6.05 **Significant real-world improvement in clinical, radiological and systemic inflammatory outcomes post CFTR modulation with elexacaftor/tezacaftor/ivacaftor in cystic fibrosis patients homozygous for the Phe508del mutation.**

Hisham Ibrahim[1,], Kevin Deasy[1,], Alexander T O'Mahony[,1], Mairead McCarthy[1], James Dorgan[1], Claire Fleming[1], Ciara Howlett[1], Yvonne McCarthy[1,], Sarah Twohig[1], Paul O'Regan[6], Laura Kirwan[6], Michael M Maher[1,], Owen J O'Connor[1], Barry J Plant[1]
1.University Hospital, Cork,6.Cystic Fibrosis Registry of Ireland

In clinical trial treatment with elexacaftor/tezacaftor/ivacaftor (ETI) in CF patients homozygous for Phe508del mutation was associated with significant improvement in FEV1, sweat chloride, weight and quality-of-life (CFQR-R).We assessed these outcomes in a real-world setting post ETI therapy in our clinic. In addition to clinical trial data, changes in ultra-low-dose CT imaging, peripheral-blood inflammatory-cytokines and patient-reported outcomes (PROMs) were measured.

The first 49 CF patients homozygous for Phe508del mutation attending our standard clinic commenced on ETI were assessed at baseline (time zero) and prospectively at three and 6 months. Table-1 summarizes the outcomes with significant improvements in FEV1, weight, BMI, and sweat chloride post-ETI treatment(*P<0.0001*). Validated patient-reported outcome measures also improved significantly for chronic rhinosinusitis/SNOTT*(P=0.0064),* respiratory quality-of-life CFQR-R(*P<0.0001*), and fatigue score*(P=0.0049).*

Ultra-low-dose CT imaging scores demonstrated reductions in peri-bronchial thickening, mucus plugging(*P<0.0001*), collapse/consolidation(*P=0.0425*), and improvements in total Bhalla score (*P<0.0001)*. Significant changes in the systemic inflammatory status of our cohort was seen with a reduction in interleukin (IL)-6 and IL-8(*P<0.0001)*, along with increasing IL-10(*P=0.0004*).Based on clinical trial parameters, ETI responders, in addition demonstrate significant improvements in CT imaging, circulating cytokines and PROMs which may be of further use to evaluate treatment response in an era of evolving CFTR modulation.

Table 1(6.5): Changes in Clinical parameters, patients-reported outcomes measures, radiological and systemic inflammatory parameters at baseline and 6 months post initiation of Elexacaftor/Tezacaftor/ Ivacaftor (ETI) therapy

	Baseline			6 months post ETI therapy			Delta (Δ)
Variable	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**	**p-value**
FEV1 %pred	49	65.5	18.6	43	75.5	19.9	*<0.0001*
FEVC %pred	48	83.9	15.8	43	92.1	15.0	*<0.0001*
Weight (Kg)	49	67.4	12.4	43	71.7	12.9	*<0.0001*
BMI	48	23.2	2.89	42	24.5	3.54	*0.000147*
CFQR-R	47	70.7	17	37	89	12.8	*<0.0001*
Sweat Cl (mmol/L)	47	79.7	15.7	41	40.4	16.3	*<0.0001*
Fatigue	48	41.5	9.21	36	44.9	8.73	*0.004925*
SNOTT	47	7.79	6.79	37	4.7	5.63	*0.006413*
IL8 (pg/ml)	49	8.03	6.65	40	4.04	2.60	*<0.0001*
IL6 (pg/ml)	49	1.48	1.17	40	0.814	0.421	*<0.0001*
IL10 (pg/ml)	49	0.910	1.48	29	4.68	16.1	*0.000451*
Total Bhala Score	22	16.1	4.06	22	13.8	4.11	*<0.0001*

Conflict of Interest: *None to declare*