A Case of Over-Exposure

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Let me introduce you to Mr John B

- 67 year old male
- Ex-smoker (25 pack year history)
- Retired sales representative
- Diagnosed with COPD by GP 2015
- Hospital admission at local hospital – reviewed by respiratory consultant and referred to Glenfield for specialist ILD review
- SOB and “troublesome” cough for 18 months prior to ILD review
- 2 years ago John could walk 4-5 miles without stopping, now approximately 50 yards

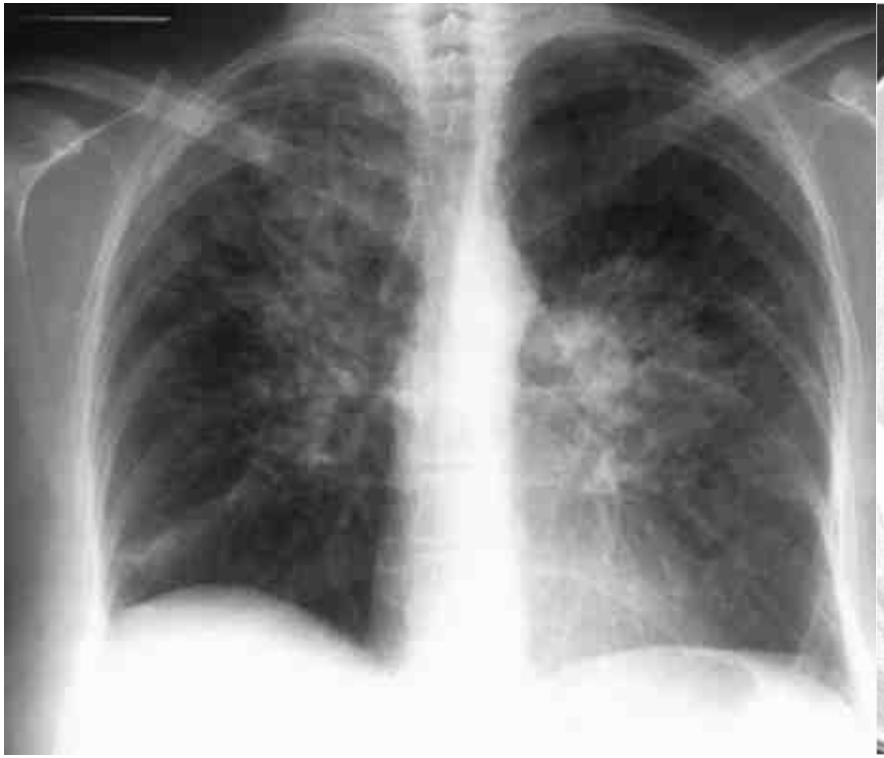
John continued …

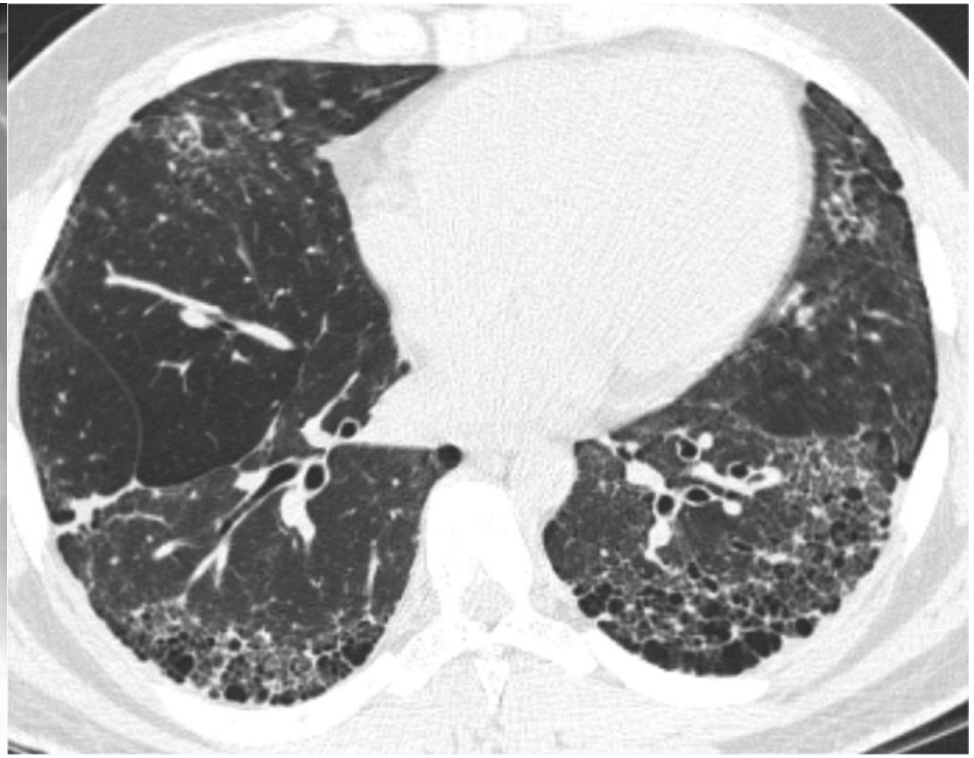
- PMH: MI (2014), CABG, AF, Hypertension
- DH: Apixiban 5mg BD
  Furosemide 40mg OM
  Omeprazole 20mg OD
  Ramipril 5mg OM
  Atorvastatin 40mg ON
  Symbicort 400/12 one dose BD
  Salbutamol MDI PRN (via aerochamber)
  No OTC/herbal medicines
  No known drug allergies, no peanut allergies

A bit more background ….

- Referral to ILD consultant end of April 2017
- Discussed at MDT (May 2017) prior to clinic visit
- CXR – volume loss
- HRCT – bilateral extensive fibrotic changes with reticulation, ground glass opacites, discreet tractions and isolated cysts of honeycombing. Consistent with pulmonary fibrosis, air trapping not typical finding for UIP
- John's daughter has had a budgie for last 2-3 years but John has little exposure
- LFTs normal, U&Es (eGFR>90 mls/min)

Radiology





Pulmonary Function Test Results

	Baseline (April 2017)
FVC	2.53 litres
FVC % predicted	62%
FEV_1	2.28 litres
FEV_1 % predicted	68%
FEV_1/FVC ratio	0.9
DLCO%	49%
TLC%	59%

Interactive

How would you manage this patient?

1. Consistent with idiopathic pulomonary fibrosis (IPF) – suitable for treatment with targeted anti-fibrotics
2. Uncertain – watch and wait
3. Uncertain – check bloods to rule out Hypersensitivity Pneumonitis (HP)
4. Uncertain – offer oral corticosteroid trial

Blood tests return negative ..

- Rheumatoid factor, ANA, ENA, ANCA,, myositis screen, anti CCP, DS-DNA
- Avian precipitans

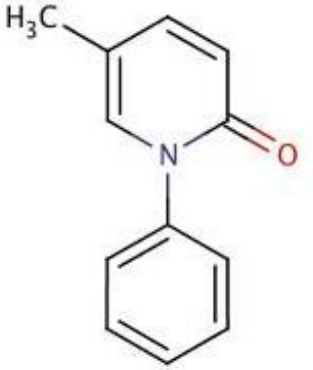
- John’s diagnosis confirmed as Idiopathic Pulmonary Fibrosis (IPF)

Interactive

How would you manage this patient now with a confirmed diagnosis of IPF?

1. Watch and wait
2. Offer choice of pirfenidone
3. Offer choice of nintedanib
4. Offer either pirfenidone or nintedanib and let John decide
5. Offer Clinical trial

John was offered Pirfenidone

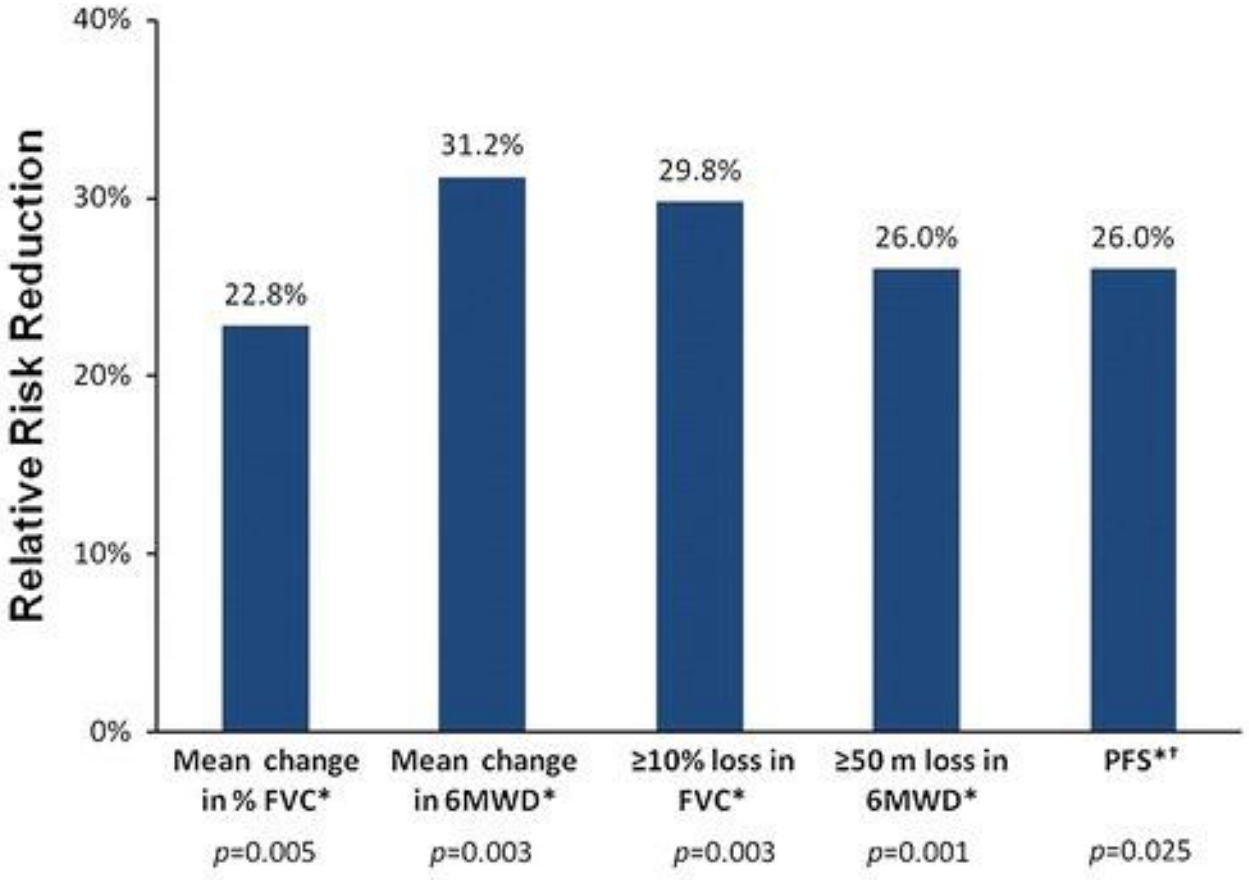


- Prescribed pirfenidone 801mg/day increased to 2403mg/day with food
  - Primarily anti-fibrotic
  - Inhibits experimental lung-, heart, liver and kidney fibrosis
  - Reduces *in vitro* fibroblast growth and collagen synthesis
  - Inhibits production of a number of cytokines important in pulmonary fibrosis
  - **The precise mechanism of action has not been fully established**
- Omeprazole changed to alternative PPI
- Symbicort/salbutamol stopped, ramipril changed to ARB
- Baseline blood test results LFTs (ALT 10, ALP 83, bilirubin 6, albumin 39), eGFR 68 mls/min
- LFTs monthly for 6 months, then test every 3 months
- Sun block SPF 50 advised to be used on a daily basis

Main studies Pirfenidone in IPF

Agent(s)	N	Duration	Primary end point	Inclusion criteria	Comments
Pirfenidone (Japanese)	275	52 weeks	ΔFVC (relative)	• Age 20–75 years • Oxyhemoglobin desaturation ≥5% on 6-MWT • SpO_2 >85% during 6-MWT	• High-dose pirfenidone group received 1,800 mg daily • Significantly improved progression-free survival
Pirfenidone (CAPACITY 004)	435	52 weeks	ΔFVC (absolute)	• Dx via HRCT or SLB • Age 40–80 years • FVC ≥50% but ≤90% pred • DLCO ≥35% but ≤90% pred • 6-MWT distance ≥150 m	• Pirfenidone cohorts dosing: – 1,197 mg daily (low dose) – 2,403 mg daily (high dose) • *P*=0.001 for placebo vs high-dose cohort ΔFVC at week 72 • *P*=0.023 for progression-free survival
Pirfenidone (CAPACITY 006)	344	72 weeks	ΔFVC (absolute)	• Dx via HRCT or SLB • Age 40–80 years • FVC ≥50% but ≤90% pred • DLCO ≥35% but ≤90% pred • 6-MWT distance ≥150 m	• Primary end point not met • Significant improvement in 6-MWT distance noted
Pirfenidone (ASCEND)	555	52 weeks	ΔFVC (relative)	• Dx via HRCT (with fibrosis extent > emphysematous change) ± SLB • Dx 6–48 months prior to enrollment • Age 40–80 years • FVC 50%–90% pred • FEV_1/FVC ≥0.80 • DLCO 30%–90% pred • 6-MWT distance ≥150 m • Symptoms present ≥12 months	• Pirfenidone dosing for treatment arm =2,403 mg daily • *P*<0.001 for FVC change (%predicted) at week 52 • *P*<0.001 for progression-free survival • *P*=0.04 for 6-MWT distance change at week 52

Consistent magnitude of treatment effect with pirfenidone across multiple clinically meaningful outcomes: CAPACITY



Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. *Noble PW, Albera C, Bradford WZ, et.al, CAPACITY Study Group.Lancet. 2011 May 21; 377(9779):1760-9.*

ORIGINAL ARTICLE

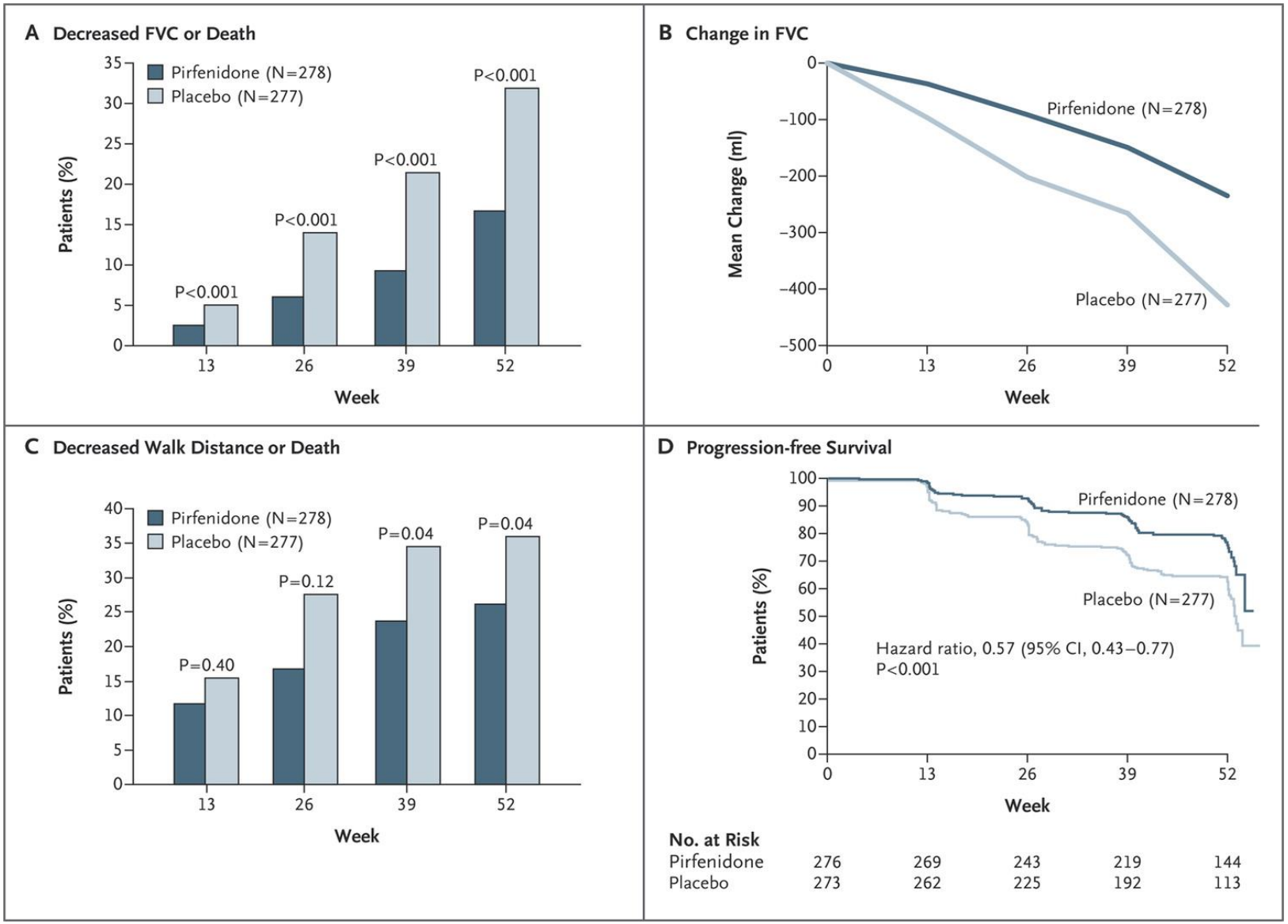
A Phase 3 Trial of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis

Talmadge E. King, Jr., M.D., Williamson Z. Bradford, M.D., Ph.D., Socorro Castro-Bernardini, M.D., Elizabeth A. Fagan, M.D., Ian Glaspole, M.B., B.S., Ph.D., Marilyn K. Glassberg, M.D., Eduard Gorina, M.D., Peter M. Hopkins, M.D., David Kardatzke, Ph.D., Lisa Lancaster, M.D., David J. Lederer, M.D., Steven D. Nathan, M.D., Carlos A. Pereira, M.D., Steven A. Sahn, M.D., Robert Sussman, M.D., Jeffrey J. Swigris, D.O., and Paul W. Noble, M.D., for the ASCEND Study Group*

"ASCEND"

King TE Jr et al. N Engl J Med 2014. DOI: 10.1056/NEJMoa1402582

ASCEND Primary and Key Secondary Outcomes



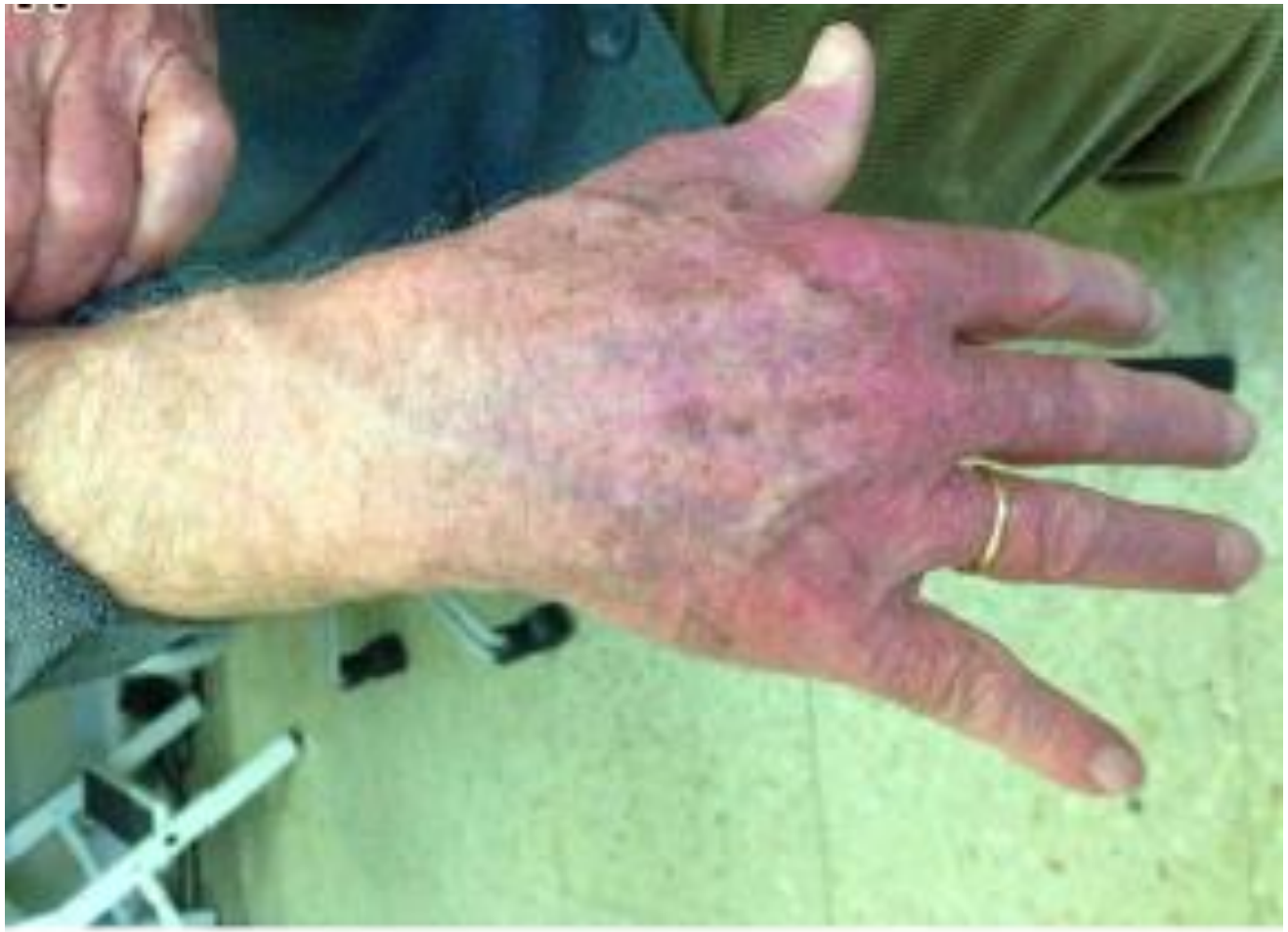
King TE Jr et al. N Engl J Med 2014. DOI: 10.1056/NEJMoa1402582

Mortality in the ASCEND and CAPACITY Trials

Variable	Pirfenidone	Placebo	Hazard Ratio (95% CI)†	P Value‡
ASCEND trial				
No. of patients	278	277		
Death — no. (%)				
From any cause	11 (4.0)	20 (7.2)	0.55 (0.26–1.15)	0.10
Related to idiopathic pulmonary fibrosis§	3 (1.1)	7 (2.5)	0.44 (0.11–1.72)	0.23
Pooled data from ASCEND and CAPACITY trials				
No. of patients	623	624		
Death — no. (%)				
From any cause	22 (3.5)	42 (6.7)	0.52 (0.31–0.87)	0.01
Related to idiopathic pulmonary fibrosis§	7 (1.1)	22 (3.5)	0.32 (0.14–0.76)	0.006

King TE Jr et al. N Engl J Med 2014. DOI: 10.1056/NEJMoa1402582

4 weeks later John phones the ILD team …



Interactive

What action would you recommend for Mr B?

1.Continue pirfenidone at 2403mg/day – its important to continue this treatment for his lungs, the photosensitivity reaction is the least of his worries

2.Stop pirfenidone and consider starting nintedanib

3.Reduce the pirfenidone dose to 1-2 capsules TDS and keep on this dose indefinitely

4.Reduce dose 1 capsule (267mg) TDS for 7 days then review

What we did ….

On discussion with John, he had recently had a chest infection and the GP had given him a weeks course of doxycycline 200mg daily.

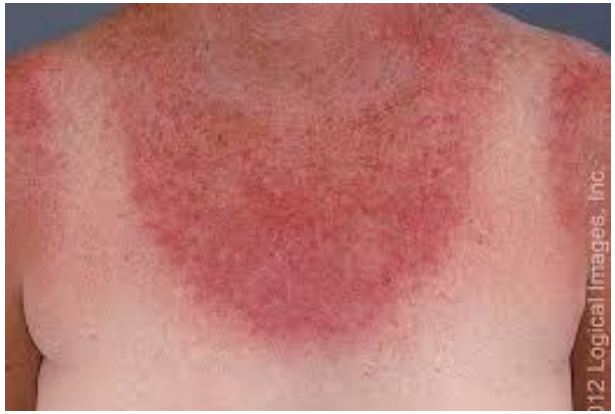
Action:

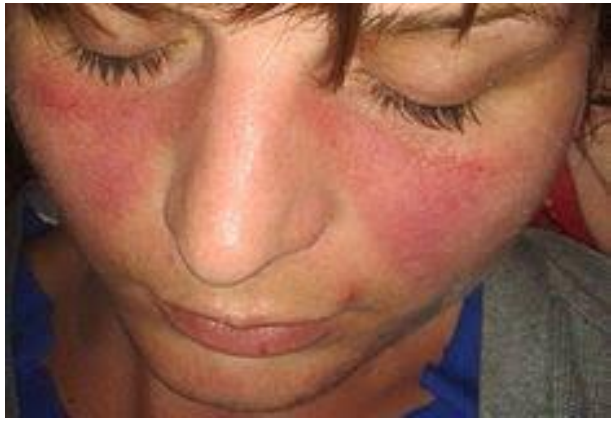
- Reduced the pirfenidone to one 267mg TDS
- Antihistamine recommended for itch
- Emollient and SPF 50 Sun block to be applied
- Arranged a follow-up review in 7 days
- Educate that tetracyclines should be avoided if possible whilst on pirfenidone

Interactive

Which one of these drugs does NOT cause photosensitivity?

1. Pirfenidone
2. Amiodarone
3. Enalapril
4. Doxycycline
5. Theophylline
6. Furosemide



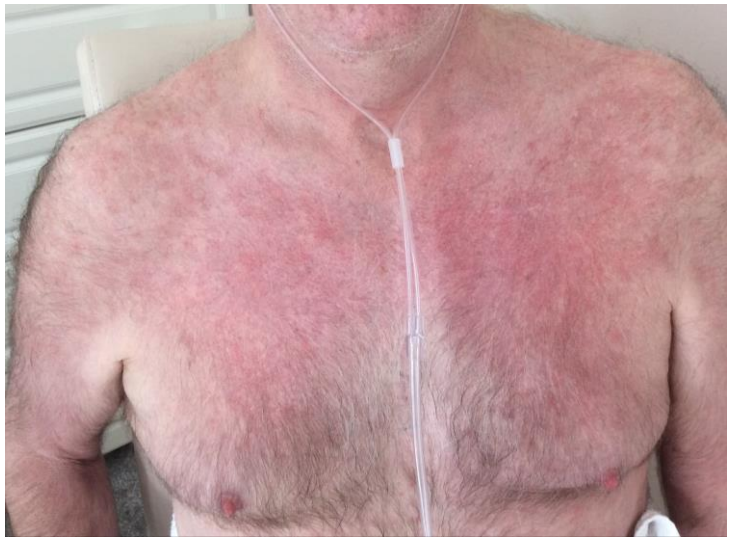


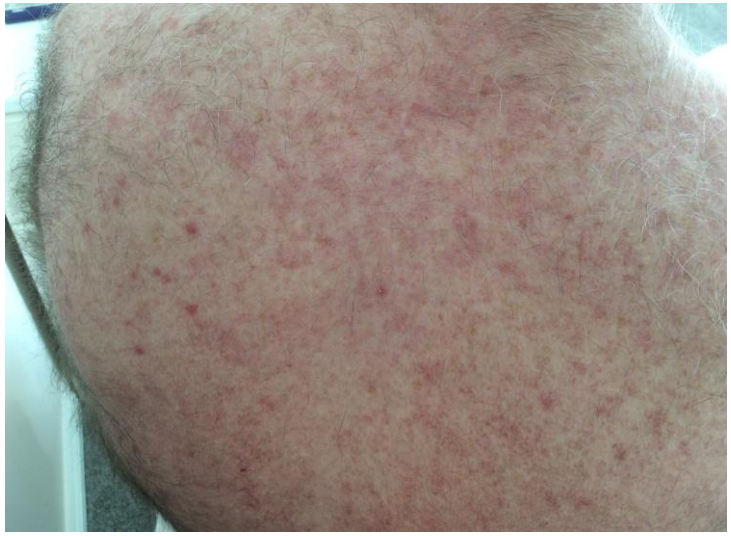
Common Photosensitivity Drugs

Class	Medication
Antibiotics	Tetracyclines–doxycycline (Vibramycin) Fluoroquinolones–ciprofloxacin (Cipro), ofloxacin (Floxin), sparfloxacin (Zagam) Sulfonamides–sulfamethoxazole/trimethoprim (Bactrim)
NSAIDs	Ibuprofen (Motrin, Advil) Ketoprofen (Orudis) Naproxen (Anaprox, Naprosyn, Aleve)
Diuretics	Furosemide (Lasix) Bumetanide (Bumex) Hydrochlorothiazide
Retinoids	Isotretinoin (Accutane) Acitretin (Soriatane)
Hypoglycemics	Sulfonylureas–glipizide (Glucotrol), glyburide (Diabeta)
Other drugs	Psoralen Amiodarone (Cordarone) Diltiazem (Cardizem) Chlorpromazine (Thorazine) Quinidine (Quinidex) Hydroxychloroquine (Plaquenil) Coal tar Enalapril (Vasotec) Dapsone (DDS) Terbinafine (Lamisil)

Pirfenidone Skin Reaction

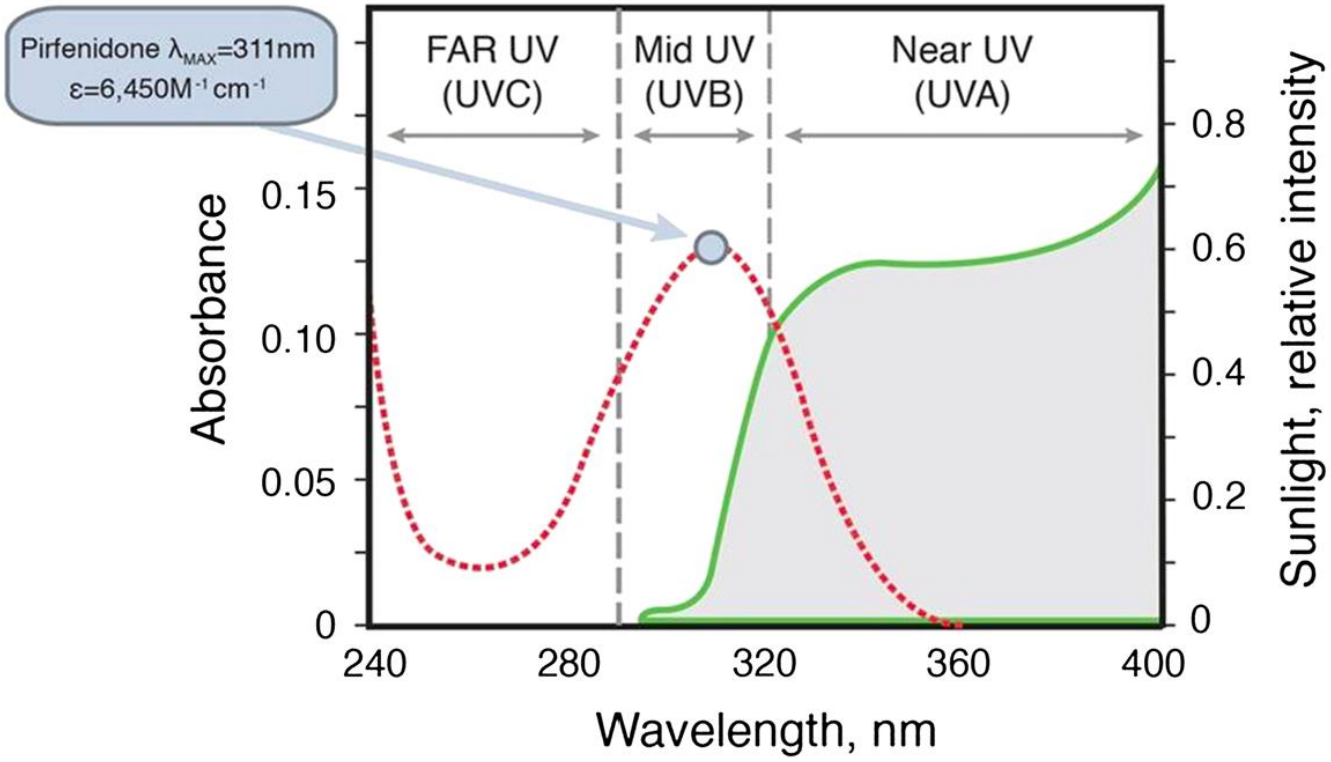
- Skin-related AEs can manifest as an erythematous (with/without edema) or as a phototoxic burn-like skin rash occuring on sun-exposed body areas
- This differs from an allergic type of eruption, which will usually affect all parts of the skin, including areas not exposed to sunlight





Phototoxic	Photoallergic
Photochemical/biological reaction	Cell mediated immune response
UVB	UVA
Hyperpigmentation and desquamation	Papular and eczematous flare and wheal
Acute e.g. tetracyclines	e.g. Sulphonamides, sulphonylureas, chloroquine
Chronic e.g. thiazides, amiodarone, sulfonamides, phenothiazomes	

Pirfenidone causes mainly phototoxic photosensitivity

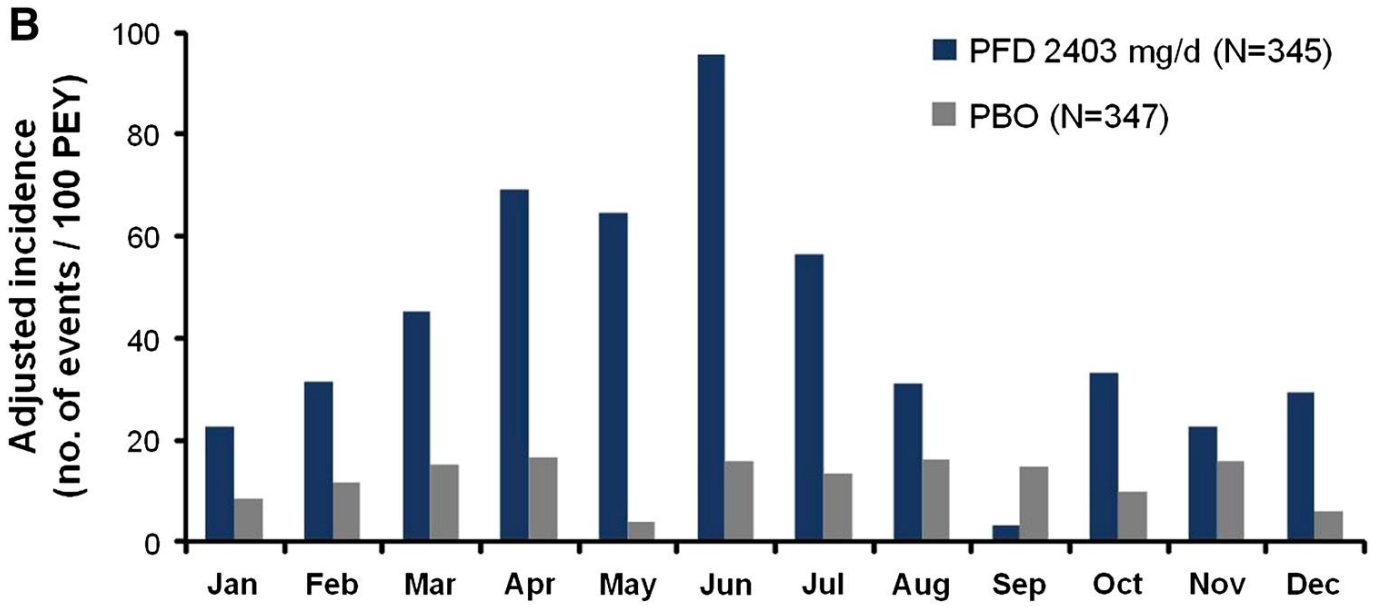


Seto Y, Inoue R, Kato M, Yamada S, Onoue S. Photosafety assessments on pirfenidone: photochemical, photobiological, and pharmacokinetic characterization. J Photochem Photobiol B. 2013;120:44–51.

Skin-related adverse effects in the CAPACITY studies

	Rash		Photosensitivity reaction	
	Pirfenidone 2,403 mg/day ($N = 345$)	Placebo ($N = 347$)	Pirfenidone 2,403 mg/day ($N = 345$)	Placebo ($N = 347$)
Grade 3 or 4 TEAEs, *n* (%)	2 (0.6)	0 (0.0)	3 (0.9)	1 (0.3)
TE SAEs, *n* (%)	1 (0.3)[a]	0 (0.0)	1 (0.3)	0 (0.0)
Deaths (*n*)	0	0	0	0
Hospitalization, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Discontinuation, *n* (%)	5 (1.4)	0 (0.0)	3 (0.9)	1 (0.3)
Dose modification, *n* (%)	42 (12.2)	5 (1.5)	19 (5.5)	1 (0.3)
Events (*n*)	159	52	60	8
Median duration (days)	38	31	88	60
Resolved, *n* (%)	132 (83)	46 (88)	47 (78)	6 (75)

Risk is all year but an increase risk is observed during the spring and summer months



European Medicine Agency. Pirfenidone CHMP assessment report.
http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_Public_assessment_report/human/002154/WC500103073.pdf

Interactive

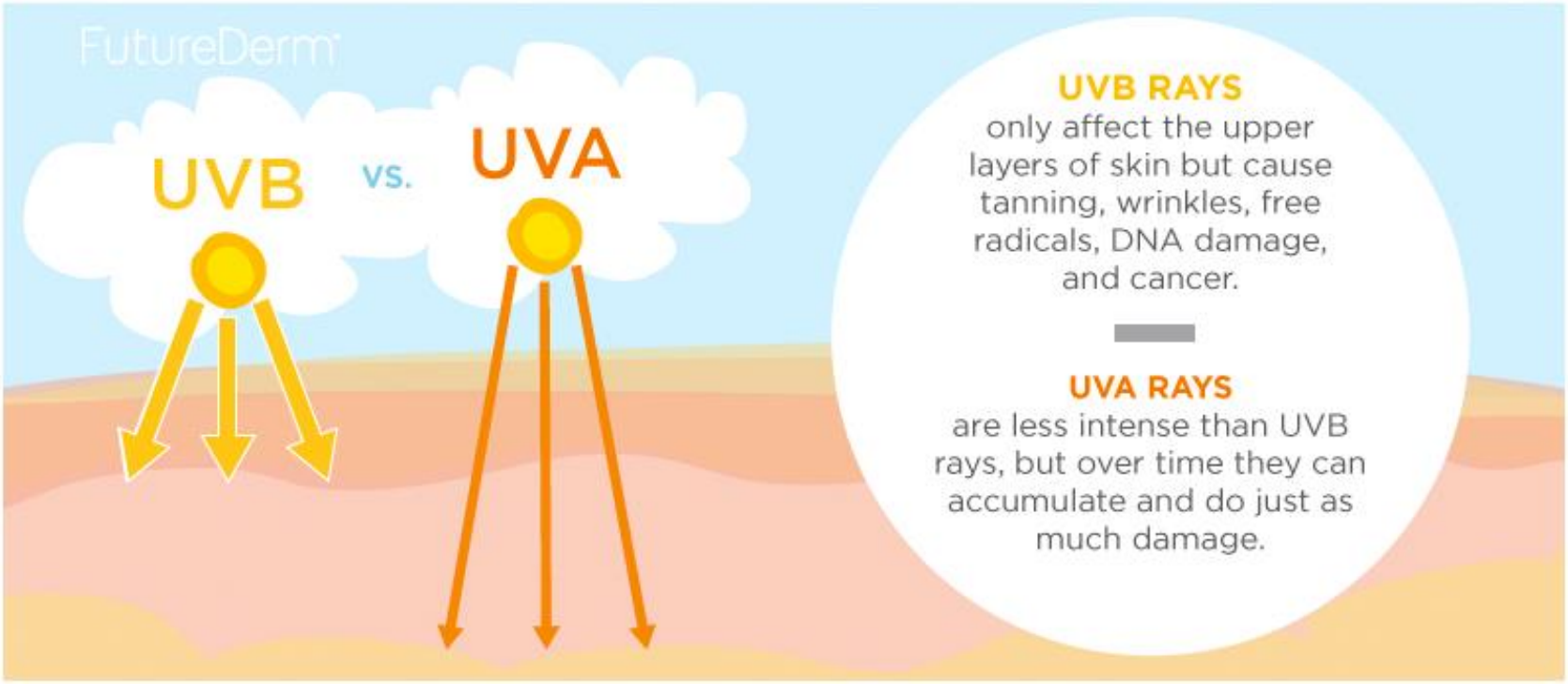
Which type of sun block would you recommend John uses?

1.SPF 30 UVB 2* UVA

2.SPF 50 UVB

3.SPF 30 UVB and UVA (5*)

4.SPF 50 UVB and UVA (5*)


FutureDerm
UVB
vs.
UVA
UVB RAYS
only affect the upper layers of skin but cause tanning, wrinkles, free radicals, DNA damage, and cancer.
UVA RAYS
are less intense than UVB rays, but over time they can accumulate and do just as much damage.

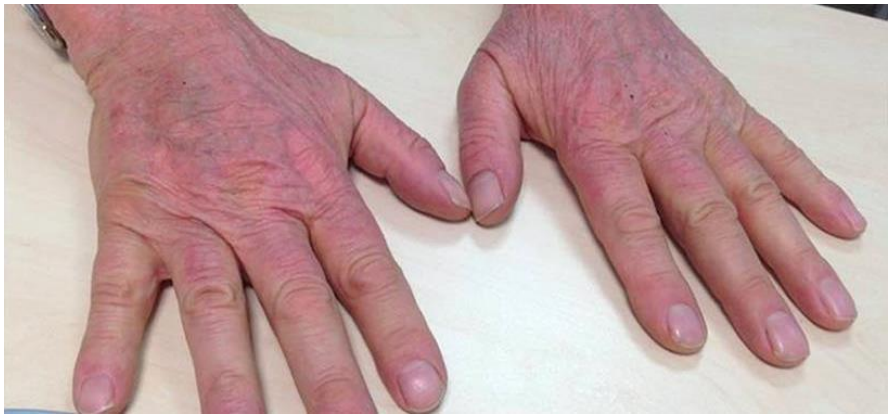
General advice about sun cream

- Apply 15 minutes before going out
- Reapply sun cream
- UVA (higher star rating) and UVB (SPF 50)
- Better to apply too much than too little – teaspoon per face/neck, teaspoon for each arm etc.
- Shelf life – 12-18 months (if stored in heat the expiry date is less)
- The sun's UV rays are strongest when your shadow is shorter than you
- UVA penetrates glass
- Vitamin D ?levels and supplementation

Once daily sun creams – Yes or No?

Once daily sun screens are NOT permitted in Australia

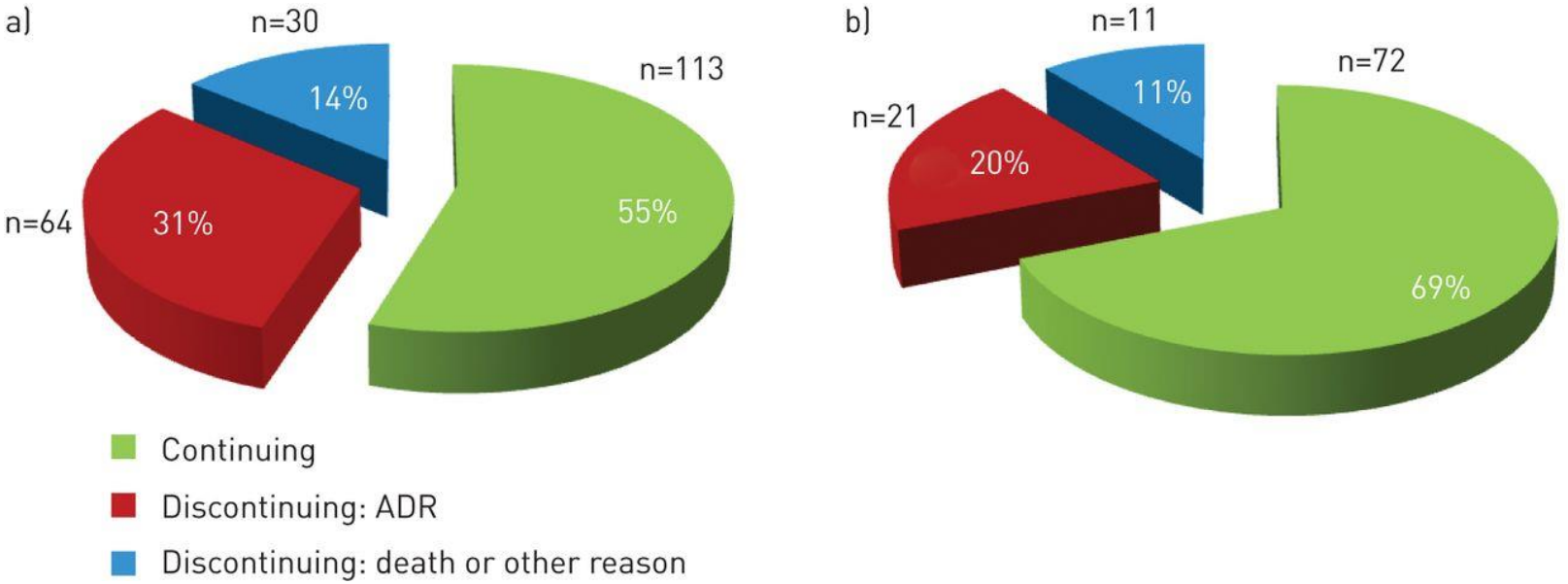
7 days later …….. improving but his skin is still red and itchy, so the pirfenidone stopped for 2 weeks …..



14 days later …….. Re-escalation of pirfenidone with the aim to increase to the full dose 2403mg/day over approx. 4 weeks

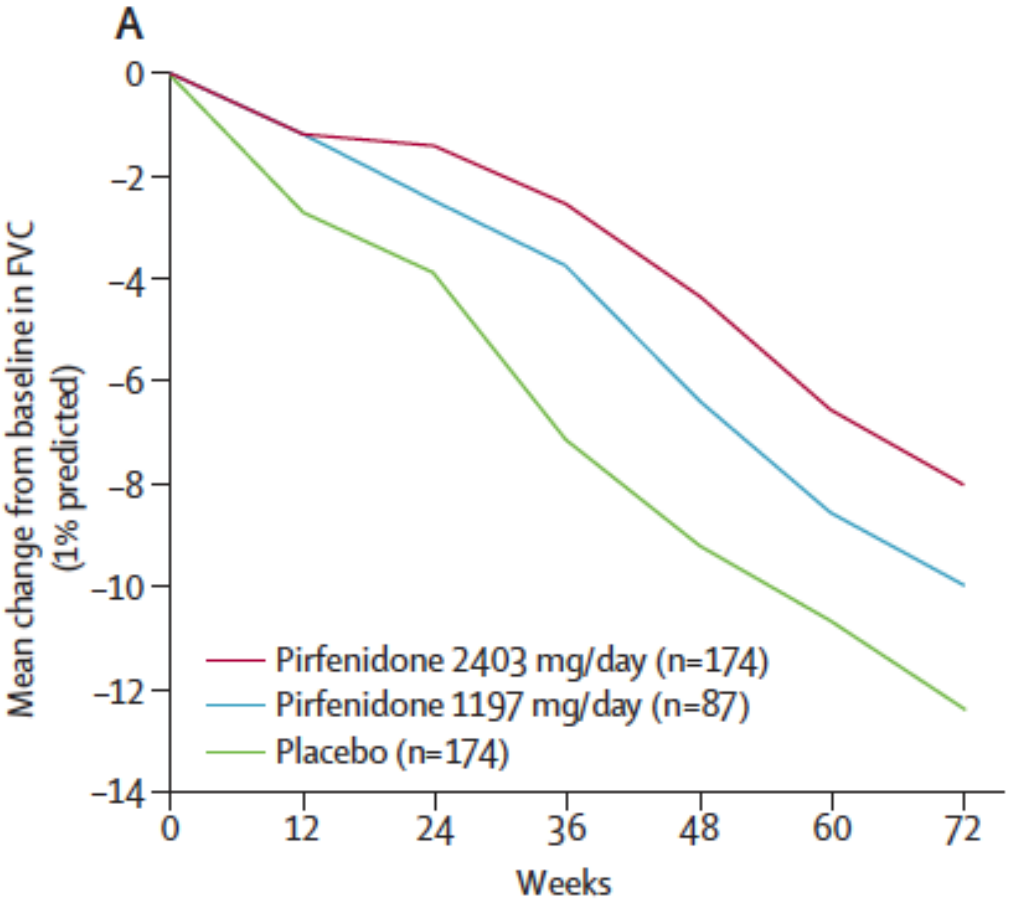
However, John would like to stay on 534mg (=2 capsules) TDS as he had no problems on the lower dose

Impact of dose adjustment in case of adverse drug reaction (ADR; includes dose interruption and/or reduction). a) No dose adjustment and b) dose adjustment.



Vincent Cottin, and Toby Maher Eur Respir Rev 2015;24:58-64

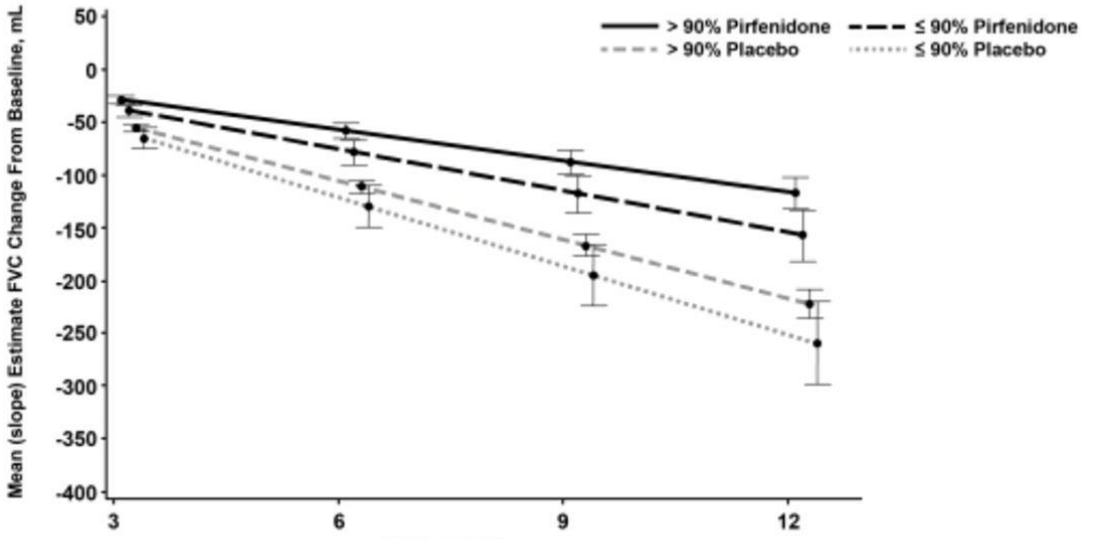
CAPACITY 004 study – lower dose



Absolute difference*	1·4%	2·5%	4·6%	4·8%	4·1%	4·4%
Relative difference*	53·5%	65·2%	63·7%	52·3%	38·3%	35·3%
p value†	0·061	0·014	0·0001	0·0009	0·0002	0·001

Impact of dose reduction on FVC

Forced Vital Capacity Volume With Linear Slope vs Time by Dose Intensity ≤ and > 90% (Based on Actual Dose) – (mITT Population)

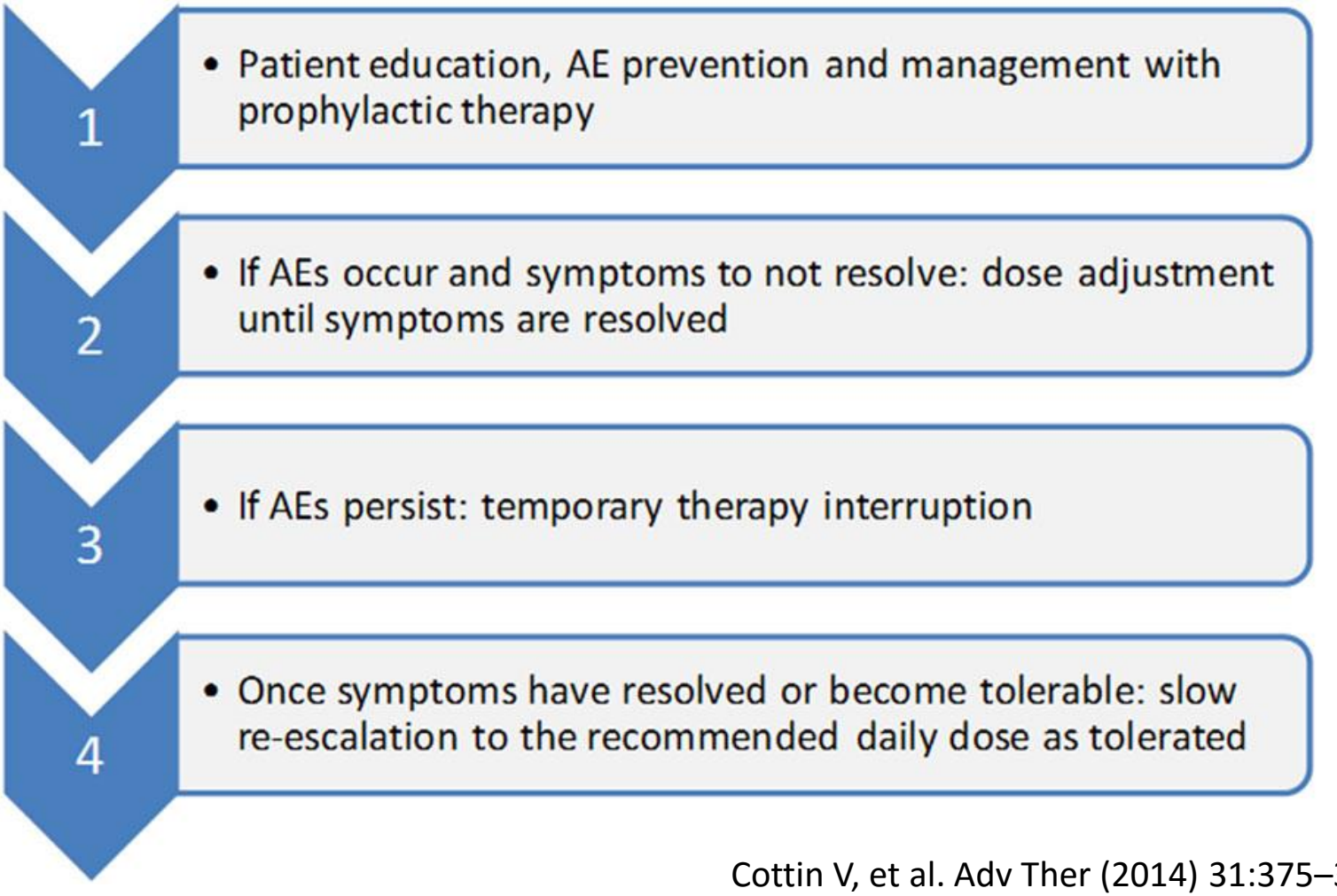


Number of Patients				
> 90% Pirfenidone	417	409	396	392
≤ 90% Pirfenidone	193	182	169	167
> 90% Placebo	545	531	508	497
≤ 90% Placebo	59	60	52	52

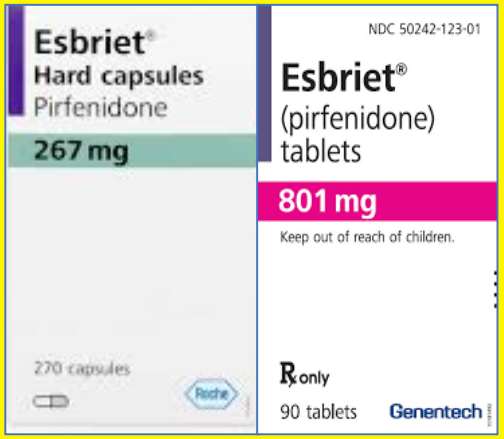
FVC, forced vital capacity; mITT, modified intent-to-treat.
Note: For missing values, no imputation was made. Months 3, 6, 9 and 12 correspond to weeks 12, 24, 36 and 48 for the CAPACITY 004 and CAPACITY 006 studies and weeks 13, 26, 39 and 52 for the ASCEND study. Calculated from the mixed linear model comparing pirfenidone 2403 mg/d with placebo, with change from baseline as the outcome variable. Study (CAPACITY 004, CAPACITY 006 and ASCEND), treatment, sex, age and height were fixed effects, whereas subject and assessment time were random effects in an unstructured variance–covariance matrix.

Steven Nathan et al. Eur Respir J 2016;48:OA1764

Stepwise approach to the prevention and management of pirfenidone-related AEs



Cottin V, et al. Adv Ther (2014) 31:375–391



Thank you

Any Questions?