

February 1, 2023

Dear Rett Community,

We are excited to provide you with some updates about Taysha’s investigational gene therapy program for Rett syndrome, which were shared in a press release this week.

What information was shared about Taysha’s ongoing investigational gene therapy clinical trial in Canada for adults living with Rett syndrome?

- As you may know, last year Taysha initiated an investigational gene therapy clinical trial - the REVEAL Adult Study - for adult females 18 years or older living with Rett syndrome
- Taysha announced that dosing of the first adult participant in the REVEAL Adult Study is anticipated in the first half of 2023
- Initial clinical data from the REVEAL Adult Study is expected to be shared in the first half of 2023, with additional planned updates (primarily safety-related) on available clinical data being shared on a quarterly basis moving forward

What is the REVEAL Adult Study?

- The REVEAL Adult Study is a Phase 1/2 clinical trial to evaluate the safety, tolerability, and preliminary efficacy of a single administration of the investigational gene therapy, TSHA-102, in adult females with Rett syndrome
- The first clinical trial site is located in Canada, with plans to open additional sites in the future
- For more details about the REVEAL Adult Study, please click here to watch the community update video that was shared with Rett patient advocacy organizations at the end of 2022

What information was shared about Taysha’s plans for an investigational gene therapy clinical trial for Rett syndrome in the United Kingdom (UK)?

- Taysha announced that it plans to submit a Clinical Trial Application (CTA) to the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK by mid-year 2023 for the investigation of TSHA-102 in pediatric females with Rett syndrome
- A CTA application must be reviewed and approved by the MHRA in order to begin a clinical trial in the UK
- It is important to note that even after an application is potentially approved, there are many additional steps required before a clinical trial can begin

What information was shared about Taysha’s plans for an investigational gene therapy clinical trial for Rett syndrome in the United States (US)?

- Taysha announced that it plans to submit an Investigational New Drug (IND) application to the Food & Drug Administration (FDA) in the US in the second half of 2023
- An IND application must be reviewed and approved by the FDA in order to begin a clinical trial in the US
- At this time, we do not have any additional details about this application to provide at this time

What are Taysha’s plans for an investigational gene therapy clinical trial for males with Rett syndrome?

- At this time, Taysha is focused primarily on running preliminary clinical trials in adult and pediatric females with hopes to demonstrate the potential safety and efficacy of this investigational gene therapy product



About Taysha’s investigational gene therapy for Rett syndrome (TSHA-102):

- What is the underlying cause of Rett syndrome?
 - In most patients with Rett syndrome, there is a mutation in *MECP2*, which is a gene that tells cells how to make a protein called Methyl-CpG-binding protein 2 (MeCP2)
 - This protein plays an important part in the development of the brain throughout childhood by maintaining normal brain function and communicating between nerve cells
 - In Rett patients with a *MECP2* gene mutation, the body does not make enough MeCP2 or produces abnormal MeCP2
- What is Taysha’s investigational approach to gene therapy for Rett syndrome?
 - Taysha’s investigational gene therapy product, TSHA-102, is designed to deliver a working copy of the *MECP2* gene to the affected cells
 - TSHA-102 uses a novel technology called miRARE, developed by Dr. Sarah Sinnet and Dr. Steven Gray of UT Southwestern Medical Center
 - The clinical trials will determine whether the working copy of the *MECP2* gene can be packaged with our miRARE technology to safely control the level of MeCP2 protein expression
- How is Taysha’s investigational gene therapy delivered?
 - The working *MECP2* gene is inserted into a delivery vehicle, called a vector, which is then injected intrathecally, into the spinal fluid in the lower back (lumbar region)
 - From there, the gene therapy is carried throughout the spinal cord and brain so that it can be transferred into the cells that need them
- What delivery vehicle is used to transfer the *MECP2* gene?
 - The vector that Taysha uses is an adeno-associated virus (AAV9) viral vector that is not known to cause disease in humans
 - AAV9 is a commonly used vector, which has been used in other investigational and approved gene therapies

If you have questions or would like to connect with a member of our team, please contact medinfo@tayshagtx.com.

As always, we are grateful for the continued support of the Rett syndrome community and the Rett patient advocacy organizations. It is a privilege to partner with you. Your continued input helps to shape the work that we do and allows us to move as quickly as possible.

We look forward to providing further updates as new information becomes publicly available.

Sincerely,
The Taysha Patient Affairs Team

