Dynacure Jun 2020

SUMMARY

- **Dynacure started the clinical development of its investigational product DYN101 into in a Phase 1-2 study in 2020**
  - **First patient received product in Q1 2020**
  - **The study could finish by end of 2022**
  - **The study is currently running in following European countries: Belgium, Denmark, France, Germany, United Kingdom and Netherlands**
- **Goal of the study: to learn about the safety and tolerability of DYN101 in patients > 16 years old with X-linked or autosomal dominant CNM (mutations in MTM-1 or DNM2).**
- **Should the results of the phase 1-2 be encouraging, then further clinical trials will be needed to show whether or not the treatment is effective in patients of all ages.**

Dear CNM Community,

At the request of several CNM patient organizations, we would like to give some information on our ongoing work to bring our investigational product DYN101 through clinical development and approval for use in the treatment of CNM patients with MTM-1 or DYN2 mutations. Please be aware that we are still in the phase of developing DYN101 and as such are limited as to what we can present according to regulations around the world. The scientific background is complex, so that we have tried to simplify it as much as possible to be understandable and there is a glossary at the end that tries to explain some of the terms used.

As you maybe are aware, DYN101 is an antisense oligonucleotide (ASO), which is expected to decrease the production of a protein, named dynamin-2, which is elevated in patients with X-linked CNM (XLCNM[1]), and thought to be overly active in patients with DYN2 mutations (ADCNM).

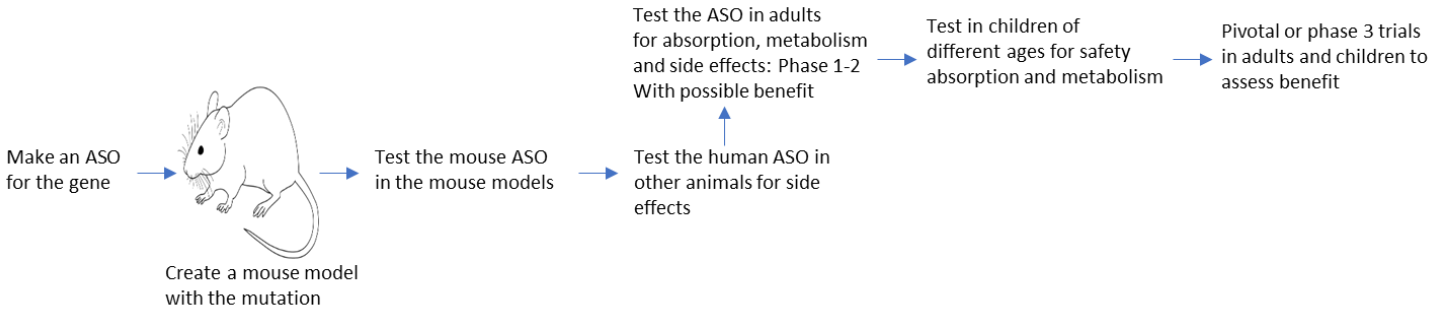
Studies in mouse models of these two types of diseases have demonstrated promising efficacy of this treatment approach, which is why Dynacure is developing the product in patients with these mutations. There are patients with other CNM mutations that are not currently planned to be treated with this therapy as there is more experimental work to be done in the laboratory before proceeding to test the drug in these other indications.

1. How does a therapy get developed?

First, the potential treatment needs to show benefit in in vitro (in a test tube) and/or animal models of the disease that have the MTM1 or DYN2 mutations. Furthermore, the treatment then needs to be tested to be sure that it will not be unacceptably harmful to humans. Based on this data, and if the treatment could be

[1] In some countries, including UK, XLCNM is referred to as x-linked myotubular myopathy

acceptable, it is then tested in a “first in human” study, or phase 1 (normal healthy volunteers) or phase 1-2 (patients with the actual disease).



These first studies look at the effect of different doses of the treatment in terms of side-effects (called safety) and tolerability (are the side effects minor or not?). In addition, the absorption of the drug, whether or not it reaches the target (for CNM, the concentration in muscle cells) in sufficient concentrations, is measured. Dynacure has selected to carry out a phase 1-2 trial to study the safety and potential beneficial effects of DYN101 in patients rather than normal healthy volunteers, in order to develop the treatment faster. This will be more relevant to see the side effects, tolerability, and whether DYN 101 reaches muscle in sufficient amounts in patients with the specific mutations. Dynacure will also evaluate whether or not there is any change in how the patients feel or whether they are able to improve on a series of tests.

Should the results of the phase 1-2 be encouraging, then further clinical trials will be needed to then show whether or not the treatment is effective in patients of all ages in a controlled fashion (which means that there will be possibly some patients on a placebo, or not effective drug without knowing it for the patient).

2. What are the goals of the Phase 1-2 clinical trial?

- To learn about the safety and tolerability of DYN101 in patients > 16 years old with X-linked or autosomal dominant CNM (mutations in MTM-1 or DYN2).
- To learn about the kinetics/distribution and excretion of the drug.- see glossary
- To learn about the extent to which the drug is available in muscle tissue.
- To determine the right dose for further development that is both well tolerated and is expected to show benefit to patients.
- If the correct dose is found, to demonstrate whether and how strongly a positive effect is seen on signs and symptoms of the disease.

3. When will the study start and where will it be run?

- First patient received product in Q1 2020
- The study could finish by end of 2022
- The study is currently running in following European countries: Belgium, Denmark, France, Germany, United Kingdom and Netherlands

4. What if I don't live in Europe, can I participate?

Dynacure is a Biotechnology company based in Europe that has decided to initiate first trials in certain European countries for the moment. Patients from outside Europe may contact investigators at sites in Europe that will be participating in the phase 1-2 trial to see if they can be included. The participating sites are published on www.clinicaltrials.gov and https://www.clinicaltrialsregister.eu once they have been selected. The phase 1-2 trial will require that patients visit the study site every week for at least 6 months and Dynacure will not be able to cover the costs for moving to Europe in order for them to participate.

5. How many patients will be included and how do patients qualify for participation?

- The study will include 18 patients aged 16 and above. 9 with the MTM1 mutation and 9 DNM2 patients
- Patients must be symptomatic, preferably be able to walk a few steps, and have mild to moderate disease. All the eligibility criteria will be on the clinical trial register: www.clinicaltrials.gov https://www.clinicaltrials.gov/ct2/show/NCT04033159?term=Unite-CNM&draw=2&rank=1

6. Why is Dynacure starting their trials in adults? Another company focuses on infants and young children.

It is Dynacure's intent to develop DYN101 to treat infants, children and adults with XLCNM as well as ADCNM (DYN2) of all ages, not just XLCNM.

In principle, new therapies should always be tested first in adults for safety and potential efficacy prior to going into children/infants. Exceptions are made if the disease only is seen in children, or if results in adults would not be useful for the paediatric population. Dynacure is testing out a new interventional pathway with DYN101, which leads to a reduction of the level of the protein DNM2, and there are adults with these mutations who can test DYN 101 prior to studying it in children.

The safety, tolerability, and efficacy of the therapy is still unknown. As the pathway that DYN101 suppresses is important for many functions in the body, it is important to ensure that a proper dose is selected that will not harm children and infants. There are adults with XLCNM and ADCNM that can participate in the initial trials, and all the necessary steps to ensure safety for this group of patients are being implemented. Once safety and a possibly effective dose is selected, then Dynacure intends to immediately start clinical trials in infants and children of all ages, as well as in adults, both for XLCNM and ADCNM.

7. Dynacure's plan looks like it will take a long time to reach infants and children. Is there no possibility to go faster?

Dynacure has evaluated many different scenarios to come up with the safest, fastest route for all patients including infants and children. Once safety and a possibly effective dose is selected, then Dynacure intends to immediately start clinical trials in infants and children of all ages, as well as in adults, both for XLCNM and ADCNM.

8. Why is Dynacure including mild-moderate patients only in their first trials?

The term “mild to moderate” is a term used by the medical profession to classify the degree of disability patients with neuromuscular disease have. It is clear to Dynacure that patients with even a “mild” classification could find that their disability is important.

Dynacure has opted to include “mild-moderately affected” patients > 16 years in the first trial for the following reasons:

- Patients who are still able to walk a few steps have potentially some muscle that can still be recovered more quickly with treatment. Those individuals who are not able to use their upper limb or lower limb muscles are possibly going to take a much longer period of time to show benefit with treatment. Furthermore, those individuals with long-standing incapacity to use upper or lower limbs are more likely to have developed contractures that would make any benefit difficult to show.
- There are many more, and different, types of tests of the upper and lower limbs to evaluate the benefit of a therapy for mild to moderate patients, than there are for more severely affected patients.
- There is a need for study participants to have enough residual muscle to allow for repeated muscle biopsies that are required in the study to evaluate whether the ASO reaches the muscle, whether the concentration of the ASO in the muscle is sufficient, and whether the ASO has normalized the look of the muscle under the microscope.
- Whether infants and children show improvement with a treatment is more difficult to assess than in adults as children are constantly acquiring new skills and normally increase their strength as they grow older.

9. Why is Dynacure developing DYN101 when there will be gene therapy to correct the cause of the disease with a single injection?

The gene therapy in development today will only treat patients with mutations in one specific gene (XLCNM) and is currently being investigated in children under the age of 5. It is also unclear if treatment at a young age will benefit patients as they become older and develop new muscle tissues. In addition, the long-term safety of gene therapy remains unknown until longer follow-up is achieved.

DYN101 is planned to be administered with an IV infusion for patients with XLCNM and ADCNM of all ages.

The testing in mice that have the same mutations as in patients with MTM1 and DYN2 mutations have shown encouraging results and it is hoped that a beneficial effect will be seen in patients with these mutations.

10. What is ASO technology?

Antisense technology aims to bind a synthetic drug to a specific messenger RNA that is involved in a particular disease and to stop unwanted proteins from being produced. For X-linked and Autosomal Dominant (DYN mutations) CNM, the ASO is created to decrease the amount of dynamin 2 protein which is too high or too active. Antisense oligonucleotides are short chemically modified strands of nucleotides (parts of DNA) .They bind to parts of the messenger RNA that produce proteins, that lead to a particular disease. In

many cases, when the ASO or antisense drug binds to the specific mRNA, it results in degradation of the mRNA, which means the targeted or unwanted protein cannot be produced. Therefore, the overall amount of the targeted protein in the cell will be reduced.

11. DYN101 is an ASO and treatments with these types of drugs have been associated with side effects, some of which are worrisome. What will Dynacure do to prevent this?

There are already several approved therapies using ASOs, particularly for rare genetic diseases. Our partner, Ionis Pharmaceuticals, is a leading developer of ASOs and have had a lot of experience and improved the technology to mitigate these safety issues.

Side effects have been seen with previous versions of ASOs, and Dynacure has been working with Ionis to mitigate the side effects observed.

Injection site reactions are expected to be lower with the type of drug that is DYN101 (a 'cEt oligo') as compared to older versions of ASOs. In addition, initial trials will be performed using the product with an IV infusion, therefore injection site reactions will be further moderated. Sub-cutaneous injections (which could eventually be self-administered) may be tested later.

Effects on platelets have been noted with other ASOs. It is planned to exclude patients with low platelet counts initially for clinical trials, however these patients may be included later depending on the ongoing investigations. From experience with other ASOs, stoppage of treatment leads usually to a reversal of platelets back to normal. Platelets will be monitored regularly in clinical trials of DYN101.

ASOs like many other therapies accumulate in the liver. Patients with abnormal liver function will be initially excluded from DYN101 trials.

ASOs are broken down for the body to then be able to get rid of them (excreted) by endonucleases that are enzymes present in almost all cells, and the degradation products (which are the small pieces left to eliminate) are then passed by the kidney. Dynacure will not include patients with any evidence of kidney malfunction in their initial trials in order to mitigate any potential untoward effects of the breakdown of the ASO.

The liver and kidney functions will be monitored in clinical trials of DYN101 to monitor the safety of the treatment.

From animal studies with this type of drug, complement activation (supportive part of immune system) and inflammatory reactions, including inflammatory effects on the heart are expected, and were indeed seen in our DYN101 animal studies too. In this study complement activation will be checked on a regular basis until it can be confirmed that these effects are limited to these animal species only.

12. When can I (or my child) participate in clinical trials?

It is Dynacure's intent to develop DYN101 to treat infants, children and adults with XLCNM as well as ADCNM of all ages.

The future trials that will include all ages will depend on the results of the phase 1-2 trial. Should the results be encouraging, it is Dynacure's intent to study patients of all ages in Europe and outside of Europe,

depending on local acceptance of the proposed clinical trials. It is too soon to give a specific date as it will depend on how long it will take to recruit the patients for the phase 1-2 trial as well as the outcome of the trial.

Priority will be given to adults and children who have participated in the Natural History Study (NHS), as it will be faster to show a benefit in patients that have been studied for a longer period and should the treatment be effective and safe, it will allow for a quicker acceptance of the treatment by the authorities and be available sooner as a treatment for you or your child.

There is the possibility to be included in trials even if you or your child have not been in the NHS. The sites where future clinical trials will be held will be available on www.clinicaltrials.gov and https://www.clinicaltrialsregister.eu websites once the phase 1-2 trial has shown that the treatment is safe and that the treatment has been able to reach muscle in the desired amount.

You can contact the doctors that are listed in these websites to see if you or your child can participate once these trials are registered.

GLOSSARY

XLCNM: X-Linked Centronuclear, or Myotubular Myopathy, or MTM1 mutation

ADCNM: Autosomal Dominant Centronuclear Myopathy, or DYN2 mutation

ASO Anti-sense oligonucleotide- it is a synthetic molecule that looks like DNA or RNA that binds to the mRNA to stop it producing an abnormal protein. Diseases that are currently approved with ASO technology include familial hypercholesterolemia (an inherited disease with extremely high cholesterol levels), severe viral infections of the eye, macular degeneration (which leads to blindness) amongst others.

CNM: Centro-nuclear Myopathies

DNA stands for deoxyribonucleic acid. DNA is present in every cell of the body and is responsible for all the functions of the cells that make up a body. Changes in the DNA or mutations, can lead to abnormalities in the proteins that are involved in the normal function of a cell.

In vitro: Investigation done in a test tube instead of in a live animal or human.

Mutation: Change in structure of a gene which is a part of DNA. A mutation can be inherited from a parent or it can occur spontaneously.

Kinetics: The uptake of a substance into the body and the subsequent elimination of it. During the study of a drug, the kinetics include how much or the drug is absorbed by the body, what are its concentrations in blood or other tissues, and how long it takes to be eliminated from the body.

Messenger RNA or mRNA: Messenger Ribonucleic Acid that translates information from DNA into a protein. For example, the MTM-1 gene has a mutation of its DNA. mRNA then translates the change in the MTM gene into an abnormal protein (an abnormal enzyme) which then leads to the X-linked form of CNM.

Degradation of mRNA: Change in structure of the mRNA so that it no longer functions properly. This usually means that the mRNA will not produce a protein.

IV infusions: Injection into a vein of a liquid substance

Platelets: Small structures in the circulating blood that aid in the clotting of blood.

END