Chair's presentation

Pirfenidone for treating idiopathic pulmonary fibrosis

3rd Appraisal Committee meeting (post appeal)

Committee B

Lead team: Sanjay Kinra, Nigel Westwood, Mark Chapman

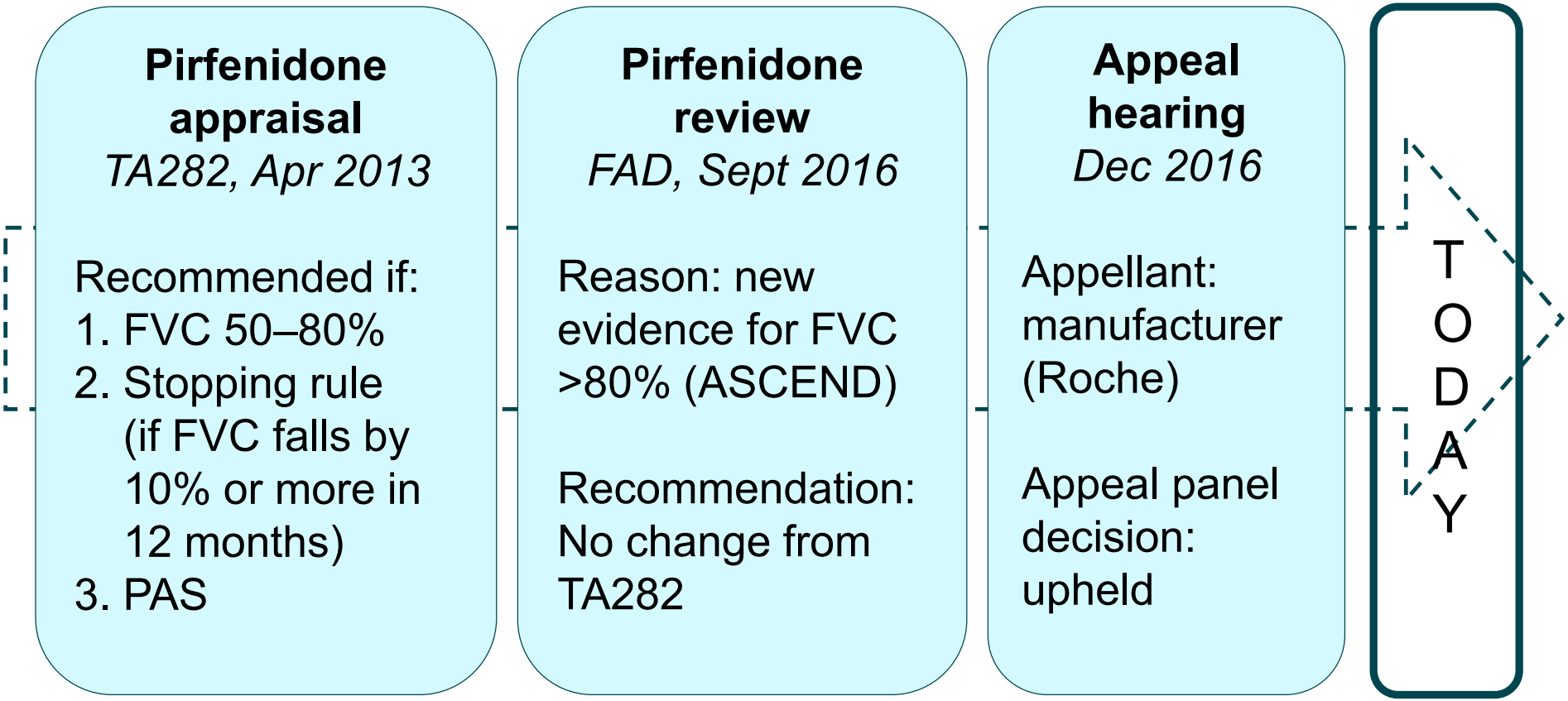
ERG: School of Health and Related Research (ScHARR), University of Sheffield

NICE technical team: Jasdeep Hayre, Sophie Cooper

Company: Roche

20 April 2017

History of pirfenidone appraisals



FVC = forced vital capacity PAS = Patient access scheme discount

Original scope for review

Population	Adults with mild to moderate idiopathic pulmonary fibrosis
Intervention	Pirfenidone
Comparator(s)	• best supportive care • nintedanib (only if % predicted FVC 50–80%)
Outcomes	• pulmonary function parameters • physical function • exacerbation rate • progression-free survival • mortality • adverse effects of treatment • health-related quality of life
Subgroups	Subgroup analysis by percent predicted FVC: 50–80% (“moderate”) and >80% (“mild”)

Appeal points from Roche

Ground 1(a): NICE has failed to act fairly
Ground 2: Recommendation is unreasonable in the light of the evidence

- Committee did not consider the totality of the data in respect of the full licensed population; considering subgroups based on FVC was inappropriate (grounds 1 and 2)
- Assessment of clinical effectiveness was perverse (ground 2)

- Determining that the subgroup of people with FVC 80–90% predicted was the relevant population for decision making (para 4.5 FAD), was inadequately reasoned, unfair and contrary to the methods guide
- There are no “know, biologically plausible mechanisms, social characteristics or other justified factors” to justify this subgroup
- Despite no evidence of a difference in pirfenidone’s effectiveness according to FVC, committee concluded that there was a difference

Summary of appeal panel considerations

- Consider full population first, with a view to making 1 recommendation
- If a product appeared acceptably cost effective in a whole population, not normally reasonable to look for cost-ineffective subgroups
  - but, hypothetically, reasonable to consider subgroups for whom the product is cost-ineffective
- Panel not yet persuaded it was reasonable to divide population into subgroups, but did not rule out a more fully reasoned approach for considering subgroups
- FVC 80% and 90% predicted acceptable thresholds to define subgroups
  - 80% represents clinical practice
  - 90% because it represents clinical trial data
- Acceptable to consider subgroups in the face of limited data for a group

Appeal panel final conclusions

Committee must take all reasonable steps to demonstrate consideration of the effectiveness and cost effectiveness of pirfenidone in the whole population as set out in the scope

Subgroups defined by predicted FVC could be considered if the treatment is not judged cost-effective in the whole population

Note: economic theory (Sculpher 2008), and the appeal panel's hypothetical considerations, support a different approach (next slide)

Appraisal committee's assessment of **clinical** effectiveness of pirfenidone in any subgroup should be clearly documented, including any uncertainty in the available evidence

Note: this will not impact cost-effectiveness, because model assumed the same relative treatment effect for both subgroups

Sculpher MJ. Subgroups and heterogeneity in cost-effectiveness analysis. Pharmacoeconomics 2008; 26 (9): 799-806

Point 1, consideration of subgroups: statement from NICE Guidance Executive

- NICE guidance executive
  - accept that committee should consider the full population,
  - disagree with the notion that subgroups can only be considered if the treatment is not cost effective in the whole population
- Instead, committee should provide a fully reasoned approach of any inclusion or exclusion of subgroups from its final recommendations

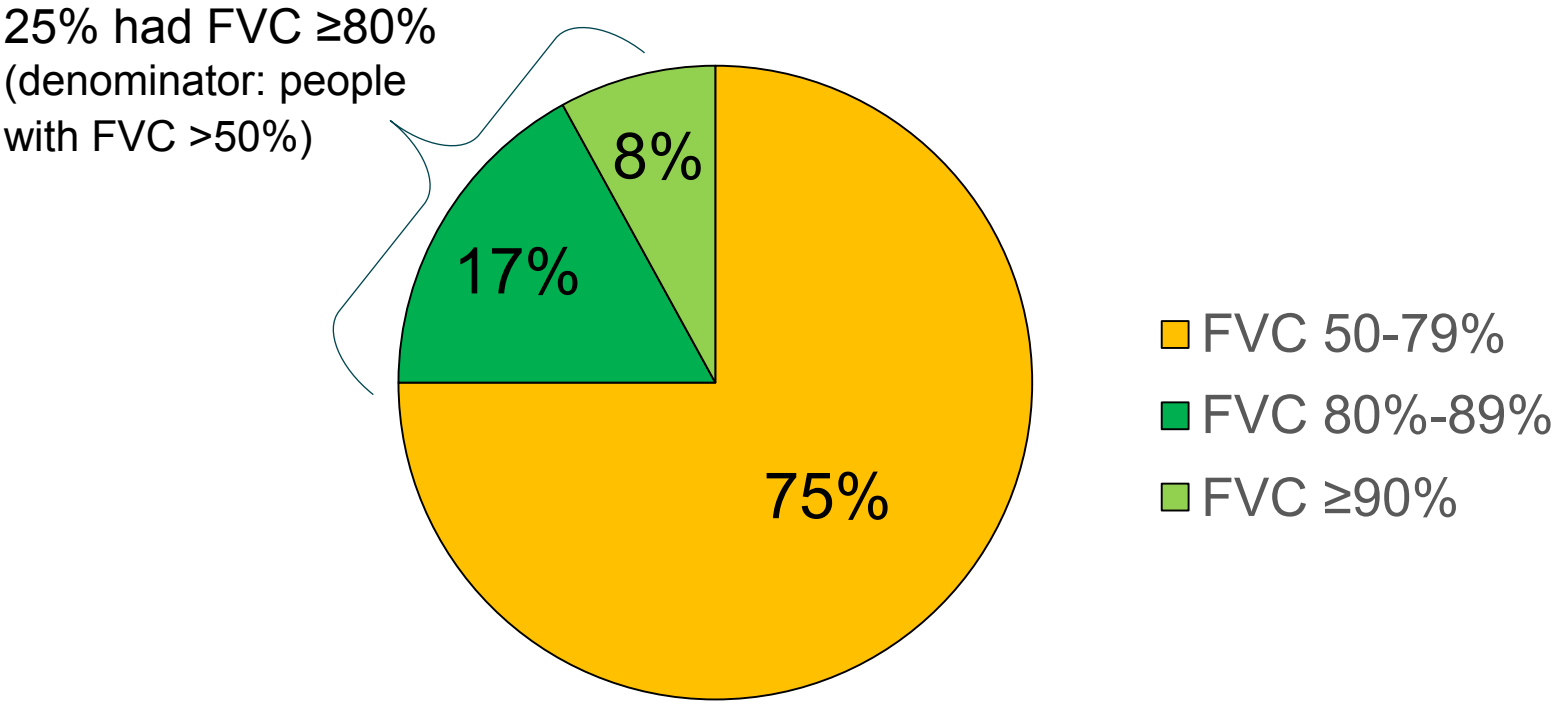
⊙ What constitutes a ‘fully reasoned approach’? For example:
Relative size of the subgroup populations
Quality of the evidence
Implications of ‘type 1 error’
Absolute risk of benefit
Others?

Point 2, clinical effectiveness: comments from NICE technical team

- Committee has already concluded on the effectiveness in subgroups
  - no new evidence has been presented
  - conclusions in the FAD will be clarified
- Doesn’t impact ICERs for subgroups
  - the model assumed same relative treatment effect for the 2 subgroups (FVC <80% and ≥80% predicted)
  - this assumption will be clearly stated in the updated FAD

Distribution of FVC in pirfenidone trials and current practice

Figure: Pooled data from ASCEND, CAPACITY 1 & CAPACITY 2 (n=1247)



Current UK practice: **41%** have FVC >80% predicted *(denominator: FVC >50%)*

(source: British Thoracic Society prospective IPF Registry, n=711, Sept 2016)

Committee's considerations

Issue	Committee's conclusion *(FAD section number)*
Clinical evidence	Evidence only generalisable to people with FVC ≤90% predicted *(4.5)*
	Nothing contradicted TA282 conclusion that pirfenidone effective *(4.11)* • reduces disease progression and may reduce mortality • compared with placebo
Effect in subgroups	FAD inconsistent and unclear, will be clarified: • no evidence of difference in pirfenidone effect between FVC >80 and ≤80% (which is assumed in the model)
Risk of death	Between Weibull & Gompertz; closer to Gompertz *(4.15)*
Treatment effect	Lasts up to 5 years *(4.16 and 4.18)*
Uncertainty in ICERs	ICERs with stopping rules underestimate true cost effectiveness because of model structure *(4.17)*

ICERs informing committee's recommendations

ICERs with stopping rule, compared with best supportive care

Population	ICER, £/QALY (5 year treatment effect)	
	Lower estimate (Weibull)	Upper estimate (Gompertz)
FVC 50–90%	£25,914	£29,036
FVC 50–80% (FAD 4.20)	£24,933	£27,780
FVC 80–90%[a] (FAD 4.18)	£32,643	£38,687
[a]No ICER was presented for FVC 80–90%; these are ICERs for FVC ≥80%		

- Upper estimate of ICERs more plausible (Gompertz)
- All ICERs underestimate true cost effectiveness because stopping rule not properly modelled, and uncertainty about duration of treatment effect
- ICERs assuming 2 year treatment duration (not reported in FAD):
  - £58,000/QALY (FVC 50–90%)
  - £54,000/QALY (FVC 50–80%)
  - £80–86,000/QALY (FVC ≥80%)

Cost-effectiveness results: full population

Table: Pirfenidone compared with best supportive care, with stopping rule

	2 year treatment effect			5 year treatment effect		
	Δ costs	**Δ QALYs**	**ICER (£/QALY)**	**Δ costs**	**Δ QALYs**	**ICER (£/QALY)**
Predicted FVC ≥ 50% (ITT)						
Weibull	£17,940	0.31	**£57,568**	£20,492	0.80	**£25,706**
Gompertz	£18,088	0.31	**£57,548**	£20,199	0.70	**£28,870**
Predicted FVC 50–90%						
Weibull	£17,665	0.31	**£57,773**	£20,244	0.78	**£25,914**
Gompertz	£17,825	0.31	**£57,504**	£19,819	0.68	**£29,036**

Source: Results from company's revised probabilistic analysis provided by ERG for 2nd committee meeting (with no changes)

Note: these ICERs were presented to committee at its 2nd meeting (the incremental QALYs and costs have been added to this slide)

Cost-effectiveness results: subgroups

Table: Pirfenidone compared with best supportive care, with stopping rule

	2 year treatment effect			5 year treatment effect		
	Δ costs	**Δ QALYs**	**ICER (£/QALY)**	**Δ costs**	**Δ QALYs**	**ICER (£/QALY)**
Predicted FVC 50–80%						
Weibull	£17,016	0.31	**£54,258**	£19,483	0.78	**£24,933**
Gompertz	£17,063	0.32	**£54,011**	£18,963	0.68	**£27,780**
Predicted FVC ≥80%						
Weibull	£21,590	0.27	**£80,217**	£24,183	0.74	**£32,643**
Gompertz	£22,095	0.26	**£86,250**	£23,734	0.61	**£38,687**

Source: Results from company's revised probabilistic analysis provided by ERG for 2nd committee meeting (with no changes)

Note: these ICERs were presented to committee at 2nd meeting (the incremental QALYs and costs have been added to this slide)