Monthly Newsletter

May 1st 2025 **CTNNB1 FOUNDATION** **Issue #2**

Dear CTNNB1 community,

This month has been quite challenging, with many deadlines approaching, but also very hopeful as we're getting closer to launching clinical trials. Being this close to the finish line is what keeps us going.

We hope you had lovely holidays and got to enjoy some quality time with your loved ones.

With the CTNNB1 Conference just around the corner, we've got lots of exciting things coming up, and we can't wait to start sharing them with you throughout May. So stay tuned!

Community news

We're excited to share some great news: our Orphan Designation Submission has been successfully validated and is now under full review by the European Medicines Agency!

At the same time, work on our clinical trial protocol is progressing steadily. Our entire team is fully committed to finalizing it over the next month, with the goal of

submitting it by **June 13, 2025**, just in time to celebrate at our International CTNNB1 Syndrome Conference in Bilbao.

Meanwhile, our toxicology and biodistribution analysis in mice and non-human primates are ongoing. We have invested the majority of our resources to thoroughly demonstrate the safety of our gene therapy product. Encouragingly, no treatment-related toxicity has been observed at our intended dose levels!

Looking ahead, a key milestone is coming up: a meeting with a competent regulatory authority is scheduled for **May 9, 2025**, where we will discuss critical aspects of our clinical trial design. Keep your fingers crossed for a positive outcome! 🤞

Dragonfly Natural History Study

Since many new families have recently joined our community, we'd love to take a moment to introduce one of our most important ongoing projects - the **Dragonfly Natural History Study (NHS)**. And if you've been thinking about joining, this is the **last chance to enroll for 2025 participation**!

❓What is the Dragonfly study?
The Dragonfly NHS is a **longitudinal, 5-year research study** that closely tracks the natural progression of CTNNB1 Syndrome. It launched in Ljubljana in 2024 and will continue through approximately 2028. The goal is simple yet powerful: to deeply understand how CTNNB1 syndrome develops over time and how it affects every part of life.
Each year, participants take part in annual medical, physiotherapy, and psychological assessments. Parents and caregivers are also invited to fill out questionnaires and participate in in-depth interviews. This comprehensive approach helps us capture a full picture of daily life with CTNNB1 syndrome - from health and development to challenges and hopes.

🌍 A Global Effort
To make the study inclusive and robust, we are collecting data from **families across the world**. The main examination period takes place alongside our **annual CTNNB1 Syndrome Conference**, which takes place in a different country each year - for example, this year in Bilbao, Spain!
In addition to Bilbao, we've arranged **multiple clinical exam locations worldwide** to make participation easier and more accessible:

- **Ljubljana, Slovenia:** May 13–14 & May 23–24
- **Bilbao, Spain:** examinations starting this month, supported by Asociación CTNNB1 España
- **Boston, MA (USA):** July 10–12 at the Embassy Suites by Hilton Boston Waltham (*Please note: This is a different Natural History Study (NHS) than the clinical assessments being organized by CTNNB1 Cure&Connect)*

🕐 *Coming soon:*

- **Sydney, Australia**: University of New South Wales (UNSW Sydney), date TBD
- **Quebec, Canada**: examinations at CHU de Québec-Université Laval Research Center planned for October (exact dates TBD)
- **Porto Alegre, Brasil:** examination planning in progress

We are immensely grateful to all families, partners, and clinicians helping us carry out this vital work. Every participant brings us one step closer to understanding CTNNB1 syndrome, and building better therapies in the future. If you're interested in enrolling your child or learning more, please contact lavra@ctnnb1-foundation.org or visit www.ctnnb1-foundation.org

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CTNNB1 Conference update

Curious about what's coming up at the conference? We're finally sharing the full conference program, which you can access through this link: https://ctnnb1-foundation.org/wp-content/uploads/2025/05/Conference-program-2025.png

We've also prepared some more sneak peeks of the presentations you'll hear in Bilbao:

🔬 **Consequences of pathogenic mutations on b-catenin conformational properties**
Sonia Bañuelos, Biofisika Institute (UPVEHU, CSIC)

What happens when β-catenin – the key protein disrupted in CTNNB1 syndrome – can't fold properly? In her upcoming talk, Sonia Bañuelos explores how pathogenic mutations affect the conformational stability of β-catenin, a crucial helical-repeat protein involved in brain development. By analyzing patient-specific variants using circular dichroism spectroscopy, her team uncovered that although some mutated forms retain partial structure, their solubility and stability are significantly compromised – possibly impairing cell adhesion and contributing to neurodevelopmental dysfunction in CTNNB1 syndrome.

🧠 **Clinical, psychological and neuropsychological characterisation of 25 CTNNB1 syndrome patients**
Merce Pallares-Sastre & Maitane Garcia-Martin, Neuro-e-motion (University of Deusto)

Merce Pallares-Sastre and Maitane Garcia-Martin will share results from a comprehensive clinical, psychological, and neuropsychological study of 25 Spanish CTNNB1 patients. Their analysis highlights common traits like microcephaly, motor and language delays, sleep disturbances, and behavioral challenges – along with a striking 60% rate of ASD symptoms. Early milestone achievement was linked to better current functioning, underscoring the critical

role of early intervention in improving outcomes and guiding personalized care strategies.

📑 **Dragonfly Natural History Study update**
Fiona Moultrie, University of Oxford

What can long-term observation tell us about CTNNB1 syndrome? Fiona Moultrie will share preliminary results from the **Dragonfly natural history study**, an international effort tracking the development of over 80 individuals with CTNNB1 syndrome and their primary caregivers. Each year, participants undergo detailed evaluations, including neurological exams, cognitive and motor assessments, communication and behaviour testing etc. Caregivers also complete questionnaires about quality of life and daily challenges. The study is already revealing valuable insights from these tools, helping to build a clearer picture of how the condition progresses, and preparing us to evaluate future treatments with greater precision.

🎙️ **Listen to the CTNNB1 conference in your language: real time translations available in 60+ languages**
We're excited to introduce a brand-new feature at this year's conference: instant translation and transcription of entire conference presentations.

Thanks to Worldly technology, participants will be able to follow presentations in real time in different languages, using just their phone or tablet. It's simple: scan a QR code we'll display at the event (or access the link we'll send you by email), and you'll immediately get live captions and voice translation during the talks. You can even plug in your headphones for a seamless listening experience!

What you need to know:

- No language barriers – we will support virtually all languages.
- Easy access – Just scan the QR code or click the link and start following along.
- Live audio or captions – You choose how you want to experience it.
- Saved transcripts – We'll also keep the original transcripts, allowing us to provide translated subtitles when we publish the conference videos later on!

We're committed to making the conference as accessible and inclusive as possible, and this new feature is another big step forward.

Research & Clinical trial updates

We also want to share the latest updates on our gene therapy program URBAGEN, developed to restore β-catenin levels in children with CTNNB1 Syndrome. Thanks to your support, we continue making significant progress

toward our clinical trial. Here's a summary of the latest research and safety results:

🧬 Non-clinical research highlights

We are proud to share that we have completed proof of concept. Patient-derived brain organoids treated with URBAGEN showed restored β-catenin function and important improvements in its phenotype. Importantly, there was no activation of cancer-related pathways, confirming the safety of our approach.

In our in vivo mouse model studies, treatment with URBAGEN led to clear improvements. Mice with CTNNB1 syndrome showed **better mobility and gait, increased spontaneous activity, and normalized motor function** scores at both mid and high doses. Molecular analysis confirmed increased β-catenin protein expression in important brain regions, including the hippocampus, cerebellum, and cortex, showing that the therapy successfully reached the brain and worked as intended.

📊 Safety studies and necropsy findings

In mice, URBAGEN was tested with long-term monitoring for up to eight months following a single brain injection with our desired dose and one time higher dose. No treatment-related toxicity was found in the study. In our regulatory enabling toxicology study in mice, no systemic treatment-related toxicity was detected based on clinical observations, bloodwork, or organ tissue analysis. At the highest dose, which was three times higher than the dose we plan to use in the clinical trial, mild inflammation of the ventricular wall and some neuronal degeneration were observed. **These findings are expected with AAV gene therapies at high doses and are considered manageable with corticosteroid treatment during the clinical trial**. Importantly, **no tumors or cancer-related changes were found in any animals**, even after extended monitoring.

In our study with non-human primates, cynomolgus monkeys received our therapeutic dose for humans and a dose three times higher to see what toxic effect we can expect in the clinic. After 90 days, **no abnormalities were seen during necropsy examinations**. Detailed tissue analysis is still ongoing, and we expect final results by May 2025.

🧬 Biodistribution studies

We have also been studying where the therapy travels in the body. So far, URBAGEN is primarily targeting the brain as intended. Some vector presence was detected in the liver, spleen, and occasionally the gonads at higher doses, and we are watching these findings closely. Early mRNA data show that the strongest gene expression remains in the brain, confirming that URBAGEN is working where it matters most.

🧐 **What's next?**
We are finalizing the GLP mouse study and awaiting the complete non-human primate histopathology results, both expected in **May 2025**. These data will help us finalize the dose selection for our first-in-human clinical trial and prepare for submission to regulatory authorities.

Our plan is to submit regulatory documentation before our 3rd International CTNNB1 syndrome conference in Bilbao. Stay tuned!

Stories of impact: Nora

This month, we share the story of a little girl who was recently diagnosed with CTNNB1 syndrome. Her journey is just beginning, and her family has bravely and inspiringly opened their hearts to show how they are navigating these early stages of diagnosis.

Nora is 14 months old – joyful, curious, sensitive, and has a voracious appetite. The first time she scooted was chasing a yogurt. She loves stories, flipping pages, and clapping along with us. Bath time, her favourite moment of the day, always fills the house with laughter.

At home, she follows her brother everywhere, spinning and scooting her way around, and reaching out to be picked up with her little hands.

From early on, Nora struggled to reach motor milestones. At first, we weren't too concerned, as her brother had also faced some delays. We thought it might be something similar – maybe joint hypermobility, maybe not enough tummy time.

But then came a series of tests: CT scan, MRI, metabolic screening... and genetic testing. We were told results could take up to a year. After five months, we opted to do them privately. Three weeks later, during a therapy session, we received an email. We opened it, hoping to read 'no alterations detected'. Instead, it said: CTNNB1 syndrome.

We didn’t know what it meant. Fear rushed in. Uncertainty became diagnosis. We desperately searched for information and found Asociación CTNNB1 España and the CTNNB1 Foundation. Reading about the syndrome was like reading about Nora. Discovering the work being done – especially the development of gene therapy – felt like spotting a lighthouse in a dark ocean. A dream. A hope. A profound sense of gratitude. Reading similar stories inspired us deeply. We believe that with work and effort, results eventually come. “When inspiration comes, may it find me working,” Picasso once said.

We’ve realized we’re facing the most challenging project of our lives. But Nora is not defined by her syndrome – she is our amazing daughter. We celebrate every little step forward, and we refuse to place limits on her future. We know our way of measuring progress will be different, but our hopes are limitless, especially with treatments already being developed.

We feel fortunate to be part of this strong, resilient community – and if there’s one thing we’ve learned, it’s that sometimes the only way not to lose a battle is to never stop fighting.

Count on us.

Written by Nora’s father, Juan

If you feel inspired to share your own family's journey with CTNNB1 or a similar rare disease, please contact **lavra@ctnnb1-foundation.org**

Lavra Debeljak
Research and Patient Relations Associate

lavra@ctnnb1-foundation.org
+386 31 457 138

Dalmatinova ulica 5
1000, Ljubljana