

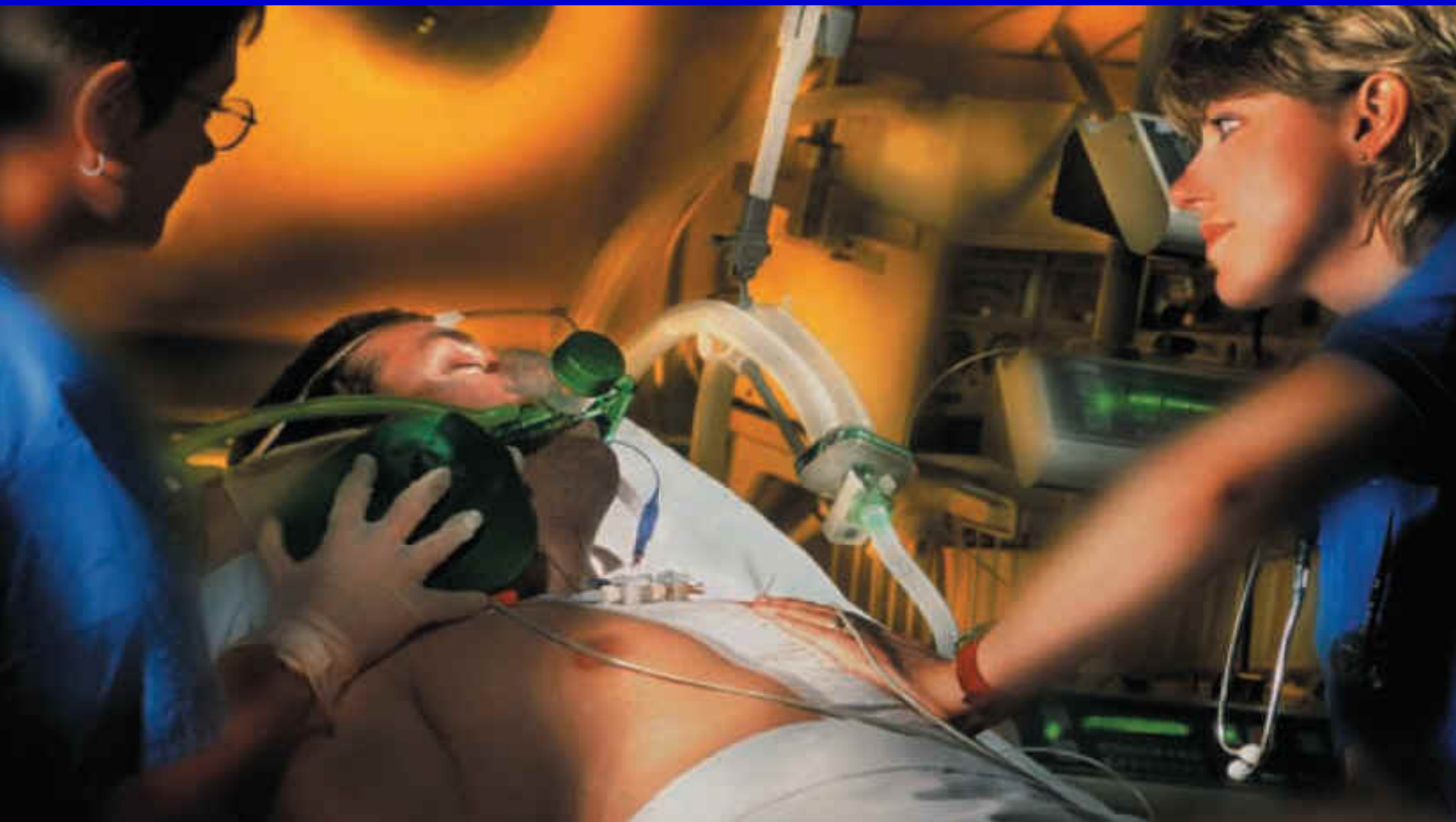
# Antifungal treatment of severe asthma

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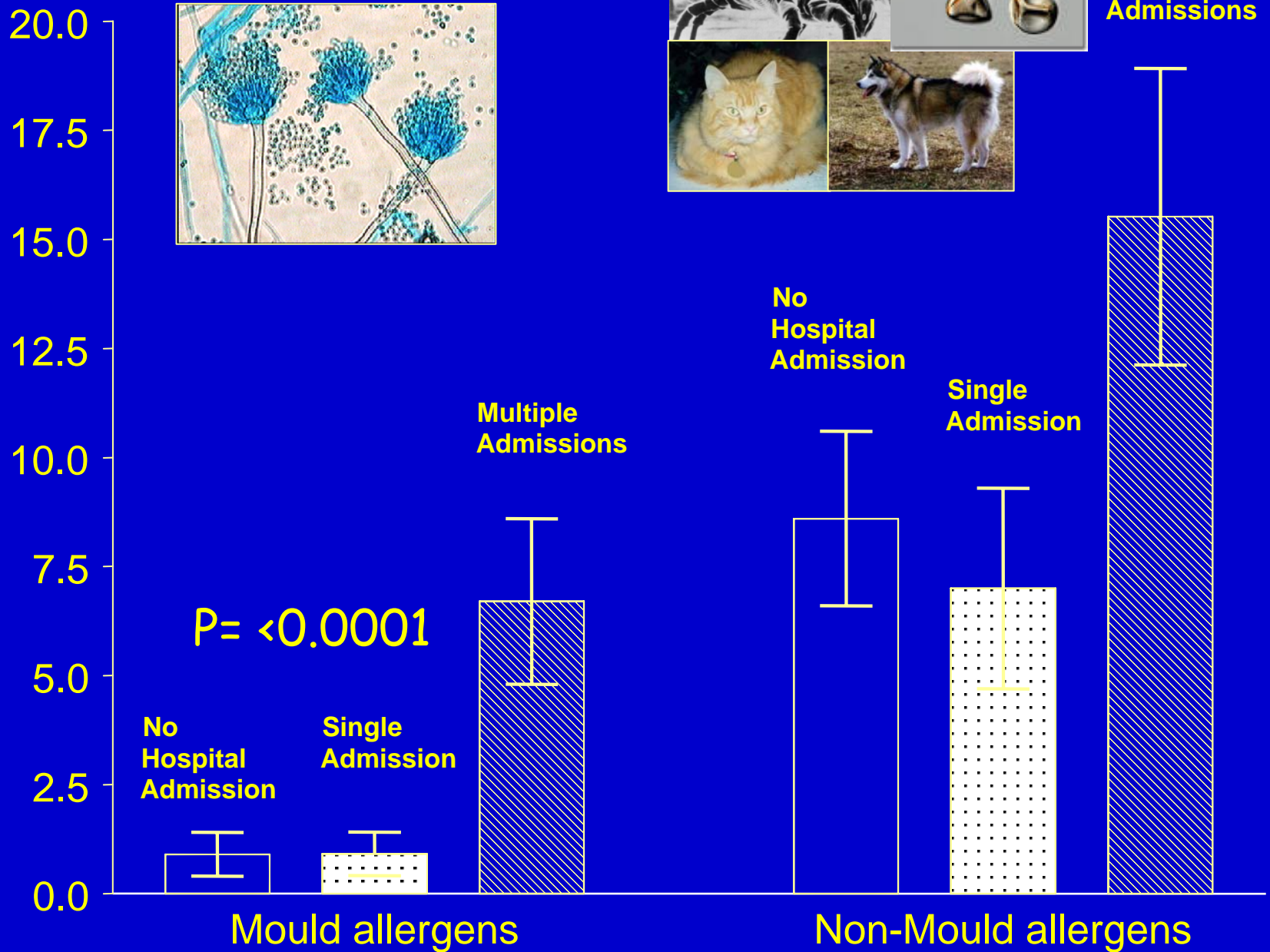
# Severe asthma



# Skin prick testing



Mean sensitization score (mm)  
(Mean and 95% CI)

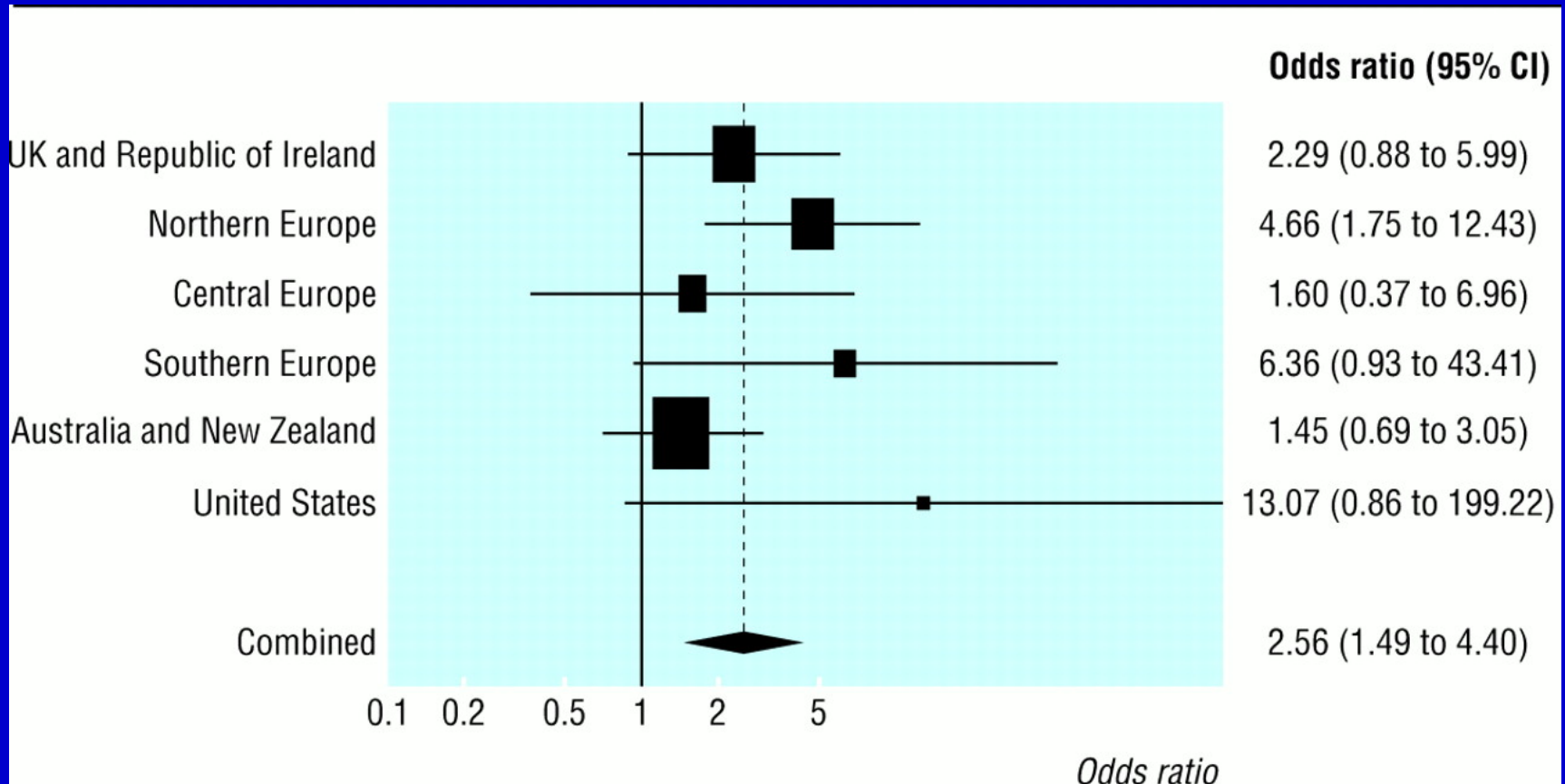


# Severe asthma and moulds

Mild asthma - 564 (50%)

Moderate asthma - 333 (29%)

Severe asthma - 235 (21%)



# Fungi and asthma

Needs new nomenclature

Asthma with fungal sensitisation

or

Severe Asthma with Fungal Sensitisation

ie

## SAFS

And what can we do about it?

Is antifungal therapy useful?



# Antifungal treatment of severe asthma with fungal sensitisation (SAFS)

11 patients with Trichophyton skin test allergy and moderate/severe asthma,

Rx with fluconazole or placebo for 5 months, then all received fluconazole.

Fluconazole v. placebo at 5 months

- Bronchial hypersensitivity reduced ( $p = 0.012$ )
- Steroid requirements reduced ( $p = 0.01$ )

Peak flow increased in 9/11 at 10 months

# Randomised trial of itraconazole in ABPA - results

Corticosteroid dependant ABPA with asthma

Phase 1 - 200mg BID v placebo, 16 weeks

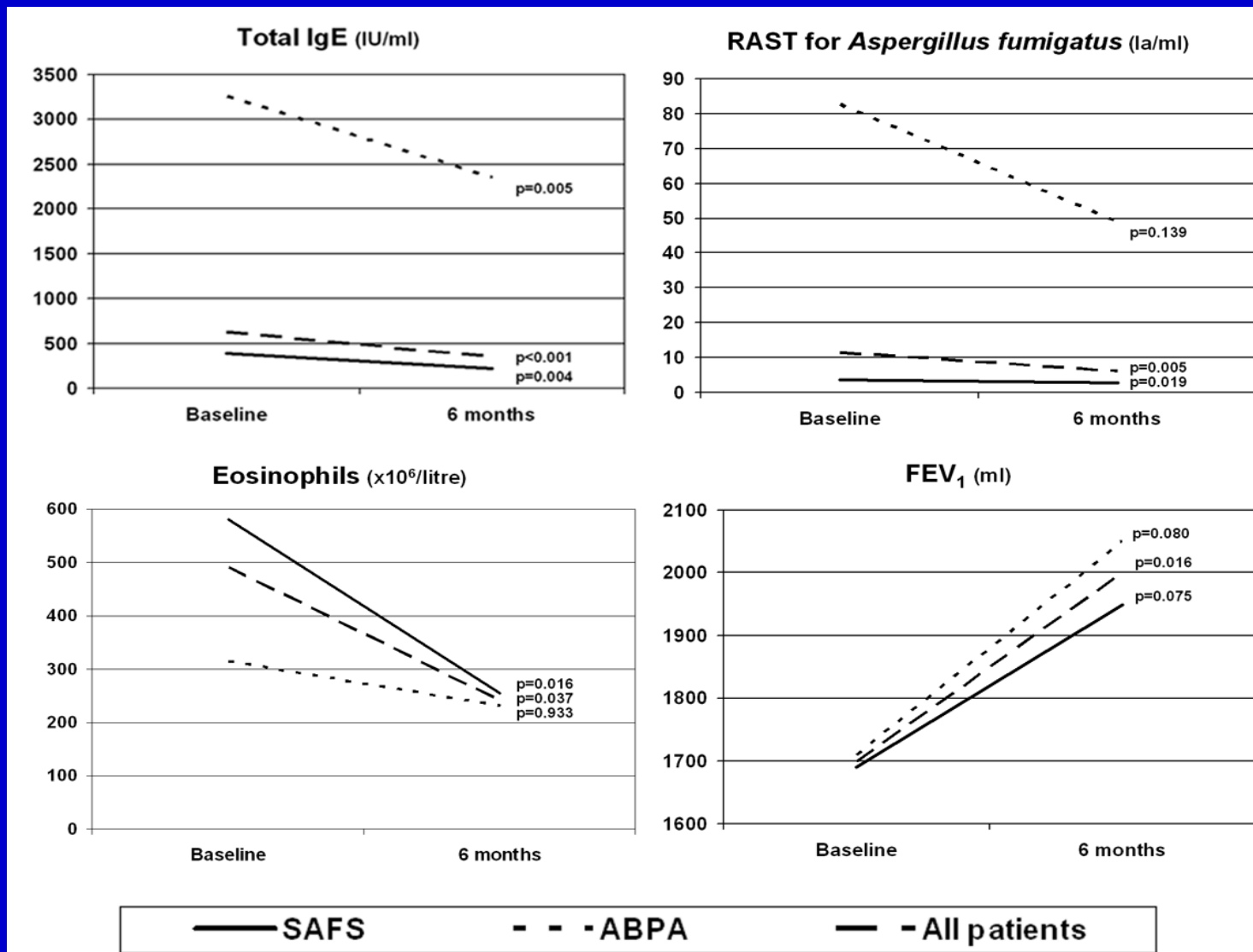
Phase II - 200mg daily in all patients, 16 weeks

	<u>Itra</u>	<u>Placebo then Itra</u>	
<u>Phase 1</u>			
Overall response	13/28 (46%)	5/27 (19%)	p=0.04
<u>Phase 2</u>			
No prior response (n=33)	4/13 (31%)	8/20 (40%)	NS



# Retrospective comparison of antifungal treatment of SAFS with ABPA

22 patients with SAFS were compared with 11 with ABPA



# Proof of concept RCT of antifungal Rx in SAFS

## Inclusion criteria

- Severe asthma [BTS 4 or 5] (ie high dose inhaled steroids, continuous oral steroids for >6 mo, or 4 courses of high dose oral/IV steroids in last 12 months, or 6 courses in last 24 mo.
- +
- Fungal sensitisation (RAST or skin test +ve) to *Aspergillus*, *Cladosporium*, *Alternaria*, *Penicillium*, *Candida*, *Trichophyton* and/or *Botrytis*

## Exclusion criteria

- Not ABPA (IgE <1000IU/mL) + -ve *Aspergillus* precipitins
- Recurrent bacterial chest infections (6 weekly)
- Prior azole therapy
- Cardiac failure
- LFTs >3x ULN

# Proof of concept RCT of antifungal Rx in SAFS - endpoints

## Primary endpoint

- Improvement in score of Asthma Quality of Life Questionnaire (AQLQ)

## Secondary endpoints

- Improvement in weekly peak flow
- FEV1 at 4, 8 and 12 months
- Exacerbation rate (both total and steroid requiring)
- Total IgE
- Rhinitis score
- Adrenal suppression indices

# Proof of concept RCT of antifungal Rx in SAFS - study plan

## Study plan

Randomised to itraconazole capsules (200mg BID) or placebo for 8 months (concealed by over-encapsulating)

Assessments are regular intervals, including scores, respiratory function, blinded itraconazole levels, LFTs

FU at 4 months post treatment

108 patients planned - 58 enrolled

# Baseline demographics - asthma

	Mean (range) or % (no.)	
	Active (n=29)	Placebo (n=29)
Gender (Male)	48% (14)	48% (14)
Age	49.2 (18, 79)	51.7 (19, 76)
Severity of asthma (BTS) <sup>1</sup> (>4)	3% (1)	11% (3)
Baseline total serum IgE (IU/L)#	212 (24,820)	245 (36,990)
Baseline eosinophilia (>0.4 × 10 <sup>9</sup> ) <sup>1</sup>	24% (7)	43% (12)
No. of hospitalisations last 12 months <sup>4</sup>		
Median (range)	0 (0, 5)	0 (0, 8)
% with none	61% (14)	83% (20)
Requiring continuous oral steroids	7% (2)	14% (4)
Requiring > 1000ug/d inhaled steroid	69% (20)	72% (21)
FEV <sub>1</sub> (L/min) <sup>1</sup>	2.15 (0.5, 4.35)	2.14 (0.65, 3.85)
FEV <sub>1</sub> (% predicted) <sup>1</sup>	71.8 (18, 121)	71.1 (27, 124)
Baseline rhinitis score	1.27 (0, 3.88)	1.29 (0, 2.70)
Baseline AQLQ score	4.12 (2.2, 7.0)	4.14 (1, 6.6)

# Baseline demographics - fungal

	Mean (range) or % (no.)	
	Active (n=29)	Placebo (n=29)
<b>Superficial fungal infection (in past)</b>		
<i>Oral thrush</i>	31% (9)	41% (12)
<i>Genital thrush</i>	17% (5)	21% (6)
<i>Fungal nail infection</i>	17% (5)	21% (6)
<i>Fungal skin rash</i>	3% (1)	3% (1)
<i>Athletes foot</i>	21% (6)	31% (9)
<i>Any of above five</i>	62% (18)	83% (20)
<b>Baseline positive fungal RAST</b>		
<i>Aspergillus</i>	52% (15)	52% (15)
<i>Cladosporium</i>	31% (9)	17% (5)
<i>Alternaria</i>	21% (6)	32% (9)
<i>Penicillium</i>	39% (11)	17% (5)
<i>Candida</i> <sup>1</sup>	52% (15)	46% (13)
<i>Trichophyton</i>	31% (8)	19% (5)
<i>Botrytis</i>	17% (5)	14% (4)

# Proof of concept RCT of antifungal Rx in SAFS - key results

Patients enrolled & randomised N = 58

Active (itraconazole) N = 29

Placebo N = 29

Withdrawal in  $\leq 4$  weeks

Active N= 3

Placebo N=1 (p=0.60)

MITT analysis set (active) N =26

MITT analysis set (placebo) N =28

**P=0.014**  
**AQLQ  $\Delta = 0.82$**

Withdrawal 4-32 weeks

Active N= 8

Placebo N=5 (p=0.25)

Per protocol analysis set (active)  
N= 18

Per protocol analysis set (placebo)  
N=23

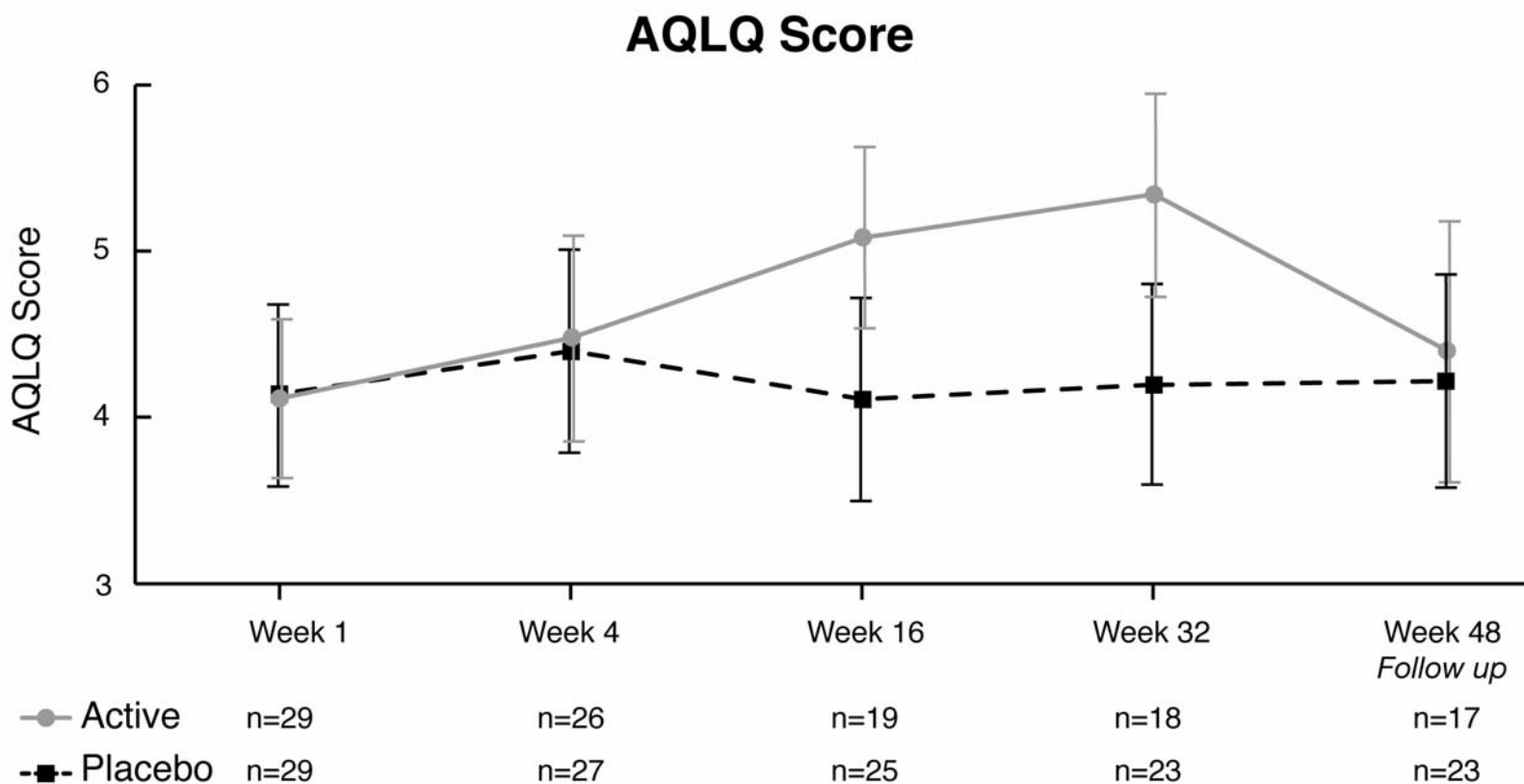
**P=0.002**  
**AQLQ  $\Delta = 1.18$**



# Proof of concept RCT of antifungal Rx in SAFS - outcomes at 32 weeks MITT

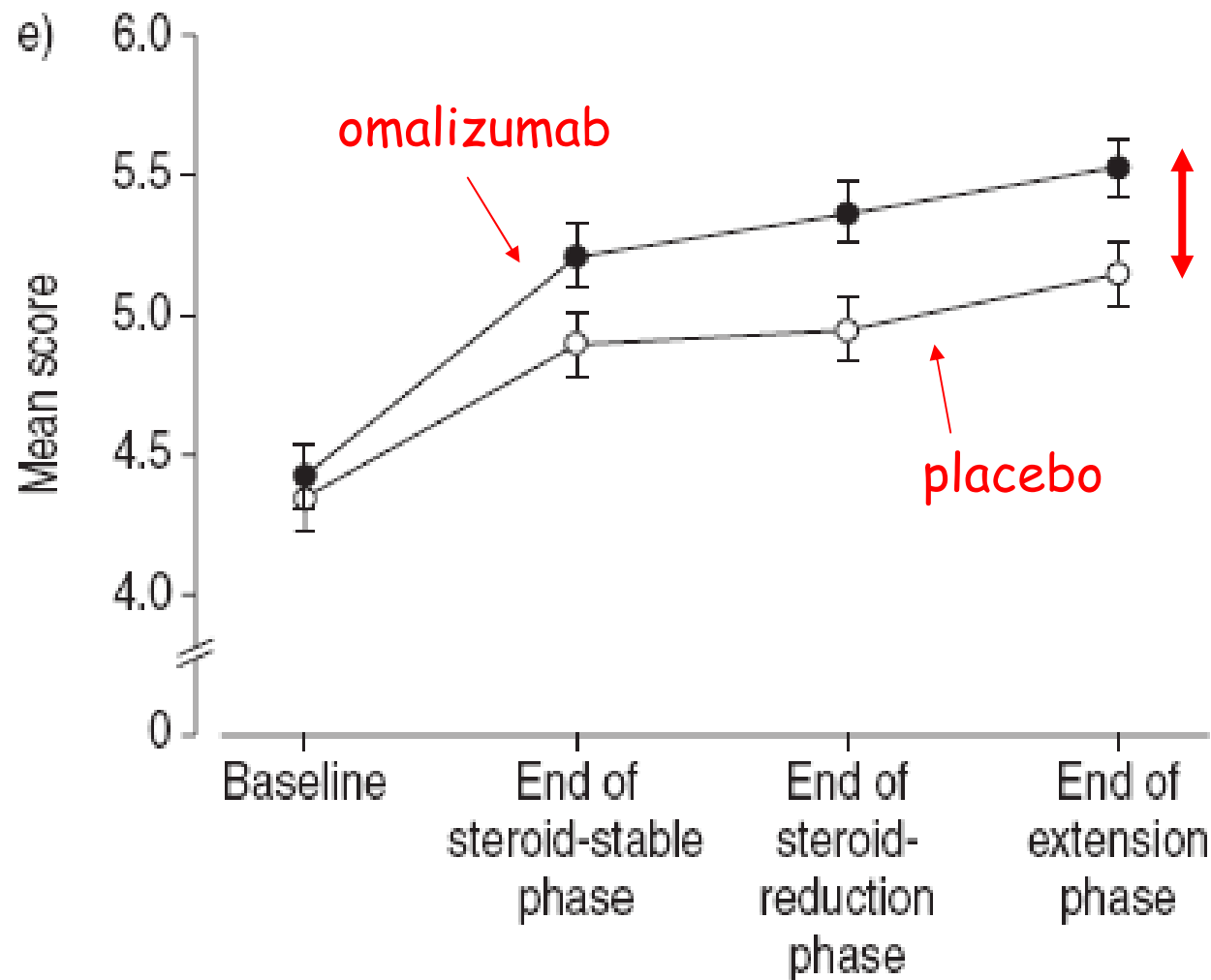
	Mean (95% CI) or % (n)		P-value
	Active	Placebo	
Change in AQLQ score	+0.85 (0.28, 1.41)	-0.01 (-0.43, 0.42)	0.014
Improvement in AQLQ score of >0.5	54% (14)	32% (9)	0.18
Percentage change in total IgE (IU/L)	-27% (-14%, -38%)	+12% (-5%, +31%)	0.001
Change in FEV1 (L/min)	-0.22 (-0.56, 0.11)	-0.02 (-0.16, 0.11)	0.22
Change in FEV1 (% predicted)	-3.66 (-9.39, 2.08)	0.13 (-3.67, 3.93)	0.24
Change in average PEFr (am)	20.8 (3.5, 38.1)	-5.5 (-21.6, 10.7)	0.028
Change in average PEFr (pm)	16.8 (1.5, 35.2)	8.9 (-33.9, 51.8)	0.74

# Proof of concept RCT of antifungal Rx in SAFS - AQLQ change



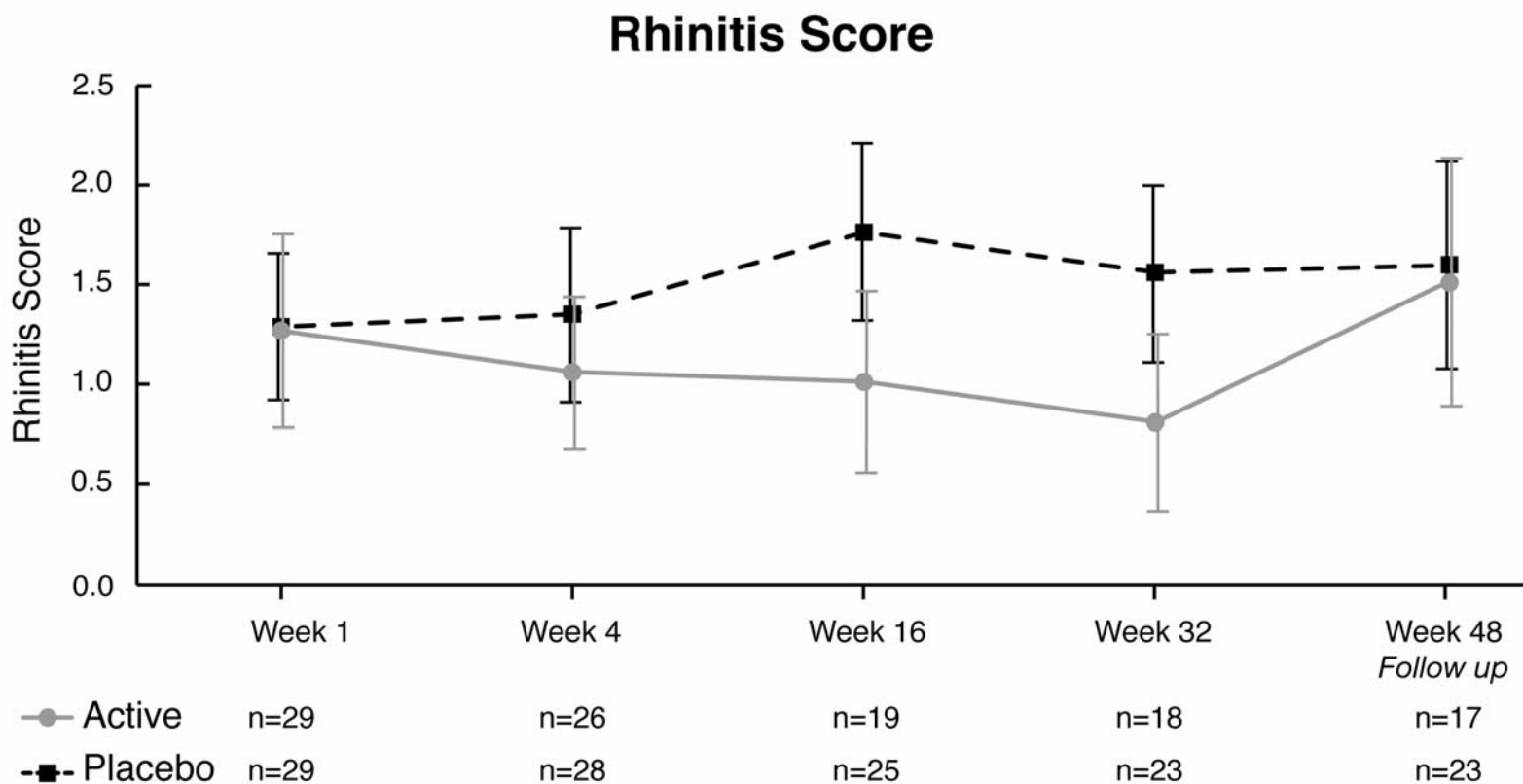
P= 0.014

# RCT of anti-IgE (omalizumab) v. placebo, moderate and severe asthma



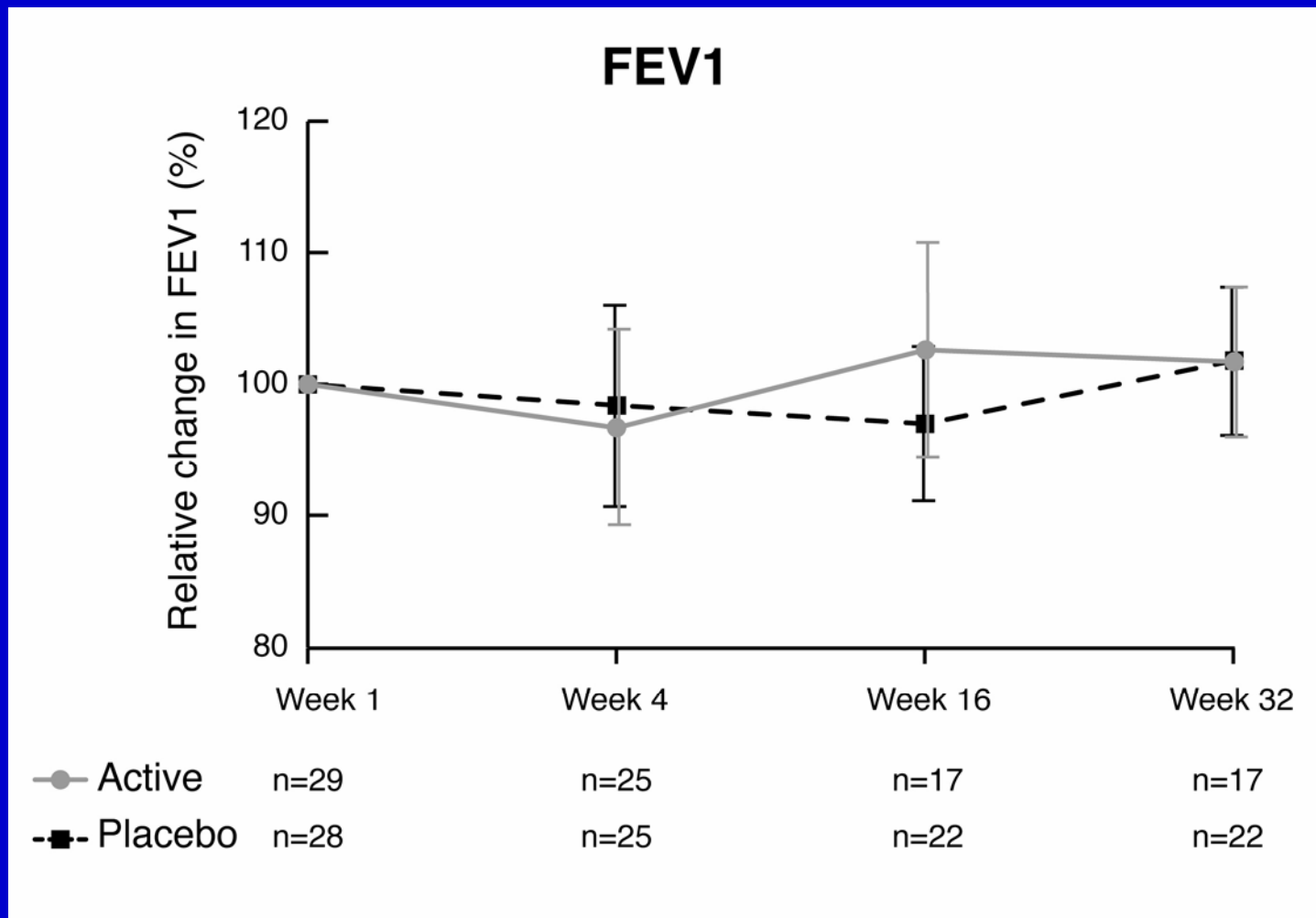
Improvement in  
AQLQ  $\Delta = \sim 0.4$

# Proof of concept RCT of antifungal Rx in SAFS - improvement in rhinitis



P= 0.013

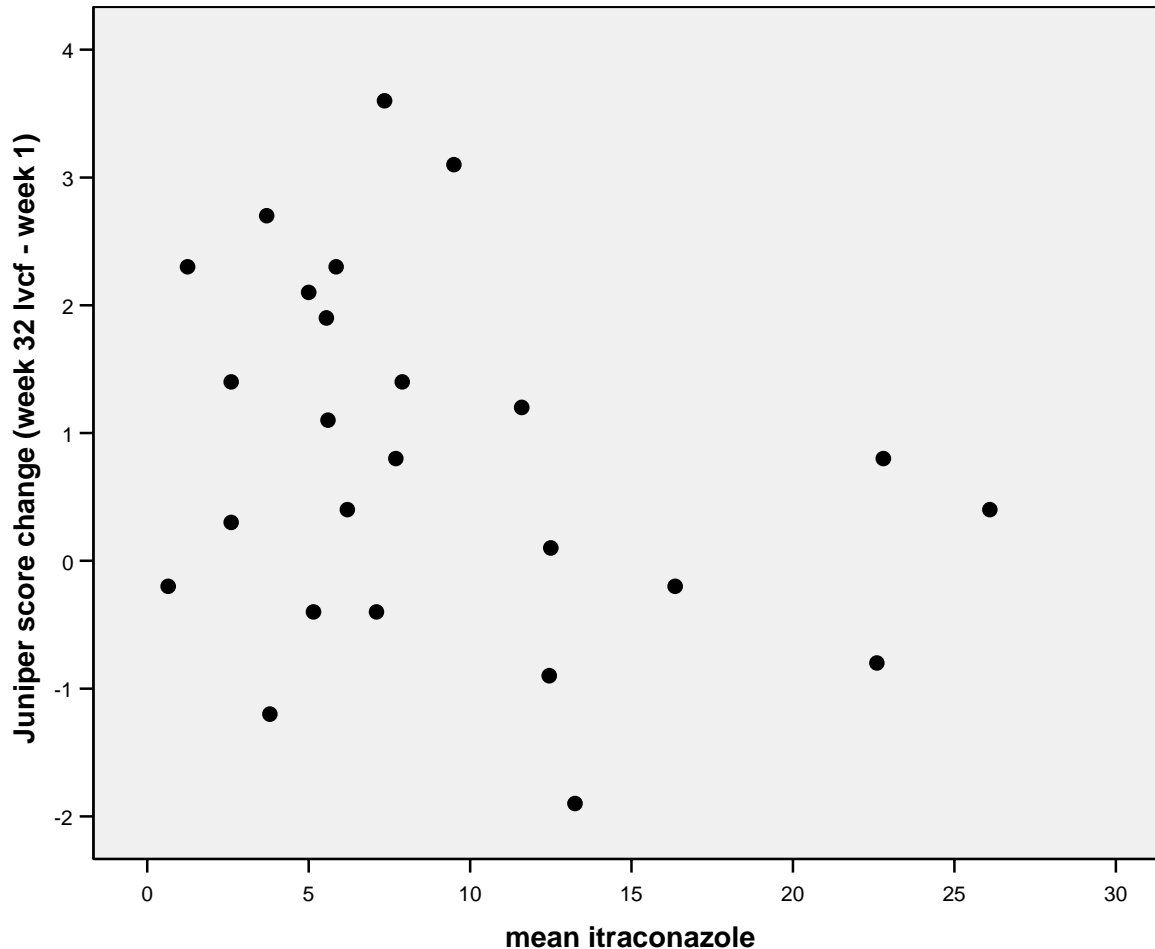
# Proof of concept RCT of antifungal Rx in SAFS - respiratory function change



P= 0.22

# Proof of concept RCT of antifungal Rx in SAFS - respiratory function change

Juniper change vs itraconazole level



No relationship  
between  
itraconazole level  
and change in AQLQ  
at wk 32  
 $p = 0.22$

# Why is antifungal therapy effective?

Three reasonable hypotheses:

- Reduction in fungal burden/exposure
- Enhanced corticosteroid effect
- Immune system effect of itraconazole

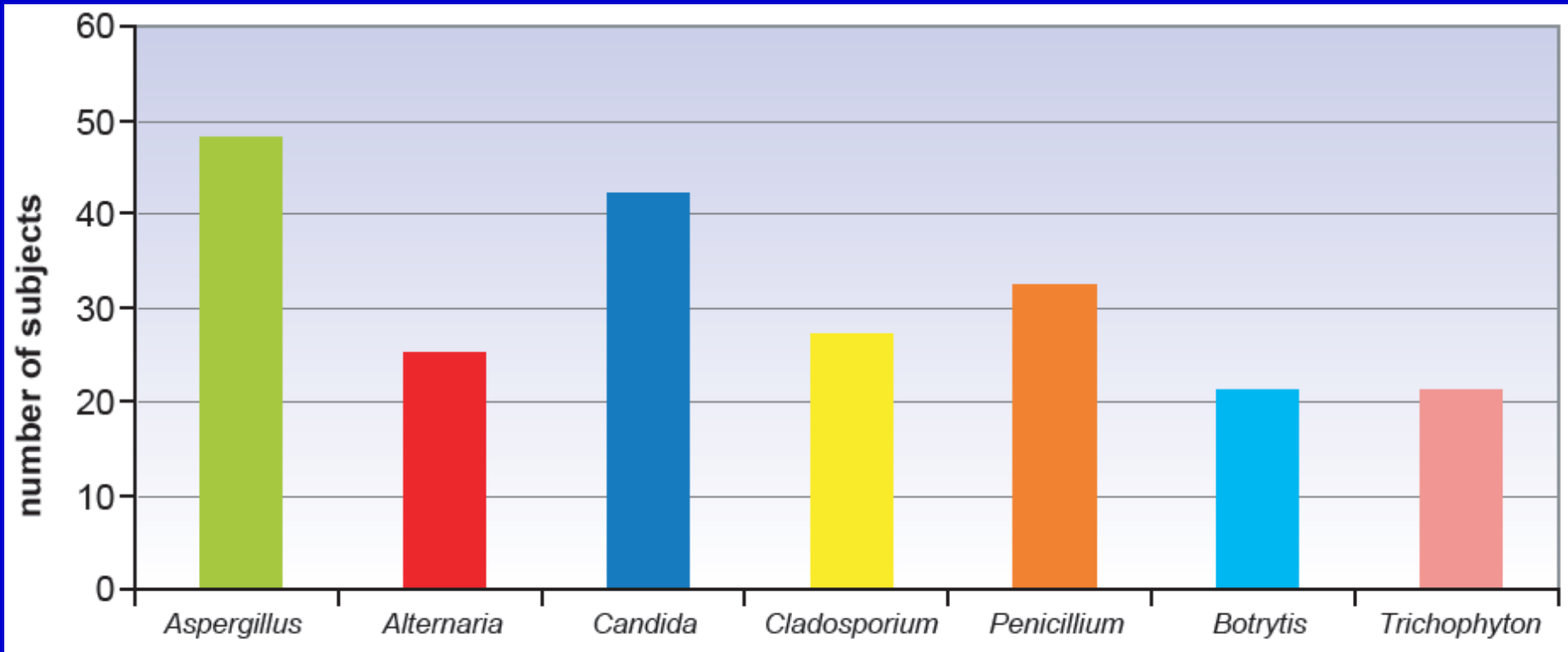


# Colonisation or infection with fungus

- Short-lived exposure to viable hyphal fragments
- Sinus colonisation
- Gut colonisation with *Candida*
- Skin infection with dermatophytes (Athlete's foot for example)

# Proof of concept RCT of antifungal Rx in SAFS

Fungi that patients are sensitised to (skin test or IgE)



# Colonisation in 'normal' lungs

Table I. Patients and pulmonary fungal carriage.

Study group	Patients (n = 74)	Fungal growth (n = 46)	No fungal growth (n = 28)
Autopsy patients	18	11 (61.1%)	7 (38.9%)
Surgical patients	56	35 (62.5%)	21 (37.5%)

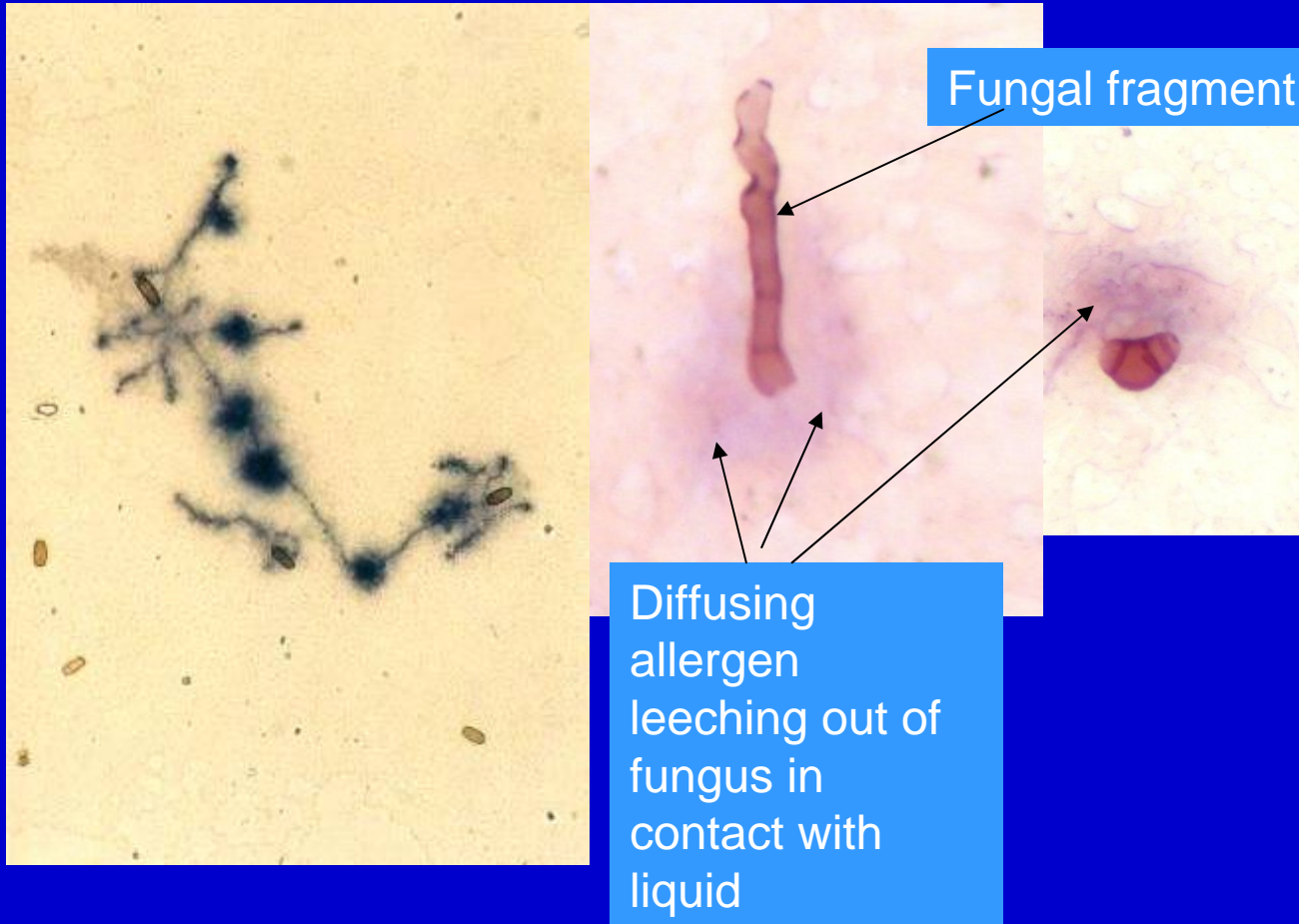
22 of 30 (73%) grew a fungus  
in both lung samples taken

10/30 (33%) grew >1 species

Table II. Presence of fungi detected.

Species	No. of patients with fungal colonization	
	Autopsy patients (n = 7)	Surgery patients (n = 23)
<i>A. fumigatus</i>	6	17
<i>A. flavus</i>	2	7
<i>A. niger</i>	1	3
<i>A. terreus</i>	1	1
<i>A. glaucus</i>	0	1
<i>Mucor</i> spp.	2	7
<i>Penicillium</i> spp.	2	5
<i>Candida</i> spp.	1	0

# Airborne fungal fragments



# Proof of concept RCT of antifungal Rx in SAFS - itraconazole inhaled steroid interaction

Study group	Plasma cortisol		
	Baseline	4 weeks	4 months post treatment
<b>Concentrations - mean (range)</b>			
Itraconazole	222.4 (92-386)	149.8 (<30- 642)	206.2 (109-907)
Placebo	518.5 (75-770)	480.6 (155-1026)	401.6 (107-539)
<b>Detectable concentrations (&gt;50 mmol/L) - number positive/number tested (%)</b>			
Itraconazole	13/13 (100)	6/12 (50)	7/7 (100)
Placebo	14/14 (100)	13/13 (100)	9/9 (100)

AQLQ score improvement in  
Itraconazole + interaction = 1.0  
Itraconazole & no interaction = 0.97

# Comparison of ABPA and SAFS

**TABLE 2** Definition of allergic bronchopulmonary aspergillosis (ABPA) and proposed definition of severe asthma with fungal sensitisation (SAFS), with some additional features

Feature	ABPA <sup>#</sup>	SAFS (proposed)
<b>Clinical features</b>		
Asthma	Any severity	Severe <sup>†</sup>
Pulmonary infiltrates (history)	Yes, which resolve with corticosteroids	No
Eosinophilia	Yes, if not on systemic corticosteroids	Not studied, but not required
Central bronchiectasis	Yes, but many patients with early disease do not have this feature	No
Thick mucous plugs	Yes, usually	Unknown
Chronic rhinosinusitis, with or without nasal polyps	Occasional	Sometimes
<b>Fungal features</b>		
<i>Aspergillus precipitins</i> positive (2 × asthma control)	Yes (almost all cases)	No
<i>Aspergillus</i> IgG test positive (2 × asthma control)	Yes	No
<i>Aspergillus</i> prick test positive (>3 mm)	Yes	Yes or no <sup>†</sup>
Other fungal skin tests positive (>3 mm)	No <sup>§</sup>	Yes or no <sup>†</sup>
Serum IgE elevated (>1000 IU·mL <sup>-1</sup> )	Yes (may be only >500 IU·mL <sup>-1</sup> , especially if on corticosteroids)	No (<1000 IU·mL <sup>-1</sup> )
<i>Aspergillus</i> -specific RAST test positive (2 × asthma control)	Yes	Yes or no <sup>†</sup>
Other fungal RAST test positive	No <sup>§</sup>	Yes or no <sup>†</sup>
Airways colonised by <i>Aspergillus fumigatus</i>	Yes	Unknown

<sup>†</sup>: at least one fungal skin or RAST test positive (better and more specific tests may emerge in the future);

# CPA and TLRs

SNP	Study groups (n)	Genotype			Allele		X <sup>2</sup>	p value	OR (95% CI)
		n (% frequency)			n (% frequency)				
TLR2		A/A	A/G	G/G	A	G			
Arg753Gln	Controls (80)	0 (0.0)	5 (6.2)	75 (93.8)	5 (3.1)	155 (96.9)			
	ABPA (22)	0 (0.0)	0 (0.0)	22 (100)	0 (0.0)	44 (100.0)	1.41	0.587	1.032 (1.004-1.061)
	SAFS (14)	0 (0.0)	2 (14.3)	12 (85.7)	2 (7.1)	26 (92.9)	1.07	0.280	2.385 (0.439-12.944)
	CCPA (40)	0 (0.0)	2 (5.0)	38 (95.0)	2 (2.5)	78 (97.5)	0.07	1.000	0.795 (0.151-4.190)
TLR4		A/A	A/G	G/G	A	G			
Asp299Gly	Controls (80)	70 (87.5)	10 (12.5)	0 (0.0)	150 (93.8)	10 (6.3)			
	ABPA (22)	21 (95.5)	1 (4.5)	0 (0.0)	43 (97.7)	1 (2.3)	1.07	0.463	0.349 (0.043-2.802)
	SAFS (14)	12 (85.7)	2 (14.3)	0 (0.0)	26 (92.9)	2 (7.1)	0.03	0.695	1.154 (0.239-5.570)
	CCPA (40)	25 (62.5)	<b>15 (37.5)</b>	0 (0.0)	65 (81.3)	<b>15 (18.8)</b>	8.93	0.003	3.462 (1.477-8.110)
TLR9		T/T	T/C	C/C	T	C			
T-1237C	Controls (80)	65 (81.2)	15 (18.8)	0 (0.0)	145 (90.6)	15 (9.4)			
	ABPA (22)	14 (63.6)	7 (31.8)	1 (4.54)	35 (79.5)	<b>9 (20.5)</b>	4.08	0.043	2.486 (1.005-6.145)
	SAFS (14)	13 (92.9)	1 (7.1)	0 (0.0)	27 (96.4)	1 (3.6)	0.03	0.474	0.358 (0.045-2.825)
	CCPA (40)	33 (82.5)	7 (17.5)	0 (0.0)	73 (91.3)	7 (8.8)	0.02	0.874	0.927 (0.362-2.373)



# Likely SAFS caseload

In 2002 - 15,960,496 adults with self-reported asthma in the USA

In Europe - >17,000,000 adults with asthma

~20% have severe asthma = 6,600,000 adults

20-50% of severe asthmatics have SAFS

SAFS cases (US +EU) = 1,320,000 – 3,300,000