Proteus Syndrome - FDA-Requested Listening Session

December 1, 2022

Objectives of Session

To gain a better understanding of the experiences living with Proteus syndrome, including the manifestations and corresponding symptoms that are most burdensome for patients and how they are currently managing the symptoms. FDA organized this listening session in order to gain a better understanding of experiences of patients living with Proteus syndrome and their caregivers, including manifestations and corresponding symptoms and patients' perceptions about participating.

Discussions in FDA Listening Sessions are informal and not meant to replace, but rather complement, existing patient engagement opportunities in the Agency. All opinions, recommendations, and proposals are unofficial and nonbinding on FDA and all other participants. This report summarizes the input provided by persons from the Proteus syndrome community at the meeting. To the extent possible, the terms used in this summary describe the health needs, perspectives, preferences, and impacts reflect those of the individual participants. This report is not meant to be representative of the views and experiences of the entire Proteus syndrome population or any specific group of individuals or entities. There may be experiences that are not mentioned in this report.

Summary of Discussion by Question

<u>Round 1: Symptoms</u>

1. **Of all the different Proteus syndrome symptoms that you/your loved one experiences, can you tell us which 1-2 symptom(s) are the most problematic or has the greatest impact on your/your loved one's life?**
    a. **How has that symptom(s) impacted your/your loved one's life?**
        - Five participants shared that the most problematic symptom for their loved ones is bone overgrowth.
            - Of those five, one participant specified craniofacial overgrowth as the main concern. Three participants said overgrowth in the legs causing leg-length discrepancy. Another caregiver mentioned overgrowth in the bone.
        - One caregiver shared that their child's most problematic symptom is delays in cognitive development causing problems with their speech and ability to understand.
        - Two participants said that the symptoms of Proteus syndrome have led to their child's knees being unable to bend causing issues with mobility.
        - Another parent said that bone overgrowth in the face could lead to issues in their child's social life (e.g., difficulty with peer relationships, bullying) as they reach adolescence.
        - Two participants noted that Proteus syndrome has led to several surgeries including, but not limited to, surgery to fix dysmetria in the legs, surgery of the ear canal to prevent hearing loss, and dermatological surgeries.
        - One participant mentioned chronic blood clots as a symptom of their child's Proteus syndrome.
        - Two participants mentioned CCTNs (cerebriform connective tissue nevi) as a problematic symptom for their children.

2. **When thinking about the most problematic or burdensome symptom(s) you/your loved one experiences, can you describe what improvement might look like to you/your child?**

- Three caregivers said that a slowing of bone growth would be the most important improvement for their child at the moment.
- Two participants stated that improving their child's mobility would be the most important.
- One parent said that an improvement in their child's ability to speak and express themself would be the most impactful development.

3. **As you think about your/your loved one's daily life, what would you consider to be a significant or meaningful improvement to your/your child's quality of life (such as looking or feeling a certain way) that currently is not being addressed?**
    - Four of the parents participating said that an improvement in their child's confidence and social skills would be the most meaningful. They all noted that overgrowth caused by Proteus syndrome has impacted their child's confidence in social settings.
    - One caregiver noted that their child would see an improvement in quality of life if they had more support from their government as it relates to kids with special needs.
    - Another participant reiterated that mobility would be the most meaningful improvement to their child's quality of life.
    - Several parents voiced concern about their child's ability to live a "normal" life living with Proteus syndrome as they are forced to deal with life-long symptoms and trips to the doctor.
    - One parent noted that improvement in her child would be slowed or reversal of growth of CCTN as well as less pain and less odor of the CCTN.

4. **How have your/your loved one's condition and symptoms changed over time?**
    - Five of the six participants noted that their child's symptoms have gotten worse over time.
        - One parent pointed out that their child's symptoms have worsened during puberty.
        - Another parent mentioned that their child initially had delays in speech development, but they now speak normally without needing to use sign language.
    - One caregiver shared that they have seen an emergence of new bone growth that hadn't appear on imaging, but other than that, their child hasn't experienced a significant change in symptoms.
    - Four participants expressed hope that their child's participation in a clinical trial will allow access to a drug that will slow, or stop, growth.

5. **Follow up from CDER's Division of Oncology II: For the patients and caregivers that had different bone and tissue growths with CCTN, did the symptoms worsen when they went through adolescence and puberty?**
    - Two of the participants mentioned that overgrowth (both bone and CCTN) worsened with puberty.
        - One caregiver shared that they asked other parents at a conference for Proteus syndrome and heard from five to six others that had experienced worsening of growth with puberty.
    - One participant said that their child hasn't seen any reduction to the CCTN, but their doctor has described it as deflating. They are hoping that the drug from a clinical trial is helping keep the CCTN less thick and puffy.
    - Only three participants responded to this follow up question.

6. **Follow up from CDER's Division of Oncology II: For the CCTN, how long after surgery did you see regrowth?**
    - One parent said that their child's CCTN was removed at age 17 and regrowth began two years after surgery. The regrowth was much slower than the original growth. Their child is in their mid-20s now and has seen growth of the CCTN within the last month.
    - Only one participant responded to this follow up question.

7. **Follow up from CDER's Division of Oncology II: Was there a reason for waiting to remove the CCTN?**
    - One caregiver shared that a healthcare provider from NIH advised against removing CCTNs right away and told them that other patients who underwent removal of a CCTN from the feet had become immobile. Unfortunately, the growth of the CCTN become so burdensome (physically and financially) that the patient eventually opted for surgery at age 17. To ensure the best chance at success, the caregiver and patient sought out opinions from multiple doctors and made sure to work with physicians known for their success with skin grafts.
    - Only one participant responded to this follow up question.

<u>Round 2: Perspectives about Clinical Trials</u>

8. **Would you participate in a randomized clinical trial, given there is a possibility that you/your child may receive the placebo, and can you explain why or why not?**
    - Two participants said that they would not want their child to participate in a clinical trial in which there is a chance for a placebo.
        - One parent said that their financial and time commitments needed to help their child live their best life with Proteus is the reason why they wouldn't want to take a chance at receiving a placebo.
        - Another caregiver said their child is at the age in their life where they need a job and health insurance. It would be too much of a risk to take off work and potentially lose benefits if there was a chance of receiving a placebo.
    - Two parents said they might consider enrolling their child in a clinical trial with the chance of a receiving a placebo. They would only take the chance after considering the potential benefits of the drug.
    - One parent said they originally answered no to this question, but after considering the impact the results of a clinical trial could have on Proteus syndrome research, they decided they would be open to their child participating in a clinical trial with a placebo.
    - Another parent said their child is currently enrolled in a trial at NIH, and if a clinical trial with a placebo was conducted through NIH, they would consider it for their child.

9. **Follow up from CDER's Division of Oncology II: We recognize that participating in a clinical trial is time consuming with other medical care. Sometimes in a randomized trial, there is an opportunity for someone to receive a placebo and then cross over to receive the test drug. If there was an option to cross-over, would that change your mind?**
    - One parent said that they would participate in a clinical trial if there was an opportunity to cross-over from placebo to the test drug.

- Another caregiver stated that they still would not participate in a trial with a placebo even if there was a chance for cross-over. Their child doesn't have the stamina to keep up with the arduous schedule of a clinical trial, and they would have to travel long distances.
- Only two participants responded to this follow up question.

10. **Follow up from CDER's Division of Oncology II: Is there a way to make clinical trials less burdensome, such as participating at a local facility?**
    - One parent said that opportunities to participate in clinical trials at local facilities would make participating in clinical trials less burdensome. Their child would be more likely to participate if travel was not an issue.
    - Another parent shared that their child is at an age where they are trying to secure employment, and as a result, would only participate in clinical trials that were available locally and didn't use a placebo.
    - Only two participants responded to this follow up question.

<u>Round 3: Optional (*time dependent)*</u>

11. **Is there anything else you would like to share with FDA about your healthcare concerns and needs?**
    - One participant shared that they have many things they'd like to share with FDA, but they believe other parents in the session touched on similar topics.
    - Another parent suggested THC as an opportunity for more investment and research as it relates to pain relief and neurological effects (both positive and negative). They also said that they hope Patient Listening Sessions will help lead to creative approaches to support members of rare disease communities such as facility locations, a no placebo consortium within a study, etc.
    - This question was not asked during the Listening Session due to time constraints, and the responses above were provided in writing after the session had ended. Only two participants responded to this question via written response.

FDA Offices & Divisions in Attendance

- Office of the Commissioner
    - Patient Affairs *(organizer)*
    - Attendees: Office of Combination Products; Office of Orphan Products Development; Oncology Center of Excellence (requestor)
- Center for Biologics Evaluation and Research (CBER)
    - Attendees: Office of the Center Director (OCD); Office of Tissues and Advanced Therapies, Division of Clinical Evaluation and Pharmacology/Toxicology (DCEPT); Office of Tissues and Advanced Therapies, Division of Clinical Evaluation and Pharmacology/Toxicology, General Medicine Branch 1 (GMB1)

- Center for Drug Evaluation and Research (CDER)
    - Office of New Drugs, Office of Oncologic Diseases, Division of Oncology II *(requestor)*
    - Attendees: Office of New Drugs, Office of Immunology and Inflammation, Division of Dermatology and Dentistry (DDD); Office of New Drugs, Office of Rare Diseases, Pediatrics, Urology & Reproductive Medicine, Division of Rare Diseases and Medical Genetics (DRDMG); Office of Translational Sciences, Office of Biostatistics, Division of Biometrics V (DBV)
- CDRH
    - Attendees: Office of Strategic Partnerships and Technology Innovation/Division of All Hazards Response, Science and Strategic Partnerships (DAHRSSP); Office of Product Evaluation and Quality, Division of Health Technology III C (DHTIIIC)

Non-FDA Attendees

- Reagan-Udall Foundation for the FDA
- National Organization for Rare Disorders

Participants Represented

- Six participants participated in this session.
- All participants in this session were parents to children with Proteus syndrome.
- Participants in this session were caregivers to children with Proteus syndrome aged 5-26.
- Participants in this session represented multiple countries across three continents.

Prior to the Listening Session, Participants Shared

- A majority of participants are currently enrolled in a clinical trial.
- A majority of participants shared that their child suffers from limb or bone growth because of Proteus syndrome.

Financial Interest

Participants did not identify financial interests relevant to this meeting and are not receiving compensation for participation in this listening session.