Cystic Fibrosis Trust

Research in focus

Long-term effects of Kaftrio

April 2022

Uniting for a life unlimited

Foreword

My son was diagnosed with cystic fibrosis (CF) when he was around nine months old. Before he was diagnosed, I can remember my husband saying that he tasted salty but we didn't make the connection with CF. It has been a lot of work to keep Matt as well as he is now. People often think CF health is only about lung health, but good lung function tests can conceal other organ challenges. Two years ago, he experienced problems with his liver and spleen and Non-Tuberculous Mycobacteria (NTM) was detected in his lungs. I was in utter despair and was advised that getting him into CFTR modulators was essential.

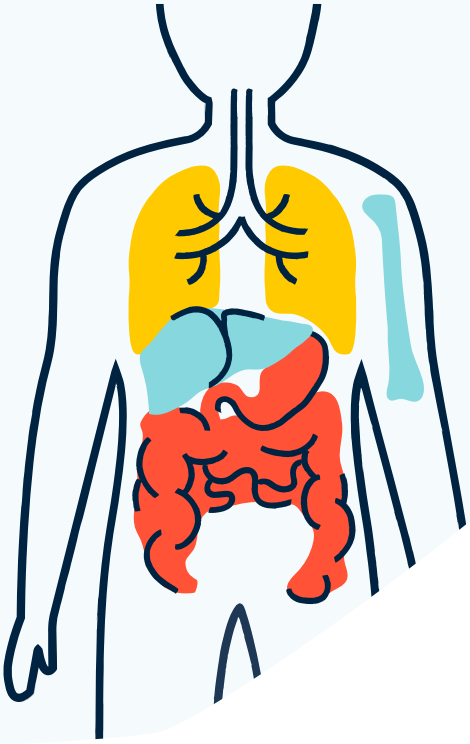
He started taking Kaftrio 15 months ago and we feel really lucky to have access to it. When he began taking it, he enrolled into the RECOVER study to help researchers understand the long-term effects of taking this medicine. Kaftrio has arrested his decline, it isn't a cure but we are realistic and grateful that his health has stablised. His lung health has always been pretty good, but there are subtle differences we've noticed since he's been taking Kaftrio, like a reduction in his sweat chloride levels. Now he's worrying about getting into college, future career plans and where he's going on holiday. He sees his life as going on forever, and we have to think like that too.

I'm very aware of how lucky we are to be offered such an expensive drug. I remember feeling left behind when everyone was getting access to CFTR modulators before my son became eligible for Kaftrio. I know there are still many people with CF who are unable to benefit from them and more research is desperately needed to make sure everyone can access the treatments they need to live longer, healthier lives.

Carolyn Thornton (centre with her family)

What is cystic fibrosis?

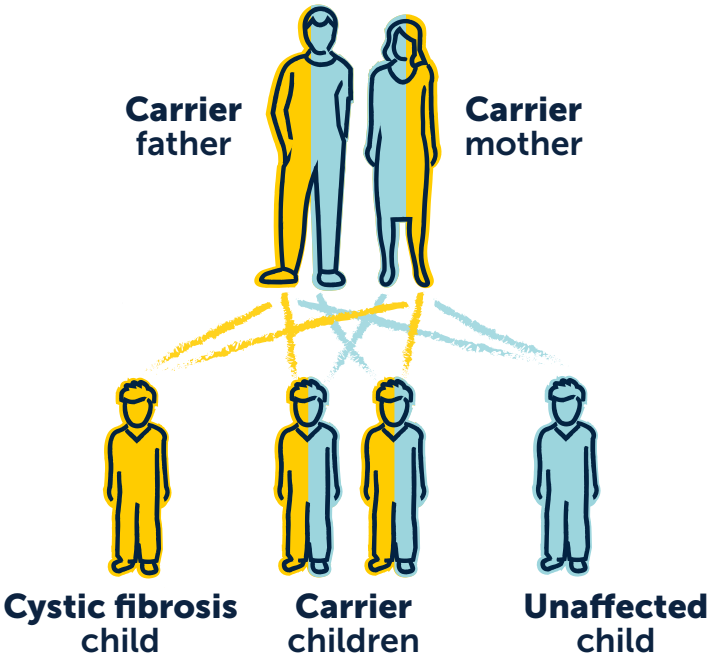
Cystic fibrosis is a rare, inherited condition that affects over 10,800 people in the UK.[1] It is caused by defects (mutations) in a gene that makes the CFTR protein, which controls the movement of salts and water in and out of cells. The defects cause the internal organs – especially the lungs and digestive system – to become clogged with thick, sticky mucus. This results in chronic infections and inflammation in the lungs, and in the digestive system, blockages, bloating and difficulty digesting food. Some adults with CF may also develop CF-related diabetes (CFRD) and forms of arthritis, bone thinning and liver problems that are related to having CF.



What causes CF?

Cystic fibrosis is caused by inheriting two damaged, or 'mutated', copies of the CFTR gene, one copy inherited from each parent. Someone's CF 'genotype' is a description of which of these mutations they carry. The CFTR gene contains the instructions on how to make the CFTR protein. When the CFTR gene is mutated, the protein made from the gene is damaged too.

Different things go wrong with production of the protein or how it works, depending on which CFTR mutations (genotype) people have. A mutation in some places within the gene means that no protein is produced. A mutation in other places means that a protein is produced, but it doesn't form the correct shape and can't move to, or can't do its job, on the surface of the cells.



How do CFTR modulators work?

The symptoms of CF are managed with a range of different medicines and treatments[2]; medicines that treat the underlying cause of CF called 'CFTR modulators' are available for some people with CF. CFTR modulators act by changing the shape of the damaged CFTR protein so it works again. These medicines only work if the damaged CFTR gene can make a CFTR protein. There are four CFTR modulator medicines: they're called ivacaftor, lumacaftor, tezacaftor and elexacaftor. They all work in different ways. Depending on their CFTR mutations, people with CF may either take ivacaftor on its own, known as Kalydeco, or a combination of ivacaftor plus one or two other drugs. (Orkambi is ivacaftor plus lumacaftor, Symkevi is ivacaftor plus tezacaftor and Katrio is ivacaftor plus tezacaftor and elexacaftor. Kaftrio is known as Trikafta in the United States). The majority of people with CF in the UK including all people with one or two copies of the commonest mutation, called 'F508del' are eligible for Kaftrio.[3]

Kalydeco = ivacaftor

Orkambi = ivacaftor + lumacaftor

Symkevi = ivacaftor + tezacaftor

Kaftrio* = ivacaftor +tezacaftor + elexacaftor

* Kaftrio is licensed as Trikafta in the United States

There are around 1 in 10 people with CF in the UK who are unable to benefit from these CFTR modulator medicines. Researchers around the world are working to develop new treatments that work in different ways to treat the underlying cause of CF in this group.[4]

What did the clinical trials of Kaftrio show?

Before medicines are approved for use, their effects are studied in clinical trials. These are conducted to ensure that the medicines are safe and they show the intended benefits. A number of different clinical trials of Kaftrio in people with CF have been conducted.[5-7] These trials have investigated the effects of Kaftrio for people with different CFTR mutations (and different combinations of CFTR mutations); and in people with CF of different ages.

The trials have shown that Kaftrio is beneficial to people with CF, as measured by improvements in lung function (measured as percent predicted FEV1) and number of exacerbations, overall CFTR protein function (as measured by sweat chloride levels) and quality of life (CFQ-R). The recent trials in children between 6-11 years old also used Lung Clearance Index (LCI) and Body Mass Index as additional measures. The trials ran for a maximum of 24 weeks (six months).

Why is more research into Kaftrio needed?

The clinical trials of Kaftrio were important to show that this medicine is beneficial for people with CF and to support a license application so they can be prescribed. However, doctors need to have a more complete understanding of how Kaftrio affects people with CF, so they can make any adjustments to CF care in the future, and identify areas where more research is needed to improve how symptoms are managed.

Doctors, researchers and health economists also need to collect evidence to show that the medicines are value for money – both to allow people with CF to continue to have access to Kaftrio, and to help ensure people in other countries which don't currently have access to it, can benefit from this medicine in the future.

To understand more about the wider and long-term benefits of Kaftrio, pharmacovigilance and Real World Evidence (RWE) research studies are happening across the world.[8]

A pharmacovigilance study is underway in the UK. This includes a data collection agreement between National Institute of Health and Clinical Excellence (NICE), Vertex Pharmaceuticals Limited and Cystic Fibrosis Trust. The results of this study will be used to inform a health technology assessment of Kaftrio in people with CF.[9,10]

A Real World Evidence study called RECOVER is taking place in Ireland and the UK.[11] In this report we explain why this study is needed, what it will tell us and the difference it will make to people with CF and their families in the future. A complementary RWE study known as PROMISE is underway in the United States.[12]

Professor Paul McNally

What is the RECOVER study all about?

The Real World Clinical Outcomes with Novel Modulator Therapy Combinations in People with CF (RECOVER) study aims to examine the impact of Kaftrio on various aspects of the lives and health of children and teens with CF aged 6-17 and adults with CF. It is funded by CF Foundation in the United States, CF Ireland and Cystic Fibrosis Trust. The study is led by Professor Paul McNally at RCSI University of Medicine and Health Sciences and Children's Health Ireland in Dublin and co-led by Professor Jane Davies at Imperial College London and the Royal Brompton Hospital, London. It involves five sites across Ireland and two sites in the UK.

"RECOVER was designed to be able to check that the results of the clinical trials hold true in a much bigger and more diverse group of people with CF, and also to look at the effects of Kaftrio on other important outcomes that weren't measured in the clinical trials. This includes things like abdominal symptoms, more sensitive and advanced ways of studying lung health and people's thoughts and habits about taking these new medicines," explained Professor McNally.

What will RECOVER tell us?

Real World Evidence studies such as the RECOVER study are research studies where people taking a new medicine are asked to take part in activities in addition to their standard care. Adults and children taking part in the RECOVER study are asked to complete questionnaires and undergo a wide range of well-established clinical tests at the hospital.

The researchers are also using some newer, more sensitive tests looking at how Kaftrio might affect health and quality of life in people with CF. The study will use tests measuring lung and gut symptoms of CF that weren't used in the CFTR modulator clinical trials. These are important to provide a more sensitive way of spotting any lung problems early and to inform how gut symptoms can be better treated in the future.

In previous studies, researchers have found that a common measure of lung function known as FEV1 doesn't work very well at spotting early lung problems in people with CF who have good lung health, such as children. To address this, research studies conducted in children with CF have used an additional, more sensitive measurement of lung health called 'Lung Clearance Index' (LCI). It is expected that more adults with CF will have good lung health now and in the future, due to taking Kaftrio. This is why the researchers in the RECOVER study are using LCI to assess the lung function in everyone taking part.

"Lung clearance index is less difficult and tiring to do than FEV1, and tells us more about what is happening in the lower airways. It requires somebody to breathe normally, but with a mouthpiece in, or a mask on if they're younger, and it measures the way gases mix within the airways of the lungs. Healthy lungs mix gases very efficiently, but in lungs with any form of disease in them, gases mix slower. The ratio or 'index' of how gases are mixed can tell us how much disease there is in the lower airway. It's very useful for us to be gaining additional data on its value in adults with CF, because now people are on modulators for longer and we need sensitive ways to pick up 'silent disease'," said Professor Jane Davies, co-lead Investigator on the RECOVER study and Director of the European CF Society LCI Core Facility.[13]

In order to detect early signs of permanent lung damage, a group of people taking part in the RECOVER study will have regular CT scans of their lungs, using a new low-radiation dose method of conducting them. (CT is a form of x-ray, that gives information about the tissue being studied in 3D, rather than a flat 2D, traditional x-ray).

More information about abdominal symptoms of CF is being collected in two ways throughout the RECOVER study, by asking people taking part about their symptoms in the form of a questionnaire and by providing a stool (poo) sample to be studied in the lab. The effects of Kaftrio on the abdominal symptoms of CF wasn't studied in the initial clinical trials. Researchers know that people with CF have identified that this is an important symptom to find out more about.[14]

A Lung Clearance Index test underway

‘Getting on Kaftrio was our best hope’

Carolyn’s son wasn’t eligible for Kalydeco, the first CFTR modulator. Initially he couldn’t benefit from Kaftrio either. When he developed the serious lung infection NTM and started having problems with his liver, she felt getting on a modulator was their best hope to try and make some difference to his life.

“My son started taking Kaftrio 15 months ago and we feel really lucky to have access to it. When he began taking it he enrolled into the RECOVER study to help researchers understand the long-term effects of taking this medicine,” said CF mum Carolyn.

“It was a big deal for us when one of the RECOVER tests showed that his sweat chloride levels had dropped, and it gave my son a massive lift! I know you can’t see it, but it means that his cells are benefitting internally from Kaftrio. I hope it’s making a difference deep in his lungs and things are moving more easily. I hope it’s benefiting other organs too like his liver and kidneys.”

Where does the RECOVER study fit in with other CF research?

“We can’t just look at the RECOVER study as an individual study answering a specific question, we should look at this as a study that’s part of an international jigsaw that’s helping us to understand CF better, understand how we should be treating it and understand what are the things that are still left for us to discover. For example, a better understanding of how Kaftrio affects CF infections, will inform future care for everyone with CF, not just those on this modulator,” said Professor Paul McNally.

The effects of Kaftrio and other CFTR modulator treatments on CF infections in the longer term are still unclear. It is thought that people with extensive lung damage and those who can’t benefit from CFTR modulators will remain vulnerable to CF infections. This is an active area of CF research around the world.[15]

“I’m very aware of how lucky we are to be offered such an expensive drug. I know there are a lot of problems in the world, but it’s thrilling that these drugs are being approved. It’s scary too, because we’re relying so much on taxpayer’s money and Governments that are stable. I hope that the results from the RECOVER study will prove to the economists that there is a gain in people taking these drugs. The more you keep people out of hospital the better!” said Carolyn.

The RECOVER study is funded by CF Foundation in the United States, CF Ireland and Cystic Fibrosis Trust.

References

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Cystic Fibrosis Trust

About us

Cystic Fibrosis Trust is the charity uniting people to stop cystic fibrosis. Our community will improve care, speak out, support each other and fund vital research as we race towards effective treatments for all.

We won't stop until everyone can live without the limits of cystic fibrosis.

For more information:

visit **cysticfibrosis.org.uk/research**

or contact **research@cysticfibrosis.org.uk**