Newsletter HIT-CF Europe

August 2023

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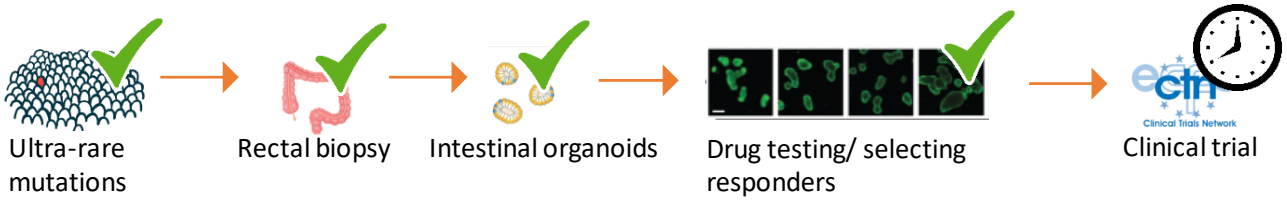

Long time no hear

A long time has passed since the last HIT-CF newsletter. We were not able to communicate earlier as there have been a lot of uncertainties. A lot has happened behind the scenes though. Some crucial issues have been cleared out now and we want to share these perspectives with all of you.

Many delays

In our previous newsletter, we informed you about the many delays the project faced. Due to the Covid-19 pandemic, many developments were temporary delayed or stopped. Some of the collaborating pharmaceutical partners in the project had to put their drug pipeline on hold or even completely stop due to lack of investors. The promising CFTR modulating compounds developed by Proteostasis Therapeutics were in danger of being lost, and a new company (Fair Therapeutics) had to be built to secure them. This new company also had to attract proper investments. Moreover, in November last year, the planned CHOICES trial was rejected by **CTIS** (Clinical Trials Information System – a procedure that is mandatory to get permission to run a trial in the European Union) because the necessary documentation on the compounds was not ready yet.

Better days ahead

But fortunately, the partners in the HIT-CF project kept searching for solutions in all possible directions. CF Europe, the European Cystic Fibrosis Society, the participating CF centres from all over Europe, and many of you, never lost faith. Indeed, we are very pleased to say that several generous investors were willing to support Fair Therapeutics, now guaranteeing that the CHOICES trial can be successfully performed. Currently we are still negotiating with the European Commission, the initial funder of the HIT-CF project. In fact, HIT-CF was supposed to officially end in December. We are very glad to see that the European Commission acknowledges the incredible value of the project. HIT-CF is a truly historic achievement as it creates new avenues of drug development for patients with ultra-rare diseases. The close collaboration of the patient community, caregivers, academia and regulators to develop drugs in an affordable way is unprecedented. We cordially hope that the Commission will soon grant an extension.

The HIT-CF team is now preparing everything to resubmit CHOICES into CTIS, and, if everything goes well, **CHOICES should start in early 2024**. This means that by the beginning of next year, the first of 52 selected HIT-CF participants (based upon organoid response) will be treated with the new drugs. Those people selected have already been informed about this. We are negotiating with other partners to set up **trials for those who cannot participate in CHOICES**. We hope to inform you about this in the next Newsletter.

To learn more about the HIT-CF project, visit www.hitcf.org or send an e-mail to HITCF@umcutrecht.nl

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Your personal results

We realise that you are very keen to find out how your organoids have responded to the tested drugs, especially to the Vertex modulator Tezacaftor/Ivacaftor (Symkevi), and we have been receiving a lot of questions about this. By the time you read this newsletter, **those HIT-CF participants not invited for CHOICES should have received a letter through their CF doctor containing their individual Symkevi result.** If you have not received this report yet, please ask your doctor about it. Not to jeopardize the continuation of the study, we cannot give you exact numbers yet, but **your organoid swelling response will be compared to the organoid swelling in a F508del/F508del control person**, in order to give you a general idea. The letter will look like this:

After stimulation with tezacaftor/ivacaftor (Symkevi) the organoids of HIT-CF ID they show a **higher/lower** swelling response than the concomitant swelling response in a F508del/F508del control subject.

Interpretation

Higher than control: The organoids showed a higher response to tezacaftor/ivacaftor (Symkevi) than the average of F508del/F508del organoids. Based on the results of this test it is likely that this person will clinically benefit from current CFTR modulator combination therapies (tezacaftor/ivacaftor–Symkevi– or elexacaftor/tezacaftor/ivacaftor –Kaftrio–) comparable or better than the clinical response to tezacaftor/ivacaftor (Symkevi) in people with F508del/F508del.

Lower than control: Organoids showed a lower response to tezacaftor/ivacaftor (Symkevi) than the average F508del/F508del organoids. Although it is expected that this person will not clinically benefit from treatment with tezacaftor/ivacaftor (Symkevi) comparable to the average person with F508del/F508del, this does not preclude clinical efficacy of such treatment. Individual responsiveness in people with F508del/F508del can vary considerably, and non responsiveness to tezacaftor/ivacaftor (Symkevi) does not preclude responsiveness to elexacaftor/tezacaftor/ivacaftor (Kaftrio). So, the result of this test should not disqualify patients from experimental treatment with CFTR modulators in the future.

Your CF doctor will guide you through this information. Don't hesitate to ask him/her for more information if something is unclear.

Important: There are 3 groups of HIT-CF participants who will not (yet) receive these personal results:

1. Those who will participate in CHOICES: To ensure the complete objectivity of the study, it is important that neither you nor the researchers know how your organoids responded on the tested drugs. This is called 'blinding'. At the end of CHOICES, you will of course also receive your personal results.
2. For a very small minority of HIT-CF participants, their organoids failed to grow well in the lab, so we could not perform drug testing on them. This unfortunately happens in experimental setups. Your CF doctor will inform you if this is the case.
3. People having only stop ("X") mutations: Symkevi was not tested on their organoids as no effect was anticipated. We will come back with more information on what these people can still expect from HIT-CF as soon as possible.