Elexacaftor-Tezacaftor-Ivacaftor treatment in the real world is associated with significant improvements in pulmonary function, nutrition, sweat chloride and exhaled nitric oxide over six months.

Real World Clinical Outcomes with Novel Modulator Therapy Combinations in People with Cystic Fibrosis | RECOVER

Poster Title

Impact of Elexacaftor-Tezacaftor-Ivacaftor (ETI) treatment on clinical outcome in people with CF in a real world setting – The RECOVER trial

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On behalf of the RECOVER study Group

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Aim

The Aim of RECOVER is to develop a deeper understanding of the impact of ETI in the lives and health of people with CF in a real world setting.

Introduction

Real world, post approval studies contribute significantly to the evidence surrounding the impact of new treatments, including CFTR modulators, but can be complex undertakings. ETI was approved by in Europe by EMA in August 2020.

Methods

RECOVER, a multi-centre post-approval study examining the impact of ETI, and conducted in 8 clinical sites in Ireland and the UK over 2 years, is designed to examine important outcomes in children and adults prescribed ETI. In addition to routine data collected as part of normal care, key RECOVER endpoints include lung clearance index (LCI), spirometry controlled CT scores, treatment adherence, GI symptoms and inflammation, liver disease markers, nasal inflammation and nitric oxide metabolism.

We present data on sweat chloride, FEV_1, lung clearance index (LCI), height, weight, BMI and exhaled nitric oxide (FeNO) from the first phase of the study – people with CF aged 12 years and above homozygous for F508del (FF) and heterozygous for F508del and a minimum function mutation (MF).

Summary of Key Outcome Data

All Participants

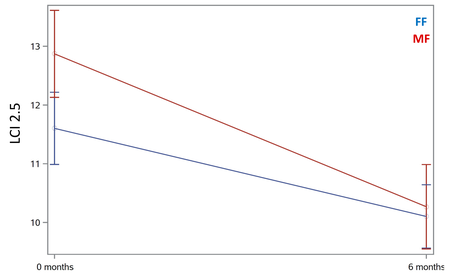
	Baseline (N=114)			3 months (N=83)			6 months (N=91)			Baseline v 3 mths	3 mths v 6 mths	Baseline v 6 mths
Variable	N	Mean	Std Dev	N	Mean	Std Dev	N	Mean	Std Dev	p-value	p-value	p-value
Sweat Chloride	89	80.51	17.808	0	.	.	62	42.1	19.005			<.0001
LCI	71	12.1	4.008	0	.	.	73	10.17	3.669			<.0001
pp FEV1	113	83.55	15.843	56	91.1	15.48	59	92.17	14.576	<.0001	0.905	<.0001
Weight z score	113	0.061	0.817	56	0.2	0.761	91	0.334	0.785	0.001	0.009	<0.001
BMI z score	113	0.084	0.818	56	0.192	0.775	91	0.383	0.775	<.0001	0.132	0.002
FeNO	112	13.86	10.407	0	.	.	82	17.15	13.193			<0.001

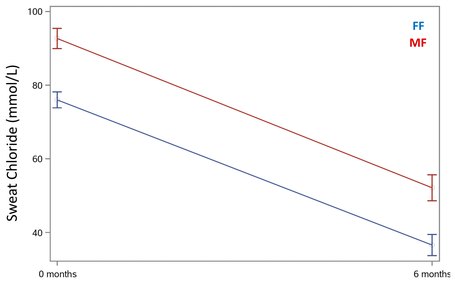
F508del/F508del (FF)

	Baseline (N=75)			3 months (N=57)			6 months (N=57)			Baseline v 3 mths	3 mths v 6 mths	Baseline v 6 mths
Variable	N	Mean	Std Dev	N	Mean	Std Dev	N	Mean	Std Dev	p-value	p-value	p-value
Sweat Chloride	64	76	17.321	0	.	.	40	36.58	18.161			<.0001
LCI	43	11.6	4.03	0	.	.	45	10.1	3.625			<.0001
pp FEV1	74	83.73	15.867	40	90.23	15.681	36	90.93	14.423	<.0001	0.983	0.003
Weight z score	74	0.088	0.912	41	0.245	0.813	57	0.343	0.873	0.003	0.038	<.0001
BMI z score	74	0.093	0.864	41	0.253	0.758	57	0.381	0.84	0	0.367	0
FeNO	73	14.55	10.584	0	.	.	52	18.79	15.567			0.007

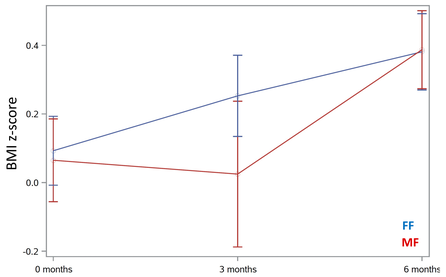
F508del/Minimum function (MF)

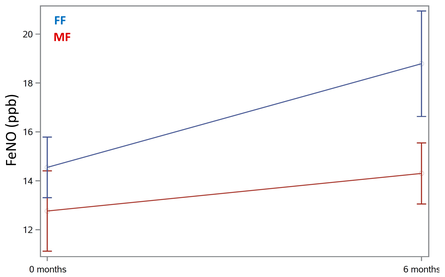
	Baseline (N=38)			3 months (N=26)			6 months (N=34)			Baseline v 3 mths	3 mths v 6 mths	Baseline v 6 mths
Variable	N	Mean	Std Dev	N	Mean	Std Dev	N	Mean	Std Dev	p-value	p-value	p-value
Sweat Chloride	24	92.67	13.417	0	.	.	22	52.13	16.531			<.0001
LCI	28	12.87	3.922	0	.	.	28	10.27	3.804			<.0001
pp FEV1	38	82.97	16.142	16	93.26	15.235	23	94.12	14.923	<.0001	0.91	<.0001
Weight z score	38	0.031	0.597	15	0.076	0.606	34	0.318	0.623	0.016	0.15	0
BMI z score	38	0.065	0.744	15	0.025	0.823	34	0.309	0.134	0.115	0.15	0.002
FeNO	38	12.76	10.13	0	.	.	30	14.3	6.839			0.463

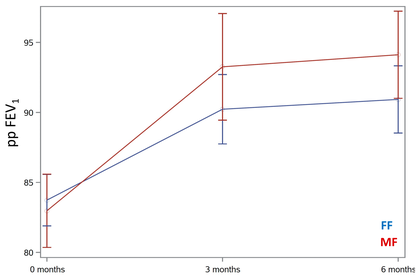




Graphical Representation of Key Outcome Data







Recruitment

Recruitment commenced in October 2020. 120 PWCF have been recruited to the study to date with 6 withdrawals. The reason for withdrawals included removal of study consent, amended ETI dosage for clinical reasons, discontinuation of ETI for medical reasons and pregnancy in one subject. Data on 114 PWCF is presented. Six of eight sites were activated for phase one of the study. Recruitment and sample collection were hampered by restrictions and delays associated with COVID-19 pandemic. Recruitment reached 88% of prespecified targets

Results

Results are presented in the central pane. It should be noted that almost all participants in the FF group started the study on dual combination CFTR modulators, whereas none of the MF group did. Significant improvements were seen across all outcome measures in the individual and combined groups apart from FeNO in the MF group. Of note, sweat chloride values at 6 months were lower in the FF group, however, apart from FeNO, other outcome measures were similar at this timepoint. Ongoing work will examine the impact of ETI on airway nitric oxide metabolism. Data on the impact of ETI on abdominal symptoms is presented elsewhere at this conference.

Acknowledgements

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Significant reduction in abdominal symptoms assessed with the CFAbd-Score over 4 weeks of treatment with Elexacaftor-Tezacaftor-Ivacaftor – first results from the RECOVER study

RECOVER
Real World Clinical Outcomes with Novel Modulator Therapy Combinations in People with Cystic Fibrosis

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INTRODUCTION

The novel CFTR modulator combination Elexacaftor-Tezacaftor-Ivacaftor (ETI) for people with CF and the 508del mutation has the potential for substantial improvements in end organ function. Studies assessing the impact of previous highly potent modulator therapies, e.g. Ivacaftor, focused on pulmonary involvement of the multiorgan-disease CF. Effects on abdominal symptoms, have not been sufficiently assessed.

For this purpose, the CFAbd-Score (cf. Fig 1) was developed and validated in line with FDA recommendations for development of a Patient Reported Outcome Measure (PROM) with input from focus groups, multidisciplinary CF specialists, people with CF and their families. It was found to correlate well with clinical characteristics, ultrasound findings and gut inflammation.

RECOVER (NCT04602468) is a multi-center, cohort study including 8 pediatric and adult sites across Ireland and the UK over a three-year period. Among other multiorgan effects of ETI, RECOVER longitudinally assesses changes of abdominal symptoms using the CFAbd-Score.

OBJECTIVES

Analyses of early changes of abdominal symptoms comparing CFAbd-Scores before, to 1 month during ETI-therapy.

METHODS

The one-sided PROM includes 28 items grouped in 5 domains (see Fig.1) as well a modified Bristol Stool Scale. Following FDA-recommendations, domains were weighted using a statistical classification algorithm and the CFAbd-Score was calculated on a scale from 0 to 100 with higher values for increasing frequency and/or severity of symptoms.

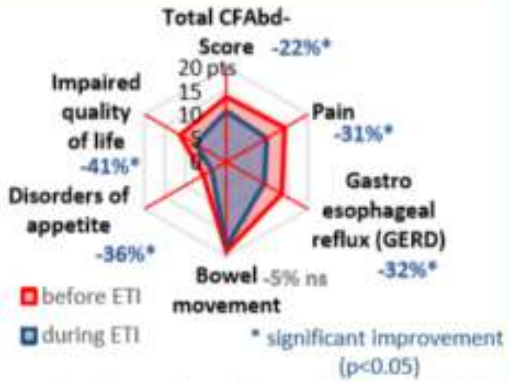

Fig. 1: design of the one-sided CFAbd-Score **Fig. 2:** changes of CFAbd-Scores after 1 month of ETI [%]

RESULTS

A total of 113 PWCF completed the baseline. 86 PWCF (mean age: 19.8±1.1, min age: 12, max age: 57), of whom 42 were female, completed the questionnaire 1 month after ETI therapy initiation. Among these, 50 (61%) previously received other CFTR-modulator therapy .

After only one month of ETI, total CFAbd-Scores reduced significantly from 13.7±1.5 to 10.7±1.2 (p<0.01)(cf. fig 2) independent from previous CFTR-modulation.

Domain	Previous CFTR-modul. therapy	Before ETI therapy	During ETI therapy (1 mo.)	p
Pain	No (32)	18.1±3.9	10.2±3.1	0.019
	Yes (50)	11.9±2.8	10.1±2.5	0.593
	p:	0.144	0.982	
GERD	No (32)	16.2±3.3	10.8±2.5	0.048
	Yes (50)	11.6±2.6	7.1±2.0	0.041
	p:	0.275	0.242	
DBM	No (32)	21.1±2.5	16.5±2.5	0.065
	Yes (50)	17.5±2.0	18.4±2.0	0.649
	p:	0.288	0.576	
DA	No (32)	7.9±1.9	5.3±1.3	0.012
	Yes (50)	4.3±1.3	3.8±1.0	0.724
	p:	0.148	0.833	
SE	No (32)	15.8±3.4	7.8±2.5	0.0005
	Yes (50)	8.2±2.7	6.5±2.0	0.336
	p:	0.085	0.668	
Total CFAbd-Score	No (32)	16.7±2.4	10.8±2.0	0.0003
	Yes (50)	11.5±1.9	10.3±1.8	0.559
	p:	0.092	0.898	

Tab. 1: ETI-related mean changes of CFAbd-Scores resulted lower with previous CFTR-modulation

Furthermore, significant improvements were seen for domains "pain" (14.3±2.1→9.9±1.9/p=0.03), "GERD" (13.6±2.0→9.3±1.6/p=0.01), "disorders of appetite" (5.6±1.1→3.6±0.7/p=0.05) and "impairment of quality of life" (11.3±2.1→7.5±1.6/p<0.01). However, in these 86 participants decline did not reach significance for "disorders of bowel movements" (19.0±1.6→18.0±1.6). Over time, reduction of ETI-induced symptoms was more pronounced in PWCF without previous CFTR-modulator therapy. Likewise, in all domains, except DBM, such changes were significant in PWCF. In contrast, symptoms reduction in PWCF, who had received lumacaftor/ivacaftor or tezacaftor/ivacaftor previous to ETI therapy, attained significance only in the GERD domain (Tab.1).

DISCUSSION

Using the CFAbd-Score, the first PROM specifically developed for assessment of CF-related abdominal symptoms, we demonstrate comprehensive improvements in gastrointestinal symptoms after initiation of the highly effective modulator therapy with ETI. As part of RECOVER, in addition to longitudinal data on abdominal symptoms, markers of gut inflammation and pancreatic status will be collected over two years of therapy.

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