20 October 2021

Update on Roche's SMA global clinical development programme: New global combination study to begin in early 2022

Dear Andi

In response to your request, we are pleased to share with you the initiation of MANATEE, a new global Phase 2/3 clinical study that aims to evaluate the safety and efficacy of GYM329 (RO7204239), an investigational anti-myostatin antibody targeting muscle growth in combination with risdiplam, in Spinal Muscular Atrophy (SMA).

Why a combination study?

This study draws on ten years of listening to and working with the global SMA community, who for a number of years now have shown a strong interest in the potential of combination treatments, the next generation in SMA research and development. By evolving our existing partnerships with the community, exploring a combination of therapies with different mechanisms of action and continuing to be curious in our approaches to treatment, we can continue to transform the lives of people living with SMA and their families.

Current available SMA therapies aim to increase the amount of survival motor neuron (SMN) protein in the body (referred to as "SMN-targeted therapies"). Low levels of SMN protein is the underlying driver of SMA. The combination of an SMN-targeted approach and a second targeting skeletal muscle (the muscle used for movement under voluntary control) may result in a complementary or added benefit by addressing the underlying cause and the symptoms of the disease concurrently[1].

About the molecule

GYM329 is an investigational anti-myostatin antibody that is designed to target skeletal muscles, potentially increasing their size and growth[2]. Myostatin plays an important role in the regulation of skeletal muscle size by controlling growth. Inhibiting myostatin may help muscles grow in size and strength. GYM329 in combination with risdiplam, which is designed to increase the amount of SMN protein throughout the body, has the potential to further improve motor function and outcomes for people living with SMA[2].

MANATEE study overview

MANATEE is a global, Phase 2/3 study that will assess GYM329 in combination with risdiplam in ambulant (able to walk independently) children with SMA aged 2-10 years. Patients who have been previously treated with either risdiplam, nusinersen or onasemnogene abeparvovec are eligible, as well as those who have not received treatment before. Other eligibility criteria exist.

The MANATEE study consists of two parts:

- Part 1 will begin first and will assess the safety of two doses of GYM329 in combination with risdiplam, with the aim of selecting the optimal dose of GYM329 for Part 2 of the study. It is expected to enrol approximately 36 participants.
- Part 2 is the main part of the study and will assess the efficacy and safety of the GYM329 dose selected in Part 1 when combined with risdiplam. It is expected to enrol approximately 144 participants. Part 2 will commence once the dose selection is complete in Part 1.

Participants will be randomly assigned to either a treatment group that receives risdiplam and GYM329, or a treatment group that receives risdiplam and a placebo. All participants in the study will receive a daily dose of risdiplam at the approved dose throughout the study, including those in the placebo group.

Approximately 15 sites have been selected to participate in Part 1 of the study in countries including Belgium, Germany, Italy, Poland, the Netherlands, the UK and the USA. Enrolment for Part 1 is anticipated to start in early 2022 and Part 2 at the end of 2023. Any patient family who has an interest in joining the study should discuss treatment decisions with their physician.

We are currently unable to confirm which UK sites will participate in Part 1 of the study. This information will be published in the coming weeks.

As we prepare to commence this next phase of the overall Roche SMA clinical development programme, we would like to take the opportunity to thank SMA Europe, our investigators and study site staff who have helped contribute to the design and preparations for the trial. We look forward to providing you with updates in the near future, and we thank you for your continued partnership.

Sincerely,

Jack Robinson

On behalf of the UK SMA team

Questions and Answers

What is myostatin?

Myostatin is a protein that occurs naturally in skeletal muscles. Its main function is to prevent skeletal muscles from growing too large in size[2].

A lack of myostatin, or treatment with anti-myostatin molecules, has been shown to be associated with a significant increase in muscle mass in several animal species, including humans. Therefore, myostatin inhibition could be a potential therapy for diseases that involve muscle loss, such as SMA[2].

Has the GYM329 molecule been investigated before? What evidence is available to indicate its potential as a viable therapy option?

GYM329 is an investigational anti-myostatin antibody designed to target skeletal muscles, helping to increase their size and growth by inhibiting myostatin, a naturally occurring protein that controls and slows the growth of skeletal muscle – making it a potential therapy approach for various types of muscle disorders[2].

The molecule has been shown to exhibit an increase in muscle volume in three different mouse disease models[2] and has been initially investigated in a select group of healthy volunteers who showed no adverse events that led to study withdrawal.

What is risdiplam?

Risdiplam is a survival motor neuron-2 (SMN2) splicing modifier designed to treat SMA by increasing and sustaining SMN protein levels both throughout the central nervous system and peripheral tissues of the body. It can be administered daily at home in liquid form by mouth or feeding tube[3].

Risdiplam is approved in over 60 countries.

How will trial outcomes be measured?

Motor function will be evaluated using the Revised Hammersmith Scale (RHS), the Motor Function Measure-32 (MFM32) and a wearable device that will measure upper and lower limb movement and activity levels during normal daily living, outside of the investigation site.

Muscle mass will be assessed using Magnetic Resonance Imaging (MRI) and Dual-Energy X-ray Absorptiometry (DXA) scans, and muscle strength measured using myometry, a process that assesses the extent of a muscular contraction. The SMA Independence Scale (SMAIS) will also be used with caregivers to assess function-related independence.

What are the eligibility criteria for participation in the trial?

The MANATEE study will enrol ambulant patients (able to walk/run 10m in ≤ 30 seconds) aged 2-10 years at screening with a confirmed genetic diagnosis of 5q-autosomal recessive SMA and symptomatic SMA disease. Participants can be any SMA type with any *SMN2* copy number. Patients who have been previously treated with either risdiplam, nusinersen or onasemnogene abeparvovec are eligible as well as those who have not received treatment before.

Patients who are receiving or have received previous administration of anti-myostatin therapies, and those who have contraindications for MRI scans are not eligible for participation in the trial. The ultimate decision of participating in a trial is between the patient and their healthcare provider. Other eligibility criteria exist. Any patient family who is interested in joining the study should review the criteria and make any decisions in partnership with their treating physician.

Why are only ambulant patients aged 2-10 years allowed to participate in the study?

We acknowledge people living with SMA are looking to participate in clinical trials, yet they may not always meet the eligibility criteria. Whilst we are committed to making our treatments available to as broad a patient population as possible, initial clinical trials must be conducted in a well-controlled environment that enables us to confirm that the treatment is safe and efficacious and that it is the treatment producing these effects, rather than other external factors or chance.

Eligibility criteria must be carefully considered to ensure the participants included in the trial are as similar to each other as possible and will remain so throughout the course of the trial. If we can show a clinically meaningful benefit in this well-controlled patient population, we will be able to understand if this approach may be helpful for others living with SMA, benefiting the community as a whole.

Do you have plans to explore this combination in other SMA patient populations?

Roche is exploring investigating the combination in other patient populations in the future, including non-ambulant patients and in a broader age range.

How can patient families enrol in the study? Where can they go for more information?

Patient families who are interested in taking part in the study must speak to their healthcare team. We are currently unable to confirm which UK sites will participate in Part 1 of the study. This information will be published in the coming weeks.

Enrolment for part 1 will begin in early 2022 in approximately 15 sites in countries including Belgium, Germany, Italy, Poland, the Netherlands, the UK and the USA. Part 2 is expected to start at the end of 2023.

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References

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[2] Muramatsu, H et al 2021. Scientific Reports, 11(1), 2160.
[3] Poirier A, et al. Pharmacol Res Perspect. 2018;6: e00447