Bottom Line:

Poster #141

PROMISE | RECOVER

Female and younger people with CF are more likely to achieve normalization of sweat chloride on ETI. Effective targeting of both alleles in a person's genotype is important for achieving greatest CFTR rescue as measured by Sweat Chloride.

Poster Title

Factors associated with significantly corrected sweat chloride in people with CF taking Elexacaftor/Tezacaftor /Ivacaftor – Results from the PROMISE and RECOVER studies.

P. McNally [1], G. Solomon [2], D. Nichols [3], S. Rowe [2], F. Ratjen [4], M. Rosenfeld [3], A. Kelly [5], L. Kirwan [6], J. Davies [7, 8], S. Heltshe [3, 9]

[1] RCSI University of Medicine and Health Sciences and Children's Health Ireland, Dublin, Ireland, [2] University of Alabama at Birmingham, Birmingham, AL USA, [3] University of Washington School of Medicine, Seattle WA, USA, [4] University of Toronto; Hospital for Sick Children, Toronto, ON Canada, [5] University of Pennsylvania Perelman School of Medicine, [6] Cystic Fibrosis Registry of Ireland, [7] National Heart and Lung Institute, Imperial College London, [8] Royal Brompton Hospital, London, United Kingdom, [9] US CFF TDNCC, Seattle Children's Research Institute, Seattle, WA USA.

Acknowledgements

We want to thank all of our study participants and parents for their time, dedication and enthusiasm, the whole PROMISE and RECOVER study teams, collaborators and staff at our clinical sites. Funding for PROMISE and RECOVER is from the Cystic Fibrosis Foundation with support from CF Ireland and the CF Trust for RECOVER. Special thanks to Morgan McCreary, CFF TDN Coordinating Center, Seattle Children's Research Institute for statistical analysis.

CYSTIC FIBROSIS FOUNDATION ADDING TOMORROWS

RECOVER PROMISE

Summary of Key Results

	PROMISE	RECOVER	Total
N	563 (79.6%)	144 (20.4%)	707
Age (in Years)			
Mean (SD)	21.5 (11.3)	14.8 (8.51)	20.1 (11.1)
Category			
< 12	121 (21.5%)	55 (38.2%)	176 (24.9%)
[12, 18)	147 (26.1%)	61 (42.4%)	208 (29.4%)
[18, 30)	172 (30.6%)	14 (9.7%)	186 (26.3%)
[30, +)	123 (21.8%)	14 (9.7%)	137 (19.4%)
Female (%)	271 (48.1%)	70 (48.6%)	341 (48.2%)
Genotype (%)			
FF	281 (49.9%)	104 (72.2%)	385 (54.5%)
FG	34 (6.0%)	0 (0%)	34 (4.8%)
FM	211 (37.5%)	40 (27.8%)	251 (35.5%)
FO	37 (6.6%)	0 (0%)	37 (5.2%)
Prior Modulator (%)			
Dual	265 (47.1%)	105 (72.9%)	370 (52.3%)
Iva	43 (7.6%)	0 (0%)	43 (6.1%)
None	255 (45.3%)	39 (27.1%)	294 (41.6%)
Baseline			
	PROMISE	**RECOVER**	**Total**
Sweat Chloride Mean (SD)	87.8 (20.4)	83.1 (19.6)	86.8 (20.3)
ppFEV1 Mean (SD)	84.7 (22.7)	86.1 (16.2)	85.0 (21.6)
CFQ-R Mean (SD)	74.0 (17.9)	78.7 (17.5)	75.0 (17.9)
6-Month Change			
	PROMISE	**RECOVER**	**Total**
Sweat Chloride Mean (SD)	-42.7 (21.1)	-44.6 (18.8)	-43.1 (20.6)
ppFEV1 Mean (SD)	8.87 (10.1)	7.78 (10.0)	8.65 (10.1)
CFQR Mean (SD)	15.4 (17.6)	11.1 (17.0)	14.2 (17.6)

Table 1. Demographic and Clinical Data by Study Cohort: The RECOVER cohort was younger than the PROMISE cohort, consisting largely of children under 18. The RECOVER cohort consisted predominately of F508del homozygous (FF) participants and participants who previously received prior dual modulator. RECOVER subjects had greater CFQ-R at baseline and less change in CFQ-R 6 months post-baseline, compared to PROMISE. No differences were observed in ppFEV1 between the RECOVER and PROMISE cohorts.

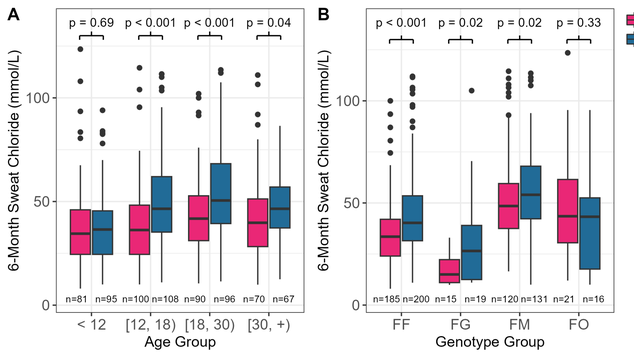


Figure 1. Sweat Chloride 6 Months Post-Baseline compared by Sex and A) Age Group and B) Genotype Group: Sweat chloride 6 months post-baseline was consistently lower in adolescent and adult females than males and greater in FF, FG, FM females than corresponding males. FF = F508del/F508del, FG = F508del/gating, FM = F508del/minimal function, FO = F508del/other.

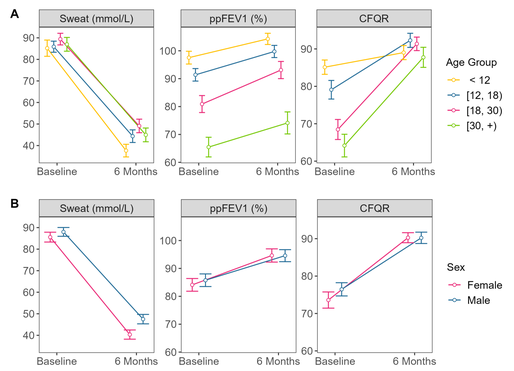


Figure 2. Average Values of Outcomes of Interest at Baseline and 6 Months Post-Baseline, Stratified by A) Age Group, and B) Sex at Birth: Outcomes of interest included sweat chloride concentration, percent predicted forced expiratory volume in 1 second (ppFEV1), and the CF Questionnaire-Revised. Vertical bars represent the corresponding unadjusted 95% confidence interval. The average sweat chloride concentration 6 months post-baseline was observed to be greater for all age groups 12 years of age and older. Similarly, sweat chloride concentration 6 months post-baseline *was observed* to be greater in males, relative to females.

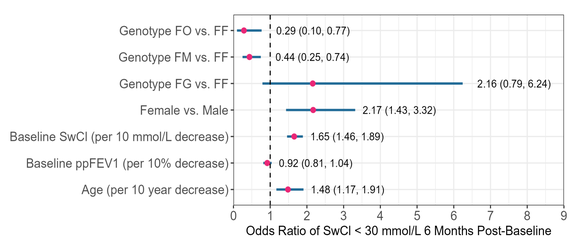


Figure 3. Multivariate Logistic Regression Results – Sweat Chloride < 30 mmol/L 6 Months Post-Baseline: Significant effects were observed for covariates corresponding to sex at birth and age. Additionally, lower odds of a 6-month post-baseline sweat chloride < 30 mmol/L was observed for FM and FO mutations, relative to F508del homozygous participants.

	SwCl ≥ 30 mmol/L	SwCl < 30 mmol/L
n	530 (75.0%)	177 (25.0%)
Age (in Years)		
Mean (SD)	21.1 (11.2)	17.1 (10.1)
Category		
< 12	109 (20.6%)	67 (37.9%)
[12, 18)	155 (29.2%)	53 (29.9%)
[18, 30)	155 (29.2%)	31 (17.5%)
[30, +)	111 (20.9%)	26 (14.7%)
Female (%)	234 (44.2%)	107 (60.5%)
Genotype (%)		
FF	266 (50.2%)	119 (67.2%)
FG	9 (1.7%)	25 (14.1%)
FM	229 (43.2%)	22 (12.4%)
FO	26 (4.9%)	11 (6.2%)
Study (%)		
PROMISE	439 (82.8%)	124 (70.1%)
RECOVER	91 (17.2%)	53 (29.9%)
Prior Mod (%)		
Dual	252 (47.5%)	118 (66.7%)
Iva	12 (2.3%)	31 (17.5%)
None	266 (50.2%)	28 (15.8%)
Baseline		
	SwCl ≥ 30 mmol/L	**SwCl < 30 mmol/L**
Sweat Chloride Mean (SD)	92.2 (15.6)	70.8 (24.1)
ppFEV1 Mean (SD)	83.5 (21.9)	89.3 (20.0)
CFQ-R Mean (SD)	74.3 (17.9)	77.2 (17.9)
6-Month Change		
	SwCl ≥ 30 mmol/L	**SwCl < 30 mmol/L**
Sweat Chloride Mean (SD)	-40.7 (19.6)	-50.2 (21.9)
ppFEV1 Change Mean (SD)	8.90 (10.2)	7.92 (9.60)
CFQR Change Mean (SD)	14.2 (17.7)	14.4 (17.1)

Table 2. Demographic and Clinical Data by Post-Modulator Sweat Chloride (SwCl): Subjects less than 12 years of age represented the largest subset of the combined cohorts with SwCl < 30 mmol/L and females comprise 60.5% of those with SwCl < 30 mmol/L despite making up 48.2% of the cohort.

Introduction

Treatment with Elexacaftor/Tezacaftor/Ivacaftor (ETI) is associated with significant improvements in sweat chloride and end organ function in people with CF. Sweat chloride (SwCl) responses to ETI among individuals are variable, with reports of on-treatment SwCl levels of <30mmol/L (in the normal range). PROMISE[1] and RECOVER[2] are prospective, multi-center post-approval studies of ETI among people with CF 6 years and older in North America and Ireland/UK, respectively. We sought to determine the frequency of on-treatment SwCl <30mmol/L after 6 months of ETI and investigate factors associated with achieving these levels.

Methods

PROMISE and RECOVER study databases were combined to increase sample size and generalizability of data. Clinical characteristics at baseline and after 6 months on ETI common to both studies include: sex at birth, CFTR genotype group, prior modulator usage, age, percent predicted forced expiratory volume in 1 second ($ppFEV_1$), SwCl, and the CF Questionnaire-Revised (CFQ-R). The values of SwCl measured at baseline and 6 months were of interest in this analysis. For those subjects with SwCl missing at 6 months, last post-baseline SwCl was carried forward to reduce missingness. Multivariate logistic regression was used to estimate features associated with achieving SwCl<30mmol/L after 6 months of ETI.

Results

- 707 participants with CF (PwCF) were in the combined analysis set (n=144 from UK/Ireland and 563 from North America). The cohort were mostly adolescents or young adults, with 176 (24.9%) under 12. The RECOVER population is younger than PROMISE (80.6% vs 47.6% under 18 years, respectively). RECOVER and PROMISE had differing genotype distributions (Table 1).
- Baseline $ppFEV_1$ was 85.0 (SD=21.6) in the combined cohort and similar across continents. Baseline SwCl was lower (p=0.012) in RECOVER compared to PROMISE and RECOVER achieved lower mean values at 6 months compared to PROMISE.
- Six month SwCl <30mmol/L was achieved in 25.0% of the cohort (n=177), but neither $ppFEV_1$ change (mean change = 8.8 vs. 7.9, p = 0.30) or CFQR changes (14.4 vs 14.2, p=0.91) were different between those below or above 30mmol/L.
- Sex at birth, genotype group, younger age, and lower baseline SwCl, were associated with SwCl<30mmol/L at 6 months: odds ratio (OR)[95% CI] was 2.2 [1.4, 3.3] for females, 0.3 [0.1, 0.8] for FO vs FF, 0.4 [0.2, 0.7] for FM vs FF. There were increased odds for normalized SwCl for every 10-year lower baseline age (OR=1.5 [1.2, 1.9]), and OR=1.7 [1.5, 1.9] for every 10 mmol/L lower baseline SwCl. Baseline $ppFEV_1$ was not associated with normalization of SwCl.

Conclusions

Our preliminary investigation has identified that female and younger PwCF are more likely to achieve normalization of SwCl. Further analysis in the entire population is required to understand the relevance of these findings. The independent association of genotype suggests that effective targeting of both alleles in a person's genotype is important for achieving greatest CFTR rescue as measured by SwCl.

References

1. Nichols DP, Paynter AC, Heltshe SL, et.al. Clinical Effectiveness of ETI in People with CF: A Clinical Trial. Am J Respir Crit Care Med. 2022 Mar 1;205(5):529-539.
2. McNally P, Lester K, Stone G, et. al. Improvement in Lung Clearance Index and Chest CT Scores with Elexacaftor/Tezacaftor/Ivacaftor Treatment in People with Cystic Fibrosis Aged 12 Years and Older - The RECOVER Study. Am J Respir Crit Care Med. 2023 Sep 13.

Bottom Line:

Poster #547

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

Elexacaftor/Tezacaftor/Ivacaftor is Associated with Improvements in Abdominal Symptom Scores in Children with CF Aged 6-11 Years over 6 Months of Treatment.

Poster Title

Reduction in abdominal symptoms measured by the CFAbd-Score over 6 months of treatment with Elexacaftor/Tezacaftor/Ivacaftor in children with CF aged 6-11 – Results from the RECOVER study

McNally, P. [1,2], Davies, J. C.[3,4], Lester, K.[1,2], Elnazir, B.[2], Williamson, M.[2], Cox, D.[2], Linnane, B.[5], Downey, D.[6,7], McKone, E. F.[8], Zagoya, C[9]. Mainz, J.G[9]. On behalf of the RECOVER study Group

[1]RCSI University, Dublin, Ireland. [2]Children's Health Ireland, Dublin, Ireland. [3]Royal Brompton & Harefield hospitals, part of Guys and St Thomas' Trust, London, UK. [4]NHLI Imperial College London, London, UK. [5]University of Limerick School of Medicine, Limerick, Ireland. [6]Belfast Health and Social Care Trust, Northern Ireland. [7]Queen's University Belfast, Northern Ireland. [8]St Vincent's University Hospital, Dublin, Ireland. [9]Brandenburg Medical School, University Hospital Brandenburg an der Havel, Germany.

Acknowledgements

We want to thank all of our study participants and parents for their time, dedication and enthusiasm, the whole RECOVER study team, collaborators and staff at our clinical sites. Funding for RECOVER is from the Cystic Fibrosis Foundation with support from CF Ireland and the CF Trust. Supported by ECFS-CTN.

Summary of Key Results

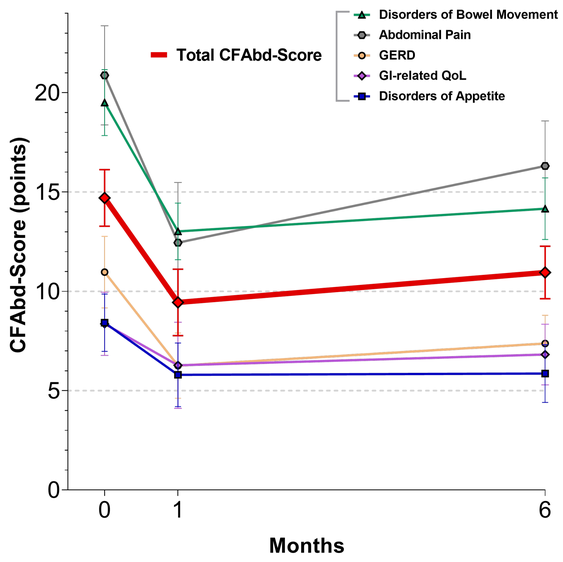


Figure 1. Mean scores (error bars, SEM) at baseline (n=76), one (n=44) and six (n=66) months of ETI therapy for: A) total CFAbd-Score, B) pain domain, C) gastroesophageal reflux disease (GERD) domain, D) disorders of bowel movement (DBM) domain, E) disorders of appetite (DA) domain and F) impairment of quality of life (QoL) domain.

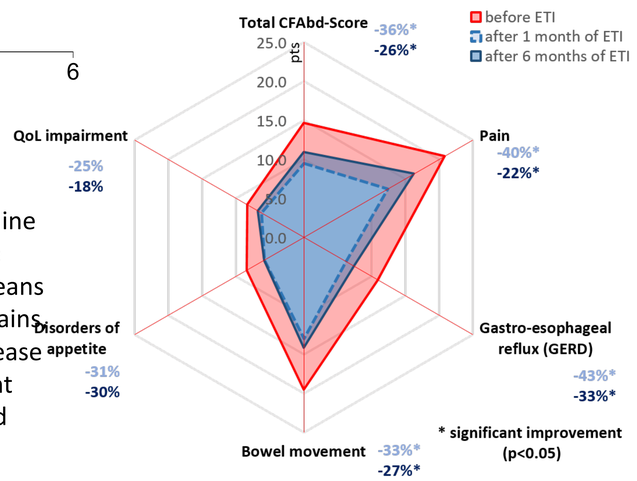


Figure 2. Spider graph outlining baseline (solid red line), 1-month (dotted blue line) and 6-month (solid blue line) means of total CFAbd-score and its five domains, i.e. pain, gastroesophageal reflux disease (GERD), disorders of bowel movement (DBM), disorders of appetite (DA) and impairment of quality of life (QoL).

		Visit	Mean	SEM	P (v. BL)
CFAbd-Score	TOTAL	Baseline	14.7	1.4	
		Month 1	9.4	1.7	**0.0002**
		Month 6	10.9	1.3	**0.0004**
CFAbd-Score domains	PAIN	Baseline	20.9	2.5	
		Month 1	12.4	3.0	**0.001**
		Month 6	16.3	2.3	**0.03**
	GERD	Baseline	11.0	1.8	
		Month 1	6.3	1.6	**0.006**
		Month 6	7.4	1.4	**0.015**
	DBM	Baseline	19.5	1.7	
		Month 1	13.0	1.4	**0.0001**
		Month 6	14.2	1.5	**0.002**
	DA	Baseline	8.4	1.4	
		Month 1	5.8	1.6	0.17
		Month 6	5.9	1.5	0.065
	QOL	Baseline	8.4	1.6	
		Month 1	6.3	2.2	0.24
		Month 6	6.8	1.5	0.25

Table 1. Mean values and standard errors of the mean for overall CFAbd scores and sub-scores at baseline, 1- and 6-month timepoints for pain, gastroesophageal reflux disease (GERD), disorders of bowel movement (DBM), disorders of appetite (DA) and impairment of quality of life (QoL).

Other Information

Introduction

The CFAbd-Score is the first CF-specific patient reported outcome measure (PROM) focusing on gastrointestinal (GI) symptoms developed and validated in line with FDA recommendations and including people with CF (PwCF), their proxies and CF-specialists from different fields (community voice). We have previously demonstrated significant improvements in abdominal symptoms (AS) using the CFAbd-Score among PwCF aged 12 years and older and treated with Elexacaftor/Tezacaftor/Ivacaftor (ETI), with improvements sustained over 12 months. Here we present first data on children aged 6-11 treated with ETI (1).

Recruitment

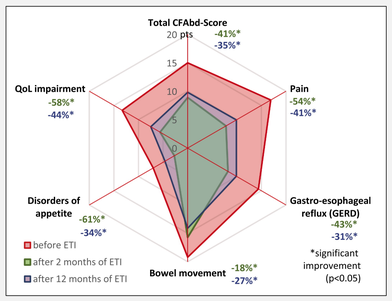
Data are currently available for n=76 participants (age at baseline (SD): 8.7(1.8) years, n=44 (57.9%) females) with baseline and n=66 with month-6 scores. For month 1, questionnaires of n=49 participants are currently available.

Methods

The CFAbd-Score, a PROM consisting of 28 questions in 5 domains, was applied prior to ETI-initiation, and subsequently at 1 and 6 months on treatment. Total CFAbd scores and domain scores range from 0 to 100 points, with higher scores indicating higher AS-burden. Total CFAbd scores and domain scores are calculated using a scoring algorithm that weights items and domains differently to optimize sensitivity. CFAbd-Score questionnaires were administered to participants by research staff at sites. Pseudonymized questionnaires were captured, processed and scored centrally at the CF Center in Brandenburg and der Havel, Germany.

Prior Work

Data previously published (1) for PwCF >12 years of age showed improvements in all domains of the CFAbd-Score.



Results

Total CFAbd scores decreased significantly over 6 months of therapy with ETI from a mean (SEM) of 14.7 (1.4) to 10.9 (1.3), p<0.001, as did scores for the domains of pain (20.9 (2.5) to 16.3 (2.3); p=0.03), GERD (11 (1.8) to 7.4 (1.4); p=0.01) and disorders of bowel movements (19.5 (1.7) to 14.2 (1.5), p=0.002). Declines for impairment of quality of life (8.4 (1.6) to 6.8 (1.5), p=0.25) as well as disorders of appetite (8.4 (1.4) to 5.9 (1.5); p=0.065) did not reach significance in this dataset (Table 1). Compared to people aged 12 years and older (Figure 2), baseline measures for QoL impairment and GERD were substantially lower in this cohort.

Ongoing Work

We are continuing to collect and process CFAbd-Scores in children aged 6-11 as part of RECOVER. Determination of stool levels of elastase, inflammatory and proliferative markers is ongoing. Stool will also be analysed for microbial community composition in this group.

Discussion

Using the CFAbd-Score, we have demonstrated improvement in abdominal symptoms over 6 months of ETI treatment in children with CF aged 6-11 included in this preliminary analysis. Specific improvement was seen in the areas of pain, GERD and disorders of bowel movement. In children aged 6-11, pain and disorders of bowel movements continue to be major symptoms with much lower scores for GERD and QoL impairment compared to older children and adults. Analysis of abdominal symptom scores from further timepoints and stool specimens for inflammatory markers and elastase is ongoing.

References

(1) Mainz JG, Lester K, Elnazir B, Williamson M, McKone E, Cox D, Linnane B, Zagoya C, Duckstein F, Barucha A, Davies JC, McNally P; RECOVER Study Group. Reduction in abdominal symptoms (CFAbd-Score), faecal M2-pyruvate-kinase and Calprotectin over one year of treatment with Elexacaftor-Tezacaftor-Ivacaftor in people with CF aged ≥12 years - The RECOVER study. J Cyst Fibros. 2023 Oct 7:S1569-1993(23)00922-0. doi: 10.1016/j.jcf.2023.10.001. Epub ahead of print. PMID: 37806792.

Bottom Line:

Poster #142

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

Elexacaftor-Tezacaftor-Ivacaftor is Associated with Improvements in PRAGMA-CF Chest CT Scores in Children with CF and F508del/F508del Aged 6-11 Over 1 Year

Poster Title

Elexacaftor-Tezacaftor-Ivacaftor (ETI) and spirometry-controlled chest CT scores in children with CF aged 6-11

Paul McNally[1,2], Karen Lester[1], Basil Elnazir[2], Michael Williamson[2], Des Cox[2], Barry Linnane[3], Eilish Twomey[2], Thara Persaud[2], David Rea[2], Siobhan McGrane[3], Tom Semple[4,8], Laura Kirwan[5], Paul O'Regan[5], Merlijn Bonte[6], Ed McKone[7], Jane Davies[4,8], Harm Tiddens[6,9]

[1]RCSI University of Medicine and Health Sciences, [2]Children's Health Ireland, Dublin, Ireland, [3]University Hospital Limerick, School of Medicine, University of Limerick, Ireland, [4]Royal Brompton Hospital, London, United Kingdom, [5]Cystic Fibrosis Registry of Ireland, [6]LungAnalysis Group, Erasmus Medical Center, Rotterdam, Netherlands, [7]St Vincent's University Hospital, Dublin, Ireland, [8]National Heart and Lung Institute, Imperial College London, [9]Thirona, Nijmegen, Netherlands

Acknowledgements

We want to thank all of our study participants and parents for their time, dedication and enthusiasm, the whole RECOVER study team, collaborators and staff at our clinical sites. Funding for RECOVER is from the Cystic Fibrosis Foundation with support from CF Ireland and the CF Trust. Supported by ECFS-CTN.

Summary of Key Results

RECOVER 6-11	Baseline			12 months			Baseline vs 12 mths	
	N	Mean	Std Error	N	Mean	Std Error	Δ (95% CI)	p-value
% Disease	26	2.73	0.305	13	1.89	0.372	0.8 (0.15 , 1.52)	**0.021**
% Bronchiectasis	26	2.04	0.281	13	1.61	0.351	0.4 (-0.24 , 1.12)	0.185
% Bronchial Wall Thickening	26	0.62	0.117	13	0.25	0.150	0.4 (0.07 , 0.68)	**0.020**
% Mucous Plugging	26	0.05	0.018	13	0.01	0.025	0.04 (-0.04 , 0.11)	0.294
% Trapped Air	23	9.49	1.456	12	3.05	1.945	6.4 (1.56 , 11.32)	**0.016**

Table 1. PRAGMA-CF CT scores and sub scores at baseline (pre-treatment) and 12 months on ETI therapy. Least-squares means and standard errors from the generalized linear mixed models are presented for each CT score outcome. Baseline is compared with 12 months using linear contrasts and results are presented as the difference (Δ) with 95% confidence interval and p-value for the 6-11 cohort. Previously published data (1) in children aged 12 and above showed improvements in all scores apart from bronchiectasis and is demonstrated in figure 2.

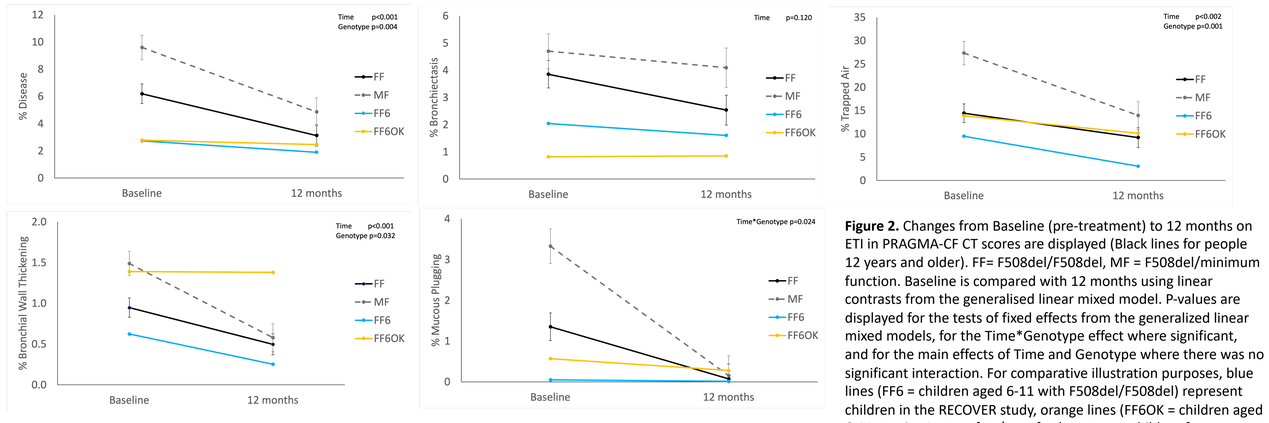


Figure 2. Changes from Baseline (pre-treatment) to 12 months on ETI in PRAGMA-CF CT scores are displayed (Black lines for people 12 years and older). FF= F508del/F508del, MF = F508del/minimum function. Baseline is compared with 12 months using linear contrasts from the generalised linear mixed model. P-values are displayed for the tests of fixed effects from the generalized linear mixed models, for the Time*Genotype effect where significant, and for the main effects of Time and Genotype where there was no significant interaction. For comparative illustration purposes, blue lines (FF6 = children aged 6-11 with F508del/F508del) represent children in the RECOVER study, orange lines (FF6OK = children aged 6-11 starting Lumacaftor/Ivacaftor) represent children from a previous study (2)(CFORMS).

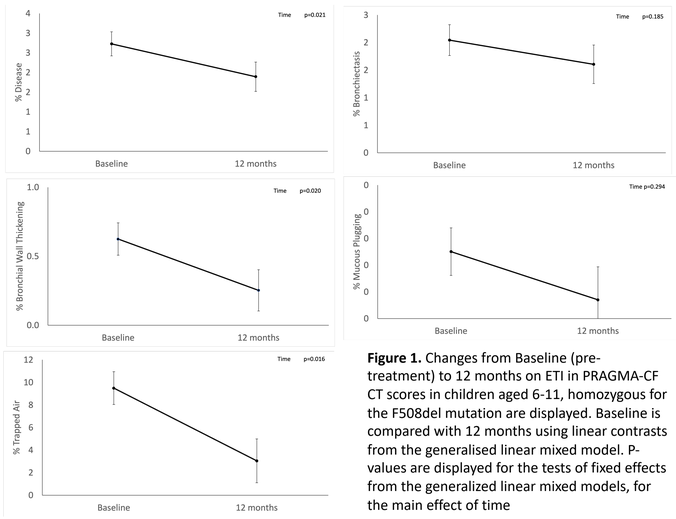
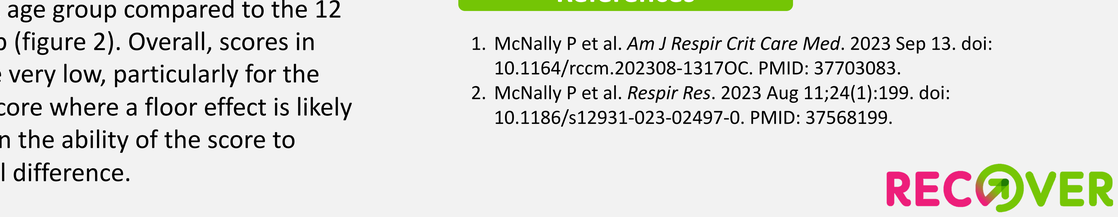


Figure 1. Changes from Baseline (pre-treatment) to 12 months on ETI in PRAGMA-CF CT scores in children aged 6-11, homozygous for the F508del mutation are displayed. Baseline is compared with 12 months using linear contrasts from the generalised linear mixed model. P-values are displayed for the tests of fixed effects from the generalized linear mixed models, for the main effect of time

Figure 3. Line graphs representing the change in PRAGMA-CF scores and sub-scores in all children with CF aged 6-11 over 12 months of ETI for whom data was available. A single very significant outlier at the baseline timepoint only was excluded from the model used to calculate the effect of time, owing to its adverse effect on the accuracy of fit of the model.



Other Information

Background

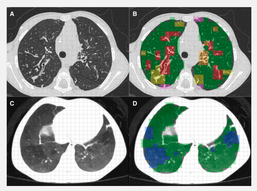
Elexacaftor-Tezacaftor-Ivacaftor (ETI) is associated with improvements in pulmonary function, sweat chloride and nutrition in people with CF (PwCF) and the F508del mutation. RECOVER (NCT04602468) is a multi-centre post-approval study examining the impact of ETI in PwCF. Structural lung damage is a key pathological finding in people with CF with advanced disease. A component of that structural lung disease is irreversible, and prevention of this irreversible pathology is a key aim of pulmonary management of people with CF. We have previously demonstrated significant improvements in chest CT scores (apart from bronchiectasis) after one year of treatment with ETI in people aged 12 years and above (1) as outlined in Figure 2 above.

Aim

The Aim of the study was to determine the changes in chest CT scores among children with CF aged 6-11 years over one year of treatment with ETI

Methods

Prior to the study, CT scanners at all sites were standardised in terms of scanning protocol and scanner output under the supervision of the European Cystic Fibrosis Society Clinical Trials Network (ECFS-CTN) CT imaging core facility at the Erasmus Medical Centre, Rotterdam. Pw CF aged 6-11 years were recruited to the study prior to initiating ETI. ETI was clinically prescribed. Spirometry controlled CT scans were performed on inspiration and exhalation at baseline and one year in subjects enrolled in this aspect of the study as per the study protocol. Further scans will be performed at 24 months in this cohort. CT scan images were anonymised and sent for analysis at Erasmus MC. CT scans were scored using the Perth Rotterdam Annotated Grid Morphometric Analysis (PRAGMA) scoring system. PRAGMA-CF scores are expressed as % of total lung volume and divided into % disease (dis), % bronchiectasis (bx), % trapped air (TA), % Mucus plugging (MP) and % bronchial wall thickening (BWT). Data are expressed as mean values. Differences in means are assessed using Mann Whitney t tests.



Results

In this subset of participants in the RECOVER study 6-11 cohort, at the time of presentation, scored CT data was available for 26 participants at baseline and 13 participants at 12 months. A significant improvement was seen in the cumulative %disease score (mean 2.73[SE 0.3] to 1.89[0.37], p=0.021). Improvements were also seen in the scores for %trapped air (9.49[1.46] to 3.05[1.95], p=0.016) and %bronchial wall thickening (0.62[0.12] to 0.25[0.15], p=0.02). There was no improvement in the scores for %bronchiectasis (2.04[0.28] to 1.61[0.35], p=0.18) or %mucus plugging (0.05[0.02] to 0.01[0.02], p=0.29). Scores for all aspects of disease were substantially lower in children in the 6-11 age group compared to the 12 and older age group (figure 2). Overall, scores in this 6-11 cohort are very low, particularly for the %mucus plugging score where a floor effect is likely to have impacted on the ability of the score to detect a meaningful difference.

Conclusions

We have demonstrated significant improvements in the overall %disease scores and scores for trapped air and bronchial wall thickening in children aged 6-11 with CF and the F508del/F508del mutation. The numbers of subjects is lower than in the older cohort, although data collection is ongoing. A floor effect is likely to have affected this analysis, particularly for %mucus plugging

Future Work

We are continuing to collect CT data in children aged 6-11. Analysis of previously collected data in people aged 6-11 and 12 and older is ongoing. Analysis of bronchial artery and airway wall thickness ratios for all groups is ongoing, as is the testing of automated analysis software for the different outcome measures.

References

1. McNally P et al. *Am J Respir Crit Care Med*. 2023 Sep 13. doi: 10.1164/rccm.202308-1317OC. PMID: 37703083.
2. McNally P et al. *Respir Res*. 2023 Aug 11;24(1):199. doi: 10.1186/s12931-023-02497-0. PMID: 37568199.

RECOVER

Bottom Line:

Poster #138

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

ETI is associated with sustained improvements in pulmonary function and nutrition in people with CF aged 12 years and older over two years of treatment in the real-world. Sweat chloride levels and LCI are significantly lower in people with two F508del mutations compared to one.

Poster Title

Clinical outcomes in people with CF after 2 years of Elexacaftor/Tezacaftor/Ivacaftor – Results from the RECOVER study.

McNally, P. [1,2], Lester, K.[1,2], Sutton, S.[1,2], Elnazir, B.[2], Williamson, M.[2], Cox, D.[2], Stone G[1,2], Linnane, B.[3], Kirwan, L.[4], O'Regan, P.[4], Saunders C.[5,6], McKone, E. F.[7], Davies, J. C.[5,6] On behalf of the RECOVER study Group

[1]RCSI University, Dublin, Ireland. [2]Children's Health Ireland, Dublin, Ireland. [3]University of Limerick School of Medicine, Limerick, Ireland. [4]Cystic Fibrosis Registry of Ireland. [5]Royal Brompton & Harefield hospitals, part of Guys and St Thomas' Trust, London, UK. [6]NHLI Imperial College London, London, UK. [7]St Vincent's University Hospital, Dublin, Ireland.

Acknowledgements

We want to thank all of our study participants and parents for their time, dedication and enthusiasm, the whole RECOVER study team, collaborators and staff at our clinical sites. Funding for RECOVER is from the Cystic Fibrosis Foundation with support from CF Ireland and the CF Trust. Supported by ECFS-CTN.

Summary of Key Results

All Participants												
	Baseline (N=117)			12 months (N=99)			24 months (N=83)			Baseline vs all FU		12 mths vs 24 mths	
Variable	N	Mean	Std Error	N	Mean	Std Error	N	Mean	Std Error	Δ (95% CI)	p-value	Δ (95% CI)	p-value
Sweat Chloride	114	86.9	1.68	94	44.8	1.87	79	51.0	2.12	-40.2 (-44.2 , -36.2)	**<0.001**	6.2 (0.7 , 11.8)	**0.029**
LCI	85	12.1	0.42	77	9.7	0.45	70	10.6	0.47	-2.5 (-3 - -2)	**<0.001**	0.9 (-0.4 , 2.1)	0.184
pp FEV_1	117	83.1	1.56	92	92.5	1.62	80	91.8	1.78	9 (6.9 , 11.1)	**<0.001**	-0.6 (-3.4 , 2.1)	0.663
pp FVC	117	92.0	1.26	92	99.5	1.33	80	98.4	1.48	6.7 (4.7 , 8.7)	**<0.001**	-1.2 (-3.8 , 1.5)	0.398
pp FEF 25-75	82	73.5	3.66	75	85.3	3.59	66	83.6	3.88	11.2 (6.1 , 16.3)	**<0.001**	-1.7 (-7.9 , 4.5)	0.596
Weight z score	117	0.04	0.082	96	0.26	0.083	82	0.22	0.087	0.2 (0.13 , 0.28)	**<0.001**	-0.04 (-0.14 , 0.06)	0.403
BMI z score	117	0.07	0.084	96	0.26	0.085	82	0.20	0.092	0.18 (0.08 , 0.27)	**<0.001**	-0.06 (-0.18 , 0.06)	0.338
CFQR-RD	115	75.0	1.49	94	88.2	1.67	81	87.4	1.87	13.8 (10.3 , 17.3)	**<0.001**	-0.8 (-5.7 , 4.1)	0.753
F508del/F508del													
	Baseline (N=78)			12 months (N=68)			24 months (N=59)			Baseline vs all FU		12 mths vs 24 mths	
Variable	N	Mean	Std Error	N	Mean	Std Error	N	Mean	Std Error	Δ (95% CI)	p-value	Δ (95% CI)	p-value
Sweat Chloride	75	77.2	1.95	64	33.8	2.11	57	40.7	2.24	-40.7 (-45.3 , -36.2)	**<0.001**	6.8 (0.8 , 12.9)	**0.027**
LCI	55	11.5	0.50	53	9.0	0.50	48	10.0	0.53	-2 (-3.1 , -0.9)	**0.005**	0.9 (-0.5 , 2.4)	0.200
pp FEV_1	78	82.7	1.81	63	90.4	1.87	58	90.7	1.96	7.8 (5.4 , 10.1)	**<0.001**	0.3 (-2.6 , 3.3)	0.832
pp FVC	78	92.7	1.45	63	97.1	1.53	58	98.0	1.61	4.6 (2.3 , 6.9)	**<0.001**	0.9 (-2 , 3.8)	0.533
pp FEF 25-75	61	69.1	3.82	54	86.6	3.87	49	83.9	4.08	15.4 (10.1 , 20.7)	**<0.001**	-2.7 (-9.1 , 3.6)	0.399
Weight z score	78	0.05	0.094	65	0.23	0.096	59	0.24	0.098	0.2 (0.11 , 0.29)	**<0.001**	0 (-0.1 , 0.11)	0.968
BMI z score	78	0.07	0.096	65	0.21	0.099	59	0.21	0.103	0.19 (0.08 , 0.3)	**<0.001**	0 (-0.13 , 0.13)	0.983
CFQR-RD	76	78.3	1.74	65	89.6	1.88	58	88.2	1.99	11.4 (7.4 , 15.5)	**<0.001**	-1.4 (-6.8 , 3.9)	0.599
F508del/Minimum function													
	Baseline (N=39)			12 months (N=32)			24 months (N=24)			Baseline vs all FU		12 mths vs 24 mths	
Variable	N	Mean	Std Error	N	Mean	Std Error	N	Mean	Std Error	Δ (95% CI)	p-value	Δ (95% CI)	p-value
Sweat Chloride	38	96.7	2.74	30	55.7	3.09	22	61.4	3.61	-39.7 (-46.2 , -33.1)	**<0.001**	5.6 (-3.7 , 15)	0.237
LCI	29	12.7	0.68	25	10.4	0.73	22	11.2	0.78	-2.2 (-3.8 , -0.7)	**0.005**	0.8 (-1.3 , 2.9)	0.462
pp FEV_1	39	83.4	2.55	30	94.6	2.65	22	93.0	2.96	10.2 (6.8 , 13.6)	**<0.001**	-1.5 (-6.2 , 3.1)	0.515
pp FVC	39	91.4	2.06	30	102.0	2.17	22	98.7	2.49	8.9 (5.6 , 12.1)	**<0.001**	-3.2 (-7.7 , 1.3)	0.162
pp FEF 25-75	21	77.8	6.25	22	84.0	6.04	17	83.4	6.61	7 (-1.7 , 15.7)	0.115	-0.6 (-11.3 , 10)	0.909
Weight z score	39	0.03	0.133	32	0.28	0.135	23	0.20	0.144	0.2 (0.08 , 0.32)	**0.0015**	-0.09 (-0.25 , 0.08)	0.310
BMI z score	39	0.07	0.136	32	0.30	0.139	23	0.18	0.152	0.16 (0.01 , 0.32)	**0.034**	-0.12 (-0.32 , 0.09)	0.262
CFQR-RD	39	71.8	2.43	30	86.9	2.77	23	86.7	3.16	16.1 (10.4 , 21.9)	**<0.001**	-0.1 (-8.4 , 8.1)	0.974

Table 1: Results of main study outcome measures at baseline (pre-treatment), 12 months and 24 months on ETI therapy for participants with CF aged 12 years and older. LCI – lung clearance index, ppFEV1 – percent predicted forced expiratory volume in 1 second, FVC – forced vital capacity, FEF25-75 – forced expiratory flow between 25% and 75% of expired volume, BMI – body mass index, CFQ-R RD – cystic fibrosis questionnaire revised, respiratory domain score. Least-squares means and standard errors from the generalized linear mixed models are presented for each outcome. Baseline is compared with all follow-up using linear contrasts and results are presented as the difference (Δ) with 95% confidence interval and p-value.

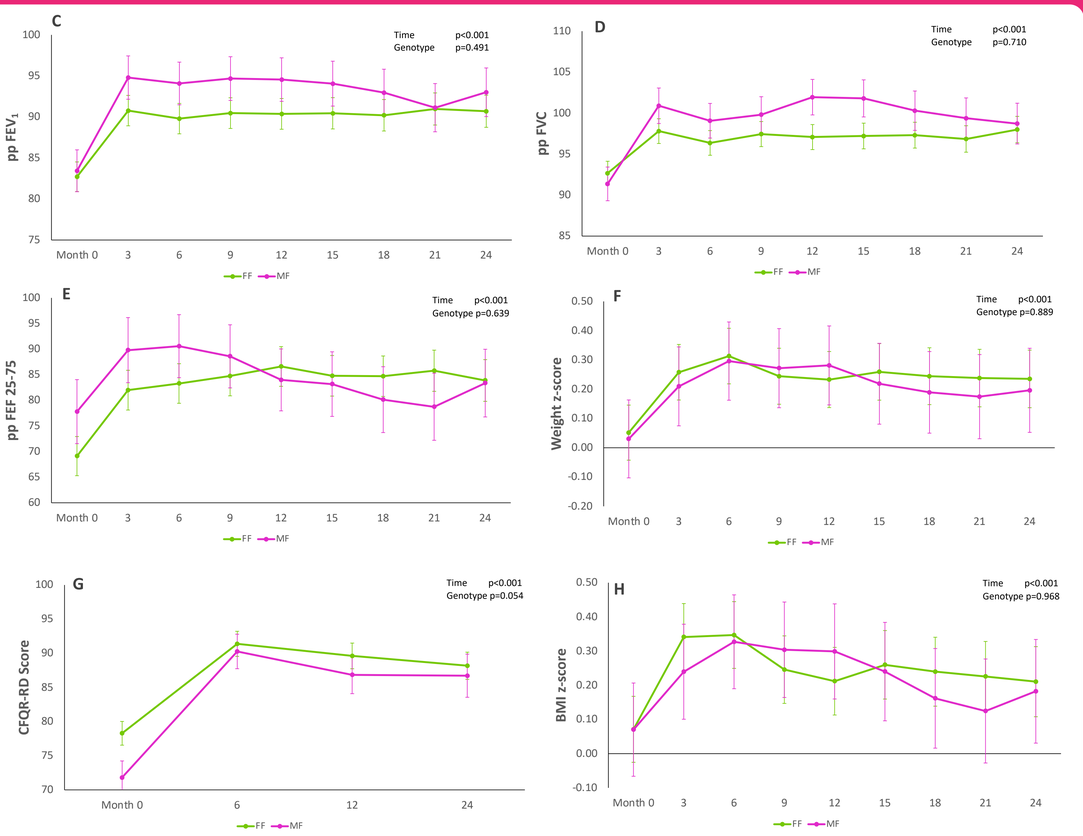


Figure 1: Figures representing main study outcome measures at baseline (pre-treatment), 3,6, 9 and 12 months on ETI therapy for participants with CF aged 12 years and older. LCI – lung clearance index, ppFEV1 – percent predicted forced expiratory volume in 1 second, FVC – forced vital capacity, FEF25-75 – forced expiratory flow between 25% and 75% of expired volume, BMI – body mass index, CFQ-R RD – cystic fibrosis questionnaire revised, respiratory domain score. Means with standard error bars are presented for each study visit. P-values are displayed for the tests of fixed effects from the generalized linear mixed models, for the Time*Genotype effect where significant, and for the main effects of Time and Genotype where there was no significant interaction. FF = F508del/F508del, MF = F508del/Min function.

Other Information

Background

The CFTR modulator combination Elexacaftor/Tezacaftor/Ivacaftor (ETI) is associated with significant improvements in sweat chloride, nutrition and pulmonary function in people with CF (PwCF). RECOVER is a multicenter post-approval study that has previously demonstrated significant improvements over one year in sweat chloride, ppFEV$_1$, lung clearance index (LCI), quality of life (CFQ-R RD) and BMI z-score in PwCF 12 years and older (1). We now present two years of outcome data from this study in people aged 12 years and older.

Aim

The aim of the study was to track the various study outcome measures in this cohort over a period of two years in the real-world.

Recruitment

Ninety-nine subjects remained in the study at 12 months and 83 at 24 months.

Methods

PwCF aged 12 years and older were recruited to the study prior to initiating ETI. The primary outcome measures was LCI, and measurement and analysis was supported by ECFS-CTN centralised training and over-reading at the Royal Brompton Hospital, London. Other outcome measures include sweat chloride, FEV1, nutritional indices and CFQR. Pulmonary function was measured clinically using GLI equations. Sweat chloride was collected with Macroduct® equipment and analysed using the Chlorocheck® system. Data management and statistical analysis was carried out by the CF registry of Ireland.

Results

Subjects heterozygous for F508del and a minimum function mutation had a higher sweat chloride at baseline, and none were on CFTR modulators. Otherwise, the groups did not differ significantly.

Results

	All (N=117)		Homozygous (N=78)		Heterozygous (N=39)		Comparison
	Median	(IQR)	Median	(IQR)	Median	(IQR)	p-value
Age (years)	15	(12 , 22)	15	(12 , 21)	15	(12 , 22)	0.951
BMI zscore	0.22	(-0.48 , 0.68)	0.15	(-0.48 , 0.74)	0.3	(-0.58 , 0.58)	0.897
FEV1pp	85.4	(74.4 , 93.1)	82.6	(75.1 , 92.3)	85.5	(73.2 , 97.6)	0.719
LCI	11.45	(8.9 , 14.1)	10.8	(8.7 , 12.9)	11.9	(9.7 , 14.1)	0.113
Sweat Chloride	85	(71 , 98)	76.8	(63.5 , 90)	96.5	(88 , 106)	<0.001
	N	(%)	N	(%)	N	(%)	p-value
Female	54	(46.2%)	34	(43.6%)	20	(51.3%)	0.431
Male	63	(53.8%)	44	(56.4%)	19	(48.7%)	
12-<18 years	76	(65.0%)	50	(64.1%)	26	(66.7%)	0.7841
≥ 18 years	41	(35.0%)	28	(35.9%)	13	(33.3%)	
Chronic PA	28	(23.9%)	16	(20.5%)	12	(30.8%)	0.523
Intermittent PA	18	(15.4%)	11	(14.1%)	7	(17.9%)	
Free PA	39	(33.3%)	28	(35.9%)	11	(28.2%)	
Never PA	32	(27.4%)	23	(29.5%)	9	(23.1%)	
ppFEV1<90%	76	(65.0%)	52	(66.7%)	24	(61.5%)	0.584
ppFEV1>90%	41	(35.0%)	26	(33.3%)	15	(38.5%)	
Dornase Alfa	88	(75.2%)	56	(71.8%)	32	(82.1%)	(24.8%)
Hypertonic Saline	90	(76.9%)	58	(74.4%)	38	(97.4%)	0.391
Pancreatic Enzymes	110	(94.0%)	75	(96.2%)	35	(89.7%)	(10.7%)
Insulin	11	(9.4%)	8	0.102564103	3	0.076923077	0.6993
Oral Antibiotics	55	(47.0%)	35	(44.9%)	20	(51.3%)	0.469
Inhaled Antibiotics	39	(33.3%)	24	0.307692308	15	0.384615385	0.3762
CFTR Modulators	77	(65.8%)	77	(98.7%)	0	(0.0%)	<0.001

Table 2: Baseline characteristics of the Study population. Data expressed as median (interquartile range) and frequency (percentage). The F508del/F508del and F508del/MF groups are compared at baseline using Wilcoxon signed rank test (medians) and Chi-square tests (frequencies).

Conclusions

Significant and sustained improvements in all outcome measures was seen in the group as a whole and this improvement was sustained for up to two years in the real-world. No significant differences were seen in outcomes between 12 and 24 months with the exception of sweat chloride in people in the FF group. The increase in sweat chloride seen here was not seen in trials and may relate to reduced treatment adherence in this group, the vast majority of whom had been on modulators for several years prior to starting ETI. The generalized linear mixed model demonstrated an effect of both time and genotype group for the outcomes of sweat chloride and LCI, suggesting a significantly lower sweat chloride and LCI in people with two F508del mutations.

References

1. McNally P et. al. Improvement in Lung Clearance Index and Chest CT Scores with Elexacaftor/Tezacaftor/Ivacaftor Treatment in People with Cystic Fibrosis Aged 12 Years and Older - The RECOVER Study. Am J Respir Crit Care Med. 2023 Sep 13.

RECOVER

Bottom Line:

Poster #485

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

Adherence to CF therapies is poor overall. Self-reporting overestimates adherence to many CF medications including Elexacaftor/Tezacaftor/Ivacaftor (ETI). Adherence to ETI reduced in the second year of treatment.

Poster Title

Measuring Adherence to Chronic Therapies over two years of Treatment with Elexacaftor/Tezacaftor/Ivacaftor in People with Cystic Fibrosis (CF) – the RECOVER Study

Sharon Sutton[1,2], John Hayden[2], Moninne Howlett[1,2], Jane Davies[4], Karen Lester[2], Basil Elnazir[1,7], Michael Williamson[1], Edward McKone[5], Des Cox[1], Barry Linnane[6], Paul O'Regan[8], Laura Kirwan[8], Alexandra Quittner[3], Paul McNally[1,2]

[1]Children's Health Ireland, Dublin, Ireland. [2]RCSI University, Dublin, Ireland. [3]Joe DiMaggio Children's Hospital, Hollywood, FL, USA. [4]NHLI, Imperial College London & Royal Brompton Hospital, UK. [5]St Vincent's University Hospital, Dublin, Ireland. [6]University of Limerick School of Medicine, Limerick, Ireland
[7]Trinity College Dublin, Ireland. [8]Cystic Fibrosis Registry of Ireland

Acknowledgements

We want to thank all of our study participants and parents for their time, dedication and enthusiasm, the whole RECOVER study team, collaborators and staff at our clinical sites. Funding for RECOVER is from the Cystic Fibrosis Foundation with support from CF Ireland and the CF Trust. Supported by ECFS-CTN.

Summary of Key Results

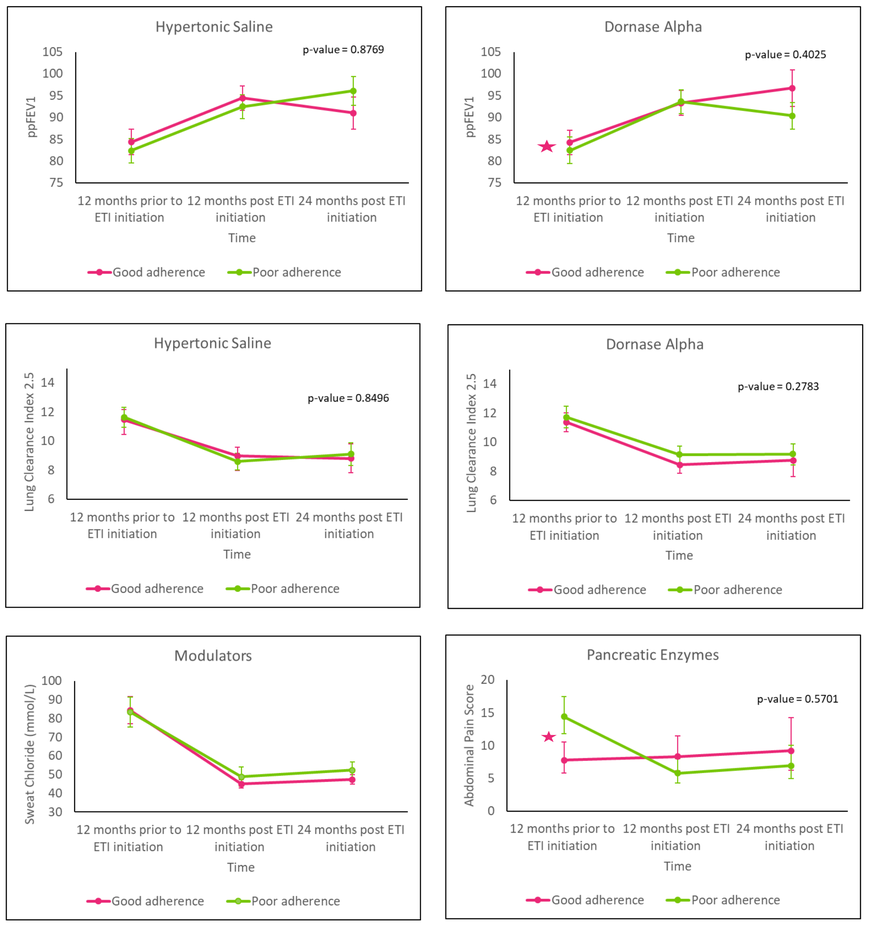


Figure 1: Modeling of adherence and outcome measures.
This model assessed MPR data (good adherence ≥80%; poor adherence <80%) and outcome measures lung clearance index, FEV1, sweat chloride and pain score from Abdominal Symptom Questionnaire at three time-points. Across the data there is no overall significant difference between good adherence and poor adherence for outcomes measures. In the 12 months prior to ETI initiation participants with poor adherence to pancreatic enzymes reported a higher pain score (p=0.0463) similarly those with poor adherence to Dornase alpha have a lower FEV1 (p=0.0494). Significant data points are highlighted with a star (★). Further analysis is underway using adherence measures as continuous variables.

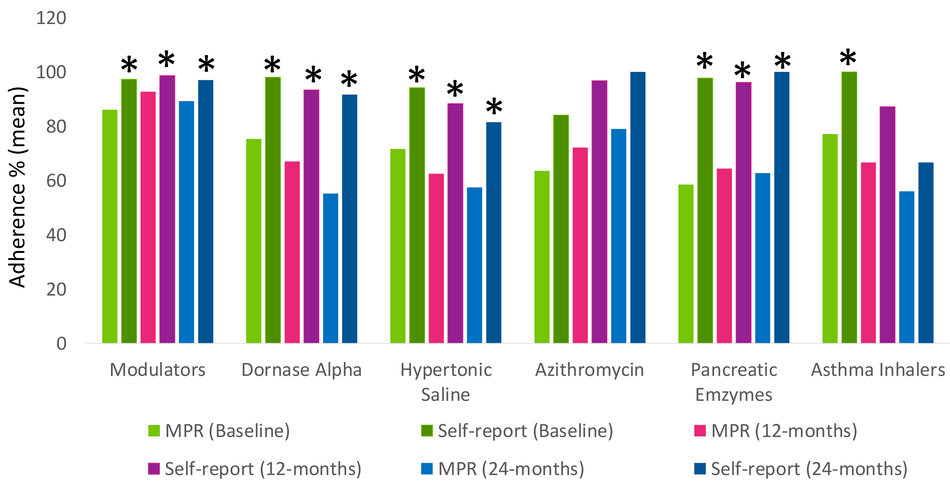


Figure 2: comparison between self–report (TAQ) and MPR
The graph compares adherence as reported in self-reported questionnaires to medication possession ratios. Significant differences between self-report and MPR are highlighted with an asterix (*).

Table 1: Medication Possession Ratio (MPR) - paired comparisons in year prior to ETI and first two years on ETI. Data in this table refers only to paired comparisons where data was available at each time point for each participant. In this paired analysis, adherence to both mucolytics hypertonic saline and dornase alpha worsened over time on ETI. Wilcoxon rank test was used, with adjusted p values due to multiple comparisons.

Medication	No. pairs	Adherence (%) baseline	Adherence (%) 12-month	Adherence (%) 24-month	p-value baseline v 12 months	p-value baseline v 24 months	p-value 12 v 24 months
Modulators	42	90.6	98.5	95.3	<0.005	>0.99	0.115
Dornase Alpha	30	83.8	77.4	57.6	>0.99	0.001	<0.005
Hypertonic saline	31	79.2	67.1	55.5	0.5	<0.05	>0.99
Azithromycin	14	63.8	71.8	73.5	>0.99	>0.99	>0.99
Pancreatic Enzymes	40	56.3	64.2	62.7	>0.99	>0.99	>0.99
Asthma inhalers	11	84.1	62.2	56.9	0.312	>0.99	>0.99

Aim

To measure adherence to CF therapies over the first two years of ETI treatment in people with CF.

Background

RECOVER is a multi-center post-approval study of clinical outcomes in PwCF prescribed ETI across Ireland and the UK. We have previously reported a decline in adherence to chronic CF treatments in people over 12 years after one year of ETI therapy. We sought to better understand adherence to therapies over two years on ETI, including measures of adherence and the impacts of adherence on clinical outcomes.

Methods

RECOVER is a multi-center non-interventional study of clinical outcomes in PwCF prescribed ETI across Ireland and the UK. Adherence in two cohorts based on ETI licensing (12+: patients ≥12 years; 6+: ≥6-<12 years) was measured over 2 years using 3 methods: 1. Treatment Adherence Questionnaire (TAQ) and Adherence Barrier Questionnaires (ABQ) – both self-reported; 2. Medication Possession Ratio (MPR) calculated from pharmacy refill data; and 3. Medication Electronic Monitoring System (MEMS®). Self-report tools and pharmacy refill data were collected for all participants. MEMS® is a direct measure used for a subset of participants in both cohorts (baseline to 12 months only). As reported previously MEMS® study recruitment and retention was challenging with only 22% (n=7) remaining at the 12 months.

Results

Data was available for 75 participants at 24 month. Analysis compared adherence at baseline to 12 months, and 12 months to 24 months, the following results were obtained for **MPR**: Dornase alpha [(83.2% to 77.4%, p=0.0012) and (77.4% to 57.67%, p=0.023)], hypertonic saline [(79.22% to 67.13%, p=0.04 and (67.13% to 55.48%%, p=>0.99)] and azithromycin [(63.9% to 71.82%, p=>0.99) and (71.8% to 73.5%, p=0.77)]. For **Self reported adherence** the following changes were noted: airway clearance [(83.5% to 75.5%, p=0.33) and (75.5% to 70.5%, p=0.10)], dornase alpha [(90.3% to 86.6%, p=0.3428) and (86.6% to 82.3%, p=0.833)], hypertonic saline [(90.1% to 84.5%, p=0.1017) and (84.5% to 72.6%, p=0.1176)] and azithromycin [(87.5% to 94.6%, p=0.2785) and (94.6% to 100%, p=>0.99)].

In cross sectional analysis of all available data, adherence to dual CFTR modulators in the year prior to baseline was calculated by MPR to be 84.5%. **Adherence to ETI at 12 months by MPR was 92.6% (p=0.0046). By 24 months adherence to ETI had reduced to 81.2% (p=0.007).** At the same time points self-reported data showed marginal changes in reported adherence: baseline (dual CFTR modulators) to 12 months of ETI (95.6% to 96.77%, p=0.57) and 12 to 24 months ETI (96.77% to 95.44%, p=0.5892). Modeling to establish whether adherence relates to outcomes is ongoing. Binary analysis (good v. poor adherence) has failed to demonstrate meaningful differences in outcomes examined to date. The data set was divided into age groups, and no statistically significant differences in adherence was observed between the adult and pediatric cohorts.

Conclusions

In this study, self-reported data showed overestimated adherence rates to most treatments, including ETI in comparison to MPR results. MPR data confirmed a **significant reduction in adherence to ETI in the second year of treatment** in the cohort overall . Adherence to routine CF therapies is poor overall and initiation of ETI may contribute to further reductions for some concomitant therapies.

Ongoing data collection in children aged 6-11 is in progress as is further analysis of the already collected data. We have established focus groups and workshops with people with CF and their families to understand attitudes to adherence and determine if new technical solutions for direct measurement are feasible in the home.

Bottom Line:

Poster #140

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

Elexacaftor/Tezacaftor/Ivacaftor improves sino-nasal MRI appearance but not rhinosinusitis symptoms in children with Cystic Fibrosis aged 6- 11 years.

Poster Title

Rhinosinusitis outcomes in children with CF after six months of Elexacaftor/Tezacaftor/Ivacaftor – Results from the RECOVER study

Stone R.G.[1,2], Lester, K.[1,2], Cox, D.[2,3], Williamson, M.[2], Elnazir, B.[2,4], Linnane, B.[5], Twomey E [2], Persaud T[2], Rea D[2], Cunney R[1,2], Davies, J. C.[6,7] McNally, P. [1,2]
On behalf of the RECOVER study Group

[1]RCSI University of Medicine and Health Sciences, Dublin, Ireland. [2]Children's Health Ireland, Dublin, Ireland. [3]University College Dublin, Dublin, Ireland. [4]Trinity College Dublin, Dublin, Ireland. [5]University of Limerick School of Medicine, Limerick, Ireland. [6]St.Vincent's University Hospital, Dublin, Ireland. [7]NHLI Imperial College London, London, UK.

Acknowledgements

We want to thank all of our study participants and parents for their time, dedication and enthusiasm, the whole RECOVER study team, collaborators and staff at our clinical sites. Funding for RECOVER is from the Cystic Fibrosis Foundation with support from CF Ireland and the CF Trust. Supported by ECFS-CTN.

Summary of Key Results

Age at enrolment (mean, range)	8.54 (5-11)
Sex (%,male) (n=37)	43%
Number of Participants	
Symptom scores	37
Nasal Swabs	26
Sinus MRI	16
CFTR Genotype	
F508del/F508del	78.4%
F508del/other	21.6%

Table 1: Demographics of study participants.

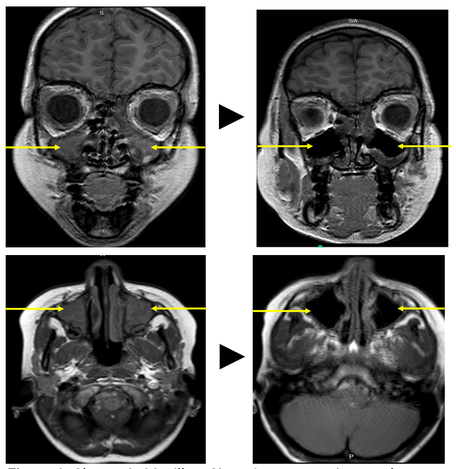


Figure 1. Change in Maxillary Sinus Appearance in a study participant aged 11 years after 6 months of ETI treatment

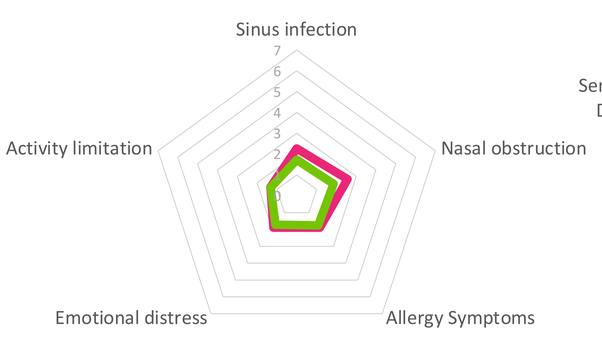


Figure 2. Change in sinonasal-5 questionnaire sub-domain scores. Scores prior to initiation of ETI are presented in pink. Scores following 6 months of ETI are presented in green.

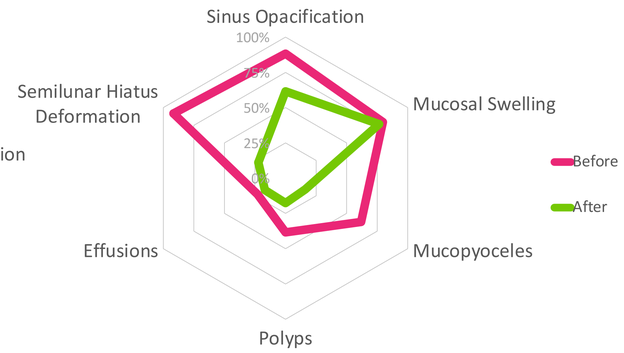


Figure 3. Change in % prevalence of MRI abnormalities. Scores prior to initiation of ETI are presented in pink. Scores following 6 months of ETI are presented in green.

	Baseline (Mean, SD)	Post-treatment (Mean, SD)	Change (Mean, SD)	p-value
Sinonasal-5 Score	1.99 (1.14)	1.68 (0.97)	-0.34 (1.07)	0.122
Rhinosinusitis related quality of life	8.65 (1.44)	9.10 (1.37)	+0.52 (1.27)	0.052
MRI Chronic Rhinosinusitis Score	33.5 (8.2)	18 (4.6)	-15.3 (6.7)	<0.001*

Table 2. Change in Sinonasal-5 Symptom Scores, Rhinosinusitis related quality of life and MRI Chronic Rhinosinusitis Scores. Means and standard deviations are presented for each outcome. Change with baseline was calculated using the Wilcoxon signed-rank test for each outcome.

	Baseline (n=26)	6 months (n=22)
Any Growth	96.2%	100%
Specific Organisms		
Commensals	69.2%	77.3%
Staphylococcus Aureus	50%	36.4%
Haemophilus Influenzae	3.8%	9.1%
Moraxella Catarrhalis	7.7%	4.6%
Corynebacterium Pseudodiphtheriticum	3.9%	4.6%
Streptococcus Pneumoniae	0%	4.6%

Table 3. Change in Nasal Swab Culture. Data is presented as % prevalence at baseline versus follow-up assessment.

MRI Interscorer Variability						
	MRI CRS Scoring			Presence vs Absence of MRI CRS Components		
Fleiss-Kappa	0.385			0.514		
% Agreement	44.7%			63.8%		
MRI Intrascorer Variability						
	Rater 1	Rater 2	Rater 3	Rater 1	Rater 2	Rater 3
Cohen's Kappa	0.988	0.753	0.722	0.993	0.837	0.785
% Agreement	99.5%	83.6%	82.3%	99.7%	91.9%	89.3%

Table 4. Interscorer and Intrascorer variability measurements for MRI Chronic Rhinosinusitis Scoring. Interrater variability was calculated using Fleiss-Kappa and % agreement statistics. Each rater re-scored 10 Sinus MRI scans (5 pre ETI and 5 post ETI) to determine intra-rater variability, which was calculated using Cohen's Kappa and % agreement statistics.

Other Information

Aim

To establish the impact of Elexacaftor/Tezacaftor/Ivacaftor (ETI) on rhinosinusitis symptom burden, imaging appearances and infection.

Recruitment

RECOVER is a multi-centre post approval study examining the impact of ETI taking place in 7 clinical sites in Ireland and the UK over 2 years. Data was included from participants attending a paediatric CF centre within Children's Health Ireland who were enrolled in the second phase of RECOVER – participants aged 6-11 years homozygous for F508del and heterozygous for F508del and a minimum function mutation.

Background

Rhinosinusitis is a common co-morbidity experienced by people with CF which decreases quality of life. ETI has been shown to substantially improve rhinosinusitis symptom burden in adult populations, however its impact in paediatric populations is not well described. ETI therapy is associated with decreased detection of recognised CF airway pathogens in the lower airways however its impact on infection within the sinonasal cavity is little understood. The Sinonasal-5 (SN-5) questionnaire has been endorsed by the Cystic Fibrosis Foundation for routine clinical use in the assessment of sinus and nasal symptoms. The MRI Chronic Rhinosinusitis Scoring System (MRI CRS) has been validated for use in children with CF over 6 years of age. While endoscopically directed middle meatus swabs are the gold standard for evaluating sinus infection, the requirement for nasal endoscopy limits their utility as a research tool in young children.

Methods

SN-5 questionnaires (Range 0-7) were administered prior to starting ETI and after at least 6 months of treatment. Wilcoxon Signed Rank Test was used to evaluate change in symptom scores. Rhinosinusitis related quality of life was rated on a visual analogue scale (Range 0 -Worst to 10 – Best). Sinus MRIs were performed using a Philips Achieva 3T MRI system prior to and after at least 6 months of ETI using the following imaging protocol: T1 Ax, T1 Cor, T2 Ax, T2 Cor and T2 FLAIR. Imaging severity was graded by 3 blinded radiologists using the MRI CRS (Range 0 -56) designed by Sommerberg et al. Interscorer and intra-scorer variability was calculated using Fleiss Kappa and % agreement statistics. Average CRS scores were evaluated for improvement using Wilcoxon Signed Rank Test. Change in MRI CRS score component presence was evaluated using Mc Nemar's Test. Sinonasal infection was determined using nasal speculum guided swabs targeting the area of the middle meatus. Bacterial culture was undertaken using blood agar, chocolate agar, MacConkey agar, Burkholderia Cepacia selective agar, and Sabourad's agar. Change in nasal swab culture was evaluated using Mc Nemar's test. Bonferroni corrections were applied to all sub-group analyses

Other Results

Interval change in SN-5 scores failed to detect a minimal clinically important difference. There were no significant changes in SN-5 subdomain scores once Bonferroni corrections were applied ($p \geq 0.012$). Follow-up SN-5 questionnaires were collected 6.0 (SD 4.26) months following commencement of ETI. Follow-up Sinus MRIs were performed 6.69 (SD 3.77) months following commencement of ETI. No significant changes in nasal culture results were observed ($p \geq 0.39$). One participant had dental braces applied during the study period which prevented analysis of the ethmoid and maxillary sinuses during follow-up MRI.

Conclusion

An overall improvement in imaging severity was observed with no significant change seen in sinonasal symptom burden or infection. Interval change in Sinonasal-5 scores failed to exceed the minimal clinically important difference, however changes in rhinosinusitis-related quality of life approached but did not achieve a p value <0.05. It is likely that a floor effect contributed to a lack of measurable improvement in rhinosinusitis symptom burden. An overall improvement in MRI CRS imaging was observed. Sub-optimal interscorer variability in imaging severity assessment limits comparability to similar studies performed in older cohorts. Similar to previously published literature a reduction in mucopyocele burden accounted for the majority of MRI CRS score reduction observed. While no measurable improvement was observed on culture-based interrogation of the sinonasal microbiome, further work is currently underway using shotgun metagenomic sequencing on nasal swabs obtained from our study cohort.

RECOVER

Bottom Line:

Poster #144

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

Exhaled Nitric Oxide levels significantly increase with ETI therapy in PwCF aged ≥12 years homozygous for F508del. This effect is not seen in children aged 6-11 with the same genotype.

Poster Title

Changes in airway nitric oxide in people with CF taking Elexacaftor/Tezacaftor/ Ivacaftor – Results from the RECOVER study

McNally, P. [1,2], Lester, K.[1,2], Elnazir, B.[2], Williamson, M.[2], Cox, D.[2], Linnane, B.[3], Kirwan, L.[4], O'Regan[4] P, McKone, E. F.[5], Davies, J. C.[6,7] Grasemann, H.[8] On behalf of the RECOVER study Group

[1]RCSI University, Dublin, Ireland. [2]Children's Health Ireland, Dublin, Ireland. [3]University of Limerick School of Medicine, Limerick, Ireland. [4]Cystic Fibrosis Registry of Ireland. [5]St Vincent's University Hospital, Dublin, Ireland. [6]Royal Brompton & Harefield hospitals, part of Guys and St Thomas' Trust, London, UK. [7]NHLI Imperial College London, London, UK. [8]Hospital for Sick Children, Toronto, Canada.

Acknowledgements

We want to thank all of our study participants and parents for their time, dedication and enthusiasm, the whole RECOVER study team, collaborators and staff at our clinical sites. Funding for RECOVER is from the Cystic Fibrosis Foundation with support from CF Ireland and the CF Trust. Supported by ECFS-CTN.

Summary of Key Results

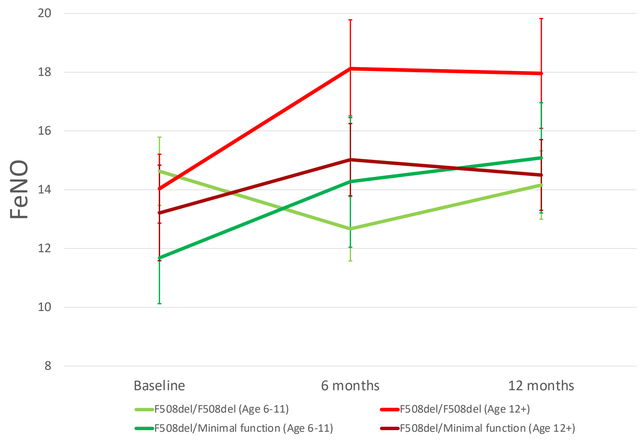


Figure 1: Graphical representation of changes in FeNO over 12 months Markers represent mean FeNo in the cohorts. Error bars reflect standard error of the mean.

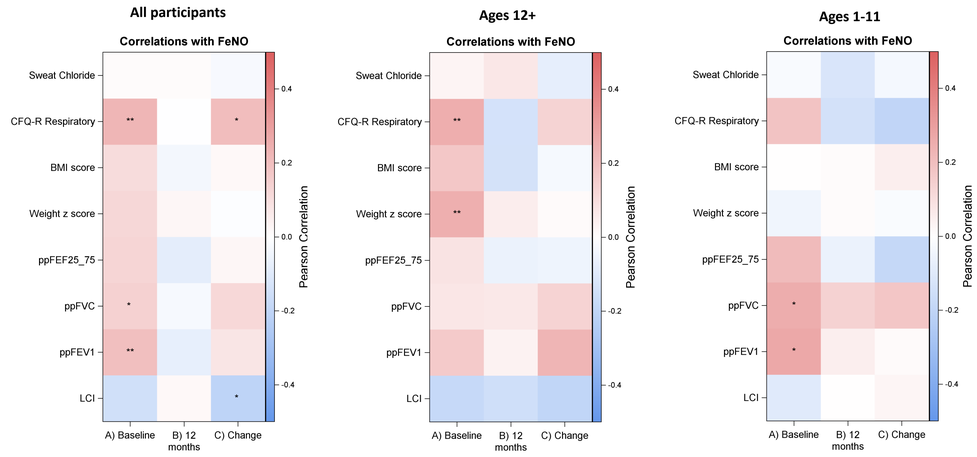


Figure 2: Correlation Heatmaps outlining relationships between FeNO and other outcome measures at baseline and 12 months (static correlations) and between changes in FeNO and changes in other outcome measures. Analysis is performed for the group as a whole and for the 12+ and 6-11 age groups. BMI – body mass index, ppFEV1 – percent predicted forced expiratory volume in 1 second, FVC – forced vital capacity, FEF25-75 – forced expiratory flow between 25 and 75% of expired volume, CFQ-R RD – CF quality of life, revised respiratory domain score, LCI – lung clearance index

FeNO (ppb) Analysis

	Baseline			6 months			12 months			Baseline vs all FU		Baseline vs 6 mths		6 mths vs 12 mths	
	N	Mean	Std Error	N	Mean	Std Error	N	Mean	Std Error	Δ (95% CI)	p-value	Δ (95% CI)	p-value	Δ (95% CI)	p-value
F508del/F508del (Age 6-11)	59	14.63	1.162	39	12.67	1.092	53	14.16	1.162	0.03 (-0.12 , 0.18)	0.701	0.08 (-0.09 , 0.24)	0.367	-0.09 (-0.23 , 0.04)	0.183
F508del/F508del (Age 12+)	77	14.04	1.172	69	18.12	1.663	65	17.96	1.868	-0.22 (-0.37 , -0.06)	**0.007**	-0.22 (-0.39 , -0.05)	**0.010**	0.01 (-0.11 , 0.14)	0.865
F508del/Minimal function (Age 6-11)	22	11.68	1.559	12	14.28	2.236	9	15.08	1.876	0.05 (-0.18 , 0.29)	0.673	0.09 (-0.17 , 0.35)	0.511	-0.07 (-0.28 , 0.13)	0.491
F508del/Minimal function (Age 12+)	38	13.21	1.625	35	15.02	1.229	31	14.50	1.203	-0.2 (-0.4 , 0.01)	0.060	-0.21 (-0.43 , 0.01)	0.061	0.03 (-0.12 , 0.18)	0.686

Table 1: FeNO Analysis among all participants. Description Least-squares means and standard errors from the generalized linear mixed models are presented for each outcome. Baseline is compared with all follow-up using linear contrasts and results are presented as the difference (Δ) with 95% confidence interval and p-value. ppb – parts per billion.

Other Information

Background

The fraction of exhaled nitric oxide (FeNO) is a well-established non-invasive airway biomarker. Low FeNO in people with CF (PwCF) is associated with lower lung function and infection with certain pathogens. FeNo can be measured quickly and repeatedly with a handheld analyzer. The CFTR modulator Ivacaftor has been shown to lead to a significant increase in FeNO in treated PwCF, suggesting that FeNO may have the potential to serve as biomarker of restored CFTR function in response to CFTR modulators. We sought to determine whether Elexacaftor/Tezacaftor/Ivacaftor (ETI) therapy was associated with changes in FeNO in treated pwCF.

We have previously reported on increased levels of exhaled nitric oxide over six months in PwCF homozygous for the F508del mutation.

Aims

The aim of the study was to establish whether use of ETI in these populations of PwCF is associated with changes in exhaled nitric oxide levels over a period of 12 months and to investigate relationships between FeNO and other outcome measures of interest.

Methods

RECOVER is a multi-center post-approval study of ETI in Ireland and the UK. FeNO was measured at baseline, six months and one year on ETI treatment using the NioX Vero® analyzer. Since ETI was approved in pwCF 12 years and older before it became available for children 6-11 years of age, the effects of ETI on FeNO were analysed separately in these two age groups. Airway secretions of participants have been bio-banked for later studies of inflammatory markers and of the L-arginine-NO metabolism.

Results

	Age 6-11				Age 12+					
	F/F (N=59)		F/MF (N=22)		F/F (N=77)		F/MF (N=38)		Age cohort	Genotype
	Median	(IQR)	Median	(IQR)	Median	(IQR)	Median	(IQR)	p-value	p-value
Age (years)	9	(7 , 10)	9	(8 , 10)	15	(12 , 21)	15.5	(13 , 22)		0.357
BMI zscore	0.27	(-0.34 , 0.66)	0.1	(-0.17 , 0.76)	0.15	(-0.4 , 0.69)	0.29	(-0.58 , 0.5)	0.546	0.841
Weight zscore	0.0	(-0.58 , 0.76)	0.2	(-0.31 , 0.65)	0.1	(-0.42 , 0.56)	0.0	(-0.29 , 0.26)	0.825	0.751
ppFEV1	93.9	(85.2 , 101.7)	95.5	(85.6 , 99.0)	85.6	(76.1 , 92.7)	85.5	(73.2 , 97.6)	<0.001	0.927
ppFVC	98.4	(88.6 , 105.7)	98.6	(89.3 , 104.9)	93.2	(86.8 , 100.6)	92.2	(81.5 , 101.0)	0.021	0.416
ppFEF 25-75	86.1	(74 , 96.3)	88	(79 , 110.2)	67.1	(45.7 , 91)	76	(55.6 , 99.4)	0.005	0.256
CFQ-R RD	91.67	(75 , 91.7)	91.67	(75 , 91.7)	83	(66.7 , 91.7)	75	(61.1 , 83.3)	0.002	0.167
LCI	6.9	(6.5 , 7.6)	7.5	(6.4 , 8.2)	10.7	(8.7 , 12.7)	11.9	(9.7 , 14.1)	<0.001	0.011
Sweat Chloride	76	(68 , 95)	104.5	(61 , 113)	76.65	(63.5 , 90)	96.5	(88 , 106)	0.924	<0.001
Sex	N	(%)	N	(%)	N	(%)	N	(%)		
Female	31	(52.5%)	8	(36.4%)	33	(42.9%)	20	(52.6%)	0.776	0.970
Male	28	(47.5%)	14	(63.6%)	44	(57.1%)	18	(47.4%)		

Table 2: Baseline characteristics. BMI – body mass index, ppFEV1 – percent predicted forced expiratory volume in 1 second, FVC – forced vital capacity, FEF25-75 – forced expiratory flow between 25 and 75% of expired volume, CFQ-R RD – CF quality of life, revised respiratory domain score, LCI – lung clearance index. Groups compared at baseline using Wilcoxon signed rank test (medians) and Chi-square tests (frequencies).

Results

FeNO was available for 131 participants in the F508del/F508del group (77 aged 12 and over and 59 aged 6-11) and 60 in the F508del/minimum function (MF) group (38 aged 12 and over and 22 aged 6-11). No participants in the F508del/MF group were taking CFTR modulators prior to starting ETI whereas all but one of the F508del/F508del participants were. In PwCF homozygous for F508del, compared to all follow up timepoints, mean FeNO increased from 14.04 (standard error 1.17) ppb at baseline to 18.12 (1.67) ppb at 6 months and 17.96 (1.87) ppb at 12 months (p=0.006).

Results

A similar effect was not seen in either the 12+ F508del/MF group or the 6-11 F508del/F508del group. Correlation heatmaps in figure 2 above do not demonstrate consistent relationships between FeNO and other outcome measures. In particular there is a notable difference in the overall pattern of correlations at baseline compared to 12 months. By 12 months, there were no significant correlations between FeNO and any other variable, in the group as a whole or in different age groups. In the group as a whole change in FeNO correlated weakly to changes in LCI and CFQR-RD. Analysis of FeNO metabolites in sputum and nasal lavage is ongoing

Conclusions

ETI therapy in pwCF homozygous for F508del and 12 years or older resulted in a significant and sustained increase in FeNO. No such change in FeNO was seen in children with CF 6-11 years of age. These data may suggest that the observed changes in FeNO were not directly related to correction of CFTR dysfunction. Further biomarker studies are needed to help explain the genotype-specific and age-dependent effects of ETI on airway NO metabolism.

RECOVER