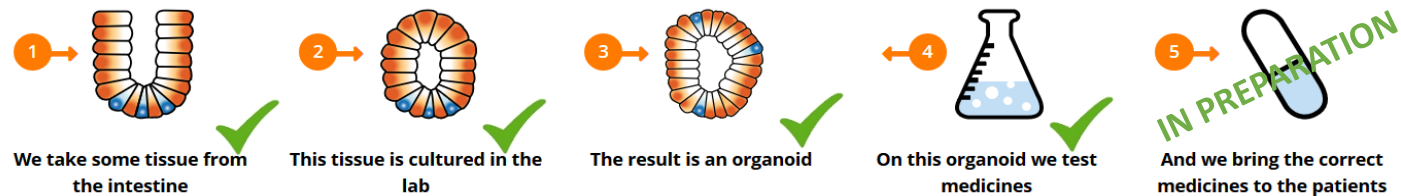


Newsletter HIT-CF Europe

February 2022



The HIT-CF Europe project aims to provide new treatment options to people with cystic fibrosis (CF) and ultra-rare genetic profiles. The project will evaluate the efficacy and safety of drug candidates provided by collaborating pharmaceutical companies in patients selected through preliminary tests in the laboratory on their mini-intestines – also called organoids.



We hope you are doing well and that 2022 is off to a good start for you and the ones you love. We are very happy that with this first newsletter of the year, we can give you more concrete information about the CHOICES trial, for which preparations are in full swing now! FAIR Therapeutics is currently busy with the “fill and finish” process, meaning that the drugs’ raw materials are processed into pills and packed in bottles. **We expect to include the first participants in CHOICES during summer.**

Who will be invited to participate in CHOICES? And when?

Participant selection for CHOICES is done very concisely and is based on the organoid response. In total, 52 people whose organoids were cultured and tested, will participate in CHOICES. These will include 26 so-called high responders, whose organoids showed a high response to the tested drugs. These people are expected to also show a good clinical response to the drugs. Also 26 ‘randomly selected’ participants will enter CHOICES. These people’s organoids showed a variety of responses to the tested drugs (both high and low). Including them into the trial is important to validate the organoid model as predictor of clinical response. **If you are invited to the CHOICES trial, you will not be told how your organoid responded to the tested drugs.** This is called “blinding”, and it is important to ensure the clinical trial results are as objective as possible. If you are selected for CHOICES, your organoid results will be communicated to you after the trial. **The HIT-CF team has already approached the caregivers of the selected patients. This means that your doctor will tell you in the coming weeks whether you are selected for CHOICES or not.**

What will the CHOICES trial look like? What can I expect?

In CHOICES, a triple modulator therapy will be tested. It consists of a potentiator (Dirocaftor), a corrector (Posenacaftor) and an amplifier (Nesolicaftor). This triple combination should increase the number of working CFTR channels on the cell surface. **CHOICES is a randomized, double-blind, placebo-controlled, crossover clinical trial.** What does this mean?

- Double-blind: this means that nor the participants, nor the study team (doctor, nurses, technicians etc.) know whether the participant receives the drug or a placebo. This is important to ensure unbiased study results. Only the researcher analyzing the results, will know which participant received what and will be able to draw conclusions.
- Placebo-controlled: this means the study drug is compared against placebo. This will permit drawing robust conclusions on the effects of the study drug.
- Crossover: this means that all study participants will receive both the study drug and the placebo in random order. After a certain amount of time, the participants that first received the study drug, will switch to placebo, and vice versa (see figure on the next page).

The study will last for a total of 42 weeks and will consist of 3 treatment periods. The first 2 treatment periods will last for 8 weeks. Between period 1 and 2, there will be a washout period of 8 weeks. This is the so-called crossover where participants switch from the study drug to placebo or vice versa, and the 8 weeks are necessary to ensure no remaining drug is left in the body of the participants. Treatment period 2 is immediately followed by treatment period 3, which lasts for 16 weeks and will enable researchers to draw longer term conclusions about the study drug.

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



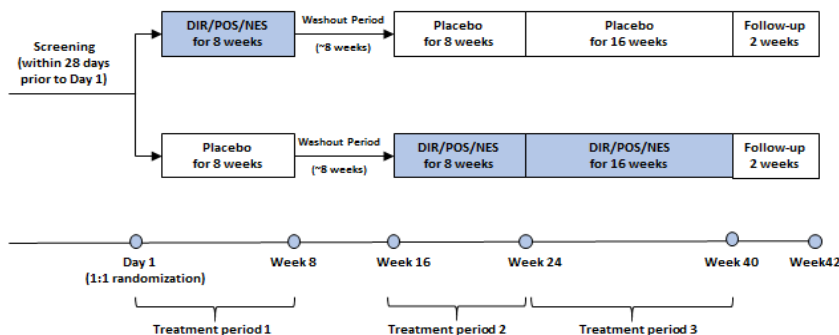
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As this is a randomized trial, it is a computer that decides (so by chance) who is in the first or second study ‘arm’ and is treated 8 or 24 weeks with the study drug. **In total, the HIT-CF team foresees that 12 study visits to the CF study centre will be necessary, completed by 5 telephone calls by the study team.**

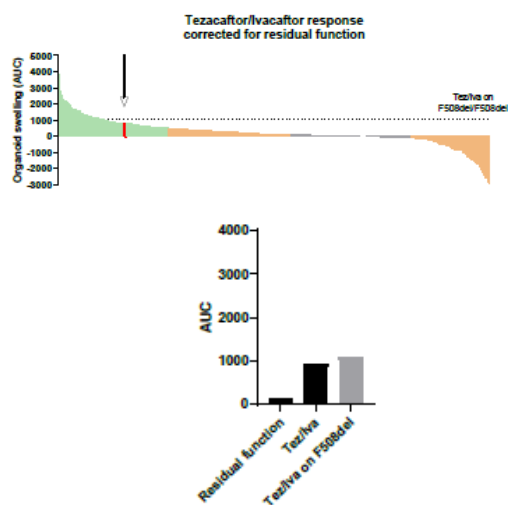


I am not selected for CHOICES, what are my options?

We are happy with a new pharmaceutical partner that joined the HIT-CF consortium. As stated in the previous newsletter, **Santhera’s Lonodelestat trial with people whose organoid did not react to any of the study drugs will start this spring.** The study protocol is currently being assessed, and CF centres will be contacted in the coming weeks. Your CF doctor will inform you about your possibilities!

Additionally, the HIT-CF team is also in contact with other companies interested in doing studies with the HIT-CF participants, including gene therapy studies. More information on this will follow. Finally, the Eloxx trial will start late 2022 – beginning of 2023.

Individual Tezacaftor/Ivacaftor (Symkevi) organoid response will be shared



Together with the study drugs, also Tezacaftor/Ivacaftor (Symkevi) was tested on the organoids. The individual organoid responses on Tezacaftor/Ivacaftor (Symkevi) will be shared with the HIT-CF participants not selected for CHOICES.

The timing will depend on the CF centre you are being followed: as only 52 people can participate in CHOICES, the trial will not run in every centre. People followed in centers that take part in the CHOICES trial will be informed after finalizing the inclusions for the CHOICES trial in autumn. This is to ensure that back-up candidates from that centre remain blinded for their organoid response until the study is up and running. People followed in the other centers will be informed about their individual results in the next coming weeks.

The report with your individual results will contain a waterfall plot (figure on the left) showing how your organoids responded compared to all other HIT-CF organoids. The lower figure compares your organoid results to that from a person with a double F508del mutation. Your CF doctor will guide you through this information. Don’t hesitate to ask him/her for more information if something is unclear!

Important: people having only stop (“X”) mutations, will **not** receive individual organoid responses, as Tezacaftor/Ivacaftor (Symkevi) was not tested on their organoids (no effect was anticipated).

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