WVE-120101

WVE-120101 is a treatment for Huntington's disease that Wave Life Sciences is developing.

It is the first therapy, together with its companion compound WVE-120102, to use a targeted approach to address the underlying genetic cause of the disease.

How WVE-120101 works

Huntington's is caused by a genetic mutation of the huntingtin (HTT) gene that contains the instructions for making the Huntingtin protein. The protein's exact function is not known, but it is thought to be essential in maintaining nerve cell health. The mutation causes the body to produce an abnormal form of the protein. The faulty protein is cut into small fragments that are toxic to nerve cells. As the toxic fragments accumulate, they cause brain cells to die, leading to the cognitive, movement, and psychiatric impairment associated with Huntington's.

There are several steps in the process of producing a protein from a gene. One is the production of a molecule called messenger RNA, or mRNA, that is essentially a copy of a gene. MRNA is produced in the nucleus of a cell, then sent outside the nucleus, where other structures read it and create a protein based on the instructions it contains. If a gene has a mutation, the mRNA copy of that gene will have the same mutation. This means that its instructions will lead to the gene producing an abnormal protein.

WVE-120101 is an antisense oligonucleotide. It works by interfering with the mutant mRNA copy of the HTT gene. It does this by binding to the mutant mRNA, preventing the cell's protein-making machinery from reading it. This prevents abnormal Huntingtin protein from being produced.

This approach is called antisense oligonucleotide targeting. The targeting must be restricted to mutant HTT mRNA. If the treatment also prevents healthy HTT mRNA from functioning, the body will not produce the healthy Huntingtin protein that nerve cells need to survive.

Making a targeted antisense oligonucleotide can be tricky. In the past, when chemists made antisense oligonucleotides in a laboratory, they ended up with a mix of stereoisomers. These molecules contain the same atoms bound together in the same order but have different shapes — and a molecule's shape affects how it functions. If a medication contains a mix of stereoisomers, its actions may be less targeted and less effective than those of one molecule alone.

Wave Life Sciences developed a proprietary technology that allows it to produce an antisense oligonucleotide that contains only one stereoisomer. This means WVE-120101 will target only mutant HTT mRNA, leaving healthy HTT mRNA to function as normal.

WVE-120101 in clinical trials

Wave Life Sciences is conducting a Phase 1/2 clinical trial (NCT03225833) to evaluate WVE-120101's safety and tolerability in Huntington's patients. Researchers are recruiting participants aged 25 to 65 in Canada and Poland who have early manifestations of the disease.

Participants will receive various doses of WVE-120101 or a placebo directly injected into the spinal canal, the cavity that encloses the spinal cord. Researchers will look at how the body processes the

medication, check for any adverse events that patients experience, and assess their symptoms using the Unified Huntington's Disease Rating Scale. The trial is expected to be completed in September 2019.