Alpha 1 Antitrypsin MZ Information & Research

News & Research Update

Jun 15, 2024

Dear Subscribers,

The Last two weeks we covered the development of a RNA inhibit and RNA editing therapeutic medication where the RNAi inhibits the expression of the "Z" mutation of the SERPINA1 gene and as such reduces the misfolded "Z" AAT protein production in the liver, and the RNA editing therapeutic medication, which allows the liver to make more of the correct "M" protein instead of the misfolded "Z" protein. Both are RNA therapeutics which are doing "something" with the messenger RNA (mRNA) and are not definitive changes in your body, which means that you need regular injections. However there are also Therapeutics in development which is changing your actual DNA, and a single dose should lead to a durable correction of the PiZ mutation, and this is what we are covering in this week Newsletter.

1. **DNA Editing therapeutics.** (Medicines)

Beam Therapeutics (June, 2024 Update from the company)

What is Beam Therapeutics Base Editing?

We all know that our inherited mutation in the SERPINA1 gene, the PiZ, is causing all our health issues, which are not only limited to the lungs and liver, but are also causing immune issues, anti-inflammatory issues and second order issues like a bile acid deficiency, causing absorption issues of important vitamins and minerals and results in the B12 and neurological issues we see in our MZ population.

To resolve this, Beam Therapeutics is working on "base editing" the SERPINA1 gene where a single dose of the BEAM-302 leads to a durable correction of the PiZ variant. (So turning the Z into an M) Base editors are like 'pencils' that enable erasing and rewriting one letter of the genome at a time."

This method has the advantage that it does not require breaking the genomic DNA strands, and thus avoids the random insertion and deletions associated with DNA strand breakage. It is therefore appropriate for precise editing, like changing the Serpina1 gene from PiZ into a PiM.

Current state of development

- Beam Therapeutics "BEAM-302" corrects the PiZ variant to PiM in a dose dependent manner in an Alpha-1 mouse model.
- SERPINA1 gene editing and AAT levels are either stable or increasing after a single dose in mouse models.
- The Phase 1/2 trial is designed to achieve clinical proof-of- concept across the spectrum of Alpha-1 is now starting and completion is expected in Q3 2027 (https://classic.clinicaltrials.gov/ct2/show/NCT06389877)

Here a link to their latest presentation related to Alpha 1 where you will find more details https://beamtx.com/media/1dljik4k/alpha-1-national-conference_june2024_final_presentation.pdf

2. Summary / Opinion

The base editing therapeutic, which is in development by Beam Therapeutics may provide for an excellent solution to prevent all the liver and lung morbidities in patients who inherited the "Z" gene(s). Their base editing therapeutic is in the Phase 1/2 clinical trial, with results expected in Q3 2027. Please note that this is a Phase 1/2 study, and it will take quite some years before this therapeutic will be available for Alpha 1 Patients.

It must be noted, that base editing has great potential, especially for the Alpha 1 community as it restores the "M" protein levels. Which means that it addresses all morbidities like liver and liver-induced issues, lung issues like emphysema, and not to forget autoimmune, anti-inflammatory and connective tissue issues.

The advantages / disadvantages we see between RNA editing and Base Editing is that RNA editing is not permanent, while base editing is permanent and is irreversible, and therefore poses a risk if an editing error occurs. The advantage is, of course, that it is a onetime treatment, while RNA editing needs regular treatment (Injections).

Note: To provide you with a bit of feeling on how much these companies are spending on development, Beam Therapeutics has spent $84.8 Mil on research and development in the first quarter of 2024.