

INFORMATION WITH REGARD TO THE SAFETY OF AAV GENE THERAPY



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Vector-based therapies from a safety perspective

Currently, there are 669 AAV therapies in clinical studies in the USA, 1250 in the EU, and 223 in the Asia-Pacific region, with numerous additional programs expected to enter clinical trials in the coming months. In the last week, the FDA granted approval for two new gene therapies: Casgevy and Lyfgenia. In addition, Zolgesma, a gene replacement therapy employing the same AAV9 virus and CBh promoter as our program, has been approved in over 47 countries and safely administered to more than 3,000 patients with Spinal Muscular Atrophy (SMA) worldwide. More recently, Upstaza (AAV2) was approved for the treatment of infant parkinsonism, a disease in which patients are not able to hold up their head, sit, or stand. Even 10 years after treatment, many patients continue to progress in development, with patients achieving important milestones, such as independent sitting and walking.

As with any other medicine, the use of AAV-based gene therapeutics can be accompanied by side effects that are considered acceptable from a risk-benefit perspective and manageable by clinicians. These are well-monitored by health authorities and reported for approved therapies, as shown in the example in the reference list. AAV gene therapy has been shown to be highly effective for various neurological diseases that cannot be treated with other drugs. Liver and Dorsal Root Ganglion (DRG) toxicities have been observed with some AAV9 gene therapies, as shown at our 1st International CTNNB1 Syndrome conference in Madrid. To mitigate this effect, our experimental AAV9-based gene replacement therapy incorporates post-transcriptional regulatory elements that prevent the expression of the vector-encoded therapeutic transgene in the liver and DRG. Moreover, the dose level established is within an appropriate safety/efficacy balance range.

What about CTNNB1 gene therapy?

To date, **no adverse side effects have been observed in our CTNNB1 animal model** following AAV9-CTNNB1 therapy. This treatment improved various aspects of the CTNNB1 phenotype. The critical brain regions in which β -catenin is normally highly expressed have been successfully restored to their functional state. Significantly, even when administered at high doses, β -catenin was not overexpressed, suggesting a robust regulation of the protein expression at the cellular level. We are currently conducting a long-term toxicity study in which we administered very high doses to healthy animals to determine the upper tolerance limit. All animals recovered well and no side effects have been observed to date, over 6 months after vector infusion. To further validate the safety of our AAV9 treatment, we have assessed beta-catenin levels in one of these animals. Remarkably, even in healthy animal exposed to the high vector dose, beta-catenin levels remained within acceptable ranges. This finding provides an additional layer of confidence in the safety profile of our AAV9-CTNNB1 treatment.

The route of administration we have chosen, intracerebroventricular administration (ICV), was determined after discussions with an expert group of the European Medicines Agency (EMA) and other experts worldwide. In addition, pre-existing immunity to the AAV is not an exclusion criterion in other clinical trials with ICV therapy.

To our knowledge, **there are currently four AAV9 gene therapy programs for neurological diseases using the same administration route.** The most recent program, Mucopolysaccharidosis type I (MPSI) demonstrated substantial neurodevelopmental progress in areas such as cognition, language, fine motor skills, and personal and social skills for daily living. Even a patient dosed at 13 years of age showed improvement in majority of the behavioural tests of this program. According to current reports, treatment via this route is **well tolerated without any significant treatment-related adverse effects.**

Regulatory agency approval is required

In addition to all of the above, we would like to stress that the **application of any sort of medication is subject to strict approval processes by regulatory bodies, which only allow to move forward onto human application when they consider the evidence strongly in favour of safety and benefit compared to risk.** With this we would like to highlight that it is not up to the Foundation or parent organization whether any of the therapies being developed, now or in the future, can be administered to patients. As the first clinical trial will take place in Europe, the European Medicines Agency is the governing body that will grant this permission, or request additional experiments if they consider it necessary. In both scenarios, **it is critical to join forces in the community to initiate the first CTNNB1 clinical trial as soon as possible.** With **only 6 months available to fundraise, the CTNNB1 foundation is encouraging everyone to support our efforts to make the first CTNNB1 therapy a reality for all the patients worldwide.**

How can I support?

Within this group, there are 430 patients who could benefit from our efforts. If each of our families would fundraise at least one thousand euros or a similar amount in US\$, we could ensure that the necessary funds are secured to initiate the first clinical trial. Together we can make a real difference to the lives of our children and families and pave the way for other effective therapies for CTNNB1 Syndrome.

Yours Sincerely,
CTNNB1 Team

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