

Achondroplasia Conference: The Development of Recifercept for Achondroplasia

Speaker: Michael P. Wajnrajch, MD, MPA (Senior Medical Director, Rare Endocrine and IEM Team Lead, Pfizer.)

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*Information compiled in this document by Victoria Garcia, RN. I have transcribed the following data that was presented at Pharmachon by the above speaker. My transcription/summarization is noted in red font. From the presentation will be my description and best understanding of the thoughts and data Dr. Wajnrajch presented. I was not given permission to share publicly the original slides shown. This document is my best attempt to summarize.

(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 or shared across platforms.)

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Where it started:

<https://pubmed.ncbi.nlm.nih.gov/24048522/>

Pfizer begins therapy trials with Recifercept.

1.) What is Recifercept? (also known as TA-46)

-The mutation expressed in Achondroplasia is FGFR3 G380R. "Because activation of FGFR3 G380R requires ligand binding, a possible treatment strategy was to use a soluble form of FGFR3 (known as sFGFR3) as a decoy receptor and titrate surrounding FGF preventing their fixation on FGFR3."

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7769458/>

****Essentially, this means that FGFR3 mutation in achondroplasia is expressed when FGF ligands (specifically ligand FGF9 and ligand FGF18) bind to FGFR3. This binding causes a suspended bone growth. Pfizer attempted to arrest this expression by injecting a soluble decoy sFGFR3 to bind to ligands FGF9 and FGF18 and in turn restore bone growth.**

From the study linked above, it was concluded that achondroplastic mice treated with injected Recifercept showed improved growth in long bones, body weight, and length. In this same study, mice skull size and foramen magnum size was drastically improved. -Victoria Garcia, RN

2.) After the initial natural history studies were conducted, a Phase 2 study was initiated.

<https://classic.clinicaltrials.gov/ct2/show/NCT04638153>

-Children with achon already enrolled in the C4181001 natural history study

-ages 3 months to 11yrs old

-53 participants randomized for 3 doses such as low, medium, high doses

-The goal for trial participants was to be in trial for 12 months with randomized controls of either placebo or drug and then go on to an open label extension. In an open label extension, participants are offered to continue treatment with Recifercept if they choose.

-A half-way analysis was conducted when 15 participants per dose had received 6 months of treatment. This half-way analysis investigates whether they are seeing expected endpoints for that point of the study.

(All of this can actually take much longer than 6 months because not every child enters enrollment on the same day or hits their 6 months of trial on the same day. There are many avenues to navigate when collecting trial data for at least 15 participants in each dose category.-Victoria Garcia, RN)

3.) Endpoints- During interim analysis the following endpoints were examined to determine if the expected improvements at that point in the study were being found.

-Primary endpoints looked at during interim analysis:

1. Safety- was it safe, tolerable
2. Efficacy- was the growth velocity above what was expected for that child historically.

-Secondary endpoints looked at during interim analysis:

1. Growth- their annualized growth velocity and change in z-score
2. Pharmacokinetics of drug- half-life of drug, immunity, antibodies
3. Proportionality- sitting height, standing height, armspan, rhizomelia, skull morphology. Have to ensure that proportionality was not worsened while on the drug.
4. Comorbidities- sleep apnea
5. Patient centered outcomes
6. Biomarkers

-Exploratory endpoints: included reports by family

- 1.) Rate of surgical intervention- hard to quantify this type of data because not all children with achon require the same type of surgical interventions or the same number of surgeries. To determine whether a trial drug has a significant impact on number of surgeries required by children with achondroplasia they would have to be on the drug for many years.
- 2.) Biomarkers- change from baseline in serum growth biomarkers such as P1N1, CTX, Pro-CNP
- 3.) 0-2yr old cohorts- was it safe in the babies, was it tolerable. Efficacy

4.) Conclusion:

-Recifercept was generally well tolerated. All adverse events were collected and looked at in-depth. The types of adverse events seen were injection site reaction, but were not bad enough to drop out of the trial. This was most common adverse side effects and no one enrolled in the trial dropped out due to injections site reactions.

-When data was collected from the half-way analysis, poor results became evident across the study cohorts such as the following:

1. **Mean Standing Height-** all 3 cohorts (low, medium and high doses) were graphed after 6 months of treatment and there was no statistically important difference in their growth velocity. This means that the children did not experience any improvements in their historical average growth velocity. Most notably from the graph depiction is the **high-dose** cohort who showed the least improvement in their growth velocity out of all cohorts. (This was a very unexpected finding. It is hard to determine if this was just incidental or if the higher dose really did perform more poorly. It was unjustified to continue the study)

2. **Sitting Height-** no statistically significant differences were seen in sitting height over the 6 months.

3. **Arm-span**- very slightly on the graph there looks to be an improvement seen in arm-span but overall not statistically significant.

****The final results of the interim 6 month analysis is that the observed increases in standing height after Recifercept treatment is comparable to the cohorts natural height increases.**

****High incidence of anti-drug antibodies (ADAs) and neutralizing antibodies (NABs). Antibodies were seen in most cohorts but antibodies do not necessarily affect treatment. It doesn't mean that the antibodies will impact overall efficacy but none-the-less they are a reported finding. Overall growth velocity was reported the same whether the child had antibodies or not, suggesting that even without antibody formation the drug was still not effective.**

5.) Efficacy and Immunogenicity Summary:

- Dosing does not affect overall standing height
- Growth velocity seen with Recifercept was significantly lower than treatment seen with Voxzogo.
- High incidence of Nabs in cohorts observed.