8th August 2017

Roche community update on our molecule, RG7916

Dear SMA Community

We've received valuable feedback requesting more information about our first oral molecule, RG7800, and how it relates to our new oral investigational medicine, RG7916.
Roche is committed to SMA. So, we want to ensure the SMA community is well informed.

About clinical studies

Before any new molecule can enter clinical studies in people, toxicology studies must be performed in animals. A molecule is tested in animals with increasing doses and duration. These studies in animals help inform us about any potential risks for humans.

Toxicology studies are conducted both at dose levels expected to be used in people (therapeutic dose levels) and also at higher dose levels.

RG7800 safety finding in animal studies

An unexpected eye finding was observed during a long-term RG7800 study in monkeys. Although this finding occurred at doses higher than those used in the Phase 2 study of RG7800 ("MOONFISH"), we decided to stop MOONFISH. We made this decision in order to thoroughly research and understand the eye safety finding in monkeys.

More specifically, we found changes in specialized cells located primarily at the periphery (edge) of the retina. The retina is a thin layer of tissue lining the back of the eye, which detects light and converts it into signals that are translated into images by the brain.

No change was observed in the central part of the monkey retina, which is involved in color vision, reading, and visual clarity. Additionally, no changes were observed in the optic nerve, which is the nerve that processes and sends visual signals to the brain.

None of these eye findings have been noted in any human receiving RG7800 or RG7916.

How is RG7916 different from RG7800?

RG7800 and RG7916 are both part of a series of investigational SMN2 oral splicing modifiers developed by Roche, PTC Therapeutics, and the SMA Foundation. It is fairly standard for multiple oral molecules in a series to be developed simultaneously until the lead molecule has progressed

into pivotal trials. Development of RG7916 has been underway since before the MOONFISH study started.

RG7916 has been optimised in how the body processes the molecule and the effect that it has in the body. RG7916 is two to three times more potent than RG7800, which means that the same effect can be achieved with lower doses of RG7916.

How do you monitor the eyes of people receiving RG7916?

Safety is Roche's top priority. Therefore, we developed – with advice from independent ophthalmology experts – an extensive eye examination protocol designed to detect and monitor eye changes in people receiving RG7916. Each participant in our studies receives regular eye examinations by ophthalmologists to ensure that we can detect any changes early.

The retinal changes that we observed in monkeys may be detected in humans using a non-invasive procedure called optical coherence tomography, or OCT. OCT is similar to ultrasound imaging, except it uses light waves instead of sound waves. OCT can help us obtain a very detailed structural view of the entire eye, and in doing so gives us the potential to detect any structural changes before symptoms are shown.

What safety measures are in place in the RG7916 clinical program?

We have three studies with RG7916, named FIREFISH, SUNFISH, and JEWELFISH. Each of these studies are currently recruiting: FIREFISH for Type 1 (1-7 months old), SUNFISH for Type 2/3 (2–25 years old), and JEWELFISH for patients previously enrolled in MOONFISH or in a nusinersen study. More information about these studies can be found at www.roche-sma-clinicaltrials.com.

The safety of participants in our studies is a priority. In our studies we only use dose levels of RG7916 that have not been associated with the eye findings in monkeys.

OCT and thorough eye examinations are precautionary measures in all our RG7916 studies to ensure that we can effectively monitor participants for any eye changes.

A Data Monitoring Committee, an independent group of experts, reviews all the data from FIREFISH, SUNFISH and JEWELFISH on a regular basis to ensure patient safety in our studies.

Have you seen any eye findings in FIREFISH, SUNFISH or JEWELFISH?

None of the eye findings observed in monkeys have been seen in any human receiving RG7916. No participant has withdrawn from any of these studies due to a drug-related side effect.

No unexpected events have occurred to date in any of the RG7916 studies. FIREFISH, SUNFISH and JEWELFISH continue to advance as planned. Some patients in SUNFISH have received RG7916 for more than six months.

We are focused on progressing our clinical studies with upmost speed and quality. We look forward to sharing more updates about RG7916.

We would like to thank all participants who take part in clinical studies - your very personal contribution is helping to advance treatments in SMA.

Best regards

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