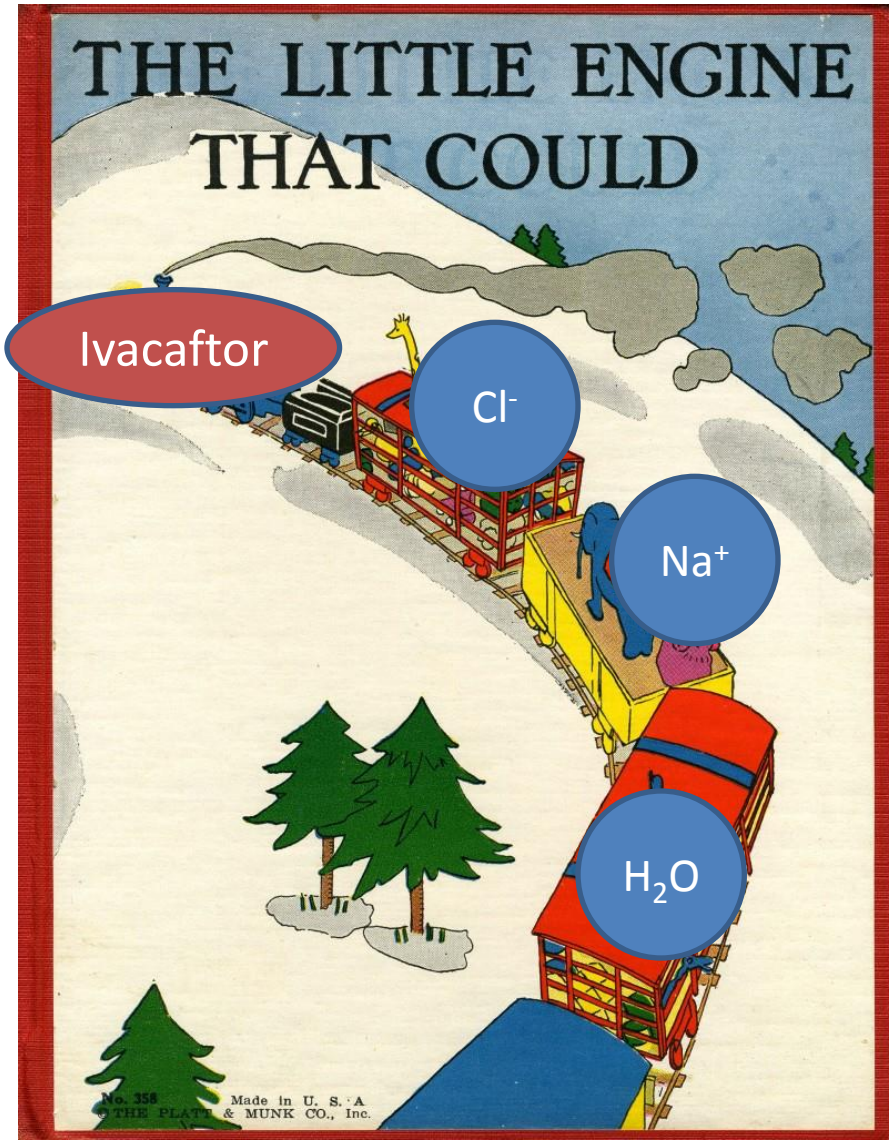


The Little Molecule That Could:

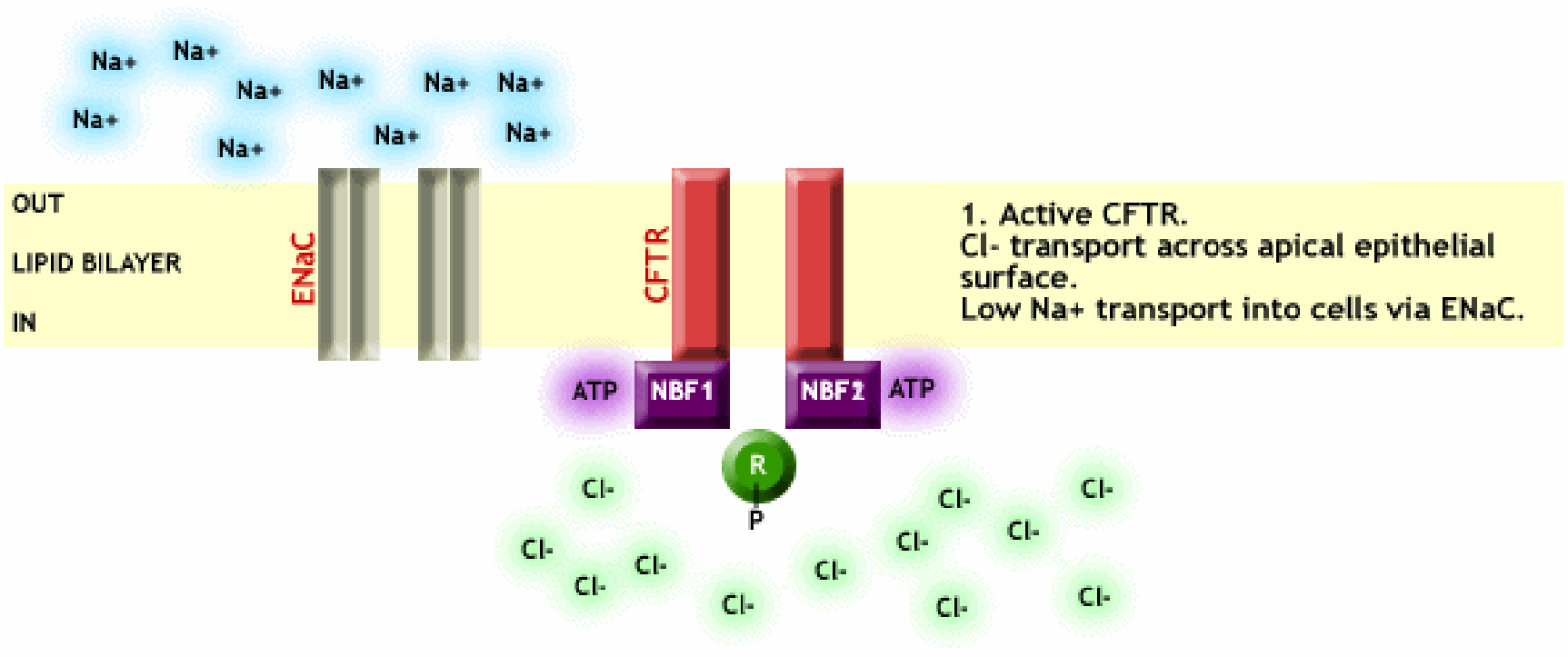
Cystic Fibrosis, Cl and Ivacaftor

Dan Rainkie
Doctor of Pharmacy Student
B.Sc(Hons), B.Sc(Pharm), ACPR

Nov 14, 2013

Cystic Fibrosis

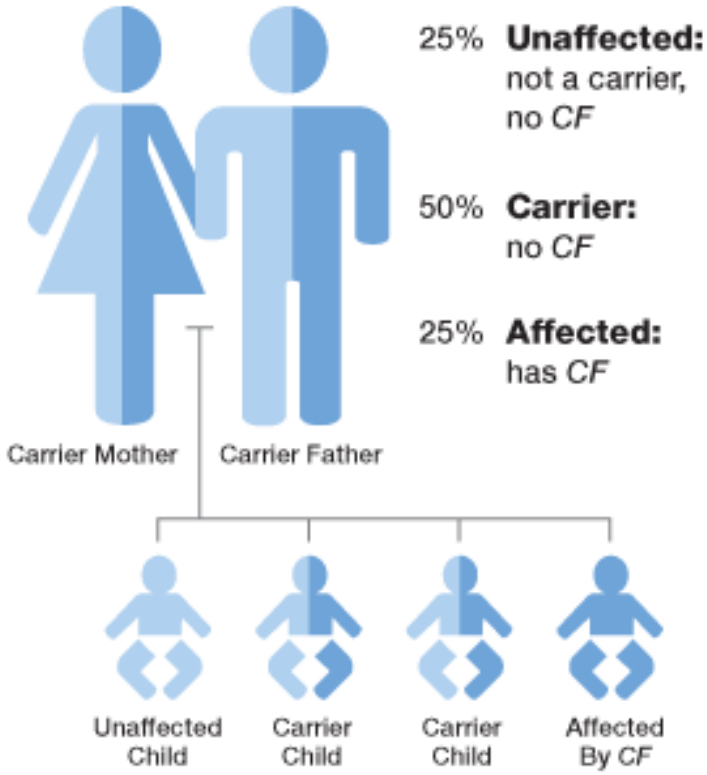
- Genetic mutation of the cystic fibrosis transmembrane conductance regulator (CFTR)



http://www.genemedresearch.ox.ac.uk/cysticfibrosis/function.html

Cystic Fibrosis

- Autosomal recessive
- ~4000 patients in Canada (2011)
- 2011 median age of survival is 48.5 years
- 60% of all people with CF are adults



Canadian Cystic Fibrosis Patient Data Registry Report 2011
http://www.inplexcf.com/images/pic_inherited_1.gif

CFTR Mutations

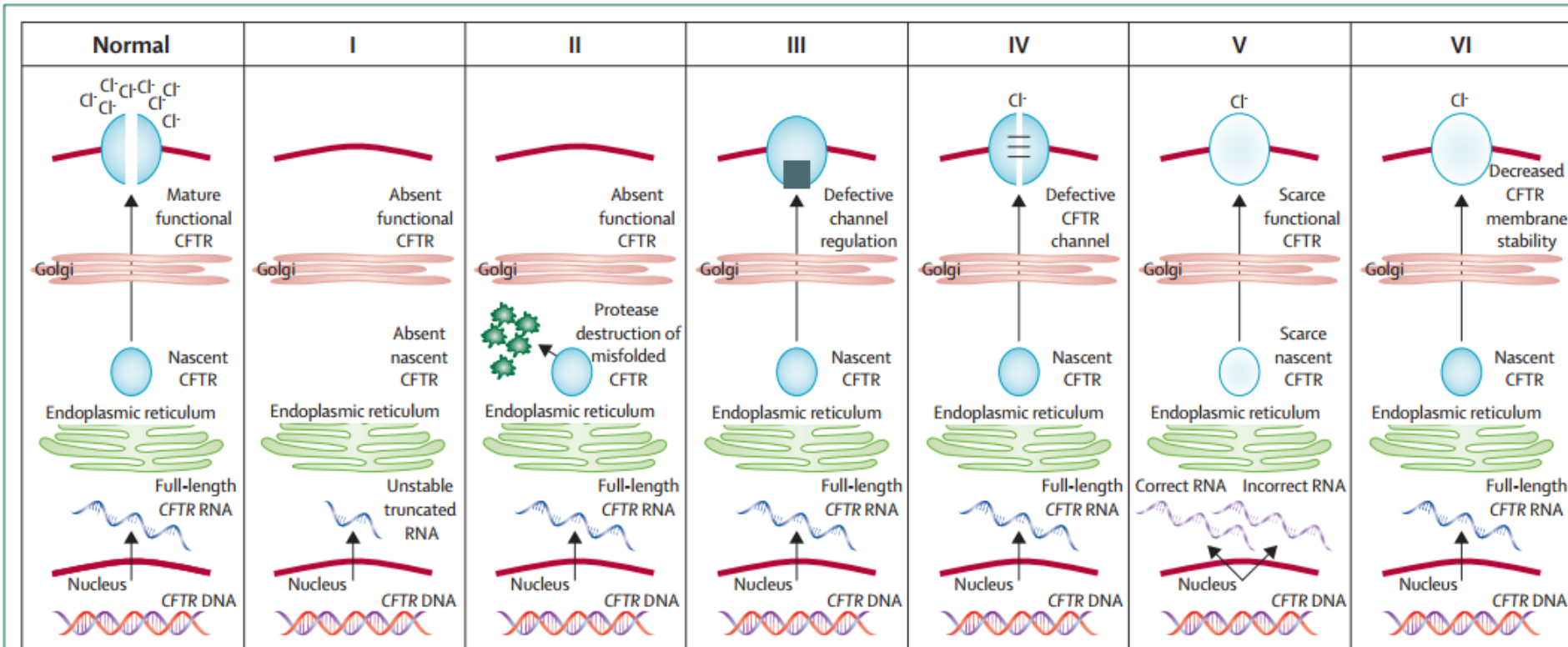
- Over 1900 mutations described

Frequency of CF mutations on one or both alleles (top five)

Genotype	Number	Percentage
DeltaF508	3,063	91.5
621+1G->T	217	6.5
G542X	134	4.0
G551D	115	3.4
711+1G->T	96	2.9

Canadian Cystic Fibrosis Patient Data Registry Report 2011
http://www.bcwomens.ca/NR/rdonlyres/776E6BBA-747A-4D9C-8447-15603FE49955/46959/CFTesting3.pdf

Six Classes of CFTR Mutations

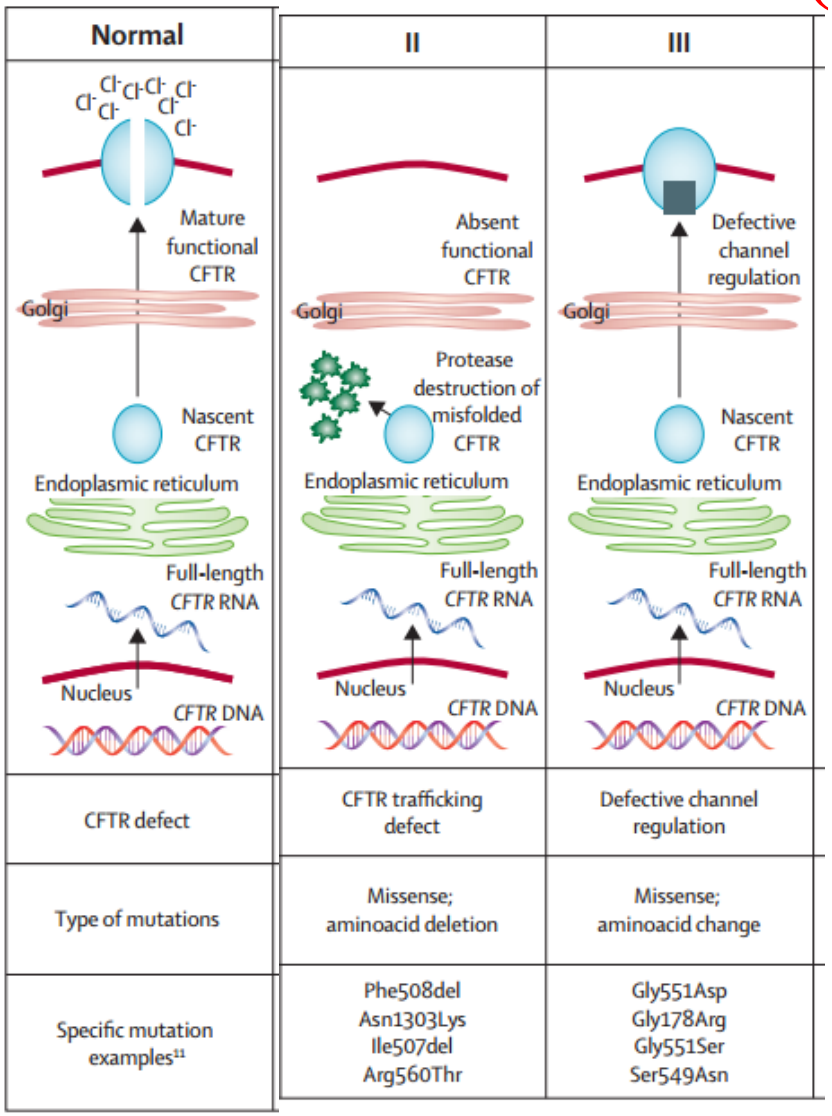


	Normal	I	II	III	IV	V	VI
CFTR defect		No functional CFTR protein	CFTR trafficking defect	Defective channel regulation	Decreased channel conductance	Reduced synthesis of CFTR	Decreased CFTR stability
Type of mutations		Nonsense; frameshift; canonical splice	Missense; aminoacid deletion	Missense; aminoacid change	Missense; aminoacid change	Splicing defect; missense	Missense; aminoacid change
Specific mutation examples[11]		Gly542X Trp1282X Arg553X 621+1G→T	Phe508del Asn1303Lys Ile507del Arg560Thr	Gly551Asp Gly178Arg Gly551Ser Ser549Asn	Arg117His Arg347Pro Arg117Cys Arg334Trp	3849+10kbC→T 2789+5G→A 3120+1G→A 5T	4326delTC Gln1412X 4279insA

Lancet Resp Med 2013; 1: 158-163

Classes of CFTR Mutations

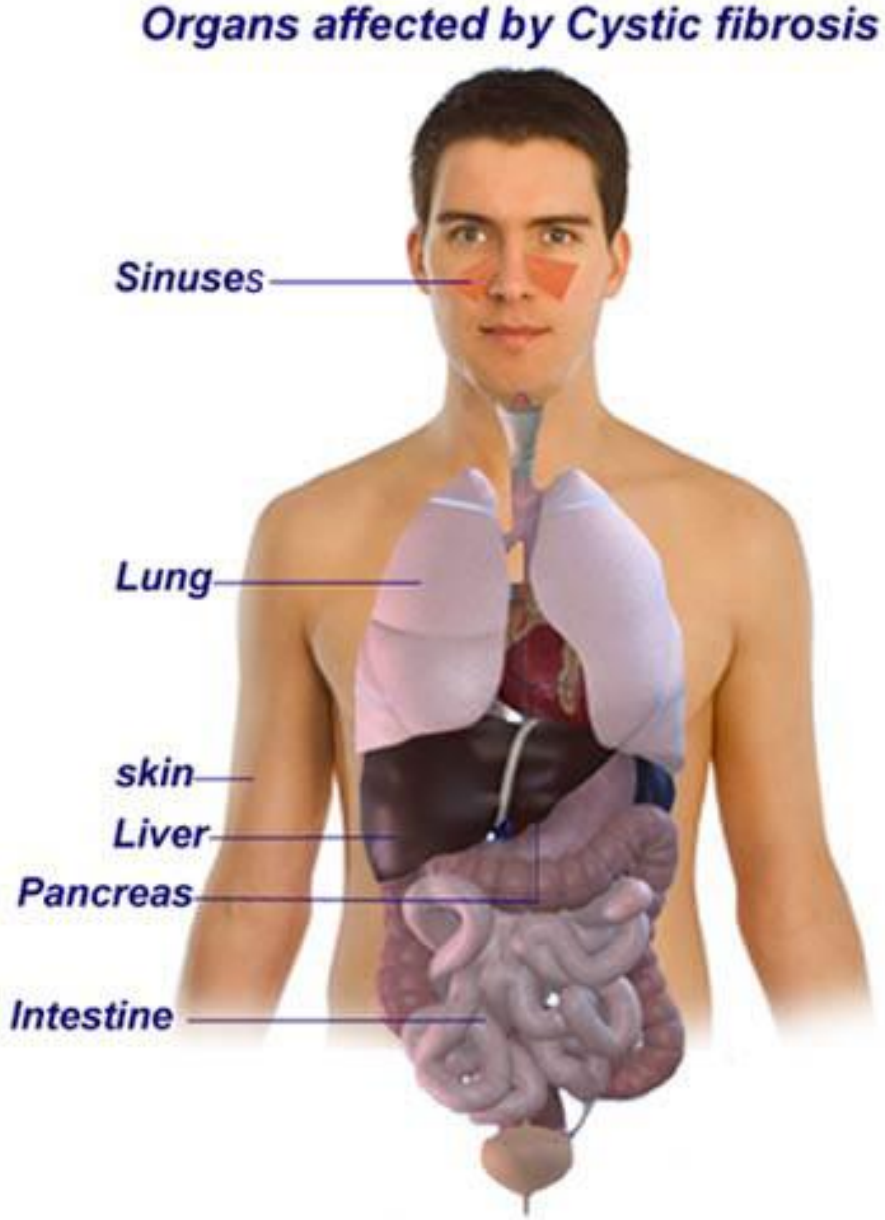
ΔF508 G551D (Ivacaftor target)



	Normal	II	III
CFTR defect		CFTR trafficking defect	Defective channel regulation
Type of mutations		Missense; aminoacid deletion	Missense; aminoacid change
Specific mutation examples[11]		Phe508del Asn1303Lys Ile507del Arg560Thr	Gly551Asp Gly178Arg Gly551Ser Ser549Asn

Lancet Resp Med 2013; 1: 158-163

CF Manifestations



Mutations and Severity

Severity	Clinical Consequence	Example Genotypes[7]
Severe	Two copies of CF-causing mutations are inherited, which are usually associated with severe pulmonary and pancreatic disease[4,5]	F508del/F508del F508del/G551D F508del/2789+5G->A R553X/G542X R1162X/R1162X
Moderate	These mutations are generally associated with pancreatic sufficiency with patients presenting with atypical CF[3]	G551D/R117H[8] F508del/A455E
Mild	Mild (or very moderate) CF mutations	A455E/R117H[9] R117H/1717–1G->A[10] R117H/F508del[11]

http://www.cftr.info/about-cf/role-of-ctfr-in-cf/cftr-mutations/the-correlation-between-cftr-mutations-and-disease-severity/cf-disease-severity/

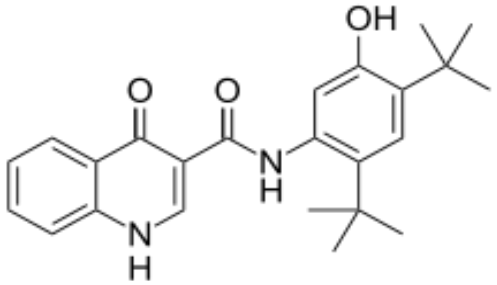
CF Treatment Options

Purpose	Medication
Nasal polyps	Intranasal corticosteroids
Mucolytic	7% NaCl inhaled
	Dornase alfa (Pulmozyme)
	Mannitol inhaled
Prevention of exacerbations	Azithromycin PO
	Tobramycin inhaled
	Colistimethate inhaled
	Aztreonam inhaled
GERD	H_2RAs
	PPIs
Delayed gastric emptying	Domperidone
	Cisapride
	Bethanechol

CF Treatment Options

Purpose	Medication
Pancreatic insufficiency	Pancreatic enzymes (Creon, Pancrease)
Liver	Ursodiol
Nutritional deficiencies	Vitamin A, D, E, K
	Calorie supplementation
CFTR Modulator	**Ivacaftor**

Ivacaftor (VX-770)



Class		CFTR potentiator
Mechanism		Potentiates opening (or gating) of G551D-CFTR protein
PK	**A**	Steady state at 3-5 days Fatty food increases exposure 2-4x
	D	99% protein bound (α_1-acid glycoprotein, albumin)
	M	**CYP 3A4** to active metabolites (~1/6th potency)
	E	65% as metabolites 88% feces, 6.6% urine $t_{1/2}$ ~ 12 hours
Dose		150 mg PO q12h
Administration		PO every 12 hours with fat-containing foods (typical CF diet)
Dose adjustment		Renal impairment < 30 mL/min use with caution

Vertex Pharmaceuticals Incorporated. Kalydeco® (ivacaftor) tablets prescribing information. Cambridge, MA; 2012 Aug

Clinical Question

P	In a cystic fibrosis patient will	
I	Ivacaftor	
C	compared to placebo	
O	Efficacy	Mortality Pulmonary exacerbations FEV_1 Weight Sweat chloride Quality of life Reduction in previous medications • B-agonist • Dornase alfa • Pancreatic enzymes • Insulin
	Safety	ADEs

Prognosis and Surrogates

- Improved survival (OR)
  - BMI 1.76
  - FEV_1 1.54
  - FVC (per 5 % increase) 1.54
- Decreased survival (OR)
  - Pseudomonas colonization 0.18
- Lung transplant candidate criteria
  - FEV_1 < 30% or rapid decline in FEV_1
  - pO_2 < 55 mmHg
  - pCO_2 > 45 mmHg
  - Life-threatening events

Eur Respir J 2010; 36(6): 1277-1283
http://www.cysticfibrosis.ca/assets/files/pdf/cf&lungtransplantationE.pdf

Ivacaftor

Databases	EMBASE, Medline, Pubmed, Google Scholar, Cochrane library, international pharmaceutical abstracts	
Search Terms	Ivacaftor	
Limits	English, human	
Results	Returned results	52
	Meta-analysis/Systematic review	0
	RCT	4 • Children in G551D • Phase 3 in G551D • Phase 2 in G551D • Phase 2 in $\Delta F508$
	Observational	1 • Insulin secretion pilot study
	Case report	3
	Other	0

To Be Covered

RCTs		Observational	Case Reports
CFTR Potentiator in Patients with Cystic Fibrosis and the G551D Mutation **(STRIVE)** NEJM 2011; 365(18): 1663-1672	Efficacy and Safety of Ivacaftor in CF patients aged 6-11 years with a G551D Mutation **(ENVISION)** Am J Respir Crit Care Med 2013; 187(11): 1219-1225	Insulin secretion improves in cystic fibrosis following ivacaftor correction of CFTR: Pilot Study Pediatric Diabetes 2013; 14(6): 417-421	NEJM 2013; 369(13): 1280-1282 Pediatric allergy, immunology, and pulmonology 2012; 25(4): 231-233 Journal of CF 2013; 12(5): 530-531

RCTs		Observational	Case Reports
CFTR Potentiator in Patients with Cystic Fibrosis and the G551D Mutation **(STRIVE)** NEJM 2011; 365(18): 1663-1672	Efficacy and Safety of Ivacaftor in CF patients aged 6-11 years with a G551D Mutation **(ENVISION)** Am J Respir Crit Care Med 2013; 187(11): 1219-1225	Insulin secretion improves in cystic fibrosis following ivacaftor correction of CFTR: Pilot Study Pediatric Diabetes 2013; 14(6): 417-421	NEJM 2013; 369(13): 1280-1282 Pediatric allergy, immunology, and pulmonology 2012; 25(4): 231-233 Journal of CF 2013; 12(5): 530-531

	STRIVE	ENVISION
Design	R, DB, PC, MC 48 week follow up	
P	n=161 **Age 25.5 (12-53)** 52% female **FEV_1 63.6 (31-98%)** 82% heterozygous (G551D/X)	n=52 **Age 8.9 years (6-11)** 52% female **FEV_1 84.2 (44-133%)** 98% heterozygous (G551D/X)
	Inclusion: CF diagnosis, G551D in at least 1 allele, FEV_1 40-90%, normal labwork	**Inclusion**: Age 6-11, CF diagnosis, G551D in at least 1 allele, FEV_1 40-105%, weight $\geq$ 15kg.
	Exclusion: Comorbidities, colonisations associated with sig PFT decline, any sickness within 2 weeks No 7% NaCl for at least 4 weeks before enrollment	**Exclusion**: 7% NaCl therapy

	STRIVE	ENVISION
I	n=83 Ivacaftor 150 mg PO BID	n=26 Ivacaftor 150 mg PO BID
C	n=78 Placebo PO BID	n=26 Placebo PO BID
Co-interventions	Continued usual therapy (not described)	Continued usual therapy (not described)

Outcome of Interest	Results (p-value)		Clinical Difference?
	STRIVE	ENVISION	
Mortality **3° outcome**	None	None	-
Exacerbations	2° outcome: Time to first Ivacaftor 67% free placebo 41% free RR 0.455 (p=0.001)	**3° outcome** Ivacaftor 4 placebo 3 events	Yes

Outcome of Interest	Results (p-value)		Clinical Difference?
	STRIVE	**ENVISION**	
FEV_1 **1° outcome**	Ivacaftor +17.5% Placebo +0.8% (p<0.0001)	2° Ivacaftor +10.7% placebo +0.7% (p<0.001)	Yes
Weight **2° outcome**	Ivacaftor +3.1 Placebo +0.4 kg (p<0.0001)	Ivacaftor +5.9kg Placebo +3.1 kg (p<0.001) BMI for age z-score +0.45 @ 48w (p<0.001)	Yes but ?result of other medication changes not reported

Outcome of Interest	Results		Clinical Difference?
	STRIVE	**ENVISION**	
Sweat chloride (mmol/L) 2° outcome	Ivacaftor -48.7 Placebo -0.6 (p<0.0001)	Ivacaftor -55.5 Placebo -1.2 (p<0.001)	Unknown significance. Used as a diagnostic tool for CF.
QoL (CFQ-R) 2° outcome	Ivacaftor +5.9 Placebo -2.7 (p<0.001)	Child = NS Caregiver = Ivacaftor +3.7 Placebo -1.2 (p=0.07)	Yes (adults only) MCID = 4
Usual CF medication use	NR	NR	-

Outcome of Interest	Results		Clinical Difference?
	STRIVE	**ENVISION**	
Adverse events	Most common ADRs > 5% difference: Headache URTI Nasal congestion Rash Dizziness	Most common ADRs > 5% difference: Oropharyngeal pain Headache Nasopharyngitis URTI Otitis media Diarrhea Increased blood eosinophil	Unknown
Drop outs	Ivacaftor = 6 (1 ADR, 2 non-compliance) Placebo = 10 (4 ADR)	Ivacaftor = 0 Placebo = 4 (1 ADR)	No

Critical Appraisal

	STRIVE	ENVISION
Randomization	stratified age, FEV_1	'randomized'
Allocation concealment		
Baseline characteristics even?		Female, FEV1 imbalance
Blinded?		
Attrition bias present?		
Statistical analysis	Mixed effects model for repeated measures Cox regression and Kaplan-Meier for time to exacerbation	Mixed effects model for repeated measures
Intention-to-treat or per-protocol?	ITT ? 1 drop out due to non-adherence	ITT
Power calculation?		
All patients accounted for		
Important outcomes considered?		
Generalizable?		
Funding source?	Vertex	Vertex

RCTs		Observational	Case Reports
CFTR Potentiator in Patients with Cystic Fibrosis and the G551D Mutation **(STRIVE)** NEJM 2011; 365(18): 1663-1672	Efficacy and Safety of Ivacaftor in CF patients aged 6-11 years with a G551D Mutation **(ENVISION)** Am J Respir Crit Care Med 2013; 187(11): 1219-1225	Insulin secretion improves in cystic fibrosis following ivacaftor correction of CFTR: Pilot Study Pediatric Diabetes 2013; 14(6): 417-421	NEJM 2013; 369(13): 1280-1282 Pediatric allergy, immunology, and pulmonology 2012; 25(4): 231-233 Journal of CF 2013; 12(5): 530-531

Insulin secretion improves in cystic fibrosis following ivacaftor correction of CFTR: a small pilot study

Pediatric Diabetes 2013: 14: 417–421

Design	Prospective, observational, single center, open-label, 1 month follow up	
P n=5	Baseline CF characteristics not reported (weight, therapies, FEV_1) **Inclusion**: CF diagnosis by sweat test, ≥1 G551D allele, ≥ 6 yrs **Exclusion**: Current ivacaftor treatment	
I n=5	Ivacaftor (Assumed 150 mg BID)	
O	1°	**IV glucose tolerance test** (0.5mg/kg, max 35g dextrose) • Insulin AUC at +10 minutes **Oral glucose tolerance test** (75g dextrose) • Serum blood glucose at 2 hours • Insulin AUC at 120 minutes
Stats	Paired t-test	

Insulin secretion improves in cystic fibrosis following ivacaftor correction of CFTR: a small pilot study

Pediatric Diabetes 2013: 14: 417–421

Patient No	History	OGTT		IVGTT
		Blood Glucose (mmol/L)	**Insulin Secretion Increase (%)**	**Acute Insulin Response Increase (%)**
1 52 F	Diabetes x 16 yrs Insulin pump	No change	No change (decrease)	Infinite Pre=0
2 14 M	New diagnosis CFRD No treatment		99%	No change (decrease)
3 40 M	Impaired glucose tolerance		~56%	~63%
4 6 F	Impaired glucose tolerance		158%	~33%
5 35 M	Normal glucose tolerance	Pre=8.2 1 mo=5.0	~100%	~330% (Pre=3, very low)
Overall	P-value	NR	P=0.07	P=0.19

Critical Appraisal

Strengths	Limitations
First study	Small sample size
Stats appropriate (could argue against using a mean instead of a median)	Baseline characteristics not reported
	Open label
	“No industry involvement in or sponsorship of this study” PFTs and sweat chloride no available since patients are being followed as part of a blinded study.

Insulin secretion improves in cystic fibrosis following ivacaftor correction of CFTR: a small pilot study

Pediatric Diabetes 2013: 14: 417–421

Conclusion

- No statistical improvement in any outcomes (?type II error)
- No data on progression to CFRD
- No outcomes on decreased insulin requirements (poor population)
- Proof of concept

RCTs		Observational	Case Reports
CFTR Potentiator in Patients with Cystic Fibrosis and the G551D Mutation **(STRIVE)** NEJM 2011; 365(18): 1663-1672	Efficacy and Safety of Ivacaftor in CF patients aged 6-11 years with a G551D Mutation **(ENVISION)** Am J Respir Crit Care Med 2013; 187(11): 1219-1225	Insulin secretion improves in cystic fibrosis following ivacaftor correction of CFTR: Pilot Study Pediatric Diabetes 2013; 14(6): 417-421	NEJM 2013; 369(13): 1280-1282 Pediatric allergy, immunology, and pulmonology 2012; 25(4): 231-233 Journal of CF 2013; 12(5): 530-531

Case Reports Summary

	NEJM 2013; 369(13): 1280-1282	Pediatr allergy, immunol, pulm 2012; 25(4): 231-233	J Cyst Fibros 2013; 12(5): 530-531
P	19, female, Ireland G551D/G551D FEV_1 24%	12, male, US ΔF508/G551D S aureus, 2x Burkholderia (1 resistant to all antibiotics) 3 month hospitalization, FEV_1 21%	39, male, US ΔF508/G551D MRSA, 3 strains pseudomonas, FEV_1 24%
I	Ivacaftor (? dose)	Ivacaftor 150 mg PO BID	Ivacaftor 150 mg PO BID
O	12 months F/U **Home O_2 D/C'd** FEV_1 40% Sweat NaCl 92 → 18 **Pancreatic enzyme ↓~60%** Serum albumin 33 → 45 6min walk distance 140m → 550m	10 weeks FEV_1 38% Baseline activity Weight + 3.1 kg Burkholderia colonized	7 months FEV_1 36% (@baseline before exacerbation) ↑QoL "He described this as "if a battery was turned on" and felt as if he was 20 years old again"

CDEC Ivacaftor Report

- List for the treatment of CF in patients 6 years and older who have a G551D mutation
  IF…
  - Substantial reduction in price
    - QALY $2-9 million
  - Clinical criteria for stopping ivacaftor if no response
    - 25% of patients failed to improve FEV_1 of at least 5%

Treatment Comparisons

Treatment	FEV_1 Changes	Pulmonary Exacerbation Reduction
Salbutamol	If response, up to 20%	-
Dornase alfa	5.8%	22%
7% NaCl	3.2%	66%
Ivacaftor	10%	55%

Cost

- Ivacaftor = $300,000 / year
- Dornase alfa = $16,000 / year
- 7% NaCl = Cheap

Summary

Efficacy	Exacerbations NNT 5 FEV_1 increase by ~10% Weight improved Sweat chloride decreased below CF diagnosis in majority QoL clinical difference in adults only ?Decrease in medication requirement (no RCTs yet)
Safety	Well tolerated, numerically less drop outs than placebo in trials CNS: Headache, dizziness HEENT: Nasal congestion, otitis media, oropharyngeal pain Resp: URTI GI: Diarrhea Heme: Eosinophilia Derm: Rash
Convenience	PO medication Typical time commitment for CF therapies: 108 min/day (SD 58 min)
Cost	~300,000/year Currently not listed by Pharmacare

Sawicki GS, Sellers DE, Robinson WM. High treatment burden in adults with cystic fibrosis: challenges to disease self-management. J Cyst Fibros 2009;8:91–96.

Comments and Questions

thought I could.
I thought I could.
I thought I could."