HIT-CF webinar

03-02-2022

Sites with potential CHOICES patients

UMC Utrecht

Welcome to the HIT-CF webinar

Agenda

New collaborations
FAIR Therapeutics
Santhera

CHOICES trial
Patient selection process
Trial design
Q-life application
Timelines

Santhera trial
Patient selection process
Trial design
Timelines

Future
Other companies: Eloxx
Individual organoid result letter

New collaborations

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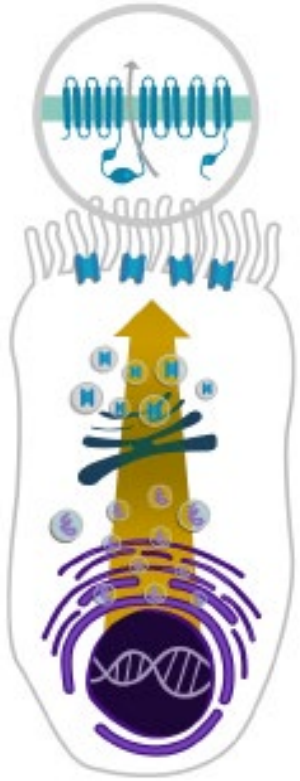
FAIR Therapeutics



Dirocaftor (DIR) is a potentiator. It enhances the ion transport activity of the CFTR protein

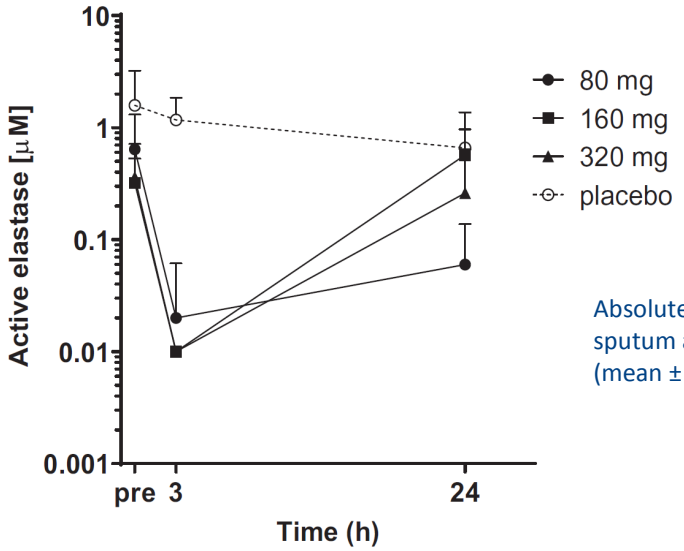
Posenacaftor (POS) is a corrector which promotes the maturation of CFTR protein to the cell surface

Nesolicaftor (NES) is an amplifier which co-translationally increases the amount of CFTR protein

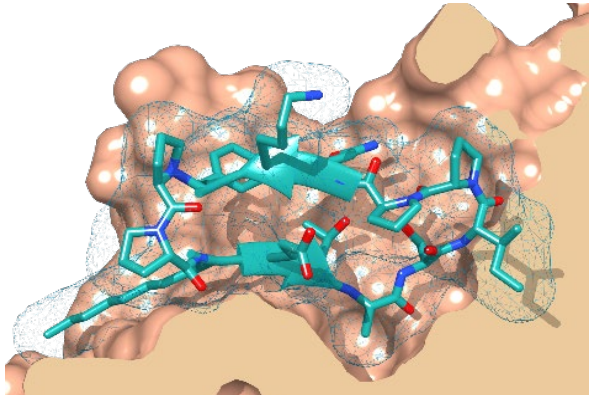
Santhera

Lonodelestat

- Targets elastase
- Highly potent, reversible and selective neutrophil elastase inhibitor
- Administration via Pari eFlow®



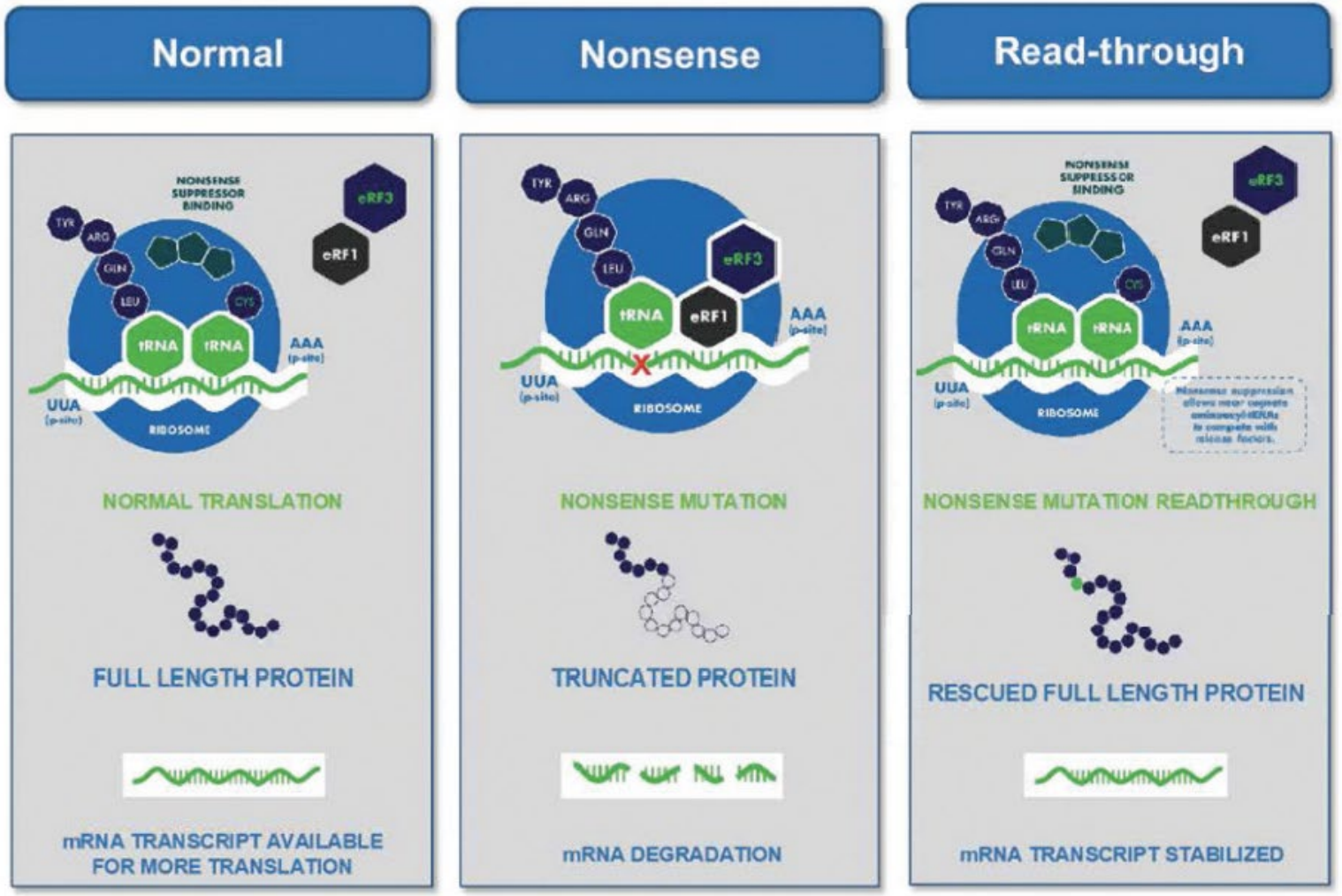
Absolute values in µM of active NE in sputum after inhalation of lonodelestat (mean ± SD values, N=6 per group).



Lonodelestat bound to elastase

Eloxx

ELX-02



Kerem (2020)

Timelines

Start CHOICES, CTIS Q2 2022

Start Santhera, Q2 2022

Start Eloxx, 2022/2023?

CHOICES Study

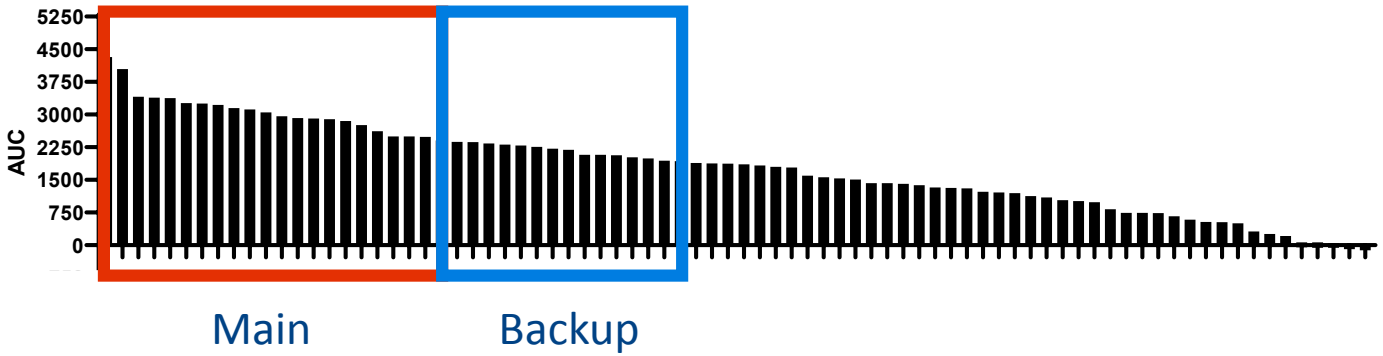
A Phase III, Multicentre, Randomised, Double-Blind, Placebo-Controlled, Crossover Study to Evaluate the Efficacy and Safety of Dirocaftor/Posenacaftor/Nesolicaftor in Subjects with Cystic Fibrosis Aged 18 Years and Older (CHOICES)

- Patient selection process
- Trial design
- Endpoints
- Timelines

CHOICES – Patient selection

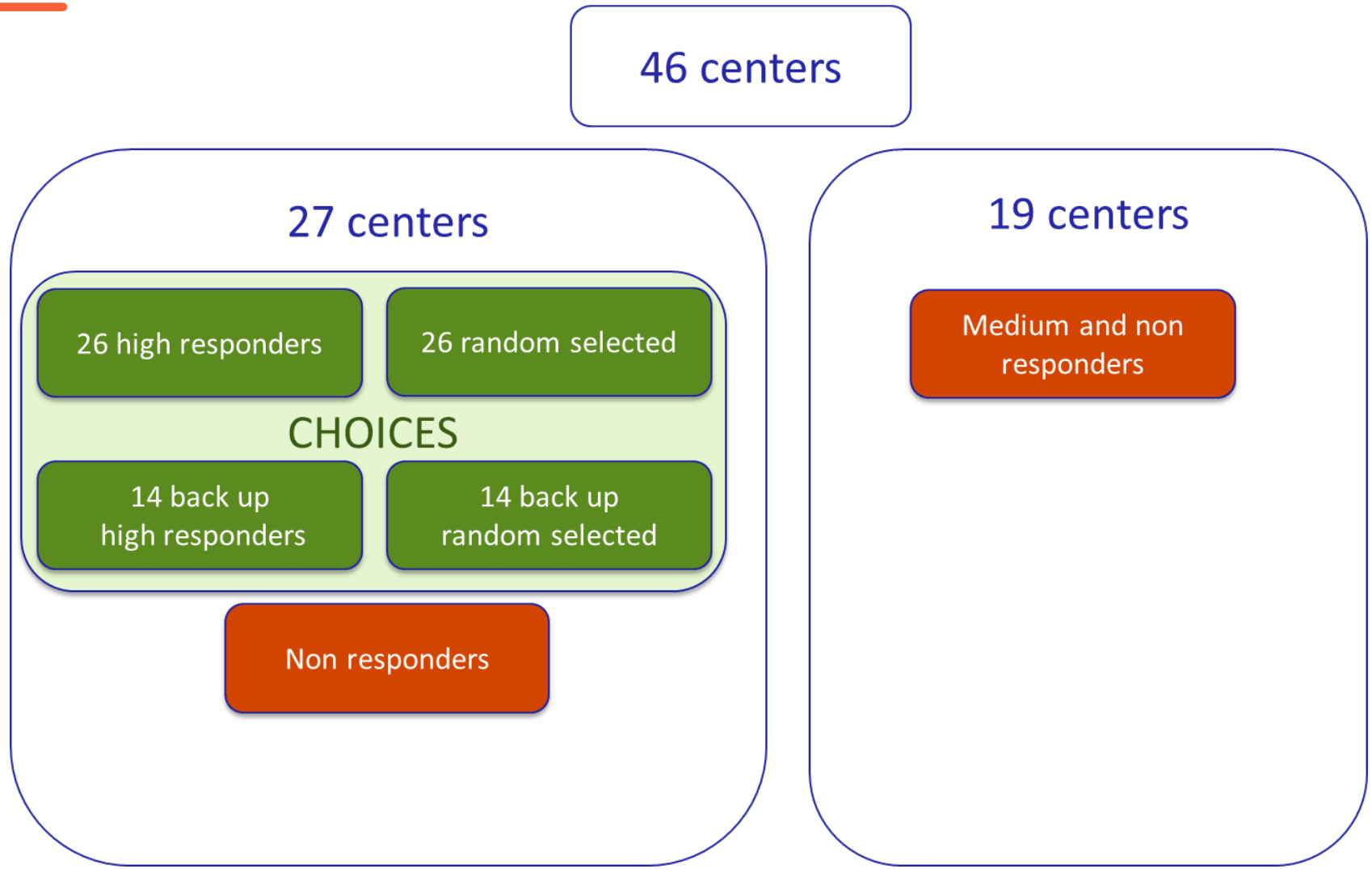
Step 1. Randomly selected patients with back up

Step 2. High responders with back up

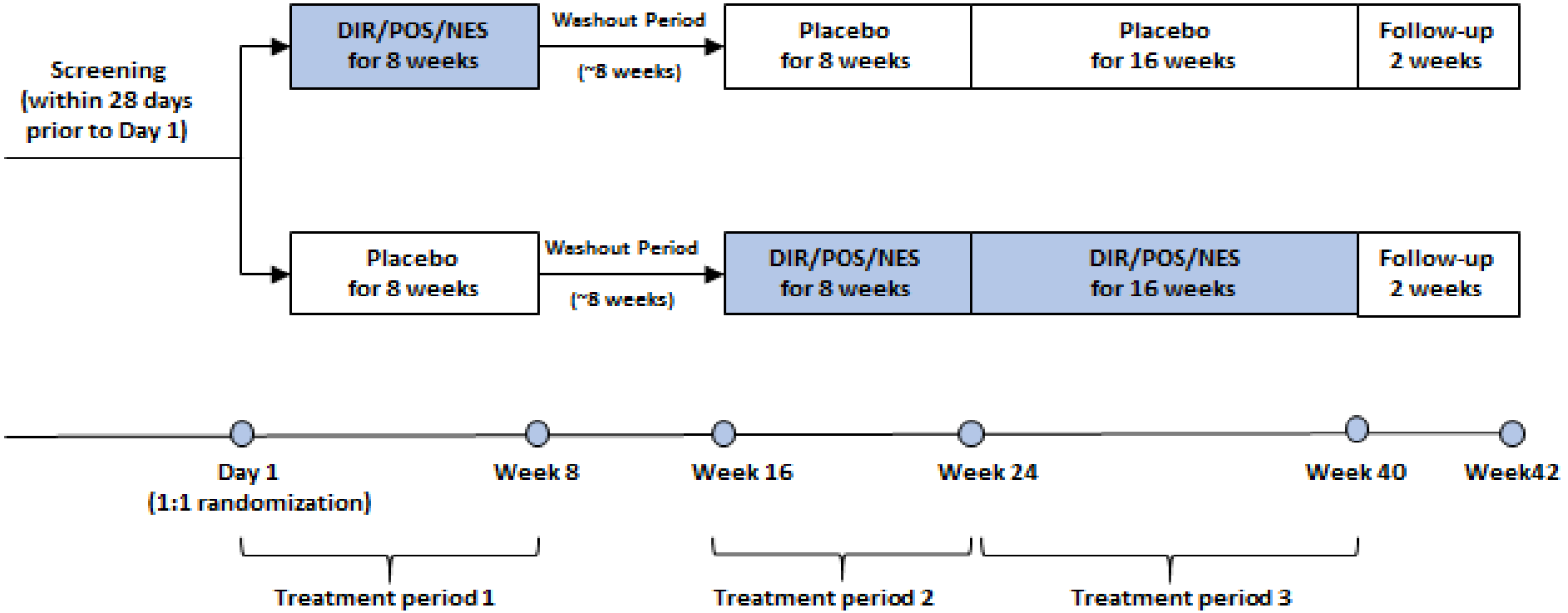


Patient selections where performed blinded for genotype and patient ID

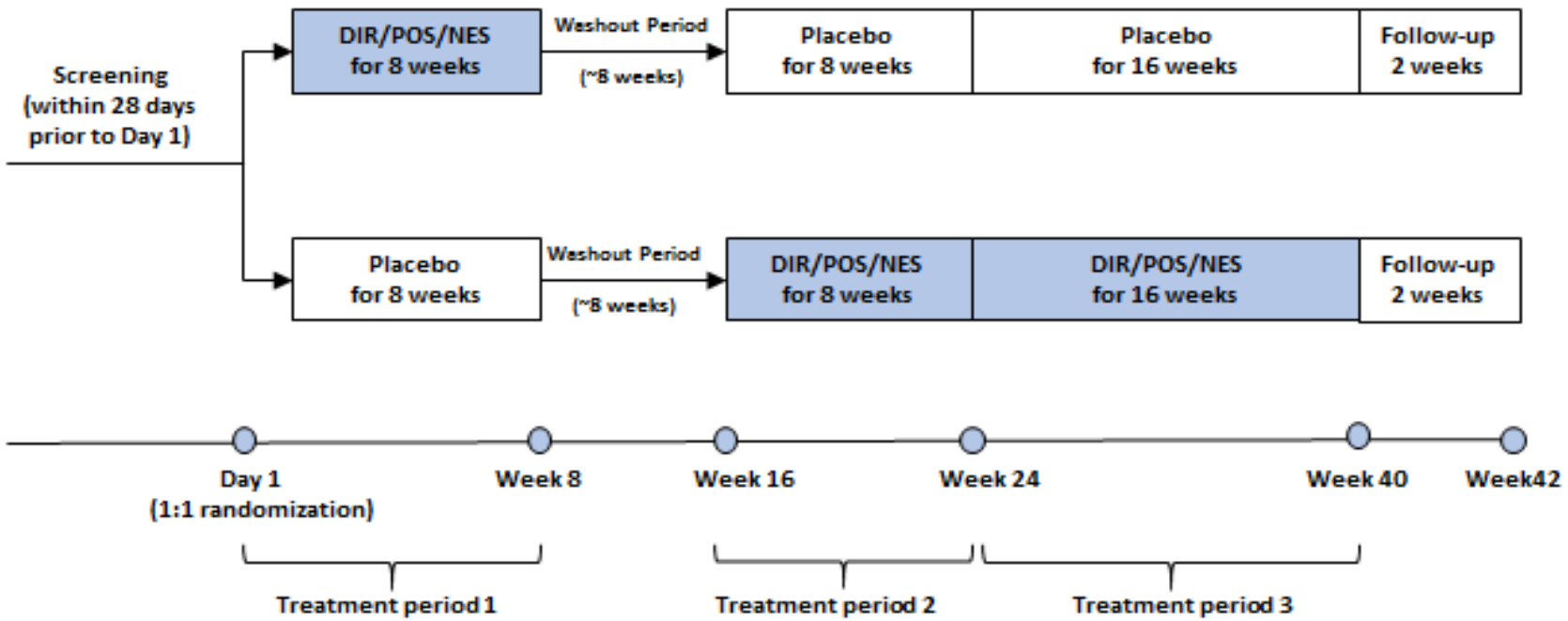
CHOICES – Patient (& site) selection



CHOICES – trial design



CHOICES – trial design



Visits:	4x	0x	4x	3x	1x
TC:	2x	1x	0x	2x	0x

Total:
12 Visits
5 TC

CHOICES – Endpoints

- **ppFEV1**
- **Sweat Chloride**
- **Weight**
- **Safety and tolerability**
- **CFQ-R**
- **Q-life**
- **Organoid response**

CHOICES – Q-life

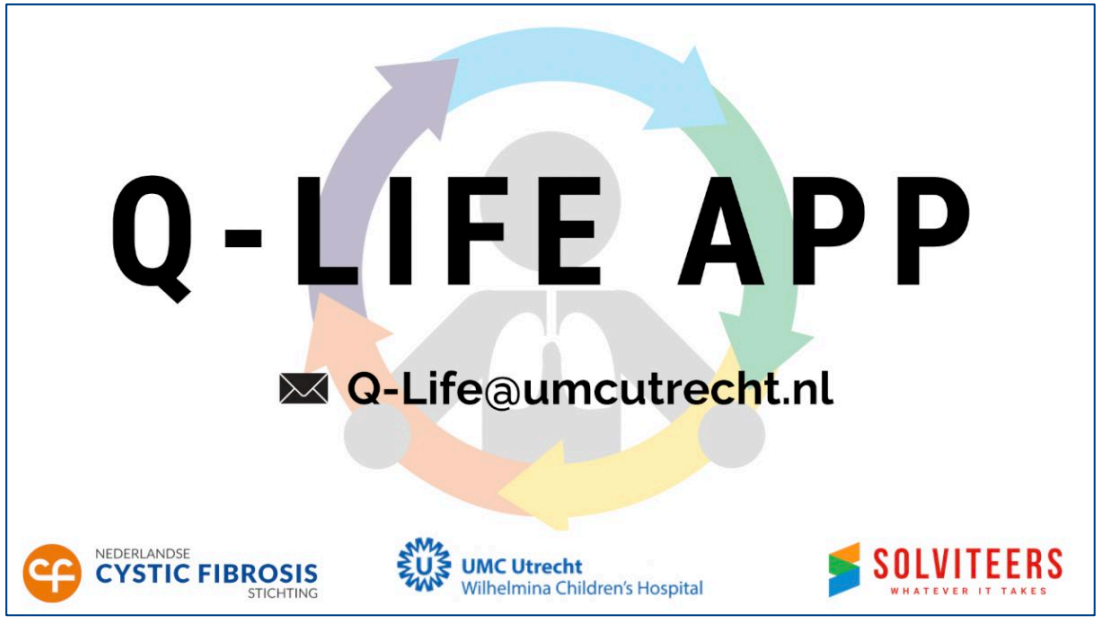
Q-Life application to assess QoL in people with CF on individual level

Available in all languages within CHOICES

Instructions and testing

- Instruction manual
- Investigator meeting

- Youtube instruction video:
- https://youtu.be/3dNTdel2TYE
- Or search for “Q-Life CF”



CHOICES - Timelines

- Fill and Finish of the capsules started
- Re-assesment of eligibility criteria – ongoing, please follow up
- Regulatory: CTIS (Apr-Jun 2022)
- Investigators meeting: July 2022
- First patient in: August 2022

Santhera

Trial in non/low organoid responders to CFTR modulators

Trial:
- Double blind, placebo-controlled multi-center study
- 12 weeks (lonodelestat placebo 2:1)
- BID 

Timelines:
- Protocol under review CTN
- Site contact in following weeks

Pending - Eloxx

Nov ’21 Results monotherapy ELX-02

Waiting resuls ELX-02 + Kalydeco

Future trial: HIT-CF + USA

Future

Additional possible trials FAIR therapeutics: residual functions, medium organoid responders, combination therapy

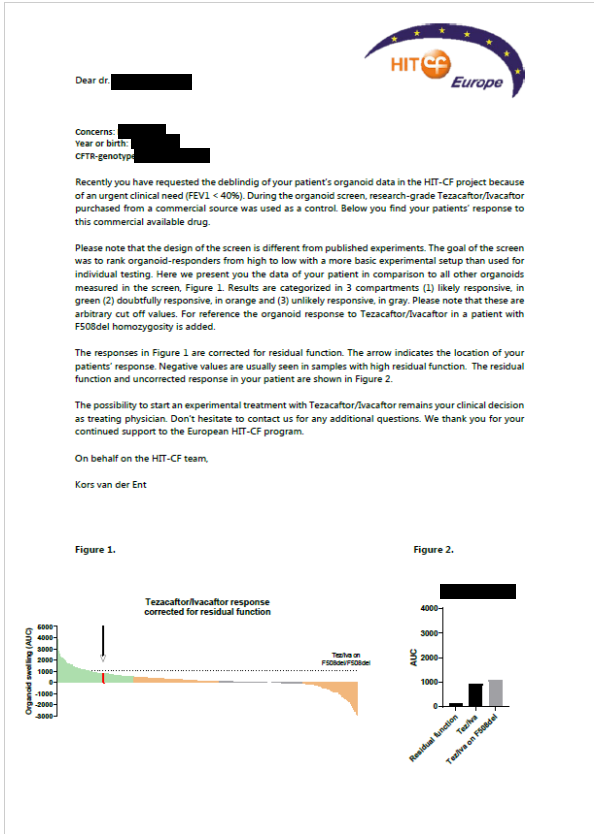
We are in contact with different companies (mRNA/genetherapy) to explore collaborations within HIT-CF project

Future – individual organoid response

- After CHOICES inclusion is closed
- Response to Tezacaftor/Ivacaftor from primary screen

- **Note:** homozygous nonsense mutations do not receive a result yet, no commercially available products were tested

Future – Individual organoid response



Dear dr. [redacted]

Concerns: [redacted]
Year or birth: [redacted]
CFTR-genotype: [redacted]

Recently you have requested the deblindig of your patient's organoid data in the HIT-CF project because of an urgent clinical need (FEV1 < 40%). During the organoid screen, research-grade Tezacaftor/Ivacaftor purchased from a commercial source was used as a control. Below you find your patients' response to this commercial available drug.

Please note that the design of the screen is different from published experiments. The goal of the screen was to rank organoid-responders from high to low with a more basic experimental setup than used for individual testing. Here we present you the data of your patient in comparison to all other organoids measured in the screen, Figure 1. Results are categorized in 3 compartments (1) likely responsive, in green (2) doubtfully responsive, in orange and (3) unlikely responsive, in gray. Please note that these are arbitrary cut off values. For reference the organoid response to Tezacaftor/Ivacaftor in a patient with F508del homozygosity is added.

The responses in Figure 1 are corrected for residual function. The arrow indicates the location of your patients' response. Negative values are usually seen in samples with high residual function. The residual function and uncorrected response in your patient are shown in Figure 2.

The possibility to start an experimental treatment with Tezacaftor/Ivacaftor remains your clinical decision as treating physician. Don't hesitate to contact us for any additional questions. We thank you for your continued support to the European HIT-CF program.

On behalf on the HIT-CF team,

Kors van der Ent

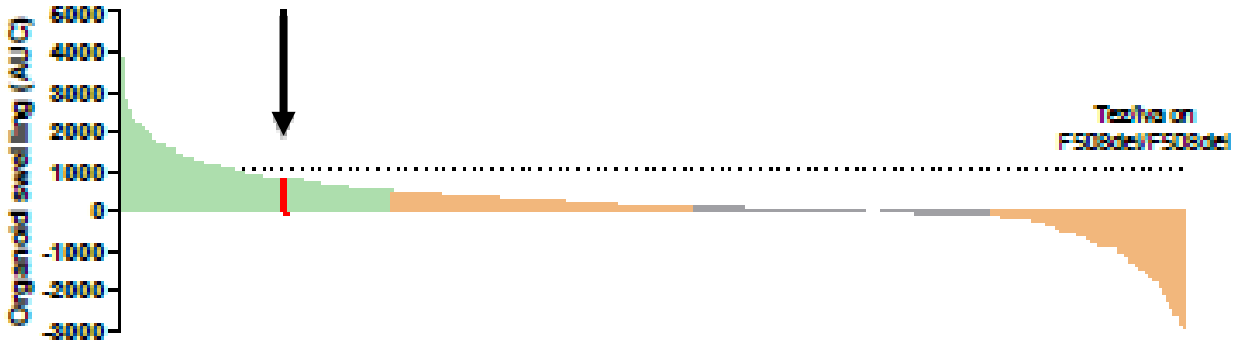
Figure 1.

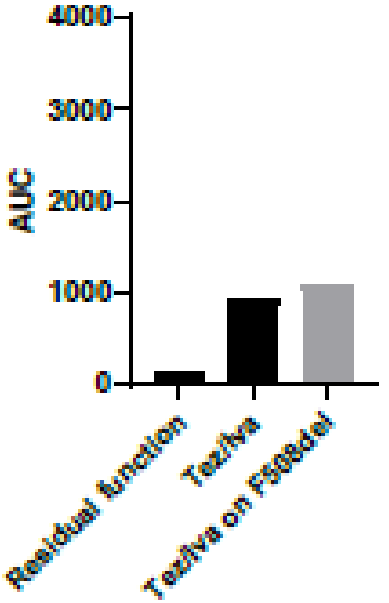
Figure 2.

Figure 1.

Figure 2.

Tezacaftor/Ivacaftor response
corrected for residual function





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Thank you all for your continuous support and looking forward to the next steps!