4 October 2022

Dear members of the FSHD Society,

We would like to share with you the initiation of our upcoming clinical trial, MANOEUVRE, as well as take this opportunity to tell you more about our company and our commitment to working with the FSHD patient community, in response to your request for such information.

MANOEUVRE: a new global Phase 2 study to begin by the end of the year
MANOEUVRE is a new global Phase 2 clinical study that aims to evaluate the pharmacodynamics*, safety, tolerability**, pharmacokinetics*** and efficacy of GYM329 (RO7204239), an investigational anti-myostatin antibody targeting muscle growth, in individuals living with FSHD.

As there are currently no approved treatments for FSHD, there remains a high unmet need for those living with the condition. This study draws on the ongoing need to assess new treatment options for FSHD and novel ways to improve muscle function and the motor abilities needed for daily living.

What is GYM329?
GYM329 is an investigational anti-myostatin antibody that is designed to target skeletal muscles, potentially increasing their size and growth. Myostatin plays an important role in the regulation of skeletal muscle size by controlling its growth. Inhibiting myostatin may help muscles grow in size and strength.

GYM329 has been engineered as a “recycling” and “sweeping” antibody, which means that it may be more efficient at removing myostatin from the blood compared to a conventional antibody.

Study overview
MANOEUVRE will assess the pharmacodynamics, tolerability, pharmacokinetics, safety, and efficacy of GYM329 in ambulant (able to walk independently) individuals aged 18-65 years with FSHD1 or FSHD2. The study plans to enrol approximately 48 participants.

This will be a placebo-controlled study, where eligible participants will receive either GYM329 or a placebo, every 4 weeks via a subcutaneous injection. The study will be double-blinded, meaning that neither the participant nor the study team will know who is receiving GYM329 or the placebo. Individuals will be asked throughout to take part in different assessments, including an MRI, muscle function and strength tests, completing questionnaires, and other evaluations. At the beginning of the study and then every 6 months thereafter, the participants will be asked to wear a digital device for a 4-week period that will help measure everyday upper and lower limb movement and capture changes to activities during normal daily living.

The study will conclude after all participants have completed 52 weeks of treatment. Participants will then have the option to continue for an additional 52 weeks, where all individuals involved will receive GYM329. Results from the trial will indicate if we move forward to a Phase 3 study.

Approximately 10 sites have been selected to participate in the study in four countries: Denmark, Italy, the UK and the United States. Enrolment is anticipated to start later in 2022. Anyone who is interested in joining the study should discuss treatment options with their physician. Further information on the MANOEUVRE study can be accessed on ClinicalTrials.gov.

About Roche and Genentech
Roche is a global biotech company focused on advancing science to improve people’s lives. We were founded 125 years ago in Basel, Switzerland, and now have a network of more than 100,000 employees working in 100+ countries. In the United States, our pharmaceutical division is called Genentech.

As a company, we believe in two key concepts:

- *Investing in and following the science.* Last year we invested CHF13.7 billion in research and development, more than any other healthcare company worldwide. We've translated that science into approved therapies that have fundamentally changed the way numerous conditions such as cancer, haemophilia, spinal muscular atrophy (SMA) and multiple sclerosis are treated.
- *Innovation and focusing on areas of unmet need.* We aim to transform how diseases can be treated and have earned various Health Authority designations – including over 30 breakthrough therapy designations from the US Food and Drug Administration. Using our existing knowledge, and with the help of your ongoing partnerships, we hope to help improve the lives of people living with FSHD.

For more than 10 years, we have been working with patient communities across different neuromuscular diseases, including SMA and Duchenne muscular dystrophy (DMD). We remain committed to supporting those living with neuromuscular diseases and we are excited to be taking our first steps to now partner with you, the FSHD community.

Partnering with the FSHD community

We are proud of our history of working with patient groups. Our goal is to be a trustworthy partner and for all partnerships to reflect common values of integrity, maintenance of independence, respect, equity, transparency and mutual benefit, in view of our common goal of meeting the needs of people living with FSHD.

We have dedicated people and teams at both the global – and country-level focused on developing sustainable collaborations with patient communities. Open and constructive dialogue is crucial. This helps us know what to expect from each other, and it helps us better understand how to support patients, carers, and physicians, and to focus our activities on areas that are most beneficial to the communities we serve.

As we move forward with our clinical development program, we would like to thank you, our investigators and study site staff who have helped contribute to the design and preparations for the trial. We are looking forward to working closely with the community and, per your request, will be providing you with regular updates on progress.

If you have any questions on the company, our pipeline or our clinical programme, please don't hesitate to get in touch.

Sincerely,

Fani Petridis

Fani Petridis, on behalf of the Roche & Genentech FSHD Team
Senior Global Patient Partnership Director, Neuromuscular Diseases

** Pharmacodynamics describes the intensity of a drug effect in relation to its concentration in a body fluid, usually at the site of drug action, or simply 'what the drug does to the body'*
*** Tolerability – the degree to which the drugs overt effects can be tolerated by the patient*
**** Pharmacokinetics is described as what the body does to the drug including the movement of the drug into, through and out of the body*

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.[1]

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

What evidence is available to indicate the potential of the GYM329 molecule as a viable therapy option?
GYM329's potential ability to inhibit the effects of myostatin and increase muscle size makes it a possible therapy approach for various types of muscle disorders.[1]

In recent studies, the molecule has been shown to exhibit increase in muscle volume in three different mouse disease models[1] and has been initially investigated in a select group of healthy volunteers who showed no adverse events leading to study withdrawal.

Are you investigating the use of GYM329 anywhere else in your pipeline?
We have also been investigating the impact of a GYM329 combined treatment for those living with spinal muscular atrophy (SMA) in our MANATEE study. For more information about this study, visit ClinicalTrials.gov.

What are the eligibility criteria for participation in the trial?
The MANOEUVRE study will enrol ambulant (able to walk unaided) individuals aged 18-65 years at screening with a confirmed genetic diagnosis FSHD1 or FSHD2. People with FSHD who have a Ricci Clinical Severity Scale score of ≥2.5 to ≤4 and who are willing to maintain the same frequency and intensity of physiotherapy, occupational therapy and other forms of exercise therapy during the clinical study may also be eligible to take part.

People living with FSHD who have received previous investigational therapy within 90 days prior to screening, or five half-lives of the drug or previous anti-myostatin therapies, and those who are unable to have an MRI scan, are not eligible for participation in the trial. Other eligibility criteria exist.

The ultimate decision of participating in a trial is between the individual and their healthcare provider. Anyone who is interested in joining the study should review the criteria and make any decisions in partnership with their treating physician.

How can people living with FSHD enrol in the study? Where can they go for more information?
Those who are interested in taking part in the study must speak to their healthcare team. Further information on the MANOEUVRE study is accessible on the ClinicalTrials.gov website here.

Enrolment for the trial will begin later in 2022 in approximately 10 sites in countries including Denmark, Italy, the UK and the US.

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[1] Muramatsu H, et al. Scientific Reports. 2021;11(1).
[2] Suh J, et al. Journal of Bone Metabolism. 2020;27 (3)