The extrapulmonary effect of CFTR Modulator Therapy

XVII National Conference of the Italian Cystic Fibrosis Society, Napoli 20-23 October 2021

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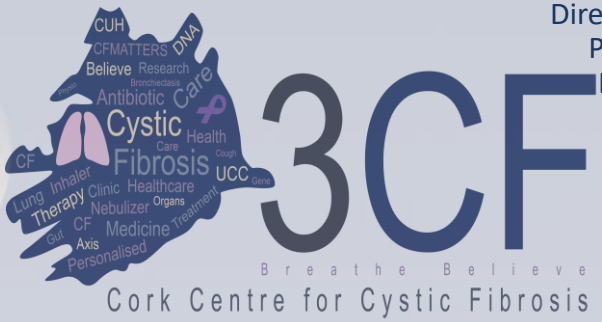
Director of Adult CF Centre, Cork University Hospital (CUH).
Professor, Dept. of Medicine, University College Cork.
Deputy Director, HRB-CRFC, University College Cork.
Executive Board Member, European CF Society.



CUH
Ospidéal Ollscoile Chorcaí
Cork University Hospital

ucc
Coláiste na hOllscoile Corcaigh, Éire
University College Cork, Ireland

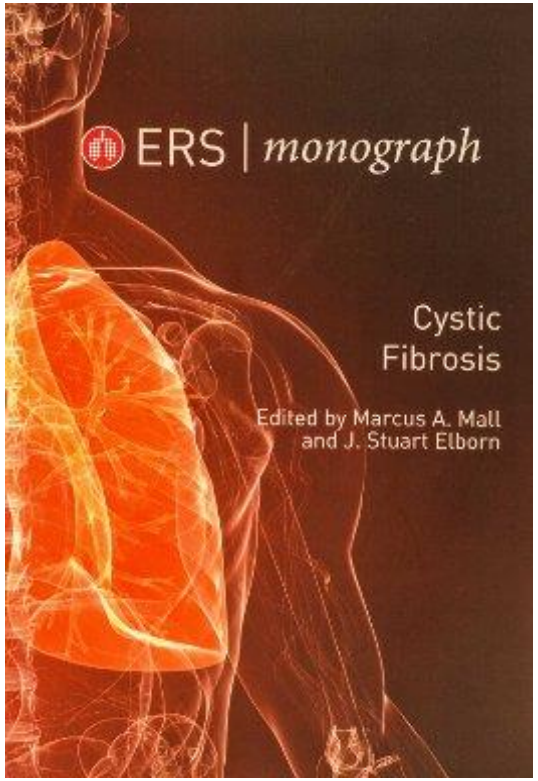
Disclosures

- I have received honoraria and speaker fees from Novartis, Gilead, Chiesi and Vertex Pharmaceuticals

Grazie Italia

- Invitation to attend this meeting
- Medical leadership and wisdom during the 1st Covid surge
- Winning UEFA EURO 2020

Cystic Fibrosis is a multisystem disease



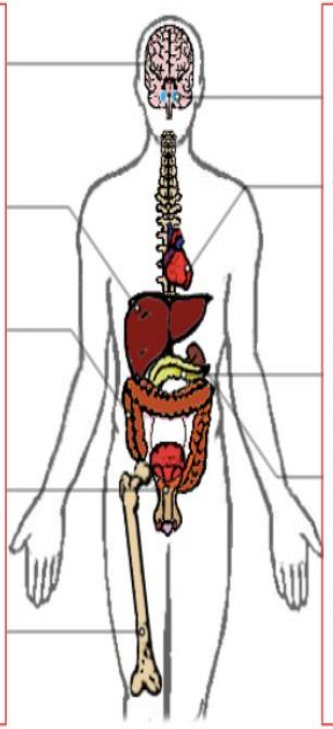
Psychosocial/psychiatric
Anxiety and depression is common

Hepatobiliary
CF liver disease gives rise to portal tract fibrosis in 5–10% of individuals

Gastro-intestinal
MI present at birth in 15% of individuals
DIOS occurs in 15% of adults
Constipation in up to 40%
GORD in 80% of children and adults

Genito-urinary
Infertility in 98% of males
Urinary incontinence in females increases with age

Bone and joint
Osteoporosis with increased risk of thoracic vertebral fractures
CF related arthropathy seen



Rhinosinus
Very common
Nasal polyps prevalence increases with age (45% in adolescents)

Vascular
Augmentation index is increased in CF adults
Possible increased risk of CAD

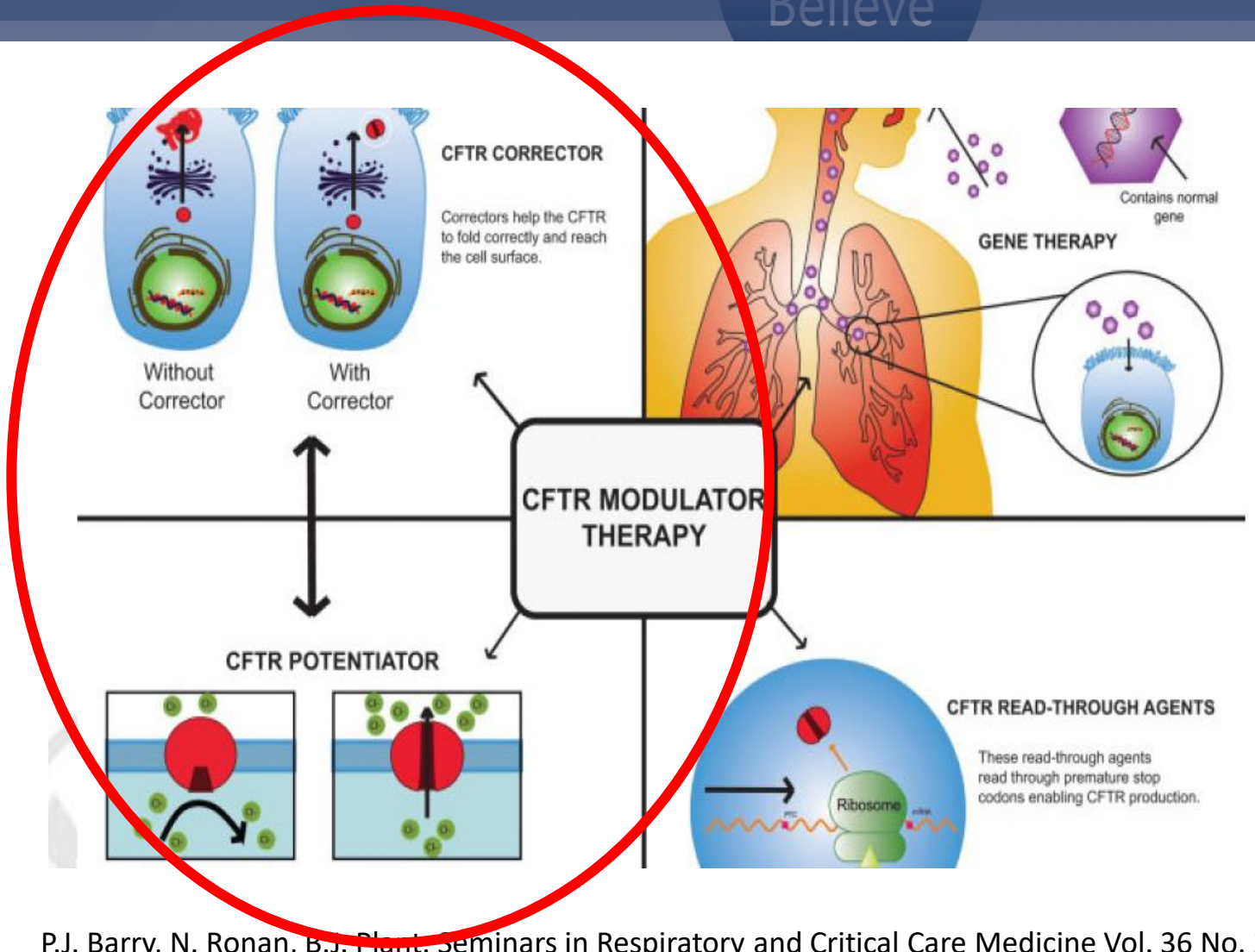
Pancreatic
80–85% of infants develop PI
Pancreatitis in 10–15% of PS CF individuals
Development of diabetes increases with age
Prevalence 40% in people over 40 years of age

Renal
Acute kidney injury common
Urolithiasis occurs in 3–6% of individuals
Chronic kidney disease increases with age, risks double with every 10 years of age

Cancer
Increase of GI cancers in CF individuals
SIR non-transplant 3.5
SIR transplant 17.3

Ch.15 “Extrapulmonary manifestations of Cystic Fibrosis” – Barry Plant & Michael Parkins (2014)

CFTR modulation over last 10 years



P.J. Barry, N. Ronan, B.J. Plant. Seminars in Respiratory and Critical Care Medicine Vol. 36 No. 2/2015

Important Considerations:

The extrapulmonary effects of CFTR modulator therapy

- All CFTR modulators are not the same
- Age of initiation variable (and dynamic)
- Duration of usage is variable
- Effect of exacerbation reduction on general phenotype cannot be overstated
- A good effect can still cause a bad outcome

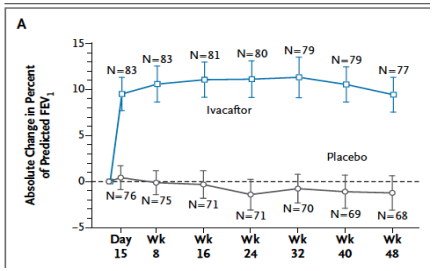
The CFTR modulator journey:

All CFTR modulators are not the same

2011-

Monotherapy

Ivacaftor (IVA)



Ramsey et al. NEJM 2002 / Wainright et al. NEJM 2015 / Midleton et al NEJM 2018

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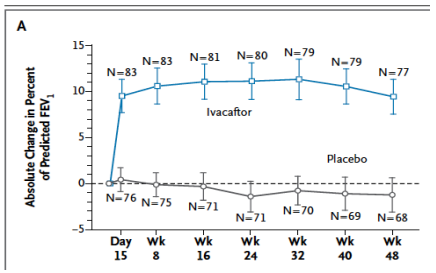
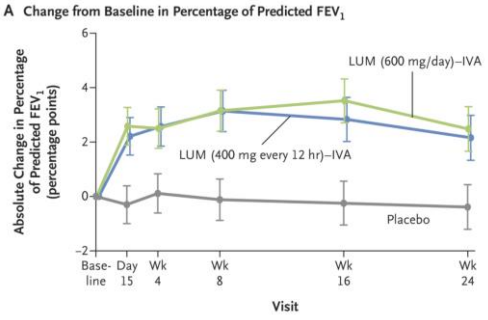


2015-17

Dual-therapy

Lumacaftor - Ivacaftor (LUM-IVA)
Tezacaftor - Ivacaftor (TEZ-IVA)



Ramsey et al. NEJM 2002 / Wainright et al. NEJM 2015 / Midleton et al NEJM 2018

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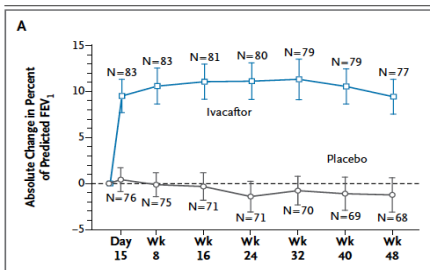

2015-17

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Lumacaftor - Ivacaftor (LUM-IVA)

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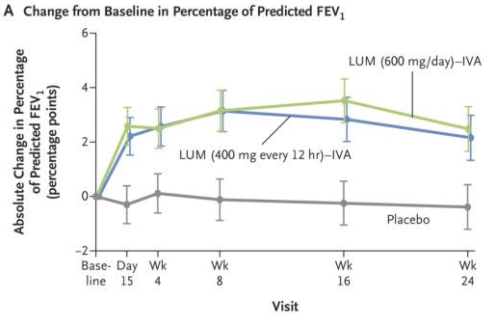
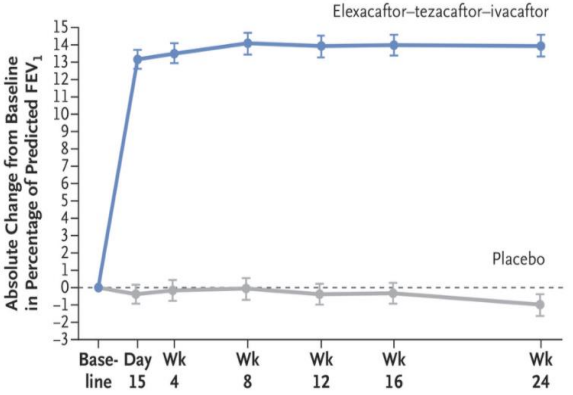


2018-

Triple-therapy

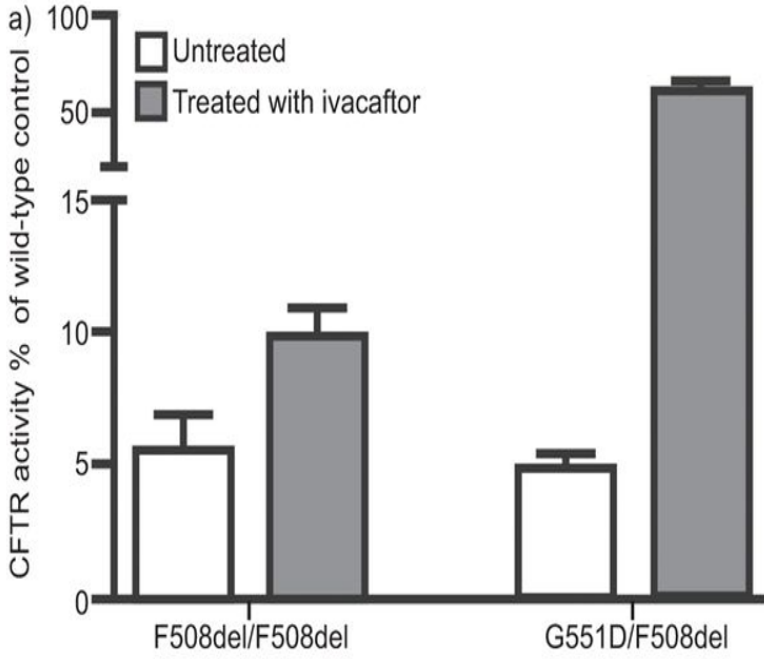
Elexacaftor-Tezacaftor-Ivacaftor (ETI)



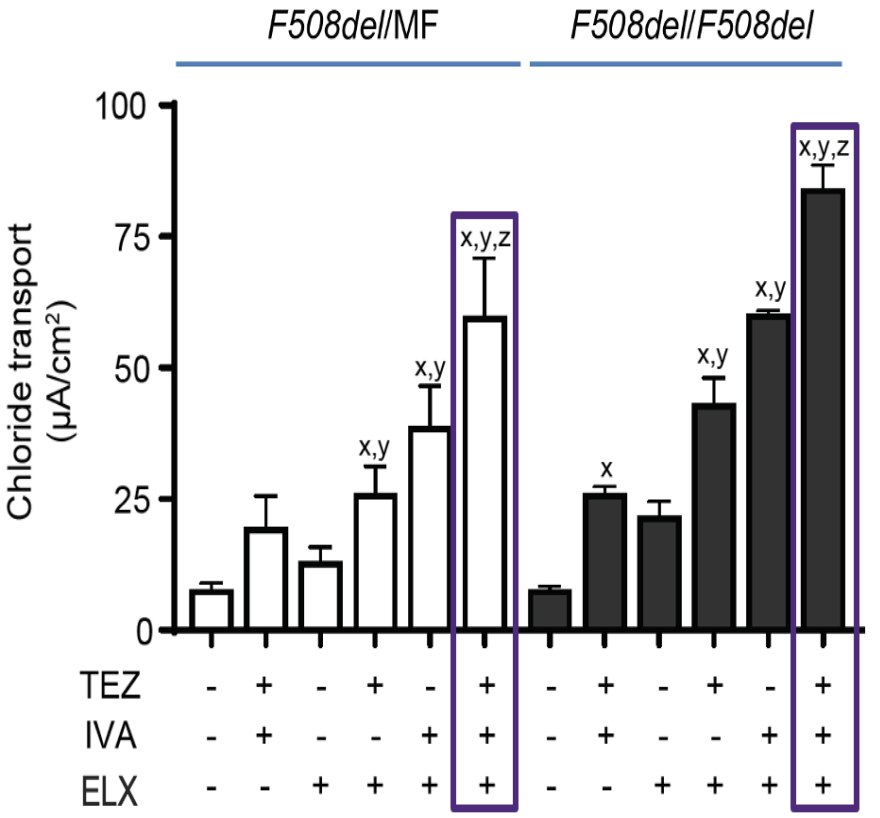
Ramsey et al. NEJM 2002 / Wainright et al. NEJM 2015 / Midleton et al NEJM 2018

The CFTR modulator journey:

All CFTR modulators are not the same



Derichs N. *Eur Respir Rev*. 2013;22(127):58–65.



$^{x}P<0.05$ vs vehicle. $^{y}P<0.05$ vs TEZ/IVA. $^{z}P<0.05$ vs ELX/IVA (paired t-test).

Keating D, et al. *N Engl J Med*. 2018;379:1612-20.

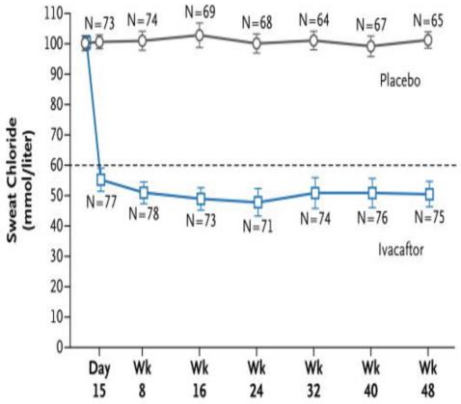
The CFTR modulator journey:

Phase 3 manuscripts and sweat test!!

Ramsey et al. NEJM 2002 / Wainright et al. NEJM 2015 / Midleton et al NEJM 2018

The CFTR modulator journey:

Phase 3 manuscripts and sweat test!!



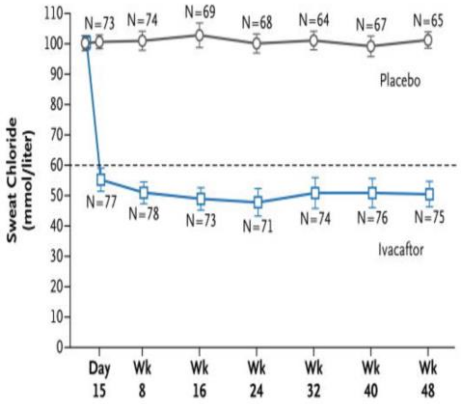
Monotherapy

Ivacaftor

Ramsey et al. NEJM 2002 / Wainright et al. NEJM 2015 / Midleton et al NEJM 2018

The CFTR modulator journey:

Phase 3 manuscripts and sweat test!!



Not reported !!

Dual-therapy

Ivacaftor/ Lumacaftor
Ivacaftor/ Tezacaftor

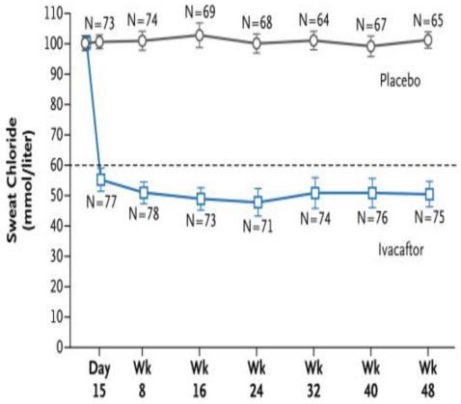
Monotherapy

Ivacaftor

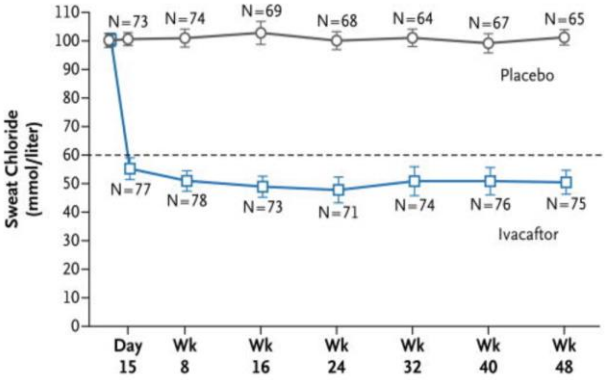
Ramsey et al. NEJM 2002 / Wainright et al. NEJM 2015 / Midleton et al NEJM 2018

The CFTR modulator journey:

Phase 3 manuscripts and sweat test!!



Not reported !!



Triple-therapy

Ivacaftor/Tezacaftor/
Effexacaftor

Dual-therapy

Ivacaftor/ Lumacaftor
Ivacaftor/ Tezacaftor

Monotherapy

Ivacaftor

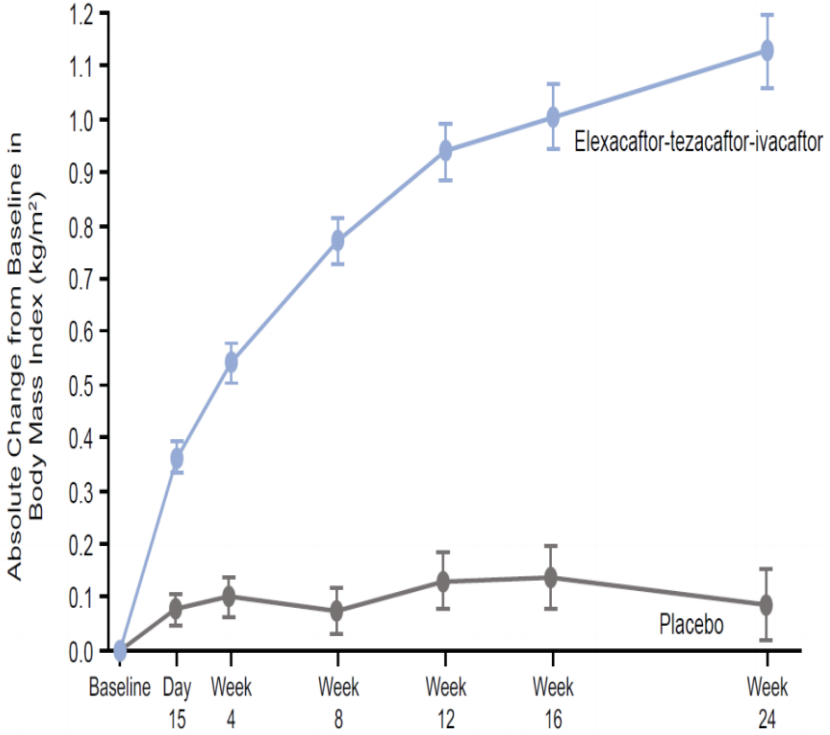
Ramsey et al. NEJM 2002 / Wainright et al. NEJM 2015 / Midleton et al NEJM 2018

Understanding the extrapulmonary effect of CFTR modulator therapy

Weight and Growth

Well recognized trial data

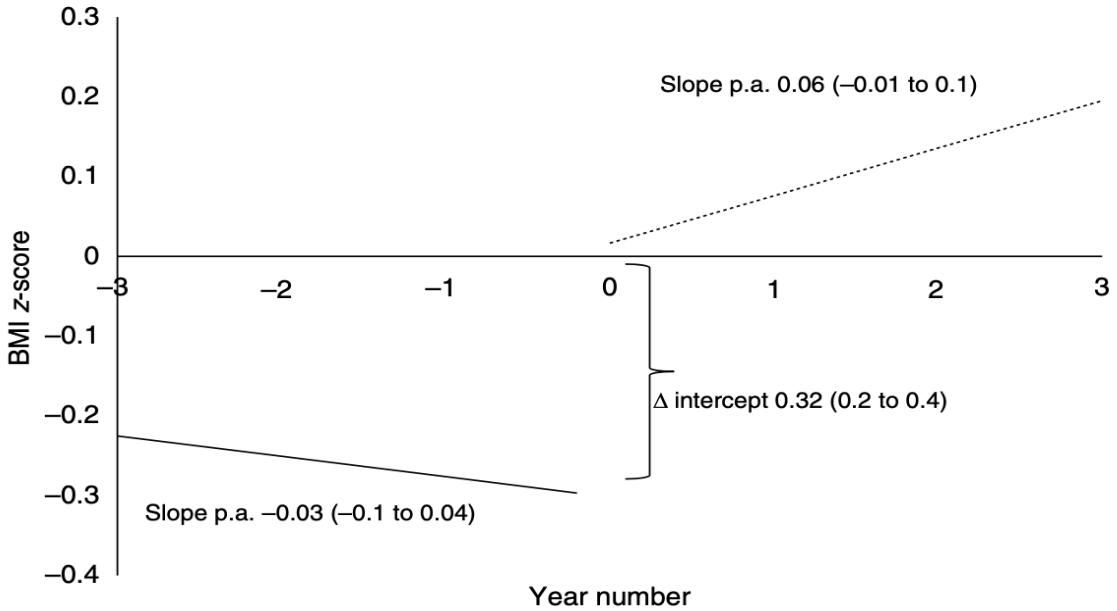
- Monotherapy (IVA)- in all age groups
- Dual-therapy (LUM-IVA)
  - modest 12 years and older
  - non significant 6-11 year old
- Dual Therapy (TEZ-IVA)
  - no significant difference
- Triple-therapy (ETI) – 12 years and older



Ramsey et al. NEJM 2002 / Wainright et al. NEJM 2015 / Ratjen et al. LRM 2017/Taylor-Cousar et al. NEJM 2017 / Midleton et al NEJM 2018

Weight and Growth

Irish registry data - 80 ivacaftor-treated patients with CF aged 6 to 56 years registered with the CF Registry of Ireland with at least 36 months of before and after commencement data.



Caveat: significant effect of FEV1% predicted on BMI z-score,

Kirwan, Fletcher, Harrington, et al.: Longitudinal Trends in Real-World Ivacaftor Outcomes. AnnalsATS Volume 16 Number 2|February 2019

Weight and Growth Mechanism

Multifactorial

- Reduced energy expenditure (less exacerbations)
- Pancreatic function

- Monotherapy (IVA) – improved IGF-1 signaling

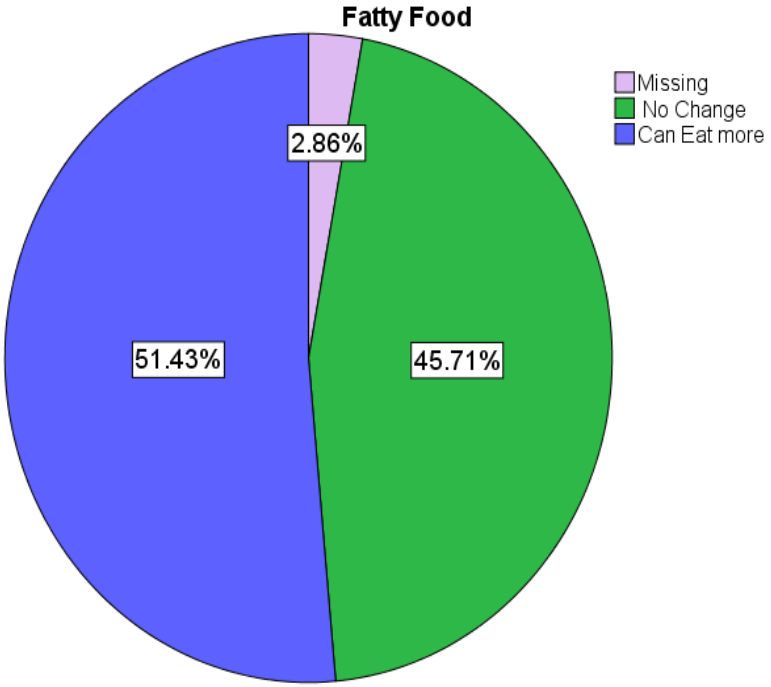
  Stanley MS. et al. *Paediatrics* 2017

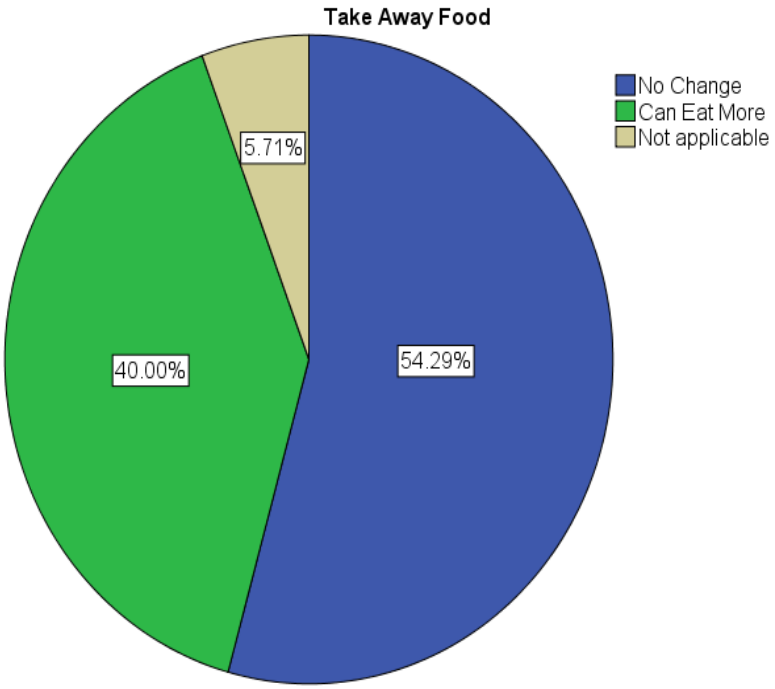
- Dualtherapy (LUM-IVA) – improved GH secretion

  Pascucci C et al. *J Endocrinol Invest* 2019

Our experiences with CFTR modulation and dietary habits

Cork data: Retrospective nutritional questionnaire in our cohort at 18 months post commencement of ivacaftor (n=46)



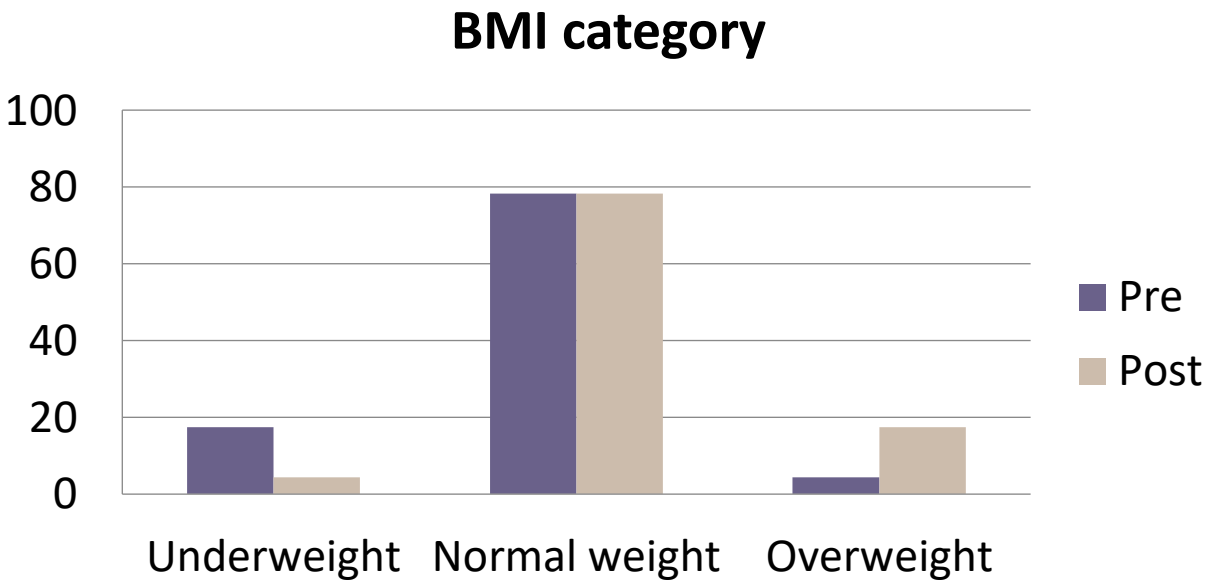


Dietary habits change!!

Howlett et al. NACFC 2015

Our experiences with CFTR modulation and BMI

Cork data: Prospective assessment (n=24) over first 12 months of ivacaftor



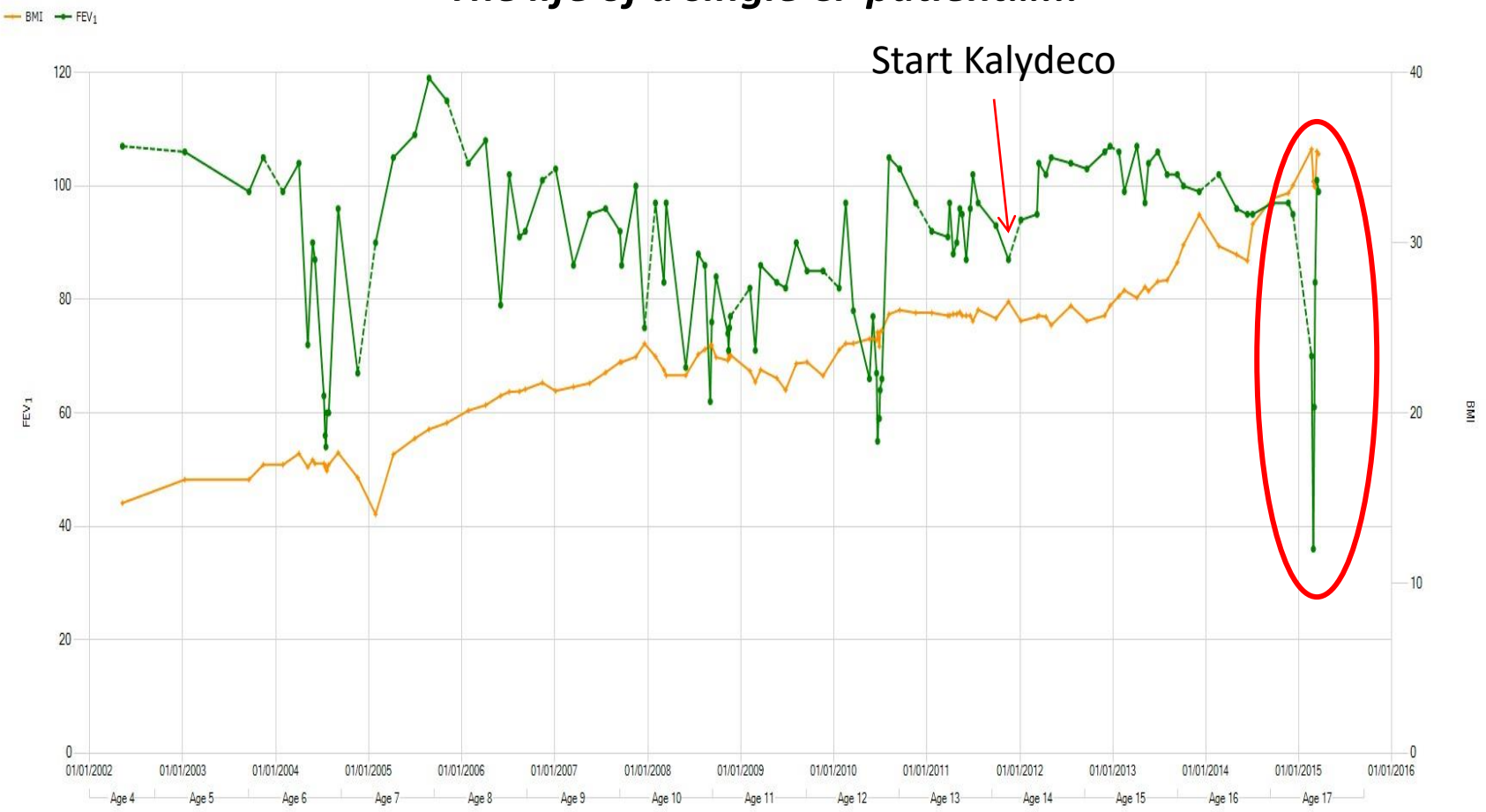
BMI goes up !!

Ronan et al. ECFS 2015

Case 1:

weight gain can have a negative effect

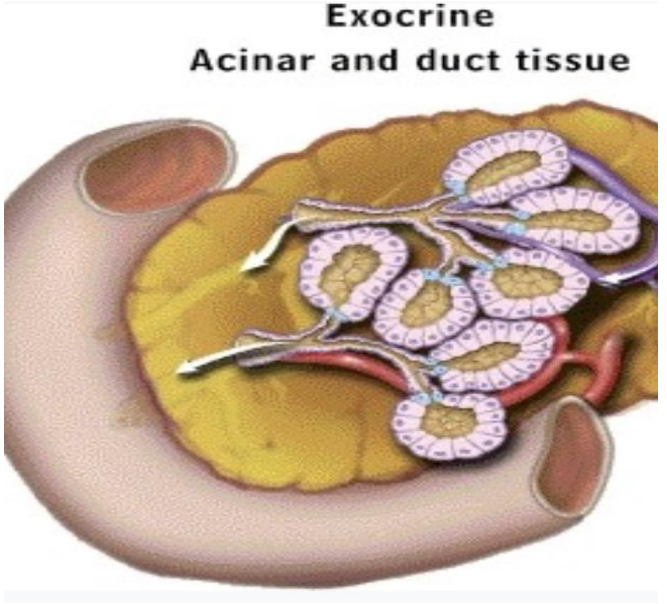
The life of a single CF patient……



Compliments: David Orenstein

Effect of CFTR modulator therapy on Pancreatic Exocrine Function

Belief : You need approx. 1-2% residual function



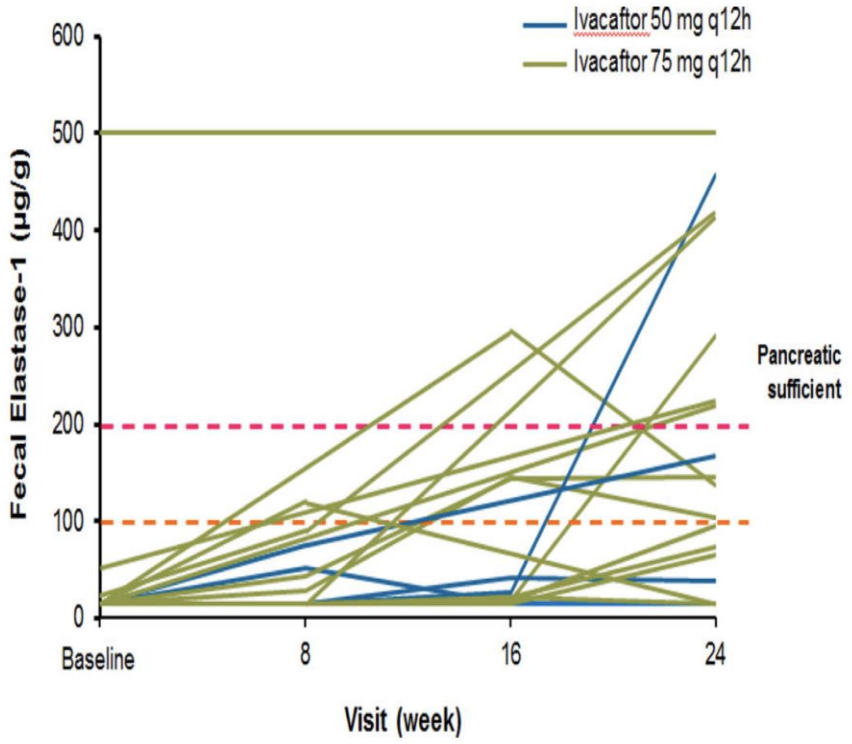
Effect of CFTR modulator therapy on Pancreatic Exocrine Function

Belief : You need approx. 1-2% residual function

KIWI: 2 to 5 years

Safety, pharmacokinetics, and pharmacodynamics of ivacaftor in patients aged 2-5 years with cystic fibrosis and a CFTR gating mutation (KIWI): an open-label, single-arm study.

Davies et al. Lancet Respir Med. 2016



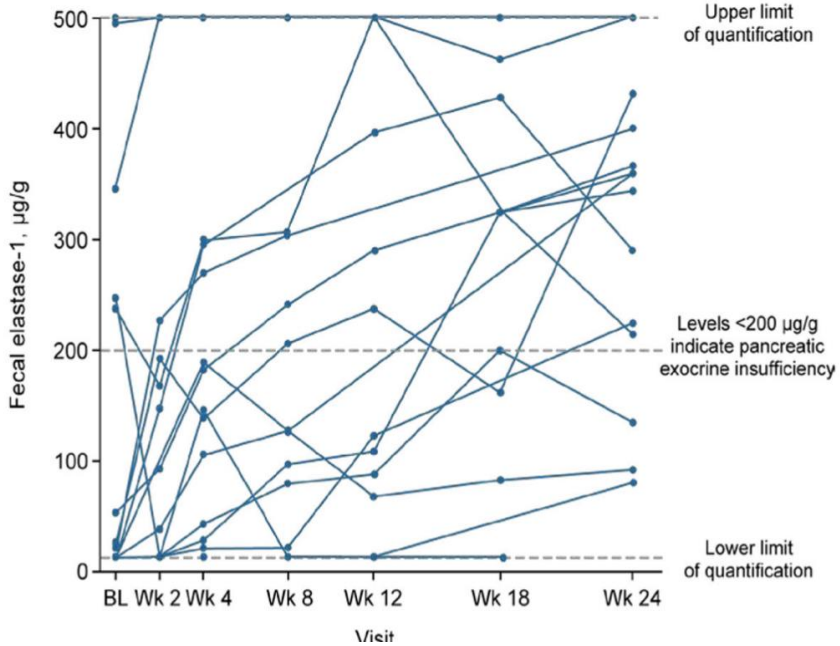
Effect of CFTR modulatory therapy on Pancreatic Exocrine Function

Belief : You need approx. 1-2% residual function

ARRIVAL: 12 to <24 months

Ivacaftor treatment of cystic fibrosis in children aged 12 to <24 months and with a CFTR gating mutation (ARRIVAL): a phase 3 single-arm study.

Rosenfeld et al. Lancet Respir Med. 2018



DUAL THERAPY (LUM/IVA). McNamara et al. Lancet Respir Med. 2019

3 of 48 with baseline FE-1 <100 improved to >200ug/g with reduction back to baseline after therapy

Older patients and exocrine effect?

Case 2: Partial restoration of exocrine pancreatic function in older child with CF

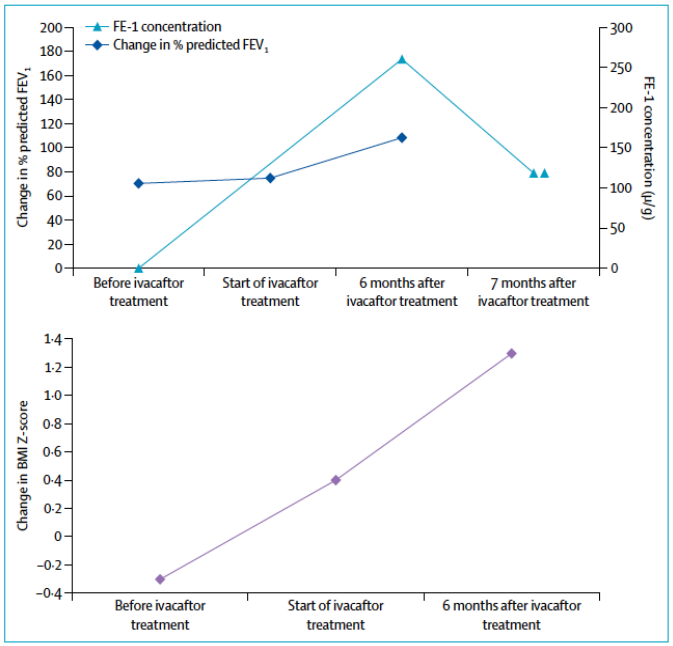


Figure: Changes in % predicted FEV_1, FE-1, and BMI Z-score after ivacaftor treatment

Howlett C, Ronan NJ, NiChroinin M, Mullane D, Plant BJ
Lancet Resp Med 2016

Case Series : Reduction of Recurrence Risk of Pancreatitis in Cystic Fibrosis With Ivacaftor:

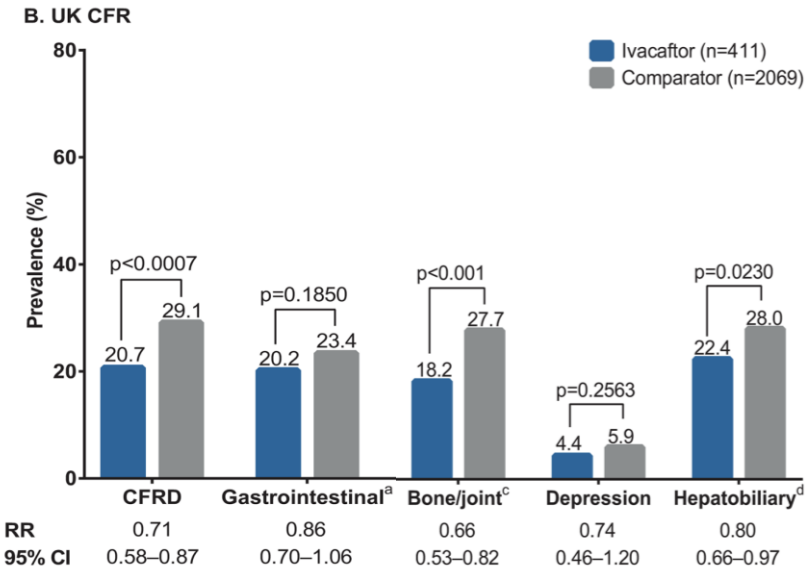
	Age, y	Fecal elastase, µg/g	Pancreatitis episodes in previous 12 mo
Patient 1	11.5	>500	5
Patient 2	13.6	232	3
Patient 3	28	Not reported	1
Patient 4	42	Not reported	2
Patient 5	43	59	2
Patient 6	60	>500	2

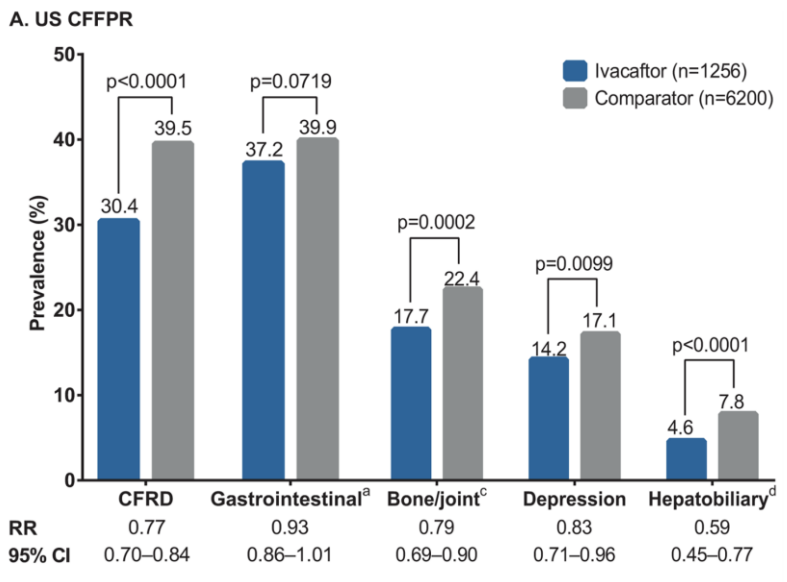
1 of the 6 patients had an episode of pancreatitis, which was managed on an outpatient basis.

Carrion A, Bvorowitz DS, Freedman SD, Siracusa CM, Goralski JL. ,
JPNG 2018

Data from the US and UK cystic fibrosis registries support disease modification by CFTR modulation with ivacaftor - Bessonova L, *et al*. *Thorax* 2018;**73**:731–740.

Incidence Cystic Fibrosis Related Extrapulmonary Conditions



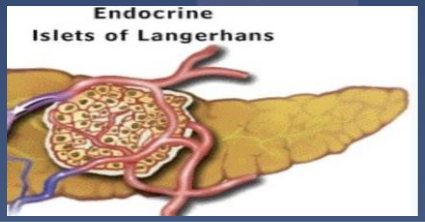


Caveat: Observational study from 2014 **did not account for differences in rates of extrapulmonary disease prior to starting therapy .**

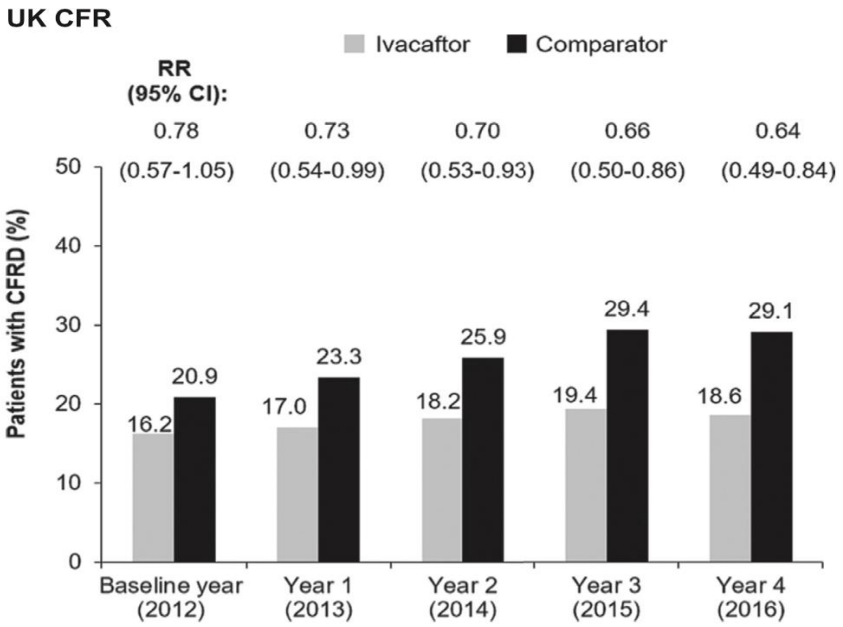
Purist : difficult to conclude a treatment effect.

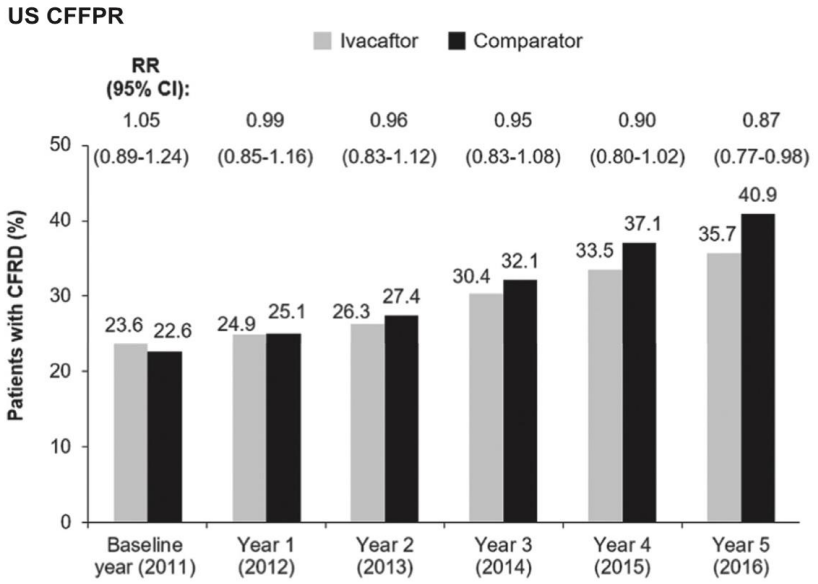
Disease progression in patients with cystic fibrosis treated with ivacaftor: Data from national US and UK registries

- ***Volkova N*** *et al. Journal of Cystic Fibrosis 19 (2020) 68–79*



Prevalence over time
Cystic Fibrosis Related Diabetes (CFRD)

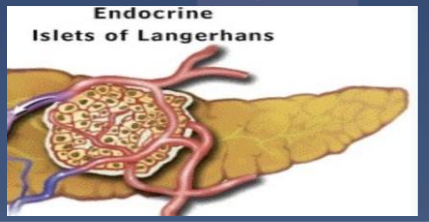




Case report 3:
Resolution of Cystic Fibrosis–related Diabetes with Ivacaftor Therapy

Hayes D Jr et al. Am J Respir Crit Care Med. 2014 Sep 1;190(5):590–1

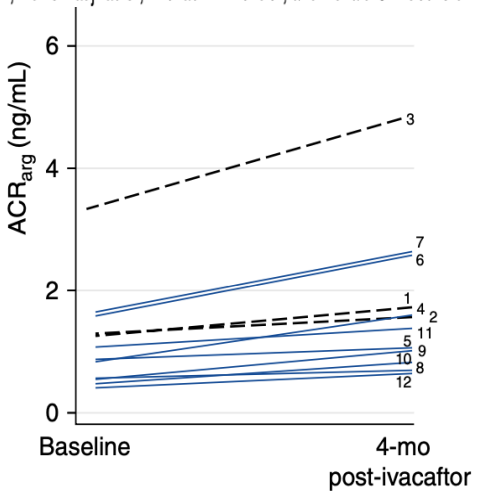
Effect of CFTR modulator therapy on CFRD



Islet Hormone and Incretin Secretion in Cystic Fibrosis after Four Months of Ivacaftor Therapy

AJRCCM 2019

Andrea Kelly[1], Diva D. De Leon[1], Saba Sheikh[2], Devaney Camburn[2], Christina Kubrak[2], Amy J. Peleckis[3], Darko Stefanovski[4], Denis Hadjiliadis[5], Michael R. Rickels[3], and Ronald C. Rubenstein[2]



Argine induced insulin secretion improved consistent with B islet cell function

CORK Study in Cystic Fibrosis

Sustained Improvements in Ultra-Low-Dose Chest CT Scores After CFTR Modulation With Ivacaftor

CHEST 2018

Nicola J. Ronan, MB, BCh; Gisli G. Einarsson, PhD; Maria Twomey, MB, BCh; Denver Mooney, PhD; David Mullane, MD; Muireann NiChroinin, MD; Grace O'Callaghan, PhD; Fergus Shanahan, MD; Desmond M. Murphy, PhD; Owen J. O'Connor, MD; Cathy A. Shortt, BSc; Michael M. Tunney, PhD; Joseph A. Eustace, MD; Michael M. Maher, MD; J. Stuart Elborn, MD; and Barry J. Plant, MD

No significant change in **HbA1C** within ivacaftor group (p=0.46) or compared to control group (p=0.7)

No significant change in **fasting glucose** (p=0.77), 2 hour post prandial glucose (0.74)

No significant change in OGTT category after ivacaftor

6 CFRD – no significant changes in **total insulin requirements** (p=0.42) or insulin/kg weight (p=0.25)

(Center experience unpublished data).

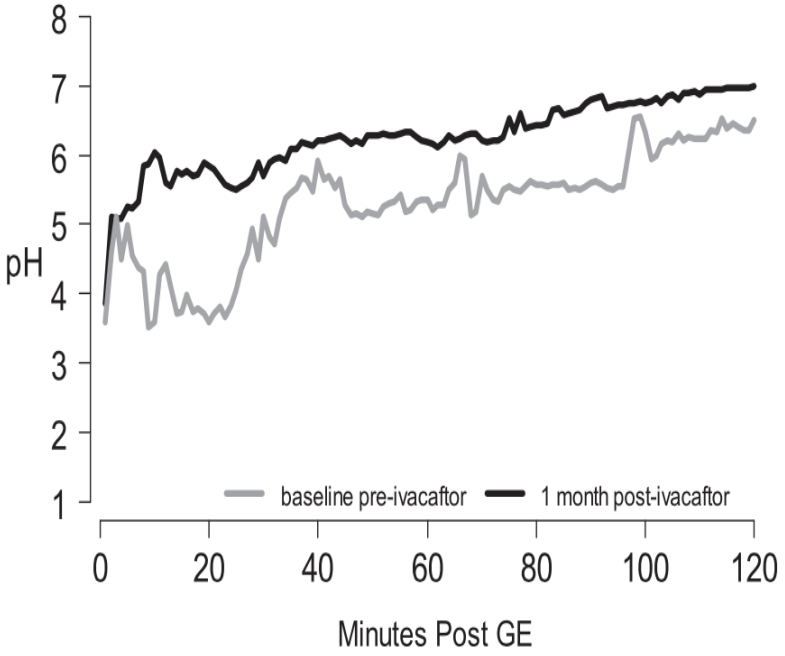
Treatment with Dual therapy **LUM-IVA** had **no consistent impact** on glucose tolerance and insulin secretion in Phe508del homozygous cystic fibrosis patients. Thomassen JC et al. JCF 2017

Effect of CFTR modulator therapy on Intestinal Tract

Clinical Mechanism of the Cystic Fibrosis Transmembrane Conductance Regulator Potentiator Ivacaftor in G551D-mediated Cystic Fibrosis

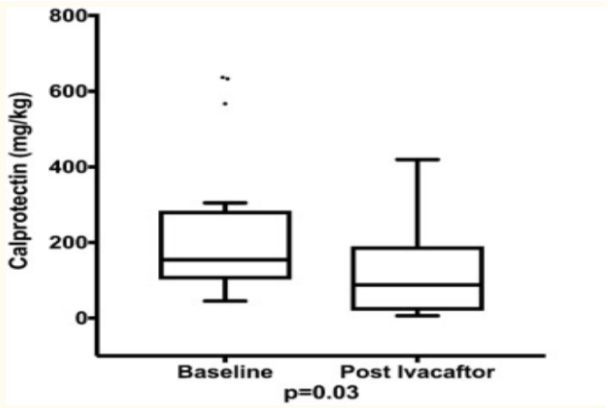
Steven M. Rowe[1], Sonya L. Heltshe[2,3], Tanja Gonska[4], Scott H. Donaldson[5], Drucy Borowitz[6], Daniel Gelfond[6], Scott D. Sagel[7], Umer Khan[3], Nicole Mayer-Hamblett[2,3], Jill M. Van Dalfsen[3], Elizabeth Joseloff[8], and Bonnie W. Ramsey[2,3]; on behalf of the GOAL Investigators of the Cystic Fibrosis Foundation Therapeutics Development Network

GOAL STUDY AJRCCM 2014



- Reduction in reflux symptoms
  n=12 over 1 year
  Zeybel GL et al. JCF 2017

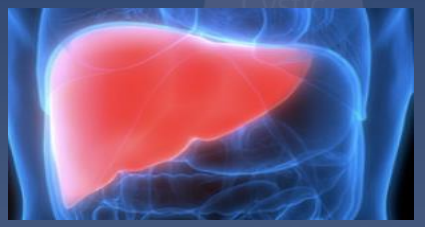
- Reduced intestinal inflammation.
  n=16 (median f/u 6.1 months)



- Increased abundance of *Akkermansia*

Ooi CY et al. *Sci Rep* 2018

Effect of CFTR modulator therapy on Hepatobiliary



Abnormal LFTs.

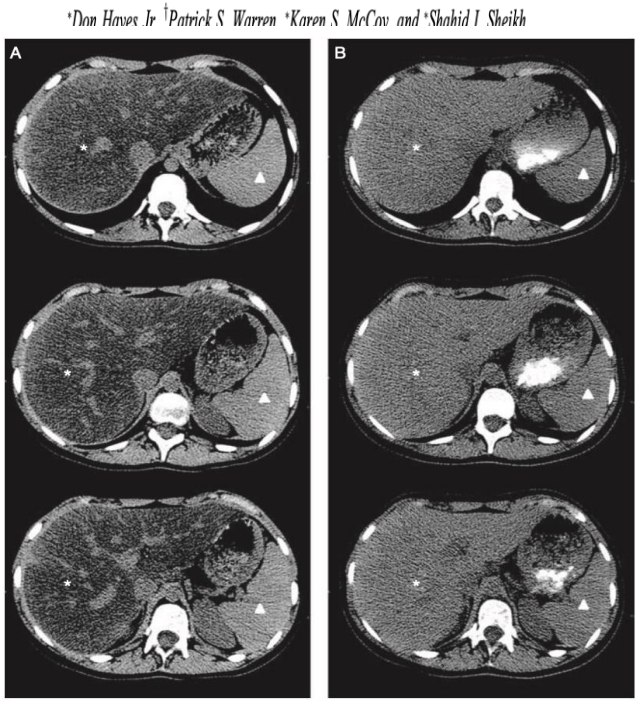
- **Monotherapy + Dual Therapy** clinical concerns transient abnormal LFTs (self limiting)

- **Triple Therapy** – "*elevated levels of alanine aminotransferase or aspartate aminotransferase that were greater than three times, greater than five times, and greater than eight times the upper limit of the normal range occurred in*

  16 patients (7.9%), 5 patients (2.5%), and 3 patients (1.5%),vs 11 patients (5.5%), 3 patients (1.5%), and 2 patients (1.0%) in the placebo group."

Case Report 4:

Improvement of Hepatic Steatosis in Cystic Fibrosis With Ivacaftor Therapy



JPGN 2015

Effect of CFTR modulator therapy on Bone/Joint

- Can't underestimate the role of increased activity

  Edgeworth et al: *Clin Sci (Lond)* 2017
  Wark et al: *BMC Pulm Med* 2019

- Reduction in energy expenditure

- Less systemic inflammation?

CORK STUDY
CHEST 2018

Results

Significant reductions

- Log10 IL-6 ($p<0.01$)
- Log10 IL-8 ($p<0.01$)
- Log10 IL-10 ($p<0.01$)
- Log10 IL-1β ($p<0.01$)
- Log10 CRP ($p = 0.015$)

Non-significant reduction in TNF-alpha ($p=0.06$)

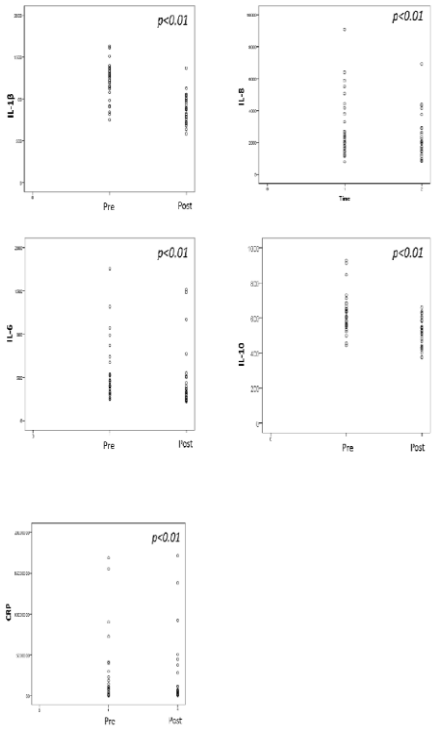


Figure 4.4 Change in blood inflammatory markers after ivacaftor

Effect of CFTR modulator therapy on Bone/Joint

- Can't underestimate the role of increased activity

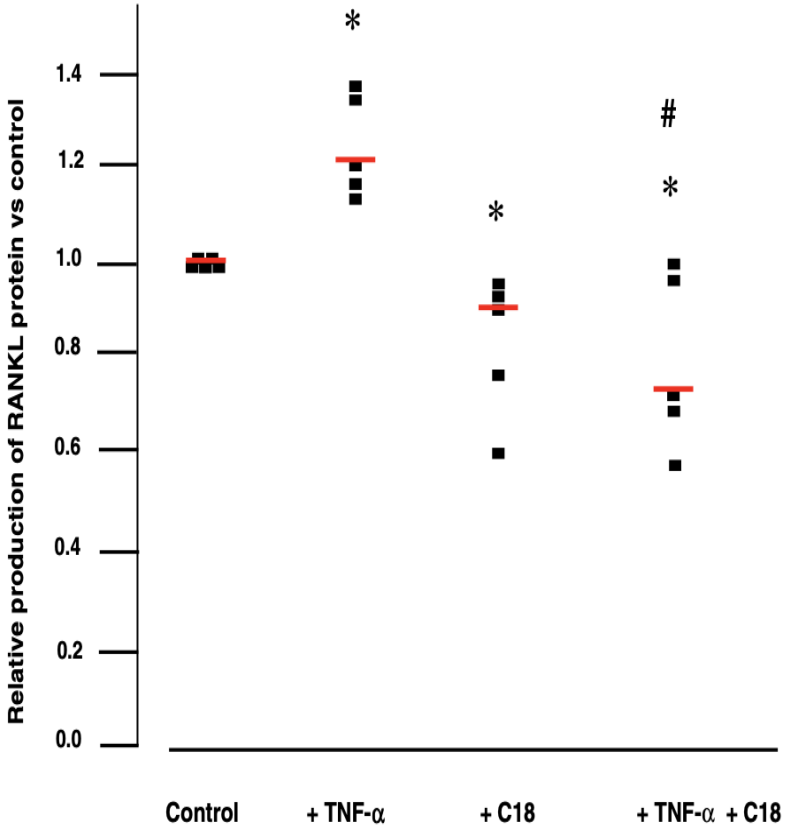
  Edgeworth et al: *Clin Sci (Lond)* 2017
  Wark et al: *BMC Pulm Med* 2019

- Reduction in energy expenditure

- Less systemic inflammation?

- Improved osteoblastic activity

  Sermet-Gaudelus et al. JCF 2016

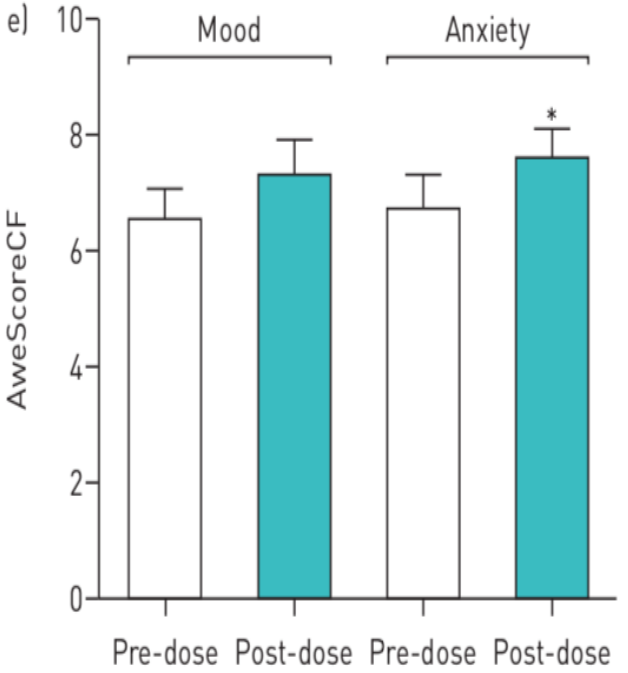


Effect of CFTR modulator therapy on Anxiety/Depression (positive)

In vitro: Ivacaftor and its two metabolites hydroxymethylivacaftor (iva-M1) and ivacaftorcarboxylate (iva-M6) demonstared positive affinity with key neurotransmitter receptors.

In vivo murine model response similar to fluoxetine

n=23 on LUM-IVA



Schneider EK et al. ERJ Open Res 2018; 4: 00127-2017.

Effect of CFTR modulator therapy on Anxiety/Depression (negative)

Exacerbation of pre-existing depression (DDI)

Antidepressants: citalopram, escitalopram, sertraline	↔ LUM, IVA ↓ citalopram, escitalopram, sertraline Due to induction of CYP3A/2C19 by LUM	A higher dose of these antidepressants may be required to obtain the desired clinical effect. Lumacaftor/ivacaftor may decrease the exposures of these antidepressants, which may reduce their efficacy.

De-novo case series LUM-IVA

McKinzie CJ et al. J Cyst Fibros 2017

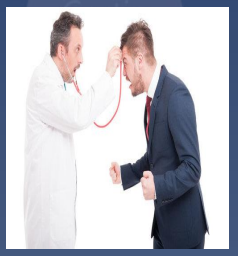
<u>Five cases in adolescent female patients</u>

Suggest a worsening of anxiety or depression associated with its use

- n= 2 experienced suicidal ideation
- n= 3 suicide attempts that resulted in psychiatric hospitalizations

ORKAMBI® (lumacaftor and ivacaftor) Approved Product Information.

Effect of **ETI** (Triple Therapy) on Anxiety/Depression ?



Difficult space

- Adjustment issues

- Introduction during COVID pandemic

Anecdotal concerns need to be taken seriously….

ORKAMBI® (lumacaftor and ivacaftor) Approved Product Information.

Extrapulmonary effect of CFTR Modulator Therapy on other drugs (DDIs)

	Ivacaftor (Kalydeco®)	Lumacaftor/Ivacaftor (Orkambi®)	Tezacaftor/Ivacaftor (Symkevi®)	Elexacaftor/Tezacaftor/Ivacaftor (Kaftrio®)
Drug-drug interactions	**CYP3A inhibitors** Strong CYP3A inhibitors ↓ Twice weekly (e.g itraconazole) Moderate Inhibitors ↓ Once daily (e.g. erythromycin)	**Substrates of CYP3A** Lumacaftor is a strong inducer of CYP3A. Administration of ORKAMBI® may decrease systemic exposure of medicinal products that are substrates of CYP3A, which may decrease therapeutic effect e.g. increased doses of **PPIs, SSRIs and systemic corticosteroids** may be required. **Antifungals** - Concomitant use of lumacaftor/ivacaftor with these antifungals is not recommended. Patients should be monitored closely for breakthrough fungal infections if such drugs are necessary. Co-administration with sensitive CYP3A substrates or CYP3A substrates with a narrow therapeutic index is not recommended e.g. **immunosuppressants**. ORKAMBI may substantially decrease **hormonal contraceptive** exposure reducing their effectiveness and increasing the incidence of menstruation-associated adverse reactions, e.g., amenorrhea, dysmenorrhea, menorrhagia, menstrual irregular. Hormonal contraceptives, including oral, injectable, transdermal, and implantable, should not be relied upon as an effective method of contraception when co-administered with ORKAMBI.	**CYP3A inhibitors** *Strong* CYP3A inhibitors ↓ morning dose to Twice weekly – no evening dose (e.g. itraconazole, clarithromycin) *Moderate inhibitors* – morning dose and evening dose held on alternate days (e.g. erythromycin)	**CYP3A inhibitors** As for Tezcaftor/Ivacaftor
	CYP3A inducers Exposure to ivacaftor is significantly decreased by the concomitant use of CYP3A inducers, potentially resulting in the loss of ivacaftor efficacy; therefore, co-administration of ivacaftor with strong CYP3A inducers is not recommended e.g. rifampicin		CYP3A inducers As for Ivacaftor	CYP3A inducers As for Ivacaftor
	P-gp substrates When used concomitantly with digoxin or other substrates of P-gp with a narrow therapeutic index, such as ciclosporin, everolimus, sirolimus or tacrolimus, caution and appropriate monitoring should be used.	**Anti-mycobacterials**: rifabutin, rifampicin, rifapentine Concomitant use of lumacaftor/ivacaftor with these anti-mycobacterials is not recommended	**P-gp substrates** As for Ivacaftor	**P-gp substrates** As for Ivacaftor

WORK CLOSELY WITH YOUR PHARMACIST !!!

Effect of CFTR modulator therapy on fertility

- Clinical trials change pregnancy rates

  - Heltshe SL et al. JCF 2017

	Pregnancy Incidence
Before Ivacaftor	34/1000 women years
During Trials	14.4/1000 women years
After Trials	38/1000 women years

- Increasing numbers of spontaneous pregnancies

  - Jones GH et al. Paediatr Respir Rev 2015

Effect of CFTR modulator therapy on fertility

safety profile encouraging

Outcomes of pregnancy in women with cystic fibrosis (CF) taking CFTR modulators – an international survey ☆

Edward F Nash [a,*], Peter G Middleton [b], Jennifer L Taylor-Cousar [c]

JCF 2020

- 44 pregnancies
- Two maternal complications were deemed related to LUM-IVA (bronchospasm)

- No modulator-related complications were reported in infants exposed *in utero* and/or during breastfeeding.

Effect of CFTR modulator therapy on fertility

safety profile encouraging

Maternal and fetal outcomes following elexacaftor-tezacaftor-ivacaftor use during pregnancy and lactation

Jennifer L. Taylor-Cousar*, Raksha Jain

JCF 2021

- 45 pregnancies
- Two maternal (Cholestasis & PE) and 3 infant complications were unknown (possible) or suspected relatedness to ETI use

- In the context of the known increased rate of complications in women with CF and their infants, data from this retrospective survey is reassuring for women who choose to continue ETI during pregnancy.

Effect of CFTR modulator therapy post transplantation

Cork experience with ETI

- Solid organ liver Tx (n=2)
- Significant improvements in FEV1 and Weight
- No LFT abnormalities

Effect of CFTR modulator therapy post transplantation

ARTICLE IN PRESS

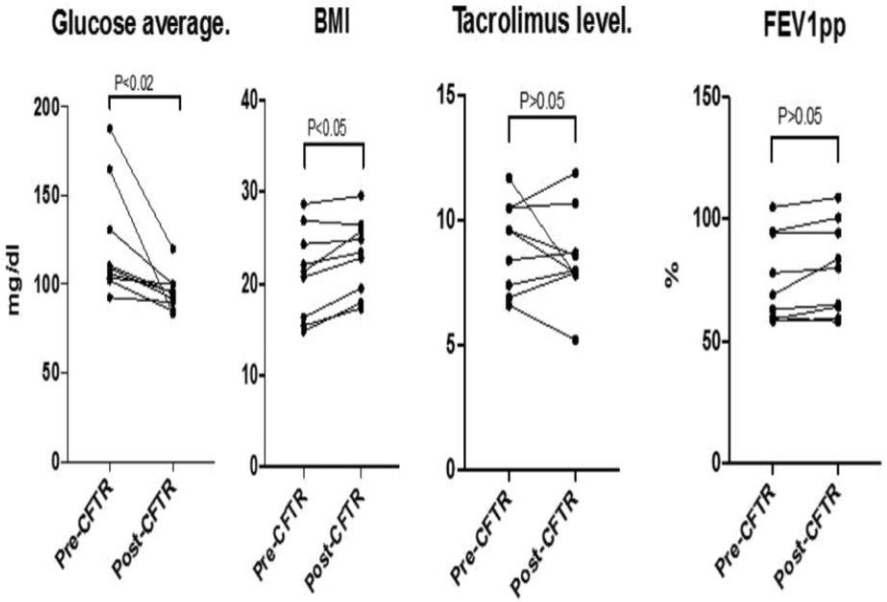
ELSEVIER

The Journal of Heart and Lung Transplantation
http://www.jhltonline.org

BRIEF COMMUNICATION

CFTR modulator use in post lung transplant recipients

Lauryn A. Benninger, DO, Cesar Trillo, MD, and Jorge Lascano, MD



Additional Effects

- **Sinus symptoms** were reported to have **improved** in 8/9 patients.
- Complaints of **GI symptoms**, including gastroparesis, fullness, bloating, and reflux, **improved** in all patients.

  No individual underwent surgical intervention for GI or sinus complications after initiation of Trikafta.
- Combined **hospital admission rates dropped** from 22 in the year prior to Trikafta to 5 after the initiation of Trikafta.
- **Antibiotic usage also decreased** with only 3 individuals requiring a single course of antibiotics after starting CFTR modulator therapy.

J Heart Lung Transplant 000;000:1–4 :2021 International Society for Heart and Lung Transplantation.

Final Case-

Final Case- Modulate as early as you can?

Final Case:

Normal pancreatic function and false-negative CF newborn screen in a child born to a mother taking *CFTR* modulator therapy during pregnancy

Fortner CN et al. JCF (online) 2021

Final Case:

Normal pancreatic function and false-negative CF newborn screen in a child born to a mother taking *CFTR* modulator therapy during pregnancy

Fortner CN et al. JCF (online) 2021

- CF Mother started ETI Nov 2018
- She and her husband (Carrier CF508) had been trying unsuccessfully to conceive a child.
- 6 weeks later –pregnancy
- She elected to remain on modulator therapy to maintain her own health.

Final Case:
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- Child was born at 39 weeks gestation.
- IRT level was 37.0 ng/ml, below the 5% threshold to reflex to molecular analysis but despite this the center tested.
- Infant had two copies of the F508del mutation / Mother breastfeeding

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- Day 10 infant assessment : above the 90th percentile for weight and above the 95th percentile in length.
- A fecal elastase collected normal (>500 µg/g)
- Sweat chloride values (measured at 5 weeks) were elevated at 60 mmol/L and 67 mmol/L.

Conclusion: The extrapulmonary effect of CFTR Modulator Therapy

Extrapulmonary effects are seen (various levels of data)

- Level of modulation
- Duration of modulation
- Age of initiation (early)

A thought:

"If you live longer and/or feel better with a chronic illness you need to look out for the unexpected."

Self discontinuation of other meds / Malignancy / Hypertension /Coronary artery disease…

(another talk!)

Thank you

Cork adult Centre for Cystic Fibrosis (CUH) & HRB Clinical Research Facility (UCC).

- Professor Joe Eustace
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- Dr. David Morrissey
- Dr. Tamara Vagg
- DR. Nicola Ronan
- Ms. Shaunagh Browne
- Ms. Yvonne McCarthy
- Mr. James Dorgan
- Ms. Claire Fleming
- Ms. Mairead McCarthy
- Ms. Claire Hickey
- Ms. Ciara Howlett
- Ms. Karen Cronin
- Ms. Sarah Twohig

Queens University Belfast.

- Professor Stuart Elbornn
- Professor Michael Tunney
- Dr. Gisli Einarsson