Achondroplasia Conference: Expert Panel Q&A for VOXZOGO

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*Questions compiled and written by Victoria Garcia, RN.
(I am not a physician and the information provided below is my best understanding of the medical data presented at the conference. It is not intended to treat or give medical advice. I do not give my permission for the information below to be edited.)

Questions:

Pharmokinetics of VOXZOGO

1. In regards to feedback regulation of CNP with Voxzogo/Vosoritide, can you describe what was seen in the trials and how often were antibodies tested for? If a child test positive for drug resistant antibodies how does that affect their treatment? As a parent, should we request a neutralizing antibody screening and how often?
    a. A biologic is a biopharmaceutical derived from biological sources. Essentially, all injected biologics will create some type of drug antibody. This data was collected and looked at during trial periods. The important types of antibodies to look for are called Neutralizing Antibodies. Even if a "Drug Resistant Antibody" is found, it does not necessarily mean that it is affecting the therapeutics of the drug. During trial periods, **no Neutralizing Antibodies** were detected. Neutralizing antibodies are the ones that can affect treatment results. Due to this, the experts on the panel agreed that it is not recommended or required to draw antibody tests for treatment with Voxzogo.

2. How long does the CNP molecule saturate the NPRB receptor? How long is CNP attached and working in the specific receptor? Is this important in regards to how often parents are rotating injection site? For example, if a child is only rotating legs for injections, is 24 hours between injection sites going to be long enough for the clearance of the CNP molecule from the receptor site before injecting that area again?
    a. Natural CNP in the body attaches and causes a response in the receptor within 2 minutes. With CNP provided from Voxzogo, the clearance time of the receptor is around 20 minutes. The experts encouraged rotation of all given injection sites.

3. For injection sites, how important is it to rotate all given injection sites?
    a. Both Biomarin representatives and expert panel agree that all sites should be rotated as instructed. Also, injection site in the same area should be spaced out by an inch or two from the last time the area was injected. For example, the site of injection in the arm should be spaced at least an inch or two from the exact

point of injection the last time that particular arm was injected. This is important because it can prevent site atrophy or scarring of subcutaneous tissues after years of injections, which could potentially affect absorption.

4. Are there any theories as to why some children respond excellently vs others who report that they are not seeing the same type of response?
    a. (See Voxzogo presentation by Dr. Ravi that I will post soon. He discusses response rates amongst age groups.) The experts did agree that with all medications you will see some clients with whom the medication works excellently for and others that do not have the same efficacy. The experts were unable at this time to give a definitive answer as to what causes this. It could be genetic component or other factors etc. Experts stated that more data throughout the years will be needed to investigate this and researched further.

5. Can you explain what causes a larger than average head circumference in children with achondroplasia? If it is due to a dysregulation between endochondral and intramembranous ossification, could this be reduced with the increased endochondral bone growth seen from treatment with Voxzogo. Could reducing the dysregulation in-turn reduce head circumference and potentially improve balance and motor development for younger children?
    a. There are several reasons for larger than average head circumference in achondroplasia. Yes, the dysregulation between endochondral and intramembranous ossification contributes to head size. When Endochondral ossification is turned down, intramembranous ossification can gear up in response, causing a larger skull. FGFR3 is also expressed in the brain and ventricles of children with achondroplasia. Their brain is larger than children without achondroplasia so the skull must accommodate this. FGFR3 affects ventricular and venous sinus spaces of the skull, which can then cause a back pressure in the brain and contribute to conditions such as hydrocephalus and increases in ventricular size. All of these are contributing factors that cause a larger than average head size. If we are correcting dysregulation of ossification we could potentially see improvements to balance, coordination, and motor milestones that are directly affected by head size. Improvements to contributing factors of hydrocephalus and foramen magnum compression are seen when endochondral bone growth is improved early enough.

6. Are there risks associated with giving CNP for several years then discontinuing therapy? Once growth plate closure happens, does the therapy have to be tapered down over time or can one simply withdraw treatment?
    a. There are no risks associated with stopping treatment. If one decides to stop treatment at any time they may. Once full therapeutic treatment is reach at growth plate closure the medication is discontinued.

7. In regards to Voxzogo, can you describe what is being reported clinically with increased appetite and weight gain? Weight gain and obesity can be a complication for individuals with achondroplasia. Does voxzogo increase the risk of obesity or is the increase in appetite a direct result of the increased caloric need from bone growth happening with Voxzogo?
    a. Dr. Ravi states that he is currently constructing a published article that will go into depth about this exact question. He did state that he will provide me with the link for the article. As soon as I read the article and gain a full understanding of it I will write up a description and share the article with the group.

8. What is the dosage being used for the 0-2 year old category in the collected data for the current trials?
    a. The data being collected on the 0-2 year old age group is the 30mcg/kg/day dosing.

9. Is there a possibility of combining therapies that work by different actions in the future?
    a. This will be looked at as more therapies become available. Drug interactions must be investigated. There is the possibility that a patient could potentially combine different therapies. Currently, there are some patients combining Voxzogo with their limb lengthening treatments.

10. Do certain age groups have more growth than other age groups? Could the older children in the studies have affected the overall results of seen for the group?
    a. Yes, age does affect results seen. Different aged cohorts had different annual growth. For the purpose of the trials, children ages ranged from 5-16. The results are based on these cohorts. (In Dr. Ravi's presentation I will breakdown the different age groups and growth seen. He has some really good charts that organize the data and growth seen for each cohort)

Barriers to treatment with VOXZOGO:

11. If Voxzogo is the standard of care for medical intervention will it preclude future clients from the other drug trials? Typically, when joining a trial they put stipulations around who can be accepted into the trial. If we are currently treating with Voxzogo will this eliminate the options of being considered for future trials of upcoming drugs?
    a. Trials are fashioned around the natural progression of disorders and treatments. Due to Voxzogo being the first approved drug and many choosing this treatment, this could affect how future trials are conducted. It does not automatically preclude a patient from being accepted into a trial. Drug companies for future trials will take note of the current market and may require things like a 6 month wash up period from current treatments. They may have more flexible criteria.

12. What is the process of getting the drug in other countries where it is not currently available?
    a. There are many variables that affect availability for countries. Every country has a type of medical agency/FDA. The drug must be accepted by the agency, there must be a demand for the drug, cost efficient, etc. (From what I understood, there isn't really a way to answer this question directly without looking into each country's process for drug approval)

13. On October 23rd, is the expansion of the drug being presenting to the FDA in the USA for ages 0 through growth plate closure, or for ages 2 through growth plate closure?
    a. The label expansion filed for October 23rd, 2023 is for approval for ages 0-5. If approved, there would no longer be a lower age restriction for Voxzogo. Everyone is hopeful for the expansion.

14. Will the cost of Voxzogo come down eventually?
    a. The longer a drug is around, the more the cost decreases over time. There is no definite answer as to when or how much that will be.

15. Will Voxzogo be available for other forms of skeletal dysplasia that the same mechanism of action would be beneficiary?
    a. Currently, multiple new drugs are being researched, including Voxzogo, to look at other forms of skeletal dysplasia for treatment. Hypochondroplasia is on the list of those being investigated. (I will discuss this more in-depth when I post the presentation notes. They did list types of dysplasia that are currently being investigated. No timeline was provided for label expansion.)