I nuovi farmaci per la Fibrosi Cistica: attualità e prospettive

Donatello Salvatore, Centro Fibrosi Cistica Regione Basilicata

CYSTIC FIBROSIS FOUNDATION
30TH ANNUAL NORTH AMERICAN
CYSTIC FIBROSIS CONFERENCE
OCTOBER 27-29, 2016 • ORANGE COUNTY CONVENTION CENTER • ORLANDO, FL

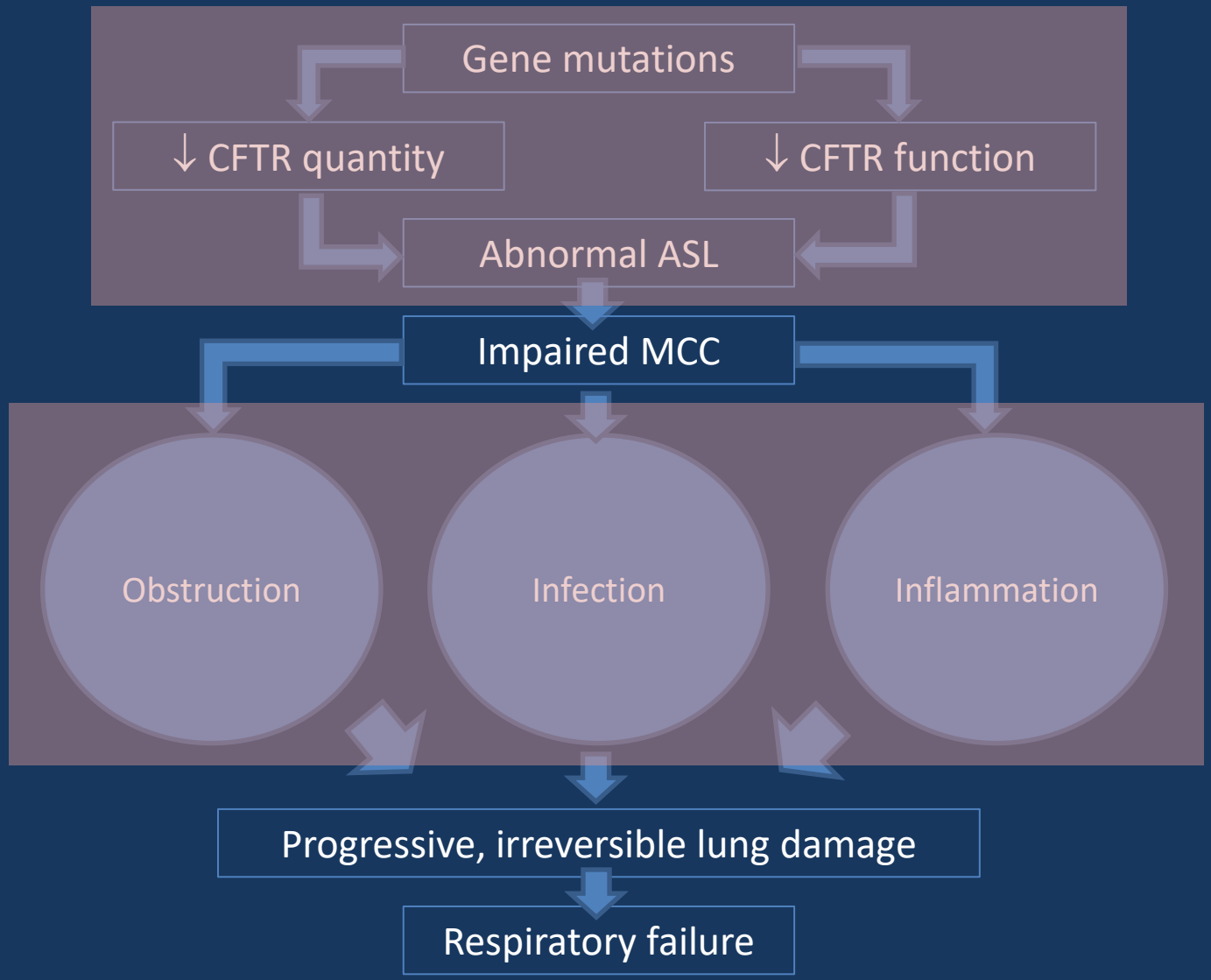
A Cure for All: Leaving No One Behind

Assuring Effective Therapies for All Patients with Cystic Fibrosis

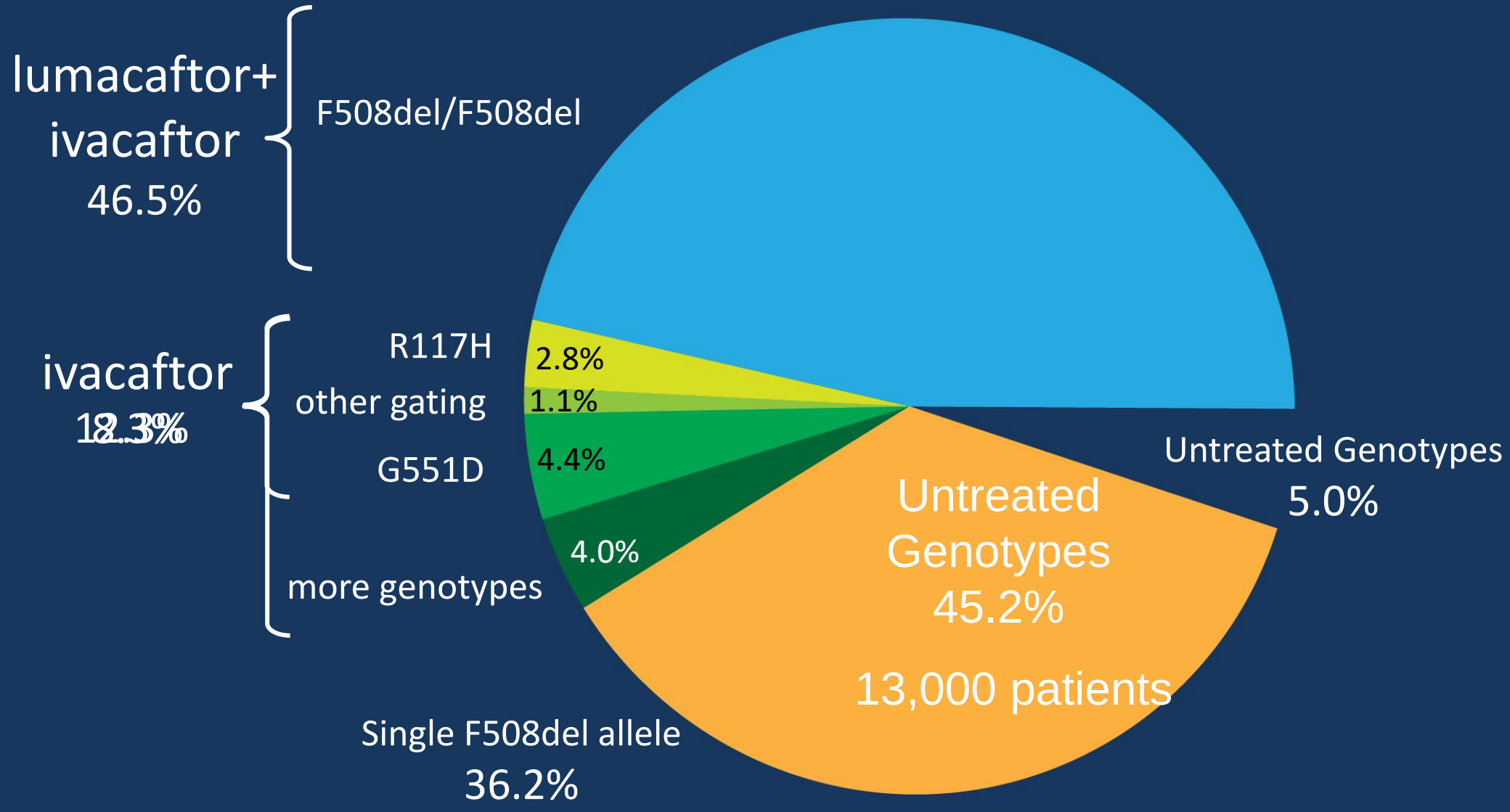
Cystic Fibrosis lung disease
-pathogenesis and targets for therapy-

New treatments address underlying CF defect
More specific, targeted

Current treatments address downstream complications of CF defect



Current US CF genotypes with approved CFTR modulators



Cystic Fibrosis Foundation Patient Registry, 2014

IVACAFTOR

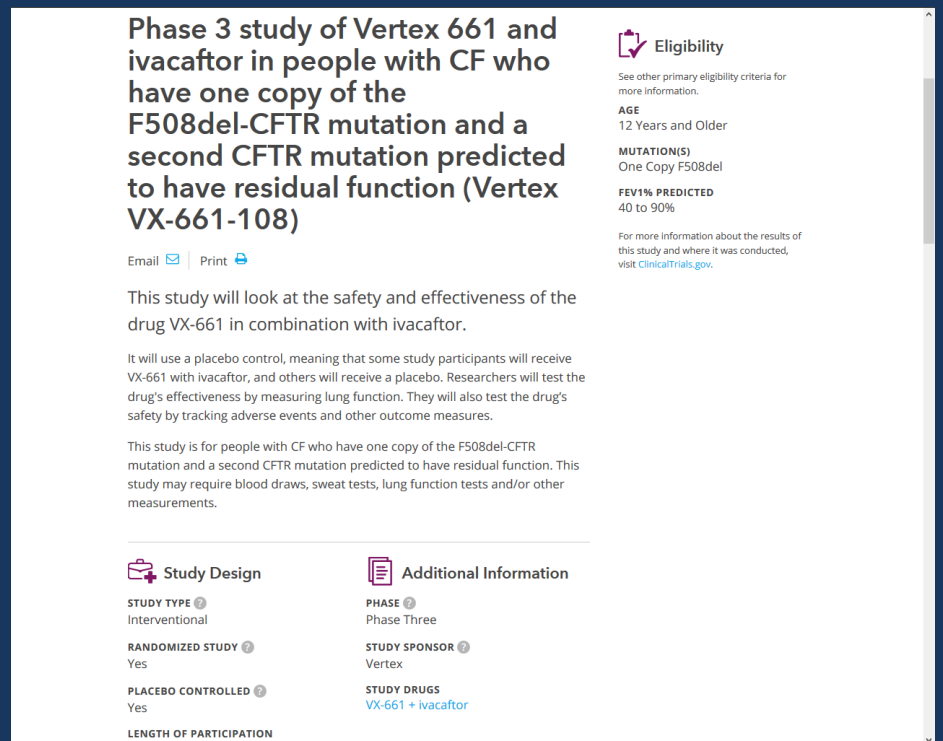
- Approvato e rimborsato per i pazienti con mutazioni di classe III (gating) *G551D, G1244E, G1349D, G178R, G551S, G970R, S1251N, S1255P, S549N, S549R* o una mutazione *R117H* in almeno un allele del gene CFTR di età pari o superiore a 6 anni
- L'estensione dell'impiego di Kalydeco alle età comprese nella fascia 2-5 anni è stata validata dall'European Medicines Agency (EMA) e l'Agenzia Italiana per i Farmaci (AIFA) ha classificato Il farmaco con l'autorizzazione alla commercializzazione e la classificazione in fascia Cnn (C non negoziata)

Table 3. Summary of Exploratory Efficacy Outcome Measures

		Absolute Change at KLIMB Week 84, Mean (SD)		
Outcome Measure	n	From KIWI Baseline	n	From KLIMB Baseline
Sweat chloride, mmol/L	20	-54.7 (26.0); P<0.0001	23	-8.5 (31.5); P=0.10
Weight *z* score	28	0.2 (0.6); P=0.11	28	0.0 (0.5); P=0.97
BMI *z* score	28	0.3 (0.6); P=0.02	28	-0.1 (0.6); P=0.50
Height *z* score	28	(0.4); P=0.18	28	0.1 (0.4); P=0.05
FE-1, µg/g	17	128.8 (170.1); P=0.005	20	56.8 (195.6); P=0.148
IRT, ng/ml	21	-15.9 (25.2); P=0.01	26	4.4 (12.2); P=0.21

Ivacaftor (2)

- Uso in pazienti con mutazioni di classe IV e V: 2789+5G->A, D110E, R352Q, A1067T, 3849+10kbC->T, D110H, A455E, R1070Q, 3272-26A->G, R117C, D579G, R1070W, 711+3A->G, E193K, S945L, F1074L, E56K, L206W, S977F, D1152H, P67L, P205S, F1052V, D1270N, R74W, R347H, K1060T
- Case report (Respir Med Case Rep 2016 Oct 18;19:193-195. eCollection 2016.)
- Studio in corso



Phase 3 study of Vertex 661 and ivacaftor in people with CF who have one copy of the F508del-CFTR mutation and a second CFTR mutation predicted to have residual function (Vertex VX-661-108)

Email | Print

This study will look at the safety and effectiveness of the drug VX-661 in combination with ivacaftor.

It will use a placebo control, meaning that some study participants will receive VX-661 with ivacaftor, and others will receive a placebo. Researchers will test the drug's effectiveness by measuring lung function. They will also test the drug's safety by tracking adverse events and other outcome measures.

This study is for people with CF who have one copy of the F508del-CFTR mutation and a second CFTR mutation predicted to have residual function. This study may require blood draws, sweat tests, lung function tests and/or other measurements.

Eligibility

See other primary eligibility criteria for more information.

AGE
12 Years and Older

MUTATION(S)
One Copy F508del

FEV1% PREDICTED
40 to 90%

For more information about the results of this study and where it was conducted, visit ClinicalTrials.gov.

Study Design

STUDY TYPE
Interventional

RANDOMIZED STUDY
Yes

PLACEBO CONTROLLED
Yes

LENGTH OF PARTICIPATION

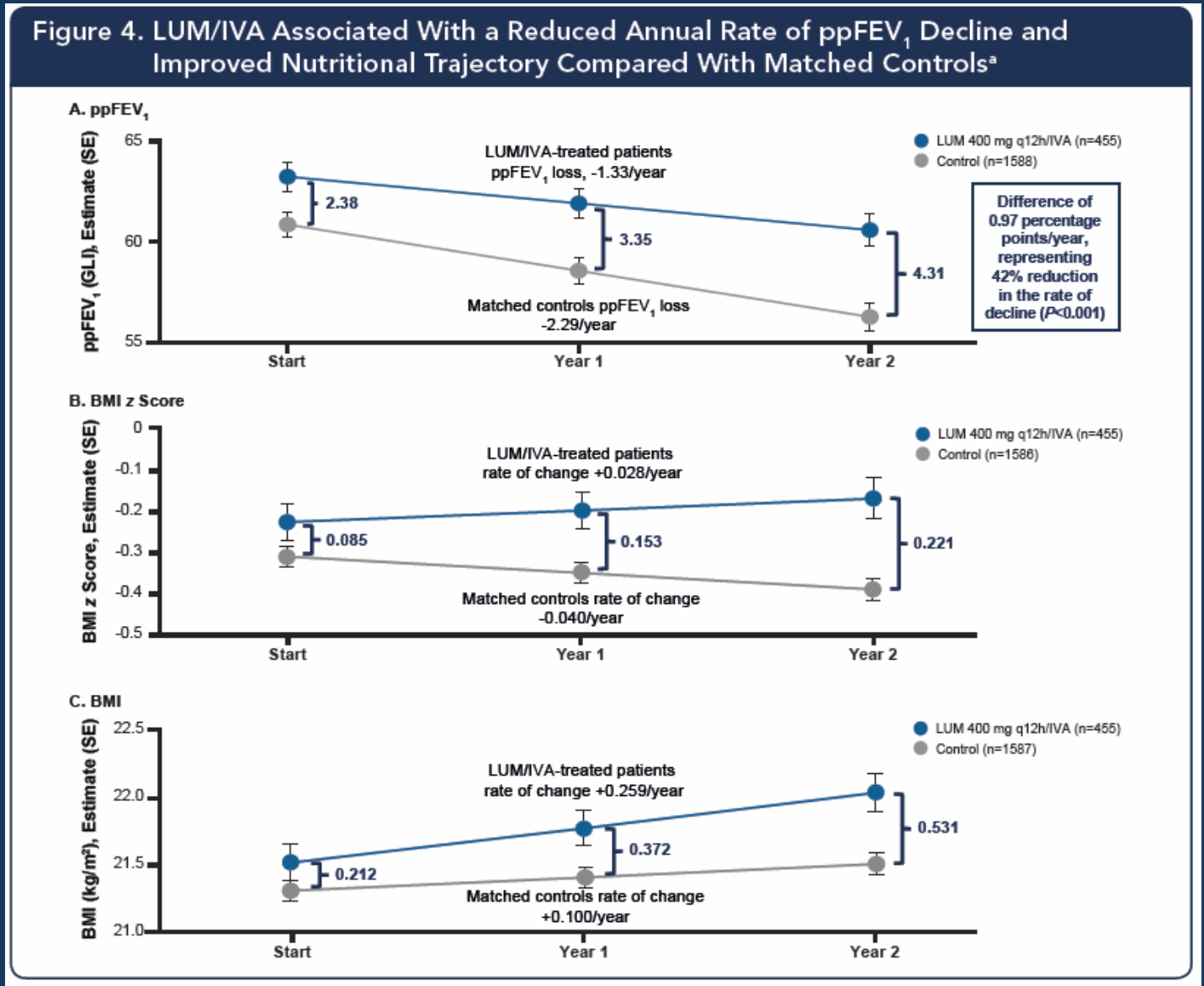
Additional Information

PHASE
Phase Three

STUDY SPONSOR
Vertex

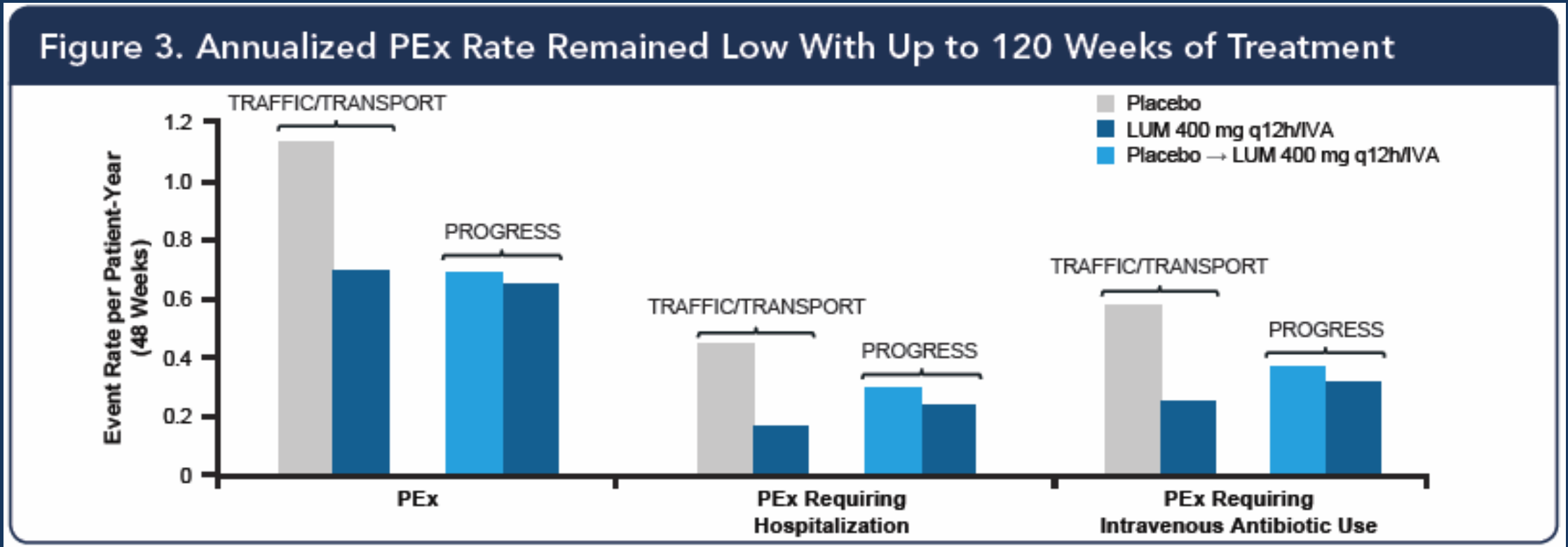
STUDY DRUGS
VX-661 + ivacaftor

Long-term lumacaftor/ivacaftor benefit in F508del homozygotes



Presented by Mike Konstan at Workshop 07 and Poster #180

Long-term lumacaftor/ivacaftor benefit in F508del homozygotes



Presented by Mike Konstan at Workshop 07 and Poster #180

Orkambi per i bambini 6-11 anni

Figure 7. Absolute Change From Baseline in $LCI_{2.5}$

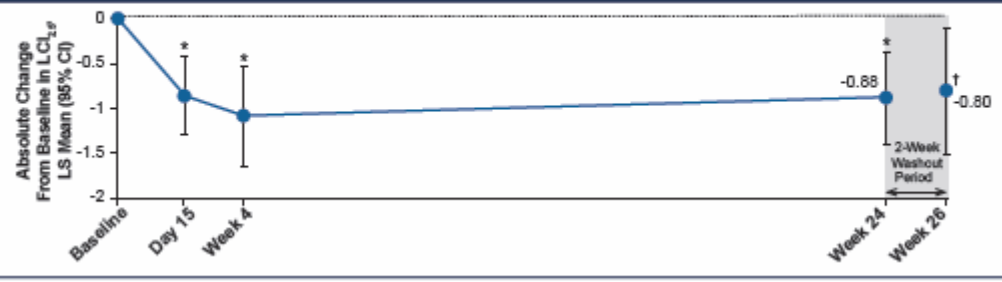


Figure 6. Absolute Change From Baseline in CFQ-R Respiratory Domain Score

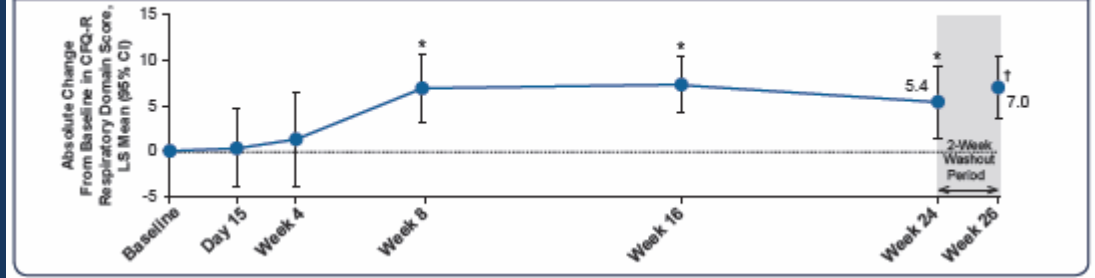


Figure 2. Absolute Change From Baseline in $ppFEV_1$

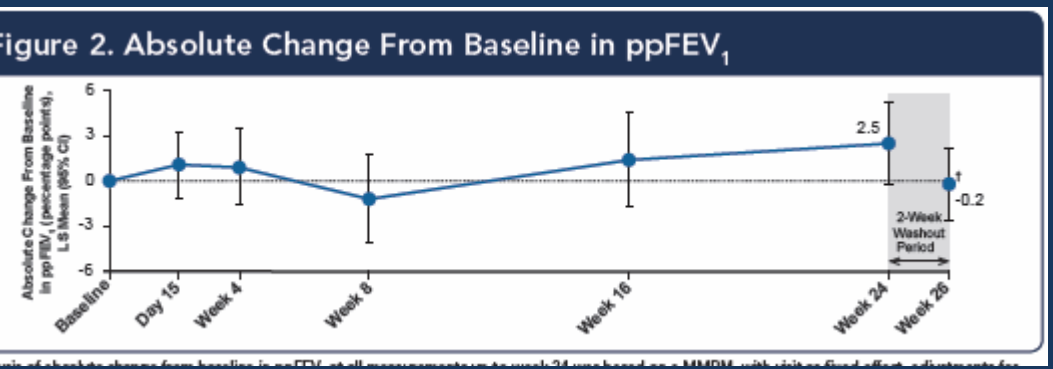


Figure 4. Absolute Change From Baseline in (A) BMI and (B) BMI z Scores

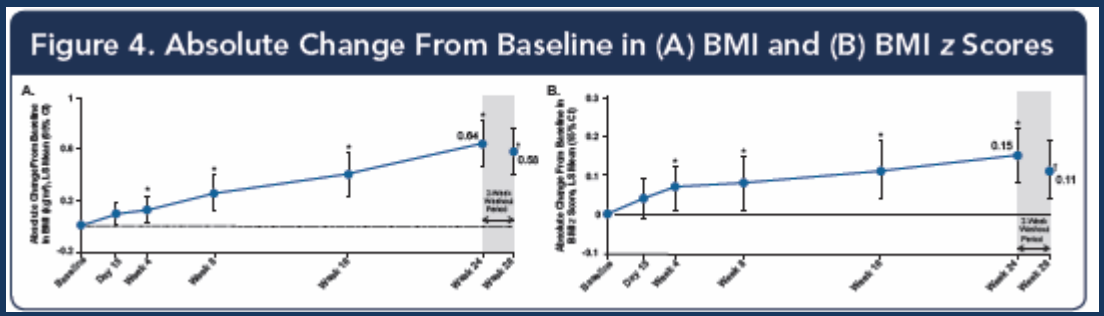
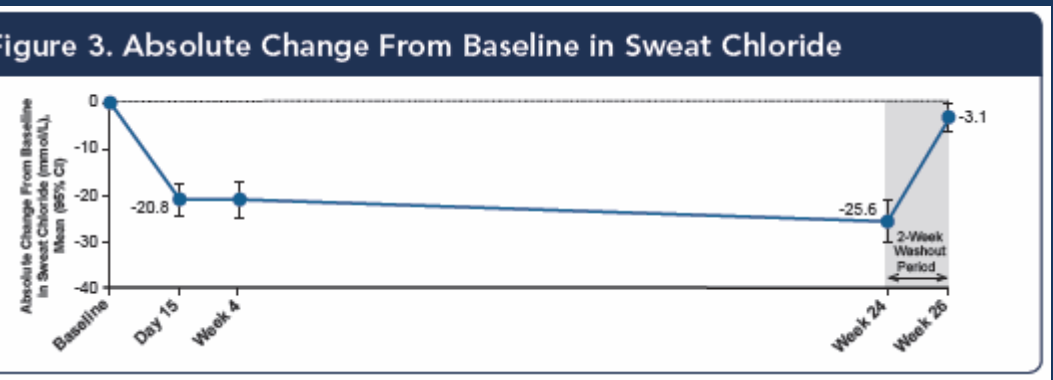


Figure 3. Absolute Change From Baseline in Sweat Chloride



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00187 Roma (Italia)
Tel.: +39 06 9779 4000
Fax: +39 06 9779 4029
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I risultati positivi di uno Studio di Fase 3 di ORKAMBI® in bambini con fibrosi cistica di età compresa tra 6 e 11 anni, portatori di due copie della mutazione F508del, supportano la richiesta di autorizzazione all'EMA (Agenzia Europea dei Medicinali) nella prima metà del 2017

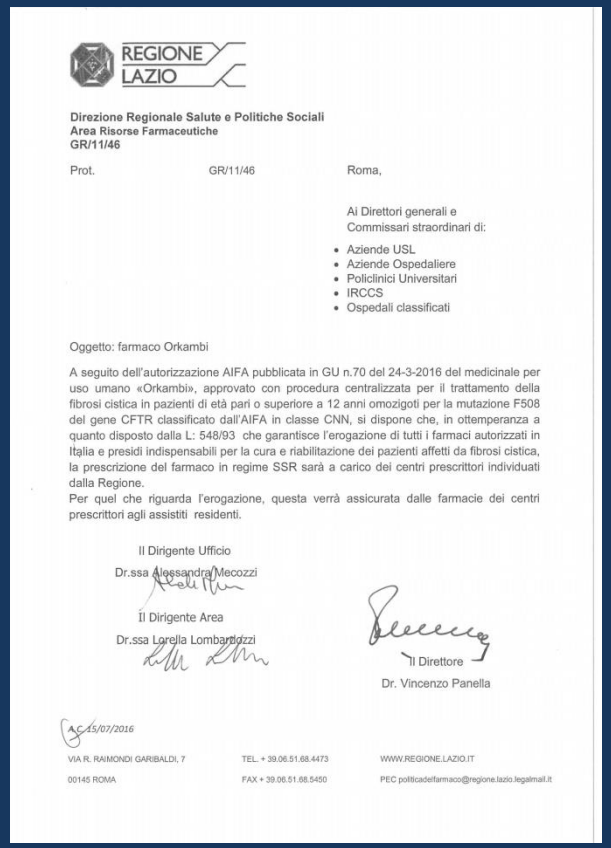
- Lo studio ha raggiunto l'endpoint primario con un miglioramento statisticamente significativo della variazione assoluta dell'indice di clearance polmonare ($LCI_{2,5}$) rispetto al placebo fino a 24 settimane di trattamento

- ORKAMBI è stato ben tollerato ed i dati relativi alla sicurezza sono risultati simili ai dati del precedente studio di sicurezza in aperto di Fase 3

- In Europa circa 3.400 bambini di età compresa tra 6 e 11 anni sono portatori di due copie della mutazione F508del

ORKAMBI (pazienti F508del OMOZIGOTI)

- In corso programma «uso compassionevole» per circa 170 pazienti; l'uso compassionevole non si interrompe finché il farmaco non sarà approvato per la rimborsabilità
- Per i pazienti dai 12 anni di età in su il farmaco è approvato in classe Cnn



REGIONE LAZIO

Direzione Regionale Salute e Politiche Sociali
Area Risorse Farmaceutiche
GR/11/46

Prot. GR/11/46 Roma,

Ai Direttori generali e
Commissari straordinari di:

- Aziende USL
- Aziende Ospedaliere
- Policlinici Universitari
- IRCCS
- Ospedali classificati

Oggetto: farmaco Orkambi

A seguito dell'autorizzazione AIFA pubblicata in GU n.70 del 24-3-2016 del medicinale per uso umano «Orkambi», approvato con procedura centralizzata per il trattamento della fibrosi cistica in pazienti di età pari o superiore a 12 anni omozigoti per la mutazione F508 del gene CFTR classificato dall'AIFA in classe CNN, si dispone che, in ottemperanza a quanto disposto dalla L: 548/93 che garantisce l'erogazione di tutti i farmaci autorizzati in Italia e presidi indispensabili per la cura e riabilitazione dei pazienti affetti da fibrosi cistica, la prescrizione del farmaco in regime SSR sarà a carico dei centri prescrittori individuati dalla Regione.
Per quel che riguarda l'erogazione, questa verrà assicurata dalle farmacie dei centri prescrittori agli assistiti residenti.

Il Dirigente Ufficio
Dr.ssa Alessandra Mecozzi

Il Dirigente Area
Dr.ssa Lorella Lombardozzi

Il Direttore
Dr. Vincenzo Panella

AC 15/07/2016

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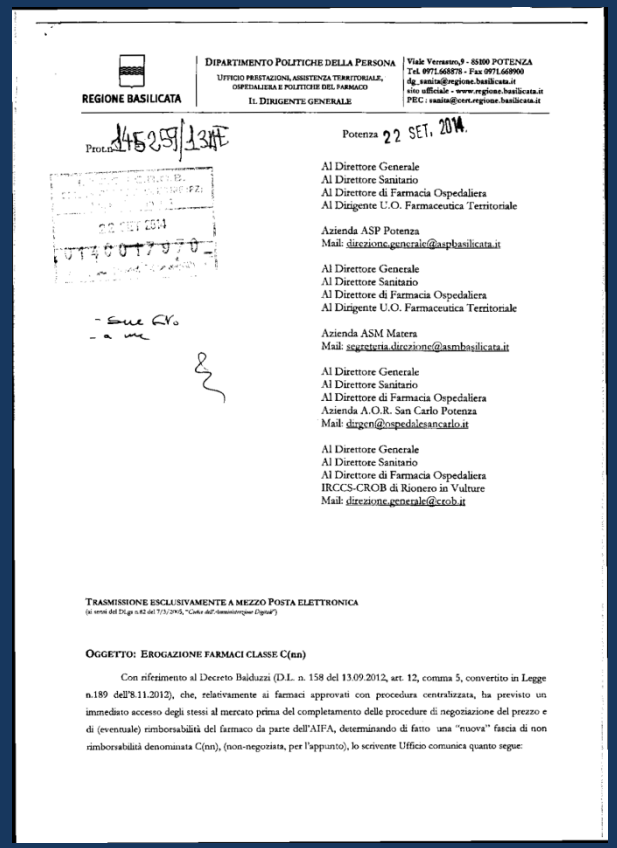
00145 ROMA FAX + 39.06.51.68.5450 PEC politicadelfarmaco@regione.lazio.legalmail.it



REGIONE BASILICATA

DIPARTIMENTO POLITICHE DELLA PERSONA
UFFICIO PRESTAZIONI, ASSISTENZA TERRITORIALE, OSPEDALIERA E POLITICHE DEL FARMACO
IL DIRIGENTE GENERALE

Viale Verrastro,9 - 85100 POTENZA
Tel. 0971.668878 - Fax 0971.668900
dg_sanita@regione.basilicata.it
sito ufficiale - www.regione.basilicata.it
PEC : sanita@cert.regione.basilicata.it

Prot. 145259/13AE

Potenza 22 SET. 2014

Al Direttore Generale
Al Direttore Sanitario
Al Direttore di Farmacia Ospedaliera
Al Dirigente U.O. Farmaceutica Territoriale

Azienda ASP Potenza
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Al Direttore Generale
Al Direttore Sanitario
Al Direttore di Farmacia Ospedaliera
Al Dirigente U.O. Farmaceutica Territoriale

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Al Direttore Sanitario
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Al Direttore Generale
Al Direttore Sanitario
Al Direttore di Farmacia Ospedaliera
IRCCS-CROB di Rionero in Vulture
Mail: direzione.generale@crob.it

TRASMISSIONE ESCLUSIVAMENTE A MEZZO POSTA ELETTRONICA

OGGETTO: EROGAZIONE FARMACI CLASSE C(nn)

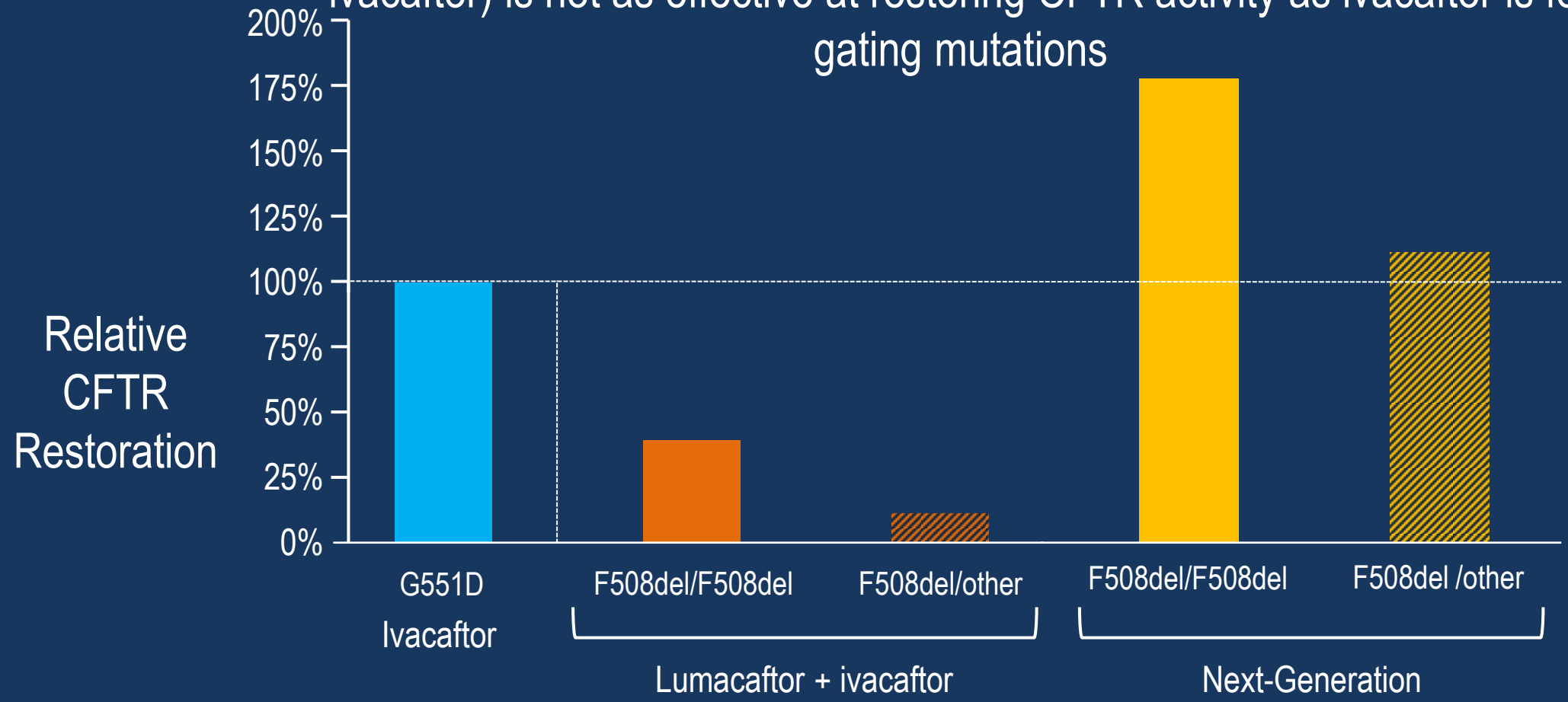
Con riferimento al Decreto Balduzzi (D.L. n. 158 del 13.09.2012, art. 12, comma 5, convertito in Legge n.189 dell'8.11.2012), che, relativamente ai farmaci approvati con procedura centralizzata, ha previsto un immediato accesso degli stessi al mercato prima del completamento delle procedure di negoziazione del prezzo e di (eventuale) rimborsabilità del farmaco da parte dell'AIFA, determinando di fatto una "nuova" fascia di non rimborsabilità denominata C(nn), (non-negoziata, per l'appunto), lo scrivente Ufficio comunica quanto segue:

Basilicata - Circolare regionale 22.09.2014
Erogazione farmaci classe C (nn)
Con riferimento al Decreto Balduzzi (D.L. n. 158 dd 13.09.201.2., art. 12, comma 5, convertito in Legge n.189 dell'8.11.2012), che, relativamente ai farmaci approvati eon procedura centralizzata, ha previsto un immediato accesto degli stessi al mercato prima del completamento delle procedure di negozlazione del prezzo e di (eventuale) rimborsabilità del farmaco da parte dell'AIFA, determinando di fatto una "nuova" fascia di non rimborsabilità denomita C (nn} (non-negoziata, per l'appumto), lo scrivente Ufficio comunica quanto segue:
- Nelle more di quanto verrà stabilito dall'AIFA, la dispensazione dci farmaci C(nn) deve essere valutata caso per caso, esclusivamente in presenza di apposita e chiara relazione del medico specialista prescrittore, supportata da idonea documentazione scientifica, opportunamente validata dal Direttore Sanitario della Azienda Sanitaria
e/o Ospedale di cura di concerto con il Direttore Sanitario della Azienda Sanitaria territorialmente competente, e da cui si evinca, tra l'altro, l'indispensabilità del trattamento terapeutico e ehe per tali i farmaci non vi è alcuna alternativa. La presente disposizione vale per i residenti della Regione Basilicata Si invia le SS..LL. in indirizzo a dare ampia e tempestiva comunicazione a tutti soggetti interessati.

Emerging (next-generation) F508del corrector molecules

Next-generation F508del correctors promise to be more effective

Today, the available corrector for F508del variants (lumacaftor + ivacaftor) is not as effective at restoring CFTR activity as ivacaftor is for gating mutations



Emerging (next-generation) F508del corrector molecules

Figure 2. VX-152 and VX-440 Increase Chloride Transport and Augment the Response to Tezacaftor/Ivacaftor

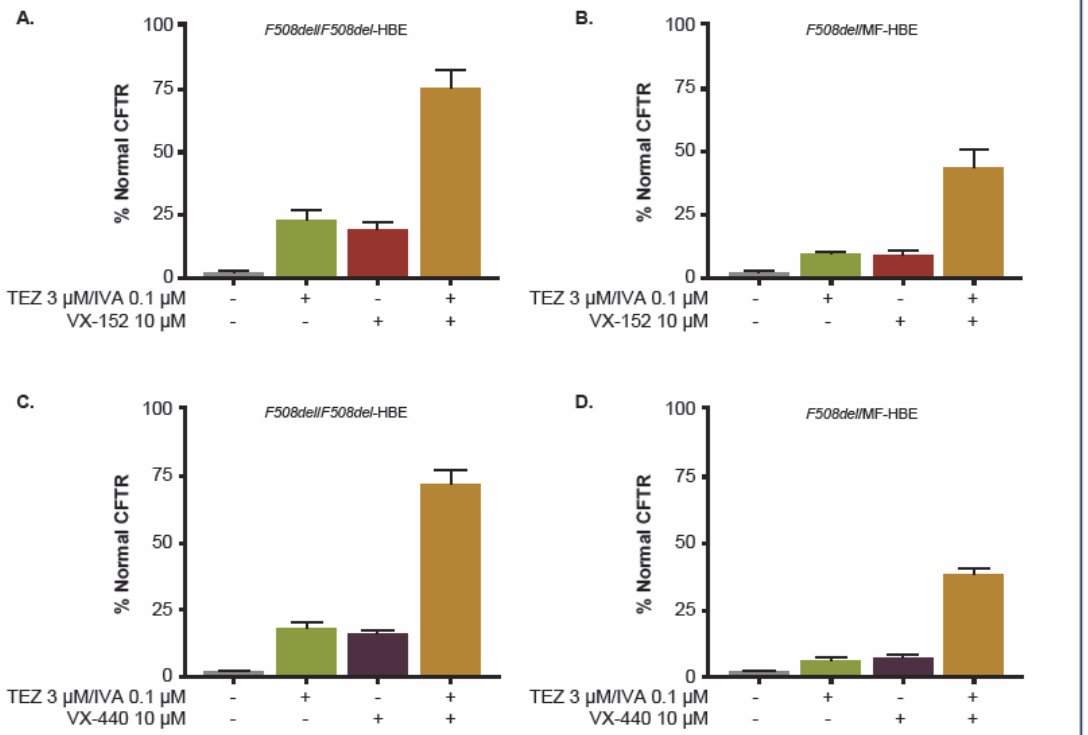
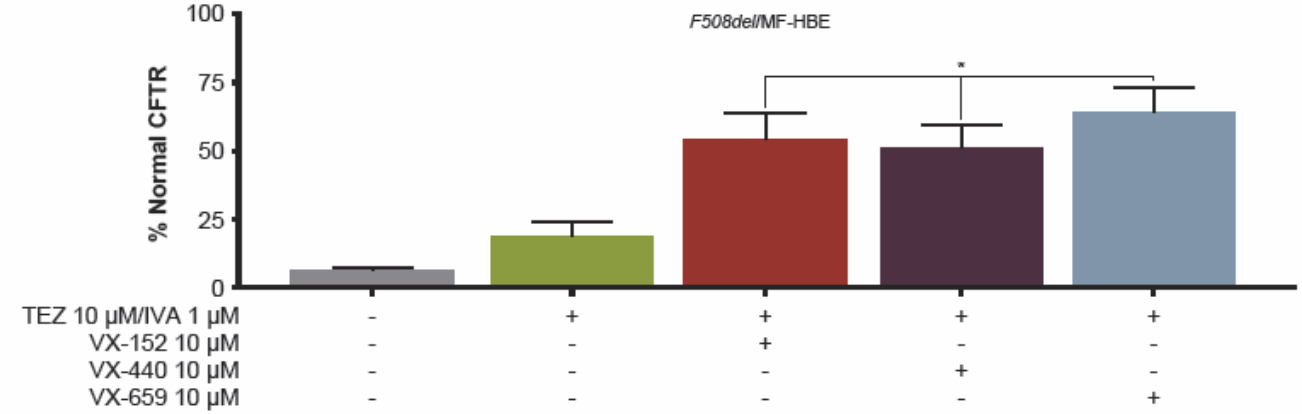


Figure 4. VX-659 Is a Next-Generation CFTR Corrector That Is More Efficacious Than VX-152 or VX-440 as a Triple Combination With Tezacaftor/Ivacaftor



CONCLUSIONS

- VX-152, VX-440, and VX-659 are next-generation correctors that could form part of a triple combination with TEZ/IVA
  - VX-152 and VX-440 are progressing to Phase 2 clinical studies
  - VX-659 is next-generation corrector entering Phase 1 clinical studies

Modulator pipeline is diversified and very robust

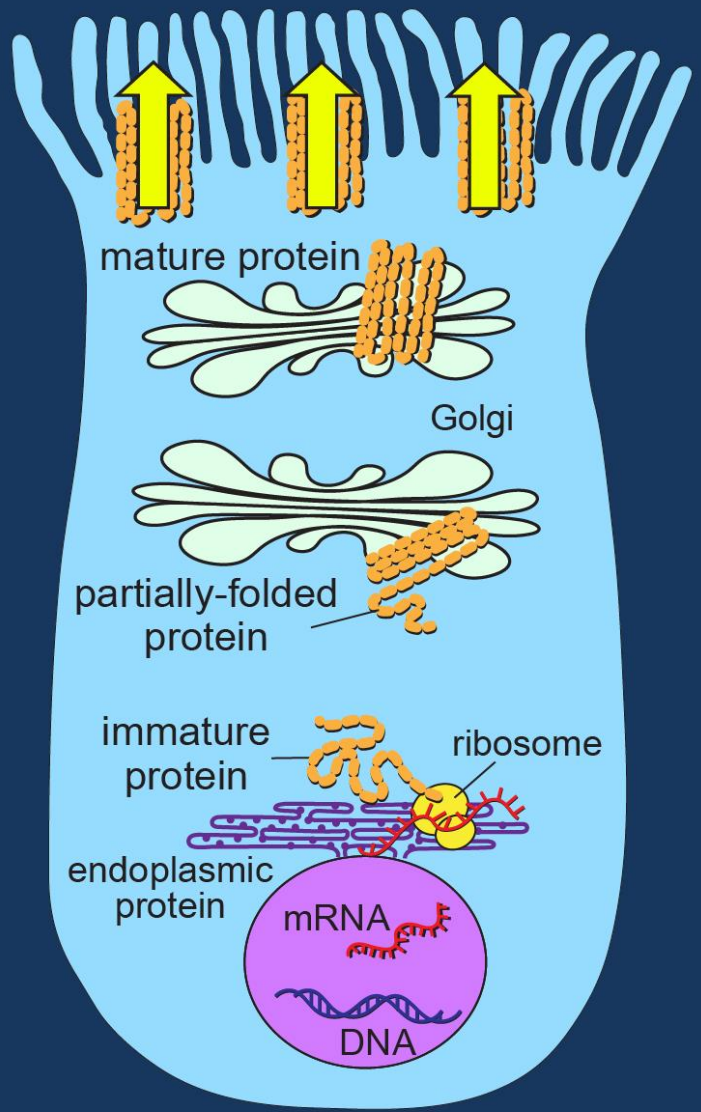
Sponsor	Drug Name	Class	R&D Stage
Genzyme		2nd gen corrector	Discovery
Reata		2nd gen corrector	Discovery
Parion		2nd gen corrector	Discovery
Flatley	FDL176	potentiator	Pre-Clinical
Pfizer		potentiator	Pre-clinical
Pfizer		corrector	Pre-clinical
Proteostasis	PTI-428	amplifier	Ph 1
Galapagos-Abbvie	GLPG2451	potentiator	Ph 1
Galapagos-Abbvie	GLPG2222	corrector	Ph 1
Galapagos-Abbvie	GLPG2665	corrector	Ph 1
Novartis	QBW267 corrector	potentiator	Ph 1
Concert Pharma	CTP-656	potentiator	Ph 2
Bayer	BAY 63-2521	corrector	Ph 2
Flatley	FDL169	1st gen corrector	Ph 2
Nivalis	N91115	GSNOR inhibitor	Ph 2
Vertex	VX-152	2nd gen corrector	Ph 2
Galapagos-Abbvie	GLPG1837	corrector	Ph 2
Vertex	VX-440	2nd gen corrector	Ph 2
Vertex	VX-661	1st gen corrector	Ph 3
Vertex	ivacaftor (VX-770)	potentiator	Available to Patients
Vertex	lumacaftor (VX-809)	1st gen corrector	Available to Patients

Approaches to increasing CFTR activity

ivacaftor

lumacaftor

ataluren



Increase the opening time of CFTR protein resulting in greater ion flow

- Potentiators

Prolong presence of CFTR protein

- GSNOR inhibitors

Facilitate processing and trafficking of CFTR protein

- Correctors
- Next-generation correctors

Increase the amount of immature CFTR protein

- Gene therapy
- DNA editing
- mRNA editing
- Read-through premature stop codons
- Amplifiers (increased translation)

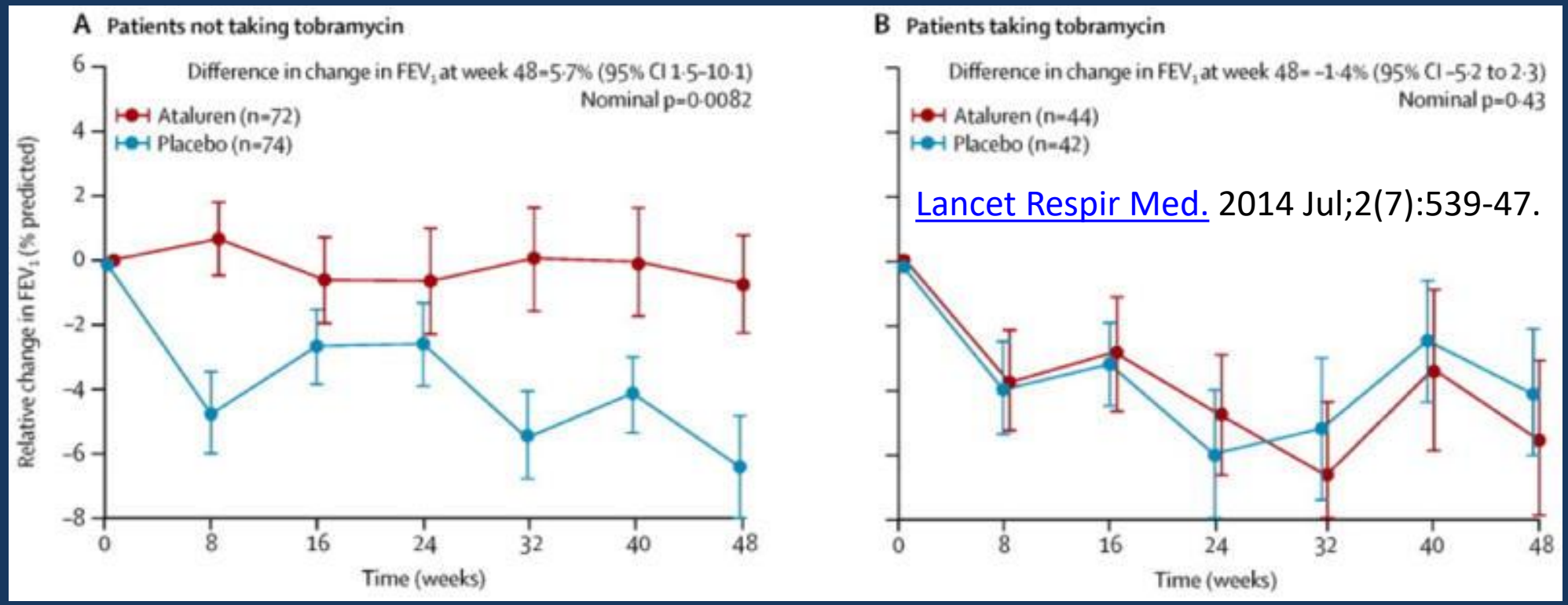
Figure adapted from Po-Shun Lee (Proteostasis)

Several programs specifically targeting premature truncation or “X” mutations

Developing drugs that read through the nonsense mutation to generate functional CFTR protein

- PTC Therapeutics - Ataluren - Primarily a read-through agent
  - Initial trial indicated interference with tobramycin
  - Second trial now concluding, data expected early 2017
- Southern Research Institute/University of Alabama, Birmingham
  - Pilot program 2014 identified several promising compounds
  - Initiated new high throughput screening program in 2015
- CFFT laboratory (Lexington, MA)
  - Major expansion in 2015 to accommodate new initiatives
  - Nonsense mutations, gene editing, stem cell biology are priorities
  - Approximately 50% of effort is directed towards X-variant therapy
- Numerous other pharmaceutical and academic groups

Ataluren (per le mutazioni che terminano in X)



Lancet Respir Med. 2014 Jul;2(7):539-47.

Results Patients not receiving chronic inhaled tobramycin (non-TOBI; n=146), showed:

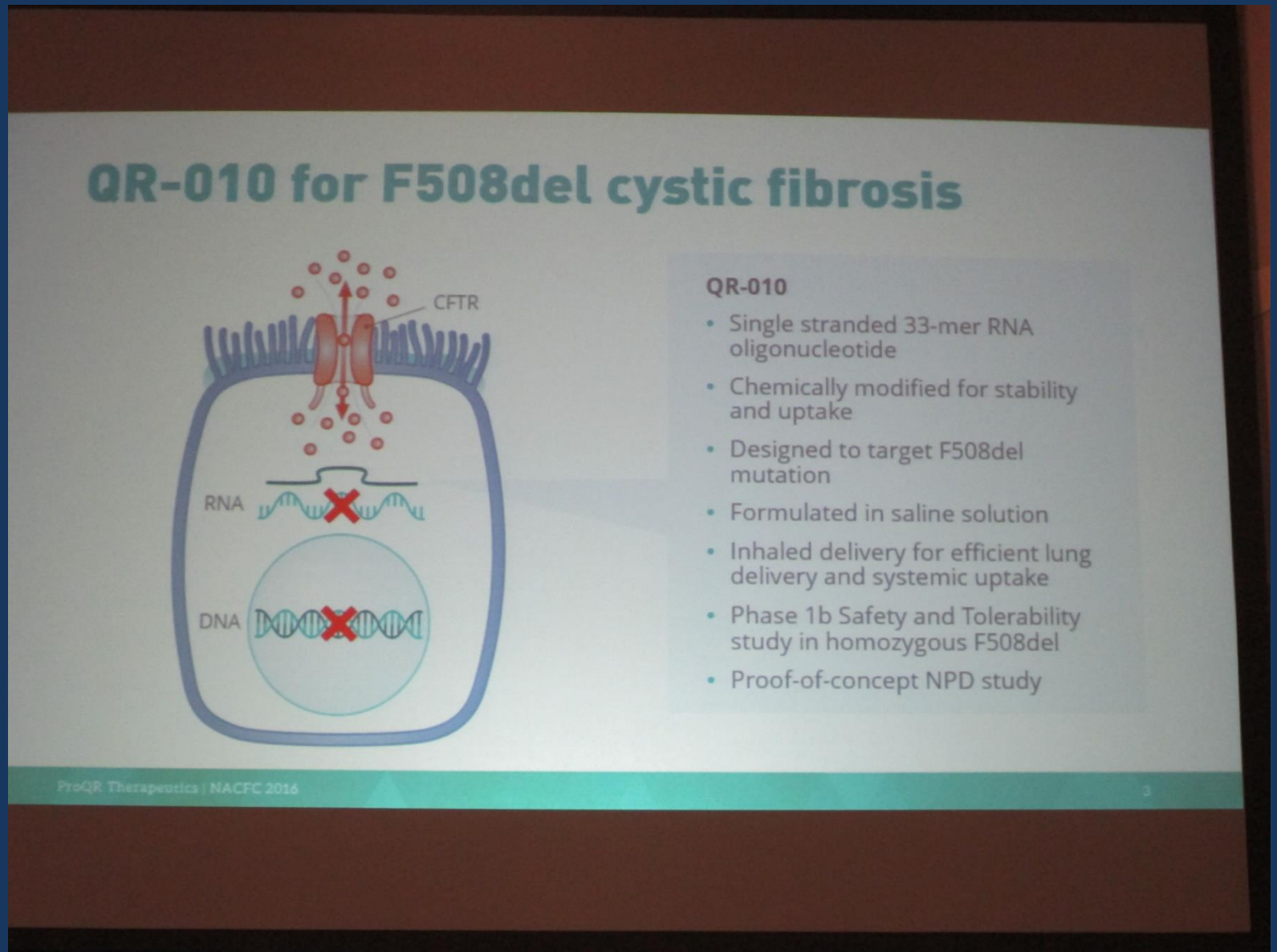
- a 5.7% difference in relative ppFEV$_1$ between ataluren and placebo (−0.7% vs −6.4%; p=0.0082)
- 40% fewer exacerbations (1.42 vs 2.18; p=0.0061).

Non-TOBI patients ≥6 to <18 years old (n=42) showed:

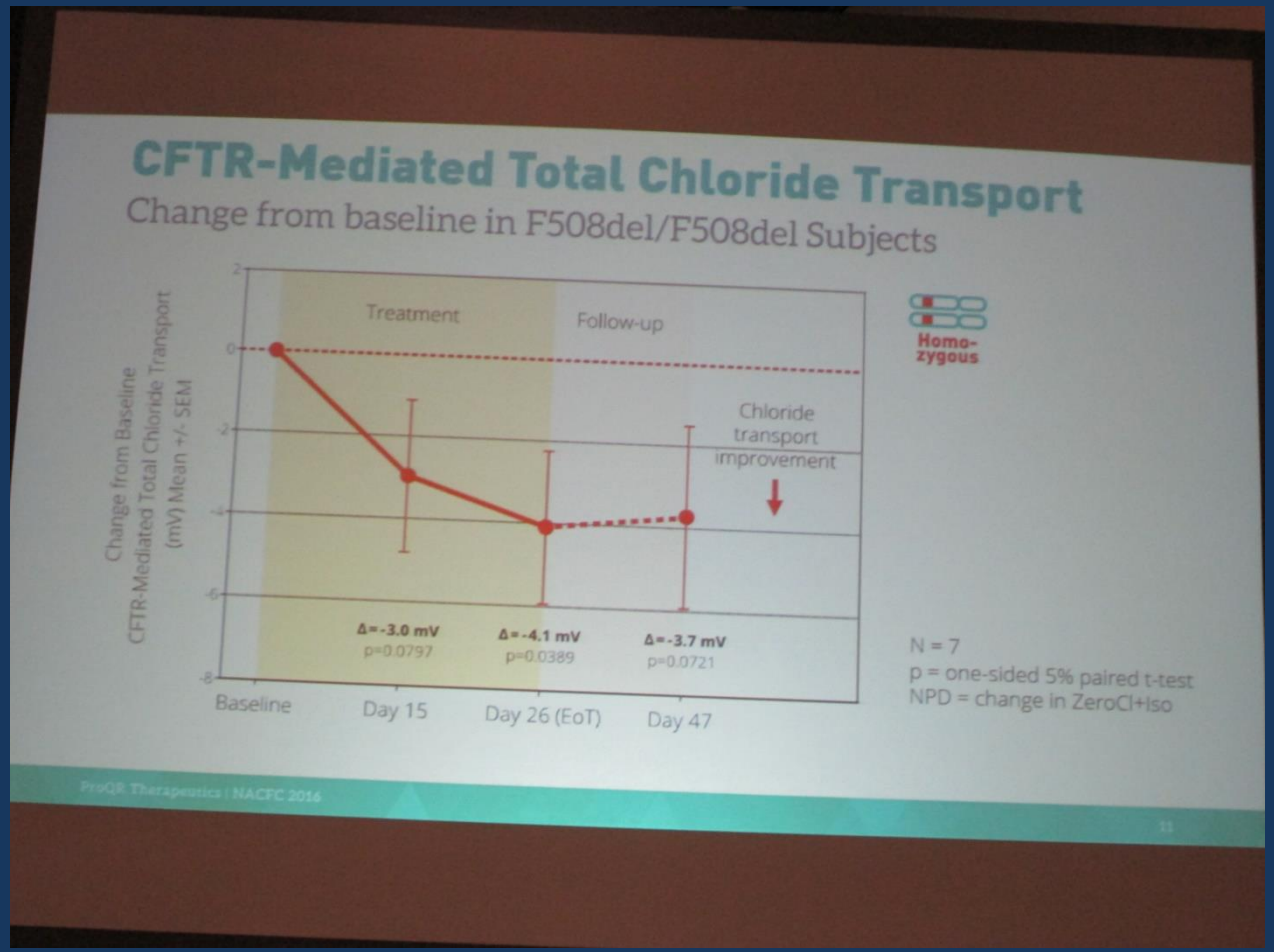
- an 8.2% difference in relative ppFEV$_1$ between ataluren and placebo (4.9% vs −3.3%; p=0.026)
- 60% lower exacerbation rate favoring ataluren (p=0.030).

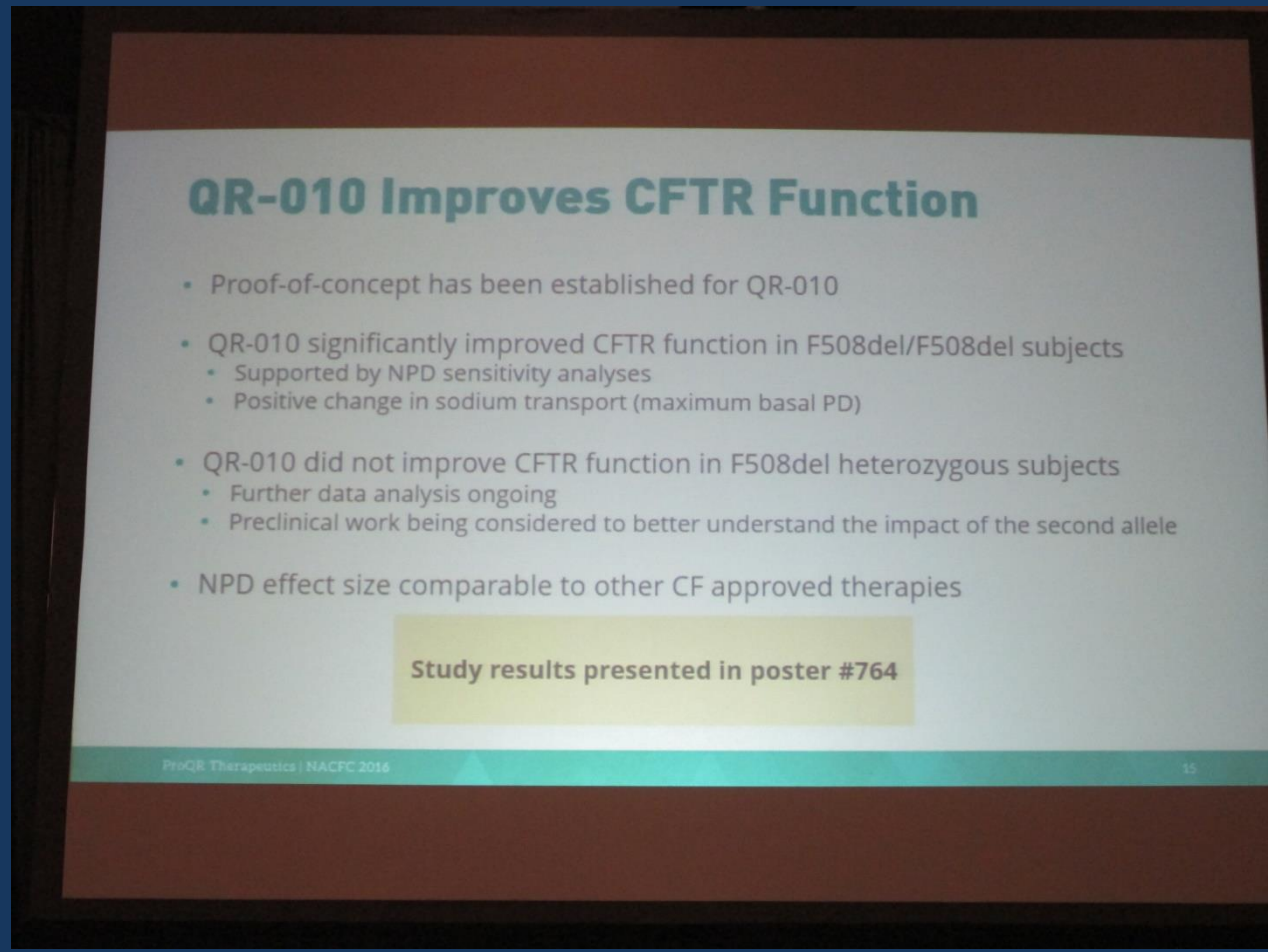
European Respiratory Journal 48(suppl 60):PA4869 · September 2016

QR-010 (mRNA editing)



QR-010 (mRNA editing)





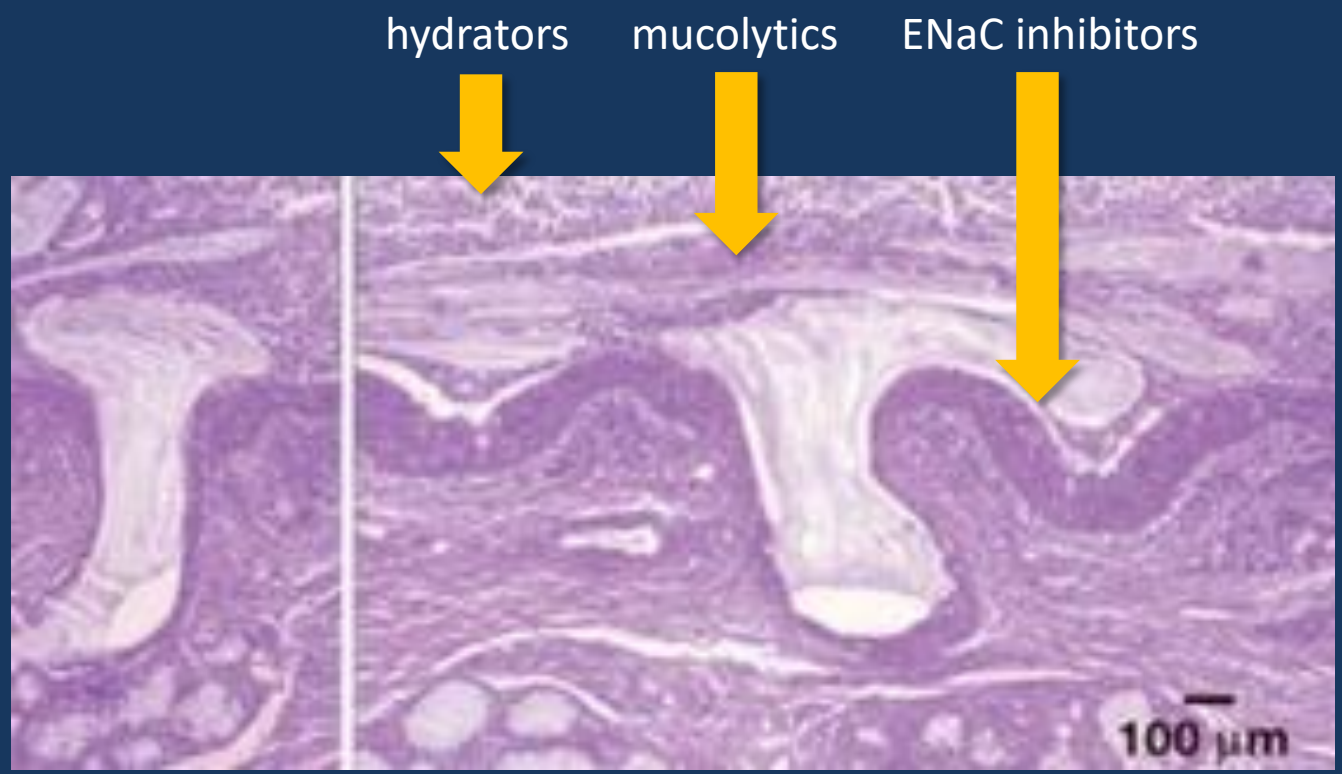
Mucociliary Clearance- and Airway Surface Liquid-focused programs
A Robust Pipeline with Available Agents
and New Compounds under Clinical Development

<u>Clinical</u>

- Hypertonic saline – available to patients
- Pulmozyme – available to patients
- Algipharma (OligoG) – Phase 2
- Novartis (ENaC inhibition) – Phase 2
- Parion/Vertex (VX-371) – Phase 2
- Pharmaxis (mannitol) – Phase 3
- Protalix (DNase) – Phase 1
- Spyryx (SPX-101) – Phase 1

<u>Preclinical</u>

- University of Iowa (THAM)
- Ionis (ENaC inhibition)
- OrPro (recombinant thioredoxin)
- Silurian (brevenal)
- Synedgen (SYGN113)



ENaC inhibition

Figure 1. The Epithelial Sodium Channel Promotes Flow of Sodium Ions and Water Out of the Airway

Without CF

Normal CFTR function ➡

Suppressed Na^+ ion flow into cells via ENaC ➡

Maintenance of normal airway water levels ➡

Normal airway hydration

With CF

Abnormal CFTR function ➡

Enhanced Na^+ ion flow into cells via ENaC ➡

Increased osmotic loss of water from airway ➡

Thick mucus, decreased mucociliary clearance ➡

Exacerbations; progressive loss of lung function

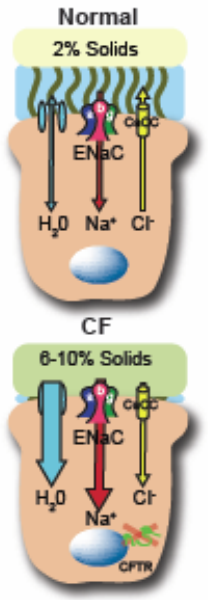


Figure 2. Effect of VX-371 With or Without Lumacaftor/Ivacaftor on Airway Surface Liquid Height in *F508del/F508del* Human Bronchial Epithelial Cells

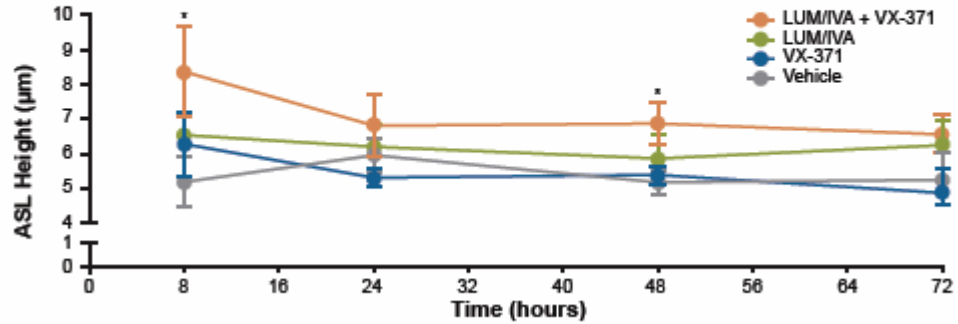
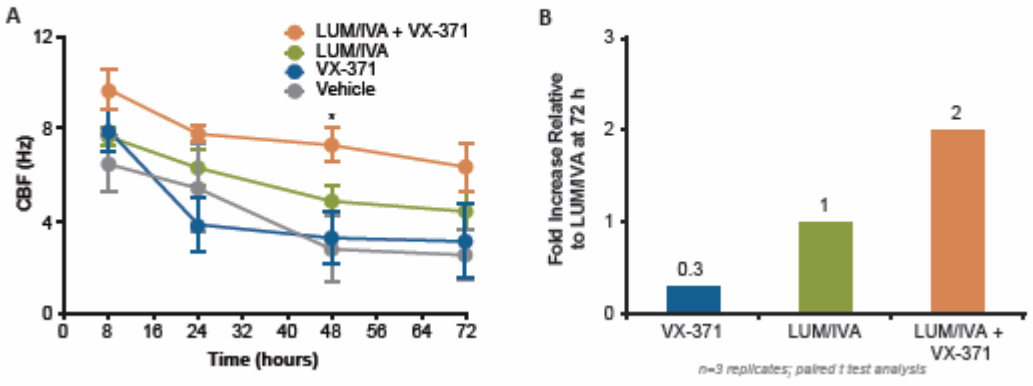


Figure 4. Effect of VX-371 With or Without Lumacaftor/Ivacaftor on Ciliary Beat Frequency in *F508del/F508del* Human Bronchial Epithelial Cells



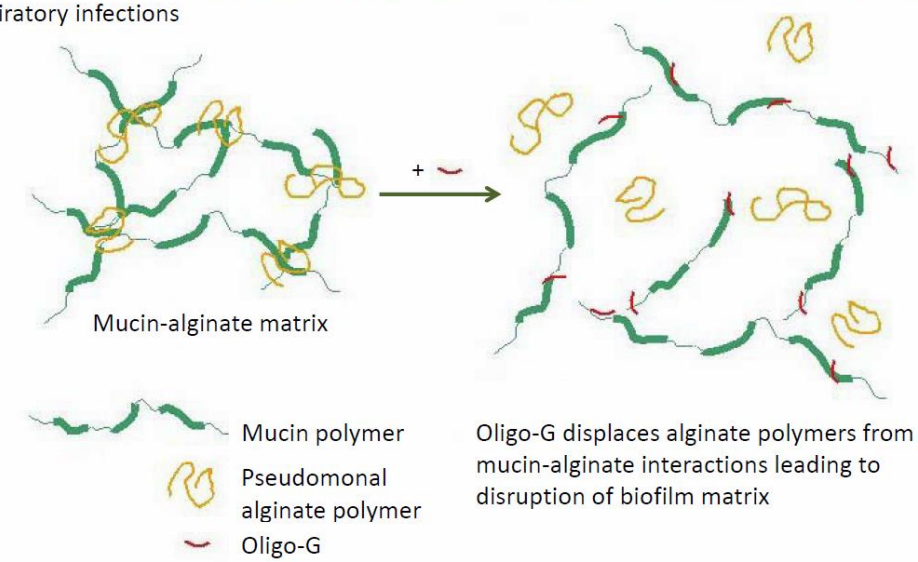
Algipharma (OligoG) – Phase 2

AlgiPharma

Oligo-G

Putative mechanism of action

Oligo-G effect on mucin pseudomonal alginate networks typically found in *Pseudomonas spp* respiratory infections

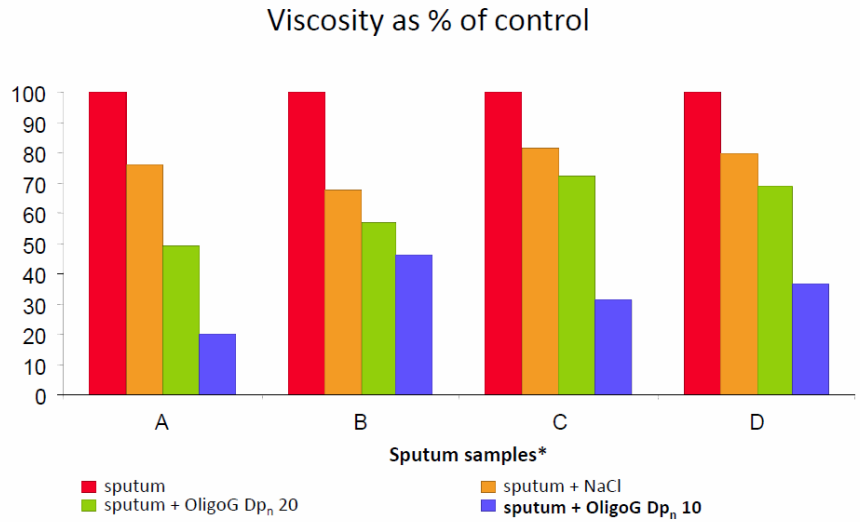


Oligo-G displaces alginate polymers from mucin-alginate interactions leading to disruption of biofilm matrix

AlgiPharma

Mucolytic properties

Reduction in viscosity of CF sputum



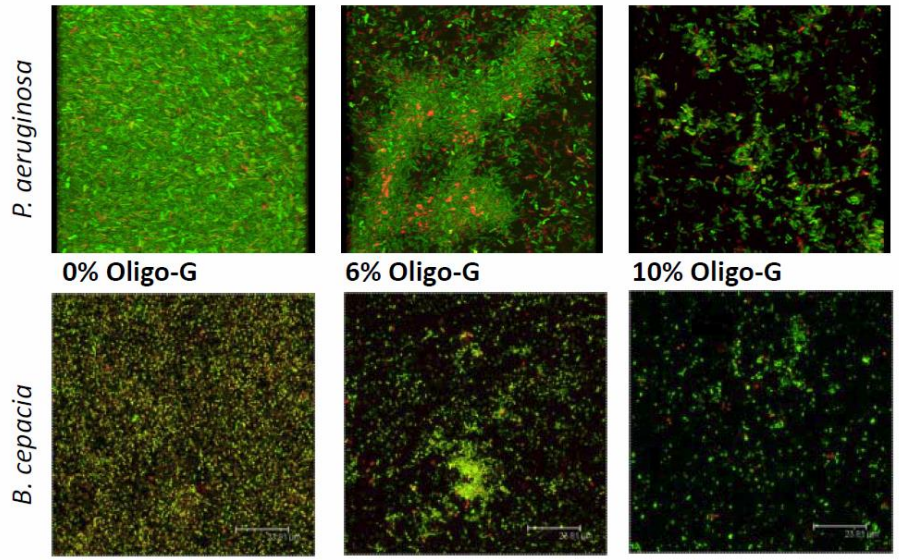
*CF sputum samples were collected from four patients at St. Olav's Hospital, Trondheim, Norway in 2005.

Algipharma (OligoG) – Phase 2

AlgiPharma

Biofilm disruption

Increasing concentration of Oligo-G disrupts biofilms

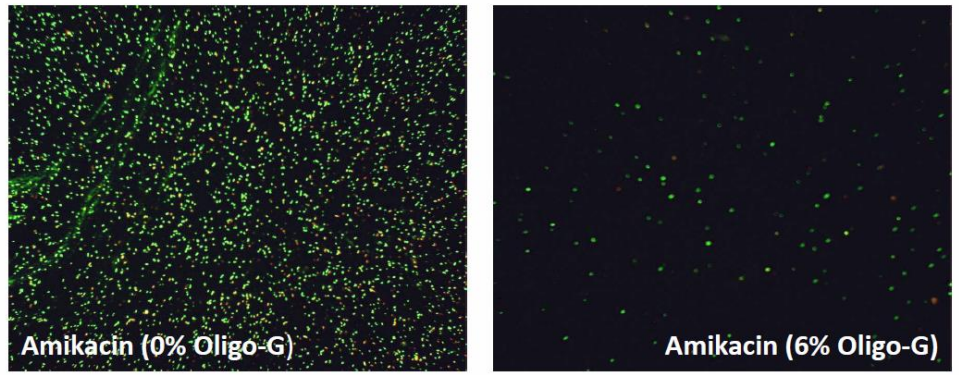


Confocal Laser Scanning Microscopy (CLSM) of *Pseudomonas spp* and *Burkholderia spp* biofilms (24h) in the presence of 0%, 6% or 10% Oligo-G

AlgiPharma

Antibiotic Potentiation

Oligo-G potentiates antibiotic activity in *Pseudomonas* biofilms



MBEC assay showing live stained (green) *Pseudomonas aeruginosa* treated with 1024 µg/ml Amikacin, with and without Oligo-G

Expanding the CF antimicrobial armamentarium

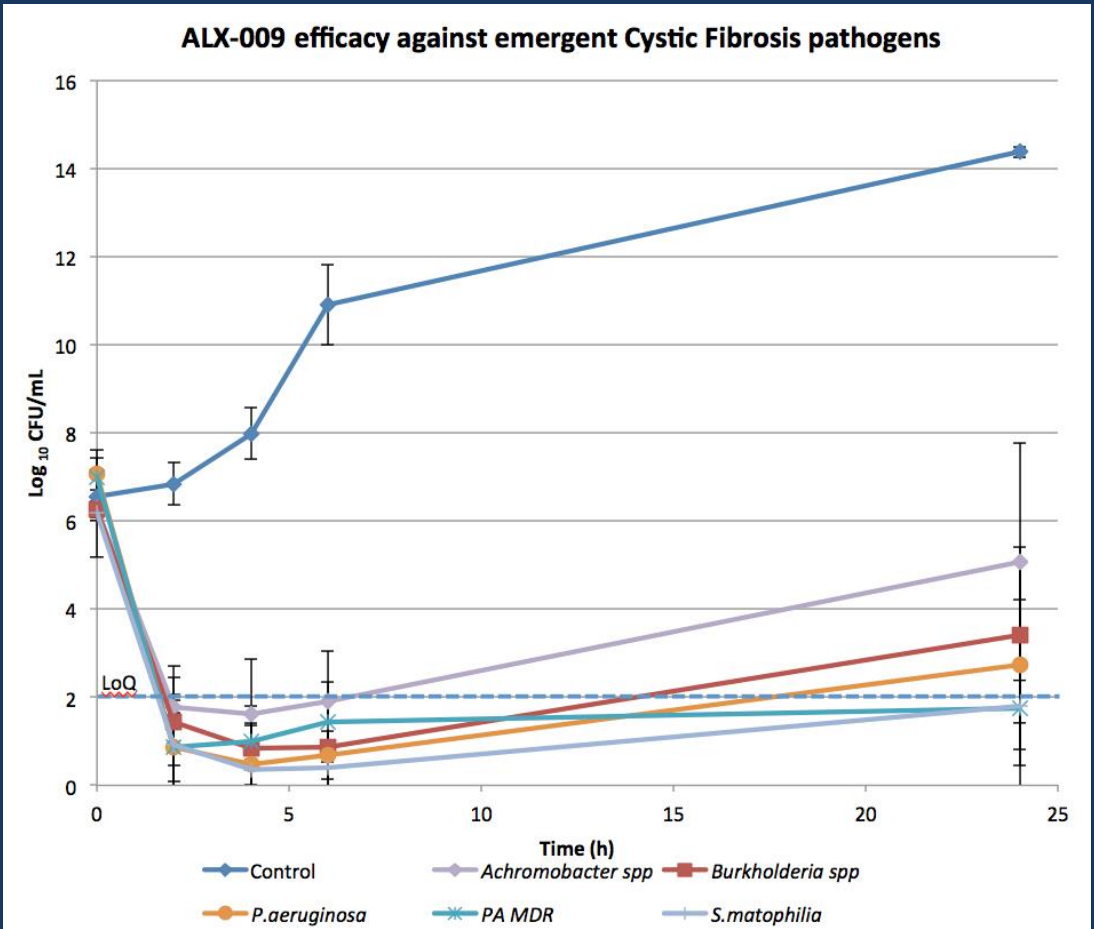
- Additional inhaled antimicrobials
  - Inhaled fosfomycin/tobramycin (FTI) inhalation solution
    - Preparing for Phase 3 (CURx)
  - Dry-powder vancomycin for chronic MRSA
    - Preparing for Phase 3 (Savara)
  - Inhaled levofloxacin (approved in Canada and EU)
    - Preparing NDA (Raptor)
  - Alaxia (nebulized $OSCN^-$/lactoferrin)
    - For *Burkholderia* spp. Eradication (Alaxia)

- Systemic antimicrobials
  - Gallium (IGNITE study)
    - Phase 2 IV trial is now enrolling

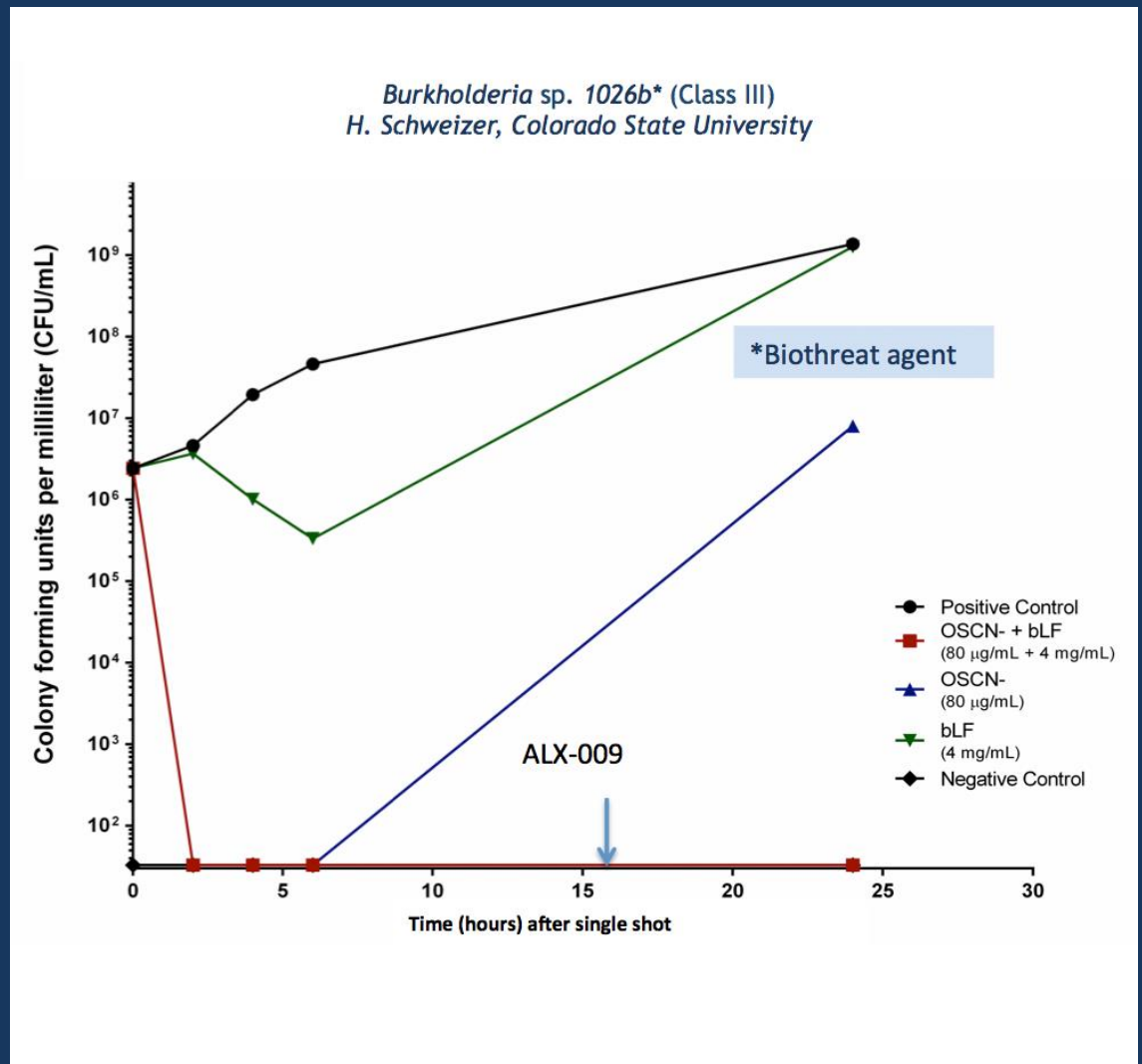
Also includes other programs targeting multi-drug resistant *Pseudomonas*, non-tuberculous mycobacteria, *B. cepacia* complex and MRSA.

ALX-009

ALX-009 is a first-in class orphan drug candidate for Cystic Fibrosis (CF) patients.
Esso consiste nella combinazione di due sostanze endogene, hypothiocyanite (OSCN-) e lattoferrina, dotate di proprietà antimicrobiche. ALX-009 si presenta come una soluzione per inalazione.

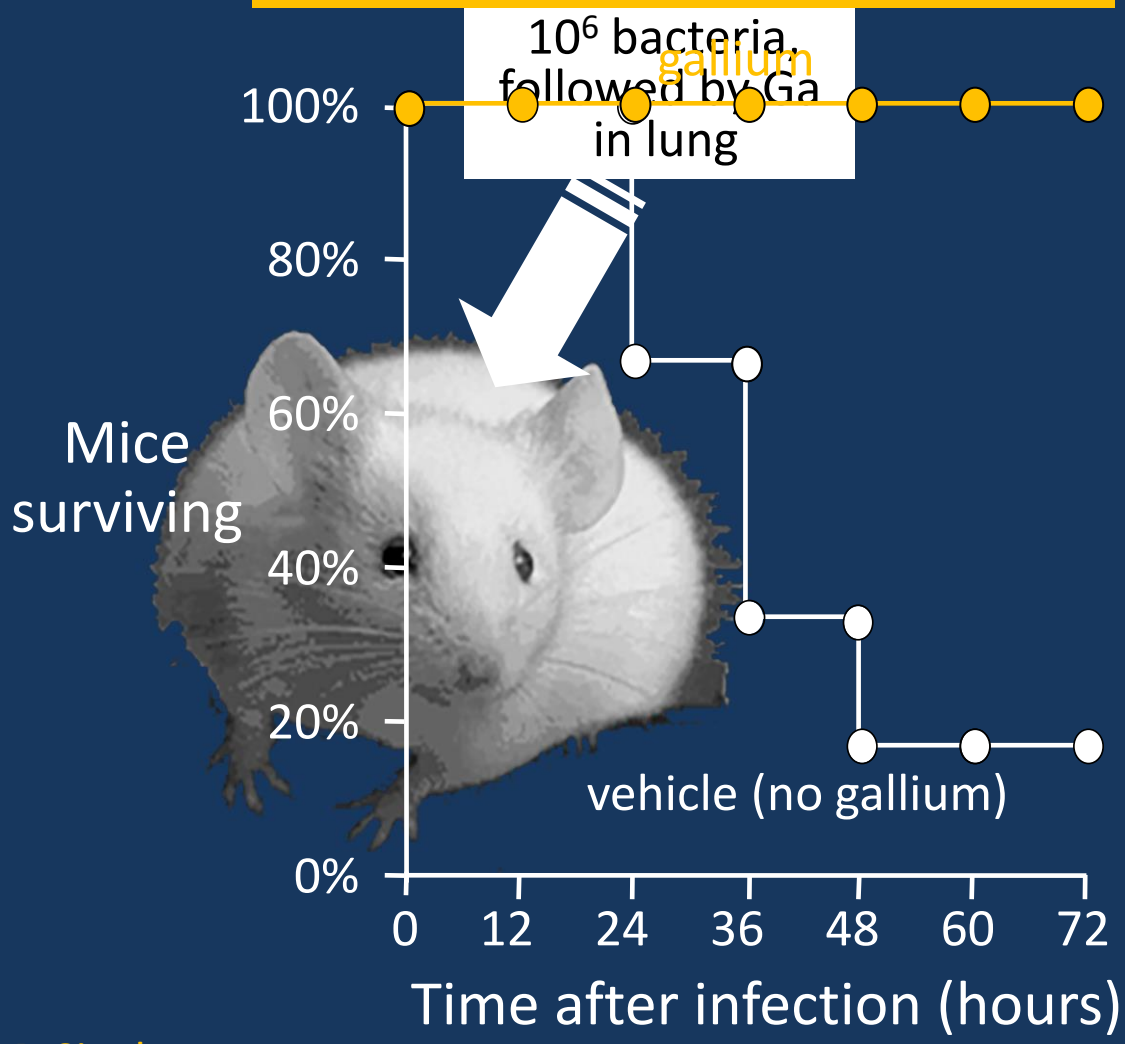


The results correspond to the compiled average values of nine *Burkholderia* spp, nine *Achromobacter* spp, nine *Pseudomonas aeruginosa*, two *Pseudomonas aeruginosa* MDR and nine *Stenotrophomonas maltophilia* clinical isolates. Each isolate was tested at least three times. Vertical bars show the standard variation for the group at the given time point. CFU: Colony Forming Unit. LoQ, Lower level of quantification

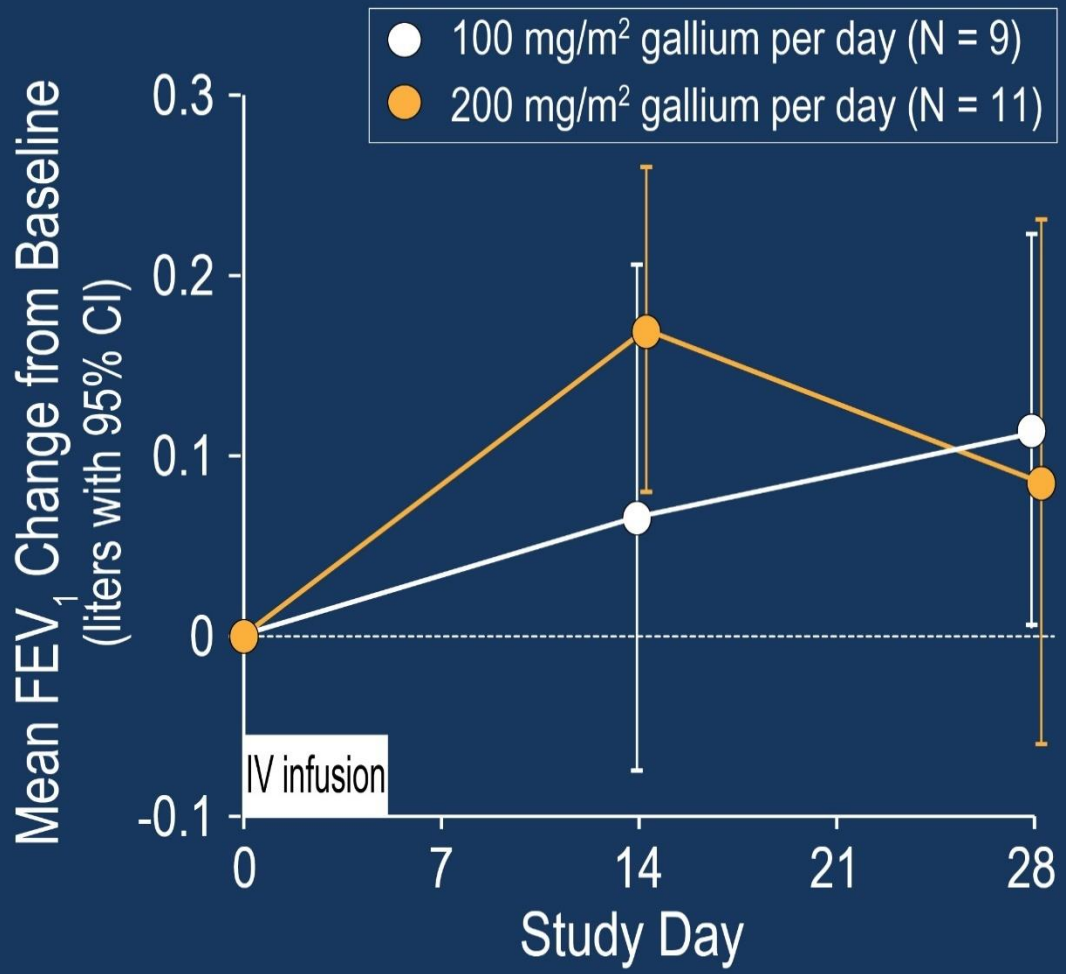


Gallium treatment of *P. aeruginosa* infection

Single dose IP Ga also prevented death, even given 12 h after infection



Ga was safe and showed an efficacy signal in CF patients



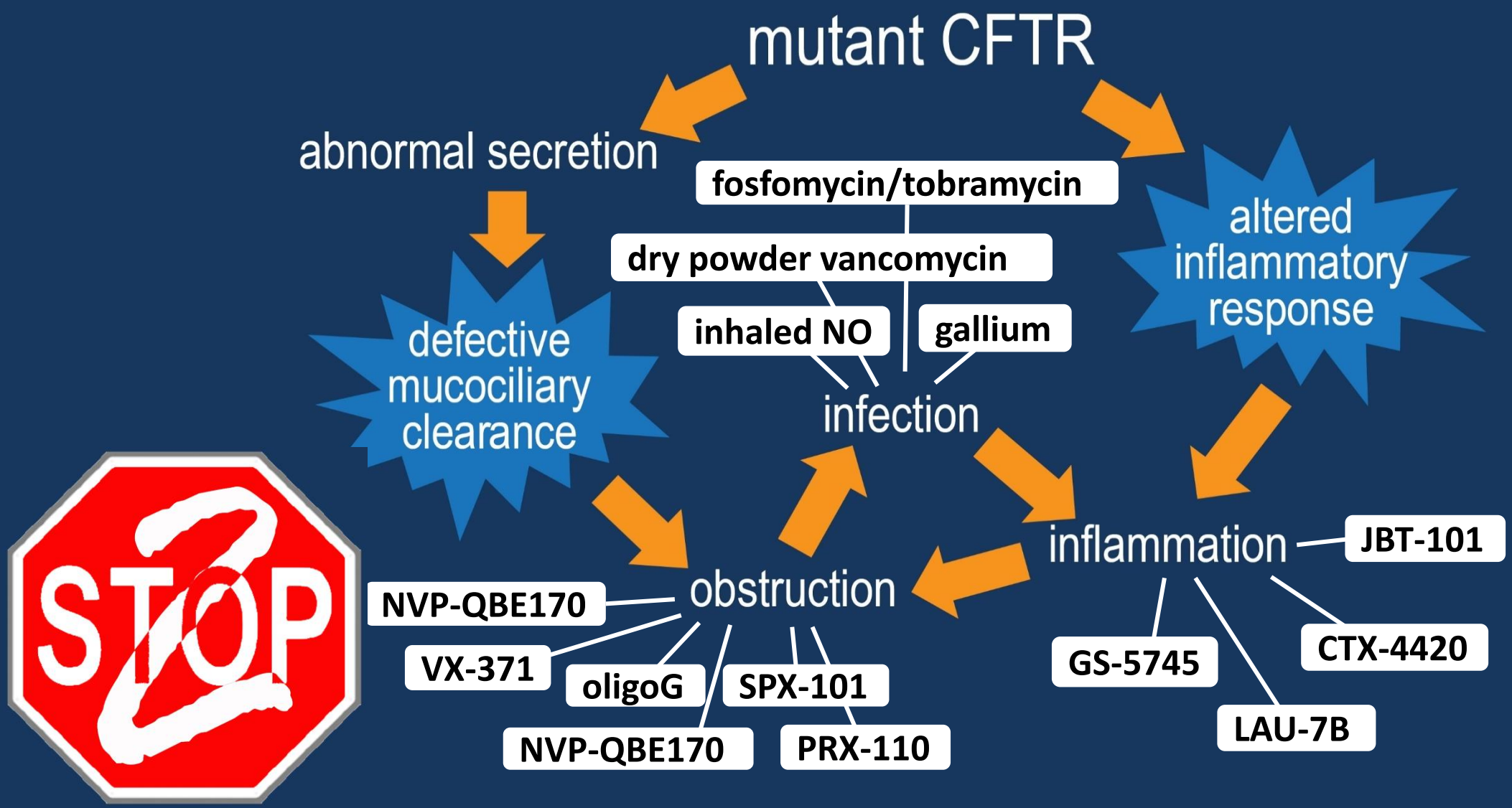
P. Singh

C. Goss, D. Hornick, N. Lechtzin, P. Singh

Emerging CF anti-inflammatory treatments

- Celtaxsys CTX-4430
  - Oral inhibitor of Leukotriene A4 Hydrolase (LTA4H)
  - Reduces neutrophil infiltration and neutrophil elastase
- Corbus JBT-101
  - Novel mechanism: cannabinoid type 2 receptor (CB2) agonist
  - Reduces pro-inflammatory mediators and induces anti-inflammatory cytokines
- Laurent LAU-7B
  - Oral corrector of AA/DHA imbalance
  - Reduces inflammatory fatty acid imbalance described for CF
- Gilead GS-5745
  - MMP-9 antibody
  - Binds pro-inflammatory mediator present in CF sputum and lung
- Polyphor POL-6014
  - Potent inhaled human neutrophil elastase (HNE) inhibitor

Don’t forget the downstream improvements as well

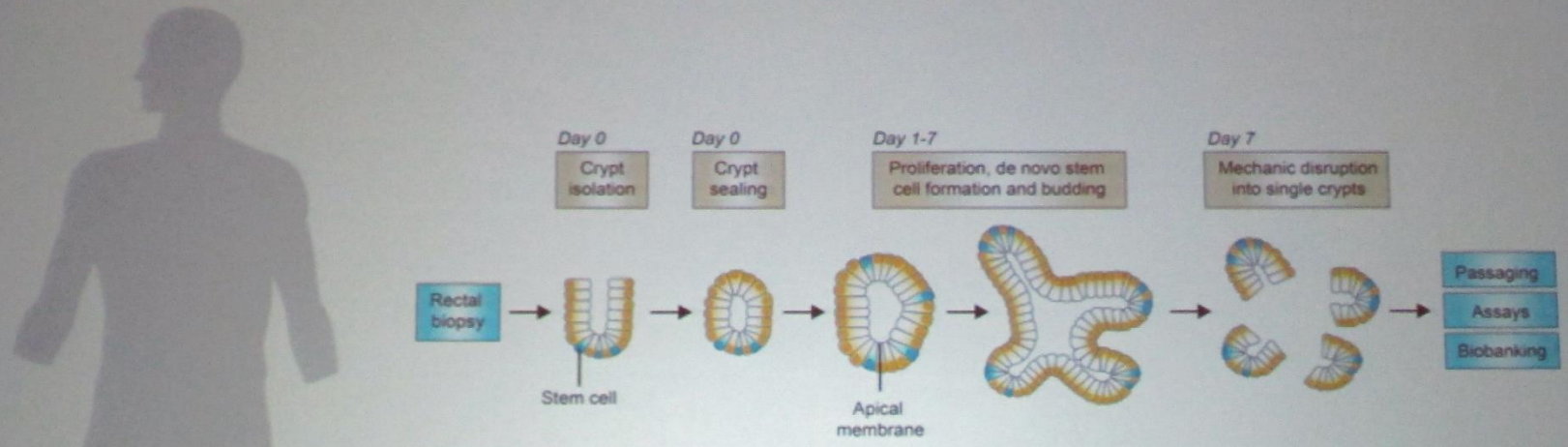


Gli organoidi

The organoid model

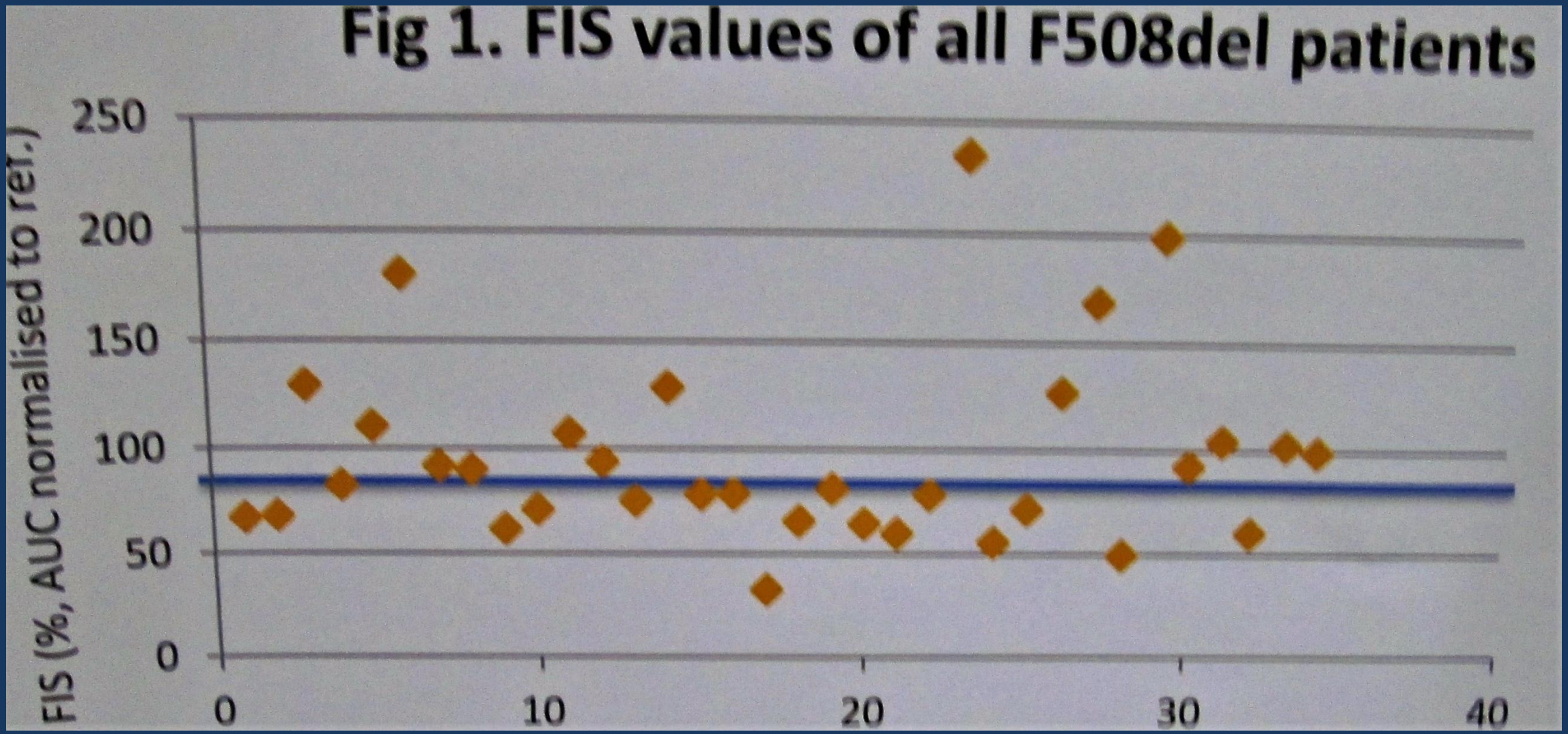
>2000 CFTR mutations

- Different phenotypes
- Different responses to therapy



Dekkers et al. Nature Medicine, 2013

Pazienti con le stesse mutazioni sono diversi fra loro



Genotype–phenotype correlation and functional studies in patients with cystic fibrosis bearing CFTR complex alleles

Vito Terlizzi,[1] Giuseppe Castaldo,[2,3] Donatello Salvatore,[4] Marco Lucarelli,[5] Valeria Raia,[6] Adriano Angioni,[7] Vincenzo Carnovale,[8] Natalia Cirilli,[9]

Genotype-phenotype correlations

Figure 1: Cystic fibrosis transmembrane conductance regulator (CFTR) gating activity measured on epithelial nasal cells in several groups of subjects. The values obtained for each sample and the groups are reported in table 2.