Lead team presentation Obeticholic acid for treating primary biliary cirrhosis – STA

1st Appraisal Committee meeting

Cost Effectiveness

Committee A

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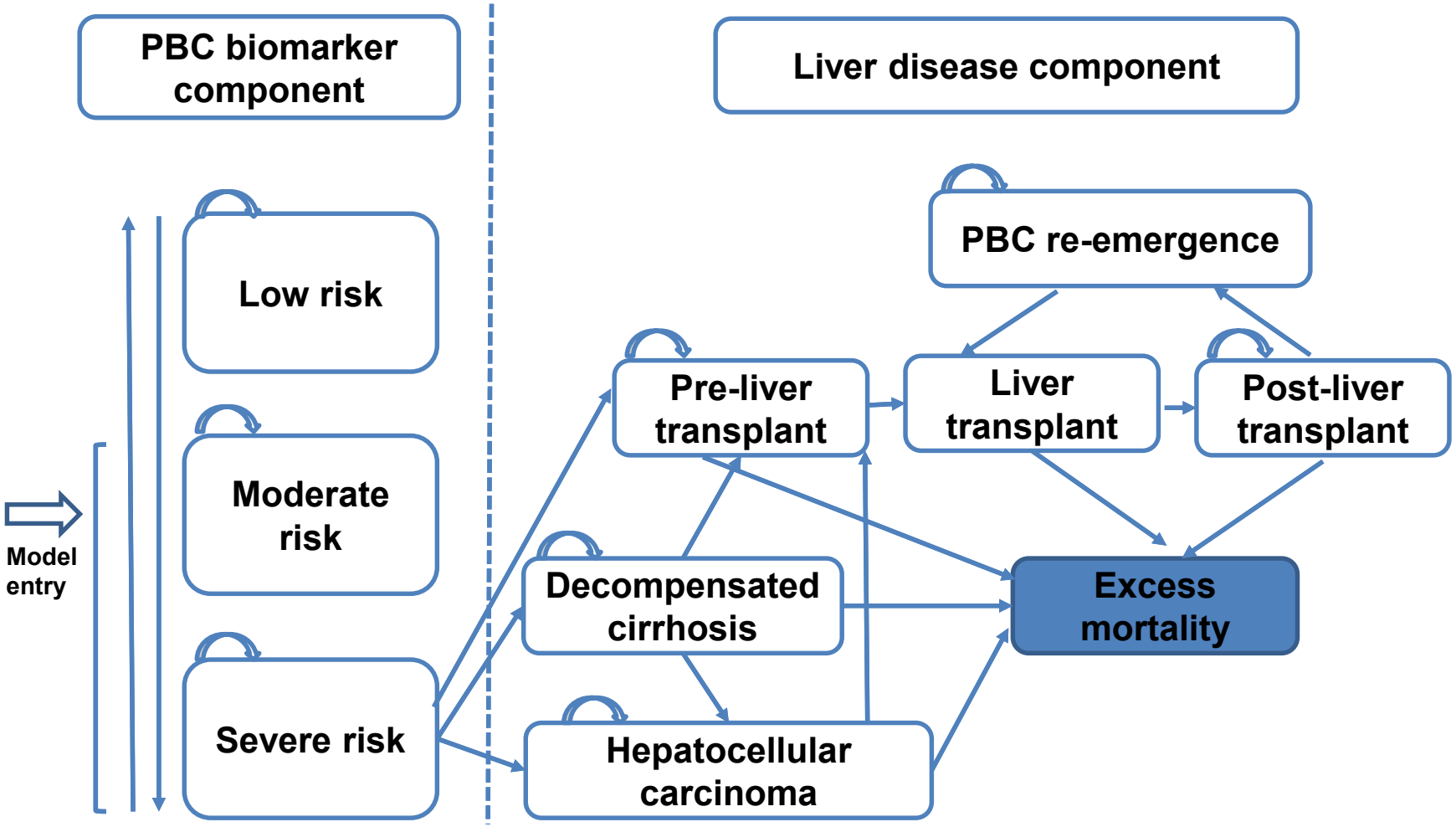
Model structure



Source: CS Figure 24

Model details

- De novo model, lifetime horizon, 3.5% discount for utilities and costs; 3 month cycle length.

- Model comprises 2 parts:
  - biomarker component: 3 health states defined by expected risk of disease progression:
    - low risk: alkaline phosphatase (ALP) ≤ 1.67 x ULN.
    - moderate risk: ALP > 1.67 x ULN and total bilirubin (TB) ≤ 1.0 x ULN.
    - severe risk: TB > 1.0 x ULN or compensated cirrhosis.
  - liver disease component: based on clinical endpoints:
    - pre-liver transplant.
    - decompensated cirrhosis
    - hepatocellular carcinoma (HCC).
    - liver transplant.
    - post-liver transplant.
    - potential PBC re-emergence
    - death.

Transition probabilities (TPs) – biomarker component

- **OCA +/- UDCA**
  - Estimated from POISE. Same TPs used for UDCA tolerant and intolerant patients, due to low number of patients who received OCA monotherapy.
  - No progression from low/moderate risk to severe risk after first year.

- **UDCA inadequate responders**
  - Calibrated TPs based on PBC-specific data from literature, using 10 year liver transplant-free survival estimated from GLOBE and UK risk scores.
  - POISE data not used because TPs could not be estimated for all health states or over full time horizon of model.

- **UDCA intolerant**
  - Estimated from Corpechot (2000) study of UDCA vs no active treatment in PBC.
  - Only 5 UDCA intolerant individuals in POISE.

TPs – liver disease component

Assumed equal for all comparators – mostly based on literature.

From:	To:	Source
Severe risk	DCC	Calibrated (CS Appendix 10)
	HCC	Assumption
	Pre-LT	Calibrated (CS Appendix 10)
DCC	Pre-LT	Calibrated (CS Appendix 10)
	Death	Calibrated (CS Appendix 10)
	HCC	Trivedi et al. 2006
HCC	Pre-LT	Wright et al. 2006
	Death	Wright et al. 2006
Pre-LT	LT	Kim et al. 2016
	Death	Kim et al. 2016
LT	Death	Wright et al. 2006
Post-LT	PBC recurrence	Lindor, 2009
	Death	Wright et al. 2006
	LT	Neuberger, 2003
PBC recurrence	LT	Assumption

CC, compensated cirrhosis; CS, company submission; DCC, decompensated cirrhosis; HCC, hepatocellular carcinoma; LT, liver transplant; PBC, primary biliary cholangitis/cirrhosis

Source: ERG report, Table 5.6

Utilities

- HRQoL data not collected in POISE, so utility values derived from either Younossi 2001 (patients with chronic liver disease due to viral infection) or Wright 2006 (patients with hepatitis C).
- Utility values assumed to remain constant over time in each of the health states of the biomarker component.
- Utility values decrease as patients move from the biomarker component to the liver disease component of the model.
- Some health states (highlighted on next slide) in the liver disease component of the model had their utility values decreased by XX%, to reflect worsened HRQoL experienced by PBC patients compared with HBV/HCV patients, based on KOL feedback.

Utilities

State	Utility	Primary source
Low risk	0.84	Younossi et al. 2001
Moderate risk	0.84	Younossi et al. 2001
Severe risk	0.55	Wright et al. 2006
Decompensated cirrhosis	XXX*	Wright et al. 2006
Hepatocellular carcinoma	0.45	Wright et al. 2006
Pre-transplant: utility at listing	XXX*	Wright et al. 2006
Pre-transplant: 3 months after listing	XXX*	Wright et al. 2006
Pre-transplant: 6 months after listing	XXX*	Wright et al. 2006
Liver transplant: 3 months post-transplant	XXX*	Wright et al. 2006
Liver transplant: 6 months post-transplant	XXX*	Wright et al. 2006
Liver transplant: 12 months post-transplant	XXX*	Wright et al. 2006
Liver transplant: 24 months post-transplant	XXX*	Wright et al. 2006
Re-emergence of PBC	XXX*	Wright et al. 2006

ALP, alkaline phosphatase; Bili, bilirubin; CC, compensated cirrhosis; CS, company submission; PBC, primary biliary cholangitis/cirrhosis
* utility decrement has been applied

Source: CS Table 61

Health-state costs and resource use

Health states	Value
Low risk ALP: ≤ 200 U/L and Bili: Normal	Staff: £221 (1x Outpatient appointment, 1x outpatient follow-up)
	Hospital costs: £27 (3 blood tests, 3 times per year, at a cost of £3)
	Total: £248
Moderate risk ALP: > 200 U/L and Bili: Normal	Staff: £345 (1x Outpatient appointment, 2x outpatient follow-up appointments)
	Hospital costs: £27 (3 blood tests, 3 times per year, at a cost of £3)
	Total: £496
Severe risk	Total: £6,254
Decompensated cirrhosis	Total: £12,509
Hepatocellular carcinoma	Total: £11,147
Pre-transplant (end stage)	Total: £18,217
Re-emergence of PBC	Total: £248
Liver transplant	Total: £65,029
Follow-up 1 year after liver transplantation	Total for 2 years divided by 2: £18,166
Follow-up 2 years after liver transplantation	Total for 2 years divided by 2: £18,166

Source: CS table 66

Company's base case deterministic results

UDCA intolerant population, using the PAS price of OCA

	Total			ICER
	Costs	LYG	QALYs	
No treatment (placebo)	£103,233	11.30	6.61	–
OCA titration	£251,671	16.68	13.56	£21,351

UDCA inadequate responder population, using the PAS price of OCA

	Total			ICER
	Costs	LYG	QALYs	
UDCA + placebo	£96,977	12.35	7.85	–
OCA titration + UDCA	£261,791	16.78	13.68	£28,281

ICER, incremental cost-effectiveness ratio; LYG, life years gained; OCA, obeticholic acid; QALY, quality-adjusted life year; UDCA, ursodeoxycholic acid.

Source: CS tables 23, 24 (erratum PAS price)

Company scenario analyses

- Scenario 1 - without XX% decrement' to HCV

	Costs	LYG	QALYs	ICER
UCDA inadequate responders				
UDCA + placebo	£96,977	12.35	8.11	–
OCA titration + UDCA	£261,791	16.78	13.72	£29,374
UCDA intolerant responders				
No treatment (placebo)	£103,233	11.30	6.91	–
OCA titration	£251,671	16.68	13.61	£22,160

- Scenario 2 - Use of alternative transition probabilities

	Costs	LYG	QALYs	ICER
UCDA inadequate responders				
UDCA + placebo	£89,666	12.00	7.67	–
OCA titration + UDCA	£260,540	16.72	13.65	£28,596
UCDA intolerant responders				
No treatment (placebo)	£94,717	10.89	6.39	–
OCA titration + UDCA	£261,791	16.78	13.72	£29,374

ICER, incremental cost-effectiveness ratio; LYG, life years gained; OCA, obeticholic acid; QALY, quality-adjusted life year; UDCA, ursodeoxycholic acid.

Source: Tables 35, 36, 37 and 38 of CS erratum PAS price

ERG comments – model structure

- **Biomarker component:**
  - Aggregation of two different health states (CC and abnormal TB count) to define “severe risk” could be problematic, since the TP to the DCC state may only apply to CC patients.
  - Patients receiving OCA who are in the low or moderate risk health states (biomarker component) at the end of the first year remain there for the rest of their lives. Although consistent with UDCA responders, long term prognosis for OCA responders is unknown and may be different.

- **Liver disease component:**
  - Company’s model diverges from those used in other appraisals (e.g. TA330); it includes an additional pre-liver transplant health state which groups patients from different health states (HCC, DCC, severe risk), who may have different HRQoL.

ERG comments - population

- 23.15% patients enter model in severe risk state, compared with 8.42% in POISE.
  - more patients in the model remain in the severe risk health state or progress to the liver disease component in the model, than if the 8.42% from POISE had been used.
  - may potentially bias model outcomes in favour of OCA.
  - Company has stated that the proportions entering the model in different health states are derived from POISE, but it is not clear how this was done.

ERG comments - transition probabilities

- Discrepancy between the TPs reported in CS Table 49 and those used in the economic model.
- Assumption of no treatment discontinuation beyond 12 months.
- Different approaches for estimation of TPs used for different comparators:
  - POISE data for OCA.
  - Literature for UDCA. Calibration methods used lack transparency and adequate justification.

ERG base case

1. Used transition probabilities in the company submission for biomarker component because of a discrepancy with the numbers used in the company's model.
2. Used uncalibrated transition probabilities from POISE for the non-OCA regimen (biomarker component).
3. Proportions in initial health states based on POISE.
4. NHS reference costs for outpatient visits.
5. Health state costs of £1,561 for compensated cirrhosis, consistent with TA330 for the severe risk health state (biomarker component), instead of £6,254 used in company's model.
6. Age-dependent utilities (from the UK general population) for the low and moderate risk health states in the biomarker component of the model is higher than .
7. Removed the XX% utility decrements.

ERG base case

UDCA **inadequate responders** – OCA PAS price

	Incremental results		
	ΔQALY	ΔCosts	ICER
Company base-case (deterministic)	5.79	£164,551	£28,425
1. Fix discrepancies between transition probabilities	5.83	£164,806	£28,280
2. Transition probabilities from POISE for the non-OCA regimen	5.20	£171,036	**£32,897**
3. POISE trial proportions in initial health states	5.55	£170,482	**£30,736**
4. NHS reference costs for outpatient visits	5.83	£165,453	£28,394
5. Health state costs consistent with TA330	5.83	£180,737	**£31,017**
6. UK age-dependent utility values	4.93	£164,808	**£33,458**
7. Remove XX% utility decrement	5.61	£164,808	**£29,377**
ERG base-case (deterministic)	4.17	£189,968	£45,541
ERG base-case (probabilistic)	4.22	£189,706	£44,945

ICER, incremental cost-effectiveness ratio; NHS, National Health Services; OCA, obeticholic acid; QALYs, quality-adjusted life years; UDCA, ursodeoxycholic acid

Source: ERG report PAS appendix, table 3

ERG base case

UDCA **intolerant patients** – OCA PAS price

	Incremental results		
	ΔQALY	ΔCosts	ICER
Company base-case (deterministic)*	6.91	£148,210	£21,438
1. Fix discrepancies between transition probabilities	6.95	£148,438	£21,351
2. Transition probabilities from POISE for the non-OCA regimen	6.56	£151,875	**£23,152**
3. POISE trial proportions in initial health states	6.89	£152,275	**£22,111**
4. NHS reference costs for outpatient visits	6.95	£149,461	£21,500
5. Health state costs consistent with TA330	6.95	£166,622	**£23,969**
6. UK age-dependent utility values	5.92	£148,441	**£25,085**
7. Remove XX% utility decrement	6.70	£148,441	**£22,162**
ERG base-case (deterministic)	5.38	£173,399	£32,217
ERG base-case (probabilistic)	5.46	£173,001	£31,682

ERG, Evidence Review group; ICER, incremental cost-effectiveness ratio; NHS, National Health Services; OCA, obeticholic acid; QALYs, quality-adjusted life years; UDCA, ursodeoxycholic acid

Source: ERG report PAS appendix table 4

ERG exploratory analyses

UDCA **inadequate responders** – OCA PAS price

	Incremental results		
	ΔQALY	ΔCosts	ICER
ERG base-case (deterministic)	4.17	£189,968	£45,541
ERG base-case (probabilistic)	4.22	£189,706	£44,945
1. Transition probabilities and model structure from TA330	3.80	£221,832	£58,412
2. Transition probabilities based on the POISE trial after 12 months for the non-OCA treatment arms	2.59	£206,182	£79,668
3. Assume that transition probabilities between biomarker health states of the OCA arm are >0%	3.75	£185,078	£49,294
4. Alternative costs for liver transplant	4.17	£191,025	£45,794

ICER, incremental cost-effectiveness ratio; OCA, obeticholic acid; QALYs, quality-adjusted life years; UDCA, ursodeoxycholic acid

Source: ERG report PAS appendix, table 9

ERG exploratory analyses

UDCA **intolerant patients** – OCA PAS price

	Incremental results		
	ΔQALY	ΔCosts	ICER
ERG base-case (deterministic)	5.38	£173,399	£32,217
ERG base-case (probabilistic)	5.46	£173,001	£31,682
1. Transition probabilities and model structure from TA330	4.91	£214,417	£43,686
2. Transition probabilities based on the POISE trial after 12 months for the non-OCA treatment arms	2.61	£202,848	£77,715
3. Assume that transition probabilities between biomarkers health states of the OCA arm are >0%	4.97	£168,979	£34,031
4. Alternative costs for liver transplant	5.38	£174,703	£32,459

ICER, incremental cost-effectiveness ratio; OCA, obeticholic acid; QALYs, quality-adjusted life years; UDCA, ursodeoxycholic acid

Source: ERG report PAS appendix, table 10

Innovation & equality issues

- OCA has the potential to make a substantial and meaningful improvement in the quality and quantity of life for patients with PBC by providing an alternative or additional efficacious treatment option that will reduce the risk of, delay, or prevent the need for liver transplant.
- OCA offers a unique therapeutic modality to patients who are currently at continued risk of hepatocellular carcinoma, fibrosis, cirrhosis and progression to liver transplantation or death.
- PBC mainly affects women, which itself presents a challenge with diagnosis since the early symptoms of PBC are often wrongly dismissed as menopausal symptoms or depression

Key issues for consideration: cost effectiveness

- Is the limited clinical evidence underpinning the cost effectiveness analysis of the UDCA intolerant group robust?
- Is the model suitable for decision making- it includes a pre transplant state which was not in previous models (TA330)?
- Should longer term literature on PBC or the POISE data be used for the natural history of PBC on UDCA?
- Is it reasonable to assume that if people in the mild or moderate state on OCA and UDCA stay in that state for a year they will not progress to the severe state?
- Is a utility value of 0.84 for the moderate and mild health states reasonable even though it is above the UK age adjusted utility?
- Is it appropriate to apply a relative XX% reduction to the utilities for Hepatitis B/C patients to estimate utilities for PBC patients?
- The model includes a higher proportion of people in the severe health state than in POISE - is this reasonable?
- Are the health state costs reasonable?