Committee, Projector and Public slides

Chairs presentation
Pirfenidone for treating idiopathic pulmonary fibrosis (review of TA282) – STA

2nd Appraisal Committee meeting

4 August 2016

Lead team: Sanjay Kinra, Nigel Westwood, Mark Chapman

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

NICE team: Jasdeep Hayre, Sophie Cooper, Rosie Lovett

Chair: Amanda Adler

Pirfenidone

Mechanism	Immunosuppressant (anti-inflammatory and antifibrotic)
Administration and dose	Oral, three 267 mg three times daily
Costs	£71.70/day (list); confidential patient access scheme exists

Reason for review:

- ASCEND trial comparing pirfenidone vs placebo people with a predicted FVC > 80% could potentially benefit from pirfenidone

History of appraisals for IPF

FVC severe <50%, moderate 50 – 80%, mild >80%

Pirfenidone
TA282, Apr 2013
Recommended if:
1. Moderate disease
2. Stopping rule - FVC falls by 10% or more in 12 months
3. PAS

Pirfenidone Review
2016
- nintedanib a comparator
- New evidence for mild disease
- increased price

Pirfenidone Review ACD
Jun 2016
- No change from TA282

TODAY

Nintedanib
TA379 Jan 2016
Recommendation: as per pirfenidone in TA282

FVC = forced vital capacity PAS = Patient access scheme discount

ACD: preliminary recommendation
no change to original guidance

- Changes proposed by the company are not recommended, specifically:
  - expanding the population to people with a forced vital capacity (FVC) above 80% predicted
  - removing the recommendation to stop pirfenidone if the disease progresses
  - a different patient access scheme (a higher price)
- Pirfenidone continues to be recommended as an option for treating idiopathic pulmonary fibrosis in adults only if:
  - person has an FVC 50% to 80% predicted
  - discount agreed in patient access scheme for TA282
- Pirfenidone should be stopped on disease progression - a decline in % predicted FVC of ≥10% in any 12-month period

Preview of key issues

- What is the relevant group with which to compare pirfenidone to best supportive care for FVC?
  - > 50% (no upper limit) *combining subgroups?*
    - *50 to 90% reflecting the evidence?*
  - ≥ 80% *the subgroup not included in existing guidance?*
- Stopping rule
  - Has the committee seen evidence to change this?
- How long does the treatment effect last?
  - 2 years, 5 years, 8 years or a lifetime?
- Which curve for overall survival curve
  - Gompertz, Weibull, ‘weighted’ or other?

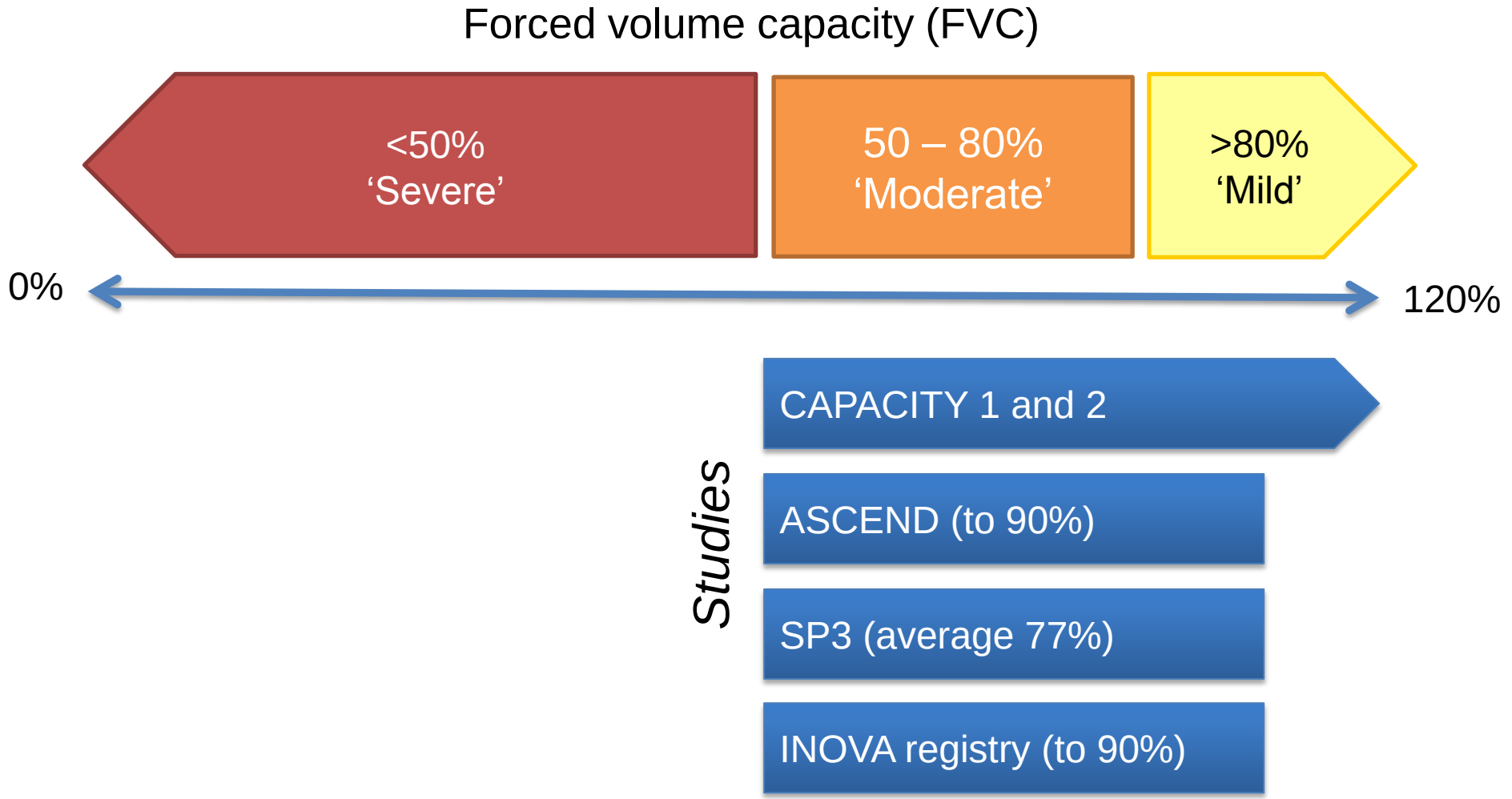
Clinical evidence for pirfenidone
4 placebo-controlled RCTs

	CAPACITY 1 (n=344)	CAPACITY 2 (n=435)	ASCEND ★ (n=555)	SP3 (n=275)
Dose mg/day	2403	1197 or 2403[a]	2403	1200 or 1800
UK sites	0	3	0	0 (Japan)
Inclusion criteria	Age 40–80 FVC ≥50% DLCO ≤90%		Age 40–80 FVC 50–90% DLCO 30–90%	Age 20–75
Exclusion	COPD or major comorbidities			Unclear
1º endpoint	Change in % predicted FVC **week 72**		Change in % predicted FVC **week 52**	Change in VC **week 52**

[a] only results for the licensed dose (2403 mg) are presented here and used in the model

★ Results from ASCEND were not available for TA282

Inclusion of ‘mild’ disease



Results: treatment effect for mortality

By trial	Week	pirfendone n (%)	placebo n (%)	HR (95% CI) 1º endpoint green
ASCEND	52	11 (4.0)	20 (7.2)	0.55 (0.26 to 1.15)
CAPACITY 1	52	Not reported (NR)		0.66 (0.24 to 1.84)
	72			0.87 (0.41 to 1.82)
CAPACITY 2	52			0.37 (0.13 to 1.05)
	72			0.51 (0.22 to 1.20)
Pooled data				
CAPACITY 1 & 2	52	11 (3.2)	22 (6.3)	0.49 (0.24 to 1.01)
	72	27 (8)	34 (10)	0.77 (0.47 to 1.28)
ASCEND, CAPACITY 1 & 2	52	22 (3.5)	42 (6.7)	0.52 (0.31 to 0.87)

SP3: no difference pirfenidone versus placebo (HR not reported)

Committee recognised different dose, population, different entry criteria

Results: ERG's network meta-analysis
ASCEND, CAPACITY 1 & 2, SP3 (ITT)

	Pirfenidone vs placebo
All-cause mortality, up to week 72 Hazard ratio (95% predictive intervals)	0.61 (0.31 to 1.13)
PFS, up to week 72 Hazard ratio (95% predictive intervals)	0.63 (0.42 to 0.94)
Acute exacerbations Odds ratio (95% predictive intervals)	0.63 (0.21 to 2.10)
Stopping treatment (all-cause) Odds ratio (95% predictive intervals)	1.28 (0.79 to 2.03)
Hazard, Odds ratios <1 are favourable for the intervention	

FVC > 80%

No difference in treatment effect by mild vs. moderate disease

Treatment effect of pirfenidone: change in % predicted FVC to week 52			
Trial	**% predicted FVC**	**Standardised treatment effect (95% CI)**	**Interaction test, p value**
ASCEND	≤80%	0.47 (0.26 to 0.68)	0.78
	>80%	0.52 (0.09 to 0.95)	
CAPACITY 1	≤80%	0.25 (−0.04 to 0.53)	0.20
	>80%	0.58 (0.14 to 1.02)	
CAPACITY 2	≤80%	0.4 (0.11 to 0.69)	0.73
	>80%	0.48 (0.07 to 0.89)	
Treatment effect: values >0 indicate a treatment benefit of pirfenidone			

- For overall survival and progression-free survival:
- treatment-by-subgroup interaction test not reported

Committee considerations FVC > 80%

ACD committee considerations
• Aware of analyses suggesting pirfenidone was associated with a benefit vs placebo
• Also noted a ‘pre-specified’ analysis showing placebo tended to have better outcomes vs pirfenidone above FVC > 80%
• No conclusive evidence in difference between subgroups i.e. no interaction, but small numbers
• Committee not seen ‘robust evidence’ that pirfenidone is clinically effective in people with FVC > 80%

Stopping rule

continued treatment benefit after disease progression (≥10% ↓ percent predicted FVC)

Outcome (%)	Pirfenidone (n=24)	Placebo (n=60)	p value
≥10% ↓ in FVC or death	1 (4.2%)	15 (25.0%)	0.032
0–10% ↓ in FVC	9 (37.5%)	23 (38.3%)	NR
No further ↓ in FVC	14 (58.3%)	22 (36.7%)	0.089
Death	0 (0%)	10 (16.7%)	0.056

ACD committee considerations
• Stopping rules followed in NHS
• Heard treatment after disease progression might be beneficial
• Substantial uncertainty in post-hoc subgroup analysis → small sample, breaks randomisation, non-informative comparison → not conclusive evidence
• Considered ICERs with and without stopping rule but concluded ICERs with stopping rule **underestimate** ICER

Committee cost effectiveness considerations

Issue	ACD Committee consideration
Model structure	Exacerbations 'disconnected' from disease progression and mortality, contrary to clinical experts' comments
	'Disconnect' between treatment duration and treatment outcomes so model
	ICERs with stopping rules underestimates (costs excluded, but treatment effect remains)
	"…serious concerns about the company's model' and so 'substantial uncertainty about the ICERs"
Mortality benefit of pirfenidone vs placebo	ERG's analysis did not show a survival benefit at 72 weeks
	Using all data available (week 72) Pirfenidone's effect on overall survival uncertain (HR 0.63; 95% predictive interval 0.32 to 1.28)
Duration of mortality benefit	Treatment effect of pirfenidone was likely to last somewhere between 2 years and a lifetime
Extrapolation	Agreed with the ERG that it was more clinically plausible to use the Gompertz distribution to estimate survival
ICERs	Not cost effective with & without stopping rules

ACD consultation responses

- Consultee comments from:
  - British Thoracic Society (endorsed by Royal College of Physicians)
  - Department of Health (no comments)
  - Royal College of Nursing
  - Roche (pirfenidone)

- Commentator comments from:
  - Boehringer Ingelheim (nintedanib)

British Thoracic Society, Royal Colleges of Physicians & Nursing

Stopping rules

- BTS/RCP: Considers FVC to define stopping rule problematic
  - 'Considerable intra-subject variability'
    - *Note: Committee aware (ACD 4.2) that clinicians 'retest FVC to confirm that the 10% drop is not temporary'*
  - Offers evidence of Nathan *et al* (*Thorax* 2016; 71:429) to support benefit beyond stopping rules
    - *Note: Committee saw this data*
  - Exacerbations make FVC worse
    - *Note: Committee aware that exacerbations:*
      - *'permanently reduce lung function' (ACD 4.1)*
      - *'..committee was concerned that acute exacerbations were 'disconnected' from disease progression and mortality..' (ACD 4.8)*
- RCN: 'We agree with the stoppage of the medication'

⊙ *Should the stopping rule be removed or changed?*

British Thoracic Society, Royal Colleges of Physicians & Nursing

- **Emphysema**
  - RCN: '…disappointing that the upper limit of forced vital capacity - FVC >80% remains because of the confounder of emphysema ..'
    - *Note: Committee aware (ACD 4.5) patients with COPD excluded from CAPACITY trials and from ASCEND*
- **Treating FVC > 80%**
  - BTS/RCP: Society supports treating patients with FVC>80%
  - RCN: '.. we already have a drug which meets the >50% <80% criteria, we need to treat the milder patients earlier and raise the upper limit to at least 90%'

Boehringer Ingelheim (nintedanib)

- Objects to term ‘mild’
  - ‘no ‘mild cancer’ terminology exists, calling a group of patients ‘early stage IPF’ more appropriate.

- ‘Urges’ NICE to look at nintedanib in ‘early stage IPF’

Comments – company (Roche)

General comments

1. Structure of model
2. FVC >80% as a subgroup defined arbitrarily
3. How long treatment continues to work
4. Modelling of overall survival

What's new

1. 'New' original (lower) patient access scheme
2. Albera is now in press (not new data)
3. New duration of treatment
4. New overall survival curves
5. New sub-groups

Comments – company (Roche)
1. Structure of model

Issue	Company's comments
Choice of model *Committee "would have preferred a model that captured the progressive nature of idiopathic fibrosis, linked clinical outcomes with each other and with time on treatment'*	• Chose to make overall survival main driver of model benefit • Simple and avoids assumptions (i.e. independent OS)
Modelling disease progression	• Very small numbers of patients to inform health states • Cannot project impact of FVC progression • Cannot fit utility and cost analysis easily • Relationship between FVC and mortality non-linear
Acute exacerbation	• Modelling 'complex' • Would require 'multiple unnecessary assumptions'

- Company has not changed the model for these issues

Comments – Company (Roche)

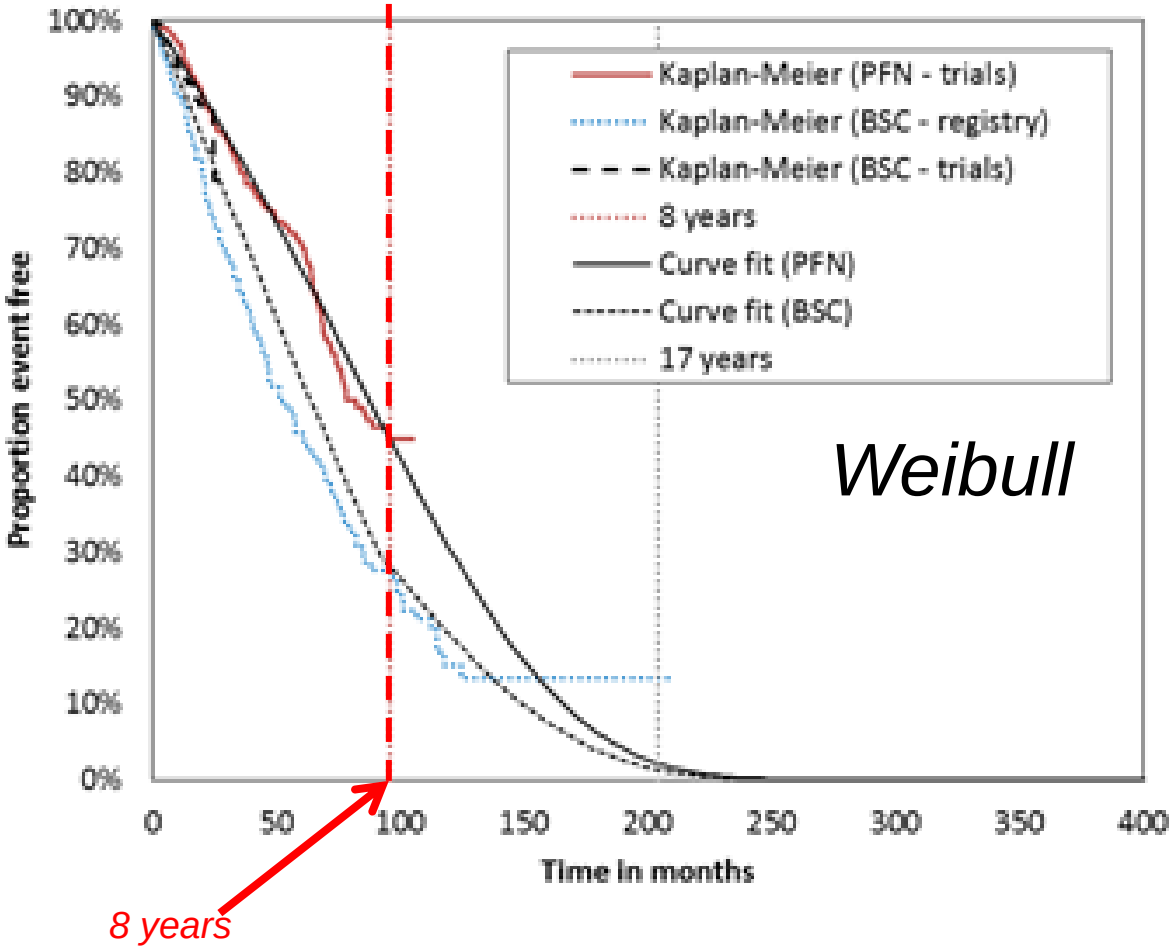
2. FVC >80% subgroup

Issue	Company's comments	ERG's comment
Analyses of FVC > 80% not seen as 'robust evidence'	• "Review seems to have been artificially limited by the historical recommendations of TA282" • No clear definition of mild' or 'moderate' • "Inappropriate focus on subgroup analyses, without evidence to support their existence" and TA methods guide: "subgroup should be clearly defined" • No biological plausible mechanism where efficacy would be different • Company proposes new subgroups **(see later)**	• Inconsistency in OS between mild (>80%) and moderate (≤80%) • Accepts it's difficult to provide biological plausibility • But subgroup reasonable if difference in baseline FVC drives prognosis which Albera 2016 shows

Comments – company (Roche)
3. How long treatment continues to work

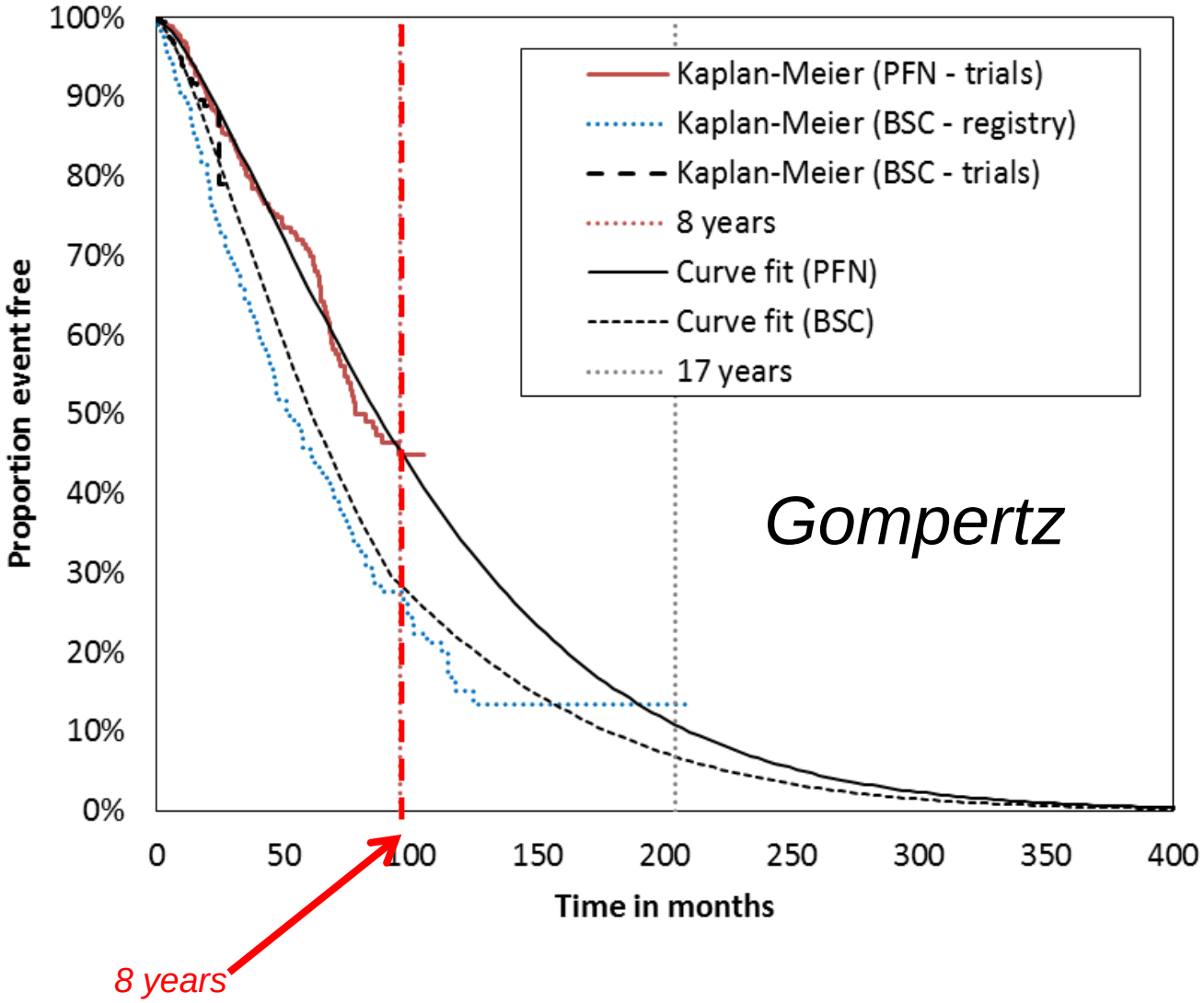
Issue	Company's comments	ERG's comments
Duration of effect	• OS data up to 8 years • RCTs + INOVA registry • Parametric curves using propensity score analysis + log-cumulative hazard plot shows treatment effect lasts for at least 8 years – **see next slides** • No significant interaction between treatment effect + time • No clinical rationale why the treatment effect would diminish in the long-term • Diminishing treatment effect not explored for nintedanib	• Analysis potential biased → data not based on randomized comparison • Propensity analysis cannot correct for unknown confounders • Data for overall survival for BSC in trials don't match data in trials in registry • 95% CI HR for pirfenidone does not contain midpoint HR from trial • Parametric curves under-predicting OS for BSC after 5 years • 'Considerable uncertainty'

Company's Kaplan-Meier plots of overall survival

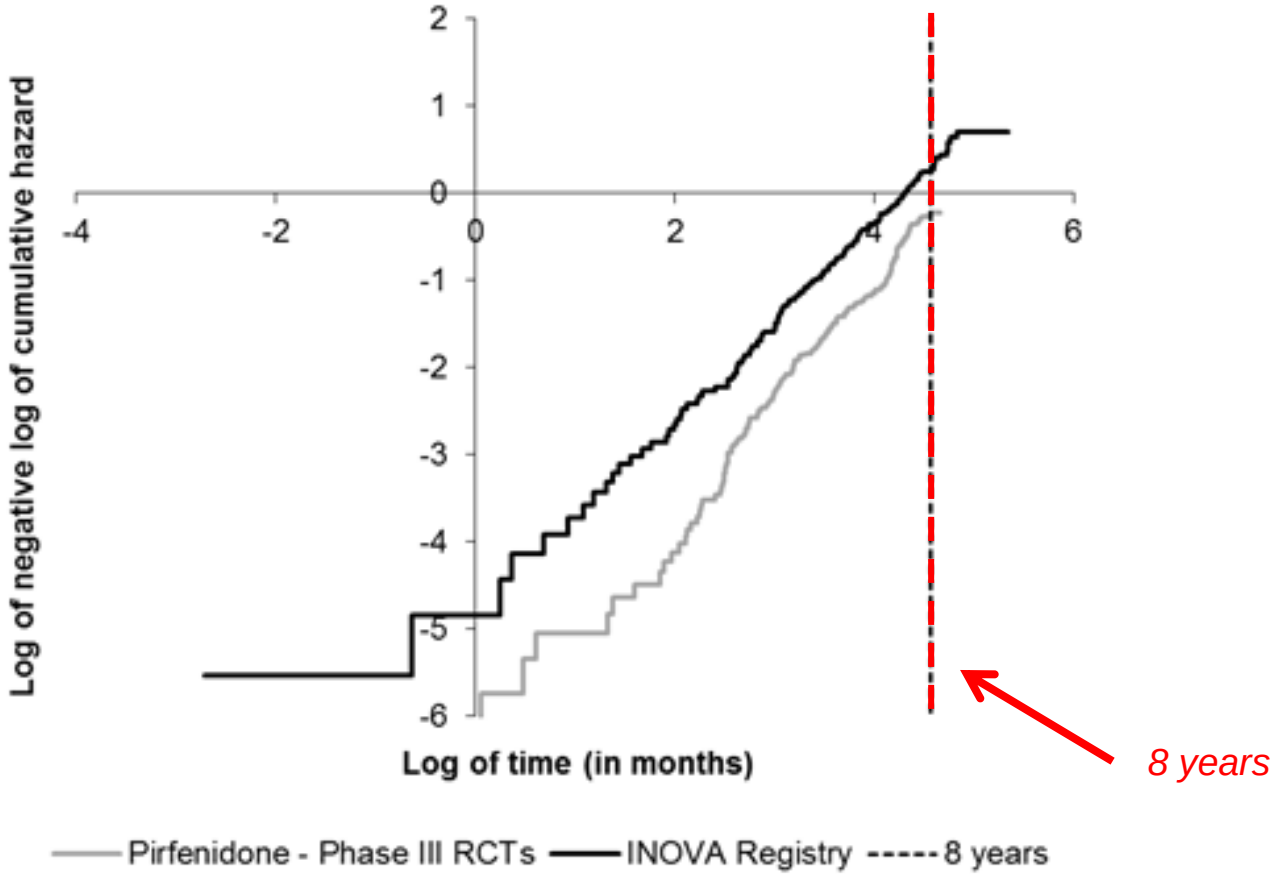


- Using ASCEND, CAPACITY 1 & 2 (and extension: RECAP) for pirfenidone and INOVA for BSC (because follow-up for BSC limited to 2 years in trials)

Company's Kaplan-Meier plots of overall survival



Comments – company (Roche)
Log-cumulative hazard plot for overall survival

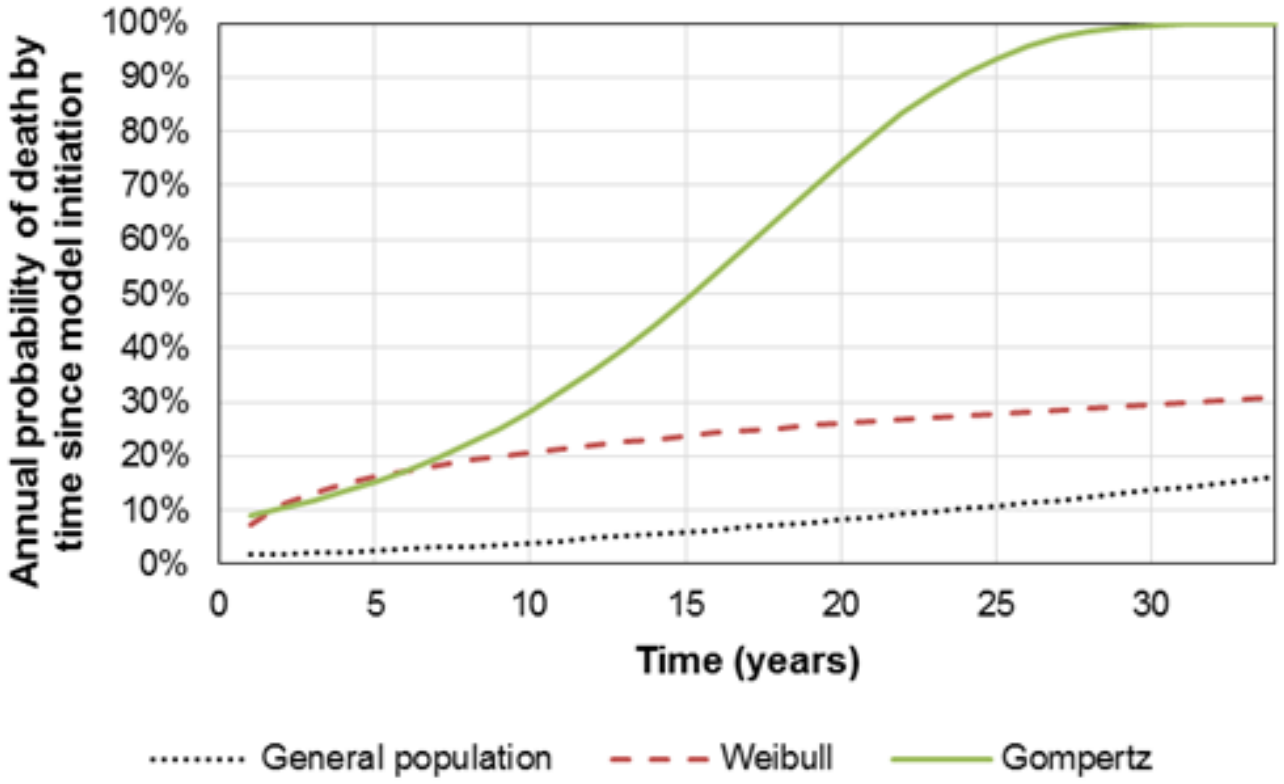


- *How long does the treatment effect last?*

Comments – company (Roche)
4. Long term data on overall survival

Issue	Company's comments
Survival curve	• *ACD 4.12: Weibull (company's preferred) "predicted a lower probability of death for older people than in the general UK population"*
	• Company: strongly disagree with committee's preferred Gompertz distribution • ERG: did not consider distribution of age at baseline • Inappropriate curve: probability of death exceed UK population only at age 90 (next slide) • Gompertz not clinically plausible: people survive for a long time after diagnosis in real life ➢ 13% of patient alive after 17 years in INOVA • Weibull takes this into account (has a tail) ➢ preferred by company

Probability of death (adjusted for age)



ERG's comments

- Adjusting for age addresses ERG's concerns
- But, at 100 months: Weibull & Gompertz predict a similar proportion surviving on BSC → ERG not convinced that Weibull more plausible than Gompertz

Overall survival curves

- What new? Company provided a new 'weighted average'

Distribution	AIC	Probability of best fit	Weight
Exponential	865.47	0%	0%
Weibull	844.15	100%	43%
Log-Normal	853.23	1%	0%
Gamma	845.78	44%	19%
Log-Logistic	844.54	82%	36%
Gompertz	851.70	2%	1%

Key: AIC, Akaike Information Criterion; OS, overall survival

Used for a 'weighted average' curve

ERG's comments

- Weighted survival curve has 'limited credibility'
- Instead - desirable to choose model supported by data & fit

⊙ *What's the most appropriate overall survival curve?*

Company's new evidence
What's new?

Change	Committee's preferred assumptions	Company's original submission	Company Revised ACD response
Patient Access Scheme (PAS)	-	Revised PAS (higher price)	Original TA282 PAS (lower price)
Different duration of treatment	2 years to lifetime	Lifetime	8 years (✓other durations available)
Overall survival curves	Gompertz	Weibull	Weibull (✓ other curves available)
Subgroups	-	FVC ≥ 50% FVC ≥ 80% FVC 50 – 80%	FVC ≥ 50% FVC ≥ 80% FVC 50 – 80% FVC 50 – 90%

Company's revised results (ICERs - £/QALY)
pirfenidone (inc PAS) vs (BSC)

	With stopping rule		*No stopping rule*	
Duration of treatment effect:	**8 years**	**Lifetime**	**8 years**	**Lifetime**
Predicted FVC 50–80%				
Weibull	£20,411	£18,508	£28,884	£25,979
Gompertz	£22,673	£21,119	£32,253	£29,771
Weighted	£18,509	£16,223	*£26,372*	£22,767
Predicted FVC ≥ 80%				
Weibull	£24,295	£19,406	£38,474	£29,874
Gompertz	£29,244	£24,494	£46,171	£37,536
Weighted	£22,862	£18,263	*£36,292*	£28,060
Predicted FVC ≥ 50% (ITT)				
Weibull	£20,587	£18,167	£30,012	£25,986
Gompertz	£23,237	£21,002	£34,222	£30,360
Weighted	£18,920	£16,533	£27,565	£23,544
Predicted FVC 50–90%				
Weibull	£20,738	£18,443	£30,432	£26,439
Gompertz	£23,188	£21,267	£34,267	£30,607
Weighted	£18,943	£16,676	*£27,685*	£23,779

Revised results (ICERs - £/QALY)
Pirfenidone vs. BSC (with stopping rule)

Duration of treatment effect	2 years	5 years	8 years	Lifetime
Predicted FVC 50–80%				
Weibull[a]	£54,258	£24,933	£20,386	£18,506
Gompertz	£54,011	£27,780	£22,793	£20,989
Weighted	£50,757	£22,691	£18,445	£16,198
Predicted FVC ≥ 80%				
Weibull[a]	£80,217	£32,643	£24,401	£19,519
Gompertz	£86,250	£38,687	£29,264	£24,236
Weighted	£77,502	£30,556	£22,896	£18,283
Predicted FVC ≥ 50% (ITT)				
Weibull[a]	£57,568	£25,706	£20,565	£18,116
Gompertz	£57,548	£28,870	£23,243	£20,832
Weighted	£51,887	£23,421	£18,946	£16,507
Predicted FVC 50–90%				
Weibull[a]	£57,773	£25,914	£20,656	£18,459
Gompertz	£57,504	£29,036	£23,312	£21,278
Weighted	£52,293	£23,471	£18,927	£16,699

Source: Results from company's revised probabilistic analysis provided by ERG (with no changes); a) Preferred by company

Revised results (ICERs - £/QALY)
Pirfenidone vs. BSC (without stopping rule)

Duration of treatment effect	2 years	5 years	8 years	Lifetime
Predicted FVC 50–80%				
Weibull[a]	£82,843	£35,902	£28,965	£25,945
Gompertz	£81,032	£40,110	£32,538	£29,719
Weighted	£78,812	£33,253	£26,436	£22,744
Predicted FVC ≥ 80%				
Weibull[a]	£138,840	£52,794	£38,703	£29,836
Gompertz	£141,482	£62,772	£46,025	£37,448
Weighted	£132,245	£49,575	£36,296	£28,058
Predicted FVC ≥ 50% (ITT)				
Weibull[a]	£90,273	£38,351	£30,080	£26,061
Gompertz	£89,253	£42,960	£34,032	£30,498
Weighted	£82,293	£35,103	£27,504	£23,537
Predicted FVC 50–90%				
Weibull[a]	£90,778	£38,529	£30,343	£26,462
Gompertz	£88,621	£43,062	£34,142	£30,779
Weighted	£82,162	£34,830	£27,619	£23,843

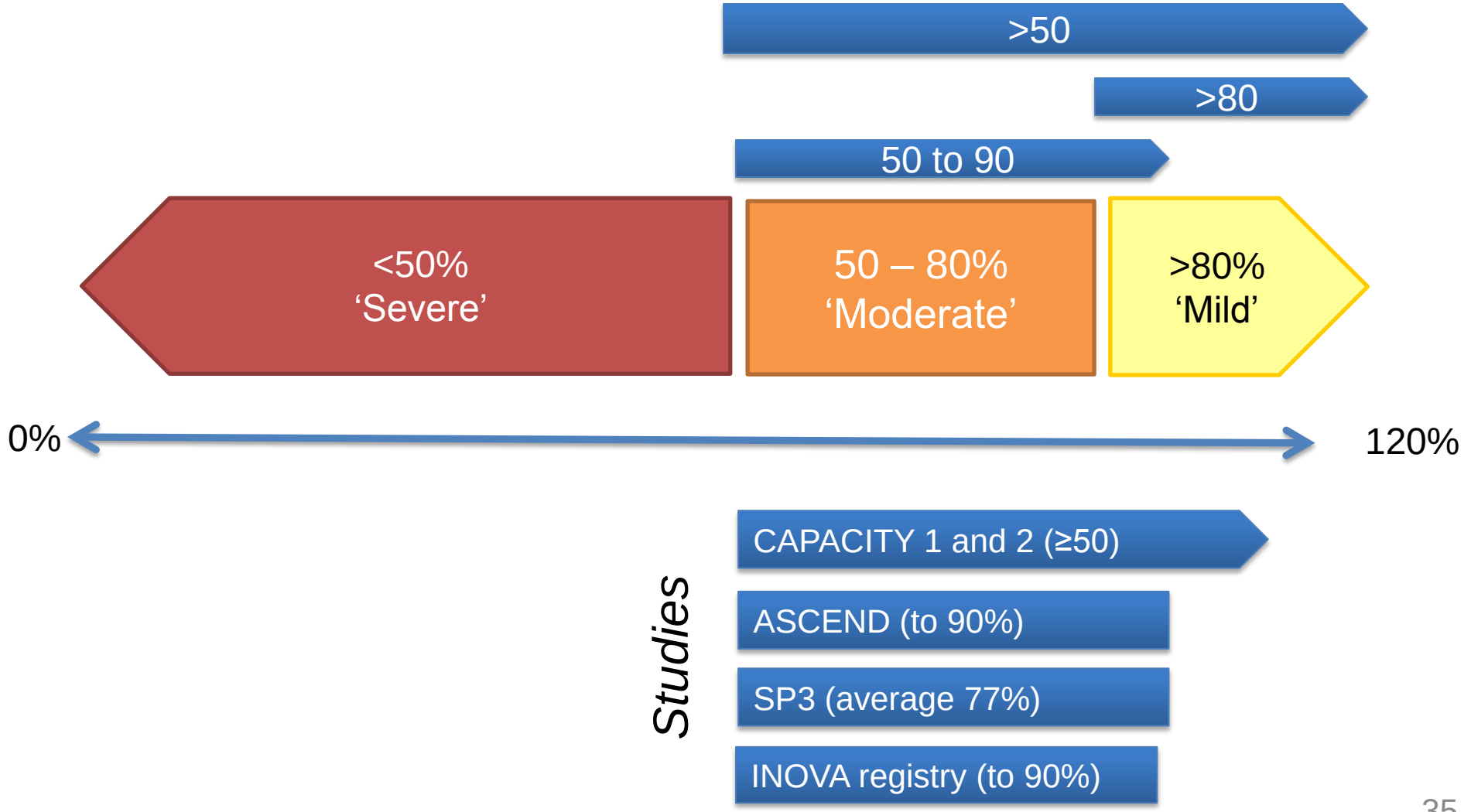
Source: Results from company's revised probabilistic analysis provided by ERG (with no changes), a) Preferred by company

Key issues

- What is the relevant group with which to compare pirfenidone to best supportive care for FVC?
  - > 50% (no upper limit) *combining subgroups?*
    - *50 to 90% reflecting the evidence?*
  - ≥ 80% *the subgroup not included in existing guidance?*
- Stopping rule
  - Has the committee seen evidence to change this?
- How long does the treatment effect last?
  - 2 years, 5 years, 8 years or a lifetime?
- Which curve for overall survival curve
  - Gompertz, Weibull, ‘weighted’ or other?

Additional back-up slides

Decision aid
What is the relevant population?



Results by baseline FVC % by subgroup

	Baseline FVC ≤80% predicted			Baseline FVC >80% predicted			Interaction test: p-value
	n (PFN / pla)	Adjusted HR	95% CI	n (PFN / pla)	Adjusted HR	95% CI	
Progression free survival from pooled trials							
52 weeks	472 / 450	0.62	0.52-0.78	146 / 168	0.54	0.35-0.75	0.4656
72 weeks		0.64	0.52-0.79		0.53	0.35-0.79	0.4106
Overall survival from pooled trials							
52 weeks	477 / 454	0.48	0.27-0.83	146 / 170	0.59	0.14-2.51	0.6452
72 weeks		0.58	0.36-0.94		0.90	0.27-2.99	0.4728

Studies pooled: ASCEND, CAPACITY 1 & 2

Source: reproduced from Tables 1 and 2 of the company's fact check response
Abbreviations: PFN: pirfenidone; pla: placebo; HR: hazard ratio; CI: confidence interval