Alpha 1 Antitrypsin MZ Information & Research

News & Research Update

Jun 8, 2024

Dear Subscribers,

Last week we covered the development of a RNAi therapeutic medication which inhibits the expression of the "Z" mutation of the SERPINA1 gene and as such reduces the misfolded "Z" AAT protein production in the liver. This is great for resolving the liver and liver related issues, but does not resolve the Alpha 1 Antitrypsin deficiency. So, you still have a low AAT level with the risk of developing lung issues like e.g. emphysema, including the auto immune, anti-inflammatory and connective tissue issues.

In this issue we will cover RNA editing therapeutic medication, which allows your liver to make more of the correct "M" protein instead of the misfolded "Z" protein.

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

Wave Life Sciences Ltd (May 9, 2024 Update)

What is Wave Life Sciences "RNA medicine"?

An RNA medicine is a short strand of synthetic ribonucleic acid (RNA) or deoxyribonucleic acid (DNA) connected by chemical linkages (also referred to as an oligonucleotide). Wave's oligonucleotides are designed to engage messenger RNA (mRNA) strands inside human cells to repair, restore, or reduce proteins to treat diseases.

WVE-006

WVE-006, is Wave Life Sciences Ltd first RNA editing program and is a first-in-class, GalNAc-conjugated and subcutaneously administered RNA editing oligonucleotide designed to correct the single base mutation in messenger RNA (mRNA) coded by the SERPINA1 Z allele, thereby enabling restoration and circulation of functional M-AAT protein.

In preclinical studies, WVE-006 demonstrated potent and durable editing of SERPINA1 Z transcript **in mice**, restoration of AAT protein up to 30 micromolar, and improvement in several markers of liver disease. WVE-006 is also highly specific with no evidence of bystander editing. Together, these data demonstrate the potential of WVE-006 to address AATD-related liver disease, lung disease, or both.

Current state (Based on recent May 9 Update from the company)

- The RestorAATion-2 clinical trial is now underway. RestorAATion-2 is a Phase 1b/2a open label study designed to evaluate the safety, tolerability, pharmacodynamics (PD) and pharmacokinetics (PK) of WVE-006 in patients with AATD who have the homozygous Pi*ZZ mutation. The trial includes both single ascending dose (SAD) and multiple ascending dose (MAD) portions. It is designed to provide an efficient path to proof-of-mechanism as measured by restoration of wild-type alpha-1 antitrypsin (M-AAT) protein in serum.

- Wave's progress in dose-escalating healthy volunteers in RestorAAtion-1 enabled the quick identification of a starting dose level in RestorAATion-2 that, based on preclinical data, is expected to engage target in patients.

- Expected upcoming milestone: Wave expects to deliver proof-of-mechanism data from RestorAATion-2 in patients with AATD in 2024

- GSK has the exclusive global license for WVE-006. Development and commercialization responsibilities will transfer to GSK after Wave completes the RestorAATion-2 study.
  Note: GSK is a large biopharma company employing 70.000 persons in 75 countries with a revenue of ~30billion pounds

Here a link to their press release related to Alpha 1 https://ir.wavelifesciences.com/news-releases/news-release-details/wave-life-sciences-announces-approval-first-clinical-trial

2. Summary / Opinion

The RNA editing therapeutics, which is in development by Wave Life Sciences may provide for an excellent solution to prevent liver and lung morbidities in patients which inherited the "Z" gene(s). This RNA editing therapeutics is in the Phase 1 clinical trial with results expected at the end of this year. Further development of WVE-006 therapeutics will transfer to GSK after completion of Phase 1 Please note that this is a Phase 1 study, and it will take years before this therapeutic will be available for Alpha 1 Patients.

According to the information on the clinical trial website: https://classic.clinicaltrials.gov/ct2/show/NCT06186492

A Phase 1, Randomized, Double-blind, Placebo-controlled, Safety, Tolerability, and Pharmacokinetic Study of Single Ascending Doses and Multiple Doses of WVE-006 in Healthy Participants.
56 participants, Start date Nov 2023, Est. Completion date Dev 2024

It must be noted, that RNA editing has great potential especially for the Alpha 1 community as it reduces the "Z" and restoring the "M" protein levels. Which means that it addresses all morbidities like the liver and liver induced issues, lung issues like emphysema, and not to forget auto immune, anti-inflammatory and connective tissue issues. However, we need to be patient (as a patient… 😊)