DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 761047

BLA APPROVAL

Ultragenyx Pharmaceutical Inc.
Attention: Min Chen Young, Ph.D., RAC
Associate Director, Regulatory Affairs
60 Leveroni Court
Novato, CA 94949

Dear Dr. Young:

Please refer to your Biologics License Application (BLA) dated March 16, 2017, received March 16, 2017, submitted under section 351(a) of the Public Health Service Act for Mepsevii (vestronidase alfa-vjbk) injection, for intravenous use.

LICENSING

We are issuing Department of Health and Human Services U.S. License No. 2040 to Ultragenyx Pharmaceutical Inc., Novato, California, under the provisions of section 351(a) of the Public Health Service Act controlling the manufacture and sale of biological products. The license authorizes you to introduce or deliver for introduction into interstate commerce, those products for which your company has demonstrated compliance with establishment and product standards.

Under this license, you are authorized to manufacture the product Mepsevii (vestronidase alfa-vjbk). Mepsevii (vestronidase alfa-vjbk) is indicated in pediatric and adult patients for the treatment of Mucopolysaccharidosis type VII (MPS VII, Sly syndrome).

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture vestronidase alfa-vjbk at your facility at Rentschler Biopharma SE, Laupheim, Germany. You may label your product with the proprietary name, Mepsevii, and will market it in 10 mg/5 mL (2 mg/mL) single-dose vials.

DATING PERIOD

The dating period for Mepsevii (vestronidase alfa-vjbk) shall be 24 months from the date of manufacture when stored at 2-8°C. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product. The dating period for your drug substance shall be (b) (4) months from the date of manufacture when stored at (b) (4).

Results of ongoing stability should be submitted throughout the dating period, as they become available, including the results of stability studies from the first three production lots.

We have approved the stability protocols in your license application for the purpose of extending the expiration dating period of your drug substance and drug product under 21 CFR 601.12.

FDA LOT RELEASE

You are not currently required to submit samples of future lots of product Mepsevii (vestronidase alfa-vjbk) to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1, requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

Any changes in the manufacturing, testing, packaging, or labeling of Mepsevii (vestronidase alfa-vjbk), or in the manufacturing facilities, will require the submission of information to your biologics license application for our review and written approval, consistent with 21 CFR 601.12.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text and with the minor editorial revisions indicated in the enclosed labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 601.14(b)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to, except with the revisions indicated, the enclosed labeling (text for the package insert). Information on submitting SPL files using eLIST may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As” at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels submitted on August 22, 2017, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format —*

Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (May 2015, Revision 3). For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved BLA 761047**." Approval of this submission by FDA is not required before the labeling is used.

RARE PEDIATRIC DISEASE PRIORITY REVIEW VOUCHER

We also inform you that you have been granted a rare pediatric disease priority review voucher, as provided under section 529 of the Federal Food, Drug, and Cosmetic Act (FDCA). This priority review voucher (PRV) has been assigned a tracking number, PRV BLA 761047. All correspondences related to this voucher should refer to this tracking number.

This voucher entitles you to designate a single human drug application submitted under section 505(b)(l) of the FDCA or a single biologic application submitted under section 351 of the Public Health Service Act as qualifying for a priority review. Such an application would not have to meet any other requirements for a priority review. The list below describes the sponsor responsibilities and the parameters for using and transferring a rare pediatric disease priority review voucher.

- The sponsor who redeems the priority review voucher must notify FDA of its intent to submit an application with a priority review voucher at least 90 days before submission of the application, and must include the date the sponsor intends to submit the application. This notification should be prominently marked, "Notification of Intent to Submit an Application with a Rare Pediatric Disease Priority Review Voucher."
- This priority review voucher may be transferred, including by sale, by you to another sponsor of a human drug or biologic application. There is no limit on the number of times that the priority review voucher may be transferred, but each person to whom the priority review voucher is transferred must notify FDA of the change in ownership of the voucher not later than 30 days after the transfer. If you retain and redeem this priority review voucher, you should refer to this letter as an official record of the voucher. If the priority review voucher is transferred, the sponsor to whom the priority review voucher has been transferred should include a copy of this letter (which will be posted on our Web site as are all approval letters) and proof that the priority review voucher was transferred.
- FDA may revoke the priority review voucher if the rare pediatric disease product for which the priority review voucher was awarded is not marketed in the U.S. within 1 year following the date of approval.
- The sponsor of an approved rare pediatric disease product application who is awarded a priority review voucher must submit a report to FDA no later than 5 years after approval that addresses, for each of the first 4 post-approval years:
  - the estimated population in the U.S. suffering from the rare pediatric disease for which the product was approved (both the entire population and the population aged 0 through 18 years),
  - the estimated demand in the U.S. for the product, and
  - the actual amount of product distributed in the U.S.

- You may also review the requirements related to this program at http://www.gpo.gov/fdsys/pkg/PLAW-112publ144/pdf/PLAW-112publ144.pdf1 (see Section 908 of FDASIA on pages 1094-1098 which amends the FDCA by adding Section 529). Formal guidance about this program will be published in the future.

ADVISORY COMMITTEE

Your application for Mepsevii (vestronidase alfa-vjbk) was not referred to an FDA advisory committee because the application did not raise significant public health questions on the role of the biologic in the diagnosis, cure, mitigation, treatment, or prevention of a disease.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the known risk of serious hypersensitivity reactions, including anaphylaxis, with use of Mepsevii (vestronidase alfa-vjbk), and to identify an unexpected long-term risk of immunogenicity, and a serious risk of pre- and post-natal developmental adverse effects.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following studies:

3271-1 A prospective, longitudinal study (Study UX003-CL401) to assess the long-term risk of immunogenicity and the risk of serious hypersensitivity reactions, including anaphylaxis, in patients with mucopolysaccharidosis type VII (MPS VII) followed for three years on Mepsevii (vestronidase alfa-vjbk). The following information will be collected and analyzed: (1) incidence rates for serious hypersensitivity reactions, (2) incidence rates for the appearance of anti-drug

antibodies (ADA) and neutralizing antibodies (Nab) against Mepsevii (vestronidase alfa-vjbk), (3) temporal associations between ADA or Nab formation and serious hypersensitivity reactions, (4) associations between beta-glucuronidase (GUSB) genotype and serious hypersensitivity reaction risk, (5) associations between intrinsic GUSB enzymatic activity and serious hypersensitivity reaction risk, and (6) assessments of the risk of immunogenicity on clinical safety outcomes. To complete these analyses, protocol UX003-CL401 will require collection of molecular genotype and intrinsic GUSB enzymatic activity (apart from any concurrent enzyme replacement). Submit annual study reports that contain results from analyses of interim data. The final study report will be based on a study population that contains at least 12 new patients (including at least six patients less than one year old) treated with Mepsevii (vestronidase alfa-vjbk) and enrolled in Study UX003-CL401.

The timetable you submitted on November 1, 2017, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	12/2017
Final Protocol Submission:	04/2018
Annual Report Submission:	01/2019
Annual Report Submission:	01/2020
Annual Report Submission:	01/2021
Annual Report Submission:	01/2022
Annual Report Submission:	01/2023
Annual Report Submission:	01/2024
Annual Report Submission:	01/2025
Study Completion:	04/2025
Annual Report Submission:	01/2026
Final Report Submission:	05/2026

3271-2 A pre- and post-natal developmental study in rats to assess the effects of Mepsevii (vestronidase alfa-vjbk) on pre- and post-natal development. The study should be designed to detect adverse effects on the pregnant/lactating female rat and on the development of conceptus and offspring from implantation through weaning. The dose levels used in the pre- and post-natal developmental study should provide adequate margins of exposure for the clinical dose.

The timetable you submitted on November 1, 2017, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	12/2017
Final Protocol Submission:	02/2018
Study Completion:	03/2019
Final Report Submission:	07/2019

Submit clinical protocol(s) to your IND 123788 with a cross-reference letter to this BLA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your BLA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: "**Required Postmarketing Protocol Under 505(o)**," "**Required Postmarketing Final Report Under 505(o)**," or "**Required Postmarketing Correspondence Under 505(o)**.**"**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 601.70 requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 601.70. We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

3271-3 In MPS VII patients enrolled in the prospective, longitudinal Study UX003-CL401 (PMR-1), to collect and analyze: (1) beta-glucuronidase (GUSB) genotype, (2) in patients without a history of Mepsevii (vestronidase alfa-vjbk) treatment, baseline intrinsic GUSB enzymatic activity apart from any concurrent enzyme replacement treatment, (3) a complete record of treatments with Mepsevii (vestronidase alfa-vjbk) pre- and post-UX003-CL401 enrollment, and (4) results from baseline and periodic tests for MPS VII clinical outcomes to include liver and spleen size measurement, pulmonary function, motor function, and neurocognitive function.

The timetable you submitted on November 1, 2017, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	12/2017
Final Protocol Submission:	04/2018
Study Completion:	04/2032
Final Report Submission:	05/2033

3271-4 To conduct studies to address the bioanalytical method validation of the assay used to measure the pharmacodynamic marker glycosaminoglycans, the Liquid Chromatography Tandem Mass Spectrometry (LC-MS/MS) method (b) (4) (b) (4). Specifically, perform incurred sample reanalysis (ISR) for samples from Study UX003-CL301, and ongoing studies UX003-CL203 and Study UX003-CL202. Complete the ongoing assessment of long-term sample storage stability and conduct a 2nd long-term sample storage stability assessment to cover the storage duration of all study samples from clinical trials. Use freshly prepared calibrator standards in conducting the ISR for samples from UX003-CL203 and UX003-CL202 and the 2nd long-term sample storage stability analysis.

The timetable you submitted on November 1, 2017, states that you will conduct these studies according to the following schedule:

ISR for samples from UX003-CL301:

Draft Protocol Submission:	11/2017
Final Protocol Submission:	12/2017
Study Completion:	01/2018
Report Submission:	02/2018

ISR for samples from ongoing studies UX003-CL203 and UX003-CL202:

Draft Protocol Submission:	03/2018
Final Protocol Submission:	05/2018
Study Completion:	10/2018
Report Submission:	12/2018

Ongoing long-term sample storage stability study:

Study Completion:	06/2018
Report Submission:	08/2018

2nd long-term sample storage stability study:

Draft Protocol Submission:	02/2018
Final Protocol Submission:	04/2018
Study Completion:	06/2020
Final Report Submission:	08/2020

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

3271-5 To conduct the bioburden and endotoxin method qualification to include a total of three lots of the following Mepsevii (vestronidase alfa-vjbk) drug substance (b) (4) (b) (4)

The timetable you submitted on November 1, 2017, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/2019

3271-6 To repeat the rabbit pyrogen test with three Mepsevii (vestronidase alfa-vjbk) drug product lots at the maximum human equivalent dose of 4 mg/kg. Provide summary data and study report.

The timetable you submitted on November 9, 2017, states that you will conduct this study according to the following schedule:

Final Report Submission: 03/2018

3271-7 To re-evaluate all Mepsevii (vestronidase alfa-vjbk) drug substance and drug product release and stability acceptance criteria when a statistically significant number of lots (25) of drug substance have been manufactured using the commercial manufacturing process and tested using commercial specifications. The corresponding data, the analytical and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided in the final study report.

The timetable you submitted on November 1, 2017, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/2035

3271-8 To perform a leachable study to evaluate leachables in the Mepsevii (vestronidase alfa-vjbk) drug product container closure system. The analysis will be performed using one drug product lot that has passed the end of shelf-life under the long term (5 ± 3 °C) and accelerated (25°C/60% RH) storage conditions. Appropriate methods will be used to detect, identify, and quantify organic non-volatile, volatile and semi-volatile species, and metals. Complete data and the risk evaluation for potential impact of leachables on product safety and quality will be provided in the final study report.

The timetable you submitted on November 1, 2017, states that you will conduct this study according to the following schedule:

Final Report Submission: 01/2019

Submit clinical protocols to your IND 123788 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should

include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

We acknowledge receipt of your submission dated March 16, 2017, of a proposed risk evaluation and mitigation strategy (REMS). We have determined that, at this time, a REMS is not necessary for Mepsevii (vestronidase alfa-vjbk) to ensure that its benefits outweigh its risks. We will notify you if we become aware of new safety information and make a determination that a REMS is necessary.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 601.12(f)(4), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80). You should submit postmarketing adverse experience reports to:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

You must submit distribution reports under the distribution reporting requirements for licensed biological products (21 CFR 600.81).

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, that may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA-3486 to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
5901-B Ammendale Road
Beltsville, MD 20705-1266

Biological product deviations, sent by courier or overnight mail, should be addressed to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
10903 New Hampshire Avenue, Bldg. 51, Room 4206
Silver Spring, MD 20903

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from

improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Jenny Doan, Regulatory Project Manager, at (301) 796-1023.

Sincerely,

{See appended electronic signature page}

Julie Beitz, MD
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling
Carton and Container Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JULIE G BEITZ
11/15/2017