CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761184Orig1s000

PRODUCT QUALITY REVIEW(S)

BLA Executive Summary
Assessment Date: June 23, 2023

1. Application/Product Information

BLA number	761184
Submission Type	Resubmission
Regulatory Pathway	NME 351(a)
Associated IND/BLA	INDs 079745 and 132494
Review Designation	Class 2
Applicant	Pfizer Ireland Pharmaceuticals
Indication	Treatment of pediatric patients aged 3 years and older who have growth failure due to inadequate secretion of endogenous growth hormone
Rx/OTC dispensed	Rx
Drug Product Name	Ngenla
	somatrogon-ghla
	FUS: RPROT P01241 (SOMA_HUMAN); RPROTFRAG P0DN86 (CGB3_HUMAN) [PF06836922]
Drug Product Description	Somatrogon drug product is a sterile, clear and colorless to slightly light yellow preserved solution formulated in citric acid monohydrate (0.3 mg), histidine (1.9 mg), metacresol (4 mg, as a preservative), poloxamer 188 (2 mg), sodium chloride (10 mg), and sodium citrate (2.8 mg) in water for injection at pH of approximately 6.6. Somatropin is a recombinant human growth hormone analog (fusion protein) comprised of the amino acid sequence of human growth hormone (hGH) with one copy of the 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. Each CTP includes multiple O-linked glycosylation sites. The glycosylation and CTP domains account for the half-life of somatrogon, which allows for weekly dosing.
Dosage Form	Liquid
Strength	24 mg/1.2 mL (20 mg/mL) or 60 mg/1.2 mL (50 mg/mL)
Route of Administration	Subcutaneous injection
Primary Container Closure System	Cartridge
Device Information	Prefilled pen

Co-packaged Product Information	None		
OPQ Review Team	Discipline	Primary	Secondary
	Drug substance	Emine Guven Maiorov	Massod Rahimi
	Drug product		
	Immunogenicity Assay	Montserrat Puig	Susan Kirshner
	Facility	Zonglin Hu	Madushini Dharmasena, Michael Shanks
	Microbiology		
	RBPM	Melinda Bauerlien	
	ATL	Massod Rahimi	
OPQ Issued Consults	CDRH OPEQ/OHT3/DHT3C – Assessment of updated batch analyses and stability data for the proposed prefilled pen		

2. Recommendation and Conclusion on Approvability
Recommendation: Approval with PMCs/PMRs

The Office of Pharmaceutical Quality, CDER, recommends approval of BLA 761184 for Ngenla manufactured by Pfizer Pharmaceuticals Ireland. The data submitted in this application are adequate to support the conclusion that the manufacture of Ngenla is well-controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under conditions specified in the package insert.

3. CMC Information for Action Letter

a. Manufacturing Location:
- Drug Substance: Pfizer Ireland Pharmaceuticals, Grange Castle Business Park, Clondalkin, Dublin 22, Ireland; FEI 3004145594
- Drug Product: Pfizer Manufacturing Belgium NV, Rijksweg 12, Puurs 2870, Belgium; FEI 1000654629

b. Fill size and dosage form: Ngenla is supplied as 24 mg/1.2 mL or 60 mg/1.2 mL solution in a prefilled pen

c. Dating Period:
- Drug Product: 36 months at 2 – 8°C
- Drug Substance: (b) (4) months at (b) (4) °C
- For packaged products: Not packaged
- Stability Option:
  - For stability protocols:

- We have approved the stability protocol in your license application for the purpose of extending the expiration dating of your drug substance under 21 CFR 601.12.

d. Exempt from lot release:
   - Yes
   - Rationale, if exempted: Ngenla is exempted from lot release per FR 95-29960.

e. Draft Phase 4 (Post-Marketing) Commitments, Requirements, Agreements, and/or Risk Management Steps, as applicable

PMC 4446-1: To perform commercial shipping studies to qualify the actual shipping conditions for the drug product (prefilled pen). The commercial shipping studies will include:

- Product quality assessment on commercial drug product in the commercial container closure system, fully packaged (primary and secondary packaging, etc.) before and after real-time shipping to evaluate the effect of handling and shipping conditions on product quality.

- Analytical testing to evaluate impact on critical quality attributes (CQAs) during shipping. Justification for the selected CQAs will be provided.

- Evaluation of container closure integrity to ensure the maintenance of sterile barrier using an appropriate method (e.g., dye ingress).

- Device functionality tests to demonstrate that the shipping conditions do not adversely impact the integrity and functionality of the device.

- Temperature monitoring of the shipping container (external and internal temperatures) recorded continuously throughout shipping from thermal couple probes placed inside and outside of the shipping container.

4. Basis for Recommendation

a. Summary:
Somatrogon binds to growth hormone receptor (GHR) and initiates a signal transduction cascade culminating in changes in growth and metabolism. Consistent with GH signaling, somatrogon binding leads to activation of the STAT5b signaling pathway and increases the serum concentration of insulin-like growth factor (IGF-1). GH and IGF-1 stimulate metabolic changes, linear growth, and enhance growth velocity in pediatric patients with growth

hormone deficiency. Potency of somatrogon is controlled using (b) (4) the biologic activity relative to an established reference material is calculated and reported.

The somatrogon drug substance (DS) manufacturing process consists of (b) (4)

The overall control strategy incorporates control (b) (4) of the DS and DP. The manufacturing processes and overall control strategies for Ngenla as described in the license are appropriately established to ensure consistency and quality of the final product; therefore, lot variability is not a concern. The assays used for immunogenicity assessment in the clinical studies to support this BLA are adequately validated and suitable for their intended purpose. Adequate descriptions of the (b) (4) (b) (4) control strategy were provided for Pfizer Ireland Pharmaceuticals (FEI 3004145594) and Pfizer Manufacturing Belgium NV (FEI 1000654629), proposed for DS and DP manufacture, respectively. All proposed manufacturing and testing facilities are acceptable based on their currently acceptable CGMP compliance status and recent relevant inspectional coverage. The BLA is recommended for approval from product quality, facility, microbiology and sterility assurance, and device constituent perspectives.

Simulated shipping studies suggest that the impact of shipping on product quality (stability) is low. The commercial shipping studies that will be conducted as a post-marking commitment will verify that the actual shipping conditions of commercial DP do not impact product quality.

b. Subdiscipline Recommendation:

Drug Substance	-	Adequate
Drug Product	-	Adequate with PMCs/PMRs
Immunogenicity Assay	-	Adequate
Facilities	-	Adequate
Microbiology	-	Adequate

c. Environmental Assessment (EA):
Categorical exclusion is claimed by the applicant and deemed acceptable.

d. Potency Assessment for Labeling:
As an initial matter, we determined that no U.S. standard of potency has been prescribed for Ngenla (i.e., there is no specific test method described in regulation for Ngenla that establishes an official standard of potency). We next considered whether potency is a factor for Ngenla within the meaning of 21 CFR 610.61(r), which requires a statement about potency on the package (carton) label if "potency is a factor" and "no U.S. standard of potency has been prescribed." We have determined that potency is not a factor for Ngenla for purposes of § 610.61(r) because lot variability is not a concern for Ngenla as Ngenla's manufacturing process is appropriately controlled to ensure the consistency and quality of the final product.

5. Life-Cycle Considerations

a. Established Conditions based on ICH Q12 principles: No

b. Drug Substance:

i. Protocols approved:
1. Validation protocol (b) (4)
2. Re-qualification (stability) protocol for the current master cell bank (MCB)
3. Re-qualification (stability) protocol for the current working cell bank (WCB)
4. Qualification protocol for new WCBs
5. Re-qualification (stability) protocol for the current primary reference material (PRM)
6. Re-qualification (stability) protocol for the current working reference material (WRM)
7. Qualification protocol for new WRMs
8. Stability protocol (b) (4)
9. Post-approval stability protocol and stability commitment

ii. Residual risk: None

iii. Future inspection points to consider: None

c. Drug Product:

i. Protocols approved:
   1. Post-approval stability protocol and stability commitment (cartridge)
   2. Post-approval stability protocol and stability commitment (prefilled pen)

ii. Residual risk: The commercial shipping studies that will be conducted as a post-marking commitment will verify that the actual shipping conditions of commercial drug product do not impact product quality.

iii. Future inspection points to consider: None

FOIA statement: More detailed assessments of the BLA submission, which are not included in this integrated quality assessment, may be requested via a Freedom of Information Act (FOIA) request.

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/s/

MASSOD RAHIMI
06/23/2023 10:50:18 PM

BLA Executive Summary
Assessment Date: April 17, 2023

1. Application/Product Information

BLA number	761184
Submission Type	Resubmission
Regulatory Pathway	NME 351 (a)
Associated IND/BLA	INDs 079745 and 132494
Review Designation	Class 2
Applicant	Pfizer Ireland Pharmaceuticals
Indication	Treatment of pediatric patients aged 3 years and older who have growth failure due to inadequate secretion of endogenous growth hormone
Rx/OTC dispensed	Rx
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	somatrogon-ghla
	FUS: RPROT P01241 (SOMA_HUMAN); RPROTFRAG P0DN86 (CGB3_HUMAN) [PF06836922]
Drug Product Description	Somatrogon drug product is a sterile, clear and colorless to slightly light yellow preserved solution formulated in citric acid monohydrate (0.3 mg), L-histidine (1.9 mg), m-cresol (4 mg, as a preservative), poloxamer 188 (2 mg), sodium chloride (10 mg), and sodium citrate ((b) (4) mg) in Water for Injection at pH of approximately 6.6. Somatropin is a recombinant human growth hormone analog (fusion protein) comprised of the amino acid sequence of human growth hormone (hGH) with one copy of the 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. Each CTP includes multiple O-linked glycosylation sites. The glycosylation and CTP domains account for the half-life of somatrogon, which allows for weekly dosing.
Dosage Form	Liquid
Strength	24 mg/1.2 mL (20 mg/mL) and 60 mg/1.2 mL (50 mg/mL)
Route of Administration	Subcutaneous injection
Primary Container Closure System	Cartridge
Device Information	Prefilled pen

Co-packaged Product Information	None		
OPQ Review Team	**Discipline**	**Primary**	**Secondary**
	Drug substance	Emine Guven Maiorov	Massod Rahimi
	Drug product		
	Immunogenicity Assay	Montserrat Puig	Susan Kirshner
	Facility	Zonglin Hu	Madushini Dharmasena
	Microbiology		
	RBPM	Melinda Bauerlien	
	ATL	Massod Rahimi	
OPQ Issued Consults	CDRH OPEQ/OHT3/DHT3C – Assessment of updated batch analyses and stability data for the proposed prefilled pen		

2. Recommendation and Conclusion on Approvability

Recommendation: Pending

The Office of Pharmaceutical Quality (OPQ), CDER, recommendation on approvability of BLA 761184 for Ngenla manufactured by Pfizer Pharmaceuticals Ireland is pending the final determination of compliance status of the manufacturing facilities, including Pfizer Ireland Pharmaceuticals (Clondalkin, Ireland; FEI 3004145594).

3. Basis for Recommendation

a. Summary:

Somatrogon binds to growth hormone receptor (GHR) and initiates a signal transduction cascade culminating in changes in growth and metabolism. Consistent with GH signaling, somatrogon binding leads to activation of the STAT5b signaling pathway and increases the serum concentration of insulin-like growth factor (IGF-1). GH and IGF-1 stimulate metabolic changes, linear growth, and enhance growth velocity in pediatric patients with growth hormone deficiency. Potency of somatrogon is controlled using (b) (4) the biologic activity relative to an established reference material is calculated and reported.

The somatrogon drug substance (DS) manufacturing process consists of (b) (4)

(b) (4)

The overall control strategy incorporates control (b) (4) of the DS and DP. The assays used for immunogenicity assessment in the clinical studies to support this BLA are adequately validated and suitable for their intended purpose. The BLA is recommended for approval from product quality, microbiology and sterility assurance, and device constituent perspectives. However, the final determination of compliance status of the manufacturing facilities, including Pfizer Ireland Pharmaceuticals (Clondalkin, Ireland; FEI 3004145594) is pending.

b. Subdiscipline Recommendation:

Drug Substance	**-**	**Adequate**
Drug Product	**-**	**Adequate with PMCs/PMRs**
Immunogenicity Assay	**-**	**Adequate**
Facilities	**-**	**Pending**
Microbiology	**-**	**Adequate**

c. Environmental Assessment (EA):
Categorical exclusion is claimed by the applicant and deemed acceptable.

d. Potency Assessment for Labeling:
Not applicable as OPQ's approvability recommendation for this application is pending.

4. Life-Cycle Considerations
Not applicable as OPQ's approvability recommendation for this application is pending.

FOIA statement: More detailed assessments of the BLA submission, which are not included in this integrated quality assessment, may be requested via a Freedom of Information Act (FOIA) request.

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/s/

MASSOD RAHIMI
04/17/2023 11:11:26 PM

Orphan Drug
Recommendation: Complete Response

BLA Number: 761184
Assessment Number: 1
Assessment Date: January 20, 2022

Drug Name/Dosage Form	NGENLA™ (somatrogon-xxxx)/for injection, solution in single-patient-use, disposable prefilled pen
Strength/Potency	24 mg/1.2 mL (20 mg/mL) or 60 mg/1.2 mL (50 mg/mL)
Route of Administration	Subcutaneous injection
Rx/OTC dispensed	Rx
Indication	Treatment of pediatric patients with growth failure due to insufficient secretion of growth hormone
Applicant/Sponsor	Pfizer Ireland Pharmaceuticals
US agent, if applicable	Gurunandan Mavinkurve (Pfizer Inc.)

Product Overview:

Somatrogon (MOD-4023) is a recombinant glycoprotein (fusion protein) produced in Chinese hamster ovary (CHO) cells. It 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 2 copies of CTP (in tandem) at the C-terminus. The glycosylation and CTP domains account for the half-life of somatrogon, which allows for weekly dosing. Somatrogon binds to the GH receptor (GHR) and initiates a signal transduction cascade leading to changes in growth and metabolism. Somatrogon binding to GHR leads to increased serum concentration of insulin-like growth factor (IGF-1). GH and IGF-1 stimulate metabolic changes, linear growth, and enhance growth velocity in pediatric patients with growth hormone deficiency.

The somatrogon drug product, NGENLA, is supplied as a sterile, colorless to slightly light yellow preserved solution in a prefilled pen containing somatrogon (24 or 60 mg), citric acid monohydrate (0.3 mg), L-histidine (1.9 mg), m-cresol (4 mg, as a preservative), poloxamer 188 (2 mg), sodium chloride (10 mg), and (b) (4) ((b) (4) mg) in Water for Injection (b) (4) at pH of approximately 6.6.

Quality Assessment Team:

Discipline	Assessor	Branch/Division
Drug Substance	Tracy Denison	CDER/OPQ/OBP/DBRR III
Drug Product	Tracy Denison	CDER/OPQ/OBP/DBRR III
Immunogenicity	Montserrat Puig	CDER/OPQ/OBP/DBRR III
Labeling	Koung Lee	CDER/OPQ/OBP
Facility	Yun Wu (DS), Madushini Dharmasena (DP)	CDER/OPQ/OPMA/DBM-2
Microbiology	Yun Wu (DS), Madushini Dharmasena (DP)	CDER/OPQ/OPMA/DBM-2
Team Lead	Massod Rahimi (OBP product quality) Susan Kirshner (immunogenicity) Candace Gomez-Broughton (facility and microbiology)	CDER/OPQ/OBP/DBRR III CDER/OPQ/OBP/DBRR III CDR/OPQ/OPMA/DBM-2
OPQ RBPM	Melinda Bauerlien	CDER/OPQ/OPRO/DRBPMI/RBPMB2
Application Team Lead	Massod Rahimi	CDER/OPQ/OBP/DBRR III
Tertiary Assessor	Susan Kirshner	CDER/OPQ/OBP/DBRR III

Multidisciplinary Assessment Team:

Discipline	Assessor	Office/Division
RPM	Sejal Kiani	CDER/OND/ORO/DROCHEN
Cross-disciplinary Team Lead	Marina Zemskova	CDER/OND/OCHEN/DGE
Medical Officer	Sonia Doi	CDER/OND/OCHEN/DGE
Pharmacology/Toxicology	Elena Braithwaite	CDER/OND/OCHEN/DPTCHEN
Clinical Pharmacology	Lin Zhou Eliford Kitabi	CDER/OTS/OCP/DCEP CDER/OTS/OCP/DPM
Statistics	Kiya Hamilton	CDER/OTS/OB/DBII

1. Names:

a. Proprietary Name: NGENLA
b. Trade Name: NGENLA
c. Non-Proprietary Name/USAN: somatrogon-xxxx/somatrogon
d. CAS Name: 1663481-09-1
e. Common Name: PF-06836922, MOD-4023
f. INN Name: somatrogon
g. OBP systematic name: FUS: RPROT P01241 (SOMA_HUMAN): RPROTFRAG P0DN86 (CGB3_HUMAN) [PF06836922]

Submissions Assessed:

Submission(s) Assessed	Document Date
STN 761184 SD 1/SN 0001 (Original submission)	10/22/2020
STN 761194 SD 8/SN 0008 (Response to 12/22/2020 IR)	01/08/2021
STN 761194 SD 9/SN 0009 (Response to 01/19/2021 IR)	01/22/2021
STN 761194 SD 10/SN 0010 (Response to 01/15/2021 IR)	01/28/2021
STN 761194 SD 12/SN 0012 (Response to 01/15/2021 IR)	02/03/2021
STN 761194 SD 16/SN 0016 (Response to 02/10/2021 IR)	02/24/2021
STN 761194 SD 17/SN 0017 (Response to 02/01/2021 IR)	02/26/2021
STN 761194 SD 20/SN 0020 (Response to 02/19/2021 IR)	03/12/2021
STN 761194 SD 21/SN 0021 (Response to 03/03/2021 IR)	03/17/2021
STN 761194 SD 26/SN 0026 (Response to 03/29/2021 IR)	04/02/2021
STN 761194 SD 27/SN 0027 (Response to 04/08/2021 IR)	04/16/2021
STN 761194 SD 35/SN 0035 (Response to 06/08/2021 IR)	06/22/2021
STN 761194 SD 36/SN 0036 (Response to 06/23/2021 IR)	06/30/2021
STN 761194 SD 37/SN 0037 (Response to 07/19/2021 IR)	07/22/2021
STN 761194 SD 45/SN 0047 (Manufacturing schedule)	08/27/2021
STN 761194 SD 49/SN 0049 (Amendment to the Integrated Summary of Immunogenicity)	09/15/2021
STN 761194 SD 60/SN 0060 (Response to 10/22/2021 IR)	10/27/2021
STN 761194 SD 63/SN 0062 (Response to 10/25/2021 IR)	10/28/2021
STN 761194 SD 66/SN 0066 (Response to 10/22/2021 IR)	11/08/2021

More detailed assessments of the BLA submission(s), which are not included in this integrated quality assessment, may be requested via a Freedom of Information Act (FOIA) request.

Quality Assessment Data Sheet:

1. Legal Basis for Submission: 351(a)

2. Related/Supporting Documents:

   A. DMFs:

DMF #	DMF Type	DMF Holder	Item referenced	Code[1]	Status[2]	Date Assessment Completed	Comments
(b) (4)	II		(b) (4)	3	N/A	N/A	No assessment required as the relevant information was in the BLA
	V			3	N/A	N/A	No assessment required as the relevant information was in the BLA
	III			3	N/A	N/A	No assessment required at this time as the relevant information related to compatibility with the product was in the BLA
	III			3	N/A	N/A	No assessment required at this time as the relevant information related to compatibility with the product was in the BLA
	III			3	N/A	N/A	No assessment required at this time as the relevant information related to compatibility with the product was in the BLA

1. Action codes for DMF Table: 1- DMF Assessed; Other codes indicate why the DMF was not assessed, as follows: 2- Assessed previously and no revision since last assessment; 3- Sufficient information in application; 4- Authority to reference not granted; 5- DMF not available; 6- Other (explain under “comments”)

2. Action codes for Status column: Adequate, Adequate with Information Request, Deficient, or N/A (There is not enough data in the application; therefore, the DMF did not need to be assessed.

B. Other documents: IND 79745, IND 132494

3. Consults:

Discipline/Topic	Date Requested	Status	Recommendation	Assessor
CDRH OPEQ/OHT3/DHT3C – Facilities inspection	12/17/2021	Completed on 05/06/2021	Not Approvable (inspection was recommended)	Robert Nakielny, Courtney Evans, Rumi Young
CDRH OPEQ/OHT3/DHT3C – Assessment of design controls, performance, stability, and suitability of prefilled pen for its intended use	01/21/2021	Completed on 05/10/2021	Approvable	Janice Ferguson, Courtney Evans, Rumi Young
CDRH OPEQ/OHT7/DCTD – Evaluate the risk of anti-CTP antibodies (and potential anti-hCG antibodies) with pregnant test interference	03/22/2021	Completed on 04/23/2021	Information provided by the Applicant is not adequate; however, drug labeling mitigations may be adequate to address the risk	Joseph Kotarek

4. Environmental Assessment of Claim of Categorical Exclusion:
The Applicant claims a categorical exclusion per 21 CFR 25.31 (c) from the environmental assessment requirements of 21 CFR 21.20. Approval of this BLA will increase the use of substances that occur naturally in the environment, but the action does not alter significantly the concentration or distribution of the substances, their metabolites, or degradation products in the environment. Categorical Exclusion is appropriate for this product.

Executive Summary:

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

Recommendation: Complete Response
The Office of Pharmaceutical Quality (OPQ), CDER, has completed assessment of STN 761184 for NGENLA manufactured by Pfizer Pharmaceuticals Ireland. The data submitted in this application are not sufficient to support a conclusion that the manufacture of NGENLA is well-controlled and will lead to a product that is pure and potent for the duration of the shelf-life. From a CMC standpoint, OPQ is recommending a Complete Response letter be issued to Pfizer Pharmaceuticals Ireland to outline the deficiencies noted below and the information and data that will be required to support approval.

B. Summary of Complete Response Issues:

The Office of Biotechnology Products (OBP) in OPQ identified multiple product quality deficiencies during the review of Module 3 of BLA 761184. The deficiencies do not support that the manufacture and testing of NGENLA is well-controlled and will lead to a product that is safe, pure, and potent for duration of the shelf-life. These deficiencies include, but are not limited to:

(b) (4)

In addition, pre-license inspections at the drug substance manufacturing site, Pfizer Ireland Pharmaceuticals (Clondalkin, Ireland; FEI 3004145594), and the drug product manufacturing site, Pfizer Manufacturing Belgium NV (Puurs, Belgium; FEI 1000654629), will be required before this application may be approved.

C. Complete Response Letter Draft Language:

Product Quality Complete Response Comments (provided by OBP):

(b) (4)

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(b) (4)

9. The MOD-4023 DP (prefilled pen) shipping qualification included shipping container qualification and simulated shipping studies. Your MOD-4023 DP shipping qualification did not include real-time shipping studies designed to qualify the actual shipping conditions of commercial DP. To verify that product quality is not impacted by worse-case shipping conditions, provide quality assessment of commercial product in the intended primary and secondary container (if applicable) prior to and after shipment. Stability-indicating critical quality attributes (CQAs) should be assessed in the commercial shipping studies. In addition, temperature monitoring data recorded continuously throughout shipping from thermal couple probes placed inside and outside of the shipping container should be provided. In the absence of commercial shipping data in the Complete Response, a shipping qualification protocol may be submitted to conduct concurrent shipping qualification.

10. Include in Sections 3.2.S.2.2 and/or 3.2.S.2.4 your definitions for regulatory terminologies used for manufacturing controls, e.g., definitions for critical material attribute (CMA), critical and non-critical parameter (CPP and non-CPP), as these are not clearly stated in the BLA (in Sections 3.2.S.2.2 and/or 3.2.S.2.4).

11. (b) (4) Provide rationale (b) (4) and clarify how the acceptable ranges were defined for the MOD-4023 commercial manufacturing process and provide supportive data.

12. In your Complete Response, provide updated data from the following studies that are on-going:

    a. (b) (4)

    b. (b) (4)

    c. The on-going MOD-4023 DS, DPS, and DP (prefilled pen) stability studies (in Sections 3.2.S.7 and 3.2.P.8).

13. In your Complete Response, provide any updated batch analysis data for DS and DPS and DP (prefilled pen) as applicable for batches released since your original BLA submission.

Additional Microbiology and Facility Inspections Comments (provided by OPMA):

1. Qualify the bioburden test method (b) (4) Method qualification will be carried out using material from 3 separate batches.

2. Inspections of the Pfizer Ireland Pharmaceuticals, Dublin, Ireland (FEI: 3004145594) and Pfizer Manufacturing Belgium NV (FEI: 1000654629) facilities are required before this application can be approved as the FDA must assess the ability of those facilities to conduct the listed manufacturing operations in compliance with CGMP. Due to U.S. Government and/or Agency-wide restrictions on travel, we were unable to complete these inspections during the current review cycle for your application. You may respond to deficiencies in this Complete Response letter while the travel restrictions remain in effect. However, even if all other deficiencies are addressed, the application cannot be approved until the required FDA inspections are completed and the findings are assessed with regard to your application.

D. Benefit/Risk Considerations:

NGENLA is indicated for the treatment of pediatric patients with growth failure due to insufficient secretion of growth hormone. Somatrogon received Orphan drug designation on September 29, 2010 under IND 79745. Based on the assessment of the efficacy and safety data, the Division of General Endocrinology (DGE), CDER, determined that the benefits of NGENLA do not outweigh the risks. More specifically, high immunogenicity and the lack of data ensuring no impact on long-term efficacy preclude the determination of the long-term benefit of NGENLA (see additional details on the deficiencies in the Complete Response letter).

The overall NGENLA control strategy incorporates control (b) (4) of the drug substance and drug product. Although the BLA is recommended for approval from a product quality microbiology and sterility assurance as well as device constituent performance perspectives, multiple product quality deficiencies were identified during the assessment period. The assessment deficiencies were not adequately addressed during the assessment period; therefore, the information and data provided in BLA 761184, and its amendments, do not demonstrate that the manufacturing process and control strategy of NGENLA are sufficient to ensure that the manufacturing process is well-controlled and leads to a product of acceptable quality to ensure drug safety and effectiveness for patients. In addition, pre-license inspections at the drug substance manufacturing site, Pfizer Ireland Pharmaceuticals, and the drug product manufacturing site, Pfizer Manufacturing Belgium NV, will be required to support BLA approval.

The technical assessments for product quality and immunogenicity assays (by OBP), microbiology and facility (by OPMA), and OBP labeling are located as separate documents in Panorama.

E. Recommendation on Phase 4 (Post-Marketing) Commitments, Requirements, Agreements, and/or Risk Management Steps, if approvable:

There are no recommended post-marketing commitments, requirements, agreements, and/or risk management steps are this time.

II. Summary of Quality Assessments:

A. CQA Identification, Risk and Lifecycle Knowledge Management

Table 1 is a summary of product-related critical quality attributes (CQA), intrinsic to somatrogon, that are relevant to both drug substance and drug product.

Table 1: Active Pharmaceutical Ingredient CQA Identification, Risk and Lifecycle Knowledge Management

CQA (type)[1]	Risk	Origin	Control Strategy	Other
(b) (4) (product-related substances)	PK	Intrinsic to the molecule and manufacturing process	(b) (4)	N/A
(b) (4) (product-related substances)	PK	Intrinsic to the molecule and manufacturing process		N/A
Identity	Safety and efficacy	Intrinsic to the molecule		(b) (4)
(b) (4) (purity)	Potency, immunogenicity, safety, and efficacy	Manufacturing process and storage		N/A
(b) (4) (product-related impurity)	Potency, immunogenicity, safety, and efficacy	Manufacturing process and storage		N/A
(b) (4) (product-related impurity)	Potency, immunogenicity, safety, and efficacy	Manufacturing process and storage		N/A
Total Related Forms (product-related substances (b) (4))	Immunogenicity	Manufacturing process and storage		(b) (4)
Potency	Biological activity, safety, and efficacy	Intrinsic to the molecule (may be impacted by the manufacturing process and storage)		

DS = Drug substance; DP = Drug product

B. Drug Substance [Somatrogon] Quality Summary

Table 2 provides a summary of the identification, risk, lifecycle knowledge management for drug substance CQAs that derive from the drug substance manufacturing process and general drug substance attributes, including process-related impurities.

Table 2: Drug Substance CQA Process Risk Identification and Lifecycle Knowledge Management

CQA (type)[1]	Risk	Origin	Control Strategy	Other

Appearance – Clarity (general)	Safety and efficacy	Intrinsic to the molecule (may be impacted by the manufacturing process and storage)	(b) (4)	N/A
Appearance – Coloration (general)	Safety and efficacy	Intrinsic to the molecule (may be impacted by the manufacturing process and storage)		N/A
pH (general)	Product stability and safety	Formulation (may be impacted by storage)		N/A
Protein Concentration (strength)	Efficacy (inaccurate dosing)	Manufacturing process and formulation		N/A
(b) (4) (process-related impurity)	Immunogenicity, safety, and PK/biological activity (degradation or modification of the product)	Manufacturing process (b) (4)		N/A
(b) (4) (process-related impurity)	Immunogenicity and safety	Manufacturing process (b) (4)		Robust and consistent (b) (4) process
Bioburden (contaminant)	Safety and efficacy (degradation or modification of the product)	Manufacturing process		N/A
Endotoxin (contaminant)	Safety	Manufacturing process		N/A
Viral Adventitious Agents (contaminant)	Safety	Raw materials and manufacturing process		N/A
Mycoplasma (contaminant)	Safety	Raw materials and manufacturing process		N/A

[1] – (b) (4)

- **Description:** Somatrogon is a recombinant glycoprotein (fusion protein) with a theoretical/observed mass of approximately 30 kDa (aglycosylated). It is comprised of the amino acid sequence of hGH with one copy of the CTP from the beta chain of hCG at the N-terminus and 2 copies of CTP (in tandem) at the C-terminus. Each CTP includes multiple O-linked glycosylation sites. The O-glycan occupancy ranges from 9-20 moieties per intact somatrogon molecule. The predominant somatrogon glycoforms include the molecule with 15 monosialyated, core-1 O-glycans or 16 monosialyated, core 1 O-glycans (theoretical/observed masses of approximately 40 – 41 kDa). Each CTP region

contains hydroxyproline residues, which range from 0-5 hydroxy additions per intact somatrogon molecule. The glycosylation and CTP domains account for the half-life of somatrogon, which allows for weekly dosing. The observed pI range is (b) (4) and the specific absorption coefficient at (b) (4) nm is (b) (4) $(mg/mL)^{-1}$ cm^{-1}.

- **Mechanism of Action (MoA):** Somatrogon binds to GHR and initiates a signal transduction cascade leading to changes in growth and metabolism. Somatrogon binding to GHR leads to increased serum concentration of IGF-1. GH and IGF-1 stimulate metabolic changes, linear growth, and enhance growth velocity in pediatric patients with growth hormone deficiency.

- **Potency Assay:** A cell proliferation assay using (b) (4) (b) (4) Relative potency for a test sample is calculated from the regression curve EC_{50} value relative to the reference material regression curve EC_{50} value.

- **Reference Materials:** A two-tiered reference standard system is applied to the commercial reference materials, consisting of primary reference material (b) (4) (b) (4) and working reference material (b) (4)

- **Critical starting materials or intermediates:** A two-tiered cell bank system consisting of a Master Cell Bank (MCB) and Working Cell Bank (WCB) is implemented for commercial somatrogon manufacturing. (b) (4) The MCB and the WCBs were adequately tested to product safety from adventitious agents. (b) (4) (b) (4)

- **Manufacturing process summary:** The drug substance manufacturing process consists of (b) (4)

(b) (4)

(b) (4)

- **Container closure:** The somatrogon drug substance is stored (b) (4) (b) (4)
- **Dating period and storage conditions:** A shelf-life of (b) (4) months when stored at -(b) (4) °C is acceptable based on available stability data from the drug substance batches manufactured (b) (4)

C. Drug Product [NGENLA] Quality Summary:

Table 3 provides a summary of the identification, risk, and lifecycle knowledge management for drug product CQAs that derive from the drug product manufacturing process and general drug product attributes.

Table 3: Drug Product CQA Identification, Risk, and Lifecycle Management

CQA (type)	Risk	Origin	Control Strategy	Other
Appearance – Clarity (general)	Safety and efficacy	Intrinsic to the molecule (may be impacted by the manufacturing process and storage)	(b) (4)	N/A
Appearance – Coloration	Safety and efficacy	Intrinsic to the molecule (may be		N/A

(b) (4)

(general)		impacted by the manufacturing process and storage)		
Appearance – Visible Particulates (general)	Immunogenicity and safety	Manufacturing process, container closure system, and storage		N/A
pH (general)	Product stability and safety	Formulation (may be impacted by storage)		N/A
Subvisible Particles (general)	Immunogenicity and safety	Manufacturing process, container closure system, and storage		N/A
Protein Concentration (strength)	Efficacy (inaccurate dosing)	Manufacturing process and formulation (may be impacted by storage)		N/A
Volume in Container (general)	Efficacy (inaccurate dosing)	Manufacturing process (may be impacted by storage)		N/A
Osmolality (general)	Product stability, safety, and patient comfort	Formulation		N/A
m-Cresol (preservative)	Safety (microbial control throughout use of prefilled pen)	Formulation (may be impacted by storage)		N/A
Syringeability/Maximum and Extrusion Force (device functionality)	Safety and efficacy	Formulation and container and closure system (may be impacted by storage)		N/A
Poloxamer 188 (composition)	Product stability and safety	Formulation		N/A
Endotoxin (contaminant)	Safety	Manufacturing process		N/A
Container Closure Integrity (contaminant)	Safety (loss of sterility) and efficacy (change on product strength due to evaporation or leakage or degradation or modification of the product)	Manufacturing process, container closure system, and storage		N/A
Sterility (contaminant)	Safety and efficacy (change on product strength due to evaporation or leakage or degradation or	Manufacturing process, container closure system, and storage		N/A

	modification of the product)		(b) (4)	
Injection Button Force/Axial Force[1] (general)	Efficacy (inaccurate dosing - users must be able to inject the dose)	Pen injector (may be impacted by storage)		N/A
Dose Accuracy[1] (general)	Efficacy (inaccurate dosing)	Pen injector (may be impacted by storage)		Pen cap removal, needle attachment, dose setting, and dose correction (related to dial torque) are inherently assessed within dose accuracy and functional operation testing
Functional Operation[1] (general)	Efficacy (inaccurate dosing)	Pen injector		
Appearance – Prefilled Pen	Efficacy (prefilled pen failure)	Pen injector, manufacturing process, and storage		The Applicant did not classify appearance as a CQA. However, there is a potential impact on efficacy

[1] – Device essential performance requirement (EPR)

- **Potency and Strength:** 24 mg/1.2 mL (20 mg/mL) or 60 mg/1.2 mL (50 mg/mL) in prefilled pens. An overfill of (b) (4) mL is included to ensure nominal volume of 1.2 mL. The potency of the drug product is determined (b) (4)

- **Summary of Product Design:** The drug product solution is a sterile, colorless to slightly light yellow preserved solution filled into a glass cartridge and further assembled into a prefilled pen for subcutaneous injection.

- **List of Excipients:** Citric acid monohydrate, (b) (4) histidine, m-cresol, poloxamer 188, sodium chloride, (b) (4) and Water for Injection.

- **Reference Materials:** Same as drug substance reference materials.

- **Manufacturing process summary:** The NGENLA drug product manufacturing process includes the following steps: (b) (4)

(b) (4)

(b) (4)

Container closure: The drug product primary container closure system consists (b) (4)

There are two mechanically identical prefilled pen presentations: 24 mg-containing prefilled pen has a lilac pen cap, dose button, and label and 60 mg-containing prefilled pen has a blue pen cap, dose button, and label. The pen is 172 mm in length and 16 mm in diameter. The pen is not novel and is similar to other pens currently on the market. Needles are not included in the carton containing the pen.

- **Dating period and storage conditions:** A shelf-life of (b) (4) months when stored at 2-8°C is not acceptable based on available stability data from the drug product solution lots manufactured (b) (4)

- **List of co-package components, if applicable:** None.

D. Novel Approaches/Precedents: None.

E. Any Special Product Quality Labeling Recommendations: NGENLA should be stored at 2-8°C and away from direct sunlight (including between each use for up to 28 days). Do not freeze, expose to heat, or shake. The prefilled pen should be stored without an injection needle attached and the cap should be placed on the prefilled pen when it is not in use. The prefilled pen should not be used more than 28 days after first use.

F. Establishment Information:

Overall Recommendation: Pre-license inspections (PLIs) will be required before this application may be approved					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
DS manufacture, DS and DPS release and stability testing, and cell bank storage	Pfizer Ireland Pharmaceuticals Grange Castle Business Park Clondalkin, Dublin 22, NA, Ireland, NA	3004145594	PLI required	N/A	Pending PLI
DS and DPS stability sample storage	(b) (4)	(b) (4)	N/A	N/A	No Evaluation Necessary
WCB and select DPS release testing		(b) (4)	N/A	N/A	No Evaluation Necessary
WCB manufacture, WCB testing, and cell bank storage		(b) (4)	N/A	N/A	No Evaluation Necessary
DPS manufacture, primary packaging, and select DPS release and stability testing DP (prefilled pen) assembly, labeling, DP (prefilled pen) release and stability testing, and secondary packaging	Pfizer Manufacturing Belgium NV Rijksweg 12 NA, Puur, NA, Belgium, 2870	1000654629	PLI required	N/A	Pending PLI
Component Manufacture	(b) (4)	(b) (4)	N/A	N/A	No Evaluation Necessary
Secondary Packaging		(b) (4)	N/A	N/A	No Evaluation Necessary

G. Facilities:

A PLI was deemed necessary for the drug substance manufacturing site, Pfizer Ireland Pharmaceuticals for the following reasons:

- The somatrogon drug substance is manufactured in the (b) (4) (b) (4) which has no FDA inspection history and no CDER-regulated biologics have been licensed using the Pfizer Ireland Pharmaceuticals facility,
- A Mutual Recognition Agreement (MRA) report was reviewed for a CGMP surveillance inspection conducted (b) (4) from (b) (4) The inspection did not provide sufficient product-specific coverage and raised concerns on microbial control of the facility,
- Past FDA inspections of the facility repeatedly identified quality-related issues, which were general GCMP deficiencies.

The Agency used its authority under Section 704(a)(4) of the FD&C to request records from Pfizer Ireland Pharmaceuticals in advance of an on-site inspection. On 10/22/2021, the Agency requested pre-inspection audit documents in support of the manufacture and testing of somatrogon drug substance and drug product (where applicable) at Pfizer Ireland Pharmaceuticals. The firm submitted the requested documents on 11/08/2021. The assessment of the manufacturing site records conducted by Dr. Yun Wu and Dr. Tracy Denison identified numerous items that require follow-up during the PLI.

A PLI was deemed necessary for the drug product manufacturing site, Pfizer Manufacturing Belgium NV (b) (4) In addition, CDRH recommended a PLI (b) (4)

Due to restrictions on travel, the Agency was not able to conduct an inspection of Pfizer Ireland Pharmaceuticals and Pfizer Manufacturing Belgium NV prior to the User Fee Date. Onsite inspections of these facilities are required before the application can be approved.

H. Lifecycle Knowledge Management:

a. Drug Substance:

i. **Protocols approved:** Not Applicable.

ii. **Outstanding assessment issues/residual risk:** See CR comments in Section I.C.

iii. **Future inspection points to consider:** A PLI at the drug substance manufacturing site, Pfizer Ireland Pharmaceuticals, will be required before this application may be approved.

b. Drug Product

i. **Protocols approved:** Not Applicable.

ii. **Outstanding assessment issues/residual risk:** See CR comments in Section I.C.

iii. Future inspection points to consider: A PLI at the drug product manufacturing site, Pfizer Manufacturing Belgium NV, will be required before this application may be approved.

c. Immunogenicity Assay Validation

i. Protocols approved: Not Applicable.

ii. Outstanding assessment issues/residual risk: None.

iii. Future inspection points to consider: None.

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/s/

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