# Request for participation in the study "Plasma cell-directed treatment in chronic fatigue syndrome (ME/CFS)

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Here is some information if you consider applying for participation in a drug study involving testing the drug daratumumab (Darzalex) as a treatment for patients with moderate to severe ME/CFS.

## Background and purpose

You have previously been diagnosed with chronic fatigue syndrome (ME/CFS) through a medical examination. We will give you more detailed knowledge about a study we want to conduct, so that you can make a proper choice whether you want to participate in the drug trial.

The reason for testing the drug daratumumab is an assumption that overactivity in the body's immune system is an important factor in the disease picture, at least in a subgroup of ME/CFS patients. In these patients, we believe the disease may be due to a faulty immune response after an infection, in which B cells in particular play a central role. B cells are a type of white blood cell blood cells that, when activated, can develop into mature plasma cells. Plasma cells produce antibodies, which are used to defend us against foreign substances such as viruses and bacteria, but plasma cells can also make antibodies that target the body's normal functions and give rise to symptoms or disease.

We further believe that this abnormal immune reaction causes disturbances in the fine regulation of blood flow to tissues, especially during exertion. Typical organs where this is felt are muscles and brain. When the organs are exposed to stress, they receive too little oxygen and nutrients. This may contribute to ME/CFS symptoms such as fatigue, "brain fog", orthostatic dizziness (when standing up), fatigue and PEM (exertional malaise).

For the past 16 years, we have conducted clinical trials with drugs that affect the immune system, with the aim of developing a treatment for the disease. Our collective experience suggests that certain subgroups of patients have an effect by either the therapeutic antibody rituximab and/or the chemotherapy drug cyclophosphamide. The largest studies we have done on rituximab, where the experience was that some of the ME/CFS patients had a good effect on the symptoms, but that this did not apply to the majority. We believe this may be related to the fact that rituximab is a medicine that specifically targets B cells, but to a too small extent affects the plasma cells, which are responsible for the production of antibodies.

Daratumumab is a medicine used to treat bone marrow cancer (myelomatosis). The medicine is not a chemotherapy drug but is (like rituximab) a therapeutic antibody that binds to a specific molecule called CD38 and destroys cells that have this molecule on their surface. CD-38-the molecule is found in large quantities on plasma cells. Treatment with daratumumab therefore has the purpose of temporarily reducing the number of plasma cells, thereby providing a lower level of antibodies.

Daratumumab has been tested in small studies in recent years in several autoimmune diseases, diseases caused by disease-causing antibodies, with good results. The patients with autoimmune diseases in these studies have often not had sufficient effect of other immunosuppressive drugs. The treatment had few side effects, but the studies conducted were small with relatively few patients.

We recently conducted a pilot study with 10 patients with moderate ME/CFS (housebound) to severe (essentially bedridden) degree of illness. These patients have received approximately 50 injections of daratumumab, and the patients have been followed up for at least 12 months. The participants have tolerated the treatment well, and there have been no serious side effects of treatment. Some patients have experienced significant improvement in a number of ME/CFS symptoms.

In such a pilot study with only 10 patients, without a control group, it is difficult to draw any firm conclusions about the effect of daratumumab in ME/CFS. However, the results from the pilot study are very interesting, and we are therefore conducting a larger clinical study that can give us more information.

The purpose of this study is to investigate how daratumumab affects the course of the disease and the symptom picture of ME/CFS, as well as obtaining further data on safety and feasibility using daratumumab given as a subcutaneous injection (under the skin).

## Study design

This study is based on, and will be conducted at, the Cancer Clinic at Haukeland University Hospital. Chief Physician, Prof. Øystein Fluge and Prof. Olav Mella are responsible. The study will include 66 patients with moderate to severe ME/CFS.

To obtain more reliable conclusions about the effects of the medication, the study should be placebo-controlled. This means that 44 of the included patients will receive active medicine with daratumumab, and 22 will receive injections without daratumumab.

Before inclusion in the study, we ask that you complete six questionnaires. You do this from home in a secure online portal, for which you will receive your own username and password. It usually takes about an hour to fill out the forms, and you don't have to fill them all out at once. There will also be a clinical assessment with physical tests of, among other things, hand strength and standing blood pressure. The physical tests will be adapted to your level of function. After inclusion in the study, all patients will first be observed in three months. During this period, you fill out three short forms in the portal every 14 days about symptoms and level of functioning. These take about fifteen minutes to answer each time. We also record physical activity level and heart rate using an activity tracker (Fitbit). The goal is to record what is normal variation in symptoms and activity for the individual patient.

Then treatment with either daratumumab or placebo is started. We give a total of five injections, the first three injections two weeks apart, and then two more injections after 24 and 26 weeks. Throughout the period of follow-up and treatment, we ask that you complete the regular forms every 4 weeks, and in addition two extra forms about function and capacity every three months.

The study will be conducted with a double-blind design, so that neither the patient nor the therapist knows which treatment the individual patient receives. The pharmacy has a coded list of the treatments, and this will be opened after the study is complete, i.e. when the last patient has been to the last visit after 72 weeks.

## Inclusion

To participate in the study, you must be diagnosed with ME/CFS according to the Canadian criteria. You must be between 18 and 64 years of age, with illness duration of at least two years. The severity of the illness must be from moderate (essentially housebound) to severe (essentially bedridden). In addition, the ME/CFS illness must have started at a defined time, typically after an infection. If you have had ME/CFS after a Covid19 infection, you are also eligible for assessment.

You cannot have other illnesses that can cause symptoms similar to ME/CFS, or that indicate that you should not receive treatment with daratumumab.

It is also a requirement that the cell values in the immune system and the level of immunoglobulins (antibodies) is above specified minimum values. We take blood samples to investigate this as part of the clinical assessment before inclusion.

You must be able to travel to Haukeland University Hospital for doctor visits, testing, physicals tests and treatments. If you live in Eastern Norway, it may be appropriate to give the treatments at Radium Hospitalet in Oslo, but you must meet in Bergen for assessment for inclusion and final control.

Pregnancy or breastfeeding excludes participation, and reliable contraception must be used from the start treatment until 24 weeks after the last injection. If you are a woman of childbearing potential, you will be asked to take a pregnancy test (blood test) regularly during the course of treatment.

## Practical implementation

Treatment with daratumumab is given at the Clinical Research Post at Haukeland University Hospital, or at Radium Hospital, Oslo University Hospital.

Blood tests are taken to rule out other diseases at the first appointment. These tests are processed as routine samples in the department and are not stored after analysis.

You will also be asked to donate blood samples to our existing approved research biobank ("Disease mechanisms in ME/CFS", with Prof. Øystein Fluge as responsible), at the start of the study and after 12, 60 and 72 weeks. The samples are used for research purposes, with the purpose of elucidating disease mechanisms in ME/CFS, and is not a mandatory part of the study. You will receive a separate information letter and consent form for biobank samples.

### Possible benefits, disadvantages and side effects

The benefit of participating in the study is that you can gain access to a treatment that may prove to be beneficial for an improvement in the symptoms of ME/CFS. If you experience a beneficial effect of the disease picture after daratumumab injections, however, we do not know how long-lasting a response will be.

Apart from our completed pilot study, daratumumab has not previously been tried as treatment for patients with ME/CFS. We therefore cannot know for sure that the drug will have a beneficial effect on the patients. Although in the pilot study we have not seen unexpected or serious side effects, we cannot exclude that rare side effects may occur.

As a participant in the study, you will contribute to increased knowledge about the disease and will thereby be able to help other patients in the future. If during the course of this pilot study you should experience a significant improvement in your ME/CFS disease, but later relapses, this study does not include the possibility of new treatment with the antibody daratumumab.

If the treatment principle proves to lead to beneficial effects on the disease picture for ME/CFS patients, it is our intention to apply for funding to conduct a new study with daratumumab for those patients who at study completion are found to have received placebo.

In order for daratumumab to be absorbed by the body, it is combined with another substance which is called hyaluronidase. Hyaluronidase is an enzyme that regulates how quickly daratumumab is taken out of the body and causes less discomfort during the injection. Hyaluronidase has been used for the same purpose in combination with other medications, and the side effects are therefore well known. The 22 patients receiving placebo will also receive injections containing hyaluronidase, but for them dissolved in saline.

## More information on side effects and precautions.

More information is provided on potential side effects and precautions.

### Voluntary participation and possibility to withdraw consent

Participation in the study is voluntary. You can withdraw at any time without giving any reason.

### Privacy and research biobank

The samples taken from you and the information recorded about you will only be used as described in the purpose of the study. All information and samples will be used in a research context and processed without name and national ID number or other directly identifiables.

Your name and code will only be kept at the study site and only by personnel responsible for the study has access to this. It will not be possible to identify you in the results of the study when these are published. The information will be stored until 31.12.2055, 25 years after the study

### Fitbit and privacy - Information recorded by Fitbit.

If you agree to use a Fitbit watch (Fitbit Charge 6), it also means that you give the company Google, which owns Fitbit, has access to some information about you, including your weight and data about your daily activity, sleep, heart rate, etc. Google can also get information about how you are using the application and the device, about your IP address and, if you choose to enable GPS, where you are located. Google uses information for various purposes described in its company privacy policy (https://policies.google.com/privacy), including for product development, to communicate with users of the service and to ensure security. Google may also share information about its users with countries that do not have as good a legal framework for personal data protection like Norway. Please note that Bergen Health HF does not have the opportunity to decide what Google uses your information for, and we do not have the opportunity to control how Google uses your information. We therefore recommend that you familiarize yourself with Google's privacy policy, and that you do not participate in the study if you have any objections to that. The company processes your information. Please note that we have not entered into a partnership with Fitbit / Google for this project. The company is bound by the European GDPR rules that protect privacy. This means, among other things, that you have the right to access, correct and delete data from your account. If you want all information registered with Google to be deleted, you can do so yourself by deleting your user account using the mobile app, or you can ask us to assist with this.

If you delete your account during the study, Bergen Health HF will also not be able to retrieve more data from the activity watch. We therefore ask that you discuss this with us first.

The study coordinator will assist in setting up a user account so that Google has access to information about you is limited. As an extra assurance for your privacy, your user account will at Google will be created under a fictitious name and date of birth, linked to a project-specific email address. Your account will be created with strict privacy settings, and we recommend that you do not activate other functions, such as connecting to such as Facebook. If you still choose to do this, the research group cannot take responsibility for any consequences for your privacy. Bergen Health HF will also assist in closing the account when the data collection is complete. If you wish, you can get a printout of the information we have extracted from your Fitbit Charge.

## Information registered by Bergen Health Centre:

By agreeing to the project, you also agree to us downloading data about the number of steps per 24-hours, resting heart rate and heart rate variability directly from your Fitbit account to a project-specific area on our secure research server. To be able to do this, we need access to usernames and password for the account. Therefore, we ask that you do not change your Fitbit account password without informing us. The list of usernames and passwords in the study is stored on a secured research server that only employees in the relevant project have access to.

### Right of access and storage of material

If you agree to participate in the study, you have the right to access what information is registered about you. You also have the right to have any errors in the information we have corrected. If you withdraw from the study, no further information will be collected. Information already collected from you will not be deleted. Samples that are collected but not yet analyzed will be deleted.

### Information about the outcome of the study

You have the right to be informed about the results of the study. Regardless of the outcome, a summary of the study results adapted to the general public are made available via the EU Clinical Trials portal Information System (CTIS) within one year of completion.

## Financing

The study and the biobank are funded by private donations and funds raised by patients and patient associations for research into the treatment of ME/CFS. We do not provide any compensation to study participants.

There is no deductible for visits or treatments at the hospital. Parking is free, and reimbursement can be sought from Patient Travel for travel expenses at regular rates. The study carried out completely without support from the pharmaceutical industry.

### Insurance

You are insured in accordance with the Product Liability Act in the Norwegian Medicines Insurance.

### Approval

The project has been approved by the Regional Committee for Medical and Health Research Ethics at the committees for Clinical Trials of Drugs and Medical Devices (REK KULMU) and of Directorate for Medical Products (DMP). Reference number in the European system for clinical studies is EU CT 2024-520094-13-00.

According to the new Personal Data Act, Bergen Health HF, Haukeland University Hospital is responsible for ensuring that the processing of your information has a proper legal basis. Processing your personal data for scientific analysis and validation in this project has a legal basis in the General Data Protection Regulation, Article 6, paragraph 1, letter e, and Article 9, paragraph 2, letter j. The project is carried out in accordance with the Health Research Act and your consent, and decisions on ethical approval from REK constitute a supplementary legal basis.

## Other

Haukeland University Hospital has applied for a patent for the plasma cell-directed treatment using the CD38 antibody daratumumab for patients with ME/CFS, and Project manager Øystein Fluge and Olav Mella are mentioned in the application as "inventors".