

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

216490Orig1s000

PRODUCT QUALITY REVIEW(S)

Tertiary Quality Review: NDA 216490
YORVIPATH® (palopegteriparatide) Injection, for Subcutaneous Use

Date	August 5, 2024
From	Mohan Sapru, M.S., Ph.D. Branch Chief/Supervisor Division of Pharmaceutical Quality Assessment-II Office of Pharmaceutical Quality Assessment-I Office of Pharmaceutical Quality (OPQ); CDER, FDA
Applicant	Ascendis Pharma
NDA Type	Type 1- New molecular entity
Type of Application	505(b)(1) NDA resubmission
Pharmacologic Class	Parathyroid hormone (PTH) analog
Presentation/ Dosage Form	Drug-device product; the prefilled pen available in three presentations
Proposed Indication(s)	Hypoparathyroidism in adults
Public Need for the Proposed Product	High; the clinical division has concluded that from a public health perspective, there is an important need for this new therapy
OPQ Recommendation*	Approval , with (b)(4) (12-month) expiration period, and informative labeling that includes label warning, limitations of use, and instruction to monitor serum calcium levels

* For details, please refer to OPQ's Integrated Quality Review (DARRTS, dated 8/5/2024).

1. Resolution of Identified Deficiencies.

Delivered Dose Inaccuracy and Overlap:

- This NME NDA involved a unique confluence of multiple challenges concerning inadequate device design, relatively concentrated formulation, and a narrow dose titration range (covering a dose range from 6 mcg to 30 mcg of PTH(1-34) in dosing increments of 3 mcg).
- Based on product specification, the conventional approach of testing dose accuracy for pen functionality per ISO 3951-1:2022 (with mechanical dialing resolution of (b)(4) μL) alone does not accurately test the accuracy of the delivered dose (a critical quality attribute), which is a function of delivered volume and the API content (assay). Due to inadequate control strategy, a significant delivered dose inaccuracy and overlap was found unacceptable from quality as well as clinical perspectives for the original NDA. As a result, the Agency issued a complete Response (CR) letter.
- In response to Agency's recommendations, for the resubmitted NDA, the Applicant has revised the control strategy, which includes use of clinically relevant asymmetrical acceptance criteria for delivered dose (i.e., asymmetrical tolerance interval) at shelf-life for low dose, middle dose, and high dose pens. CDRH review team's conclusion is that device performance meets the release specification as well as revised asymmetric specification criteria for deliverable dose at shelf-life. It is important to note that based on revised specifications for the delivered dose, the device will deliver a range of delivered doses at each dose setting, with certain degree of dose overlap. However, the clinical review team has concluded that the revised specifications, including the asymmetrical acceptance criteria for delivered dose (i.e., asymmetrical tolerance interval) at shelf-life for low dose, middle dose, and high dose pens are acceptable from patient safety/clinical perspective. Specifically, the clinical review team has concluded that although

there is slight dose overlap at the extremes of the percent variability of the administered dose is low, this dose overlap is expected to occur primarily when the patient gets one extreme of a dose range followed by the other extreme, the probability of which is low. Even in situations when this does occur, the inadvertent dose change that the patient will experience, is not expected to result in significant fluctuations in serum calcium levels. In conclusion, from clinical perspective, the benefits of palopegteriparatide outweigh its risks based on the above considerations.

2. Risk mitigation strategy to address potential for delivered dose inaccuracy and overlap:

- From CMC perspective, the risk mitigation strategy involves granting of (b) (4) expiration period of 12 months for the proposed product to minimize dose overlap at shelf-life.
- In the interest of informative label and accuracy in labeling, Section 3 of Prescribing Information will include tabulated information about deliverable dose range at each dose setting based on device performance.
- From clinical perspective, the label will include a) warning and precautions statement concerning potential relative variability of the delivered dose and unintended changes in serum calcium levels, b) instructions for rigorous monitoring of serum calcium levels to mitigate the risk of occasional extreme variability, which could result in blood calcium that is too low (hypocalcemia) or too high (hypercalcemia), and c) instructions to avoid use of 2 pens, which could exacerbate the dose variability.
- The Applicant's initial approach (b) (4)

To address this deficiency, the Applicant has amended the NDA to indicate that this NDA will only involve use of the UV method-based assay principle for the reference standard and calculation of batch analysis data (i.e., assay) and deliverable dose variability based on application of the reference standard, which was originally used to calculate the development standard content values for the clinical study batches. This scientifically validity approach enables linking the data from the clinical batch (thereby, the product quality) with that of the future commercial batches. Under a post-marketing mechanism, the Applicant has the option to seek approval for using a new reference standard based on additional supporting data and in compliance with the draft guidance for industry, "Analytical Procedures and Methods Validation for Drugs and Biologics – 2015".

3. Conclusion:

As discussed above, the Applicant has incorporated tighter control strategy, which includes a) product specification to test dose accuracy for pen functionality, b) specification for testing the delivered dose at release, and c) use of clinically relevant asymmetrical acceptance criteria for delivered dose at shelf-life, which are acceptable from the clinical perspective in the context of risk mitigation strategy listed above. So, OPQ recommends product approval, with (b) (4) (12-month) product expiration period, and informative labeling that includes label warning, tabulated description of deliverable dose range at each dose setting, statement about limitations of use, and instruction to monitor serum calcium levels.

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/

MOHAN K SAPRU
08/05/2024 06:05:59 PM



Title:	NDA IQA Template Title Page- EXEC SUMMARY	
Document ID:	OPQ-ALL-TEM-0040	
Effective Date:		Revision: 00
Total Pages:	8	



Template Revision: 03

Office of Pharmaceutical Quality

New Drug Application (NDA) Integrated Quality Assessment Template

NDA Executive Summary

1. Application/Product Information

NDA Number	216490
Applicant Name	Ascendis Pharma Bone Diseases A/S
Drug Product Name	Yorvipath (palopegteriparatide) injection, 300mcg/mL
Dosage Form	Injection
Proposed Strength(s)	300mcg of teriparatide per mL (equivalent to 3456 mcg of palopegteriparatide per mL). Yorvipath is available in 3 strengths: • 168 µg/0.56mL, for delivering labeled doses of 6, 9, or 12µg • 294 µg/0.98mL, for delivering labeled doses of 15, 18, or 21µg • 420µg/1.4 mL, for delivering labeled doses of 24, 27, or 30µg
NDA Classification	Type 2 – New Active Ingredient
Route of Administration	Subcutaneous
Maximum Daily Dose	30µg once daily
Rx/OTC Dispensed	Rx
Proposed Indication	For the treatment of adults with hypoparathyroidism
Drug Product Description	Clear, colorless solution available in single-patient-use prefilled pens in three presentations: • Pen with blue push button: 168 mcg/0.56 mL prefilled pen, for delivering labeled doses of 6, 9, or 12 mcg • Pen with orange push button: 294 mcg/0.98 mL prefilled pen, for delivering labeled doses of 15, 18, or 21 mcg • Pen with burgundy push button: 420 mcg/1.4 mL prefilled pen, for delivering labeled doses of 24, 27, or 30 mcg
Co-packaged product information	Provided as a pack containing 2 prefilled pens and 30 Ypsomed Click fine AutoProtect 31G x 5mm needles.

Device information	Yorvipath pen consists of a pen injector assembled with 1.5mL glass cartridge containing palopegteriparatide) injection, 300mcg/mL. It is a disposable, 14-dose single patient use pen injector.		
Storage Temperature/ Conditions	2°C to 8°C		
Review Team	Discipline	Primary	Secondary
	<i>Drug Substance</i>	Dan Jansen	Zhengfu Wang
	<i>Drug Product/ Labeling</i>	Akm Khairuzzaman	Muthukumar Ramaswamy
	<i>Manufacturing</i>	Sateesh Sathigari	Vidya Pai
	<i>Biopharmaceutics</i>	-	-
	<i>Microbiology</i>	Xia Xu-	-
	<i>Other (specify)</i>	-	-
	<i>RBPM</i>	Oluwafunmike (Funke) Ajomale	
	<i>ATL</i>	Muthukumar Ramaswamy	
Consults	CDRH: Shreya Tarafdar/Shruti Mistry CDER Biometrics (CMC Stat consult): Tengfei Li/ Shaobo Liu/ Chao Wang		

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating: A shelf-life of 12 months from the date of manufacture is granted for Yorvipath (palopegteriparatide) injection, 300mcg/mL provided as prefilled pen, when stored at long-term storage conditions of 2 to 8°C.

b. Additional Comments for Action- none

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

The Office of Pharmaceutical Quality Review team has assessed the Chemistry, Manufacturing, and Controls (CMC) information for NDA 216,490 resubmission and determined that the NDA meets all applicable standards to support the

quality and purity of the drug product. As such, OPQ recommends approval of this NDA from a quality perspective.

NDA 216490 was originally submitted on August 31, 2022, for Yorvipath (palopegteriparatide) injection, 300µg/mL. The drug substance, palopegteriparatide, is a new molecular entity. It contains a branched methoxypolyethylene glycol moiety and a linker conjugated to the N-terminal portion of teriparatide. The proposed drug product is a clear, colorless, sterile solution provided as disposable 14-dose pen in a 1.5mL cartridge filled with 0.56mL or 0.98 mL or 1.4 mL of product and intended for delivering the following labeled doses: 6, 9, 12, 15, 18, 21, 24, 27, and 30mcg. The strength of the drug product is expressed in terms of equivalent teriparatide content (mcg) per dose or per mL. For example, 3456 mcg of palopegteriparatide is equivalent to 300mcg of teriparatide.

The pen has a dialing resolution of (b) (4). Accordingly, the dose volume specification for each dose setting, as defined in the original specification was target dose volume $\pm$ (b) (4). The dispensed dose (mcg) for each dose setting depends on dispensed dose volume and the product concentration (API content) at the time of use. Since the dispensed dose volume for each setting is a range controlled by pen design and the content of the drug will change during storage, the dose in mcg dispensed from the device for each setting will also be a range and needs to be controlled within target (b) (4), to avoid potential to significantly overlap. The Applicant's product design did not take into consideration the potential for dose overlap. Also, the applicant's quality control specifications for dose accuracy, a critical quality attribute, were not sufficiently tight to assure a narrow dose variability, so that it does not cause dose overlap significantly.

The OPQ recommendation for the original submission was complete response, primarily due to dose variability/overlap issue. A Complete Response (CR) Letter was issued to the Applicant on 04/28/2023. Other significant issues outlined in the CR letter included a) lack of data to support the feasibility of the revised assay and delivered dose volume specification to limit the variability to be within (b) (4) at each dose setting, b) anticipated high-level of batch failure based on applicant's proposed specifications, which was indicative of inadequate formulation and device design, and c) inadequate stability data to support shelf-life determination of the proposed product per the revised specification for the delivered dose. There were no product quality issues related to the drug substance, manufacturing process, microbiology, and facility issues for the NDA. Please refer to Dr. Khairuzzaman's OPQ integrated quality review dated 3/17/2023 in DARRTS for the original submission.

The applicant resubmitted the NDA 216490 on 11/14/2023 with revised product specification but did not make any changes to the product formulation or pen design. Instead, the applicant revised the dose volume range specification (i.e., from target (b) (4) μL to target (b) (4) μL) and assay (i.e., (b) (4) % at release).

To address the potential net dose variability issue, the applicant revised the delivered dose specification, after multiple rounds of information requests. Delivered dose specification represents (b) (4)

- For the low dose pen (168 mcg/0.56 mL) used for delivering labeled doses of 6, 9, or 12 μg , the Applicant agreed to set the quality control delivered dose specification to target (b) (4) μg at release and stability.
- For the middle dose pen (294 μg /0.98mL) delivering labeled doses of 15, 18, or 21 mcg, the applicant agreed to target (b) (4) at release and an asymmetric specification of target (b) (4) to target (b) (4) for stability.
- For the high dose pen (420 μg /1.4 mL) delivering labeled doses of 24, 27, or 30 mcg, the applicant agreed to target (b) (4) at release and an asymmetric specification of target (b) (4) mcg to target (b) (4) for stability.

The Applicant has included “Net difference” as an additional test parameter to ensure that the maximum dose variability within a batch for all 3 pen presentations will be $\leq \Delta$ (b) (4) mcg. While this parameter limits the dose overlap when a patient switches to a pen obtained from the same batch, the risk of overlap persists when a patient switches to a pen from a different batch. The probability of dose overlap as per the CDER statistical simulation is in between 6%-45% for the high dose pen, when two different batches are used. This is primarily due to assay difference between a new batch and end of expiry batch. The potential for dose overlap and range of delivered dose at each dose setting is described in section 3 of prescribing information so that the provider is aware of such dose variability/overlap.

The NDA contains stability data from 3 PPQ batches, and six (6) registration and clinical study batches. Since there was a significant difference in stability profile of PPQ batches versus the registration and clinical batches, only stability data available for registration and clinical study batches were considered for granting shelf-life. It was noted that a switch in the reference standard contributed to the differences in the assay (content) and slope of the three PPQ batches, with PPQ batches performing better with respect to deliverable dose variability.

It was discovered that potential differences in assay principle used to determine reference standard content can impact the accurate calculation of content of the drug product during release and stability as well as delivered dose variability. To establish a link between the clinical batches and commercial batches, the

applicant was advised to use the UV absorption method for reference standard content determination for marketing purposes.

The applicant was informed that under a post-marketing mechanism, the applicant has the option to seek approval for using a new reference standard based on additional supporting data and in compliance with the draft guidance for industry, “Analytical Procedures and Methods Validation for Drugs and Biologics – 2015”, which recommends a) that a new batch of the reference standard material be qualified/calibrated against the current reference standard, and b) to consider orthogonal methods for reference material characterization. Per this guidance, in certain specific cases, a two-tiered approach to qualify a new reference standard (to prevent a drift in the quality attributes) may be more useful, which involves a comparison of each new reference standard with a primary reference standard so that it is linked to clinical trial material and the current/commercial manufacturing process.

Based on real-time stability data and CDER’s statistical simulation of dose failure rate for the registration and clinical batches, a shelf-life of 12 months is granted for the product stored at 2-8°C and after first use, a 14-day in-use period is granted when stored at room temperature below 30°C. Please refer to Dr. Khairuzzaman’s CMC drug product and CMC labeling reviews for this application in Panorama dated 8/2/2024 .

CDRH evaluated the device portion of the drug-device combination product and reviewed the sponsor’s revised specifications for pen deliverable dose at stability using an asymmetric approach and concluded that the device performance meets the sponsor’s set specification criteria of deliverable dose. CDRH also deferred to CDER to make the decision if the new asymmetric approach of delivered dose specification is clinically relatable and acceptable. Please refer to CDRH consult reviews dated July 25, 2024, and April 5, 2024, in DARRTS.

It is to be noted that even with this control strategy, there could be still as high as 11% failure rate for the deliverable dose at the end of 12 months for the high dose pen, but the middle dose and low dose pen can have much lower than 5% failure rate. After discussion with clinical team, this risk is considered acceptable, when considering the patient need for this product. Considering clinical assessment and labeling instructions, the clinical review team indicated that they do not anticipate that this degree of dose variability and resulting fluctuations in serum calcium levels should preclude approval of this product for patients with this rare disease, who have very limited options. To mitigate the risk of occasional extreme variability, which could result in blood calcium that is too low (hypocalcemia) or too high (hypercalcemia), the clinical review team has instructed to rigorous monitoring of serum calcium levels in the label. The risk of

hyper- and hypocalcemia will also be included in the Warnings and Precautions section.

- Risk of Unintended Changes in Serum Calcium Levels Related to Number of Daily Injections and Total Delivered Dose: Using two YORVIPATH injections to achieve the recommended once daily dosage increases the variability of the total delivered dose. Use only one YORVIPATH injection to achieve the recommended once daily dosage.
- Serious Hyper and Hypocalcemia: Serious hyper- and hypocalcemia have occurred with YORVIPATH. Periodically measure serum calcium and monitor for signs and symptoms of hyper- and hypocalcemia.

The label will also emphasize avoiding the use of 2 pens, which would exacerbate the dose variability. Dosage and Administration, (b) (4)
Section (See below for proposed language in the draft label).



- Dosage and Administration : Use only one injection to achieve the once daily recommended dosage. Using two injections to achieve the recommended once daily dosage increases the risk of unintended changes in serum calcium levels, hypocalcemia, and hypercalcemia.

The OPMA process and facility review concluded that the process and facilities information provided in the NDA is adequate. The Panorama screen shot of facility assessment is shown below (recorded on 8/5/2024).

NDA-216490-ORIG-1-RESUB-56

Planned Completion: Aug 14, 2024 | Status: Current | Condition: On Target

Project Summary | Project Details | Application Life Cycle | Received Documents | **Inspection View** | Tasks | Submission Facility Status View

Inspection View | As of Aug 5, 24, 1:40 pm E

Inspection View - Overall

Export

Task Number	Task Name	Comments	Assignments	Pin Comp	Act Comp	Task Status	Actions	Additional Information
10	Overall Manufacturing Inspection Recommendation	No changes to facilities in resubmission	Sateesh Kumar Satnigari	11/2/23	4/5/24	Complete	Go to Form	Approved

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

Drug Substance - Adequate
Drug Product - Adequate
Quality Labeling - Adequate

Manufacturing - Adequate
Biopharmaceutics - N/A
Microbiology - Adequate

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No

Comments:

Comparability Protocols (PACMP): No

Comments:

Additional Lifecycle Comments:

None

Muthukumar Ramaswamy 8-5-2024

Application Technical Lead Name and Date:



Muthukumar
Ramaswamy

Digitally signed by Muthukumar Ramaswamy
Date: 8/05/2024 02:27:38PM
GUID: 508da7210002a0c0870017f6c83398f4

41 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page



Title:	NDA IQA Template CHAPTER IV-LABELING
Document ID:	OPQ-ALL-TEM-0045
Effective Date:	18 Sep 2023 Revision: 00
Total Pages:	20



Template Revision: 03

CHAPTER IV: LABELING

NDA Number	NDA-216490-Resubmission
Assessment Cycle Number	<u>1</u>
Drug Product Name	YORVIPATH™ (palopegteriparatide) injection, for subcutaneous use

Assessment Recommendation: Adequate

Item	Assessment Conclusion	SDN # where labeling is adequate (“N/A” otherwise)
Prescribing Information Labeling	Adequate	0084
Patient Information	Adequate	0084
Instruction for Use (IFU)	Choose an item.	0084
Container Labels	Choose an item.	0080
Carton Labeling	Choose an item.	0080

Brief Description of Outstanding Issues:

Submissions being reviewed:

Document Reviewed (eCTD #, SDN #)	Date Received	Information Provided
0084	06/13/2024	Package insert, medication guide, Information, Instruction for use
0080	04/08/2024	Labeling – container-carton

1.0 PRESCRIBING INFORMATION¹

Assessment of Product Quality Related Aspects of the Prescribing Information:

¹ [Labeling Review Tool \(LRT\) \(March 2022\)](#), including use of consistent terminology for dosage form and unit of measure for strength in the product title and DOSAGE FORMS AND STRENGTHS heading in Highlights, in the DOSAGE AND ADMINISTRATION, DOSAGE FORMS AND STRENGTHS, DESCRIPTION, and HOW SUPPLIED/STORAGE AND HANDLING sections (see page 2 of LRT)

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

BRAND NAME YORVIPATH™ (palopegteriparatide) injection, for subcutaneous use

Initial U.S. Approval: N/A

Item	Item in Proposed Labeling (choose “Adequate”, “Inadequate”, or “N/A”)	Assessor’s Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Product Title in Highlights² [21 CFR 201.57(a)(2)]		
Established name(s) ³	Adequate	YORVIPATH™ (palopegteriparatide) injection, for subcutaneous use
Route(s) of administration	Adequate	for subcutaneous use
Controlled drug substance symbol (if applicable)	N/A	N/A
Initial U.S. Approval [§201.57(a)(3)]	Adequate	New drug, not previously approved in USA
Dosage Forms and Strengths Heading in Highlights [§ 201.57(a)(8)]		
Dosage form(s) ⁴ and strength(s) in metric system ⁵	Adequate	Injection 168 mcg/0.56 mL pen, delivering doses of 6, 9, or 12 mcg 294 mcg/0.98 mL pen, delivering doses of 15, 18, or 21 mcg 420 mcg/1.4 mL pen, delivering doses of 24, 27, or 30 mcg
If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride). ⁶	N/A	Not a salt.

² Draft guidance: *Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products — Content and Format* (January 2018)

³ Established name = [Drug] [Route of Administration] [Dosage Form]. Do use not “USP” descriptor in the product title or within the Highlights (see page 3 of LRT).

⁴ Draft guidance: *Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products — Content and Format* (January 2018); USP <1151>; USP Nomenclature Guideline

⁵ Labeling Review Tool (March 2022, page 13), include limited packaging information; USP <7>

⁶ Guidance: *Naming of Drug Products Containing Salt Drug Substances* (June 2015); MAPP 5021.1

Item	Item in Proposed Labeling (choose “Adequate”, “Inadequate”, or “N/A”)	Assessor’s Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state “functionally scored.” ⁷	N/A	
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package. ⁸	Adequate	Currently states, “Injection in a single-patient-use prefilled pen”.

Assessment: *Adequate*

(Provide any revision, if applicable, e.g., different color font, strikethrough, etc.) **Any issues should be listed at the end in “OUTSTANDING ISSUES AND RECOMMENDATIONS”**

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)⁹

Item	Item in Proposed Labeling (choose “Adequate”, “Inadequate”, or “N/A”)	Assessor’s Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents)	N/A	N/A

⁷ Guidance: *Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation* (March 2013)

⁸ Guidance: *Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use* (October 2018); USP <659>

⁹ See § 201.57(c)(3); draft guidance: *Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (January 2023); Labeling Review Tool (March 2022, page 25)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
and/or soft food ¹⁰ , storage conditions needed to maintain the stability of the reconstituted or diluted product).		
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food).	N/A	N/A
For parenteral products: include statement: <i>"Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit."</i> ¹¹	N/A	The drug product is a prefilled pen, which contains a prefilled syringe. Therefore, visual inspection is not possible.
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. ¹² Note the labeling requirement may be applicable to another section of the PI (e.g., Section 11).	N/A	N/A
For radioactive products, include radiation dosimetry for the patient and healthcare practitioner(s) who administer the drug	N/A	N/A
For hazardous products, include the statement <i>"DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures."</i> ^x with x numerical citation to "OSHA Hazardous Drugs."	N/A	N/A

¹⁰ Draft Guidance: [Use of Liquids and/or Soft Foods as Vehicles for Drug Administration: General Considerations for Selection and In Vitro Methods for Product Quality Assessments](#)

¹¹ §201.57(c)(3)(iv)

¹² USP General Notices 2.30 Legal Recognition

Assessment: Adequate

(Provide any revision, if applicable, e.g., different color font, strikethrough, etc.) **Any issues should be listed at the end in “OUTSTANDING ISSUES AND RECOMMENDATIONS”**

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)¹³

(b) (4)



Item	Item in Proposed Labeling (choose “Adequate”, “Inadequate”, or “N/A”)	Assessor’s Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Adequate	Injection
Strength(s) in metric system	Inadequate	168 mcg/0.56 mL, 294 mcg/0.98 mL and 420 mcg/1.4 mL. The solution

¹³ See § 201.57(c)(4); [Labeling Review Tool \(March 2022, page 29\)](#)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
		concentration across all three pen is the same, which is 300 mcg/ml. Deliverable dose should be included. See suggested table above.
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance . Clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride). No equivalency statement.	N/A	Not a salt
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable.	Adequate	It's a prefilled pen in an auto injector, therefore identifying characteristics are not visible by a patient. Refer to section 11 for description of the solution.
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."	N/A	N/A
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package (see USP <659>).	Adequate	Should read as "Injection: Clear, colorless solution available in single-patient-use prefilled pens in three presentations:

Assessment: *Adequate*

(Provide any revision, if applicable, e.g., different color font, strikethrough, etc.) **Any issues should be listed at the end in "OUTSTANDING ISSUES AND RECOMMENDATIONS"**

1.2.3 Section 11 (DESCRIPTION)¹⁴



(b) (4)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DESCRIPTION section		
Proprietary and established name(s) ¹⁵ [§ 201.57(c)(12)(i)(A)].	Adequate	YORVIPATH (palopegteriparatide) injection

¹⁴ See § 201.57(c)(12); [Labeling Review Tool \(March 2022, page 56\)](#)

¹⁵ Use of "USP" descriptor is not required to be included next to the established name throughout Prescribing Information (PI) labeling. If an applicant wants to use the "USP" descriptor next to the established name in the PI, recommend limiting its use to the product quality sections of the Full Prescribing Information (FPI) (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING) (see page 3 of LRT).

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Dosage form(s) and route(s) of administration [§ 201.57(c)(12)(i)(B)].	Adequate	Should read as "YORVIPATH is a sterile, clear and colorless solution in a glass cartridge which is preassembled in a single-patient-use prefilled pen for subcutaneous administration."
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per Salt Guidance and MAPP . For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)" [§ 201.57(c)(12)(i)(C)].	N/A	Not a salt. it's a prodrug. Appropriate equivalence statement is in place as follows: "Each mL of YORVIPATH solution contains 3456 mcg of palopegteriparatide, equivalent to 300 mcg of teriparatide (PTH(1-34))". The following statements are added under section 11: Each pen of 0.56 mL contains 168 mcg teriparatide equivalent to 1935 mcg palopegteriparatide. Each pen of 0.98 mL contains 294 mcg teriparatide equivalent to 13387 mcg palopegteriparatide. Each pen of 1.4 mL contains 420 mcg teriparatide equivalent to 4838 mcg palopegteriparatide.
List inactive ingredients (not required for oral use, except for colorant) by the USP/NF names in alphabetical order. ¹⁶ Avoid brand names. [§ 201.57(c)(12)(i)(C)].	Adequate	41.7 mg mannitol, 2.5 mg metacresol, 0.13 mg sodium hydroxide, 1.18 mg succinic acid, and water for injection.
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and	Adequate	See above

¹⁶ Per § 201.100(b)(5)(i) and (ii), flavoring and colorants may be designated as such without naming their components except for FD&C Yellow No 5 and FD&C Yellow No 6, which must be listed per § 201.20. Per § 201.100(b)(5)(iii), trace amounts of harmless substances added solely for individual product identification need not be named. If an applicant wants to use the National Formulary (NF) descriptor next to excipients, recommend limiting its use to the product quality sections of the FPI (see page 3 of LRT). Do not list brand names, e.g., Opadry, Eudragit, Polistirex, etc.

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
statement of effect. [§ 201.100(b)(5)(iii)].		
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F. (15.56 °C) [§ 201.10(d)(2)].	N/A	N/A
Sterility statement (if applicable) [§ 201.57(c)(12)(i)(D)].	Adequate	Identified as a sterile solution
Pharmacological/Therapeutic class ¹⁷ [§ 201.57(c)(12)(i)(E)].	Adequate	parathyroid hormone analog
Chemical name ¹⁸ , structural formula, molecular weight [§ 201.57(c)(12)(i)(F)].	Adequate	Provided
If radioactive, statement of important nuclear characteristics [§ 201.57(c)(12)(i)(G)].	N/A	N/A
Other important chemical or physical properties (such as pKa or pH) [201.57(c)(12)(ii)].	Adequate	YORVIPATH has a pH of 3.7 to 4.3.
For oral prescription drug products, include gluten statement ¹⁹ (if applicable).	N/A	N/A
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity").	N/A	N/A
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable	N/A	N/A

¹⁷ Listed before "indicated for" in INDICATIONS AND USAGE of Highlights section [§ 201.57(a)(6)]; can also search the term "FDA EPC Text Phrases" in [FDA's Labeling Resources for Human Prescription Drugs](#) for the most recent EPC list.

¹⁸ Chemical names do not need to be capitalized unless it appears at the beginning of a sentence (see *Preferred IUPAC Names Provisional Recommendation*, September 2004; Chapter 1, par. 16 Name writing, p.80-90).

¹⁹ Draft guidance: [Gluten in Drug Products and Associated Labeling Recommendations \(December 2017\)](#)

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
to another section of the PI (e.g., Section 2).		

Assessment: *Adequate*

(Provide any revision, if applicable, e.g., different color font, strikethrough, etc.) **Any issues should be listed at the end in "OUTSTANDING ISSUES AND RECOMMENDATIONS"**

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)²⁰



²⁰ See § 201.57(c)(17); [Labeling Review Tool \(March 2022, page 70\)](#). Consider including proprietary name and established name.

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s) [§ 201.57(c)(17)].	Adequate	YORVIPATH is available in a prefilled, disposable, 14-dose pen-injector.
Strength(s) in metric system. [§ 201.57(c)(17)(i)] If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance . Clearly state whether the strength is based on the active moiety. No equivalency statement.	Adequate	Each pen contains a clear and colorless solution of 3456 mcg/mL of palopegteriparatide equivalent to 300 mcg/mL of teriparatide.
Available units (e.g., bottles of 100 tablets) [§ 201.57(c)(17)(ii)].	Adequate	Each pack contains 2 prefilled pens and 28 needles for 28 injections (plus two spare needles).
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s) [§ 201.57(c)(17)(iii)].	Adequate	Provided (see above)
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored."	N/A	N/A
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package (see USP <659>).	Adequate	14-dose pen-injector

Item	Item in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g., to protect from light or moisture, to maintain stability, etc.). For hazardous drugs, state "DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures. ^x " with x numerical citation to "OSHA Hazardous Drugs." [§ 201.57(c)(17)(iv)]	Adequate	Do not freeze. Store away from heat. Keep YORVIPATH in the packaging to protect from light.
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature. (see USP <659>).	Adequate	Until first use, store YORVIPATH in the refrigerator between 2°C to 8°C (36°F to 46°F). After first use, store YORVIPATH for 14 days at room temperature below 30°C (86°F).
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free." ²¹	N/A	N/A
Include information about child-resistant packaging ²² (if chosen by manufacturer).	N/A	N/A

²¹ Guidance: [Recommendations for Labeling Medical Products to Inform Users that the Product or Product Container is not Made with Natural Rubber Latex](#) (December 2014)

²² Guidance: [Child-Resistant Packaging Statements in Drug Product Labeling](#) (August 2019)

Assessment: Choose an item.

(Provide any revision, if applicable, e.g., different color font, strikethrough, etc.) **Any issues should be listed at the end in “OUTSTANDING ISSUES AND RECOMMENDATIONS”**

1.2.5 Other Sections of Labeling

Patient counseling information under section 17 (Subject to review by DMEPA and clinical)

1.2.6 Manufacturing Information After Section 17 (for drug products)²³

Item	Item in Proposed Labeling (choose “Adequate” or “Inadequate”)	Assessor’s Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Manufacturing Information After Section 17		
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer.	Adequate	Manufactured by: Ascendis Pharma (b) (4) A/S Tuborg Boulevard 12 Hellerup Denmark DK-2900 (b) (4)

Assessment: Adequate

(Provide any revision, if applicable, e.g., different color font, strikethrough, etc.) **Any issues should be listed at the end in “OUTSTANDING ISSUES AND RECOMMENDATIONS”**

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guides, Instructions for Use, Patient Information):

Item	Item in Proposed Labeling (choose “Adequate”, “Inadequate”, or “N/A”)	Assessor’s Comments about Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name ²⁴	Adequate	palopegteriparatide
Special preparation instructions (if applicable).	N/A	N/A

²³ § 201.1(h)(5) and 201.1(i); [Labeling Review Tool \(March 2022, page 74\)](#)

²⁴ Established name = [Drug] [Route of Administration] [Dosage Form]

Item	Item in Proposed Labeling (choose “Adequate”, “Inadequate”, or “N/A”)	Assessor’s Comments about Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Storage and handling information (if applicable).	Adequate	Before first use, store in a refrigerator between 2 °C – 8 °C (36°F to 46°F). Do not freeze. Store away from heat. Store in the original package with the pen cap on in order to protect from light. After first use, store below 30 °C (86°F). Keep the pen cap on the prefilled pen in order to protect from light. Throw away each pen 14 days after first use.
If the product contains a desiccant, ensure the desiccant has a warning (e.g., “Do not eat.”) and the size and shape of the desiccant differ from the dosage form.	N/A	N/A
Active ingredient(s) (if applicable).	Adequate	palopegteriparatide
Alphabetical listing of inactive ingredients (if applicable).	Adequate	mannitol, metacresol, sodium hydroxide, succinic acid, and water for injection
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer.	Adequate	Manufactured by: Ascendis Pharma Bone Diseases A/S, Denmark

Assessment: Adequate

(Provide any revision, if applicable, e.g., different color font, strikethrough, etc.) **Any issues should be listed at the end in “OUTSTANDING ISSUES AND RECOMMENDATIONS”**

3.0 CONTAINER AND CARTON LABELING²⁵

1 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

²⁵ [Carton and Container Labeling Resources](#)



Fig. Outer Carton

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
Proprietary name and established name ²⁷ , (font size and prominence) [§ 201.10(g)(2)].	Adequate	Yes	

²⁷ Established name = [Drug] [Route of Administration] [Dosage Form]

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
Strength(s) in metric system [§ 201.100(b)(4) & 201.100(d)]. ²⁸	Adequate	Yes	
Route(s) of administration, not required for oral use [§ 201.100(b)(3)].	Adequate	Yes	
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP [§ 201.10(d)(1) & 201.100(b)(4), USP <1121>].	Adequate	Yes	
Net contents (e.g., tablet count, volume of liquid) [§ 201.51(a)]. ²⁹	Adequate	Yes	
"Rx only" displayed on the principal display [§ 201.100(b)(1)].	Adequate	Yes	
NDC (requested, but not required for all labels or labeling) [§ 201.2 & 207.35].	Adequate	Yes	
Lot number and expiration date [§ 201.18 & 201.17].	Adequate	Yes	
Storage conditions. If applicable, include a space on the carton labeling for the user to write the beyond-use-date (BUD).	Adequate	Yes	
For injectable drug products for parenteral administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms	Adequate	Yes	

²⁸ Express as "XX mg per tablet" or "XX mg per capsule" for strength of professional samples of solid oral dosage form with small net quantities per container (e.g., 5 or less) or blister pack/carton. See [Guidance: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors \(May 2022\)](#)

²⁹ § 201.51(h): A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled "sample", "physician's sample", or a substantially similar statement and the contents of the package do not exceed 8 grams.

Item	Item in Proposed Carton Labeling (choose "Adequate", "Inadequate", or "N/A")	Is item in Container Labels same as that of Carton Labeling?	Assessor's Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
include pharmacy bulk package and imaging bulk package, and these products require a "Not for direct infusion" statement. (See USP <659>).			
Name of all inactive ingredients, in alphabetical order [§ 201.10(a)] [except for oral drug per § 201.100(b)(5) or limited space per § 201.10(i)(2)].	Adequate	No	Absent on pen labeling; limited space
For parenteral injectable dosage forms, include quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect. [§ 201.100(b)(5)(iii)].	Adequate	No	List of inactive ingredients not present due to limited space
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol at 60 °F. (15.56 °C) [§ 201.10(d)(2)].	N/A	Yes	
Linear Bar code [§ 201.25(c)(2)]. ³⁰	Adequate	Yes	
Adequate directions for use: "Recommended Dosage: See Prescribing Information" [§ 201.5 & 201.55].	Adequate	Yes	
Name of manufacturer/distributor /packer [§ 201.1(a), 201.1(h)(5)].	Adequate	Yes	
"Keep out of reach of children" statement, optional for Rx,	Adequate	No	not present due to limited space

³⁰ See § 201.25(b)(1)(i) for a list where bar code is not required, e.g., prescription drug samples, medical gases, radiopharmaceuticals, etc.

Item	Item in Proposed Carton Labeling (choose “Adequate”, “Inadequate”, or “N/A”)	Is item in Container Labels same as that of Carton Labeling?	Assessor’s Comments about Container Labels and Carton Labeling (If an item is Inadequate or different, provide more details, as appropriate)
required for OTC [§ 201.66(c)(5)(x)].			
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	Adequate	Yes	
No text on Ferrule and Cap over seal of a vial of injectable products unless a cautionary statement is required. (USP <7>).	N/A	Yes	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	N/A	Yes	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label. ³¹	N/A	Yes	
And others if space is available.	N/A	Yes	

Assessment of Carton Labels and Container Labeling: Adequate

Any issues should be listed at the end in “OUTSTANDING ISSUES AND RECOMMENDATIONS”

³¹ USP General Notices 3.20 Indicating Conformance

4. OUTSTANDING ISSUES AND RECOMMENDATIONS

Assess consistency of product-quality information in prescription drug labeling (PI, c/c labeling, and FDA-approved patient labeling). See [Carton/Container Labeling Specific Resources](#) for a presentation about inappropriate inconsistencies of product quality information between labeling. If there are inappropriate inconsistencies between the labeling (e.g., established name, strength(s), package type term, discard statement, identifying characteristics, storage, reconstitution/dilution instructions), please list these issues in this section.

Primary Labeling Assessor Name and Date: Akm Khairuzzaman, Ph.D., 07/29/2024

*Secondary Assessor Name and Date (and Secondary Summary, as needed):
Muthukumar Ramaswamy, Ph.D., 07/29/2024*



Akm
Khairuzzaman

Digitally signed by Akm Khairuzzaman
Date: 8/02/2024 02:21:40PM
GUID: 502d1ab500002aef5afaa6f74ddf7e69



Muthukumar
Ramaswamy

Digitally signed by Muthukumar Ramaswamy
Date: 8/02/2024 02:22:13PM
GUID: 508da7210002a0c0870017f6c83398f4

46 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page



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

Date:	7/24/2024		
To:	Oluwafunmike Ajomale		
Requesting Center/Office:	CDER/OPQ	Clinical Review Division:	Other
From:	Sreya Tarafdar OPEQ/OHT3/DHT3C		
Through (Division): *optional	Shruti Mistry OPEQ/OHT3/DHT3C		
Subject:	Consult for Submission: NDA216490		
Recommendation:	Approvable Please refer to page 7 for detailed discussion.		

Digital Signature Concurrence Table		
Reviewer	Team Lead (TL)	Division (optional)
Sreya Tarafdar -S	Shruti N. Mistry -S	2024.07.24 17:29:47 -04'00'

1. SUBMISSION OVERVIEW

Table 1. Submission Information	
Consult Identification #	ICCR#01000802
Consult Request Link	01000802 Case Salesforce
ICC tracking #	ICC2400595
Submission Number	NDA 216490
Sponsor	Ascendis Pharma Bone Disease Division, A/S
Drug/Biologic	palopegteriparatide inj
Indications for Use	for the treatment of hypoparathyroidism in adults
Device Constituent	Pen-injector
Related Files	ICC2200569, ICC2200738, ICC2200739, ICC2301092, ICC2400045

2. CDRH REVIEW

ICC Review Request from CDER/OPQ, Other:

We have received a new CMC amendment for this NDA on June 21st 2024 (SN # 0084). The Applicant has further tightened the pen deliverable dose at stability using an asymmetric approach as follows. Note that the deliverable dose at batch release remains the same, i.e., (b) (4) μg at all dose level up to 30 μg . PLEASE SEE THE TABLE IN THE ATTACHMENT While this asymmetric approach is new with respect to deliverable dose from an injectable product, from CMC point of view this approach may be reasonable as long as they are acceptable to the clinical division. Therefore, the CMC reviewer had discussions with the clinical reviewer on this new limit and the Applicant's justification on this range (based on clinical trial dose variability data). It appears that the clinical division is OK with this range from their point of view. We also wanted to let you know that the OPQ's evaluation regarding the dose overlap with this proposed range will be based on whether or not such a dose variability range is clinically significant. While we are waiting for an official email from the clinical division on this proposed range, we are requesting you to take a look in this CMC amendment and let us know if the device can perform on stability with this newly proposed asymmetric limit and please let us know whether or not you need new device verification data for this newly proposed limit. On an additional note, we want to let you know that our statisticians have simulated a dose failure rate based on this applicant's newly proposed limit. According to their simulation the probability for dose failure at 12 months of shelf life with this newly proposed limit is less than 1% for the low dose pen (1st pen), less than 5% for the middle dose pen (2nd pen) and it is ~11% for the high dose pen (3rd pen). (b) (4)



Device Presentation(s) being evaluated:

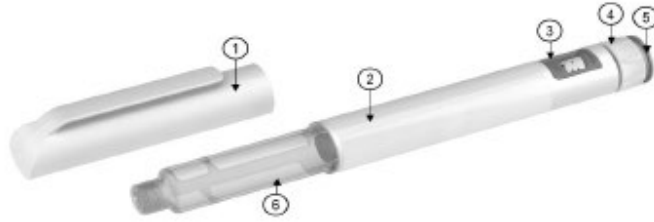
Palopegteriparatide is supplied as solution for injection in a 1.5 mL cartridge (primary container closure) assembled in a single-patient-use pen (secondary container) intended for daily subcutaneous (SC) administration. The prefilled pen is available in three presentations, covering a dose range from 6 to 30 μg of PTH(1-34) in dosing increments of 3 μg , each intended to deliver three distinct dose levels of palopegteriparatide drug product for 14 days of use:

Table 1: The Palopegteriparatide Prefilled Pen Presentation With Respective Dose Levels

Prefilled Pen Presentation		Dose ^a (Dose Volume)		
Palopegteriparatide prefilled pen 168 μg /0.56 mL		6 μg (20 μL)	9 μg (30 μL)	12 μg (40 μL)
Palopegteriparatide prefilled pen 294 μg /0.98 mL		15 μg (50 μL)	18 μg (60 μL)	21 μg (70 μL)
Palopegteriparatide prefilled pen 420 μg /1.4 mL		24 μg (80 μL)	27 μg (90 μL)	30 μg (100 μL)

^a Dose expressed in content of PTH(1-34)

Figure 1: The Palopegteriparatide Prefilled Pen Components (User-facing)



The component names are: 1) Pen cap, 2) Housing, 3) Dose setting window, 4) Dose Sleeve, 5) Push button, 6) Cartridge holder.

For detailed device description please refer to CDRH memo for ICC2200738-739

Objective of this Memo:

To determine and provide a review of whether the device functions as intended with the new tightened the pen deliverable dose at stability.

CDRH Review

Due to the short timeline provided on this ICC consult, CDRH is providing this streamlined memo as formal feedback for this ICC2400595.

Comments:

Sponsor has revised the specifications for pen deliverable dose at stability using an asymmetric approach as shown in table 14 and 18 below (tables have been retrieved from NDA216490 Seq# 0084 SD#085 1.11.4 Multiple Module Information Amendment). We note that the specification for deliverable dose at **batch release** remains the same, i.e., ^{(b) (4)} μg for all doses.

Table 14: Revised Delivered Dose and New Net Difference Acceptance Criteria

Test Parameter	Analytical Procedure	Acceptance Criteria	
		Release	Shelf Life
Delivered Dose (µg PTH(1-34))	Data Assessment A-PTH-071		
Tolerance interval ^a			
168 µg/0.56 mL		6 µg: (b) (4) 9 µg: 12 µg:	6 µg: (b) (4) 9 µg: 12 µg:
294 µg/0.98 mL		15 µg: 18 µg: 21 µg:	15 µg: 18 µg: 21 µg:
420 µg/1.4 mL		24 µg: 27 µg: 30 µg:	24 µg: 27 µg: 30 µg:
Net difference ^b		(b) (4)	

^a (b) (4)

^b Difference between the calculated upper and lower values of the Delivered dose tolerance interval for a given batch

Table 18: Delivered Dose Specification and Difference Between and Within Batches

Presentation	Doses (µg)	Release Acceptance Criteria Delivered Dose (µg)	Shelf Life Acceptance Criteria Delivered Dose Tolerance Interval (µg)	Maximum Difference Between Upper and Lower Criteria <i>Between Batches</i> (µg)	Maximum Net Difference ^a Between Upper and Lower Values <i>Within a Batch</i> (µg)
168 µg / 0.56 mL	6 – 9 – 12				(b) (4)
294 µg / 0.98 mL	15 – 18 – 21				
420 µg / 1.4 mL	24 – 27 – 30				

^a Net difference is calculated as the difference between the observed upper and lower value of the Delivered dose tolerance interval for a given batch.

Sponsor has revised their tolerance intervals of delivered dose acceptance criteria for stability studies such that for middle doses (15, 18 and 21) the lower limit is (b) (4) and for higher doses (24, 27, 30) the lower limit is (b) (4) as shown in table 18. As shown in table 14, likewise the yellow highlighted numbers show, for example, for a dose of 15 ug the lower limit tolerance levels would be (b) (4) = (b) (4) ug.

(b) (4)

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

Moreover, CDER in their email stated that *“While this asymmetric approach is new with respect to deliverable dose from an injectable product, from CMC point of view this approach may be reasonable as long as they are acceptable to the clinical division. Therefore, I had discussions with the clinical reviewer on this new limit and the Applicant’s justification on this range (based on clinical trial dose variability data). It appears that the clinical division is OK with this range from their point of view. I also wanted to let you know that the OPQ’s evaluation regarding the dose overlap with this proposed range will be based on whether or not such a dose variability range is clinically significant.*

On an additional note, ... statisticians have simulated a dose failure rate based on this applicant’s newly proposed limit. According to their simulation the probability for dose failure at 12 months of shelf life with this newly proposed limit is less than 1% for the low dose pen (1st pen), less than 5% for the middle dose pen (2nd pen) and it is ~11% for the high dose pen (3rd pen).

(b) (4)

CDRH’s scope of review is limited to reviewing whether the device is able to perform and meet the specification criteria set by the sponsor. CDRH is unable to comment on whether the asymmetric approach of setting the specification limits for the pen deliverable dose is clinically acceptable, from the perspective of how much drug is being delivered to the patient and what impact can it have on the patient with their dosing being variable. From CDER’s email, CDRH notes that CDER CMC would find this asymmetric specification criteria acceptable, contingent upon approval from the CDER clinical team. We also note that the CDER clinical team has also indicated that they are OK with the sponsor’s approach. CDRH also notes that CDER statistics division simulated the probability of dose failure at 12 months of shelf life and found the rate of failure to range from 1% to 11 % for the low to high dose

	pens. CDER indicated in their email that they would accept this failure rate, due to favorable risk benefit analysis, provided the applicant can assure that their pen dosing variability will remain within the proposed ranges and they will have appropriate control strategies in place to release successful batches selectively into the market (and not release the batches that incur failure). We defer to CDER to make the final review recommendation. We also defer to CDER to make the decision if the new asymmetric approach of delivered dose specification is clinically relatable and acceptable.
Review Recommendation:	Given the sponsor's revised specifications for pen deliverable dose at stability using an asymmetric approach, and the sponsor updating their claimed shelf life to (b) (4) – our review indicates that the device performance meets the sponsor's set specification criteria of deliverable dose.

---END OF REVIEW---

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/

OLUWAFUNMIKE O AJOMALE
07/25/2024 07:53:52 AM

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/

MUTHUKUMAR RAMASWAMY
08/05/2024 02:57:11 PM



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

Date:	4/3/2024		
To:	Ajomale, Oluwafunmike		
Requesting Center/Office:	CDER/OPQ/OPRO/DRBPMIII	Clinical Review Division:	N.A
From:	Sreya Tarafdar OPEQ/OHT3/DHT3C		
Through (Division): *optional	Shruti Mistry, Assistant Director, Injections Team OPEQ/OHT3/DHT3C		
Recommendation:	Not approvable (please refer to CDRH comments to CDER team in Section 2)		

Digital Signature Concurrence Table		
Reviewer	Team Lead (TL)	Division (optional)
Sreya Tarafdar -S	Shruti N. Mistry -S	2024.04.04 17:00:21 -04'00'

1. SUBMISSION OVERVIEW

Table 1. Submission Information	
Consult Identification #	ICCR# 00967152
Consult Request Link	https://force-dsc.my.salesforce.com/5003d00000AQew7
ICC tracking #	ICC2400045
Submission Number	NDA 216490
Sponsor	Ascendis Pharma Bone Disease Division, A/S
Drug/Biologic	palopegteriparatide inj
Indications for Use	for the treatment of hypoparathyroidism in adults
Device Constituent	Pen Injector syringe
Related Files	ICC2200569, ICC2200738, ICC2200739, ICC2301092

2. CDRH REVIEW

ICC Review Request from CDER/OPQ,	Consult for Submission: <i>A consult (ICCR# 00958392) was entered for this resubmission on November 28, 2023 (was previously CR'd – ICCR 00868197). On December 18, 2023, CDRH indicated that the sponsor's response constitutes an incomplete response to the CR issued April 2023.</i> <i>The CMC received new CMC data and per the reviewers, the CMC amendment includes delivered dose data at release as well as on stability. The reviewers would like to know if</i> <i>If these data can serve as the device performance data with respect to their capability at (b) (4) mcg</i> <i>If not, how they Applicant should conduct the device testing to demonstrate their performance capability at (b) (4) mcg range?</i> <i>At what stability time point the device performance start to fall outside of the (b) (4) mcg criterion?</i> <i>The assigned CDRH assessor will be invited to the CMC team meetings (Mid-cycle, Touch points, and Wrap-up) and to the OND Team meetings.</i>
Device Presentation(s) being evaluated:	Pen injector
Objective of this Memo:	Review new CMC data to determine if it demonstrates that their device performs and meets the revised limits of delivered dose specifications (b) (4) mcg and (b) (4) ul, as is deemed as an acceptable specification limit by CDER.
CDRH Comments to CDER review team:	The provided delivered dose data appears to meet the (b) (4) mcg specification limits for the (b) (4) doses (<30 mcg) through early time points in the stability studies (<12 months). However, we noted that several delivered dose data appears to fail the (b) (4) mcg specification limits for the (b) (4) doses (24 mcg upwards) through the stability studies and also for (b) (4) doses of 12 mcg at the later time points in the stability studies (>12 months). The provided data does not completely demonstrate that the existing device is capable of consistently meeting the earlier proposed (b) (4) µg dose delivered

	specification for all dose settings at release and stability per the revised quality control strategy. We defer to CDER to make the final review recommendation. We also defer to CDER to make the decision if the (b) (4) mcg specification limits would be applied to the higher doses and later time points of stability testing.

BACKGROUND:

CDER issued a CR letter to the sponsor on April 28, 2023 as follows: [CR NDA 216490 final.pdf](#)

FDA stated :

You have revised your delivered dose specifications during the NDA review and are proposing tightening your assay (active pharmaceutical ingredient) acceptance limits to (b) (4) (at shelf) and pen delivered volume limits to (b) (4) μ L at every dose setting. Based on these specifications, the amount of delivered drug can vary by as much as (b) (4) between pens of two different lots, and the amount of delivered drug can vary by as much as (b) (4) for a single pen. This large degree of variability could lead to dosing inaccuracy and dose overlapping (i.e., where the actual dose delivered at one dose level is the same as the actual dose that could be delivered at a lower dose level or higher dose level). We are concerned this can cause erratic dosing leading to efficacy and safety concerns (episodic hypocalcemia when a lower than intended amount of drug is administered and episodic hypercalcemia when a higher than intended amount of drug is administered). You have not provided data to assure that the anticipated dose variability and dose overlapping will not impact patients adversely.

You acknowledge “that the revised dose accuracy and content acceptance criteria are insufficient for achieving a net delivered daily dose variability of less than (b) (4) μ g (corresponding to (b) (4) μ g from the target dose) and eliminating the risk of dose overlap calculated from release specifications”. Therefore, you propose to apply a new test/control in the specification to limit the variability of the deliverable dose to (b) (4) μ g at each dose setting (so that the delivered drug amount does not vary by more than (b) (4) μ g). You propose to reject batches that do not meet this (b) (4) μ g criterion even if they meet the acceptance limits of (b) (4) % (at shelf) and pen delivered volume limits of (b) (4) μ L. However, this approach does not appear to be viable because of the extent of variability possible with the assay and volume specifications (for example, dosing variability could be as high as ~ (b) (4) (b) (4)). You have not provided design verification testing data confirming that the (b) (4) μ g dose delivered specification can be consistently achieved by your device per your quality control strategy. In fact, per your delivered dose specification criteria, approximately one-half of your developmental batches (including some registration stability batches) failed with respect to either content/assay and/or deliverable volume. We have no assurance that the released batches will reliably and consistently meet the delivered dose specification for every pen at every dose setting. In addition, because there are no stability data with respect to the delivered dose, it is unclear if acceptable batches that are released will meet the shelflife criteria. Note that Good Manufacturing Practices regulations require that the manufacturing processes be designed and controlled to assure that the finished drug product meets predetermined quality requirements and does so consistently and reliably.

As a path forward, FDA provided the sponsor with two alternatives, as follows:

To resolve the identified deficiencies, we recommend the following:

(b) (4)

Alternatively, you could address the above-listed CMC deficiencies and provide data verifying that your existing device is capable of consistently meeting your proposed (b) (4) µg dose delivered specification at release and stability per your revised quality control strategy.

Regardless of the approach chosen, you will also need to provide a statistical control plan for lot release testing of device Essential Performance Requirements.

Information request issued by CDER CMC on January 4, 2024

Reviewer comments:

Sponsor provided stability data in response to CDER's IR# 1 and all delivered dose data appears to meet the (b) (4) µg specification limits, except one batch ASTL021A – highlighted in pink. The out-of-specification results were with the 30ug dosing at 0 and 12 months stability testing.

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

Reviewer comments:

Sponsor provided individual dose results at **release** from retrospective calculations. However, several delivered dose data appears to **fail the** ^{(b) (4)} **µg** specification limits, highlighted in pink and yellow.

Though there are instances of failures in the 12 , 15 and 18 ug doses (highlighted in yellow.), the failure to meet the spec limit is seen more in the higher doses at 21 mcg - highlighted in pink.

Reviewer comments:

Sponsor provided individual dose results **at stability** from retrospective calculations. However, several delivered dose data appears to **fail the** ^{(b) (4)} **µg** specification limits, highlighted in yellow.

The failure appears to be more frequently occurring at the stability time point of 12 months and greater.

Reviewer comments:

Sponsor provided individual dose results **from commercial batches**. It is not clear why the table is labelled for dose accuracy results in ul. However, the data appears to be delivered dose in ug and delivered dose data appears to **meet the** ^{(b) (4)} **µg** specification limits.

Reviewer comments:

Sponsor provided delivered dose results at stability from registration batches. In the summarized data table above, the delivered dose data from 6 batches appears to **meet the** (b) (4) **µg** specification limits, but these data have been recorded only at time point = 0 and not tested for the shelf-life stability points of 24 or 36 months.

In Table 2, sponsor provided delivered dose results at stability from registration batches. The delivered dose data start to fall out-of-specification limits at higher doses (b) (4)



Reviewer comments:

Sponsor provided dose accuracy results at stability. However, the dose accuracy data appears to **meet the** (b) (4) **µl** specification limits.

Reviewer comments:

Sponsor provided delivered dose results at stability. However, several delivered dose data appears to **fail the** (b) (4) **µg** specification limits, highlighted in yellow.

---END OF REVIEW---

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/

OLUWAFUNMIKE O AJOMALE
04/05/2024 07:53:52 AM

Tarafdar, Sreya

From: Tarafdar, Sreya
Sent: Monday, December 18, 2023 12:33 PM
To: Ajomale, Oluwafunmike (Funke)
Cc: Mistry, Shruti
Subject: ICCR# 00958392 NDA 216490 Palopegteriparatide - CDRH feedback

Hi Funke ,

As discussed earlier with the CMC team, please consider this email as our formal feedback for this ICC2301092.

The sponsor has provided a new proposed wider specification limit in response to the deficiency regarding the overlapping dose variability issue. The sponsor has provided design verification testing supporting their new specified specification limits for dose variability. However, upon discussion with the CMC review team, the new proposed specification limit is not acceptable due to continued overlapping risks having not been mitigated. Moreover, the sponsor has not provided data verifying that the existing device is capable of consistently meeting the earlier proposed (b) (4) µg dose delivered specification at release and stability per the revised quality control strategy, as outlined in the CR letter. Thus we concur with CDER/CMC that the sponsors response constitutes an incomplete response to the CR letter issued during April 2023.

~ Sreya

Sreya Tarafdar, Ph.D.

Infusion Devices Team
DHT3C: Division of Drug Delivery, General Hospital Devices and Human Factors
OHT3 | Office of Product Evaluation and Quality
Center for Devices and Radiological Health
U.S. Food and Drug Administration
Phone 3017967540 | sreya.tarafdar@fda.hhs.gov



Sreya Tarafdar -S

Shruti N. Mistry -S
Digitally signed by
Shruti N. Mistry -S
Date: 2023.12.18
19:53:43 -05'00'

Excellent customer service is important to us. Please take a moment to provide feedback regarding the customer service you have received:
<https://www.research.net/s/cdrhcustomerservice?ID=1532&S=F>

From: OLUWAFUNMIKE AJOMALE <oluwafunmike.ajomale@fda.hhs.gov>
Sent: Tuesday, November 28, 2023 2:13 PM
To: Khairuzzaman, Akm <Akm.Khairuzzaman@fda.hhs.gov>; Ramaswamy, Muthukumar <Muthukumar.Ramaswamy@fda.hhs.gov>; Jairath, Meghna <Meghna.Jairath@fda.hhs.gov>; Sapru, Mohan <Mohan.Sapru@fda.hhs.gov>; CDRH—Combination Product Consults-3 <CDRHComboConsult3@fda.hhs.gov>
Cc: Ajomale, Oluwafunmike (Funke) <Oluwafunmike.Ajomale@fda.hhs.gov>; Intercenter Consult <IntercenterConsult@fda.hhs.gov>
Subject: ICCR# 00958392 has been SUBMITTED to CDRH - NDA 216490 Palopegteriparatide

ICCR# 00958392 has been SUBMITTED to CDRH.

***** CENTER FOR DEVICES AND RADIOLOGICAL HEALTH PLEASE ASSIGN A REVIEWER USING THE LINK BELOW *****

*****If you believe this ICCR has been routed in error, contact: [CDRH PJO](#)*****

To view the ICCR, copy and paste this link into Chrome: <https://force-dsc.my.salesforce.com/5003d000009z5La>

Lead Center: CENTER FOR DRUG EVALUATION AND RESEARCH

ICCR Requester/Org: OLUWAFUNMIKE AJOMALE

Product Information: NDA 216490 Palopegteriparatide

Applicant/Sponsor: Ascendis Pharma Bone Disease Division, A/S

ICCR Request Type(s):

Consult Expertise/Keywords: Delivery Devices (e.g., autoinjector, non-insulin delivering infusion pump, nasal spray devices)

Consult Sub-Type: Technical engineering/Device design

Request Details: Request consult for this resubmission (was previously CR'd), please review applicant's response in resubmission.

The assigned CDRH assessor will be invited to the CMC team meetings (Kick-off, Mid-cycle, and Wrap-up) and to the OND Team meetings.

CMC Kick-off meeting is currently scheduled for December 4, 2023, OND meeting is scheduled for 12/6/2023

ICCR Submitted Date: 11/28/2023

ICCR Due Date: 12/15/2023

Indications for Use: (b) (4) for the treatment of hypoparathyroidism in adults

If there are routing issues related to this ICCR, contact OLUWAFUNMIKE AJOMALE.

Contact(s) for this ICCR:

Lead Center Requester: OLUWAFUNMIKE AJOMALE

Lead Center Submission Contact: OLUWAFUNMIKE AJOMALE

Receivers: CDRH Combo 3-(cdrhcomboconsult3@fda.hhs.gov)

Reviewers:

Others Notified: Akm.Khairuzzaman@fda.hhs.gov; Muthukumar.Ramaswamy@fda.hhs.gov;

Meghna.Jairath@fda.hhs.gov; mohan.sapru@fda.hhs.gov

Additional Helpful Information:

- If the ICCR was submitted to the wrong receiver or office/division/group in the Consulted Center, reroute the ICCR to the correct group in your Center ([view instructions](#)).
- If the consult due date is too short, request a consult due date extension ([view instructions](#)).
- If there are not enough details to understand the product or consult request, reach out to the Lead Center Requester and Lead Center Submission Contact for additional details. Contact your [Center PJO](#) for assistance if needed.
- If you do not think a consult is needed per an [established agreement or MOU](#) between Centers, reach out to the Lead Center Requester and Lead Center Submission Contact to share your thinking, and ask the Lead Center Requester to withdraw the consult. Consider including your Center PJO on the communication.

-----THIS IS A SEND ONLY ACCOUNT. DO NOT RESPOND TO THE SENDER.-----

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/

OLUWAFUNMIKE O AJOMALE
12/20/2023 01:32:05 PM



Title:	New Drug Application (NDA) Integrated Quality Assessment Template		
Document ID:	OPQ-ALL-TEM-0004		
Effective Date:	04 Nov 2022	Revision:	08
Total Pages:	11		



Template Revision: 03

RECOMMENDATION

☐ Approval
☐ Approval with Post-Marketing Commitment
☒ Complete Response

NDA 216490 Assessment # 1

Drug Product Name	Yorvipath (Palopegteriparatide) injection
Dosage Form	Injection
Strength	168 µg/0.56mL, 294 µg/0.98mL, 420µg/1.4 mL
Route of Administration	Subcutaneous
Rx/OTC Dispensed	Rx
Applicant	Ascendis Pharma Bone Diseases A/S, Denmark
US agent, if applicable	Ascendis Pharma, Inc., Palo Alto, CA

Submission(s) Assessed (eCTD Sequence)	Document Date	Discipline(s) Affected
0005	09/26/2022	Quality
0007	10/06/2022	Quality
0010	10/24/2022	Quality
0012	11/09/2022	Quality
0013	11/10/2022	Quality
0016	11/21/2022	Quality
0023	11/30/2022	Quality
0029	12/13/2022	Quality
0032	12/19/2022	Quality
0034	12/22/2022	Quality
0037	01/05/2023	Quality
0042	01/13/2023	Quality
0043	01/25/2023	Quality/Clin Pharm
0044	01/27/2023	Quality/Clin Pharm
0045	02/08/2023	Quality/Clin Pharm
0047	03/09/2023	Quality/Clin Pharm/PMC



Title:	New Drug Application (NDA) Integrated Quality Assessment Template
Document ID:	OPQ-ALL-TEM-0004
Effective Date:	04 Nov 2022 Revision: 08
Page 2 of 11	



Template Revision: 03

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance	Daniel Jansen	Zhengfu Wang
Drug Product	Akm Khairuzzaman	Mohan Sapru
Manufacturing	Sateesh Sathigari	Vidya Pai
Microbiology	Xia Xu	Nandini Bhattacharya
CDRH	Sreya Tarafdar	Alan Stevens
Biopharmaceutics	<i>None</i>	
Regulatory Business Process Manager	Nowrin Kakon	
Application Technical Lead	Akm Khairuzzaman	
Laboratory (OTR)	Jamie Mans Hongbin Zhu	Cynthia Sommers
Environmental	Akm Khairuzzaman	Mohan Sapru



Title:	New Drug Application (NDA) Integrated Quality Assessment Template
Document ID:	OPQ-ALL-TEM-0004
Effective Date:	04 Nov 2022 Revision: 08
Page 3 of 11	



Template Revision: 03

QUALITY ASSESSMENT DATA SHEET

For more details about the items in this template, please see the [Quality Assessment Data Sheet chapter of the NDA IQA Guide](#)

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	III	(b) (4)	(b) (4)	Adequate	1/30/2023	All technical information has been provided in the NDA. They are found to be adequate to support this NDA.
	III			Adequate	1/30/2023	

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
Letter of Authorization	510(k) file# K152514	Clickfine AutoProtect Pen Needle
Meeting minutes	IND- 133469	Meeting minutes

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
CDRH	Completed	Complete Response	1/21/2023	Sreya Tarafdar Alan Stevens



Title:	New Drug Application (NDA) Integrated Quality Assessment Template		
Document ID:	OPQ-ALL-TEM-0004		
Effective Date:	04 Nov 2022	Revision:	08
Page 4 of 11			



Template Revision: 03

EXECUTIVE SUMMARY

For more details about the items in this template, please see the [Executive Summary chapter of the NDA IQA Guide](#)

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

From the chemistry, manufacturing, and controls (CMC)/quality perspective, NDA 216490 (palopegteriparatide injection, for subcutaneous use) is recommended for Complete Response (CR) because there are currently unresolved deficiencies concerning i) significant variability about the delivered dose, a product critical quality attribute, ii) lack of adequate data to support feasibility of revised assay and delivered volume specification, iii) high-level of batch failure, indicative of inadequate formulation and device design, and iv) inadequate stability data to support shelf-life determination of the product per revised specification for the delivered dose. Specifically:

- (a) For the proposed drug device combination product presentation, there is a significant concern about dosing variability leading to dose overlapping from a single pen presentation and/or between pens of different lots.*
- (b) Only 3 out of 9 proposed doses have been tested in the narrowly designed Phase 3 clinical trial. The observed dose variability in the clinical batches appears very minimal compared to the expected variability from the commercial products based on specification range, including the lower and upper acceptance limits of the range. There are no data available to assess how the other yet-to-be-delivered doses will behave in the real world.*
- (c) The underlying variabilities contributing to dosing inaccuracy and dose overlapping are PTH content (assay) and pen functionality. Per a series of amendments submitted, the Applicant acknowledges i) "only a limited number of batches were used in the clinical program", and ii) "that the revised dose accuracy and content acceptance criteria are insufficient for achieving a net delivered daily dose variability of less than $(b)(4)$ μg (corresponding to $(b)(4)$ μg from the target dose) and eliminating the risk of dose overlap calculated from release specifications". Therefore, the Applicant proposed a new test for "delivered dose" with a limit of not more than $(b)(4)$ μg . This approach doesn't appear to be viable because based on the currently proposed limits for these underlying variables, dosing variability could be as high as $(b)(4)$. Per Applicant's delivered dose specification criteria, approximately half of the developmental batches (including some registration stability batches) failed with respect to either content/assay and/or deliverable volume. None of the failed batches were dosed in the Phase 3 clinical trial. This approach may be indicative of a kind of cherry-picking of the most ideal batches for getting tighter results. Note that GMP regulations require that the manufacturing processes be designed and controlled to assure that the finished drug product meet predetermined quality requirements and do so consistently and reliably.*



Title:	New Drug Application (NDA) Integrated Quality Assessment Template
Document ID:	OPQ-ALL-TEM-0004
Effective Date:	04 Nov 2022 Revision: 08
Page 5 of 11	



Template Revision: 03

(d) (b) (4)
Importantly, the viability of Applicant's proposed revised specification for assay and delivered volume is not currently supported by any device design verification testing data to verify that the delivered dose specification can be consistently achieved by the device at release and on stability.

(e) *The proposed device has a poor dialing resolution of ^{(b) (4)} μL which is not very suitable to deliver a small volume concentrated dose like this. For a drug device combination product/pen, the delivered dose (D) = C x V, where "C" is the API content/assay and "V" the deliverable volume. Applicant's claim that the key driver for variability in delivered dose/patient exposure to drug is ^{(b) (4)} is unjustified.* (b) (4)

(f) *key deficiency flagged by CDRH's review).* (b) (4)

II. SUMMARY OF QUALITY ASSESSMENTS



Title:	New Drug Application (NDA) Integrated Quality Assessment Template		
Document ID:	OPQ-ALL-TEM-0004		
Effective Date:	04 Nov 2022	Revision:	08
Page 6 of 11			



Template Revision: 03

A. Product Overview

Yorvipath (Palopegteriparatide) injection is a “combination drug product”. Palopegteriparatide is a new chemical entity, and a synthetic prodrug consisting of 34 amino acids. The proposed drug product is a sterile injectable solution for subcutaneous administration. The strength is expressed as the parathyroid hormone, “teriparatide” but supplied as “palopegteriparatide” solution (300 mcg per mL) in single-patient-use prefilled pens covering doses of 6 to 30 mcg PTH(1-34) to be administered as a once-daily subcutaneously. Each vial is in an autoinjector that contains multidose for 14-day supply. There are three (3) different pen presentations to deliver nine (9) different doses as follows:

- 168 mcg/0.56 mL pen, delivering doses of 6, 9, or 12 mcg
- 294 mcg/0.98 mL pen, delivering doses of 15, 18, or 21 mcg
- 420 mcg/1.4 mL pen, delivering doses of 24, 27, or 30 mcg
- Patients will receive 14 injections from one pen

Each mL of the solution contains 3456 mcg of palopegteriparatide, corresponding to 300 mcg of teriparatide (PTH(1-34)) as active ingredient, and the following inactive ingredients: 1.18 mg succinic acid, 41.7 mg mannitol, 2.5 mg metacresol, 0.13 mg sodium hydroxide, and water for injection. The critical quality attributes for this combination drug product includes assay, identification, release profile, related impurities, (b) (4) content, sterility, bacterial endotoxin, pH, osmolality, subvisible particles, dosing accuracy for pen functionality and delivered dose. For this product presentation, the dosing accuracy is considered as the most critical issue because the dose delivery is dependent on the pen functionality and content (assay) of the solution in the vial. Considering both, the drug product reviewer’s calculation shows that the maximum expected range for the dosing variability between two different pens of two different lot could be as high as (b) (4) % from the target label claim of the lowest dose (6 mcg) and (b) (4) % from the target label claim of the highest dose (30 mcg) (b) (4). This is consistent with the Applicant’s calculation as well. However, all clinical batches (phase II and III batches) showed a very consistent dose delivery. Dr. Khairuzzaman pointed out that with the existing control strategy almost half of the developmental batches are failing. Although the Applicant’s strategy is that they will only release batches that pass the acceptance criteria, there is not adequate confidence whether the “good batches” will meet the criteria on shelf. Therefore, there is a significant concern with feasibility of their approach and manufacturability of the product. GMP regulations require that the manufacturing processes be designed and controlled to assure that the finished drug product meet predetermined quality requirements and do so consistently and reliably. While the clinical impact of this large variability is subject to review by the clinical division, the variability is also expected to lead to dose overlapping or overdosing. This is a significant quality issue. To resolve this issue, the Applicant may take approaches such (b) (4)



Title:	New Drug Application (NDA) Integrated Quality Assessment Template	
Document ID:	OPQ-ALL-TEM-0004	
Effective Date:	04 Nov 2022	Revision: 08
Page 7 of 11		



Template Revision: 03

(b) (4)

Proposed Indication(s) including Intended Patient Population	Hypothyroidism
Duration of Treatment	Long term
Maximum Daily Dose	(b) (4) per day
Alternative Methods of Administration	None

B. Quality Assessment Overview

Drug Substance: Adequate

Drug Product: Inadequate

There is a significant issue with the dosing accuracy

Labeling: Inadequate

The product presentation is supposed to be changed as per the Applicant's PMC proposal.

Manufacturing: Adequate

Biopharmaceutics: N/A

Microbiology (if applicable): Adequate



Title: New Drug Application (NDA)
Integrated Quality Assessment
Template

Document ID: OPQ-ALL-TEM-0004

Effective Date: 04 Nov 2022 Revision: 08

Page 8 of 11



Template Revision: 03

Risk Assessment

CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Assessment Cycle #	Comments
Assay	High	(b) (4)	Medium	(b) (4)
Degradation impurities	High		Medium to low	
Content of (b) (4)	Medium		Low	
pH	Medium		Low	
Osmolality	Low		Low	
Bacterial Endotoxin	High		-	
Sterility	High		-	
Leachable Extracts	Medium to low		Low	
Dosing efficiency/Dosing variability/Delivered dose	High		High	



Title:	New Drug Application (NDA) Integrated Quality Assessment Template	
Document ID:	OPQ-ALL-TEM-0004	
Effective Date:	04 Nov 2022	Revision: 08
Page 9 of 11		



Template Revision: 03

D. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies (*Deficiencies that affect multiple sub-disciplines*)

Please see list under Drug product Deficiencies below

2. Drug Substance Deficiencies

None

3. Drug Product Deficiencies

A drug device combination product needs to meet product quality standards, including viable specification for critical quality attributes, control strategy for manufacturability, reproducibility of delivered dose (dose accuracy), and should be supported by appropriate device design verification data. Several deficiencies listed below concerning these requirements are currently unresolved:

a) We note that the viability of your proposed control strategy that includes revised specification for assay and delivered volume is not currently supported by any device design verification testing data to ensure that the delivered dose specification can be consistently achieved by the device at release and on stability

b) We note that the proposed limit of (b) (4) μ L for pen functionality cannot assure the target delivered dose of (b) (4) μ g (i.e., a net of (b) (4) μ g) because the net dose variability is expected to occur at all dose settings as follows: (b) (4)

(b) (4) respectively, when pens are performing at their extreme ends of specification. Similarly, the variability is expected to be double for (b) (4)

c). Only three (3) out of nine (9) proposed doses were tested in the Phase 3 clinical trial. The observed dose variability in the clinical batches appears very minimal compared to the expected variability from the commercial products based on specification range, including the lower and upper acceptance limits of the range. There are no data to assess how the other yet-to-be-delivered doses will behave in the real world. Additionally, your current testing



Title:	New Drug Application (NDA) Integrated Quality Assessment Template		
Document ID:	OPQ-ALL-TEM-0004		
Effective Date:	04 Nov 2022	Revision:	08
Page 10 of 11			



Template Revision: 03

methodology involves use of very limited pens, and each pen is tested for three doses only. Therefore, to improve reliability, we recommend you update your testing methodology for pen functionality to include dosing accuracy on all the doses from a single pen (b) (4) at release and on stability. You may apply a bracketing approach once you demonstrate that the variability between all the doses is not significant.

d) We acknowledge your effort of tightening the assay specification and manufacture of PPQ batches and two additional commercial batches. However, your approach of controlling the dose variability (i.e., delivered dose with a limit of (b) (4) µg) is not adequately supported by batch analysis data, which indicate that (b) (4) % batches failed with respect to delivered dose and a total of (b) (4) % batches failed based on revised assay and delivered volume specification. Absent device design verification data, the precision of the deliverable volume from the pen at release and on stability doesn't appear to be suitable for this low dose concentrated product presentation. Due to these underlying variabilities and the proposed control strategy, the dosing accuracy is not assured based on current device and formulation design for the to-be-released batches.

e) Unusually tight specification for assay (API content) and delivered volume, resulting in a significant batch failure, is generally indicative of an inadequate formulation and device design. To comprehensively address the current deficiencies, we acknowledge your future plan (b) (4)

(b) (4) We recommend you include this information in your NDA resubmission.

f) Currently, there are no available data concerning the "delivered dose" from the registration stability batches. Therefore, it is unclear if your proposed control strategy is feasible from a shelf-life perspective (b) (4)

There is concern that a batch that is released with the criterion of (b) (4) µg for delivered dose may not meet the same criterion at the end of your proposed shelf life (i.e., (b) (4)) because the assay can drop, and the pen functionality may also change over time (as evident from the stability data).

4. Labeling Deficiencies



Title:	New Drug Application (NDA) Integrated Quality Assessment Template	
Document ID:	OPQ-ALL-TEM-0004	
Effective Date:	04 Nov 2022	Revision: 08
Page 11 of 11		



Template Revision: 03

Not Applicable at this Stage because of a CR recommendation

5. Manufacturing Deficiencies

None

6. Biopharmaceutics Deficiencies

N/A

7. Microbiology Deficiencies

None

8. Other Deficiencies (Device-related deficiencies from the CDRH review team).

a. In your response to the FDA CMC Information Request dated 03 February 2023, you have stated your intent to modify the pen dose delivered specification to (b) (4). However, you have not provided data verifying that your device is capable of consistently meeting this new specification. You also state on page 5 of your response that you plan (b) (4) (b) (4) " Please provide design verification testing data verifying the (b) (4) dose delivered specification is consistently achieved by your device per your quality control strategy.

b. Please provide a statistical control plan for lot release testing of device EPRs.

Application Technical Lead Name and Date:

Akm Khairuzzaman, Ph.D. 3/16/2023 *Akm Khairuzzaman*

121 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

CHAPTER IV: LABELING

[IQA NDA Assessment Guide Reference](#)

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Items	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	Yorvipath	Acceptable
Established name(s)	TRADENAME (palopegteriparatide) subcutaneous injection	PI is edited as follows: TRADENAME (palopegteriparatide) injection, for subcutaneous use
Route(s) of administration	Subcutaneous injection	Acceptable
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Subcutaneous injection in a single-patient-use prefilled pen • 168 mcg/0.56 mL pen, delivering doses of 6, 9, or 12 mcg • 294 mcg/0.98 mL pen, delivering doses of 15, 18, or 21 mcg • 420 mcg/1.4 mL pen, delivering doses of 24, 27, or 30 mcg	Acceptable
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	(b) (4) the term "single patient use" is used.	(b) (4) Acceptable
Special instructions for product preparation (e.g., reconstitution and resulting	None	Acceptable

concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)		
Available dosage form(s)	Subcutaneous Injection	Acceptable
Strength(s) in metric system	Subcutaneous injection in a single-patient-use prefilled pen • 168 mcg/0.56 mL pen, delivering doses of 6, 9, or 12 mcg • 294 mcg/0.98 mL pen, delivering doses of 15, 18, or 21 mcg • 420 mcg/1.4 mL pen, delivering doses of 24, 27, or 30 mcg	Acceptable
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	Not applicable	Acceptable
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single patient- use). Other package type terms include pharmacy bulk package and imaging bulk package.	“(b) (4) the term “single patient use” is used.	(b) (4) Acceptable

1.2.3 Section 11 (DESCRIPTION)

Items	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	TRADENAME (palopegteriparatide) injection, for subcutaneous use	Acceptable
Dosage form(s) and route(s) of administration	Subcutaneous	Acceptable
If the active ingredient is a salt, apply the USP Salt Policy and include the	Not applicable	Acceptable

equivalency statement per FDA Guidance.		
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Provided	Acceptable
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	Provided under section 11 of the labeling as follows: <i>“Each mL of TRADENAME solution contains 3456 mcg of palopegteriparatide, equivalent to 300 mcg of teriparatide (PTH (1-34)), and the following inactive ingredients: 41.7 mg mannitol, 2.5 mg metacresol, 0.13 mg sodium hydroxide, 1.18 mg succinic acid, and water for injection.”</i>	Acceptable
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	Not Applicable	Acceptable
Statement of being sterile (if applicable)	Yes	Acceptable
Pharmacological class	Yes	Acceptable
Chemical name, structural formula, molecular weight	Yes	Acceptable
If radioactive, statement of important nuclear characteristics.	Not Applicable	Acceptable
Other important chemical or physical properties (such as pKa or pH)	Section 11 says, <i>“It has a pH of 3.7 to 4.3.”</i>	Acceptable
Remove statements that may be misleading or promotional (e.g., “synthesized and developed by Drug Company X,” “structurally unique molecular entity	None present	Acceptable

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

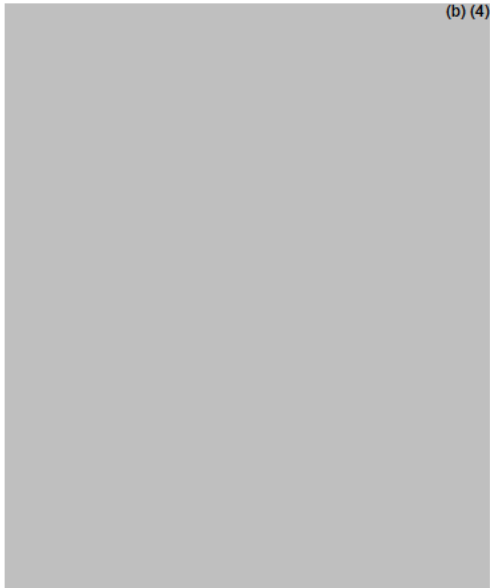
Items	Information Provided in the NDA	Assessor's Comments																
HOW SUPPLIED/STORAGE AND HANDLING section																		
Available dosage form(s)	Subcutaneous Injection	Acceptable																
Strength(s) in metric system	Provided (see below)	Acceptable																
Available units (e.g., bottles of 100 tablets)	<table border="1"> <thead> <tr> <th data-bbox="643 533 808 573">Prefilled Pen Presentation</th> <th data-bbox="813 533 899 573">Doses</th> <th data-bbox="904 533 990 573">Content of Pack</th> <th data-bbox="995 533 1109 573">NDC</th> </tr> </thead> <tbody> <tr> <td data-bbox="643 579 808 722">TRADENAME (168 mcg/0.56 mL) identified by blue push button</td> <td data-bbox="813 579 899 722">6, 9, and 12 mcg</td> <td data-bbox="904 579 990 722">2 prefilled pens 30 needles</td> <td data-bbox="995 579 1109 722">73362-100-01</td> </tr> <tr> <td data-bbox="643 728 808 871">TRADENAME (294 mcg/0.98 mL) identified by orange push button</td> <td data-bbox="813 728 899 871">15, 18, and 21 mcg</td> <td data-bbox="904 728 990 871">2 prefilled pens 30 needles</td> <td data-bbox="995 728 1109 871">73362-101-01</td> </tr> <tr> <td data-bbox="643 877 808 993">TRADENAME (420 mcg/1.4 mL) identified by burgundy push button</td> <td data-bbox="813 877 899 993">24, 27, and 30 mcg</td> <td data-bbox="904 877 990 993">2 prefilled pens 30 needles</td> <td data-bbox="995 877 1109 993">73362-102-01</td> </tr> </tbody> </table>	Prefilled Pen Presentation	Doses	Content of Pack	NDC	TRADENAME (168 mcg/0.56 mL) identified by blue push button	6, 9, and 12 mcg	2 prefilled pens 30 needles	73362-100-01	TRADENAME (294 mcg/0.98 mL) identified by orange push button	15, 18, and 21 mcg	2 prefilled pens 30 needles	73362-101-01	TRADENAME (420 mcg/1.4 mL) identified by burgundy push button	24, 27, and 30 mcg	2 prefilled pens 30 needles	73362-102-01	Acceptable
Prefilled Pen Presentation	Doses	Content of Pack	NDC															
TRADENAME (168 mcg/0.56 mL) identified by blue push button	6, 9, and 12 mcg	2 prefilled pens 30 needles	73362-100-01															
TRADENAME (294 mcg/0.98 mL) identified by orange push button	15, 18, and 21 mcg	2 prefilled pens 30 needles	73362-101-01															
TRADENAME (420 mcg/1.4 mL) identified by burgundy push button	24, 27, and 30 mcg	2 prefilled pens 30 needles	73362-102-01															
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Provided (see table above)	Acceptable																
For injectable drug products for parental administration, use appropriate package type term (e.g., single dose, multiple-dose, single-patient use). Other package terms include pharmacy bulk package and imaging bulk package.	Following statement provided: <i>"TRADENAME is available in a prefilled, disposable, 14-dose pen-injector"</i>	Acceptable																
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a	Following statements are provided: "Do not freeze. Store away from heat. Keep TRADENAME in the packaging to protect from light.	Acceptable																

statement to “Dispense in original container,” provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	Until first use, store TRADENAME in the refrigerator between 2 °C to 8°C (36°F to 46°F). After first use, store TRADENAME for 14 days at room temperature below 30°C (86°F). After each use, remove the needle and put the pen cap on to protect from light. Discard the prefilled pen 14 days after first use“	
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Provided. See above row.	Acceptable
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: “Not made with natural rubber latex. Avoid statements such as “latex free.”	Not Applicable	Acceptable
Include information about child-resistant packaging	Not Acceptable	Acceptable

1.2.6 Manufacturing Information After Section 17 (for drug products)

Items	Information Provided in the NDA	Assessor’s Comments
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Manufactured by: Ascendis Pharma (b) (4) A/S, Tuborg Boulevard 12 Hellerup Denmark DK-2900 (b) (4)	Acceptable

2.0 PATIENT LABELING



Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use): The medication guide provides detailed step-by-step instruction on how to use the pen device and how to select the dose. There is very limited CMC information on the medication guide except for the above instruction regarding storage condition. These are found to be Acceptable from CMC point of view.

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label (Pen label)



Note: The two other pen presentations have identical information except for dose, NDC number & box color to differentiate strengths.

3.2 Inner carton labeling

(b) (4)



Note: The two other lower strengths have identical information except for strength, NDC number & box color to differentiate strengths [redacted] (b) (4)

[redacted]

1 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page



Note: The two other lower strengths have identical information except for strength, fluid volume, API amount, NDC number & box color to differentiate strengths.

Items	Information Provided in the NDA	Assessor's Comments
Proprietary name, established name, and dosage form (font size and prominence)	TRADENAME (palopegteriparatide) for injection	Unacceptable. Should read as TRADENAME (palopegteriparatide) injection, for subcutaneous use

Dosage strength	(b) (4)	Acceptable
Route of administration	Subcutaneous Injection	Acceptable
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	Not applicable	Acceptable
Net contents	0.56 ml, 0.98 ml, and 1.4 mL per presentation	Acceptable
"Rx only" displayed on the principal display	yes	Acceptable
NDC number	yes	Acceptable
Lot number and expiration date	yes	Acceptable
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	(b) (4)	Acceptable
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single patient-use)	Provided	Acceptable
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	Not applicable	Acceptable
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	Not Acceptable	Acceptable
Name of manufacturer/distributor	Distributed by: Ascendis Pharma Endocrinology Inc. Princeton NJ 08540 USA Manufactured by: Ascendis Pharma Bone Diseases A/S Tuborg Boulevard 12, DK-2900 Hellerup	Acceptable
Medication Guide (if applicable)	Not Applicable	Acceptable
No text on Ferrule and Cap Overseal	Not Applicable	Acceptable
When a drug product differs from the relevant USP	Not Applicable	Acceptable

standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.		

Assessment of Carton and Container Labeling: Will be adequate once the Applicant changed the product name on the labeling.

1. *The drug product name needs to be revised to read as: "TRADENAME (palopegteriparatide) injection, for subcutaneous' instead of "TRADENAME (palopegteriparatide) for injection"*

ITEMS FOR ADDITIONAL ASSESSMENT

None

Overall Assessment and Recommendation: *Package insert, Carton and Container Labeling comment should be sent out to the Applicant.*

Primary Drug Product Assessor Name and Date: Akm Khairuzzaman, Ph.D., 1/4/2023.

Secondary Assessor Name and Date (and Secondary Summary, as needed): Mohan Sapru, Ph.D., 1/4/2023



Akm
Khairuzzaman

Digitally signed by Akm Khairuzzaman
Date: 3/15/2023 09:39:21AM
GUID: 502d1ab500002aef5afaa6f74ddf7e69



Mohan
Sapru

Digitally signed by Mohan Sapru
Date: 3/15/2023 11:13:25PM
GUID: 504f821600000ec6d20b59d2b68eb3d2

45 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

CHAPTER VII: MICROBIOLOGY

For more details about the items in this template, please see [Chapter VII \(Microbiology\) of the NDA IQA Guide](#)

Product Information	(b) (4) for the treatment of hypoparathyroidism in adults. (The drug product is a prodrug providing sustained release of parathyroid hormone (PTH(1-34)).)
NDA Number	216490
Assessment Cycle Number	01
Drug Product Name/ Strength	Palopegteriparatide prefilled pen, 168 µg/0.56mL, 294 µg/0.98mL, 420µg/1.4 mL
Route of Administration	Subcutaneous Injection
Applicant Name	Ascendis Pharma Bone Diseases A/S
Therapeutic Classification/ OND Division	Division of General Endocrinology
Manufacturing Site	(b) (4)
Method of Sterilization	

Assessment Recommendation: Adequate

Assessment Summary: (b) (4)

(b) (4). The process validation meets the product quality microbiology review criteria.

List Submissions Being Assessed (table):

Document(s) Assessed	Date Received
Supporting document # 1 (Seq-0001)	08/31/2022
Supporting document # 16 (Seq-0016)	11/21/2022

Highlight Key Issues from Last Cycle and Their Resolution: None.

Remarks: 505(b)(1) application. Priority review. Information provided in Seq-0025 is the same as Seq-0016, but under a different drug product folder.

Concise Description of Outstanding Issues: None.

Supporting Documents: None.

S DRUG SUBSTANCE

The palopegteriparatide drug substance, manufactured by (b) (4) is supplied as non-sterile (b) (4). This section is therefore not reviewed for sterilization process validation. Acceptance criteria for microbiological quality of drug substance are listed below:

- Total Aerobic Microbial Count (TAMC): ≤ (b) (4) CFU/100 mg
- Total yeasts and molds count (TYMC): ≤ (b) (4) CFU/100 mg
- Bacterial endotoxins: ≤ (b) (4) EU/mg

Assessment: {Adequate}

Microbiological quality acceptance criteria for drug substance comply with those specified by USP <1111> for non-sterile substances for pharmaceutical use.

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

Description of drug product

The drug product is a sterile, (b) (4), (b) (4), 0.3 mg PTH(1-34)/mL solution for injection packaged in a 1.5 mL multi-dose glass cartridge which is assembled in a single-patient-use pen injector for daily subcutaneous injection. There are three different fill volumes. Each prefilled pen presentation is intended to deliver three distinct dose levels of palopegteriparatide drug product for 14 days of use.

Prefilled pen presentation	Dose (Dose Volume)		
	Palopegteriparatide 168 µg/0.56 mL	6 µg (20 µL)	9 µg (30 µL)
Palopegteriparatide 294 µg/0.98 mL	15 µg (50 µL)	18 µg (60 µL)	21 µg (70 µL)
Palopegteriparatide 420 µg/1.4 mL	24 µg (80 µL)	27 µg (90 µL)	30 µg (100 µL)

* Dose expressed in content of PTH(1-34).

Drug product composition

Ingredient	Reference to standard	Function	Nominal quantity (per mL)
Palopegteriparatide	In-house	Prodrug form of PTH(1-34)	0.3 mg PTH(1-34)*
Succinic acid	USP-NF, JPE	(b) (4)	1.18 mg
Mannitol	USP-NF, Ph. Eur., JP		41.7 mg
Metacresol	USP-NF, Ph. Eur.		2.5 mg
Sodium hydroxide	In-house		(b) (4) mg**

(b) (4)		
WFI	USP-NF, Ph. Eur., JP	(b) (4) q.s. to 1.00 mL

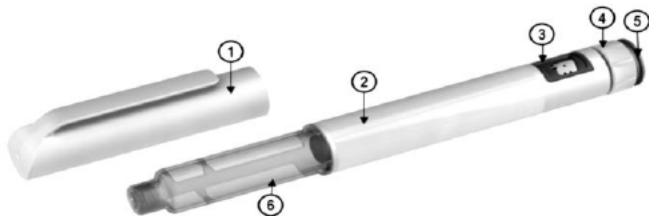
* Content for palopegteriparatide is declared as the equivalent amount of PTH(1-34). Palopegteriparatide is a prodrug, consisting of PTH(1-34) transiently conjugated to an inert carrier via a TransCon Linker. Active PTH(1-34) is released from the prodrug under physiological temperature and pH via an auto-cleavage reaction. Therefore, the content, concentrations and dose levels of the palopegteriparatide prodrug are expressed as equivalent amounts of the physiologically active substance PTH(1-34). To qualify the content or concentration of the equivalent palopegteriparatide drug substance, a (b) (4) is used.

Description of container closure system

Packaging Component	Material	Supplier
Primary packaging	1.5 mL cartridge	(b) (4)
	Rubber plunger	
	Crimp cap	
Secondary packaging	Pen injector	

* The address for each supplier is not provided.
 ** Consists of a pen cap, a cartridge holder, and a dosing mechanism with a pen push button and a dose sleeve (pages 3-4 of 6, 3.2.P.7 Container Closure System, Secondary Packaging).

Figure 1: The Palopegteriparatide Prefilled Pen Components (User-facing)



The component names are: 1) Pen cap, 2) Housing, 3) Dose setting window, 4) Dose Sleeve, 5) Push button, 6) Cartridge holder.

Injection needles (Ypsomed Clickfine AutoProtect 31GX5mm needles) are co-packaged with the palopegteriparatide prefilled pen. Each pack of product contains 2 prefilled pens and 28 needles for 28 injections (plus two spare needles). The pen needle is CE marked and is cleared by FDA in a 510(k) [K152514] for use with pen injectors devices. They are sterile, non-pyrogenic, single-use replaceable (individually packaged) stainless-steel needles. Prior to administration, the needle is mounted to the cartridge holder of the pen and

discarded after use. The prefilled pen is discarded 14 days after first use. The drug product is not in direct contact with any of the pen components during storage and during use (3.2.P.2.6 *Comptability*).

Assessment: {Adequate}

The drug product composition and container-closure system are adequately described. The container-closure system is adequate for the drug product subcutaneous route of administration.

P.2 PHARMACEUTICAL DEVELOPMENT

P.2.5 MICROBIOLOGICAL ATTRIBUTES

(b) (4)



Xia
Xu

Digitally signed by Xia Xu
Date: 1/04/2023 10:21:21AM
GUID: 585c30e50015a0ac941cb21671c188ce



Nandini
Bhattacharya

Digitally signed by Nandini Bhattacharya
Date: 1/04/2023 10:35:42AM
GUID: 508da70c00028f454473851fced0e9d4



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

Date	10/24/2022 Recommendation Updated on 02/21/2023
To:	Nowrin Kakon
Requesting Center/Office:	FDA/OC/CDER/OPQ/OPRO/DRBPMI/RBPMB2/
From	Sreya Tarafdar OPEQ/OHT3/DHT3C
Through (Team)	Courtney Evans, Team Lead, Injection Team OPEQ/OHT3/DHT3C
Through (Division) *Optional	CPT Alan Stevens, Asst Director, Injection Team OPEQ/OHT3/DHT3C
Subject	NDA 216490 , Palopegteriparatide ICC2200738-739 00868187-97
Recommendation	Filing Recommendation Date: 10/24/2022 ☐ 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: 11/4/2022 ☐ 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: 1/6/2023 Recommendation Updated on 02/21/2023 ☐ 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)
Sreya Tarafdar -S Digitally signed by Sreya Tarafdar -S Date: 2023.02.23 11:39:41 -05'00'		

1. SUBMISSION OVERVIEW

Submission Information	
Submission Number	NDA 216490
Sponsor	Ascendis Pharma Bone Disease Division, A/S
Drug/Biologic	Palopegteriparatide
Indications for Use	(b) (4) for the treatment of hypoparathyroidism in adults
Device Constituent	Pen-Injector
Related Files	

Review Team	
Lead Device Reviewer	<i>Sreya Tarafdar</i>

Important Dates	
Final Lead Device Review Memo Due	01/03/2023
Interim Due Dates	
Meeting/Due Date	
Filing	10/28/2022
74-Day Letter	11/11/2022
CMC Mid-Cycle	11/04/2022
CMC wrap-up	01/04/2023

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 <u>Notes</u>
	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	deferred to DMEPA
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:

CDRH defers to CDER the review of biocompatibility, reprocessing related to the primary container closure, since review of primary container closure is beyond the scope of CDRH review.

2.2. Complete Response Deficiencies

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

CDRH is providing the following 'letter-ready' Deficiencies written so they can be directly communicated to the Sponsor:

1. In your response to the FDA CMC Information Request dated 03 February 2023, you have stated your intent to modify the pen dose delivered specification to (b) (4). However, you have not provided data verifying that your device is capable of consistently meeting this new specification. You also state on page 5 of your response that you plan “ (b) (4) ” Please provide design verification testing data verifying the (b) (4) dose delivered specification is consistently achieved by your device per your quality control strategy.
2. Please provide a statistical control plan for lot release testing of device EPRs.

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

1.	SUBMISSION OVERVIEW.....	2
2.	EXECUTIVE SUMMARY AND RECOMMENDATION.....	3
2.1.	Comments to the Review Team.....	3
2.2.	Complete Response Deficiencies.....	3
2.3.	Recommended Post-Market Commitments/Requirements.....	4
3.	PURPOSE/BACKGROUND.....	7
3.1.	Scope.....	7
3.2.	Prior Interactions.....	7
3.2.1.	Related Files.....	7
3.3.	Indications for Use.....	7
3.4.	Materials Reviewed.....	7
4.	DEVICE DESCRIPTION.....	8
4.1.	Device Description.....	8
4.2.	Steps for Using the Device.....	15
4.3.	Device Description Conclusion.....	17
5.	FILING REVIEW.....	17
5.1.	Filing Review Checklist.....	17
5.2.	Facilities Information.....	18
5.3.	Quality System Documentation Triage Checklist.....	24
5.4.	Filing Review Conclusion.....	25
6.	LABELING.....	25
6.1.	General Labeling Review.....	25
6.2.	Labeling Review Conclusion.....	26
7.	DESIGN CONTROL SUMMARY.....	26
7.1.	Summary of Design Control Activities.....	26
7.2.	Design Inputs and Outputs.....	27
7.3.	Applicable Standards and Guidance Documents.....	35
7.4.	Design Control Review Conclusion.....	36
8.	RISK ANALYSIS.....	36
8.1.	Risk Management Plan.....	36
8.2.	Hazard Analysis and Risk Summary Report.....	38
8.3.	Risk Analysis Review Conclusion.....	43
9.	DESIGN VERIFICATION REVIEW.....	44
9.1.	Performance/Engineering Verification.....	44
9.1.1.	Essential Performance Requirement Evaluation.....	47
9.2.	Design Verification Review Conclusion.....	70
9.3.	Discipline Specific Sub-Consulted Review Summary.....	71
10.	CLINICAL VALIDATION REVIEW.....	71
10.1.	Review of Clinical Studies Clinical Studies.....	71
10.2.	Clinical Validation Review Conclusion.....	73
11.	HUMAN FACTORS VALIDATION REVIEW.....	74
12.	FACILITIES & QUALITY SYSTEMS.....	74
12.1.	Facility Inspection Report Review.....	74

12.2.	Quality Systems Documentation Review	74
12.2.1.	Description of the Device Manufacturing Process.....	74
12.2.2.	cGMP Review	78
12.2.3.	Corrective and Preventive Action Review	80
12.3.	Control Strategy Review	81
12.4.	Facilities & Quality Systems Review Conclusion.....	83

3. PURPOSE/BACKGROUND

3.1. Scope

Ascendis Pharma Bone Disease Division, A/S is requesting approval of Palopegteriparatide. 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:

ICC2200739 OPQ requests CDRH review for this NDA because this NDA is for a drug device combination product (prefilled syringe). Therefore, we need CDRH consult for their evaluation on the device part focusing on the followings: device constituent design inputs and outputs, device specifications with objective acceptance criteria such as dose accuracy, activation force or break loose / glide force, needle length / gauge and other attributes as necessary, design validation, device design risk assessment, biocompatibility, reprocessing / cleaning / disinfection validation (if any) and device performance stability. The assigned CDRH assessor will be invited to the CMC team meetings (Kick-off, Mid-cycle, and Wrap-up) and to the OND Team meetings. ICC2200738 Request consult for device facility --this is a drug device combination product (prefilled syringe). The assigned CDRH assessor will be invited to the CMC team meetings (Kick-off, Mid-cycle, and Wrap-up) and to the OND Team meetings.

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

Device performance, design validation/verification, facilities information for sites involved in final finished device manufacture/assembly

This review will not cover the following review areas:

the primary container closure system, Biocompatibility of PFS cartridge, 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

3.2.1. Related Files

3.3. Indications for Use

Combination Product	Indications for Use
Palopegteriparatide	(b) (4) for the treatment of
Pen-Injector	hypoparathyroidism in adults Delivery of the Drug Product

3.4. Materials Reviewed

Materials Reviewed	
Sequence	Module(s)

1.14	Labeling
2.2	Introduction
2.3	Quality Overall Summary
2.7.3	Clinical Summary
3.2.P.2.3	Manufacturing Process Development
3.2.P.2.4	Container Closure System, Functional Secondary Container Closure,
3.2.P.3	Manufacture
3.2.P.5.1	Specifications
3.2.P.5.6	Justification of Specifications
3.2.P.5.6	Control Strategy
3.2.P.7	Container Closure system (secondary)
3.2.P.8.1	Stability Summary and Conclusions
3.2.R	DEVICE Design and Development
3.2.R	DEVICE Design Verification
3.2.R	DEVICE Labeling and IFU
3.2.R	DEVICE Relevant standards
3.2.R	DEVICE Quality systems regulation summary
3.2.R	DEVICE Risk Management
3.2.R	DEVICE Ypsomed Manufacturing and Assembly
3.2.R	DEVICE (b) (4) Manufacturing and Assembly

4. DEVICE DESCRIPTION

4.1. Device Description

Palopegteriparatide is a prodrug designed to provide sustained release (within the physiological range for 24 h per day) of parathyroid hormone (PTH) (b) (4) in adults with hypoparathyroidism with the proposed indication:

TRADENAME is a prodrug with sustained release of parathyroid hormone (PTH 1-34) indicated for (b) (4) treatment of adult hypoparathyroidism

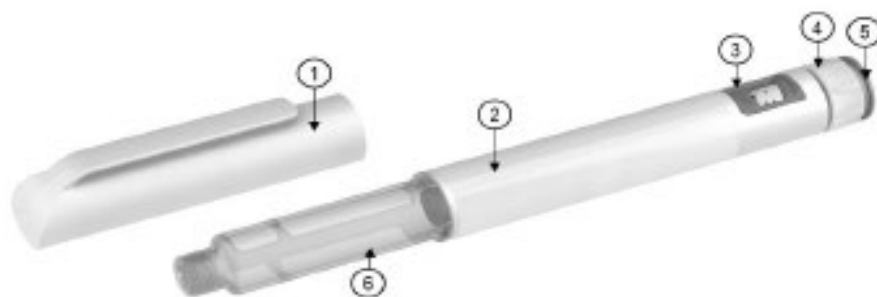
Palopegteriparatide is supplied as solution for injection in a 1.5 mL cartridge (primary container closure) assembled in a single-patient-use pen (secondary container) intended for daily subcutaneous (SC) administration. The prefilled pen is available in three presentations, covering a dose range from 6 to 30 µg of PTH(1-34) in dosing increments of 3 µg, each intended to deliver three distinct dose levels of palopegteriparatide drug product for 14 days of use:

Table 1: The Palopegteriparatide Prefilled Pen Presentation With Respective Dose Levels

Prefilled Pen Presentation		Dose* (Dose Volume)		
Palopegteriparatide prefilled pen 168 µg/0.56 mL		6 µg (20 µL)	9 µg (30 µL)	12 µg (40 µL)
Palopegteriparatide prefilled pen 294 µg/0.98 mL		15 µg (50 µL)	18 µg (60 µL)	21 µg (70 µL)
Palopegteriparatide prefilled pen 420 µg/1.4 mL		24 µg (80 µL)	27 µg (90 µL)	30 µg (100 µL)

* Dose expressed in content of PTH(1-34)

Figure 1: The Palopegteriparatide Prefilled Pen Components (User-facing)



The component names are: 1) Pen cap, 2) Housing, 3) Dose setting window, 4) Dose Sleeve, 5) Push button, 6) Cartridge holder.

The development of the prefilled pen is based on the Ypsomed AG (Ypsomed) UnoPen platform pen device. The prefilled pen, as the sponsor has noted will be co-packaged with a safety needle, Ypsomed ClickFine® AutoProtect™.

Sponsor has stated examples of other companies who applied this pen platform to develop customized prefilled pen solutions of which at least one is being marketed in the US includes (b) (4)

Each pen is characterized by specific, tailored maximum dose stop, specific dose sleeve labeling and a unique push button color. All three pens must be primed before first use. This is done by dialing two clicks on the pen. Following this, the dose setting (before an actual injection) takes place by dialing the dose on the pen. A specific dose corresponds to a number of clicks on the pen, as described below in the table.

Table 1: Palopegteriparatide Prefilled Pen Presentations

Pen Presentation	Palopegteriparatide 168 µg/0.56 mL	Palopegteriparatide 294 µg/0.98 mL	Palopegteriparatide 420 µg/1.4 mL
Deliverable doses	6, 9 or 12 µg	15, 18 or 21 µg	24, 27 or 30 µg
Min. deliverable dose/volume	(b) (4)		
Max. deliverable dose/volume			
Total extractable volume (=14 x max dose)	0.56 ml	0.98 ml	1.4 ml
Pen Clicks	Corresponding Dose	Corresponding Dose	Corresponding Dose
0	0	0	0
2	Priming	Priming	Priming
(b) (4)			

Figure 1: Representative Prefilled Pen Parts Overview

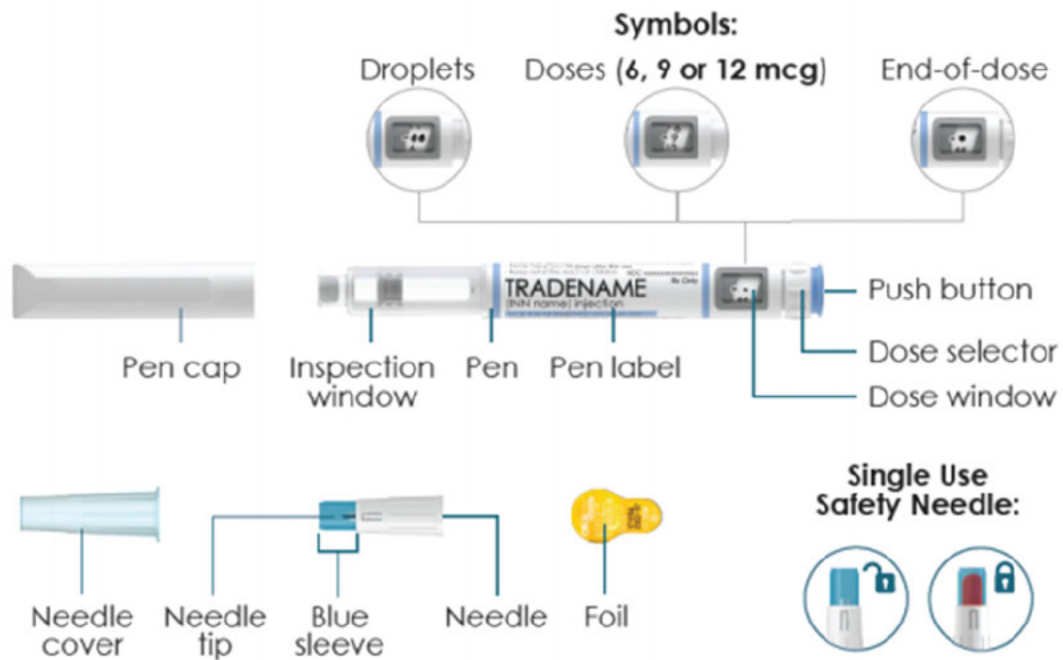
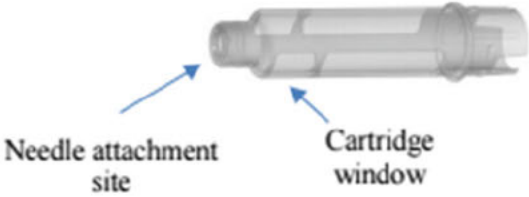
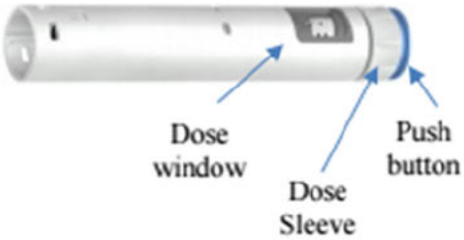


Table 3: Pen Components and Functions

Component	Supplier	Function	Representative image
Pen Cap	Ypsomed	- Attaches to the prefilled pen. - Protects prefilled pen between uses	
Cartridge holder	Ypsomed	- Contains the prefilled drug cartridge - Provides site for needle attachment	
Dosing mechanism	Ypsomed	- Multi-component sub-assembly that allows the user to prime the pen and set the dose. - The push button is color coded for each pen variant. - The dosing mechanism includes a dose sleeve that is visible through the dose window. The dose sleeve has customized printing of the dose levels for each variant.	
Cartridge	(b) (4)	- Prefilled primary container closure for the drug constituent - Non-replaceable multi-dose container	

A summary of the technical characteristics are provided in Table 3.

Table 3: Palopegteriparatide Prefilled Pen Technical Specifications

Technical Characteristics	
Size	Length: 172 mm Diameter at push button: 17 mm Diameter at pen cap: 19.5 mm
Dose accuracy	According to ISO 11608-1:2014
Shelf life	(b) (4) and 14 days
Use Conditions	
In use temperature with palopegteriparatide drug product	Below 30°C
Storage and transportation temperature until first use	Between 2°C to 8°C
Light protection	Store in box until first use. Attach pen cap after injections during 14 days in-use time.

Each prefilled pen consists of

(b) (4)

The Palopegteriparatide Prefilled Pen Components (with Arbitrary Colouring)

(b) (4)

INTENDED ENVIRONMENT OF USE :

v05.02.2019

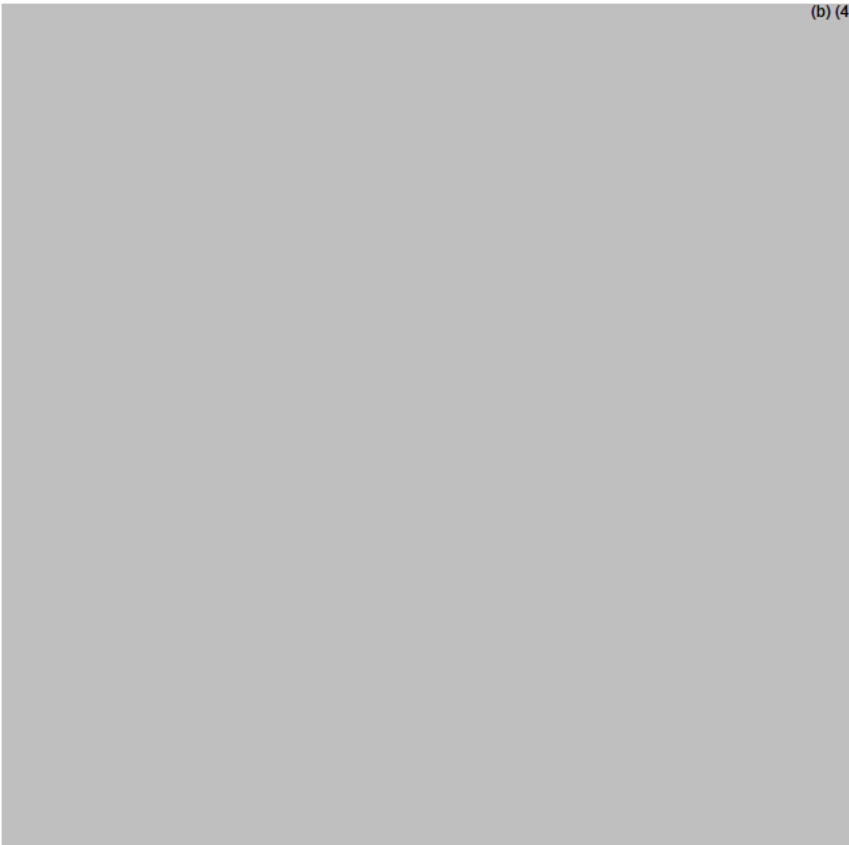
Intended for use both at home and/or in clinical environment by the patients and/or caregivers and/or healthcare providers (HCPs).

PACKAGING :

The prefilled pen will be co-packaged with injection needles which include safety needle with a needle shield locks out the needle after the use, significantly lowering the risk for needle stick injuries and prohibiting reuse.

The palopegteriparatide prefilled pen consists of a disposable, multiple dose, prefilled pen that is co-packaged in a box with 15 single-use needles (14 needles for single-use and one spare single-use needle). Two boxes with a prefilled pen and needles will be packaged in a commercial sales box which also will containing the prescribing information leaflet and the instructions for use (IFU). Hence, the commercial sales box provides supplies for 28 days.

(b) (4)



DESCRIPTION OF THE CO-PACKAGED NEEDLES

The co-packaged Ypsomed Clickfine AutoProtect 31Gx5mm needles are sterile, non-pyrogenic, single-use replaceable needles intended for subcutaneous administration of liquid pharmaceuticals.

The Ypsomed Clickfine AutoProtect 31Gx5mm needle complies with the standard ISO 11608-2:2012 "Needle-based injection systems for medical use – Part 2: Needles" and is cleared by FDA under 510(k) [K152514] for use with pen injector devices for the injection of liquid pharmaceuticals. It is a sterilized, single use, stainless-steel needle with a 31-gauge outer diameter and 5 mm length. It is designed for use with pen injectors such as

the palopegteriparatide prefilled pen and must be mounted on the cartridge holder of the pen using the threads on needle and cartridge holder, respectively. The needles have a safety mechanism, in which a shield covers the needle after withdrawal from the body post-injection. This mechanism prevents the user from re-using the needle and minimizes the risk of patient injury from the needle.

Sponsor has provided a LOA from Ypsomed for referencing all information form the cleared 510K K152514

Ascendis Pharma A/S
Tuborg Boulevard 12
2900 Hellerup
Denmark

Ypsomed AG
Brunnmattstrasse 6
P.O. Box
3401 Burgdorf / Switzerland
Tel +41 34 424 41 11
Fax +41 34 424 41 22
www.ypsomed.com
info@ypsomed.com

Burgdorf, 15 July 2020

RE: Authorization to Clickfine AutoProtect Pen Needle 510(k) file # K152514

To Whom It May Concern

This letter authorizes the Food and Drug Administration to include by reference all required information in our Clickfine AutoProtect Pen Needle 510(k), file number K152514, to support the TransCon PTH submission filed by Ascendis.

Yours sincerely
Ypsomed AG

[Redacted signature block] (b) (6)

I.A.
Sabine Sonleitner
Regulatory Affairs Specialist

I.V.
Dr. Andrea Sparti
Head of Regulatory Affairs

Reviewer's comment : upon checking K152514, it was noted that the clickfine autoprotect needle (5 mm x 31G) was verified for functional compatibility with the following pens systems :

[Redacted list of pen systems] (b) (4)

However, the Ypsomed Unopen which is the device constituent to be used with palopegteriparatide is not among the list. It is not clear if the Unopen device is compatible with the Clickfine pen needle. IR issued to Sponsor asking them to clarify if the needles were used during their design verification/EPR testing to demonstrate compatibility. If not, we will ask the sponsor to provide compatibility testing. Please refer to section 9.

4.2. Steps for Using the Device



(b) (4)

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

4.3. Device Description Conclusion

DEVICE DESCRIPTION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☐ No ☐ N/A	Mid-Cycle Deficiencies: ☐ Yes ☐ No ☐ N/A	Final Deficiencies: ☐ Yes ☐ No ☐ N/A
<u>Reviewer Comments</u> The Device description provided by the sponsor is sufficient and acceptable. Compatibility of the Unopen with the clickfine needle is not clarified by the sponsor. An IR was sent out on January 4. Please refer to Section 9.2 for details on the IR and the sponsor response.		
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	☐

5.1. Filing Review Checklist

Filing Review Checklist		Present		
Description		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		
Quality Systems/ Manufacturing Controls Check	Description of Device Manufacturing Process	X		
	Description of Quality Systems (Drug cGMP-based, Device QSR-based, Both)	X		
	CAPA Procedure	X		
	Control Strategy provided for EPRs	X		

Reviewer Comment

This application is fileable.

5.2. Facilities Information



(b) (4)



5.3. Quality System Documentation Triage Checklist

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.

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:	
<u>Reviewer Comments</u> This submission is acceptable for filing.	

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 (deferred to DMEPA)		
Electrical Safety Labeling/Symbols			X
EMC Labeling/Symbols			X
Software Version Labeling			X
<u>MRI</u> Labeling/Symbols			X
RF/Wireless Labeling/Symbols			X



Reviewer Comments

The labeling contains all required elements (as listed above) and the instructions for use are acceptable. The labeling is acceptable from a device perspective.

Please note that a human factors evaluation and a detailed review of the step by step instructions for use of the devices is deferred to DMEPA.

6.2. 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
<u>Reviewer Comments</u> The labeling contains all required elements (as listed above) and the instructions for use are acceptable. The labeling is acceptable from a device perspective. Please note that a human factors evaluation and a detailed review of the step by step instructions for use of the devices is deferred to DMEPA.		
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			
Design Inputs/Outputs	Yes	No	N/A
Design requirements / specifications document present (essential performance requirements included)	X		
Design Verification / Validation Attributes	Yes	No	N/A
Validation of essential requirements covered by clinical and human factors testing	X		
To-be-marketed device was used in the pivotal clinical trial		X	
Bioequivalence Study utilized to-be-marketed device		X	
Verification methods relevant to specific use conditions as described in design documents and labeling	X		
Device reliability is acceptable to support the indications for use (i.e. emergency use combination product may require separate reliability study)	X		
Traceability demonstrated for specifications to performance data	X		

Reviewer Comments
 The overall design control process is acceptable. Please see below for a review of the risk analysis that includes a general overview of the design control activities.

7.2. Design Inputs and Outputs

Table 3: Essential Performance Requirements

EPR	Name	Requirement	Acceptance criteria
# 1	Dose accuracy		(b) (4)
# 2	Injection force		
# 3	Torque to set/correct dose		
EPR	Name	Requirement	Acceptance criteria
# 4	Needle gauge		(b) (4)
# 5	Needle length		

ICC2200738-739
NDA 216490 ,Palopegteriparatide
Ascendis Pharma Bone Disease Division, A/S

*** Please see IR sent by CDER to sponsor, requesting for a bracketing approach to demonstrate that all pen injector configurations deliver accurately.

CDER IR dated October 26, 2022

(b) (4)

Reviewer [Comments](#)

[Redacted] (b) (4)

In the dose accuracy for pen functionality testing, at release of commercial batches at [Redacted] (b) (4)

[Redacted] However this control strategy for sampling size seems inadequate. Sponsor should provide a statistical control method strategy for release testing, addressing their chosen sampling size, based on the release lot size, irrespective of the pen presentation. We will add a PMC comment in our feedback for the sponsor. Please refer to Section 2.3.

UPDATE January 27 , 2023 : An informal teleconference was held with the sponsor on 1/19/23 wherein CDER/FDA explained our concerns to the sponsor. Briefly concerns from Clin Pharm review teams involved issues like :- the wide dose variability is bound to lead to dose overlapping and, in some case, excess dose delivery. Additionally, some of the lower proposed doses have not been tested during the clinical trials.

Based on our multidisciplinary discussion with the Applicant (via t-con), the Applicant acknowledged these deficiencies and decided to propose a revised control strategy [Redacted] (b) (4)

[Redacted] (b) (4)

[Redacted] (b) (4)

- Given that the device has a poor dialing resolution of (b) (4) μL , there are no data to indicate that the device can function with the revised (tightened) delivered volume limit of (b) (4) μL . In fact, some phase 2 and phase 3 clinical batches will fail based on these revised limits using the same device. Also, there are no data from registration and stability batches to supports this new strategy.
- It is obvious that with the current product presentation, dosing variability could be as high as [Redacted] (b) (4). Unless the Applicant changes their current device to a new one with better dialing resolution (example: (b) (4)) the risk of dose variability would continue to be significant.
- Therefore, OPQ's Integrated Quality Assessment (IQA) is heading towards a Complete Response (CR) recommendation.

[Redacted] (b) (4)

UPDATE February 3, 2023 : Since the sponsor has not provided any data supporting their revised specification limits, we sent out another IR on 02/03/23.

The FDA has carefully reviewed your revised proposal regarding dosing accuracy (ref: NDA 216490; eCTD# 0044; SDN# 44, dated 1/27/2023). Regarding design verification data in your revised Module 3, dated January 27, 2023, in Section 3.2.R, you state that results from the dose accuracy testing of the three presentations verified that your prefilled pen dispenses the selected dose with a dosing accuracy (USL and LSL specification limits) of (b) (4) μL . While you have provided a summary of the dosing accuracy test results in Table 2, however, we could not find/locate the actual data reports. In addition, we note that your proposal is still not adequate due to the following reasons:

1. The delivered dose is a function of two independent variables: assay and pen functionality. There is a disconnect between the proposed delivered dose specification (target (b) (4) μg) and the proposed dose volume accuracy specification (target (b) (4) μl) for each dose setting and the assay range (b) (4). Therefore, it is unclear how you would meet the delivered dose specification of target (b) (4) μg for your commercial product when a single pen is used, or pens of different lots are used to achieve a higher dose.
2. There still is a significant concern with dose overlapping between the calculated maximum and minimum delivered dose (μg) at each setting.
3. Regarding the design of the pen, the proposed device has a poor dialing resolution of (b) (4) μL , which may not be very suitable to deliver a small dose volume based on your current product presentation. It is obvious that with the current product presentation, dosing variability could be as high as (b) (4). The dosing variability may be best addressed by changing your current device to a new one with better dialing resolution to minimize the risk of dose variability and achieve the desired dose accuracy.

UPDATE February 7, 2023 : Sponsor Ascendis Pharma provided the design verification data results verifying the dose accuracy for the three pen presentations against the (b) (4) μL specification limits are provided in 3.2.R Dose Accuracy Verification.

The sponsor also discusses the approach for addressing the dose variability for the commercial batches: The sponsor modified the pen dose delivered specification to (b) (4). Ascendis provided a summary of the Delivered dose calculation and an example calculation using data from clinical batch ASRI011A.

(b) (4)

(b) (4)

UPDATE February 15 , 2023 : However, the IR response does not include data verifying they are capable of consistently meeting this new specification. Sponsor also states on page 5 of the IR response that they “
[REDACTED] (b) (4)
[REDACTED] (b) (4)
.” This implies that the data are currently unavailable to verify performance to
Please refer to CR deficiency in Section 2.2

7.3. Applicable Standards and Guidance Documents

Sponsor provided this information in 3.2.R DEVICE relevant standards

Generally Applicable Standards and Guidance Documents:

Standard or Guidance	Conformance (Y/N/NA)
AAMI / ANSI / ISO 14971:2019 medical devices - applications of risk management to medical devices	Yes
Standard Practice for Performance Testing of Shipping Containers and Systems; ASTM D4169-16	yes
IEC 60601-1-11	yes
IEC 62366-1:2015 Medical devices – Part 1: Application of usability engineering to medical devices	Yes
ISO 11608-1:2014 Needle-based Injection Systems for Medical Use – Requirements and Test Methods – Part 1: Needle-based Injection Systems	Yes
Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products (2017)	Yes
Mobile Medical Applications Guidance for Industry and Food and Drug Administration Staff (2015)	N/A
Guidance for Industry and FDA Staff – Medical Devices with Sharps Injury Prevention Features (2005)	Yes
Use of International Standard ISO 10993-1: 2018, Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process"	Yes
Applying Human Factors and Usability Engineering to Medical Devices	Yes

Reviewer Comments

Sponsor has identified and defined 5 EPRs as listed above related to the NIS. Dose accuracy, Injection force, and Torque to set/correct dose relate directly to the prefilled pen operation and the performance of an injection. The Needle gauge and length relate to subcutaneous injection and the performance of the needle.

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 <u>Comments</u> Sponsor has declared conformance to ISO 11608-1:2014. Recently ISO 11608-1:2022 was released which cancels and replaces the third edition (ISO 11608-1:2014). However, we are still accepting (with DHT3C management concurrence) 11608-1:2014 through until July 2023. Thus no deficiency will be issued to the sponsor and the sponsor's conformance to 11608-1:2014 is acceptable.		
CDRH sent Design Control Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☐ No		

8. RISK ANALYSIS

8.1. Risk Management Plan



Table 1: Risk Management Responisibilities

Responsible Organization	Deliverable
(b) (4)	

Reviewer Comments

Risk activities are compliant with ISO 14971:2019 Medical Devices – Application of Risk Management to Medical Devices. The benefits of the use of the palopegteriparatide prefilled pen combination product outweigh the contributions of all identified risks; therefore, the overall residual risk is acceptable.

8.2. Hazard Analysis and Risk Summary Report

[Link to Infusion Pump SAC Reviewer Guide](#)

(b) (4)



4 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

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 A systematic and documented risk management process has been applied to the development of the palopegteriparatide prefilled pen. The planned risk management activities defined in the RMP is acceptable.		
CDRH sent Risk Analysis Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☐ No		

9. DESIGN VERIFICATION REVIEW

9.1. Performance/Engineering Verification

25 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

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 Sponsor has not provided compatibility testing of the palopegteriparatide prefilled pen with the intended co-packaged clickfine needle, intended to be used with.		
UPDATE Jan 5, 2023 : Sponsor responded to the issued IR confirming that the verification testing for E PR's (dose accuracy and injection force) were conducted using the device constituent prefilled pen in combination with the Clickfine® Autoprotect™ needle 31Gx5mm. sponsor also provided additional needle compatibility testing report and confirmed that their E PR testing and compatibility testing complies with the requirements per ISO 11608-1 and 11608-2.		
CDRH sent Design Verification Deficiency or Interactive Review Questions to the Sponsor: ☐ Yes ☐ No		
IR sent to sponsor on January 4, 2023		



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

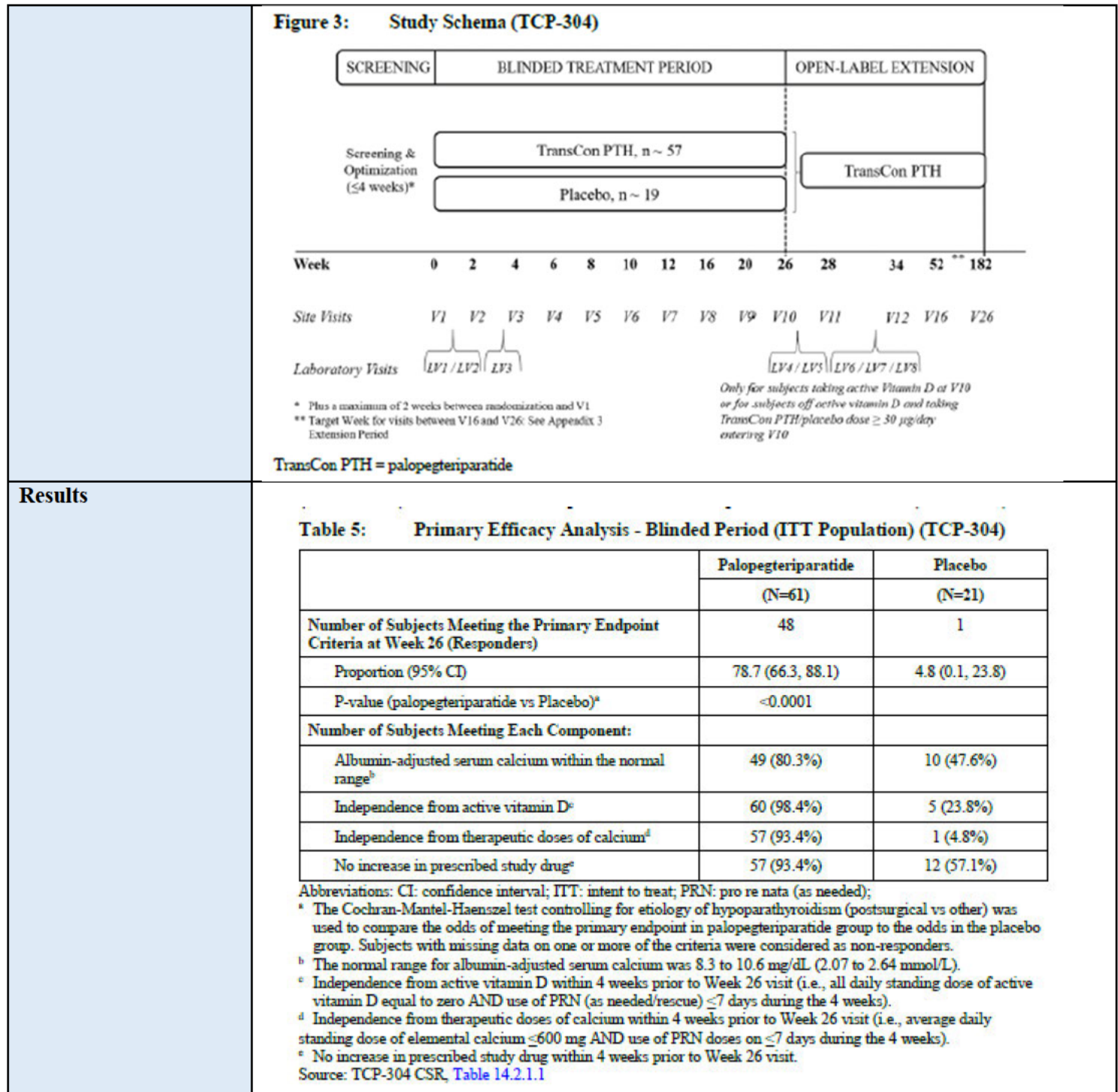
10.1. Review of Clinical Studies Clinical Studies

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

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

Study Name	Pivotal Phase 3 TCP-304 (PaTHway) Trial
Study Type	Ongoing ; The pivotal Phase 3 TCP-304 (PaTHway) trial is ongoing to evaluate the efficacy, safety, tolerability, and quality of life (QoL) of palopegteriparatide in adult patients with hypoparathyroidism. The study is a 26-week multicenter, randomized, double-blind, placebo-controlled study with a 3-year open-label extension.
Objectives/Endpoints	The primary objective of trial TCP-304 was to assess the treatment effect of daily palopegteriparatide on serum calcium levels, and therapeutic doses of active vitamin D (i.e., calcitriol or alfacalcidol) and calcium at 26 weeks of treatment. Efficacy endpoints : At 26 weeks of treatment, the proportion of subjects with: • Albumin-adjusted serum calcium measured within 4 weeks prior to and on the Week 26 visit are within the normal range (8.3-10.6 mg/dL)a; and • Independence from active vitamin Db and

	• Independence from therapeutic doses of calcium (i.e., taking calcium supplements ≤ 600 mg/day)c, and • No increase in prescribed study drug within 4 weeks prior to Week 26 visitd <u>Secondary objectives:</u> • To assess the safety and tolerability of daily palopegteriparatide • To assess the treatment effect of daily palopegteriparatide on HPES and Short Form-36 (SF-36) domain scores • To assess the treatment effect of daily palopegteriparatide on PD markers (including serum calcium) and active vitamin D and calcium doses • To assess the treatment effect of daily palopegteriparatide on serum phosphate, serum calcium$\times$serum phosphate (albumin-adjusted serum calcium$\times$serum phosphate product), and serum magnesium • To assess anti-PTH, anti-palopegteriparatide and anti- PEG antibody responses • To assess the treatment effect during the Extension Period • To assess the treatment effect of daily palopegteriparatide on: – BMD and TBS by DXA – Bone turnover markers (serum P1NP and CTx) • To assess the effect of treatment on patient-reported health-related quality of life (HRQoL) and a clinician reported outcome assessment
Drug/Device Studied	Palopegteriparatide
Number and Type of Subjects	61 subjects Subjects were male and female, ≥ 18 years of age with postsurgical chronic hypoparathyroidism, or autoimmune, genetic, or idiopathic hypoparathyroidism for at least 26 weeks; treated with either calcitriol ≥ 0.5 $\mu\text{g}/\text{day}$ or alfacalcidol ≥ 1.0 $\mu\text{g}/\text{day}$ and elemental calcium ≥ 800 mg/day for at least 12 weeks prior to Screening; and a 24-hour urine calcium excretion ≥ 125 mg/24 h. Diagnosis of hypoparathyroidism was established based on a history of hypocalcemia in the setting of inappropriately low serum PTH levels.
Brief description of protocol	The trial consisted of: • Screening Period (supplement optimization): Up to approximately 4 weeks (plus a maximum of 2 weeks between randomization and Visit 1) • Blinded Treatment Period (study drug and optimization of conventional therapy): 26 weeks • Extension Period (open-label palopegteriparatide treatment): 156 weeks Subjects were randomized in a 3:1 ratio into 2 treatment groups: • Palopegteriparatide 18 $\mu\text{g}/\text{day}$*, co-administered with conventional therapy • Placebo for palopegteriparatide (excipient solution) 18 $\mu\text{g}/\text{day}$, co-administered with conventional therapy <i>*Dose of palopegteriparatide refers to dose of PTH(1-34) administered</i>



10.2. Clinical Validation Review Conclusion

CLINICAL VALIDATION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☐ No ☐ N/A	Mid-Cycle Deficiencies: ☐ Yes ☐ No ☐ N/A	Final Deficiencies: ☐ Yes ☐ No ☐ N/A
Reviewer Comments		

CDRH sent Clinical Validation Deficiencies or Interactive Review Questions to the Sponsor: Yes No

11. HUMAN FACTORS VALIDATION REVIEW

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

12. FACILITIES & QUALITY SYSTEMS

12.1. Facility Inspection Report Review

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

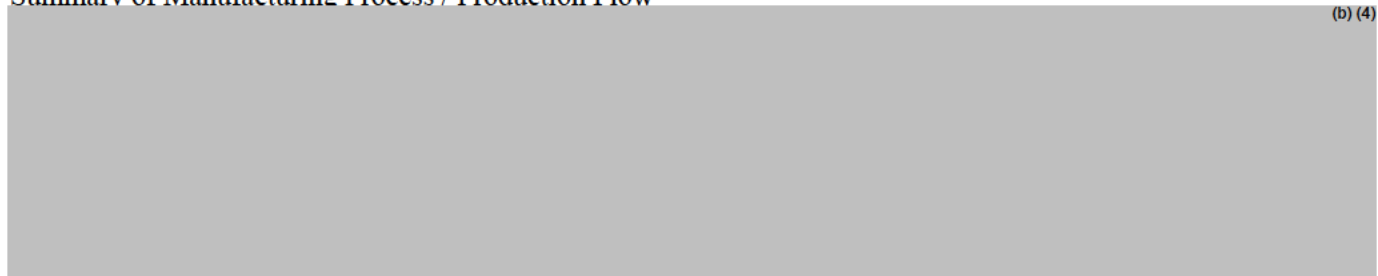
12.2. Quality Systems Documentation Review

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

(b) (4)



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

Reviewer Comments

The Sponsor provided a full description of the drug and device manufacturing processes. This is acceptable.

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

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**)

Sponsor declares in 3.2.R DEVICE Quality systems Regulations summary :

Ascendis Pharma has implemented a quality management system (QMS) that applies to all Ascendis Pharma personnel and sites. The QMS complies with the following US regulations:

- *21 CFR Part 210, Current Good Manufacturing Practice in Manufacturing Processing, packing, or Holding of Drugs*

- 21 CFR Part 211, Current Good Manufacturing Practice for Finished Pharmaceuticals.
- 21 CFR Part 4, Regulation of Combination Products (subpart A: cGMP, Subpart B: PMSR for combination products)

21 CFR 820.20 Summary of Management Responsibility	Firm(s): Ascendis Pharma	(b) (4)
21 CFR 820.30 Summary of Design Controls	Firm(s): Ascendis Pharma	
21 CFR 820.50 Summary of Purchasing Controls	Firm(s): Ascendis Pharma	
21 CFR 820.100 Summary of Corrective and Preventive Actions	Firm(s): Ascendis Pharma	Reviewer Discussion – Reviewed in Section 12.2.3 .
21 CFR 820.170 Summary of Installation	Firm(s):	Reviewer Discussion – N/A

21 CFR 820.200 Summary Servicing	Firm(s):	Reviewer Discussion – N/A
Subpart F – Identification and Traceability	Firm(s):	Reviewer Discussion – N/A
Subpart G – Production and Process Controls	Firm(s):	Reviewer Discussion – Reviewed in Section 12.3
Subpart H – Acceptance Activities	Firm(s):	Reviewer Discussion – N/A
Subpart I – Nonconforming Product	Firm(s):	Reviewer Discussion – N/A

Reviewer Comments

To comply with the quality system requirements of 21 CFR Part 4, the firms have established a streamlined drug cGMP quality system. The streamlined quality system complies with the drug cGMPs (21 CFR 210 & 211) in addition to the applicable sections of the medical device quality system regulation (21 CFR 820). The applicable sections of the QSR as specified in 21 CFR 4.4(b)(1) include the following:

- 21 CFR 820.20 Management Responsibility
- 21 CFR 820.30 Design Controls
- 21 CFR 820.50 Purchasing Controls
- 21 CFR 820.100 Corrective and Preventive Actions (CAPA)

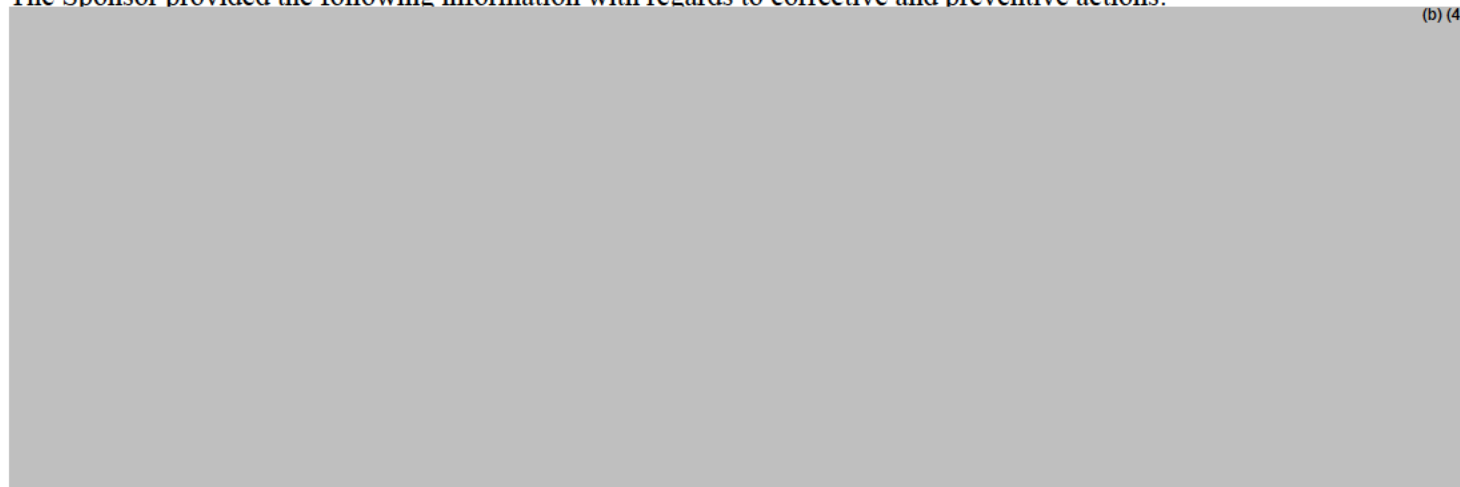
All sites are in compliance with current Good Manufacturing Practices (cGMP).

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

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



(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:

Essential Performance Requirements Control Strategy Table

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

Control Strategy Conclusion		
The Sponsor provided adequate information to support the manufacturing control activities for the essential performance requirements of the combination product.	☒ 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		
CDRH sent Facilities & QS Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☐ No		

<<END OF REVIEW>>

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/

NOWRIN S KAKON
02/23/2023 12:58:03 PM
CDRH review is uploaded on behalf of CDRH assessors.

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/

AKM KHAIRUZZAMAN

03/17/2023 02:16:11 PM

This NDA is recommended for a Complete Response (CR) from CMC and Drug Device perspective

MOHAN K SAPRU

03/17/2023 02:48:23 PM