do not indicate any unexpected or important effects of somatrogon on the QTc interval at clinically relevant exposures associated with the proposed dose.

2 Background

Pfizer Inc. is developing somatrogon as a long-acting recombinant growth hormone analog for treatment of pediatric patients (who have growth failure due to an inadequate secretion of endogenous growth hormone). Somatrogon (MOD-4023; molecular mass of the protein without O-glycosylation: ~30465 Da) is comprised of the amino acid sequence of human growth hormone

(hGH) with one copy of the C-terminal peptide (CTP) from the beta chain of human chorionic gonadotropin (hCG) at the N-terminus and two copies of CTP (in tandem) at the C-terminus. Each CTP includes multiple O-linked glycosylation sites. This glycoprotein is produced by recombinant DNA technology.

Somatrogon is expected to bind to the growth hormone receptor initiating a signal transduction cascade culminating in changes in growth and metabolism. The product is formulated as solution (1.2 mL, delivered using disposable prefilled pen; for single-use) containing somatrogon (24 mg / 1.2 mL or 60 mg / 1.2 mL) for subcutaneous administration. The proposed maximum dose for the present indication is 0.66 mg/kg of body weight to be administered once weekly (on the same day each week; at any time of day). The peak concentrations of 690 ± 261 ng/mL (Tmax: ~8 h; half-life: ~28 h) are expected at steady-state with the maximum proposed dose of 0.66 mg/kg once weekly (POP-PK Predicted; Pediatric Population). No significant accumulation is expected at steady-state with the proposed maximum dose (Racc: ~1.02).

Sponsor highlights that somatrogon is primarily eliminated by proteolytic catabolism and indicates that it has no PK drug interaction liabilities. Clinical pharmacology studies characterizing potential worst-case scenario due to organ impairment (renal impairment or hepatic impairment) have not been studied (m2.7.2).

The sponsor did not submit the highlights of clinical pharmacology and clinical safety. Refer to the sponsor's non-clinical overview (m2.4). The hERG data for somatrogon is not included in the submission.

Safety pharmacology endpoints, which included electrocardiogram parameters (heart rate, RR interval, PR interval, QRS duration, QT interval, and corrected QT) were incorporated into the pivotal toxicity studies in rhesus monkeys (Study 1592-004 and Study 1592-006), and effects on the central nervous system and respiratory systems were evaluated (via clinical observations) in the pivotal toxicity study in rats (Study 1592-003) and rhesus monkeys. There were no test article-related effects on the central nervous, respiratory, or cardiovascular systems.

Refer to the sponsor's clinical overview (m2.5) and the sponsor's summary of clinical safety (m2.7.4).

No clinically significant shifts from baseline were observed with regard to ECG and vital signs, and there were generally no differences between the somatrogon and Genotropin treatment groups in both Studies CP-4-006 and CP-4-004, main and OLE periods (Module 2.7.4). Both studies included 12-month main study periods as well as ongoing OLE periods.

- Phase 3 registration study, CP-4-006, A Phase 3, Open-Label, Randomized, Multicenter, 12 Months, Efficacy and Safety Study of Weekly MOD-4023 Compared to Daily Genotropin® Therapy in Pre-Pubertal Children with Growth Hormone Deficiency.
- Phase 2 supportive study, CP-4-004, Safety and Dose Finding Study of Different MOD-4023 Dose Levels Compared to Daily r-hGH Therapy in Pre-Pubertal Growth Hormone Deficient Children.

Study # CP-4-006

ECGs for somatrogon subjects were taken 7-12 hours post dose. Changes in vital signs assessments were similar between somatrogon and Genotropin. Both treatment groups had similar mean

baseline values and mean changes from baseline across the ECG parameters (HR, PR interval, QRS interval, QT interval, RR interval, QTc interval and QTcF interval).

Four subjects (2 somatrogon and 2 Genotropin) had QTcF interval above 450 msec at 6 months: In the somatrogon group, 1 subject (b) (6) had a QTcF interval of 480 at baseline that decreased to 462 msec at 6 months and another subject (b) (6) had a QTcF interval of 452 msec at 6 months; In the Genotropin group, subject (b) (6) had a QTcF interval of 454 msec at 6 months and Subject (b) (6) had a QTcF interval of 550 msec at 6 months. None of the QTc intervals for these 4 subjects were considered to be clinically significant (Module 5.3.5.1, CSR CP-4-006, Section 12.5.2).

Descriptive statistics for observed and change from baseline ECG measurements at each visit are summarized in Module 5.3.5.1, CSR CP-4-006, Tables 14.3.6.1.1 and 14.3.6.1.2, respectively. Neither treatment group had any shifts from normal baseline values to out-of-range values at 6 months or anytime postbaseline. No clinically significant shifts from baseline at 6 months or anytime postbaseline for either treatment group. No consistent pattern was observed in the physical examination findings.

Overall, no trends in vital sign abnormalities have been observed in the CP-4-006 OLE period. Also, there have been no clinically meaningful changes in ECGs. Changes in vital signs assessments were consistent with the main study CP-4-006. All subjects had similar mean baseline values and mean changes from baseline across the ECG parameters (HR, PR interval, QRS interval, QT interval, RR interval, QTc interval and QTcF interval).

In the CP-4-006 main study period, no clinically significant shifts from baseline were observed with regard to ECG, vital signs, and physical findings, and there were no differences between the somatrogon and Genotropin treatment groups. A similar trend with regard to these parameters was observed in the CP-4-006 OLE period, up to the data cutoff date of 01 November 2019.

Study # CP-4-004

Mean values for the vital signs (systolic / diastolic BP in a seated position, RR, pulse rate, and body temperature) were within normal ranges for all parameters for all visits, and no meaningful changes in the mean values from baseline values were noted.

With regard to ECG parameters, no subject was found to have clinically significant abnormal results at either Screening or the Month 12 visit. Collectively, 23 of the 42 subjects (54.8%) in the somatrogon cohorts had abnormal results at Screening and 19 somatrogon subjects (45.2%) had abnormal results at the Month 12 visit, but these were not clinically significant. Similarly, 7 of the 11 Genotropin subjects (63.6%) had abnormal results at Screening while 6 of the 10 Genotropin subjects tested at Month 12 had abnormal results; however, these ECG results were not clinically significant.

In Study CP-4-004 OLE there were no subjects with clinically meaningful changes from baseline in terms of vital signs, ECG parameters (including after transition to pen), or ECG shifts Module 5.3.5.1, CSR CP-4-004 OLE, Tables 14.6.3.1 and 14.6.3.2.

In the CP-4-004 main study and OLE period (up to the data cutoff date of 01 November 2019), the trend in shifts from baseline in ECG, vital signs, and physical findings was similar to that observed in the CP-4-006 main study and OLE period. The few clinically significant shifts from baseline in physical findings in the CP-4-004 main study period were mild, and not related to study treatment.

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

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/

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