A clinical trial* to establish the safety, tolerability and pharmacokinetics (how a medicine works in the body) of different doses of an investigational medicine called taldefgrobep alfa (RG6206 – an anti-myostatin adnectin) in boys with Duchenne Muscular Dystrophy (DMD) – THUNDERJET

DM-XX-00003399
Date of preparation: November 2020

*Referred to as a 'study' throughout this summary document. See the end of the document for the full title of the study.

About this summary

Thank you to those who took part in this clinical study. This was a clinical study for an investigational medicine called taldefgrobep alfa (RG6206), known as an anti-myostatin adnectin. An investigational drug (often described as an experimental drug) is one that is still being studied to see how it works and has not been approved by an authority such as the U.S. Food and Drug Administration (FDA) or the European Medicine Agency (EMA). The aim of the study was to investigate the safety and tolerability of taldefgrobep alfa (RG6206) in boys with Duchenne Muscular Dystrophy (DMD) and to assess how it worked in the body.

The study was not completed in full. A pre-planned analysis of the initial results of the SPITFIRE study – another study of the same investigational drug – showed that taldefgrobep alfa (RG6206) was not as effective as had been hoped. It was well tolerated, however. As a result, THUNDERJET was stopped early.

All studies contribute to the better understanding of diseases. Despite the fact that the THUNDERJET study was stopped early, it has provided valuable information about DMD and how potential medicines may work in DMD patients. Roche remains committed to supporting this area in the future and is exploring other potential treatments for DMD, such as the investigational gene therapy drug SRP-9001.

This document provides a summary of the THUNDERJET study. This summary was written after the study ended and is intended for members of the public and people who took part in the study.

Key information about this study

The aim of the study was to investigate the **safety and tolerability of a potential treatment for DMD,** and how it is processed by the body (pharmacokinetics)

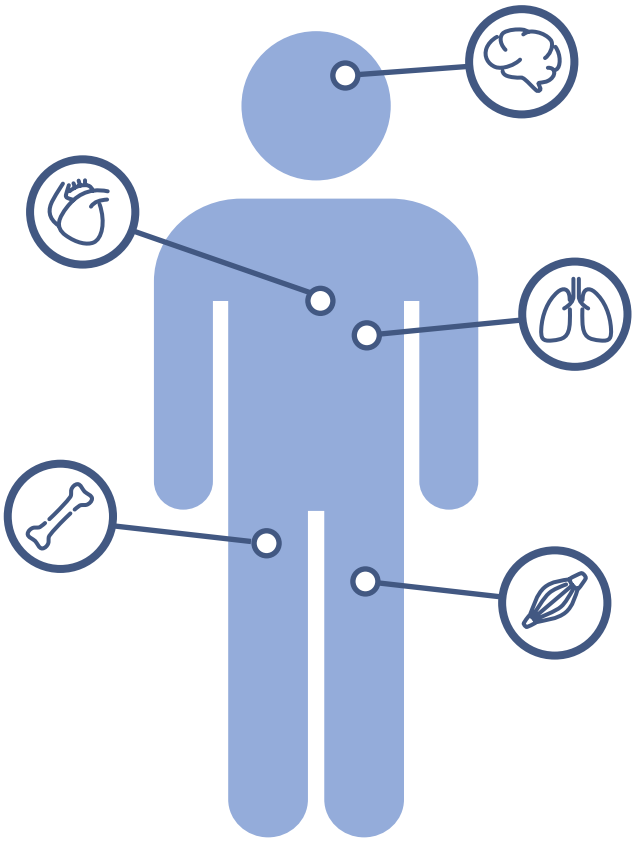
This study included **43 boys aged 5–10 years in the United States and Canada**

The study was divided into two parts. In Part 1 of the study, participants were given either the study medicine, called **taldefgrobep alfa (RG6206)**, or a **placebo** (dummy treatment). It was decided by chance which treatment each person would receive. Part 2 of the study was 'open label', meaning all participants had the option to take the active medicine

The study started in December 2015 and was stopped early in November 2019. The reason for this was that analysis of the initial results of another study using the same drug showed that it did not work as well as expected

Why was the study carried out?

Duchenne Muscular Dystrophy (DMD) is a genetic disease that causes muscle weakness and wasting. It is usually diagnosed before the age of 5 and predominantly affects boys.



DMD can affect many different parts of the body, including the heart, lungs and nervous system (brain and spinal cord), as well as the skeleton and muscles. Symptoms tend to worsen with age and can impact on every aspect of daily life. There is no cure for DMD. Current treatment options for DMD patients are limited and are mainly designed to reduce symptoms, reduce the risk of heart and lung complications, slow progression and improve survival. There is a clear need for effective new treatments for DMD.

Taldefgrobep alfa (RG6206) is known as an anti-myostatin adnectin. It blocks a protein called myostatin which prevents muscle growth. In healthy people, it is needed to prevent muscles from growing too large. It is thought that blocking the action of myostatin could lead to increased muscle size and strength in patients with DMD.

The purpose of the study was to find out how different doses of taldefgrobep alfa (RG6206) affected boys with DMD and to see whether it caused any side effects.

General information about the study

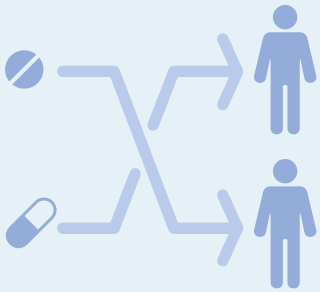
What was the study timing?	
Duration	Part 1: 24 weeks Part 2: 48 weeks, with an option to continue taking the active medicine for up to 228 weeks
Start date	December 2015
End date	April 2020. The study was stopped early in November 2019 but follow up visits continued until April 2020 to check on the participants

Who took part?	43 boys with DMD Aged 5-10
What were the **inclusion criteria** (who could take part)? 	■ Aged between 5 and 10 years ■ Male ■ Genetic diagnosis of Duchenne ■ Able to walk without assistance (ambulatory) ■ Able to walk up 4 stairs in 8 seconds or less (4SC score) ■ Taking a regular regimen (medication plan) of corticosteroids for DMD
What were the **exclusion criteria** (who could <u>not</u> take part)? 	■ An ejection fraction (measure of the percentage of blood leaving the heart each time it contracts) of less than 55% ■ Behaviour or mental issue affecting the ability to complete study procedures ■ Use of certain medications including androgens or human growth hormone ■ Use of a ventilator during the day ■ Inability to have blood samples taken or to receive an injection under the skin ■ Treatment with exon skipping therapies (therapies that aim to correct mutations in the affected gene) ■ 6 months prior to the study start ■ Treatment with ataluren or any investigational drug

How was the study designed?

The study consisted of a 24-week **double-blind** phase and then a 48-week **open label** part with the option of continuing in the open label part for up to 228 weeks. This is known as an **open label extension**.

Double-blind phase



In a **double-blind study**, participants are randomly assigned to receive either the drug being investigated or placebo (a dummy drug with no active ingredient). Neither participants nor researchers know whether participants are receiving the active medicine or a placebo.

In this study, participants were divided into four groups and were randomly assigned to receive either placebo or one of three different doses of the study drug: 11 participants received placebo; 7 participants received 4 mg of the study drug; 6 participants received 12.5 or 20mg of the study drug; and 19 participants received 35 or 50mg of the study drug) for a period of 24 weeks. Within each group, the dosage of the study drug was adjusted within a specific range to take account of the participant's body weight. The medicine or placebo were given subcutaneously (injected under the skin) once a week.

Open label phase

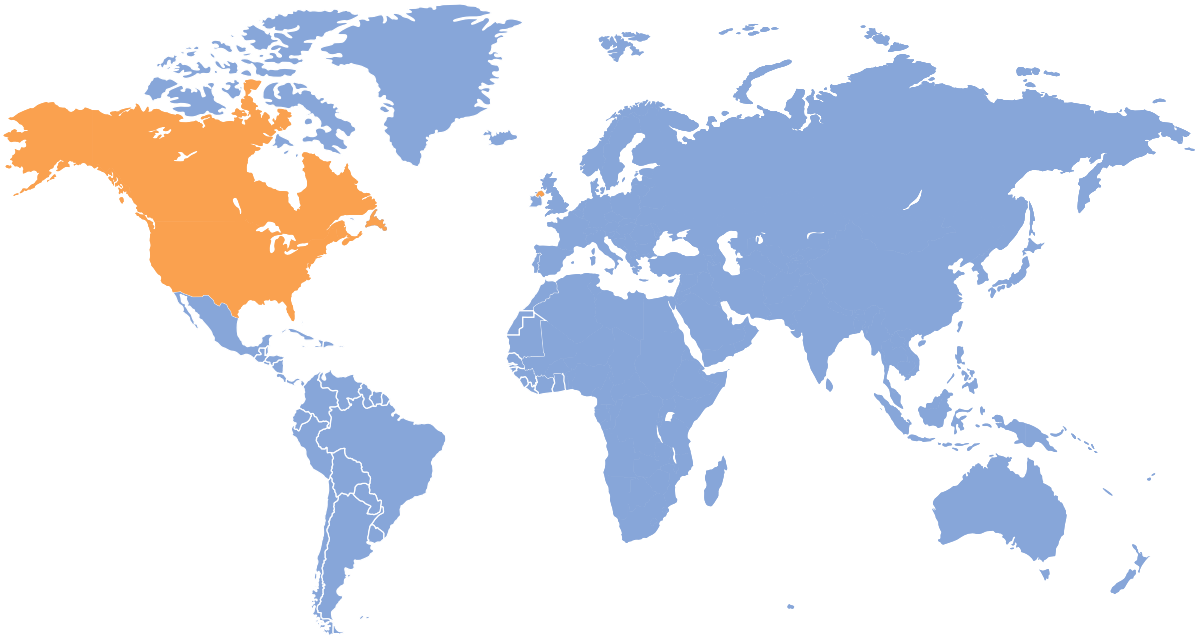
In an **open label study**, both researchers and participants are told who is receiving active treatment and who is receiving placebo.

In this study, all those who had taken part in the double-blind phase had the option to enter the open label part of the study. All participants in this open label phase received the active treatment (9 at the lowest dose, 8 at the middle dose, 26 at the highest dose).

The **open label phase** was due to last for an initial 48 weeks, with the option to continue taking the active treatment for up to 228 weeks, **an open label extension**.

The THUNDERJET study was a **phase 1/2** study. This means that it was one of the first studies using taldefgrobep alfa (RG6206).

Where was the study carried out?



The study was carried out in the United States and Canada

What was the study trying to find out?

What was the main question the researchers wanted to answer?

The main aim (primary endpoint) was to find out whether different doses of taldefgrobep alfa (RG6206) were safe in boys with DMD and whether they caused any side effects.

What other questions did the researchers want to answer?

Researchers also wanted to explore a number of other areas (secondary endpoints) in terms of how the study medicine worked in the body. The trial included measures to assess:

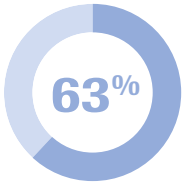
- the **pharmacokinetics** of the study drug (how it was absorbed, distributed, processed and excreted)
- the **immunogenicity** of the study drug (whether it produced an immune response)
- how the study drug affected **levels of myostatin** (a specific protein involved in the development of muscle)
- how the study drug affected **muscle mass**.

What were the results of the study?

How safe was the trial drug?

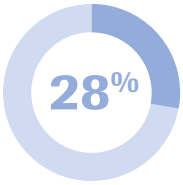
The study drug was considered generally safe and well tolerated with mild to moderate adverse events (AEs) (side effects). No new safety concerns were identified.

Side effects are medical problems that happen during a study. Doctors checked to see if the drug affected the number of medical problems participants had When someone has a health problem during a study, it can be hard to tell exactly what caused it. Sometimes the health problem is a side effect of one of the treatments. Other times the health problem can be caused by a patient's long-term disease, or by a new illness.

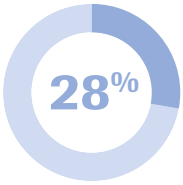


of participants had adverse events (AEs) (side effects) that were considered by the researchers to be related to study drug treatment. All were mild in intensity apart from 4 moderate events (injection site redness, injection site discomfort, injection site swelling, and headache). None of the related events were considered as serious

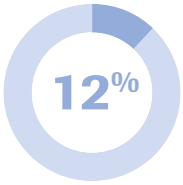
Of the side effects considered to be related to study drug treatment, **the most frequently reported were related to the injection site**:



Bruising



Skin redness



Skin irritation

A **serious adverse event (SAE)** is one that is life-threatening, requires hospital care or causes lasting problems. Eight SAEs were reported but the study investigators did not consider these to be related to treatment.

What did the study show about the drug's pharmacokinetics (how it works in the body)?

The study showed that, as expected, the study drug decreased levels of myostatin circulating in the blood. Myostatin levels further decreased as the dose of the study drug increased.

Imaging results from THUNDERJET suggested a positive effect on muscle mass and composition.

It was hoped that by decreasing myostatin, muscle size and strength in people with DMD would increase, but this theory was not proven in a larger study (SPITFIRE) designed to measure the effectiveness of the study drug.

How has this study helped researchers?

For a disease like DMD, where treatment options are limited, it is important to investigate potential new treatments in order to advance care. The valuable data collected during this study will be used to help advance understanding of DMD and to develop future therapies.

Where can I find more information?

Full title of study:	A clinical trial* to establish the safety, tolerability and pharmacokinetics (how a medicine works in the body) of different doses of an investigational medicine called taldefgrobep alfa (RG6206 – an anti-myostatin adnectin) in boys with Duchenne Muscular Dystrophy (DMD) – THUNDERJET
Short name of study:	THUNDERJET
National Clinical Trial number:	NCT02515669
European Clinical Trial number (EudraCT):	2015-005455-28
Study start date:	December 2015
Study end date:	April 2020

You can find more information about this study via the ClinicalTrials.gov website listed below:

https://clinicaltrials.gov/ct2/show/NCT02515669

If you or your child have took part in this study and have any questions about the results, please speak with your doctor or other medical staff at your study site.

If you have any further questions, please contact a representative at your local Roche office.

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