A clinical trial* to establish the effectiveness and safety of an investigational medicine called taldefgrobep alfa (RG6206 – an anti-myostatin adnectin) in boys with Duchenne Muscular Dystrophy (DMD) – SPITFIRE

DM-XX-00003400
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 effectiveness, safety and tolerability of taldefgrobep alfa (RG6206) in boys with Duchenne Muscular Dystrophy (DMD).

The study was not completed in full. A pre-planned analysis of the initial results of SPITFIRE showed that the drug did not meet the stated aims of the researchers. In this study, taldefgrobep alfa (RG6206) was found to be less effective than expected, although it was well tolerated by those taking part. As a result, the study was stopped early.

All clinical research contributes to the better understanding of diseases. Despite the fact that the SPITFIRE 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 SPITFIRE 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 **effectiveness, safety and tolerability of a potential treatment for DMD**

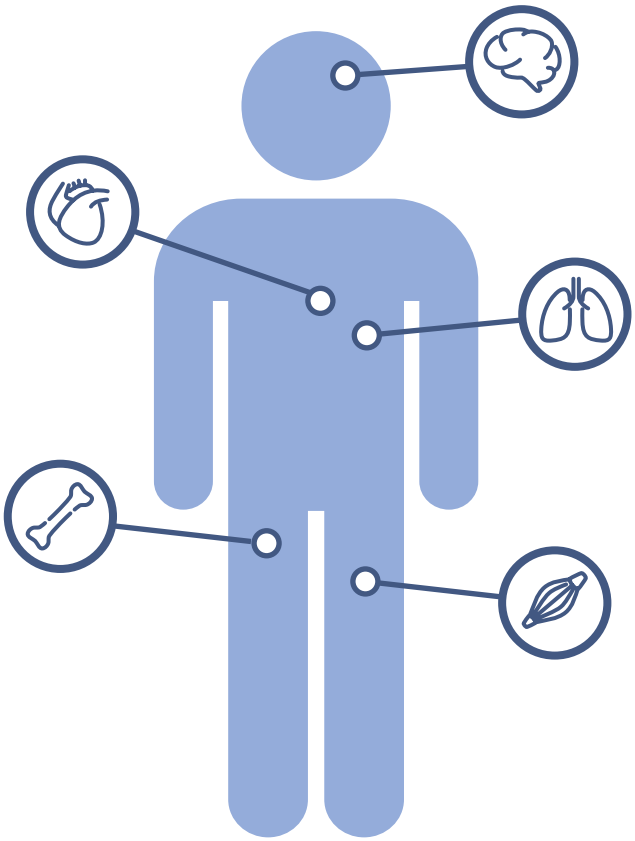
This study included **166 boys aged 6-11 in 13 countries**

In this 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, which is known as a 'randomized' study

The study started in July 2017 and stopped early in November 2019 as taldefgrobep alfa (RG6206) 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	48 weeks, with a further open label extension
Start date	July 2017
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

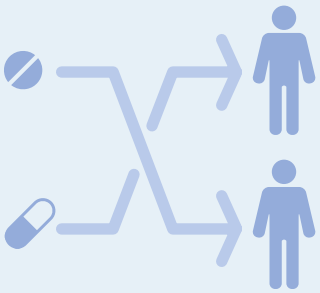
Who took part?	166 boys with DMD Aged 6–11
What were the **inclusion criteria** (who could take part)? 	■ Aged between 6 and 11 years ■ Male ■ Genetic diagnosis of DMD ■ Able to walk without assistance (ambulatory) ■ Minimum NSAA* score of 15 ■ Able to walk up 4 stairs in 8 seconds or less (4SC score) ■ Weight of 15 kg (33 lbs) or over ■ Taking a regular regimen (medication plan) of corticosteroids for DMD
What were the **exclusion criteria** (who could not take part)? 	■ 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 ■ Current or previous participation in a gene therapy study

***The NSAA (North Star Ambulatory Assessment) is a 17-item rating scale used to measure motor function abilities (e.g. how well the muscles work) in children with DMD, to a maximum score of 34. Even a 1-point change can make a significant difference to a child or parent's life in terms of gaining relative independence on a specific measure, such as being able to sit up by themselves.**

How was the study designed?

The study was designed in two parts: a **double-blind** phase and then an **open label** part. However, the study was stopped early, before all patients had completed the double-blind phase, after pre-planned analysis of the initial results showed that the drug being studied was less effective than expected.

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 trial, participants were divided into three equal groups (2 groups of 55 participants and 1 group of 56 participants) and chosen at random to receive a lower dose of the study drug (7.5 or 15mg), a higher dose of the study drug (35 or 50mg), or placebo. The medicine or placebo were given subcutaneously (injected under the skin) once a week.

A **futility analysis** was carried out, using data from all patients, when the first 49 participants had completed the double-blind phase. This means the initial results of the first part of the study were assessed to see how well the study drug was performing, if it is likely to meet its aims and to decide whether it would be appropriate to continue.

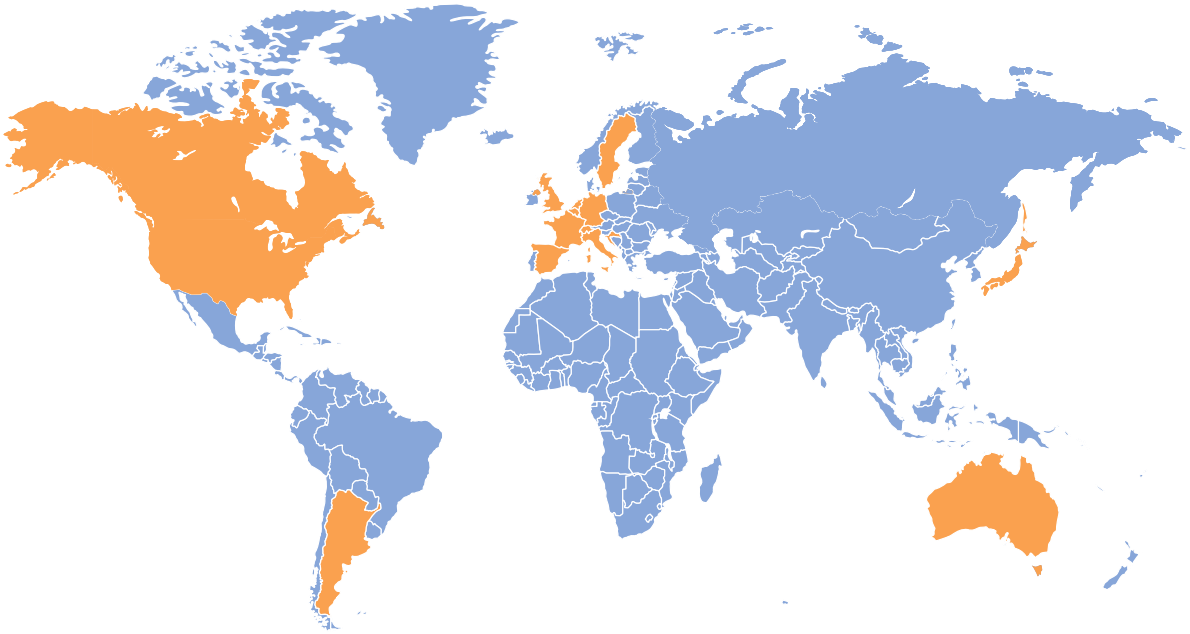
Open label phase

In an **open label study**, both researchers and participants are told who is receiving active treatment and who is receiving placebo. In the SPITFIRE study, all those who took part in the open label phase received the active treatment.

The open label phase of the study started as planned but was stopped early following the results of the futility analysis.

The SPITFIRE study was a **phase 2/3** study. This means that taldefgrobep alfa (RG6206) had been tested in a number of people with DMD before this study. It is also described as a **pivotal** study. This means it was designed to demonstrate the safety and effectiveness of the drug being investigated in order to support regulatory approval to make the drug available to patients around the world.

Where was the study carried out?



The study was carried out in Argentina, Australia, Belgium, Canada, France, Germany, Italy, Japan, Netherlands, Spain, Sweden, United Kingdom, United States

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 see whether participants improved according to the North Star Ambulatory Assessment (NSAA) scale. This is a scale used in children with DMD to measure motor function skills such as standing, climbing stairs, hopping and jumping.

What other questions did the researchers want to answer?

Researchers also wanted to explore a number of other areas (secondary endpoints). Participants were assessed to see whether they had improved in a series of tests of physical ability:

- The time taken to climb 4 stairs (4SCV)
- The time taken to stand up from lying down (stand from supine velocity)
- The time taken to walk or run 10 m
- Distance walked in 6 minutes (6MWD)
- Assessment according to PODCI, a questionnaire to measure basic mobility
- Muscle strength when extending and flexing the knee, measured using a device called ActiMyo

A further exploratory endpoint was to measure changes in lean body mass index.

What were the results of the study?

How effective was the trial drug?

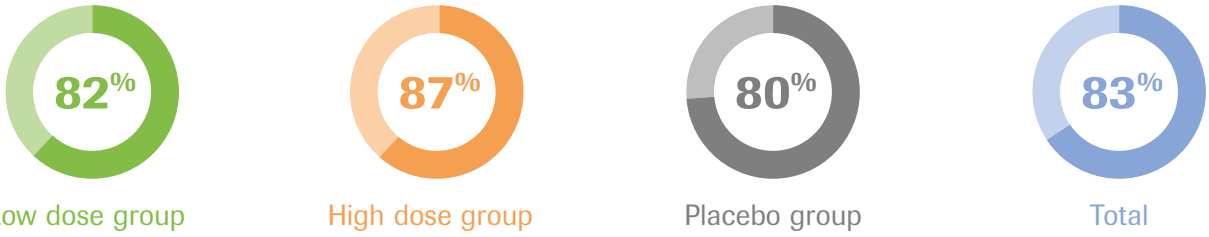
- The early analysis of the results did not meet a specified threshold established by the investigators, (an improvement of 1.5 points in the NSAA score versus placebo), which indicated there was a low chance to show an improvement in the NSAA scale at the end of the study .
- There were no meaningful differences in the secondary endpoints.
- This means that the drug being studied was not as effective as expected.

Safety

The study drug was well tolerated with mild adverse events (AEs) (side effects).

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.

In the double-blind phase of the trial, the percentages of boys experiencing side effects was as follows:



The most common side effects were (total number of boys with a side effect across all groups – taking drug or placebo):

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

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 effectiveness and safety of an investigational medicine called taldefgrobep alfa (RG6206 – an anti-myostatin adnectin) in boys with Duchenne Muscular Dystrophy (DMD) – SPITFIRE
Short name of study:	SPITFIRE
National Clinical Trial number:	NCT03039686
European Clinical Trial number (EudraCT):	2016-001654-18
Study start date:	July 2017
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/NCT03039686

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.

Address and telephone number for the sponsor of this trial:
F. Hoffmann-La Roche Grenzacherstrasse 124 CH-4070 Basel, Switzerland
+41-61-688-1111