a joint effort by your family advocates & the DCAA research team

Newsletter

CONTENT

G'day!

Welcome to the second newsletter about Dutchtype CAA in Australia! Have you read the first on that came out in July 2023? A lot has happened since and we would love to catch you up! Who are we?

My name is Sanne van Rijn and I am a member of a DCAA family in the Netherlands. The Dutch patient association was initiated by my mum, who is a gene carrier and patient. In 2007, she recognised the lack of information, support, healthcare and research, and decided to jump in. I have been there from the start and since then, our work and role continues to grow. Since 2021 I have been working parttime as a professional patient advocate.

Since our kickoff in 2007 we have built amazing relationships with researchers working on Dutchtype CAA, including the team in Perth. Together with them and researchers from Leiden and Boston and pharmaceutical company and partner Alnylam, we are in a consortium that works on TRACK DCAA, a study you might be part of. If so, thank you very much!

That study gave us a lot of information (and continues to) about how DCAA actually acts in the brain and how to measure the progress of the disease as effectively as possible. The other goal of the study has always been to be a 'trial run in' study, a sort of testcase for setting up a drug trial. Alnylam has been working on an RNA therapy, ALN-APP, now known as Mivelsiran, that hopefully helps reduce the production of amyloid precursor protein (APP), a precursor to the troublesome amyloid beta that causes DCAA.

To bring that study to both the Netherlands and Australia, I have been working closely with Alnylam's team members. Together we have worked on what the protocol should look like, how to make participation as comfortable as possible, how to communicate about the study and how to include DCAA family members perspective in all that is being done.

To be able to support families on both sides of the globe, I spent 4 months in Freo and Albany in 2023. During that time, I spent time with Dini and Dorinda (who you know as Plug family members) and Helen and Carol de Jong (who are from a different W.A. family with DCAA), who have been actively advocating for Australian Dutchtype CAA families for years now.

Together with them, I also met with many of the Plug family members, including during two family barbeques. Part of that was to be able to support you and get a grip on what you actually need. The other part was to get your perspective on participation in research and to find out what actually helps you to participate and what holds you back.

To everyone who has met with me and took the time to engage, I am very grateful. I know it is not easy to have DCAA on the forefront of your mind and I thank you for opening up. Your input has helped us in many ways to promote DCAA research in Perth. A special thanks to Carol and Rob, and their commitment to hosting the barbeques.

In the meantime, I worked closely with the research team (Ralph, Kevin, Hamid, Samantha, Dan and Ana) and helped them to bring their amazing research efforts into DCAA and your perspective and needs closer together. It is incredible to realise that for an ultrarare disease like Dutchtype CAA, there is extensive research going on in two places in the world.

Now, you might wonder where that leads to. And I have to honour to bring you incredible news: Dutchtype CAA family members WILL be able to take part in the phase II drug study with Mivelsiran!
The Perth team now has approval from the Australian regulators to move forward, which means the protocol has been reviewed by professionals and has been deemed safe (enough) and ethical, the information gathered so far by Alnylam has shown enough effect of the drug to move forward and the design of the study reflects what needs to be done to further investigate whether the drug does what we hope it does and what is being asked of participants outweighs potential advantages.

This does not mean that gene carriers and patients will get effective treatment, but it does mean we can contribute to the development of a potential treatment. This newsletter is our effort to explain you everything you need to know about what a phase II drug study means, what the study looks like, who can participate and why, and what participation looks like for you as an individual.

Unfortunately, European regulators have not (yet) approved the drug study, which means you as Australian family members will have an opportunity that Dutch DCAA families do not have (yet). That means it is the first time in the history of DCAA research, that you are actually ahead of the Netherlands when it comes to research into the disease.

Speaking from a DCAA family member perspective: being able to be part of a drug trial and working towards a potential treatment has been something we could not have dreamed of only 5 years ago. I have great hope that many of the Dutch and Australian will work together to make this study successful and will give participation serious thought.

Being part of a Dutchtype CAA family can be hard and we are doing what we can to support you. On behalf of the whole team: thanks for taking the time to read this newsletter. If you have any questions, please don't hesitate to let us know!

With warm regards,
Sanne

WHO ARE WE?

Sanne van Rijn, Msc.
Psychologist & DCAA family advocate

Prof Hamid Sohrabi
Director of the Centre for Healthy Ageing at Murdoch University

Kevin Taddei
Research Manager Neuroscience Research Group

Dr Samantha Gardener
Research fellow

Dr Dorinda 't Hart
Research Associate in Social Sciences & DCAA family advocate

Prof Ralph Martins,
Foundation Chair in Aging and Alzheimer's Disease

Dini Plug, Msc.
School teacher &
DCAA family advocate

Carol Harper
Entrepeneur &
DCAA family advocate

Dr Helen de Jong
Clinical Research Coordinator &
DCAA family advocate

Alzheimer's Research Australia

HCHWA-D
VERENIGING KATWIJKSE ZIEKTE

WHAT DOES MIVELSIRAN DO?

Mivelsiran is an RNAi therapy that is being developed by Alnylam. The company has pioneered in developing these therapies since 2002. They have been on the forefront of developing therapies that silence disease causing genes. In 2018, the world's first RNAi therapeutic —and Alnylam's first commercial medicine—was approved.

Their RNAi therapeutics are currently available in more than 60 countries.
Mivelsiran is one of the therapeutics Alnylam is currently developing. As you might know, our DNA contains many messages, including what proteins to produce. That message is brought to production parts of our cells by messenger RNA. Mivelsiran potentially silences the message for producing amyloid precursor protein (APP), a protein that eventually leads to amyloid beta, and can help reduce the levels of the toxic protein in the brain.

The potential treatment does not target the specific mutation that causes Dutchtype CAA, it targets APP production in general. That means that the drug potentially has an effect on sporadic CAA (the non-genetic version of CAA that effects 1 in 4 older adults) and Alzheimer's disease (AD) as well. Therefore, in the phase I study the company conducted, patients with early AD were included, and in phase II both people with Dutchtype CAA AND people with sporadic CAA can participate.

What Are RNAi Therapeutics?

RNAi therapeutics are a type of gene-silencing medicine.

They represent an innovative, clinically-validated approach to treating rare and common diseases.

How Do RNAi Therapeutics Work?

RNAi therapeutics silence the genes that cause or contribute to disease.

Many genes contain the instructions for making proteins. Proteins are the "workers" in the biochemistry of life and are responsible for almost all cellular and body functions.

Sometimes a mutation in a gene results in a faulty protein that causes disease, or other times, a normal gene produces a protein that contributes to disease. RNAi therapeutics can treat disease in both scenarios by interfering with the production of these unwanted proteins.

They use specially designed small interfering RNA (siRNA) to target messenger RNA (mRNA) that genes use to tell the body how to make the unwanted proteins. The mRNA molecules are degraded before they can pass the message.

How Do RNAi Therapeutics Differ From Conventional Medicines?

They act before proteins are made.

Most conventional pills, injections and infusions work by directly targeting proteins involved in disease after they are already made. In contrast, RNAi therapeutics disrupt the production of unwanted proteins, acting **before** they are made. If a disease is compared to a leaking tap, then RNAi provides a new way of fixing the leak, rather than mopping up the floor after the leak has occurred.

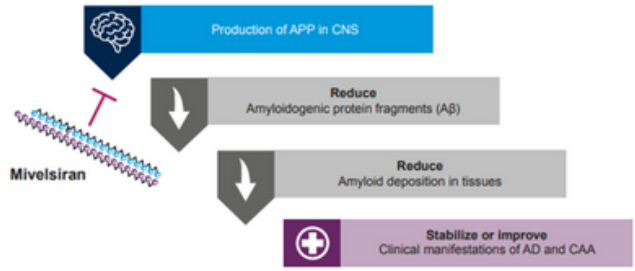
They are long-lasting.

Many conventional medicines must be taken daily to be effective. In contrast, a single dose of an RNAi therapeutic can reduce the levels of a protein for months, which means that it can be administered infrequently—every three or six months, for example. Patients can be prescribed and administered an RNAi therapeutic to optimally treat their disease without worrying about having to take a daily dose.

How Does RNAi Differ from Other Genetic Medicines?

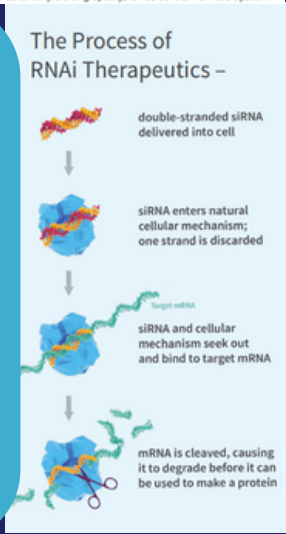
RNAi therapeutics are a class of medicines within the broader category of genetic medicines that employ DNA and/or RNA to treat disease but they differ in an important way.

Unlike some genetic medicines such as CRISPR-based treatments, RNAi therapeutics don't permanently alter the genes (DNA) within cells. This is a key safety feature of the RNAi approach to treating disease.



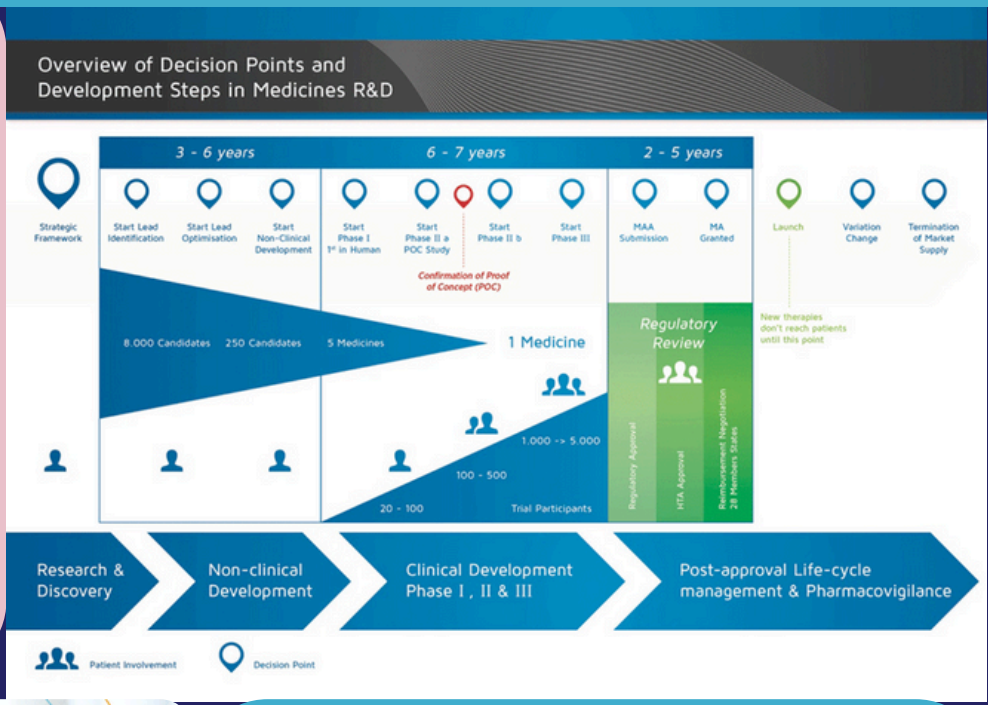
Aβ, amyloid beta; AD, Alzheimer's disease; APP, amyloid precursor protein; CAA, cerebral amyloid angiopathy; CNS, central nervous system.

Click here for Alnylam's video explaining RNA therapies



PHASE II AND MIVELSIRAN

Drug development is a complicated process. On average, it takes on average over 12 years and costs over €1 billion to do all the research and development necessary before a new medicine is available for patients to use. The development of a new medicine can be divided into 10 different steps.



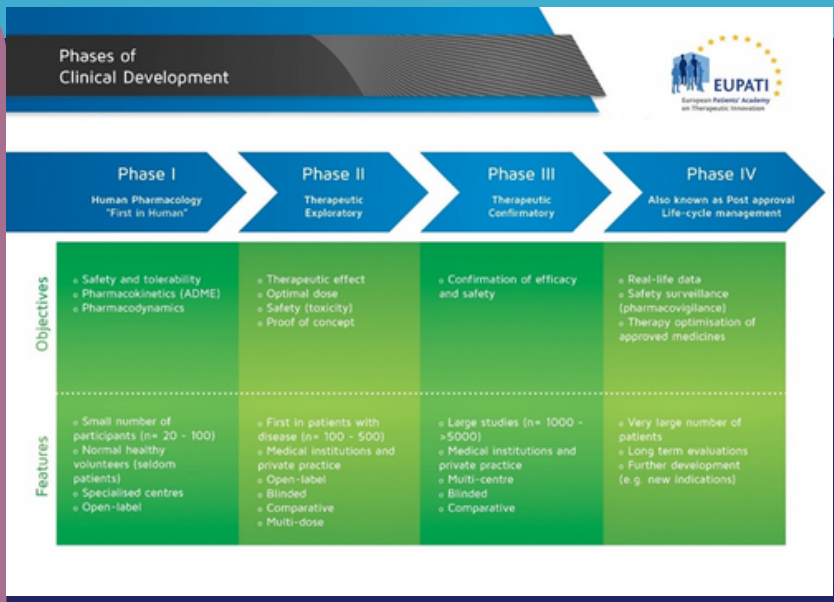
Part of this was also explained by Alnylam's team during the webinar 'A potential treatment: introducing ALN-APP' on August 10th 2023. Click here for the recording

To ensure safety and efficacy, drug companies like Alnylam go through these phases of research before a drug is actually eligible "to go to market". That starts with non-clinical development, meaning not in humans. Alnylam's Mivelsiran was first tested in a lab, in petri dishes under a microscope for example, and was then tested on animals. Because this proved successful, meaning the drug did not cause concerning adverse effects and showed an effect, Alnylam was able to move forward to study the drug in humans. In the first phase of their study, Alnylam studied Mivelsiran in patients with early Alzheimer's. Before we go into those results, let us explain what a phase I and II look like and why.

PHASE II AND MIVELSIRAN

What is Early Clinical Development?

Early Clinical Development refers generally to the first studies of a medicine in humans – typically known as Phase I and Phase II trials. The stages of clinical development are usually represented as consecutive phases, as shown in the image.



What are the objectives of Early Clinical Development?

Studies in early clinical development focus on the safety and tolerability of a new drug. They also try to show that the drug can have the intended effect. The following key questions must be answered during early clinical development.

Phase I

·Is the drug safe in humans? At what levels? (Tolerance)

·What does the body do to the drug? (Pharmacokinetics (PK))

·What does the drug do to the body? (Pharmacodynamics (PD))

·Does the drug do what we expect it to do?

Phase II

·Is the drug safe in patients? (Safety)

·What does the drug do to the body? (Pharmacodynamics (PD))

·Does the drug seem to work in patients? At what dose(s)? (Effect)

·How should confirmatory trials be designed? (Endpoints, target population, other medications being taken (concomitant), etc.)

·What interactions are there? (Drug-Drug interactions, interactions with food and drink, etc.)

PHASE II AND MIVELSIRAN

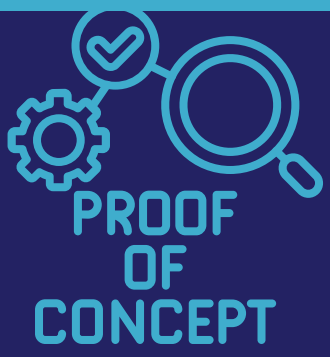
What are the requirements for early clinical development?

Before early clinical development of a drug can begin, there must be enough data from non-clinical studies supporting the drug's safety for human administration. Then, a clinical development plan must be compiled which:

·Establishes the objectives of the clinical programme.

·Sets out the requirements that must be fulfilled in order to consider a Proof of Concept as positive.

·Describes the design and conduct of Phase I and Phase II clinical studies.



How are decisions made during early clinical development?

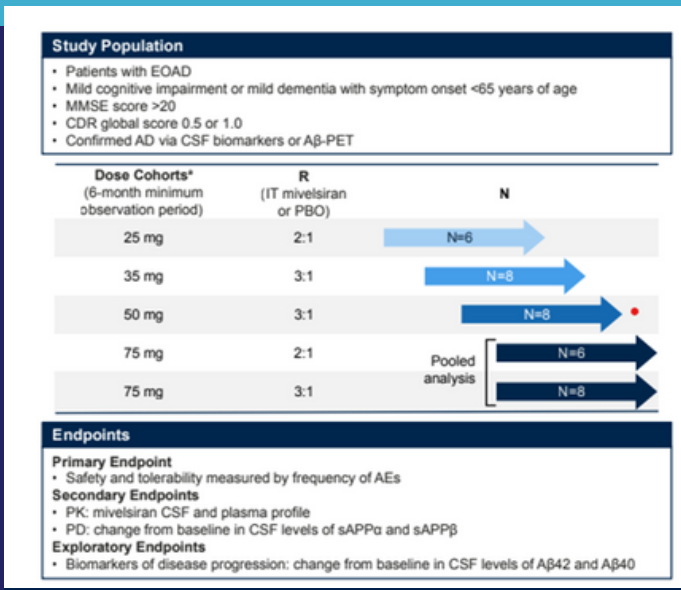
Development decisions are data-driven. The results of studies are carefully considered before development continues. The Proof of Concept must be achieved and a dosage schedule selected before further development can continue. If early clinical development of a drug returns positive results, then more testing of the drug can continue. Unclear results during early clinical development require further testing and assessment before decisions can be made. If early clinical development of a medicine returns negative results – for instance, if the concept is not adequately proven or unacceptable safety issues arise – then development of the medicine stops.

MIVELSIRAN AND PHASE I RESULTS

A number of early AD patients received different dosages of Mivelsiran in the first study of the drug in humans. Trying different dosages of a drug is a regular thing to do in early clinical phases, because in this way, the developers get an understanding of if a drug actually reaches its target (in this case APP production) and what dosage is necessary to cause an effect.

As you read on the previous page, the goal of a phase I study is not necessarily to study the effect of the drug, the main focus is to see if it can be safely processed in the body. The phase I study is ongoing for over a year now, and Alnylam has published their first results, and presented these to AD and CAA researchers during conferences.

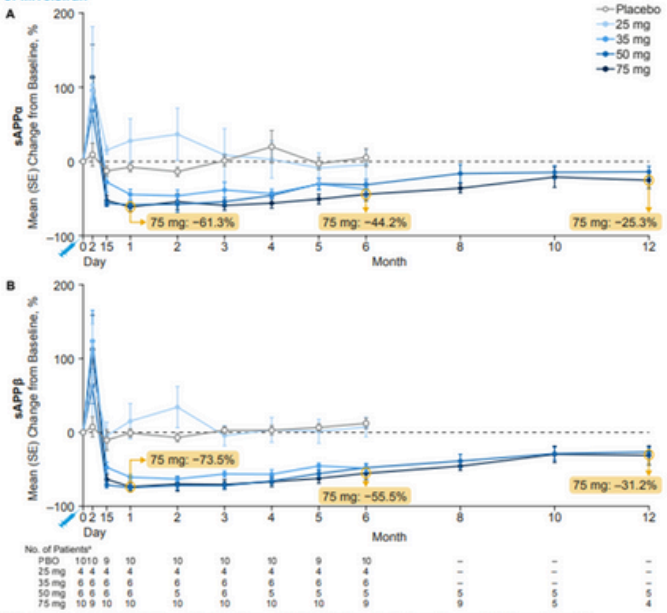
So far, the drug seems to be processed by the body safely, because none of the participants experiences adverse events related to having the drug administered. Some did feel uncomfortable after the lumbar puncture (had a headache), which we know from TRACK DCAA can happen. Also, the drug seems to reach its target and lower APP production, in some dosages even up to 12 months.



Pharmacodynamics – CSF sAPPα and sAPPβ

- A single dose of mivelsiran above 25 mg rapidly reduced CSF sAPPα and sAPPβ levels.
  - Peak mean reductions from baseline with mivelsiran 75 mg were 61.3% for sAPPα and 73.5% for sAPPβ at Month 1 (**Figure 3**).
- Dose-dependent reductions were sustained through Month 6.
- Reductions were observed through 12 months with single 50 mg or 75 mg doses.

Figure 3. Robust and Durable Reductions from Baseline in CSF sAPPα and sAPPβ after Single Dose of Mivelsiran

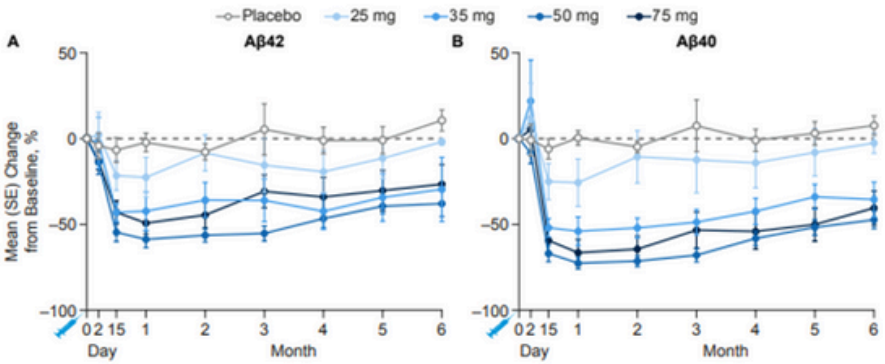


Data shown as of July 10, 2024. Time points with n≤3 are not plotted. *Numbers of patients are the same for both panels A and B.
CSF, cerebrospinal fluid; PBO, placebo; sAPP, soluble amyloid precursor protein; SE, standard error.

Exploratory Biomarkers – CSF Aβ42 and Aβ40

- A single dose of mivelsiran above 25 mg reduced CSF Aβ42 and Aβ40 levels.
  - Peak mean reductions with mivelsiran 75 mg were –49.3% for Aβ42 and –66.5% for Aβ40 at Month 1.
- Reductions were sustained through Month 6 at doses of 35 mg or higher (**Figure 4**).

Figure 4. Marked Reductions from Baseline in CSF Aβ42 and Aβ40 after Single Dose of Mivelsiran



Data shown as of July 10, 2024. Placebo: n=10, except Days 2 and 15, Months 5 and 6: n=9; 25 mg mivelseran: n=4; 35 mg mivelsiran: n=6, except Month 6: n=4; 50 mg mivelsiran: n=6, except Months 4–6: n=5; 75 mg mivelsiran: n=10, except for Aβ42 assessment on Day 2: n=9.
Aβ40, amyloid beta peptide length 40 amino acids; Aβ42, amyloid beta peptide length 42 amino acids; CSF, cerebrospinal fluid; PBO, placebo; SE, standard error.

WHAT DOES PHASE II LOOK LIKE?

How long does the trial take?

Being part of a drug study can be quite intense. Because safety and efficacy are so important to prove, drug studies look very different from what we call “natural history studies”, like TRACK DCAA, that focus on how a disease progresses. During a drug study, there are more study visits.

Alnylam’s called this drug trial cAPPricorn-1 and the phase II will be done in 70 sites around the world. The design of the study was informed by a group of experts called a steering committee, that included experts on both sporadic AND Dutchtype CAA.

Learnings from TRACK DCAA were largely informing what methods are used in cAPPricorn-1 to measure disease progress. To date, 10 sites around the world are already active, and 3 sporadic CAA participants have been randomised into the study. Let’s start by explaining what the schedule looks like.

		TREATMENT PERIOD		
	SCREENING PERIOD	DOUBLE-BLIND PERIOD	OPEN-LABEL PERIOD	FOLLOW-UP PERIOD
DURATION	UP TO 60 DAYS	24 MONTHS	18 MONTHS	1 YEAR AFTER LAST DOSE
NUMBER OF VISITS	1–3 VISITS	12 VISITS	5 VISITS	1 VISIT
STUDY MEDICATION ADMINISTRATION	NONE	MIVELSIRAN OR PLACEBO EVERY 6 MONTHS	MIVELSIRAN EVERY 6 MONTHS	NONE

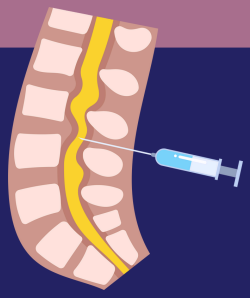
WHAT DOES PHASE II LOOK LIKE?

How long does the trial take?

When you participate in the trial, you will be asked to be part of it for at least 24 months. During that time you will have 12 visits. During some of those visits, you will receive a dosage of Mivelsiran. Your heart rate and blood levels will be monitored, to get further information on how the body processes the drug.

Unfortunately, Mivelsiran can only be administered through a lumbar puncture. There is no other way to make the drug reach the place that actually matters: the brain. That means that when you participate in the study, you will be asked to undergo a number of them. Some of the LP's in the study protocol are to administer the drug, others are to look into safety markers and biomarkers in your cerebral spinal fluid (CSF).

After those 24 months, there is an "open label extension" which means everyone who participated can receive Mivelsiran for a continuing 18 months if they choose to. This will give everyone the opportunity to receive the study drug and also helps Alnylam gather further data. There are 6 more visits during the open label extension period.



24

WHAT DOES PHASE II LOOK LIKE?

Does everyone receive Mivelsiran?

No, half of the people in the study get a placebo. During phase II studies, there are usually two treatment groups. One group gets the active drug and one group receives either a current other available treatment or a fluid that does not have an active ingredient, otherwise known as an placebo. Because there is no other treatment available to compare Mivelsiran to, there is a placebo group.

We understand that if can be difficult to wrap your head around being part of a drug study for such a long time, undergoing lumbar punctures and MRI's and other things, and potentially not receiving Mivelsiran. Adding a placebo group has been part of many discussions between experts, representatives, and Alnylam. Eventually, everyone felt the study would be way more robust if there was a placebo group included, meaning that the results of the study would be way more powerful and that helps when a company tries to continue to further phases of development and to get a drug to market eventually.

Continues on the next page.

WHAT DOES PHASE II LOOK LIKE?

Does everyone receive Mivelsiran?

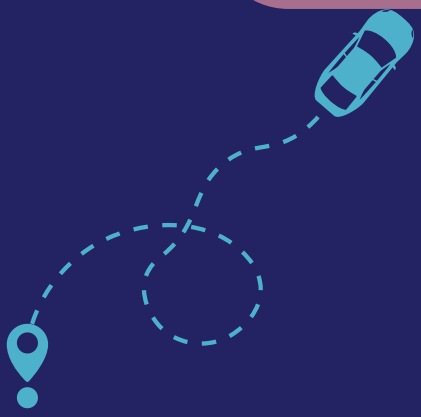
"Placebo-controlling" is very common practice in drug trials. This phase II study with Mivelsiran is a placebo-controlled, double-blind and randomized. That means the following:

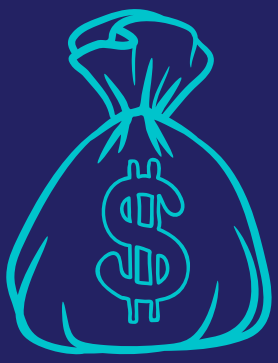
- 'Double-blind' means that both the study research team and the participant do not know who is receiving the active druge or placebo.
- 'Randomised' means that people are randomly assigned to either the treatment group or the placebogroup. This is usually done with a computer that generates a random code. It cannot be influenced by the study research team or anyone else.
- 'Placebo-controlled' means that some participants will receive a placebo given under the exact same conditions as the active drug. This allows the effects related to the drug to be separated. For example, if a participant in a study complains of a headache it is important to know if that is related to the active drug. If the same number of participants receiving placebo complain of headaches, this shows that the headache cannot be due only to the active drug.

WHAT DOES PHASE II LOOK LIKE?

How many days does one study visit take?

We know some of you have to travel wide and far to get to Perth. Also, some of you have to take time off work, sometimes several days, to participate in research. We appreciate all of you who have made that effort so far. Being part of cAPPricorn-1 means an even bigger commitment. Therefore, we are looking into how to plan visits as economically as possible, making it easier for you to be part of it if you want to. As we speak, the research team is working on the planning of the trial and when we know more, we will tell you more about what that looks like. Some visits might only require one day at the research center, others will require up to three days. Your travel and accommodation costs will be covered by the study as with TRACK DCAA.





When can I enroll?

The research team is currently working out the logistics of the trial on their site. Our expectation is that DCAA family members can start screening assessments for the study early in 2025.

2025

WHO CAN BE PART OF THE STUDY?

Earlier, we shared an info sheet with you, about who can participate in the study and why. Some of this information will be a repetition of that info, some of it is new.

From what age can you participate?

30

The minimum age to participate in the study is 30 years. This age is based on what researchers have learned from studies such as DIAN and TRACK DCAA. From the age of 30 onwards, they see more changes in what we call 'biomarkers', ways to measure disease progress.

Do you need to know whether you carry the gene?

Only people who know that they are gene carriers can participate in the drug research, unlike TRACK DCAA. This is partly because it is safer, because it gives better results, because it 100% prevents people from discovering their genetic status because of side effects and because this way the study can be conducted faster. We will go further in to that on page.....

Is there a maximum age?

There is no maximum age up to which you can participate in the study. There are a number of limits: for example, how far DCAA has progressed. That is why, before you can participate, a screening assessment is done at the research centre.

WHO CAN BE PART OF THE STUDY?

If you are in TRACK DCAA, are you automatically in cAPPricorn-1?

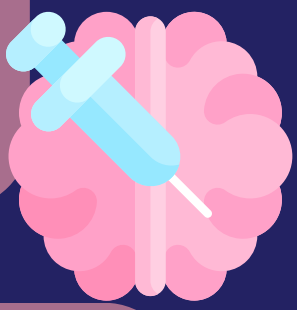
The inclusion criteria for TRACK DCAA and the drug study are not exactly the same. This is because Alnylam has learned a lot from research so far, thanks to you, and is applying this to the cAPPricorn-1 study. Anyone who participates in TRACK DCAA, knows that he or she is a gene carrier and is 30 years and older is invited for a screening assessment. It's up to you to decide whether or not you want to be part of the trial.

Various tests will be used to determine whether you can participate. If not, you will be asked to continue in TRACK DCAA, unless you already finished your last visit of the study. We are currently discussing the continuation of TRACK DCAA with Alnylam.

Are lumbar punctures part of the drug study?

Mivelsiran is administered through a lumbar puncture, because that is the only way it ends up in the right place: the brain. Therefore, you can only participate in the study if you agree to a number of lumbar punctures. Some of the LP's in the study protocol are to administer the drug, others are to look into ...kers and biomarkers in your cerebral spinal fluid (CSF).

Want to learn more about how a lumbar puncture works? Check this video.



Are there other inclusion criteria?

In addition to the most important criteria mentioned earlier, there are a number of other things that determine whether you can participate, such as your body mass index and pregnancy.

WHO CAN BE PART OF THE STUDY?

Are there criteria on family planning?

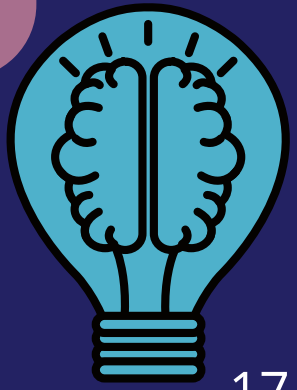
It is very common in drug trials to exclude females who are pregnant or are planning to expand their family during the course of the trial, because of uncertainties around the effect of the drug on conception and unborn babies. This also applies to male participants and their partners. Practically this means participants won't be able to have children over a period of 24 months, 36 months if they want to be part of the open label extension. We understand this is potentially a big ask, especially for younger DCAA family members.

Do you miss out on a treatment when you are not eligible?

No, we do not yet know whether Mivelsiran works, which is why it is being investigated. If you choose to participate in the study, you have a chance that you will receive something that slows down the disease, but we will only know after the study finished whether or not that is true.

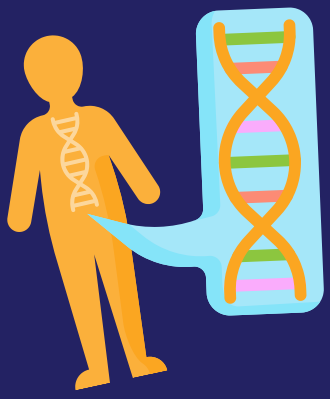
if you have any questions about these criteria or want to speak to someone about them, feel free to contact Samantha Gardener at s.gardener@ecu.edu.au

Alnylam visited the Dutch CAA famlies to explain the inclusion critera. Click here to watch the recording.



TRIAL PARTICIPATION AND GENETIC TESTING

Why can only known genecarriers participate in the trial?



Alnylam decided, partially based on the input of DCAA family members during Community Conversations in July 2023 and partly due to ethical considerations, to only include people who know they are gene carriers (through testing or symptoms) in cAPPricorn-1. They had several reasons for this

- It is safer to only administer the drug to people who carry the gene and have increased levels of amyloid beta.
- The result of the study will be better when only people with the disease can take part in it.
- Because risk carriers are not enrolled and the drug is only being researched in groups that can actually be found a result in, phase II can be finished faster, which means the entire drug development process will go faster.

But the most important reason for Alnylam is this!

There is a small chance of something happening to the body when taking part in a trial. When that happens, the doctor overseeing the trial might have to “unblind” you to see if the drug is having the negative effect or something else unrelated to the drug.

If the drug is given to people who do not know their genetic status (are 50% at risk), only gene carriers would receive the drug, while non-carriers (people who do not carry the gene, but don’t know this themselves) would only receive the placebo. If somebody who doesn’t know their genetic status but is a gene carrier and therefore receiving the drug needed to be “unblinded,” the doctor would have to make known whether they are in the drug or placebo group and in that way, they would find out whether they are a gene carrier or not, without going through the regular process, that includes counseling.

Because the decision to get tested is such a big one, and the process around it is regulated because of that, it is very important that there is no way to find out through participation in a trial.

TRIAL PARTICIPATION AND GENETIC TESTING

What does genetic testing look like?

Nicole de Jong is part of the Dutch patient association. She went through the testing process in the Netherlands and made a beautiful podcast about her process. You can listen to the subtitled episodes, following her from making the decision to get tested, getting her referral from her GP, to her counselling sessions and getting her test result, click here.

Genetic testing can be done through the public system or through private companies. Because of waiting lists in the public arena, we are looking into referring DCAA family members who want to undergo genetic testing to a private company.

This means that you can actually start the process in a shorter timeframe, making it easier to enroll in the trial early on.

The actual procedure might look a bit different between different places, but usually entail several steps.

Continues on the next page

TRIAL PARTICIPATION AND GENETIC TESTING

What does genetic testing look like?

1) The first step is to get a referral, either through your GP or the research team.

2) After, you will be invited to undergo counselling at least once, face to face or online. During this conversation, together with the counsellor, you will go into your reasons for wanting to know your genetic status, your coping mechanisms, your personal situation and your social situation / support system.

3) If you both feel confident you are highly motivated and are in the right situation to find out your genetic status, the next step is the testing itself. This means that you will need to donate blood, that will be send to a testing facility to investigate whether you carry the mutation for Dutchtype CAA or not.

4) It usually takes 4 to 6 weeks to get back results from the lab. After, you have another counseling session in which you receive your test result. For both a positive AND negative result it is important to have a safe space to process and to look forward. How are you going to cope with the result? How are you informing the people around you? What do you need short term and long-term?

TRIAL PARTICIPATION AND GENETIC TESTING

Genetic testing in the context of a drug trial

We all know that predictive genetic testing is a huge dilemma when being a DCAA family member. A small percentage of people in general (+/- 17%) of people from a family with a genetic neurodegenerative disease (for example Huntington's and genetic Alzheimer's) choose to undergo testing.

Because only people who know their genetic status can be part of the phase II trial, we understand that undergoing testing might be a more prevalent question now.

To help you make an informed decision, check this overview of what the process looks like and what the pro's and con's are in the context of drug development.

POTENTIAL ADVENTAGES

- It is important that as many people as possible participate in the drug trial. Because we do not know exactly how many DCAA family members are willing to, Alnylam has decided that the goal for the DCAA group, outside of the number of sporadic CAA patients enrolling, is 'up to 48'. That means that the study has not failed when that number is not reached, but if we can get to 48 DCAA members, it would make the study more powerful. Therefore, the more people from DCAA family members participating, the better. The enrolment for Dutchtype CAA family members will close as soon as the recruitment for the sporadic CAA part of the study is complete (152 patients), with a maximum of 18 months. Practically that means that we cannot give a timeframe on how much time is available for family members who need time to think about participating or genetic testing.

- Participating means potentially having a benefit from receiving Mivelsiran. We emphasize the word POTENTIALLY, because we do not yet know whether the drug has a beneficial effect, as it is being studied.

- When taking part of the study, you contribute to scientific knowledge about DCAA and the development of a potential treatment.

- Participation might not only benefit you, it is also important to future generations.

TRIAL PARTICIPATION AND GENETIC TESTING

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POTENTIAL DISADVENTAGES

- Being part of the study does not mean you get a treatment, especially not one altered to your individual situation.

- You will be screened to see if you can take part in the study. That means that even after getting your test result, you might not be eligible to take part in the study.

- The drug might be proven to be effective in DCAA and still not work in individual situations.

- There is a 50/50 chance you will be part of the placebo group, meaning you will only receive Mivelsiran in the open label extension period, if you choose to take part in it.

- In any phase of the study, results might inform Alnylam to discontinue developing Mivelsiran. This means you still carry the effect of knowing your genetic status, without there being a (potential) treatment.

- Even if Mivelsiran proves to be successful, it will take a number of years to make the drug available through your physician.

TRIAL PARTICIPATION AND GENETIC TESTING

Considerations concerning genetic testing in the context of participating in a drug trial

There are a number of things that are important to consider when you are thinking about genetic testing, because you want to take part in cAPPricorn-1.

During a family meeting with the Dutch CAA family members, psychologist Sanneke van Rooden from the clinical genetics department from the Leiden hospital gave a presentation about genetic testing in the context of a drug trial. Click here to watch the subtitled recording (from 1:35:00)

- It is very important you are well informed on what the study actually entails and whether or not you are willing and able to take part in it.

- Make sure you are informed on what the screening entails. You might be able to go through this with the research team and learn more about whether or not you are eligible to enrol.

- The predictive genetic testing process is about more than taking part in a drug study. It is vital that you pay enough attention to whether or not you are in the right place and mindset to find out your genetic status, and all those personal factors should be taken into consideration.

- Take some time to think about what a positive test results means outside of the drug trial. What will happen to you and your life short- and long-term if you find out you carry the gene and there is no treatment on the horizon?

LEARN MORE

We are currently working on organising a family meeting with the Alnylam team that develops Mivelsiran, either online or in person, early 2025. This means you will have a chance to ask your questions directly. Sanne will try to be present as well.

Get in contact with the research team, specifically Sam, through s.gardener@ecu.edu.au. She can arrange a call with you to go through all your questions.

Check out www.stopdcaainaustralia.com and the FAQ. You can also reach out to Sanne, she is a psychologist and has talked to over a 100 DCAA family members about their experiences with the disease and their questions about research.

stopdcaainaustralia.com

Check this website for more information on the cAPPricorn-1 study protocol.

OTHER NEWS: CAA RESEARCH AND CONFERENCE

Every two years, researchers from around the world gather at the international CAA (Cerebral Amyloid Angiopathy) conference. The Dutch DCAA patient association usually sends two representatives to learn about the latest research, network with researchers and physicians, and voice the perspectives of families affected by Dutch-type CAA.

This October, we met in Munich. Since the conference was "close to home," as the patient association, we had extra room in our budget (aka our government subsidy), allowing a larger part of our board to attend. This year, Maike, Koos, Janny, Martina, Nicole, and Sanne were all present.

The conference was intens, interesting and exciting as always. Sanne wrote a summary for you, read it here.

Want to learn more about what is being done in CAA research and about studies that potentially effect Dutchtype CAA as well? Sign up for this webinar.

CAA LIVE Webinar Saturday November 23rd 12noon EST/9am PST
Hosted by Amyloidosis Support Groups and the International CAA Association

1. Welcome and introductions – 5min
Muriel Finkel - on behalf of Amyloidosis Support Groups
Eric Smith, MD PhD (University of Calgary, Canada) & Susanne van Veluw, PhD (Massachusetts General Hospital, Boston, US) - on behalf of the International CAA Association

2. General overview of CAA (clinical symptoms and pathology) – 15min
Steven Greenberg, MD PhD (Massachusetts General Hospital, Boston, US)

3. Recap of the 9th International CAA Association conference – 15min
Gargi Banerjee, MD PhD (University College London, UK)

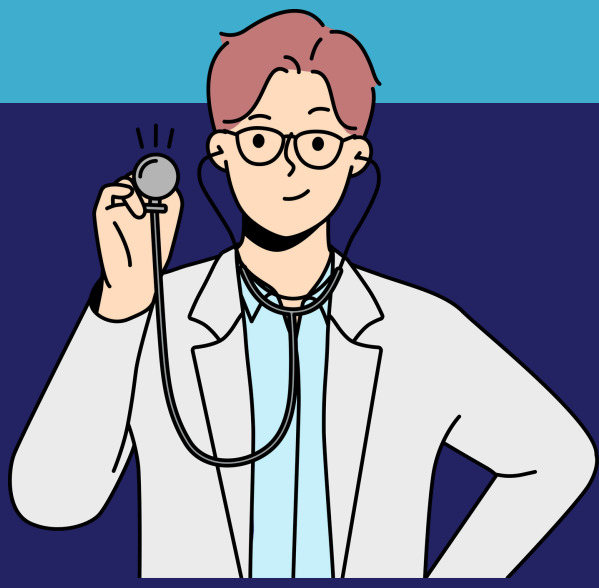
4. Ongoing studies in CAA – 15min
Mariel Kozberg, MD PhD (Massachusetts General Hospital, Boston, US)

5. Q&A / panel discussion – 35min
Eric Smith, Susanne van Veluw, Steven Greenberg, Gargi Banerjee, and Mariel Kozberg
Moderated by Muriel Finkel

Please Scan QR Code to Register
(if any problems or issues please email Info@AmyloidosisSupport.org)

caa FORUM

OTHER NEWS: NEUROLOGIST DAN CLARKE AND CCIP



Stroke neurlogist doctor Daniel Clarke has been a great addition to the team! He is available for clinical care every Monday afternoon. This service is generously sponsored by the Alzheimer's Research Australia. The clinical service is also available for DCAA family members who do not participate in TRACK DCAA. You can make an appointment through Samantha: s.gardener@ecu.edu.au

Alzheimer's Research Australia

GOVERNMENT OF WESTERN AUSTRALIA

Western Australian Future Health Research & Innovation Fund

FHRI Fund Consumer and Community Involvement Support application

The FHRI Fund Consumer and Community Involvement Support program (the Program) aims to support consumer and community involvement (CCI) in research and innovation activity.
Funding will be provided on a competitive basis to support CCI involvement in research and/or innovation ideation, development and writing of grant applications and for ongoing involvement in FHRI Fund and nationally supported research and innovation activities.
We are currently applying for this grant to enhance CCIP activities (like family meetings, community converstations and this news letter) in WA.