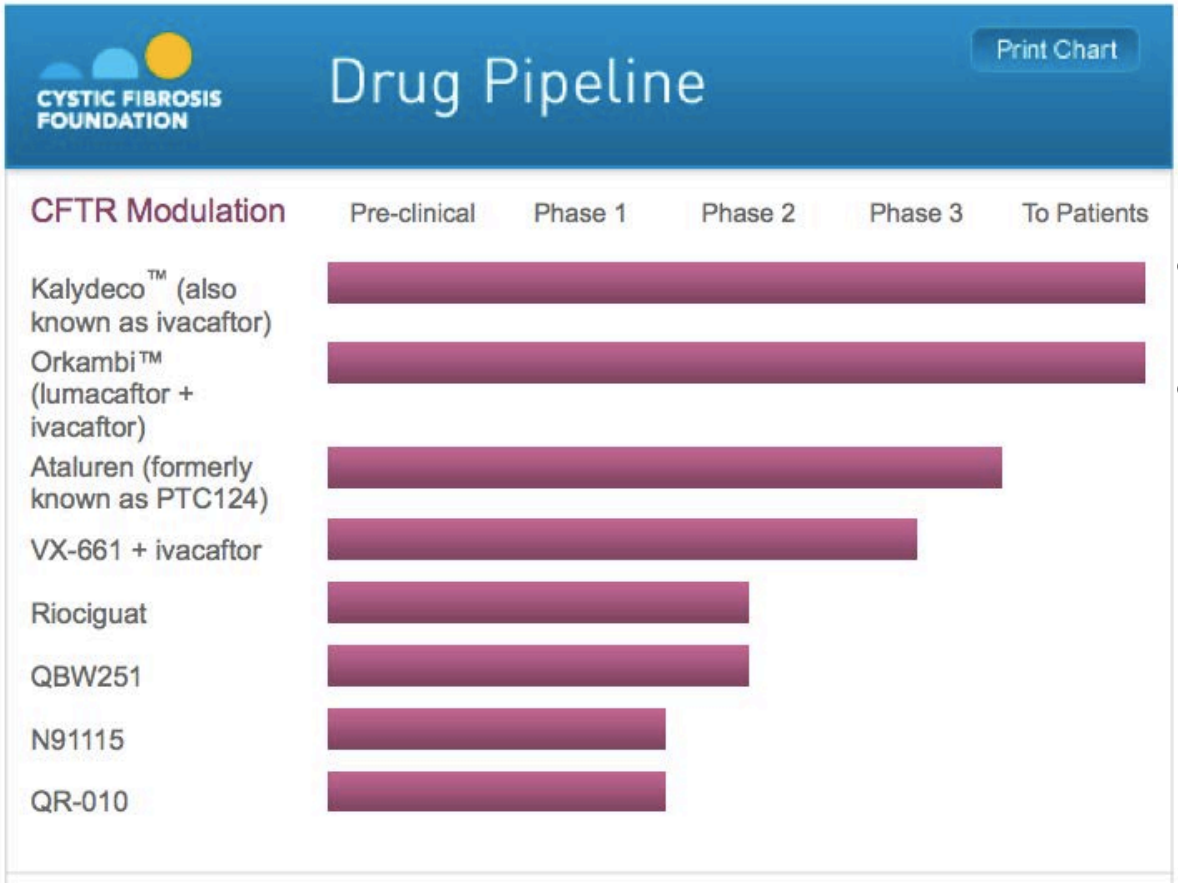
Disclosures

- I am Director of the ECFS Clinical Trial Network
- I have not received any fees or payments from Pharma related to CF Therapies
- I am subject to several confidentiality agreements with different Pharma related to Protocol Review and Feasibility activity for ECFS-CTN related to this topic
- Data I present today is all in the public domain

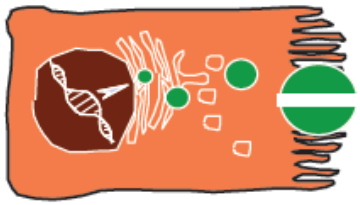
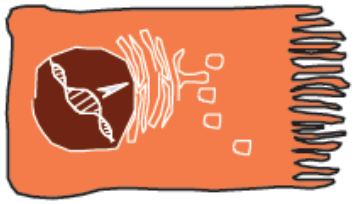
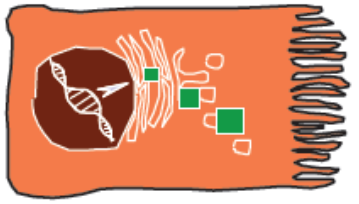
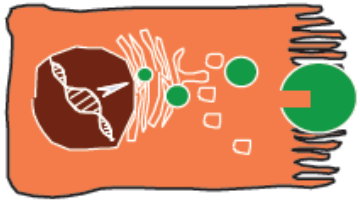
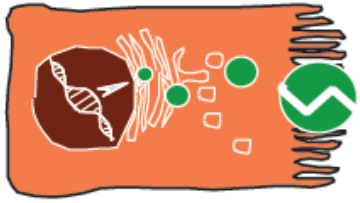
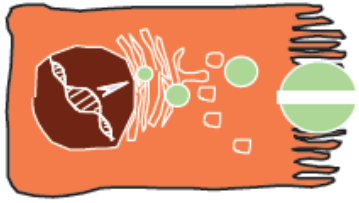


- ClinicalTrials.gov
- 60 studies involve CFTR modulators

Overview of CFTR Modifier Pipeline

Tim Lee, United Kingdom

ECFS-CTN Director

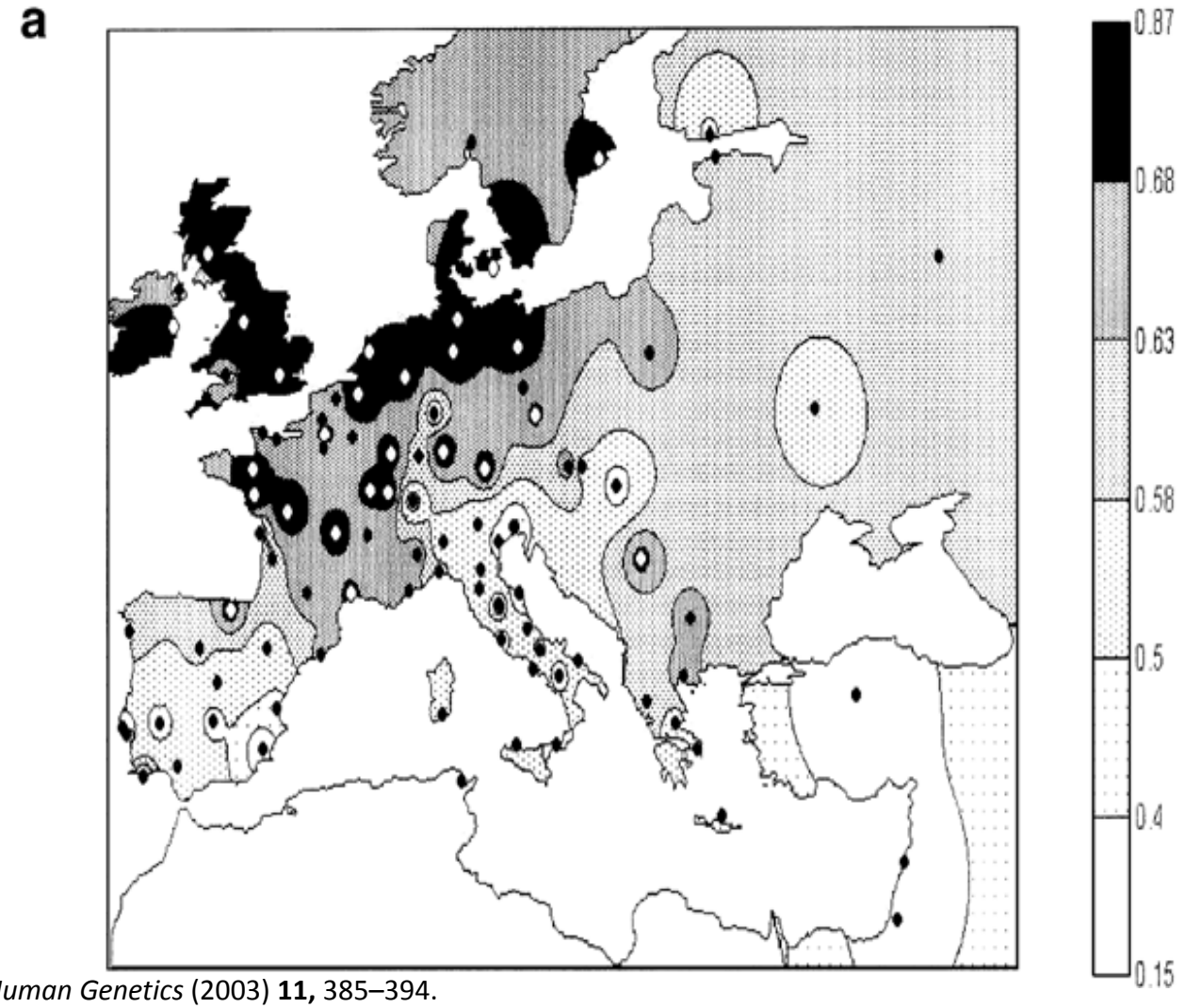
CFTR Mutation Classes	Approach
 • Normal	
 • Class 1 Stop mutations	• Corrector (or suppressor of premature termination eg Ataluren) ? also potentiator??
 • Class 2 (phe508del) Defective Processing	• Corrector eg VX 809/VX 661/Riociguat/N91115/inhaled QR-010 ? with potentiator eg Orkambi™
 • Class 3 (G551D) Defective regulation	• Potentiator eg Ivacaftor, QBW251
 • Class 4 Defective conductance	• Potentiator eg Ivacaftor, QBW251
 • Class 5 Reduced synthesis	• Rare: Corrector? ?QBW251

Images from Johns Hopkins Medicine CME "Ahead of the Curve"

Serious CF extra pulmonary manifestations

- Pancreatic insufficiency
  approx 90% of people with CF
- CF Liver disease in up to 41%
  Cirrhosis in 7.8%, transplant 2%
  Lamireau et al J of Hepatology 2004
- CF related diabetes
  2% of children, 19% of adolescents, and 40-50% of adults
  Dunitz 2009; 32 (9): 1626-31

Geographical distribution of phe508del mutation in Europe



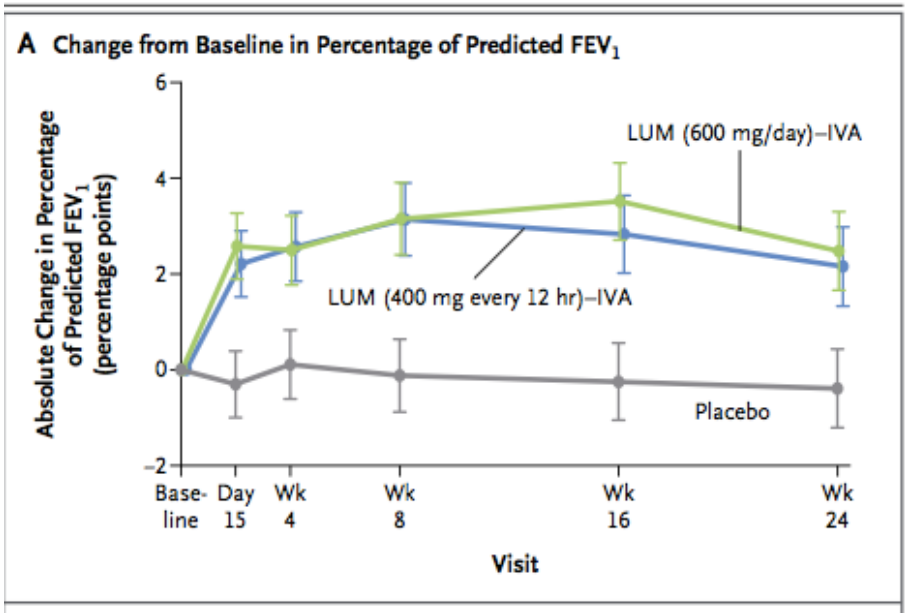
European Journal of Human Genetics (2003) **11,** 385–394.
Spatial patterns of cystic fibrosis mutation spectra in European populations
Lao O *et al.*

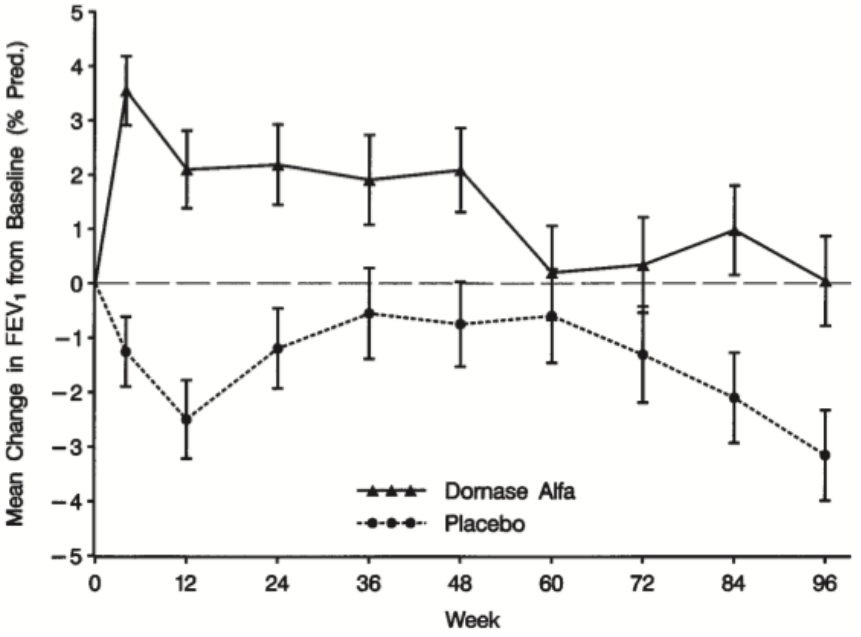
VX-809 (Lumacaftor) plus VX-770 (Kalydeco™, Ivacaftor) for phe508del/phe508del Phase 3: Orkambi™

- 2 large double blind RCTs (TRAFFIC and TRANSPORT)
- 1108 patients (mean baseline FEV1 = 61% pred)
- Lumacaftor (600 mg once daily or 400 mg every 12 hours) in combination with ivacaftor (250 mg every 12 hours) or matched placebo for 24 weeks
- Primary end point: Absolute change from baseline in % predicted FEV1 at week 24

Wainwright C *et al.* 2015: Lumacaftor-Ivacaftor in patients with cystic fibrosis homozygous for the phe508del CFTR.
NEJM DOI: 10.1056/NEJMoa1409547

VX-809 (Lumacaftor) plus VX-770 (Kalydeco™, Ivacaftor) for phe508del/phe508del
Phase 3: Orkambi™





Range from 2.6 to 4 percentage points
P<0.001 for all comparisons
Change by Day 15, sustained through 24w
Seen in all subgroups including FEV1 <40%

3.2% improvement over placebo
P=0.006
Change by Day 28, sustained through 96w
Younger patients (8 years, FEV1 95%)

Wainwright C et al. 2015: Lumacaftor-Ivacaftor in patients with cystic fibrosis homozygous for the phe508del CFTR. NEJM DOI: 10.1056/NEJMoa1409547

Quan JM et al. 2001: A two year randomised placebo-controlled trial of Dornase-alpha in young patients with cystic fibrosis with mild lung function abnormalities. J Pediatrics 139: 813-20

VX-809 (Lumacaftor) plus VX-770 (Kalydeco™, Ivacaftor) for phe508del/phe508del
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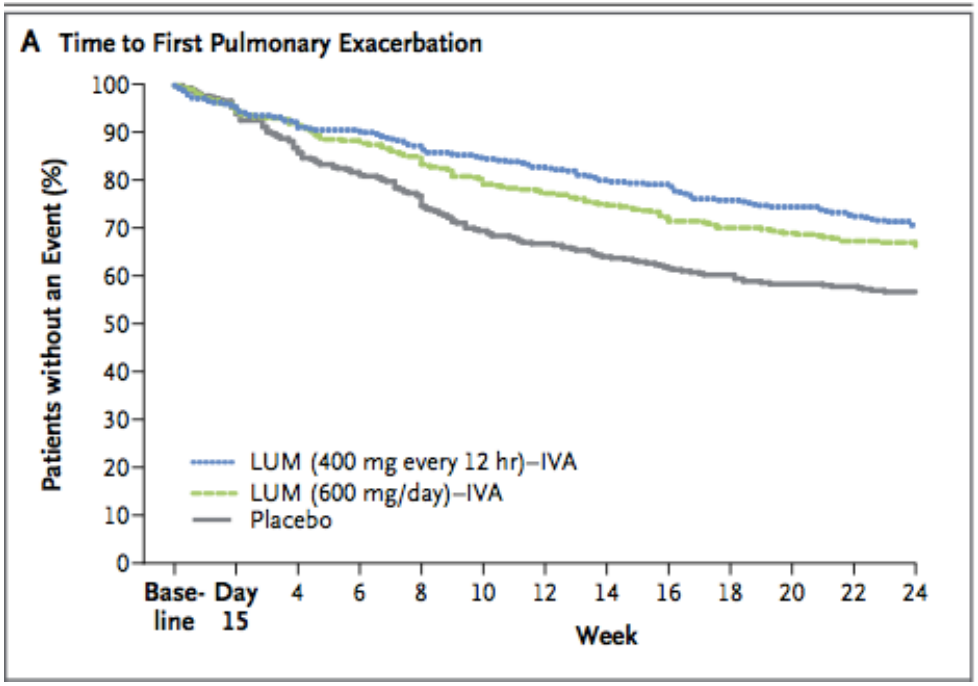
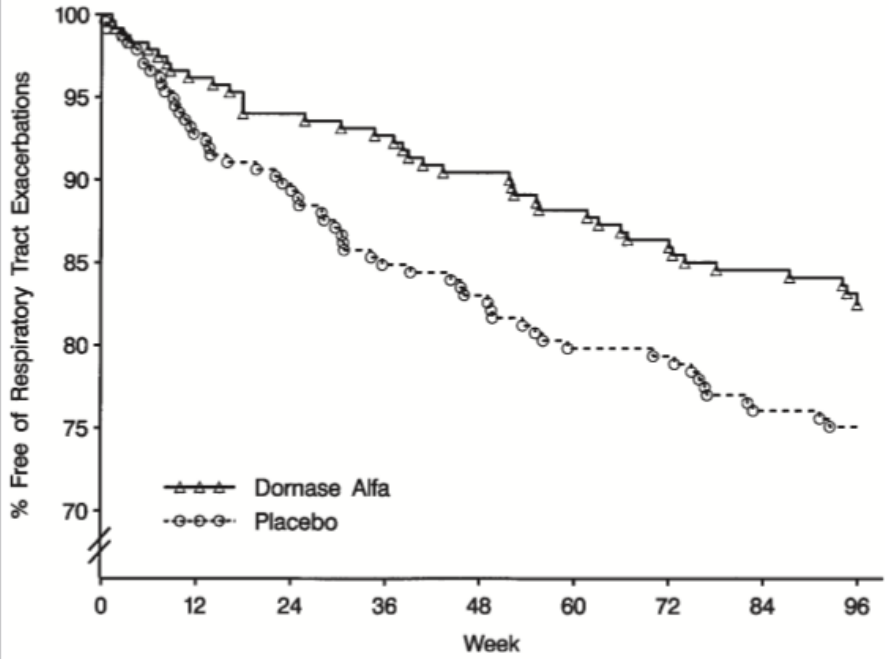


30-39% reduction in pulmonary exacerb.
P= and <0.001 respectively
45-56% reduction in requirement for iv antibiotics
P <0.001

Wainwright C et al. 2015: Lumacaftor-Ivacaftor in patients with cystic fibrosis homozygous for the phe508del CFTR. NEJM DOI: 10.1056/NEJMoa1409547



34% reduction in RTE
P=0.048
RTE= Resp symptoms req. iv antibiotics
Younger patients (8 years, FEV1 95%)

Quan JM et al. 2001: A two year randomised placebo-controlled trial of Dornase-alpha in young patients with cystic fibrosis with mild lung function abnormalities. J Pediatrics 139: 813-20

What do we know about VX-661 plus Ivacaftor Combination Programme?

VERTEX

March 23, 2015

Vertex Announces Data from 12-Week Phase 2 Safety Study of VX-661 in Combination with Ivacaftor in People with Cystic Fibrosis Who Have Two Copies of the F508del Mutation

- 39 adults with 2 copies phe508del
- Mean within-group absolute improvement from baseline in %pred FEV1 of 4.4 percentage points (p=0.009) at week 4 and 3.0 (p=0.026) at week 12
- Pulmonary exacerbation occurred in 38% of patients who received VX-661 and 44 percent of those who received placebo (NS)
- Moving on to four Phase 3 studies:
  - *People with two copies of the F508del mutation (began enrollment in February)*
  - *People with one F508del mutation and a second gating mutation (Class 3)*
  - *People with one F508del mutation and a second residual function mutation (Class 4)*
  - *People with one F508del mutation and a second mutation that results in minimal CFTR function (eg Class 1, Class 2)*

Extended Evaluation of Ivacaftor Treatment in Pediatric Patients With Cystic Fibrosis and a *CFTR* Gating Mutation

Margaret Rosenfeld, MD[1]; Sarah Robertson, PharmD[2]; Yulia Green, MBChB[3]; Jon Cooke, MSc[3]; Mark Higgins, MD[3]; Jane C. Davies, MD, MBChB[4]; on behalf of the KIWI Study Group

1. Seattle Children's Hospital, Seattle, WA, USA; 2. Vertex Pharmaceuticals Incorporated, Boston, MA, USA; 3. Vertex Pharmaceuticals (Europe) Limited, London, UK; 4. Royal Brompton & Harefield NHS Foundation Trust, London, UK

Poster 247, North American CF Conference, October 2015

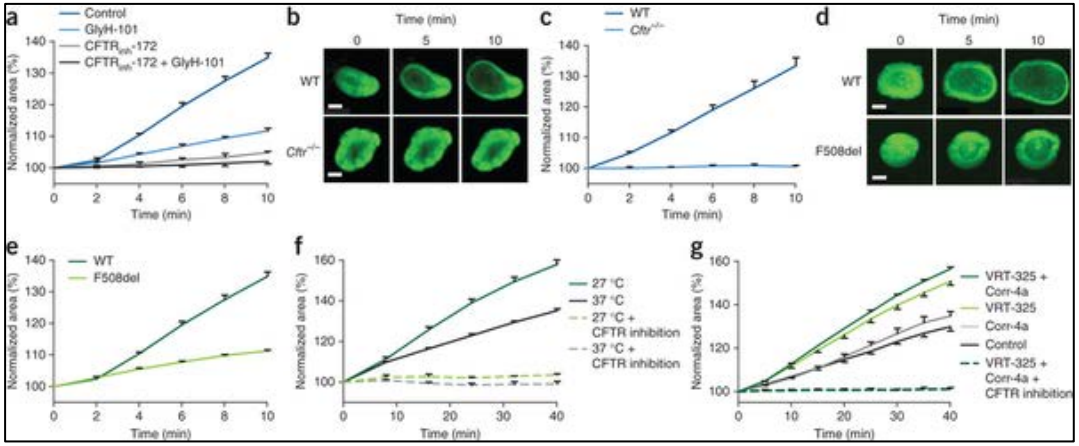
Mean increase in faecal elastase 99.8 ug/g at 24 weeks,
101.9 after 72 weeks
34.6 of patients PI at baseline had one or more value >200 ug/g

Mean reduction in IRT (marker of pancreatic stress) of 20.7 ng/ml after 24 weeks.

What about CF patients with rare mutations?

- Organoids appear a good personalized predictor of response to CFTR modulator therapies
- For people with CF who have rare mutations then n of 1 /very small number studies using organoid results as screening criteria seems a very appropriate and feasible way forward
- We have a responsibility to consider carefully how people with rare mutations are not excluded from eventual access to better treatments for CF

Dekkers et al.
Nature Medicine **19**, 939–945 (2013)



Challenges/Opportunities

- Assessing efficacy in children
- People with rare CF mutations – need for n of 1 methodology
- Assessing improved CFTR modifiers over and above existing approved CFTR modifiers that become “standard of care”
- Addressing other important CFTR related disease especially gastro-intestinal, liver, pancreas, CF Related Diabetes.

ECFS-CTN Steering Committee