SKIP-NMD (Skipping exon 53 of the dystrophin gene) PROJECT UPDATE

The SKIP-NMD project was originally funded by a European Union (EU) grant that allowed the completion of the first phase of this first-in-human Phase I/II clinical trial, 4053-101. It was an international project coordinated by Professor Francesco Muntoni of Great Ormond Street Hospital in London, involving a consortium of 10 academic partners across Europe (UK, France, Belgium and Italy) and the US. It also included the involvement of several companies Sarepta Therapeutics, Inc., Consultants for Research and Imaging (CRIS), and SYSNAV (expertise in indoor/outdoor robust navigation and positioning systems) who provided their new advances and techniques in translational Duchenne research, and six patient organizations: Action Duchenne, Association Française contre les Myopathies**,** Duchenne Family Support Group, Duchenne Parent Project France, Duchenne Parent Project Onlus, and Muscular Dystrophy UK.

The EU grant funding the SKIP-NMD project ended in April 2016, after which Sarepta Therapeutics, Inc. stepped in to fund and conduct an extension phase to the clinical trial. The extension phase of the trial will continue until October 2019. Many of the original academic partners and companies are still involved in the extension phase of the study.

The aim of the entire project is to develop a potential treatment for Duchenne Muscular Dystrophy by designing and testing a novel investigational drug developed by Sarepta Therapeutics, Inc. to restore dystrophin production in young people living with Duchenne who are amenable to exon 53 skipping, missing sections (or "exons") in the dystrophin gene such as: exons 52, 45-52, 47-52, 48-52, 49-52, 50-52, or others. The investigational therapy, SRP-4053, is an antisense oligonucleotide* of the morpholino type, i.e., a *PMO (phosphorodiamidate morpholino oligomer)*[1] and designed to 'skip' exon 53 of the dystrophin gene to permit production of a shortened, partially functional form of dystrophin protein. Approximately, 8% of all young people living with Duchenne have one of these mutations.

Objectives of the SKIP-NMD programme:

- Select the PMO that is most effective at skipping exon 53 and use the PMO (SRP-4053-101, the one selected) to perform required safety studies in animals before dosing patients in a clinical trial. This part was completed in the first part of 2014.
- Design and perform a clinical trial of SRP-4053 in 3 EU countries (UK, France and Italy). In the UK, two centres were involved: Great Ormond Street Hospital, led by Professor Francesco Muntoni and in Newcastle University Hospital by Professor Volker Straub. In France at the Institute de Myologie, Paris, led by Dr Laurent Servais and in Italy at the Policlinico Universitario A Gemelli, Rome, by Professor Eugenio Mercuri.

[1] *A synthetic antisense oligonucleotide is an artificial version of DNA or RNA that is used to modify gene expression. Gene expression is a process by which instructions in the DNA are converted to a working copy of RNA that directs production of a protein in a cell.*

- The clinical trial started at the end of 2014. Its aims were to examine the safety of SRP-4053 and its ability to increase production of shorter but functional dystrophin protein in muscle; and to explore the effect on walking ability (ambulation) and muscle function.
- Validate new outcome measures.[2]
- Assess the role of non-invasive *biomarkers 2** such as muscle MRI (magnetic resonance imaging), MRS (magnetic resonance spectroscopy), and serum biomarkers.

Part 1 (between October 2014 and June 2015)

- Designed to assess safety, tolerability and pharmacokinetics (levels of drug in the body and how the drug is cleared from the body).
- A 12-week, randomised, double-blind, placebo-controlled[3] dose-titration[4] study.
- 12 ambulant young people living with Duchenne, aged 6-15 years took part.
- Young people living with Duchenne were randomized 2:1 (SRP-4053: placebo).
- To be eligible, young people with Duchenne had to have a baseline six-minute walk distance (6MWD) of more than 250 m with a less than 15% difference from their screening 6MWD. A North Star Ambulatory Assessment total score of more than 17 *or* a rise time (getting up from the floor) of less than 7 seconds.
- Those randomized to SRP-4053 received weekly intravenous (IV) infusions at successively higher doses of the drug (from 4 mg to 30 mg per kilo of patient weight, with dose increases every 2 weeks).

A data and safety monitoring committee (DSMC) met in June 2015 to review safety data from Part 1 before endorsing continuation to Part 2.

Part 2 (started in June 2015 and is ongoing):

- A long-term Phase II open-label study (patients and researchers know that treatment with SRP-4053 is being received) at the dose identified in Part 1, to evaluate safety and efficacy.
- The 12 patients from Part 1 continued onto Part 2 of the study with an additional 13 treated patients that were newly enrolled.

---

[2] *Outcome measures are tests (for example how far somebody can walk in 6 minutes) that help researchers and clinicians monitor disease progression and effects of an investigational treatment. Non-invasive biomarkers are markers of disease and treatment response that can be measured without taking surgical or other hard-to-obtain samples. Serum biomarkers are molecules in the bloodstream whose level is affected by a condition and which can be easily measured (for example by a blood test). Together, these can be used to measure the effectiveness an investigational method of treatment in clinical trials.*

[3] *Placebo-controlled means some patients receive active drug and others receive a version (placebo) that contains no drug.* Randomised means that patients are assigned by chance to receive either active drug or placebo. Double-blind means *neither the patient nor the researcher knows whether the patient is receiving the active drug or placebo.*

[4] *Dose-titration means the dose is gradually increased over a period of several weeks until the target dose is reached.*

- The 25 treated patients are currently receiving 30 mg per kilo body weight per week of open-label SRP-4053.
- They will be compared to an untreated control group consisting of 14 patients who are not amenable to exon 53 skipping. This group will periodically complete the same set of functional assessments as the treated patients.
- Adverse event recording and safety monitoring are being completed for both the treated and untreated groups.
- The planned 48 weeks for Part 2 has been extended to 144 weeks. This is due to lessons learned in the development of eteplirsen, another PMO for exon 51 skipping that recently received accelerated approval by the US Food and Drug Administration.

Outcome Measures

- Primary outcome measures in Part 2 are the 6MWT and the % of dystrophin-positive fibres shown by immunohistochemistry (IHC).[5]
- Additional outcome measures include, but are not limited to, heart function testing, monitoring aspects of leg and arm movement during daily activities (actimetry)[6*], dystrophin intensity by IHC, dystrophin protein by *western blot*[6], and exon skipping by reverse transcription polymerase chain reaction (RT-PCR).[7]

A data and safety monitoring committee met to review Part 2 safety data in April 2016. No major safety signals were identified and it was recommended to continue the study with no change. At that time, approximately 600 intravenous infusions of SRP-4053 had been completed.

As of September 19, 2016, enrollment was considered complete with 25 treated and 14 untreated patients enrolled. The first patient's infusion was administered on 13 Jan 2015, and the last patient's last visit is expected to take place in May 2019. The projected completion date for the clinical study report (CSR) is October 2019. The outcome of dystrophin production in the muscle, comparing the baseline muscle biopsy to the one performed at Week 48, will be communicated prior to the finalization of the CSR.

Additional resources:

1) SKIP-NMD website: http://www.skip-nmd.eu/
2) SKIP-NMD webinar (September 2014): https://www.youtube.com/watch?v=P7q-MLPdKM4
3) Exon skipping round table Action Duchenne conference 2016: http://www.actionduchenne.org/wp-content/uploads/2017/02/Annemieke-Aartsma-Rus.pdf

---

[5] *(an analytical technique to measure amounts of specific proteins)*

[6] *home-based walking analysis and also adapting the technology/apparatus for assessing the motor activity of the upper limbs*

[7] *(a method to look at RNA expression and size – exon skipped RNAs are smaller)*