מרכז שניידר לרפואת ילדים בישראל
مركز شنايدر لطب الأطفال في اسرائيل
Schneider Children's Medical Center of Israel

CLALIT 100 over years
The Best For Your Family

Israel CF conference, Caesaria, October, 2017

Cystic Fibrosis: Current and long term safety data with innovative and future treatments

Hannah Blau, MBBS

Schneider Children's Medical Center of Israel

Disclosures

- I am a member of the Cystic Fibrosis Foundation Therapeutics Data and Safety Monitoring Board participating in Data Monitoring Committees for several Vertex trials

- I have not further disclosures

New CFTR modulating therapies

- Exciting
- “almost a cure”
- Address an unmet need
- Change a person’s life
- A dream come true –
  - For the patients
  - For the families
  - For the CF physicians and team

- Therefore….

Monitoring safety….

- Tolerance levels very high
- No one wants to be taken off a trial
- No one wants to stop a drug that is even normalizing their sweat test

What is known to date?

- In general, CFTR modulating therapies so far, demonstrated acceptable safety profiles
  - Ivacaftor studies[1,2]
  - Lumacaftor/Ivacaftor studies[3]
  - Ataluren studies[4]

- What about longer term follow up?
- What about post marketing data?

- What of drugs in earlier stages of development?
- Teratogenicity?

1. Accurso FJ, et al. N Engl J Med 2010; 363: 1991–2003 2. Davies JC, et al. Am J Respir Crit Care Med. 2013; 187(11): 1219–1225 3. Wainwright CE, et al. N Engl J Med 2015; 373(3): 220–231
4. Eitan K, et al. Lancet Respir Med 2014; 2(7): 539–547

Why are these drugs well-tolerated?

- May be related to the specificity to CFTR
- What about effects of metabolism (e.g CYP)?
- How do these effect Drug- Drug interactions?

Safety Monitoring – Who's responsibility is it?

- The European Medicines Agency (EMA): key role in safety monitoring of medicines in the European Union (EU)
  - "Coordination of the European pharmacovigilance system to provide advice on the safe and effective use of medicines."[1]
- In Israel – Ministry of Health
- In the US – Food and Drug Administration (FDA)[2]

1. European Medicines Agency. Safety monitoring of medicines. Available at http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000456.jsp&mid=WC0b01ac05801ae8fb 2. FDA. Drug Safety Priorities 2015–2016. Available at http://www.fda.gov/downloads/Drugs/DrugSafety/UCM523486.pdf

PATIENT SAFETY IN CF CLINICAL TRIALS

Before enrollment

Food and Drug Administration (FDA)

FDA provides guidelines for study supervision, reviews previous studies to assess safety and approves drug to be tested in humans

Study Sponsor

Sponsor develops a study plan (protocol), which includes a guide for how safety will be monitored

Therapeutics Development Network (TDN) Scientific Review

CF research experts from the TDN and community representatives assess the merit of the study drug, study design and safety

Data Safety Monitoring Board (DSMB)

CF experts from the DSMB review safety data and make a plan to monitor safety during study

During the study

Food and Drug Administration (FDA)

FDA receives ongoing notification from sponsor about the safety of the study and provides federal oversight

Study Sponsor

Sponsor's medical expert reviews adverse events in real time

Therapeutics Development Network (TDN) Study Oversight

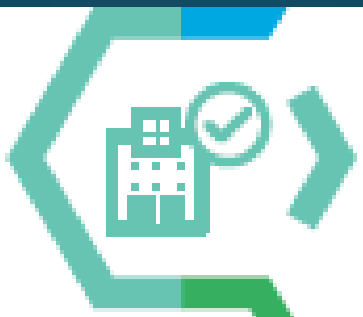
CF researchers from the TDN rely on the DSMB to monitor the study

Data Safety Monitoring Board (DSMB)

CF experts from the DSMB monitor all study data and take action if a safety risk is found

Institutional Review Board (IRB)

IRB at the research site reviews the study to evaluate possible benefits and risks



Institutional Review Board (IRB)

IRB at the research site provides general oversight and monitoring during the study

Site Study Team

Doctor at the research site reviews your health to see if you can safely participate in the study

Site Study Team

Study doctor and research coordinator monitor your health during the study, and can pull you out of the study if your health is a concern

Patient's Role

In the informed consent process, you are given all the available information about the study plan as well as possible risks and benefits, and your questions are answered

Patient's Role

You follow the study plan as explained during the consent process, and you keep your physician informed about how you're feeling and any concerns you have

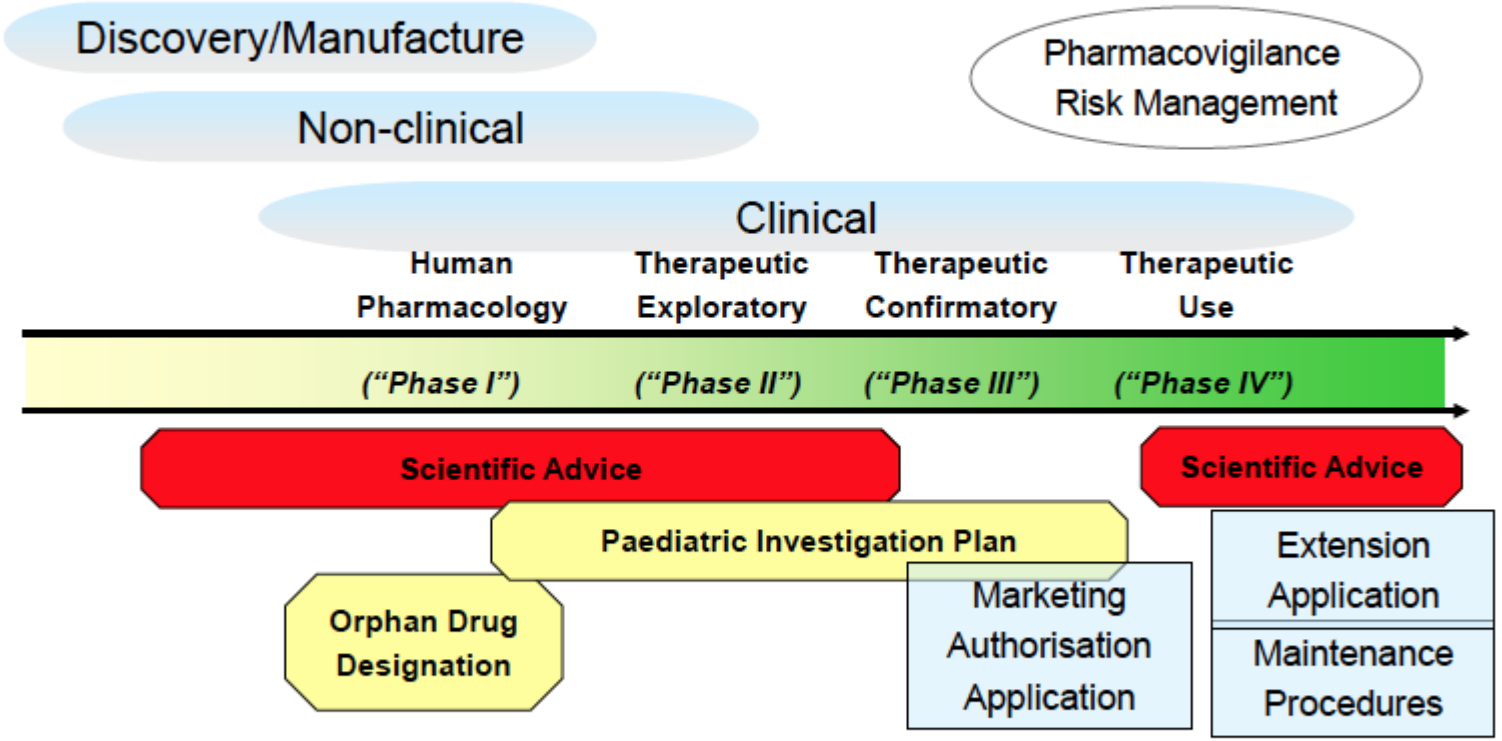
For more information visit CFF.org/safety.

These safeguards are in place for all trials performed through the CFFT Therapeutics Development Network.

CYSTIC FIBROSIS FOUNDATION

Drug Development Overview

EUROPEAN MEDICINES AGENCY

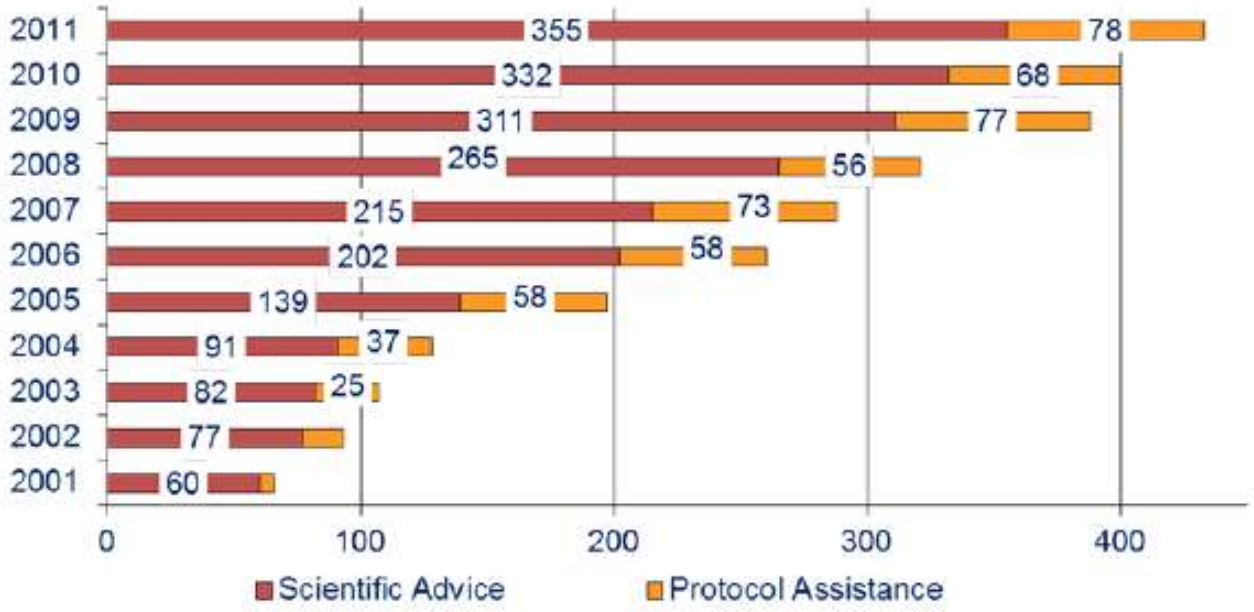


3

From: EMA workshop : 'Experience with CF in Scientific advice' E. Manolis, 2010

SAWP activities

EUROPEAN MEDICINES AGENCY



- **Product related**
- **Qualification of novel methodologies**
- **HTA-EMA parallel advice**
- **FDA–EMA parallel advice**
- **Workshops**
- **1998-Sept 2012: 53 letters on CF products**

SAWP = Scientific Advice Working Party

From: EMA workshop : 'Experience with CF in Scientific advice' E. Manolis, 2010

Pharmacovigilance

Monitoring of

- Adverse Drug Reactions
- Safety/toxicity profile of drugs
- Lack of efficacy

During

- Clinical use
- Overdose/ abuse/ non-approved use
- Drug withdrawal
- Pregnancy
- Infant of a nursing mother

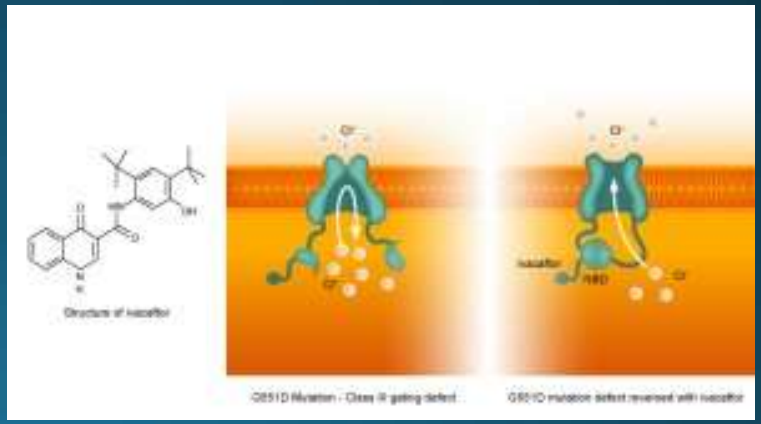
Precision medicine in CF: targeting the defect in CFTR in a genotype-specific manner

3 Main targeted approaches:

- Potentiators: recover CFTR function at the epithelial cell apical surface for class III and IV mutations.
  - Ivacaftor; FDA approval 2012
- Correctors: Improve intracellular processing of CFTR to increase surface expression for class II mutations
  - Lumacaftor/Ivacaftor combination; FDA approval 2015
- Production correctors: promote transcription (read through) for class I mutations
  - Ataluren in trials

Ivacaftor: a CFTR potentiator

- Increases chloride transport by potentiating the channel-open probability (or gating) of the CFTR protein at the cell surface.
- Acts on excised membrane patches, therefore appears to act directly on CFTR
- High CFTR selectivity (pharmacodynamics drug interactions unlikely)



<u>Dosage and administration</u>

- 150 mg oral tablet every 12 hours with fat-containing food[1]

1. Vertex Pharmaceuticals. Summary of product characteristics: Kalydeco 2016.

Ivacaftor: phase III RCT studies for patients with ≥1 GLy551Asp allele

- STRIVE: Ramsey et al, N Eng J Med 2011.
  - 48w, ≥ 12y, ≥1 GLy551Asp allele
- ENVISION: Davies et al, Am J Resp Crit Care Med, 2013.
  - 48w, 6-11y, ≥1 GLy551Asp allele

- Adverse events:
  - all similar in ivacaftor and placebo groups across trials
  - fewer serious adverse events (SAEs) in ivacaftor vs placebo groups across trials
  - 1 patient in STRIVE discontinued treatment - raised liver enzymes

- PERSIST: McKone et al, Lancet Respir Med, 2014
  - 144 week roll over of above studies. Adverse event rate similar. No further safety concerns. Sustained efficacy.

Ivacaftor: phase III RCT studies with mutations other than GLy551Asp

- KONNECTION: De Boeck et al, J Cyst Fibros, 2014.
  - 24w, ≥ 6y, ≥1 non GLy551Asp gating mutation
- KONDUCT Moss et al, Lancet Respir Med, 2015.
  - 24w, ≥6y, ≥1 Arg117His mutation

- Adverse events:
  - Similar in ivacaftor and placebo groups across trials

Ivacaftor and hepatic impairment

- Monitor ALT and AST before starting, 3 monthly in 1st year and then yearly
  - if levels become elevated, monitor closely till resolve.
  - if ALT or AST values rise to >5 ULN, interrupt therapy till return to normal.
  - weigh the benefits and risks of restarting ivacaftor.

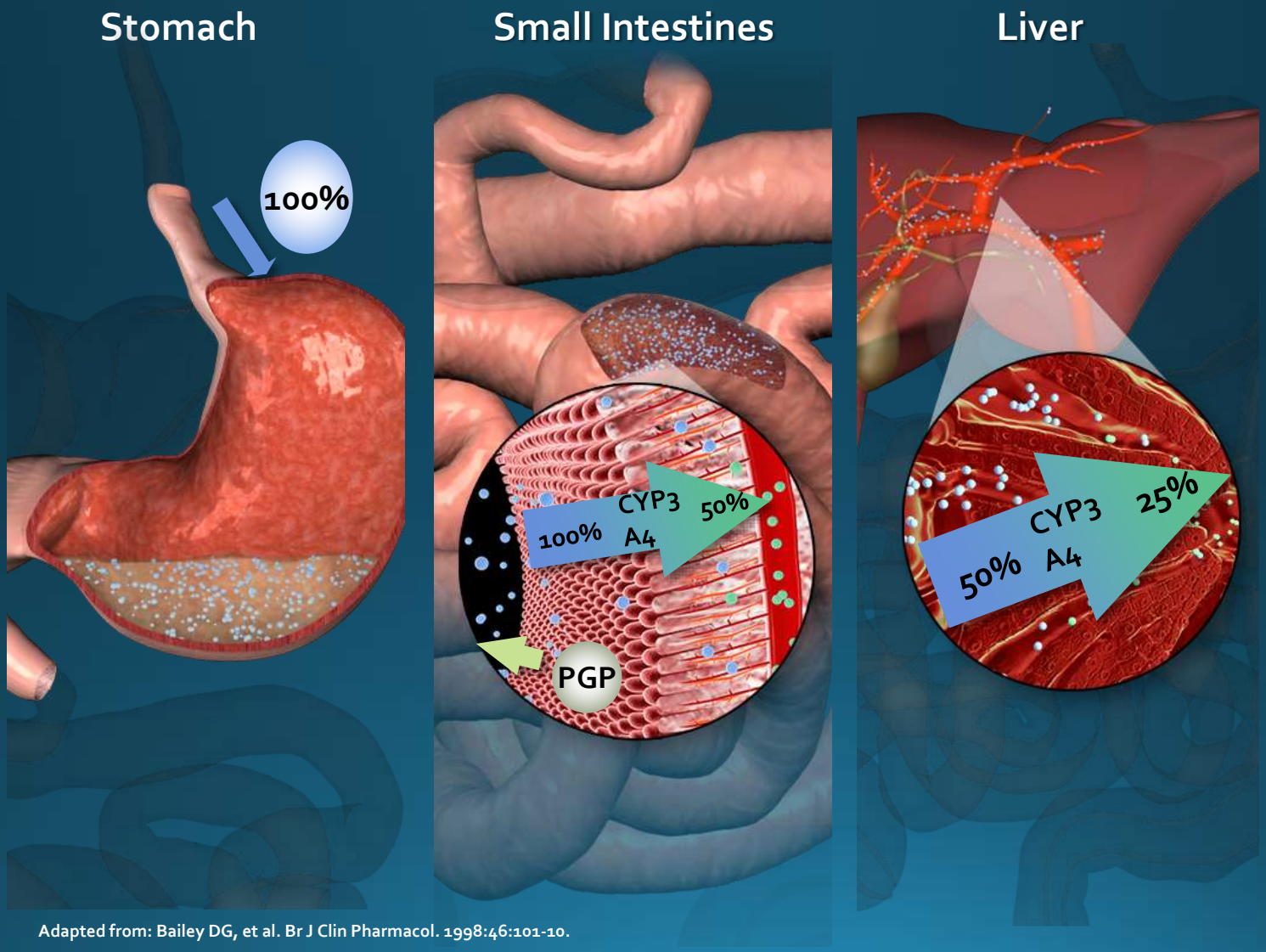
Degree of hepatic Impairment	Mild	Moderate	Severe*
Child-Pugh class (score)	A (score 5 to 6)	B (score 7 to 9)	C (score 10 to 15)
Ivacaftor dose adjustment*	None	Reduce to 150 mg once daily†	Use with caution at a dose of 150 mg every other day or less frequently after weighing the risks and benefits of treatment†

*Use of Ivacaftor is not recommended in patients with severe hepatic impairment unless the benefits are expected to outweigh the risks of overexposure.

†Dosing intervals should be modified according to clinical response and tolerability.

Vertex Pharmaceuticals. Summary of product characteristics: Kalydeco 2016.

Ivacaftor metabolism: Cytochrome CYP3A most relevant



Adapted from: Bailey DG, et al. Br J Clin Pharmacol. 1998:46:101-10.

Ivacaftor drug–drug interactions

Class	Drug examples	Recommendation
Potent inhibitors of CYP3A (⇑⇑ Ivacaftor level)	Ketoconazole, itraconazole, posaconazole, voriconazole, telithromycin, clarithromycin	Ivacaftor should be administered at a dose of 150 mg twice a week
Moderate inhibitors of CYP3A (⇑ Ivacaftor level)	Fluconazole, erythromycin (and grapefruit, Seville oranges)	Ivacaftor should be administered at a single daily dose of 150 mg
Strong CYP3A inducers (⇓⇓ Ivacaftor level)	Rifampicin, rifabutin, phenobarbital, carbamazepine, phenytoin and St. John's Wort *(Hypericum perforatum)*	Co-administration with Ivacaftor is not recommended
Weak to moderate CYP3A inducers (⇓ Ivacaftor level)	Dexamethasone, high-dose prednisone	Use with caution as it may reduce Ivacaftor efficacy
CYP3A, P-gp or CYP2C9 substrates*	Midazolam, alprazolam, diazepam or triazolam	Use with caution and monitor for benzodiazepine-related side effects
	Digoxin, cyclosporine or tacrolimus	Use with caution and appropriate monitoring
	Warfarin	Monitor the INR (International Normalized Ratio)

Vertex Pharmaceuticals. Summary of product characteristics: Kalydeco 2016.

***Kalydeco is a mild CYP3A inhibitor**

Ivacaftor safety assessment, EMA 2012

Derived from pooled safety assessment on 700 subjects in 23 studies as of 2011:

"The treatment with ivacaftor appears to be well tolerated. Few subjects have discontinued treatment due to adverse events. The majority of adverse events associated with ivacaftor were mild to moderate in severity. There were no deaths in any ivacaftor studies. Population from 6 to 11 years-old) is very limited, therefore safety in these subgroups is addressed with additional pharmacovigilance activities."

EMA Kalydeco Assessment report, EMA/473279/2012; Committee for Medicinal Products for Human Use (CHMP)

Ivacaftor safety assessment, EMA 2012

- Related AE leading to study discontinuation: 1.7% for Ivacaftor and 3.8% for placebo
- Increase in ALT (3.1%) and AST (4.1%) was similar to placebo
- a Pregnancy Category B drug and caution is recommended for breastfeeding mothers.
- Caution is recommended with severe renal impairment (no studies; minimal renal excretion)
- Lens opacities were seen in juvenile rats, but human lens more complete at birth. Unlikely relevant for children >6y . However, as cataracts are seen in CF, baseline and follow up opthalmological examinations are recommended
- A five year safety surveillance study is ongoing in the US and Europe to better understand long term safety

EMA Kalydeco Assessment report, EMA/473279/2012; Committee for Medicinal Products for Human Use (CHMP)

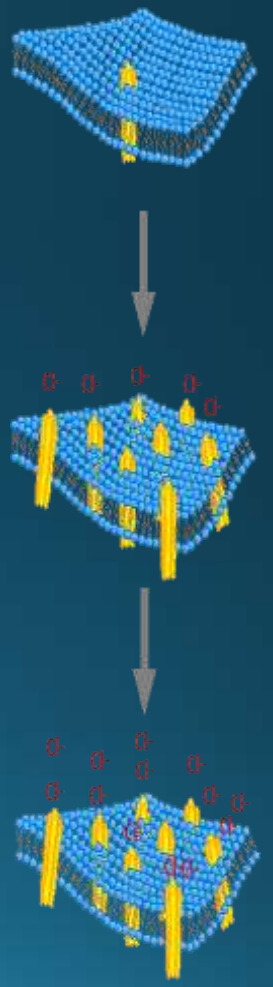
Lumacaftor/Ivacaftor

Lumacaftor is a CFTR 'corrector'

Improves the conformational stability of Phe508del-CFTR, resulting in increased processing and trafficking of mature protein to the cell surface

Ivacaftor is a CFTR 'potentiator'

Facilitates increased chloride transport by potentiating the channel-open probability (or gating) of the CFTR protein at the cell surface



Phase II RCT lumacaftor/ivacaftor

- Improvement 3-4% in absolute FEV1 over 56d
- Adverse event :
- a dose dependent trend towards a decline in FEV_1% predicted for the groups assigned to higher lumacaftor doses, which was associated with increased dyspnea and chest tightness;
- this finding was later determined to be an off target adverse event because it was replicated in healthy volunteers.

Boyle et al. Lancet Respir Med 2014

Lumacaftor/Ivacaftor: phase III RCT studies for homozygous Phe508del CF patients

- TRAFFIC: Wainwright et al, N Eng J Med, 2015.
  - 24w, 559 patients ≥ 12y
- TRANSPORT: Wainwright et al, N Eng J Med, 2015.
  - 24w, 563 patients ≥ 12y

- Dosage: lumacaftor either 400mg BID or 600mg QD and ivacaftor 250mg BID

Adverse Events Summary: TRAFFIC/TRANSPORT

- For all groups, pulmonary exacerbation was by far the most common SAE:
  - placebo, 24.1%;
  - pooled LUM/IVA groups, 13.0%
- It was the only SAE reported in ≥10 patients in any treatment group
- No deaths were reported during the study

Wainwright et al, N Eng J Med, 2015.

Adverse Events: TRAFFIC/ TRANSPORT study	Placebo N=370	LUM (600 mg qd)/ IVA (250 q12h) N=369	LUM (400 mg q12h)/ IVA (250 mg q12h) N=369
Patients reporting any AE, n (%)	**355 (96)**	**356 (97)**	**351 (95)**
Patients who discontinued due to an AE, n (%)	**6 (2)**	**14 (4)**	**17 (5)**
Patients reporting a serious AE, n (%)	**106 (29)**	**84 (23)**	**64 (17)**
Most common AEs, n (%)	**182 (49)**	**145 (39)**	**132 (36)**
Infective pulmonary exacerbation	**148 (40)**	**121 (33)**	**104 (28)**
Cough	**58 (16)**	**58 (16)**	**58 (16)**
Headache	**70 (19)**	**55 (15)**	**54 (15)**
Sputum increased	**29 (8)**	**55 (15)**	**48 (13)**
Dyspnea	**22 (6)**	**40 (11)**	**32 (9)**
Respiration abnormal	**50 (14)**	**52 (14)**	**50 (14)**
Hemoptysis	**31 (8)**	**36 (10)**	**45 (12)**
Diarrhea	**28 (8)**	**29 (8)**	**46 (13)**
Nausea			

Wainwright et al, N Eng J Med, 2015.

Summary of Liver Function Test Elevations: TRAFFIC/TRANSPORT

- Elevated LFTs (AST or ALT >3 times the ULN) seen in 5.2% of patients receiving LUM/IVA and 5.1% of placebo patients

- In the active group, the 3 bilirubin elevations were accompanied by >3x ULN ALT/AST elevations. These episodes occurred in patients with underlying severe liver disease and/or alternative etiologies

- SAEs related to abnormal liver tests occurred in 0 placebo patients and 7 LUM/IVA patients. Following discontinuation or interruption, LFTS returned to baseline for 6 patients and improved substantially in the other 1.

Wainwright et al, N Eng J Med, 2015.

Lumacaftor/Ivacaftor Pharmacokinetics

Lumacaftor	Ivacaftor	Co-administration of Lumacaftor with Ivacaftor
• Strong inducer of CYP3A	• Sensitive CYP3A substrate • Weak inhibitor of CYP3A when given as monotherapy	• Due to the induction effect of lumacaftor on CYP3A the net exposure of ivacaftor is not expected to exceed that when given in the absence of lumacaftor at a dose of 150 mg every 12 hours, the approved dose of ivacaftor monotherapy

Vertex Pharmaceuticals. Summary of product characteristics: Orkambi 2016.

Lumacaftor/Ivacaftor and CYP3:

- When initiating Lumacaftor/Ivacaftor in patients taking strong CYP3A inhibitors,
  - e.g.Ketoconazole, posaconazole, voriconazole, clarithromycin, reduce Lumacaftor/Ivacaftor to 1 tablet daily lumacaftor 200 mg/ivacaftor 125 mg for 1st week till steady-state induction effect of lumacaftor.
  - Following this period, continue with the recommended daily dose.
- CYP3A inducers will decrease the Lumacaftor/Ivacaftor availability: e.g. rifampin (↓lumacaftor,↓↓↓ ivacaftor), phenytoin, St John's wort, carbamazepine. Efficacy of these drugs may also be reduced
- May need a higher dose of systemic corticosteroids, ibuprofen, consider alternative to benzodiazepines ;
- Avoid us of Lumacaftor/Ivacaftor with cyclosporine, everolimus, sirolimus, tacrolimus as their efficacy may be reduced

European Public Assessment Report (EPAR) of the EMA, Summary of Product Characteristics: Orkambi, 2016
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003954/WC500197611.pdf

Lumacaftor 200mg bid /Ivacaftor 250mg bid 24w, 6-11 y, n=58

Improvements in Sweat Chloride, BMI, LCI, CFQR resp. Not in FEV1pp

- AEs were mild to moderate in severity. The most frequently reported AEs were cough (n=29), nasal congestion (n = 12), infective pulmonary exacerbation (n=12), and headache (n=12).
- Respiratory symptom-related AEs were infrequent and not associated with any discontinuations or serious AEs.
- Two patients discontinued treatment due
  - Rash (n=1)
  - Elevated liver transaminases (n=1)
  - Both AEs resolved following discontinuation.
- No new safety concerns were identified compared with older subjects.

Milla et al, Am J Resp Crit Care Med, November 2016

Tezacaftor (VX-661)

- Tezacaftor (VX-661) is an investigational, first-generation CFTR corrector
  - Compared with lumacaftor (VX-809), VX-661 has a similar mechanism of action but different pharmacologic properties, including a longer half-life and fewer drug interactions (no cytochrome P450 3A induction)
- Currently, it is taken in combination with Ivacaftor in the clinical trials: over 1000 patients with either Phe508del homozogotes or heterozygotes with minimal function, residual function and gating mutations

- Unlike Lumacaftor, not associated with bronchospasm in healthy volunteers[2]

1. Joseph Pilewski, MD, NACFC 2014
2. Data on file. Boston, MA: Vertex Pharmaceuticals Incorporated; 2014

Tezacaftor (VX-661)

Characteristic	Monotherapy				Combination				Placebo
	VX-661 10 mg	VX-661 30 mg	VX-661 100 mg	VX-661 150 mg	VX-661 10 mg Ivacaftor 150 mg	VX-661 30 mg Ivacaftor 150 mg	VX-661 100 mg Ivacaftor 150 mg	VX-661 150 mg Ivacaftor 150 mg	
n	8	8	8	9	18	19	17	17	24
Patients reporting any AE, n (%)	8 (100)	7 (87.5)	7 (87.5)	8 (88.9)	15 (83.3)	18 (94.7)	10 (58.8)	17 (100)	22 (91.7)
Patients reporting any serious AE, n (%)	1 (12.5)	1 (12.5)	0	0	1 (5.6)	2 (10.5)	2 (11.8)	2 (11.8)	4 (16.7)
Serious pulmonary exacerbation	1 (12.5)[a]	1 (12.5)	0	0	1 (5.6)	1 (5.3)[b]	2 (11.8)	1 (5.9)[c]	4 (16.7)
Discontinuation due to AE	1 (12.5)	0	0	0	1 (5.6)	0	2 (11.8)	1 (5.9)	0

1. Joseph Pilewski, MD, NACFC 2014
2. Data on file. Boston, MA: Vertex Pharmaceuticals Incorporated; 2014

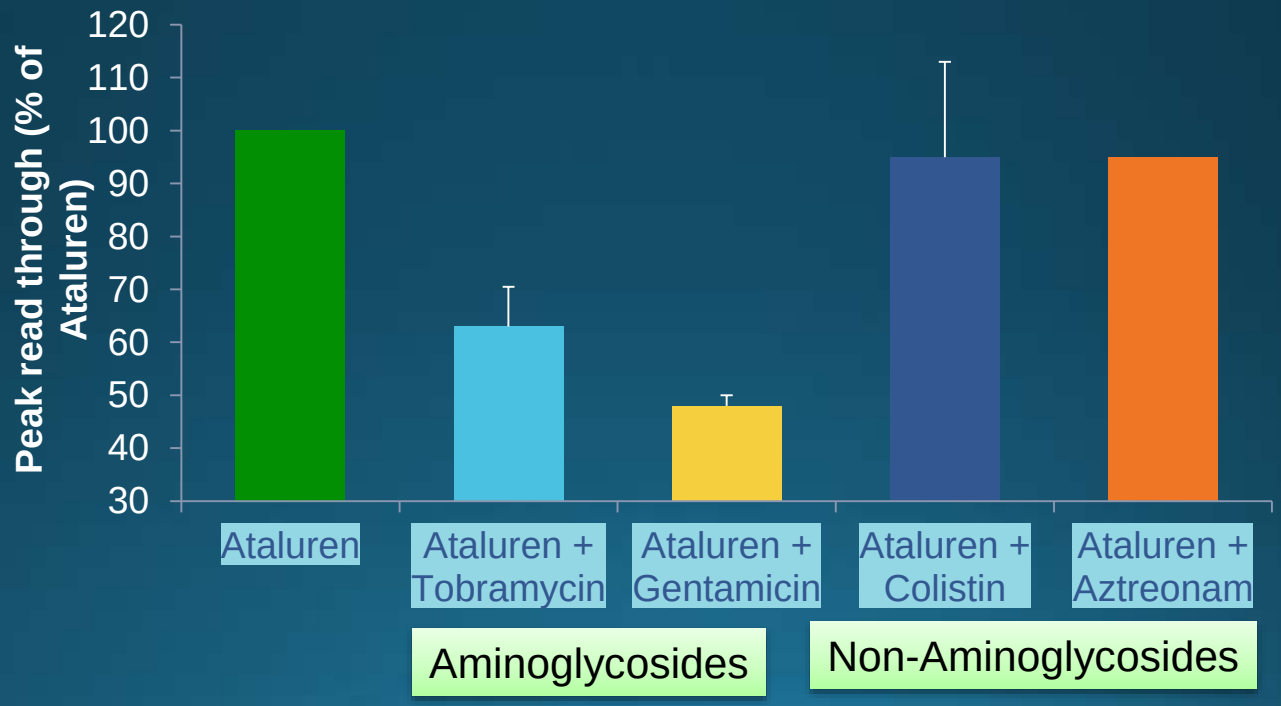
Study 009: Ataluren safety profile

- Generally well tolerated
- Side-effects generally mild-to-moderate, with similar profile to placebo
- Reversible increase in creatinine concentrations (ie, acute kidney injury) occurred in 18 (15%) of 118 patients in the ataluren group compared with one (<1%) of 120 patients in the placebo group.
- 3 were reversible grade 3-4 creatinine increases in patients who were treated with systemic antibiotics (aminoglycosides and vancomycin) for pulmonary exacerbations, and in some cases were associated with dehydration.
  - Preventing this addressed the issue as the trial proceeded.
- A similar profile was observed in the non-tobramycin group at post hoc analysis

Kerem E, et al. Lancet Respir Med. 2014 Jul;2(7):539-47

Chronic aminoglycosides (i.e. tobramycin) inhibit the activity of ataluren in CF patients

- In vitro assay work demonstrated that aminoglycosides inhibit the read-through activity of ataluren



Kerem E, et al. Lancet Respir Med. 2014 Jul;2(7):539-47

ELX-02: synthetic drug aminoglycoside-based scaffold

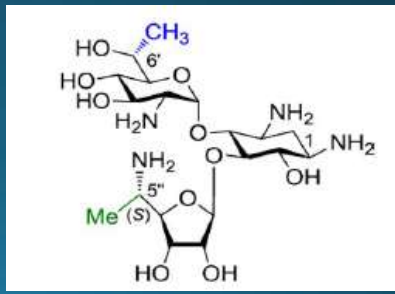
Eloxx Pharmaceuticals

- binds preferentially to the eukaryotic ribosome (improving read-through activity
- low affinity for the prokaryotic ribosome
- decouples the antibacterial activity from read-through activity.
- When compared to gentamicin: 100-fold lower antibacterial activity and 9-fold higher read-through activity

(Shalev, Rozenberg et al. 2015)

- <u>Target organs of toxicity:</u>
- Kidney: some AE at X6-10 dose in rat and dog
- Ear: (Oto- and vestibular-) no ototoxicity in rats in X14 dose for 4wks
- Injection site

- Human studies on going….



Ways to Avoid Drug-Drug Interactions

- Always be vigilant for DDIs when starting new therapies
  - Keep an updated list of ALL prescriptions, OTC and herbal products in medical record
  - Review medication list at each clinic visit
  - Be aware of drugs with "narrow" therapeutic indexes, long half-lives and/or that are potent cytochrome P450 inducers or inhibitors
- Be familiar with metabolic pathways of all agents being used
- Know where to locate information about interactions
  - On-line
  - Health-care resource (e.g. pharmacist)
  - Medical reference book
- Seek advice from other healthcare professionals, e.g. pharmacist, if possible, to help minimize DDIs
  - The more "eyes" the better
- Patients should have all new medications, OTC and herbal products reviewed by their HCP prior to initiation

THANK YOU