NICE National Institute for Health and Care Excellence

Metreleptin for lipodystrophy

Chair's presentation

3rd evaluation committee meeting

ERG: Kleijnen Systematic Reviews (KSR)

Chair: Peter Jackson

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Company: Amryt

Highly Specialised Technologies, 11 November 2020

Overview

- History of metreleptin evaluation
- Recap:
  - Evidence
  - Considerations/recommendations from ECD and withdrawn FED
- Reconsideration: re-submission
  - Technical engagement (TE) - overview of issues
  - Patient group response to TE - patients and carers experience
  - Key issues
    - to be discussed
    - resolved
    - remaining/unresolvable uncertainties

History of metreleptin evaluation

ECM1 - 28 June 2018

Metreleptin not recommended; ECD developed

ECM2 - 12 Feb 2019

Committee considered comments received during consultation, including additional evidence and analyses from company

Metreleptin not recommended; FED developed

Company* and patient group **appealed** the decision; initial scrutiny noted some valid points; reconsideration step: company proposed to **resubmit** evidence and analyses in response to committee's FED critique; **FED withdrawn**

ECM3 – today

- New SLR, analyses (to establish metreleptin's relative effectiveness), and modelling approach in response to concerns raised in (withdrawn) FED
- Updated PAS

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*Aegerion was the marketing-authorisation holder of metreleptin at 1st and 2nd committee meetings; Amryt acquired Aegerion last year and is now the current marketing-authorisation holder; Abbreviations: ECD: Evaluation Consultation Document; FED: Final Evaluation Document; PAS: patient access scheme; SLR = systematic literature review

Recap: nature of the condition

Lipodystrophy (LD)

- Lipodystrophy is a heterogeneous group of syndromes characterised by complete or partial loss, or absence of, subcutaneous adipose tissue

Loss of subcutaneous adipose tissue → leptin hormone deficiency → abnormal lipid accumulation → progressive organ abnormalities

- Symptoms include:
  - hyperphagia characterised by ever present pursuit of food, resulting in food access issues - reduction in the ability to regulate hunger, and energy storage;
  - metabolic abnormalities including diabetes mellitus;
  - fatigue which has an impact on the daily life;
  - mood and sleeping problems;
  - reproductive dysfunction
- Patients can also experience progressive organ abnormalities in multiple organs, including the liver, kidneys, pancreas, and heart
- Lipodystrophy is generally classified on the basis of the extent or pattern of fat loss (**generalised** or **partia**l) and whether the disease is genetic or acquired

Recap: current treatment options

No standard clinical pathway

- There is no standard clinical pathway and no licensed treatments available
- The disease is currently managed with lifestyle modifications: such as a low fat diet and exercise; cosmetic surgery; and medications to manage the metabolic disturbance associated with leptin deficiency, including lipid lowering drugs (fibrates and statins) and medications for diabetes (metformin, insulin, sulphonylureas, and thiazolidinediones)
- Treatment with metreleptin is currently provided, as part of an early access programme (*EAP*), under the National Severe Insulin Resistance Service at Addenbrooke's Hospital, Cambridge University Hospitals NHS Foundation Trust
  - [redacted] patients currently receiving metreleptin ([redacted])
- It is assumed that [redacted] new patients each year would be eligible for metreleptin [redacted]

Abbreviations: GL = generalised lipodystrophy; PL = partial lipodystrophy

Recap: metreleptin (Myalepta, Amryt)

Marketing authorisation	Myalepta is indicated as an adjunct to diet as a replacement therapy to treat the complications of leptin deficiency in lipodystrophy (LD) patients: • with confirmed congenital generalised LD (Berardinelli-Seip syndrome) or acquired generalised LD (Lawrence syndrome) in adults and children 2 years of age and above • with confirmed familial partial LD or acquired partial LD (Barraquer-Simons syndrome), in adults and children 12 years of age and above for whom standard treatments have failed to achieve adequate metabolic control.
Mechanism of action	Metreleptin is an analogue of the human hormone leptin, which is secreted into circulation from adipocytes
Administration & dose	Recommended daily dose is based on body weight, with starting dose: • Males and females ≤40 kg: 0.06 mg/kg (injection volume: 0.012 ml/kg) • Males >40 kg: 2.5 mg (0.5 ml), Females >40 kg: 5 mg (1 ml)
List price	List price: £2,335 per vial 11.3mg (10mg dose) Previously simple PAS in place, discount has now been increased in resubmission
Source: Company submissions	

Abbreviation: PAS= patient access scheme

GL and PL – MA and company evidence

Marketing authorisation

congenital and acquired generalised lipodystrophy (GL) ≥ 2 years

+

familial and acquired partial lipodystrophy (PL) ≥ 12 years – not restrictive

Company's definition of "overall PL" and "PL subgroups"

- **"Overall PL" included in NIH follow-up study and used for ITC:**
- Defined as:
  - leptin <8.0 - 12.0 ng/mL in females, <6.0 - 8.0 ng/mL in males; <6 ng/mL in children 6 months- 5 years
  - presence of at least 1 of following metabolic abnormalities:
    - Presence of diabetes mellitus **(HbA1c ≥6.5%)**
    - Fasting insulin >30 µU/mL #
    - Fasting TG >2.26 mmol/L, or postprandially elevated TG
    - **TG >5.65 mmol/L** (not fasting)

- **"PL subgroup proposed post TE": HbA1c>7.5%** and/or **fasting TG >5.0 mmol/L**
- ERG: no evidence for its clinical or economic effectiveness

- **EAP used to inform patient distribution in model,** inclusion criteria for PL:
- **Baseline leptin <12 ng/mL, HbA1c ≥6.5%, and/or TG ≥5.65 mmol/L**

- **"PL subgroup" used for economic model inputs:** defined only by **HbA1c ≥6.5% and/or TG ≥5.65 mmol/**L

Recap on clinical evidence

Types	Technology	Study

Clinical trials	Metreleptin	• **NIH 991265/20010769** (pivotal, N= 107, GL=66, PL **overall** =41, PL subgroup (post-hoc) = 31 (1 patient from UK)
		• Mean change in HbA1c to Month 12 (metreleptin arm)
		  • GL patients= -2.2% (95% CI: -2.7 to -1.6, p<0.001)
		  • PL overall = -0.6% (95% CI: -1.0 to -0.2, p=0.005)
		  • PL subgroup= -0.9% (95% CI: -1.4 to -0.4, p<0.001)
		• FHA101 (supportive, EAP in the US, GL=9, PL=32)

Observational studies	Metreleptin Comparator	• **NIH Follow-up study** (n=112, GL=68, PL=44) • **GL/PL Natural History study** (N=178, GL=56, PL=122)
	Metreleptin	**EAP** has been running for 10+ years; results reported at 36 months follow-up*; n=31 patients received metreleptin since EAP initiation

		PL SG[a] N = 18	PL overall N = 21	GL N = 10
HbA1c % change from baseline at Month 36[b]	n	3	4	5
	Mean (SD)	-1.1 (6.88)	-1.6 (1.52)	-1.2 (1.61)
Triglycerides % change from baseline at Month 36[c]	n	3	3	4
	Mean (SD)	-57.6 (28.02)	-19.9 (42.02)	-23.9 (35.24)

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* Evidence submitted for ECM3; PL subgroup (SG)= patients with baseline leptin <12 ng/mL and HbA1c ≥6.5% and/or triglycerides ≥5.65 mmol/L (see issue 1); [b] Defined as any visit to Addenbrooke's Hospital between Month 30 and Month 42
Abbreviations: EAP = early access programme GL = generalised lipodystrophy; PL = partial lipodystrophy; SG = subgroup; SoC = standard of care

Recap: ECM1/2 - main concerns / considerations

Lack of relative effectiveness evidence

ECM1	• Insufficient evidence on relative effectiveness of metreleptin; • Company encouraged to systematically identify comparator evidence that allows a robust comparison between metreleptin and standard of care; • Committee requested data from the EAP
ECM2	• New systematic literature review may have missed some studies; • No evidence on change in patient experience and disease progression in people who did not have metreleptin; • EAP data presented, but no long term data, or patient reported outcomes (such as hyperphagia); new evidence did not improve committee's understanding of metreleptin's relative effectiveness in either short or long term; • Scarcity of evidence on relative effectiveness of metreleptin on disease progression or important outcomes such as hyperphagia

Recap: ECM1/2 - main concerns / considerations

Company's modelling approach

ECM1	• Markov model has significant uncertainties and lack of justification • Uncertainties include 13 disease attributes modelled independently (rather than interlinked); • The matching of the NIH cohort to the GL/PL natural history cohort not sufficiently robust; • Methodological issues with getting disutilities from DCE study and lack of validity; • Effect of hyperphagia on QoL need further exploring; carers disutilities should be explored; • Diabetes or fatty liver disease models as the basis for modelling would be more reliable
ECM2	• Partitioned survival model: focused on mortality, did not capture important aspects of the condition and oversimplified its underlying progression; • Committee's suggestion on model structure from ECM1 not followed; • Starting and stopping criteria not incorporated in model; should reflect population most likely to have metreleptin in clinical practice in England; • The matching exercise: concerns remained about its robustness; important outcomes such as hyperphagia not captured; • Rescaled* utility estimated from DCE more plausible than original DCE; • Vignette (elicited) utilities presented; value elicited from clinicians based on taking treatment rather than health state descriptions; • SF-6D scores presented although based on small PL patient sample (n=8); • Carer utility decrement based on literature, only applied to standard of care (SoC) arm; • A hyperphagia utility decrement applied to SoC arm (company scenario analysis) could have led to double counting, because some of its effect may have been captured in EQ-5D used for scoring in the vignette study

* Company anchored results at the lowest possible EQ-5D-3L tariff (−0.594) and adjusted peoples' responses in the analysis to account for anyone taking survey shortcuts because of the complexity involved

Recap: FED* recommendations

*The committee **was unable to make recommendations** on metreleptin as an option for treating lipodystrophy*

- The committee's key concerns included:
  - Scarcity of evidence on relative effect of metreleptin on disease progression and important outcomes such as hyperphagia
  - Lack of clear understanding of disease progression and experience of people with lipodystrophy; aspects important for patients and carers other than mortality not captured in economic model
  - Substantial uncertainty about model inputs; utility values were highly uncertain because of elicitation methods used
- Committee has not been presented with evidence or framework on which to judge metreleptin's clinical effectiveness and value for money
- Committee recommended further data collection, capturing other aspects of treatment effect beyond metabolic outcomes, research on disease progression without metreleptin, and experience of people with lipodystrophy

**The FED has been withdrawn to allow reconsideration of this topic and allow the company to undertake further evidence collection and to present this back to the HST committee.*

The committee key concerns reported in the FED still prevail.

Re-submission and technical engagement

Company resubmitted evidence including:

Updated clinical and economic systematic literature reviews	De novo indirect treatment comparison	De novo economic model	Further evidence on impact of disease on carers (*UK Lipodystrophy Patient and Caregiver Survey*)

Technical engagement took place between company, NICE technical team and chair, and ERG.

A separate engagement was done with 3 clinical experts

Response to TE: patients' & carers' experience/concerns

Concerns about treatment discontinuation/treatment withdrawal:

- ***Fear of hunger*:**
  - *Fear of hunger cannot be overstated* […] hunger is a roadblock to achieving quantifiable results of HbA1c, lipid profiles etc. Metreleptin is only wrecking ball we have to get rid of that obstacle."
  - *"I am terrified of losing access and going back to constant hunger and being sick 3 out of every 4 weeks. I will not be able to maintain my employment."*
- ***General health deterioration/complications:***
  - *"devastating and my general health would deteriorate, I would be very frightened about my future without Leptin, I believe it has delayed crisis outcomes."*
  - *"I feel I would have more premature health complications and a less likelihood of surviving these complications if I was not on Leptin"*
  - *"heart disease would progress further, particularly as the combination of ezetimbe, atorvastatin. The familial PL 2 and complications would resurface. Medication would be required for my diabetes. The ischemic , bezafibrate and restricted diet was not enough to keep my diabetes and mixed hyperlidaemia under control, which in turn would result in my ischemic heart disease progressing further and an early death"*

Benefits of metreleptin treatment

- "Feeling satisfied by food for the first time in my life."
- "Life changing! No longer have to [inject] huge amounts of insulin daily. Kept my weight down so no yo-yoing. Very liberating as most of my LD health issues have been easily controlled."
- "Diabetes is under control, no longer require conventional diabetes medication"

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Source: from LDUK response to technical report

Response to TE: patients' & carers' experience/concerns (contd.)

Impact of LD on families and carers:

- The impact of caring for a child with lipodystrophy has far reaching implications for the entire family unit and can be all consuming, especially for example, if a child experiences severe organ abnormalities.
- This is a particular problem for families of children with generalised lipodystrophy. Organ damage and associated complications can have a lifelong impact on those affected (both for the patient and the carer), with the need for continuing care.

Source: from LDUK response to technical report

Overview of issues

Issues	Summary
1. Population eligible for metreleptin	For discussion
2. Representativeness of clinical studies	For discussion
3. Relative treatment effect / indirect treatment comparison	For discussion
4. Long-term treatment effect of metreleptin (while on treatment)/surrogate relationships	For discussion
5. Discontinuation rate	Resolved during TE
6. Baseline transition probabilities and pathway through organ sub-models	For discussion
7. HbA1c post-discontinuation	For discussion
8. Liver complications post-discontinuation	For discussion
9. Quality of life/utility differential post-discontinuation	For discussion
10. Number of carers	For discussion

Discussed together

Key issues: clinical

Issue 1: PL population eligible for metreleptin

- Are PL patients in the proposed subgroups (HbA1c>7.5% and/or fasting TG >5.0 mmol/L) likely to gain more or less benefit than those in the NIH PL subgroup (HbA1c ≥6.5% and/or TG ≥5.65 mmol/L)?

Issues 2 and 3: Representativeness of clinical studies and indirect treatment comparison

- Given the apparent differences in response in patients in the NIH and EAP populations, which is the best for the ITC?
- Does the limited adjustment in the ITC produce an acceptable comparison?

Issue 4: Long-term effect (while on treatment) and surrogate relationships

- Does the committee consider that in long-term metreleptin is likely to
  - reduce the risk of damage of organs (such as kidney, liver, and heart)?
  - improve hyperphagia and QoL?
- Is HbA1c a satisfactory surrogate for damage to heart/kidneys/eyes?
- Are ALT/AST* satisfactory surrogates for damage to liver?

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*ALT/AST are liver enzymes

Issue 1: Population eligible for metreleptin

Background: unclear which PL patients would receive metreleptin in clinical practice in submission

- **NIH studies**: a PL subgroup defined as baseline HbA1c ≥6.5% and/or TG ≥5.65 mmol/L; company considers the PL subgroup a more severe group than overall PL population;
- **The ITC** (see issue 3) used overall PL population; while the economic model inputs were based on the PL subgroup, including baseline metabolic levels and change in HbA1c from baseline
- **EAP** : PL subgroup defined as baseline leptin <12 ng/mL, HbA1c ≥6.5%, and/or TG ≥5.65 mmol/L, used to inform the baseline patient distribution in the model (prevalence of GL and PL in EAP assumed to be representative of eligible patients in the UK)

Company response to TE:

- **PL patients eligibility criteria**: as **HbA1c**>7.5% and/or **fasting TG** >5.0 mmol/L, comparable to the PL subgroup in NIH studies; **leptin levels not recommended** as eligibility component;
- **HbA1c could be lower in cases of extreme hyperphagia** and/or intolerance of standard diabetes treatment;
- If recommended, propose to initiate metreleptin in more severe PL patients aligned to the PL subgroup in the NIH studies alongside stopping rule
  - Stopping rule implemented in model: *At 9 months after metreleptin initiation, a specialist service review will determine whether treatment should be stopped if the following metabolic criteria have not been met: an HbA1c reduction of at least 0.75% from baseline, or a fasting TG reduction of at least 50% from baseline.*
- Severity of baseline metabolic status (HbA1c, TG) is a good predictor of response to metreleptin
- NIH study was considered as generalisable to UK by committee in ECM1

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Abbreviations: PL= partial lipodystrophy; TG= triglyceride

Issue 1: Population eligible for metreleptin (contd.)

Clinical experts (CE)

- Natural history of PL subgroup (HbA1c ≥6.5%, TG ≥5.65 mmol/L) and overall PL should be the same
- Minimal HbA1c improvement expected in patients with better baseline HbA1c levels; PL patients with lower leptin at baseline could possibly do better than those with higher leptin but no evidence for this
- **CE1:** no current consensus on definition of PL patients eligible for treatment; PL subgroup criteria in NIH studies were post-hoc, no evidence of how treatment effect on this subgroup would differ from that of overall PL patients; difficult to define "extreme hyperphagia"
- **CE3** (**CE2** in agreement with starting criteria): criteria broadly accepted by EU LD centres

	Start criteria	Stop criteria
GL	*Specialist service review is mandatory before start* • Confirmed GL (> 2 years) • Attendance dietary education session	• At 6-9 months after starting metreleptin or anytime thereafter: specialist service review • Stop metreleptin therapy if poor compliance/non-engagement with appointments

PL	*Specialist service review is mandatory before start*
	• To start metreleptin **all** criteria below must be met:
	  • Confirmed PL (> 12 years)
	  • Attendance of dietary education session
	  • Maximal standard anti-diabetic and lipid lowering therapies including insulin therapy
	  • HbA1c>7.5% (58mmol/mol) and/or fasting TG >5.0mmol/l
	  • Leptin < 10ng/ml
		• At 6-9 months after starting metreleptin: specialist service review
		1. Stop metreleptin if poor compliance/non-engagement with appointments
		2. Stop metreleptin if **no** HbA1c reduction of at least 0.5% from baseline or a fall in fasting TG of at least 50% from baseline.
		
		NB: The specialist service may agree to continue leptin therapy in occasional patients with PL who have not met the above metabolic criteria but who are judged by the specialist service to have had other significant treatment benefits such as a very significant reduction in concomitant medication, significant improvement in fatty liver disease, and/or a significant improvement in quality of life due to for example a significant appetite reduction, or in whom a trial of dose escalation is thought to be required.

Issue 1: Population eligible for metreleptin (contd.)

ERG comments

- Company have narrowed population (although unclear why reported levels were chosen) and defined exceptional circumstances.
  - Company's proposed criteria (HbA1c>7.5% and/or fasting TG >5.0 mmol/L) different from their initial submission (HbA1c ≥6.5% and/or TG ≥5.65 mmol/L)
- Difficult to predict the impact on metreleptin effectiveness. Create issue around application of data sources on UK clinical practice
- Unclear population size given lack of information on number of patients who would actually fulfil these criteria including the exceptions

Issues 2 and 3: Representativeness of clinical studies and indirect treatment comparison

Background

- Because no head-to-head trial, company performed ITC to estimate relative difference in key clinical outcomes* between metreleptin (NIH follow-up) and SoC (GL/PL natural history)
- ERG note discrepancies in metreleptin's effects between EAP data and NIH 991265/20010769 studies, and NIH follow-up study in terms of absolute change in TG level (change from 6.4 to 4.6 (about -1.8) mmol/l [EAP] vs. -10.54 mmol/l [NIH follow-up])
- With the availability of EAP data in the resubmission, ERG raised concerns about generalisability of the NIH follow-up populations to people with LD in England and recommend to perform the ITC using EAP data
- Regarding the ITC, concerns with selection of covariates used; no prognosis variables such as baseline HbA1c, TG, leptin levels, and baseline pancreatitis were adjusted for. Company argued that these factors were not confounding because they were not related to treatment allocation. Company stated that a sensitivity analysis using additional covariates was explored but not feasible due to either small sample size or too many variables covariates included

Company response to TE:

- Important to consider % reductions rather than absolute change as it shows greater consistency (e.g., TG levels at month 12: Mean (SD): -48.4% (20.30) EAP vs. -32.7% (71.28) NIH 991265/20010769 studies)
- Reason for discrepancies between EAP and NIH follow-up: severity of patients eligible for EAP in past was lower than would be today, due to patients changing and growing evidence

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*Key clinical outcomes: change in HbA1c, TG, ALT and AST from baseline to Month 12; incidence of pancreatitis, and all-cause mortality or self explanatory in ITC result slide. Abbreviations: EAP=early access program; ITC=indirect treatment comparison; GL=generalised lipodystrophy; LD= lipodystrophy; PL= partial lipodystrophy; SoC=standard of care; TG=triglycerides

Issues 2 and 3: Representativeness of clinical studies and indirect treatment comparison (contd.)

Clinical experts

- EAP not a research study, based on 'compassionate use' rather than formal clinical criteria. Eligibility criteria currently used were not in place when EAP was set up; criteria for PL patients only set up 2 years ago. Insufficient patient numbers, PL patients did not have poor enough metabolic status at baseline to be representative of effect of metreleptin; EAP has very few GL patients' response to metreleptin so no efficacy conclusion can be made from EAP data.
- Difference in metreleptin effect between EAP and NIH follow up study is due to wide range of TG levels in patients in NIH follow-up causing larger absolute change in TG compared to EAP (which included patients with relatively restricted TG range)
- **CE2**: NIH 991265/20010769 and GL/PL natural history populations are reasonably representative of UK clinical practice with restriction on PL patients
- **CE1 and CE3**: baseline HbA1c and TG levels could have an impact on treatment effect of metreleptin (the higher the baseline levels, the larger the treatment effect)
- Given EAP limitations, ITC better informed by NIH study

ERG comments

- Agree with company on consideration of % reduction change but note that lower absolute change in TG might be due to lower baseline values in EAP patients
- Remain doubts on eligibility criteria of PL patients to metreleptin
- ERG reiterate EAP data is more applicable to UK clinical practice than NIH 991265/200110769 (due to including UK patients and eligibility criteria for PL patients are still unclear from issue 1)
- ERG note company report 2 reasons for not excluding additional covariates: lack of feasibility and loss of precision. ERG reiterate they would like to see a full report of sensitivity analysis

Indirect treatment comparison results (metreleptin vs. standard of care)

Results using Inverse probability weighting (IPW)

Outcome	ATE	Robust standard error (%)	95% CI	p-value
Mean change in HbA1c at 12 months	-1.52	0.38	-2.28 to -0.77	<0.001*
Mean change in TG at 12 months, mg/dL [mmol/L]	-915.30 [10.34]	225.95 [2.55]	-1358.15 to -472.44 [-15.35 to -5.34]	<0.001*
Mean change in ALT at 12 months	-44.13	11.06	-65.81 to -22.46	<0.001*
Mean change in AST at 12 months	-27.79	6.93	-41.38 to -14.20	<0.001*
Odds ratio, pancreatitis	0.94	0.026	0.89 to 0.98	0.01*
Hazard ratio, all-cause mortality	1.38	0.40	0.88 to 20.37 (lower limit corrected by ERG)	0.42

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; ATE, average treatment effect; IPW, inverse probability weighting; CI, Confidence interval; SC, Supportive care; TG, triglycerides
*denotes significance at the p<0.05 level

- 3 methods explored: IPW, multiple regression analysis and naïve comparison
- Results consistent for 3 methods
- Overall PL population data from NIH follow-up study (with worse outcomes than PL subgroup)

Source: ERG report table 1.1 pp 14-15
HbA1c, TG, liver enzyme (ALT and AST) levels and mortality are only outcomes consistently captured and reported in NIH Follow-up and GL/PL Natural History study therefore these were only outcomes considered feasible to include as outcomes of interest

Issue 4: Long-term treatment effect and surrogate outcomes

Background

- Little information about long-term treatment effects of metreleptin, particularly in relation to patient-perceived (hyperphagia) and hard clinical outcomes (e.g. liver damage);
- Mean follow-up times: NIH 991265/20010769/NIH follow-up: GL: 8 years, PL 7.7 years; GL/PL natural history study: GL 9.5 years, PL 6.5 years;
- Although only ITC estimate effects at 12 months reported, mainly on surrogate outcomes HbA1c, TG, ALT/AST
- **ERG**: improvements in surrogate outcomes are likely to predict long-term impacts on future health but evidence is derived from different populations than LD population
- Development of neutralising antibodies and its potential effects remain unclear; could impair metabolic control and immune function.

Company response to TE:

- Relationship between HbA1c and long-term hard clinical outcomes is established and widely accepted based on 30-year follow-up of diabetes in DCCT/ EDIC and UKPDS study.
- Neutralising antibodies reported in 4% of patients (NIH studies 991265/200110769 and FHA101) and therefore not anticipated to affect significant proportion of patients. Not anticipated to affect outcomes such as HbA1c and TG levels in long-term

ERG comments

- No new evidence presented and lack of long-term evidence for metreleptin (for metabolic outcomes at 36 months, and only from EAP)
- No evidence on correlation between surrogates and organ complications in LD, apart from Delphi panel

Abbreviations: DCCT=Diabetes Control and Complications Trial; EDIC= Epidemiology of Diabetes Interventions and Complications; LD=lipodystrophy; TG= triglycerides; UKPDS= UK Prospective Diabetes Study

Issue 4: Long-term treatment effect and surrogate outcomes (contd.)

Clinical expert comments

Metreleptin's long term treatment effect on clinical outcomes including organ damage, hyperphagia, and QoL (while on treatment):

- **CE1**: improvement in leptin deficiency could have positive effect on hyperphagia, and QoL but there is no simple relationship between eating less or more and QoL, so the impact of this treatment effect on utility will be difficult to measure.
- **CE2**: NIH studies have been using leptin since around 2000 so many patients should have follow up data for many years; it is known that very low leptin levels have a major impact on hyperphagia so leptin is very likely to affect GL patients and less PL patients; leptin expected to reduce mortality in line with improvements in HbA1c and TG
- **CE3**: unclear if metreleptin therapy has any direct effect on organs
  - unclear whether risk of liver cirrhosis/ HCC is reduced by metreleptin but seems likely; published data show metreleptin improves fatty liver, proteinuria (kidney), and women's reproductive status;
  - likely that if blood glucose/lipid control is improved with metreleptin that there is reduction in macrovascular and microvascular complications associated with diabetes;
  - in clinicians and patients experience, metreleptin usually improves (reduces) hyperphagia and improves QoL
  - hyperphagia: no long term benefit expected if metreleptin is stopped; symptoms will probably return after a few days

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Abbreviations: HCC = hepatocellular carcinoma; QoL = quality of life

Issue 4: Long-term treatment effect and surrogate outcomes (contd.)

Clinical expert comments (contd.)

HbA1c, TG levels, and ALT/AST as surrogate for hard clinical outcomes (organ damages) in people with LD:

- **CE1 and CE2:** HbA1c and TG levels are reasonable surrogate for long-term outcomes in LD, however overall risk of dying young is still greater for people with LD vs people with T2 diabetes/metabolic syndrome.
- **CE1:**
  - HbA1c strongly linked to renal disease and less strongly to liver & cardiovascular outcomes
  - TG weakly linked to cardiovascular outcomes and more strongly to pancreatitis
  - Liver enzymes weakly linked to rates of liver disease
  - No good marker to predict effects on reproductive dysfunction

Neutralising antibodies are rare events, relevant to some but have not appeared to be a frequent problem in clinical practice. Same issues seen in other metabolic disease but does not affect drug efficacy. Should still be monitored once metreleptin is approved.

Abbreviations: HCC = hepatocellular carcinoma

Issue 4: Long-term treatment effect and surrogate outcomes (contd.)

LDUK comments

- Long-term treatment associated with slowed down development and reduced severity of organ abnormalities, providing many additional years of good quality of life.
- Report of impact of metreleptin in patients with chronic pancreatitis: now have had no further instances of pancreatitis; with female reproductive dysfunction: return to normal menstruation
- *“Incredible. My hunger disappeared almost over night. The fat in my liver reduced by over 75%;*
- *“TG back to normal, appetite back to normal, no more fatty liver”;*
- *“Significant improvements in hyperphagia, significant improvement in immune system, significant improvement in fatty liver, improvement in triglycerides and HbA1c”*

Key issues: clinical

Issue 1: PL population eligible for metreleptin

- Are PL patients in the proposed subgroups (HbA1c>7.5% and/or fasting TG >5.0 mmol/L) likely to gain more or less benefit than those in the NIH PL subgroup (HbA1c ≥6.5% and/or TG ≥5.65 mmol/L)?

Issues 2 and 3: Representativeness of clinical studies and indirect treatment comparison

- Given the apparent differences in response in patients in the NIH and EAP populations, which is the best for the ITC?
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  - improve hyperphagia and QoL?
- Is HbA1c a satisfactory surrogate for damage to heart/kidneys/eyes?
- Are ALT/AST satisfactory surrogates for damage to liver?

Key issues: economic

Issue 6 : Transition probability

- Is the committee satisfied with how the transition probabilities were modelled for;
  - kidney disease, cardiovascular disease, retinopathy, and neuropathy (use of data from other metabolic disease, and adjusted with absolute change in HbA1C at 12 months from NIH studies)?
  - liver disease (direct estimate from Delphi panel vs. ITC estimate for ALT/AST)?

Issues 7, 8 and 9: Post-discontinuation treatment effect and utilities from literature

- Does the committee accept;
  - utilities for model states derived from non-LD sources?
  - an LD-specific disutility in addition to model states to reflect symptoms such as hyperphagia?
- If metreleptin is discontinued;
  - will protection of heart/kidneys/eyes (via HbA1c) persist?
    - if so, for how long?
  - will protection of the liver persist?
    - if so, for how long?
  - will LD-specific disutilities return?
    - if so, after how long?

Key issues: economic (contd.)

Issue 10: number of carers

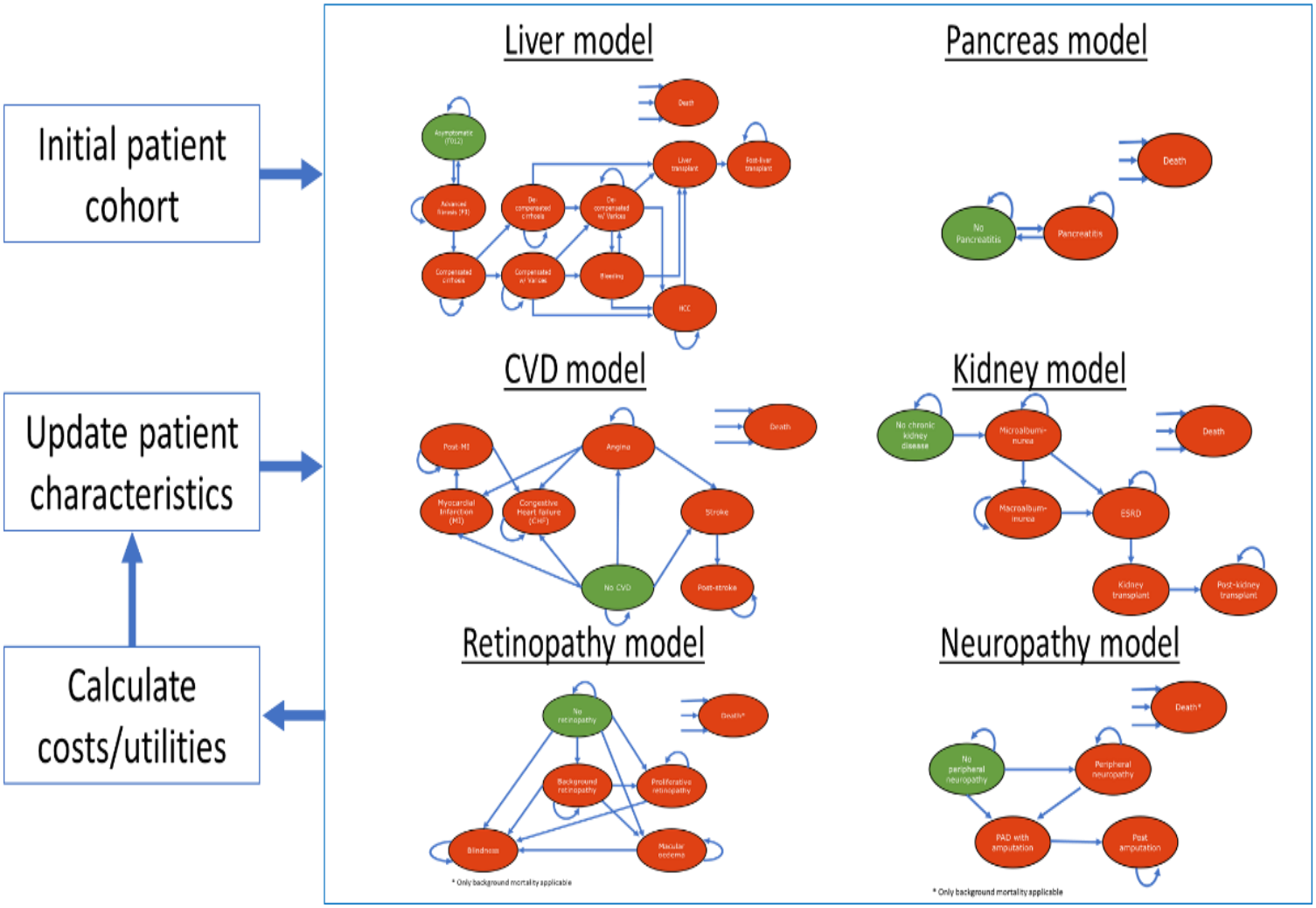
- Which assumption on number of carers (ERG's vs. the company's) does the committee consider appropriate?

What is the committee's preferred ICER?

Does QALY weighting apply?

Population indicated for metreleptin include children, are there any additional considerations required?

Economic model - structure



- De-novo individual patient level model consisting of 6 Markov sub-model
- 6 sub-models simulating progression of disease on organs affected by LD: pancreas, liver disease, cardiovascular disease, kidney, neuropathy and retinopathy
- 1 year cycle; lifetime horizon; NHS and PSS perspective; costs and QALYs discounted at 3.5%.
- Patient simultaneously in single health state in each 6 independent sub-models

Company resubmission p.21: structure is informed by that Sheffield diabetes model and one cited in NICE non-alcoholic fatty liver disease (NAFLD) guidelines

Economic model - evidence sources and assumptions

Initial patient distribution	• Baseline from NIH 991265/200110769 study for SoC and metreleptin • PL characteristics based on PL subgroup (i.e. patients with baseline HbA1c ≥ 6.5% and/or TG ≥ 5.65 mmol/L) from safety analysis of NIH 991265/20010769 • PL/GL patient distribution based on EAP
Transition probabilities for sub-models	Metreleptin arm: baseline transition (from literature) **adjusted** to account for risk reduction of organ complications, which is assumed to continue post-discontinuation • Pancreas: baseline rate of pancreatitis (from GL/PL natural history) adjusted using odds ratios estimated from ITC • Liver: baseline rate of liver disease (from fatty liver) adjusted using direct risk reduction estimated from Delphi panel (base case) or ITC (scenario analysis) • Other 4 organs: baseline rate of complication (from diabetes) adjusted using absolute change in HbA1c level from baseline to 12 months from NIH 991265/20010769
Treatment discontinuation	Metreleptin arm: • Treatment non-compliance: discontinuation rate from NIH studies (annual rate of 1.50% for GL patients and 3.86% for PL patients)
Mortality	• All-cause mortality in LD patients from UK Life tables (ONS); assumed that patient with no complications have similar risk of death as general population • Each organ: mortality risks aggregated to create single probability of death

Economic model - evidence sources and assumptions

Adverse events (AE)	Not included; company report that AE were mild or moderate with low frequency so impact on cost and utility is minimal
Utility decrements (applied to age specific UK population)	• **Pancreas**: from DCE of original submission • **Other organs**: from literature based on non-LD population • **Utility differential**: company also accounted for impact of LD specific symptoms not captured in sub-organ models (i.e., hyperphagia, PCOS, inability to work and impaired physical appearance): differential in utility (vs SoC) of 0.12, based on DCE
Number of carers	• Used of median N carer = 2 per patient (rounding of mean 1.67; sourced from *Lipodystrophy Caregiver Disease Burden Survey* using EQ-5D in carers of LD patients) • If patient discontinued metreleptin: assumed that 50% of 0.12 treatment differential and 50% of benefit to carers is maintained post-discontinuation
Costs	Metreleptin: • drug administration (home delivery + self-administration training) not included since funded by company. • dosage assumptions based on EAP data (and supportive care costs based on NIH studies). Routine monitoring costs based on Delphi panel. Costs of organ complications usually identified in previous NICE guidelines or technology appraisals

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Abbreviation: DCE = discrete choice experiment; LD=lipodystrophy; PCOS= Polycystic ovary syndrome

Issue 6: Baseline transition probabilities and pathway through organ sub-models

Background

- Diabetes-related baseline transition probabilities used for diabetes-related complications, i.e. cardiovascular, kidney disease, neuropathy and retinopathy, and HbA1c used to adjust probabilities
- Considerable uncertainty on assumptions of company new model structure:
  - patients with diabetes or elevated TG levels, due to LD, will follow similar course to patients with similar metabolic conditions but different aetiology.

Company response to TE

- Delphi Panel, which included UK clinicians, reached consensus that early-onset T2 diabetes is closest of diabetes observed in LD patients
- Baseline transition probabilities were adjusted using risk ratios for organ-specific complications derived from literature for T1 vs early-onset T2 diabetes
- Transition probabilities may be an underestimate of CV risk because TG not taken into account (hypertriglyceridemia is a risk factor of CV disease)

Abbreviations: CV = cardiovascular; LD=lipodystrophy; TG= triglycerides

Issue 6: Baseline transition probabilities and pathway through organ sub-models (contd.)

Clinical experts

- Using transition probabilities from other disease areas may under-estimate true values because specific features of LD that could worsen outcomes may not be captured, especially progression of fatty liver, macrovascular disease, episodes of pancreatitis due to hyperinsulinaemia, severe hyperglycaemia and lipid abnormalities.
- No alternative approach to modelling, however, LD more likely to accentuate clinical outcomes from identified metabolic dysfunctions, but size of accentuation cannot be estimated. Unique features of LD (cosmetic, hyperphagia issues) may not be adequately captured by modelling against other common metabolic disease.

ERG comments

- No new evidence provided besides reiterating clinicians' consensus from Delphi Panel study
- ERG note that expert opinion on early-onset type 2 diabetes being the closest form of diabetes observed in LD patients does not mean that the transition probabilities in model closely reflect the disease trajectory of LD patients
- Uncertainty remains that inputs from non-LD populations are generalisable to LD patients
- ERG usually prefers trial data, however, use of risk reduction estimated from Delphi panel (literature) or ITC (trial data) for liver disease does not seem to be a big issue in this case (as very small impact on ICER)

Abbreviations: LD=lipodystrophy

Issue 7: Long-term treatment effect (post-discontinuation) – HbA1c

Background

- No data available on metreleptin's benefit for HbA1c levels post discontinuation
- Company assumed discontinuation had no impact on efficacy: patients receive full benefit at treatment initiation (in 1st cycle) and then HbA1c rises at same rate as patients taking SoC (annual increase of 0.15%; source NICE TA315); therefore relative efficacy post discontinuation remain constant over lifetime in 4 sub-models using HbA1c to determine transition probabilities
- ERG considered assumption unrealistic; ERG base case assumed complete reversal of HbA1c in cycle post discontinuation to remove assumption of continued effect post discontinuation

Company response to TE

- Elevated levels of HbA1c are marker of glucose control over time and reflect levels over several months; lack of glucose control is the cause of diabetes related complications
- Clinically implausible to assume patients return immediately to rates of SoC post discontinuation, including the 0.15% annual drift (as implemented in ERG's base case)
- Company explored scenario where HbA1c level returns to baseline of metreleptin arm immediately post discontinuation (excluding 0.15% annual drift)
- Full relative efficacy for HbA1c is only maintained until ceiling of 12% is reached in SoC group, after which relative efficacy wanes until it is null when metreleptin patients reach ceiling
- Company conducted 2 scenarios: all patients experience (i) 0.1% annual HbA1c increase and (ii) 0.05% annual HbA1c increase.

Abbreviations: SoC= standard of care

Issue 7: Long-term treatment effect (post-discontinuation) – HbA1c (contd.)

Clinical expert comments

- After discontinuation of metreleptin, HbA1c level will reverse to baseline (or more) over 6 to 12 months. In type 1 diabetes, a period of good metabolic control may confer long-term benefits on clinical outcomes (so-called 'metabolic memory' effect); may not apply to LD

ERG comments

- Incorrect company claim on HbA1c reversal being immediate in ERG base case; it is modelled as full efficacy is assumed in the year of discontinuation (on average patients receive an additional 6 months full or 1-year waning efficacy)
- Company provided no evidence to justify the longer period of post-discontinuation efficacy
- Company claims lag between glucose control (marked by HbA1c) and impact on risk of complications but have not modelled it at beginning of treatment, where patients are at higher risk due to poor previous glucose control than level of risk suggested by their drop in HbA1c
- No evidence for company base-case assumption, which results in long term treatment efficacy for both GL (an average of 20 years full and 4 years waning) and PL patients (an average of 20 years full and 6 years waning) maintained
- ERG updated base case (also a company scenario) now assuming HbA1c level returns to baseline (not including 0.15% annual drift) immediately post discontinuation

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Abbreviations: LD=lipodystrophy

Issue 8: Long-term treatment effect (post-discontinuation) – Liver

Background

- No evidence of metreleptin's effect on liver post-discontinuation
- Company assumed liver benefits maintained post discontinuation by assuming that the short-term reduction in fatty deposits and accumulation in liver will yield a longer-term benefit

Company response to TE:

- Sought UK clinician opinion: residual liver benefit is retained post-discontinuation
- Not clinically plausible that level of liver damage would immediately reverse to baseline, it would take several years
- ERG base case removed post-discontinuation liver benefit
- Company explored scenarios of treatment benefit modelled for 1, 5 and 9 year post discontinuation

Clinical expert

- Some sustained slowing of liver damage may be maintained for some months post-discontinuation
- Published data show improvement in fatty liver with metreleptin
  Unclear whether risk of liver cirrhosis/ HCC is reduced but this seems likely
- Liver enzymes (ALT/AST) weakly linked to rates of liver disease

Abbreviations: HCC=hepatocellular carcinoma

Issue 8: Long-term treatment effect (post-discontinuation) – Liver (contd.)

ERG comments

- Incorrect company claim on liver risk reversal being immediate in ERG base case; it is modelled as full efficacy assumed for the year of discontinuation (6 months full or 1-year waning efficacy)
- No reference provided for expert opinion on residual liver benefits will be retained
- Company base case (treatment benefit for lifetime) and scenarios (treatment benefit for 5 and 9 years) do not match claim it takes several years to return to baseline
- ERG remains uncertain on true period and level of post-discontinuation efficacy
- ERG's updated base case includes 1 year efficacy post-discontinuation (on top of 6 months full or 1-year waning efficacy) to reflect possibility that it takes several years to return to baseline risk

Issue 9: Utilities from literature & long-term treatment effect (post-discontinuation) – QoL & utility differential

Background

- Model disutilities on organ complications mostly obtained from literature in non-LD populations
- No evidence on metreleptin's effect on QoL post-discontinuation
- Company's model accounted for impact of LD-specific symptoms not captured in organ model (i.e., hyperphagia, PCOS, inability to work and impaired physical appearance) with a utility differential (vs SoC) of 0.12, based on DCE; carer disutility also modelled
- Company assumed maintenance of 50% of 0.12 differential and 50% of benefit to carers post-discontinuation over the patients' lifetime
- ERG base case removed assumption of 50% continued lifetime treatment effect because its inclusion meant lower incidence of hyperphagia, inability to work, PCO and impaired physical appearance, but no evidence exists to support this

Company response to TE:

- Metreleptin benefit accrued during treatment and translates into reduction of symptoms and risk in multiple complications, generating QoL benefit to carer and patient; average time to treatment discontinuation estimated (in ERG base case) as 8.61 years
- Company performed 3 scenarios exploring continuation of QoL treatment benefit for 1, 5 and 9 years post-discontinuation (assumed average time to treatment discontinuation)
- Because of lack of LD-specific utility, company model used previously NICE-accepted utilities from similar metabolic abnormalities but caused by different underlying diseases
- Company argued that utilities in model are representative of LD complications because utility decrement of specific symptom is not significantly influenced by cause of condition.

Abbreviations: LD=lipodystrophy; PCOS= Polycystic ovary syndrome; QoL=quality of life

Issue 9: Utilities from literature & long-term treatment effect (post-discontinuation) – QoL & utility differential

ERG comments

- Company applied both organ-specific utilities and LD-specific utilities, however, it should be noted that a patient transitioning to more progressed states in organ sub-models receives relevant utility decrement, separate to utility differential observed between patients on metreleptin and SoC
- ERG question the maintenance of utility differential in model; hyperphagia and inability to work account for 80% of differential according to company's rescaled DCE, and those will return quickly post-discontinuation
- ERG note that the way QoL is modelled in their base-case means that the risk of complications and treatment differential remain with patients treated with metreleptin until cycle after discontinuation, implying 6 months full efficacy post-discontinuation or 1-year waning efficacy. No evidence has been provided that justifies a period of efficacy after 1 year
- ERG does not consider there is a strong argument for long term post-discontinuation treatment differential for patients and kept it removed in their updated base case (as well as carer benefit)

Clinical experts comments

- **CE1:** no simple relationship between eating less or more and QoL, so impact of metreleptin on utility is difficult to measure; treatment with leptin is very likely to affect hyperphagia in GL patients and to a lesser extent in PL patients
- **CE2:** in our experience and opinion expressed by patients and families, metreleptin usually improves (reduces) hyperphagia and improves QoL; no long term hyperphagia benefit expected if metreleptin is stopped; symptoms will probably return after a few days

Abbreviations: LD=lipodystrophy; GL= generalised lipodystrophy; QoL=quality of life; SoC= standard of care

Issue 10: Number of carers

Background

- Company base case assumed that each patient had carers
- Number of carers reported in *Lipodystrophy Caregiver Burden Survey* data: 1.67 per patient
- Company base case used average carer scenario (rounded value): N= 2 carers per patient
- ERG base-case used average value of 1.67

Company response to TE

- Value of 2 is the **median**
- Median has less impact of potential outliers than the mean
- Median is more likely to be representative of average number of carers in UK clinical practice
- Validated by UK patient experts

ERG comments

- Reiterates that **mean** should be included in model to reflect average numbers of carers

Company updated base case (deterministic*)

Revised base case deterministic results after technical engagement (with PAS), include following assumptions

- HbA1c maintained until ceiling of 12% is reached in SoC group, after which relative efficacy wanes until it is null + 0.15% annual drift
- Liver: lifetime benefits maintained post-discontinuation
- QoL: lifetime maintenance of 50% treatment differential and carer utility gain post-discontinuation
- Liver transition probabilities sourced from Delphi panel
- Annual discontinuation rate (from NIH studies)
- Utilities are now UK-specific
- N=2 carers

Intervention	Incr. cost (£)	Incr. QALY (discounted)	Incr. QALY (undiscounted)	ICER (£/QALY)
GL metreleptin	[redacted]	[redacted]	[redacted]	£91,407
PL metreleptin	[redacted]	[redacted]	[redacted]	£158,351
overall	[redacted]	[redacted]	[redacted]	£118,895

Source: Company's response to technical engagement; *QALY weighting applied; GL = generalised lipodystrophy; ICER = incremental cost effectiveness ratio; PAS=patient access scheme; PL = partial lipodystrophy; QALYs = quality adjusted life years; QoL= quality of life; SoC=standard of care.

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updated probabilistic results not provided

Company scenario analyses (overall population)

Scenarios		Incremental Costs	Incremental QALYs disc.	Incremental QALY undisc.>10	ICER
Company base case	-	[redacted]	[redacted]	-	£118,895
1. Post-discontinuation HbA1c	Reversion to baseline level	[redacted]	[redacted]	-*	£119,997
2. Maintain of liver benefit post-discontinuation	1-year post-discontinuation	[redacted]	[redacted]	-*	£138,087
	5 years post-discontinuation	[redacted]	[redacted]	-*	£132,380
	9 years post-discontinuation	[redacted]	[redacted]	-*	£128,492
3. Maintain 50% QoL benefit post-discontinuation and carer benefits	1-year post-discontinuation	[redacted]	[redacted]	-	£180,575
	5 years post-discontinuation	[redacted]	[redacted]	-	£167,551
	9 years post-discontinuation	[redacted]	[redacted]	-	£157,755
4. Reversal of HbA1c to baseline, maintenance of liver benefits, and 50% QoL benefits for patients and carers post-discontinuation	1-year post-discontinuation	[redacted]	[redacted]	-	£194,263
	5 years post-discontinuation	[redacted]	[redacted]	-	£175,917
	9 years post-discontinuation	[redacted]	[redacted]	-	£163,130
5. HbA1c annual drift	0.1% annual increase	[redacted]	[redacted]	[redacted]	£110,223
	0.05% annual increase	[redacted]	[redacted]	[redacted]	£101,368

NICE *Undiscounted ICER for GL population is >10 (see details in appendices); Based on model updated from the company's response to technical engagement. Abbreviations: GL = generalised lipodystrophy; ICER = incremental cost effectiveness ratio; PL = partial lipodystrophy; QALYs = quality adjusted life years; QoL= quality of life.

ERG updated base case (deterministic)

ERG updated base case (post TE) include following assumptions:

- **correction of number of carers to 1.67 (rather than 2 in company base case)**
- use of ALT/AST data to adjust transition probabilities in liver model (rather than Delphi data)
- **removal of assumed lifetime maintenance of 50% of QoL treatment differential and carer utility gain post-discontinuation from metreleptin**

Additional assumptions based on company technical engagement's response:

- reversal of HbA1c to baseline level after discontinuation (excluding 0.15% drift)
- updated utilities based on UK Tariff (carried out differently in company base case)
- **additional 1 year of post-discontinuation efficacy in liver model**

Intervention	Incr. cost (£)	Incr. QALYs (discounted)	Incr. QALYs (undiscounted)	ICER (£/QALY)
GL metreleptin	[redacted]	[redacted]	[redacted]	£185,088
PL metreleptin	[redacted]	[redacted]	[redacted]	£252,765
overall	[redacted]	[redacted]	[redacted]	£217,128

Probabilistic ICERs were aligned to deterministic ICERs, although more variation for PL subgroup

Based on model updated from the company's response to technical engagement.[1]
Abbreviations: GL = generalised lipodystrophy; ICER = incremental cost effectiveness ratio; PL = partial lipodystrophy; QALYs = quality adjusted life years; QoL= quality of life.

ERG scenario analyses (overall population)

Scenarios		Incremental		ICER	Impact
		Costs	QALYs*		
ERG updated base case (post TE)	-	[redacted]	[redacted]	£217,128	-
1. Post-discontinuation HbA1c	Full reversal (including 0.15%drift) *ERG original base case (pre TE)*	[redacted]	[redacted]	£222,836	↑
	No reversal *Company updated base case (post TE)*	[redacted]	[redacted]	£216,890	↓
2. Post-discontinuation benefits liver	No additional years *ERG original base case (pre TE)*	[redacted]	[redacted]	£220,366	↑
	5 years post-discontinuation	[redacted]	[redacted]	£216,406	↓
	Lifetime *Company updated base case (post TE)*	[redacted]	[redacted]	£213,358	↓
3. Post-discontinuation benefits QoL	1-year post-discontinuation	[redacted]	[redacted]	£214,396	↓
	5 years post-discontinuation	[redacted]	[redacted]	£198,723	↓↓
	Lifetime	[redacted]	[redacted]	£162,105	↓↓↓

NICE *Incremental QALY undiscounted are not presented as all are <10; Abbreviation: ICER = incremental cost effectiveness ratio; QALYs = quality adjusted life years; QoL= quality of life.

↓↓ Shows larger decrease than ↓

ERG scenario analyses (overall population)

Scenarios		Incremental		ICER	Impact
		Costs	QALYs*		
ERG updated base case (post TE)	-	[redacted]	[redacted]	£217,128	-
4. Post-discontinuation benefits HbA1c, liver and QoL scenarios combined	No additional years and full reversal of HbA1c (including 0.15% drift)	[redacted]	[redacted]	£223,713	↑
	1 additional year and reversal of HbA1c to baseline (not including drift)	[redacted]	[redacted]	£214,396	↓
	5 additional years and reversal of HbA1c to baseline (not including drift)	[redacted]	[redacted]	£196,173	↓↓↓
	9 additional years and reversal of HbA1c to baseline (not including drift)	[redacted]	[redacted]	£182,696	↓↓↓
	Lifetime and no reversal of HbA1c	[redacted]	[redacted]	£143,340	↓↓↓↓
5. Number of carers	2 carers ***Company updated base case (post TE)***	[redacted]	[redacted]	£205,452	↓↓
6. Source of liver transitions	Delphi Panel ***Company updated base case (post TE)***	[redacted]	[redacted]	£215,530	↓

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*Incremental QALY undiscounted are not presented as all are <10; Abbreviation: ICER = incremental cost effectiveness ratio; QALYs = quality adjusted life years; QoL= quality of life.

↓↓ Shows larger decrease than ↓

QALY weighting

- For ICERs above £100,000 per QALY, recommendations must take into account the magnitude of the QALY gain and the additional QALY weight that would be needed to fall below £100,000 per QALY
- To apply the QALY weight, there must be compelling evidence that the treatment offers significant QALY gains

Lifetime incr. QALYs gained	Weight
Less than or equal to 10	1
11–29	Between 1 and 3 (using equal incr.)
Greater than or equal to 30	3

Issues resolved during technical engagement

	Summary	Stakeholder responses	Technical team consideration
	Issue 5: Discontinuation rate; company assumes that patients will only stop treatment for non-compliance (from NIH study 991265/20010769)	• ERG believes that declining annual rate of discontinuation (from NIH study) is more appropriate. • Company agree these are plausible alternative discontinuation rates that have been previously accepted by NICE Committee	• Compliance should not be the only reason for discontinuation of metreleptin treatment • Agree with ERG

Unresolvable uncertainties

- Utilities for pancreatitis and other LD specific symptoms (e.g. hyperphagia) sourced from original DCE
- Committee previously concluded that DCE is associated with substantial limitations including issues around the method and validity of utilities estimated
  - Company attempted to address issues on validity by rescaling utilities, and presented results at ECM2. Committee considered rescaled utilities were more plausible than original DCE utilities
- ERG noted it is unclear to what extent input values are generalisable to LD patients and therefore utility estimates are subject to uncertainty. However, ERG concluded that no changes to utility values or decrements can be made by as no better alternatives are available

Factors affecting the guidance

- In forming the guidance, committee will take account of the following factors:

Nature of the condition	Clinical effectiveness
• Extent of disease morbidity and patient clinical disability with current care • Impact of disease on carers' QoL • Extent and nature of current treatment options	• Magnitude of health benefits to patients and carers • Heterogeneity of health benefits • Robustness of the evidence and the how the guidance might strengthen it • Treatment continuation rules
Value for money	**Impact beyond direct health benefits**
• Cost effectiveness using incremental cost per QALY • Patient access schemes and other commercial agreements • The nature and extent of the resources needed to enable the new technology to be used	• Non-health benefits • Costs (savings) or benefits incurred outside of the NHS and personal and social services • Long-term benefits to the NHS of research and innovation • The impact of the technology on the delivery of the specialised service • Staffing and infrastructure requirements, including training and planning for expertise

Key issues: economic

Issue 6 : Transition probability

- Is the committee satisfied with how the transition probabilities were modelled for;
  - kidney disease, cardiovascular disease, retinopathy, and neuropathy (use of data from other metabolic disease, and adjusted with absolute change in HbA1C at 12 months from NIH studies?
  - liver disease (direct estimate from Delphi panel vs. ITC estimate for ALT/AST)?

Issues 7, 8 and 9: Post-discontinuation treatment effect and utilities from literature

- Does the committee accept;
  - utilities for model states derived from non-LD sources?
  - an LD-specific disutility in addition to model states to reflect symptoms such as hyperphagia?
- If metreleptin is discontinued;
  - will protection of heart/kidneys/eyes (via HbA1c) persist?
    - if so, for how long?
  - will protection of the liver persist?
    - if so, for how long?
  - will LD-specific disutilities return?
    - if so, for after how long?

Key issues: economic (contd.)

Issue 10: number of carers

- Which assumption on number of cares (ERG's vs. the company's) does the committee consider appropriate?

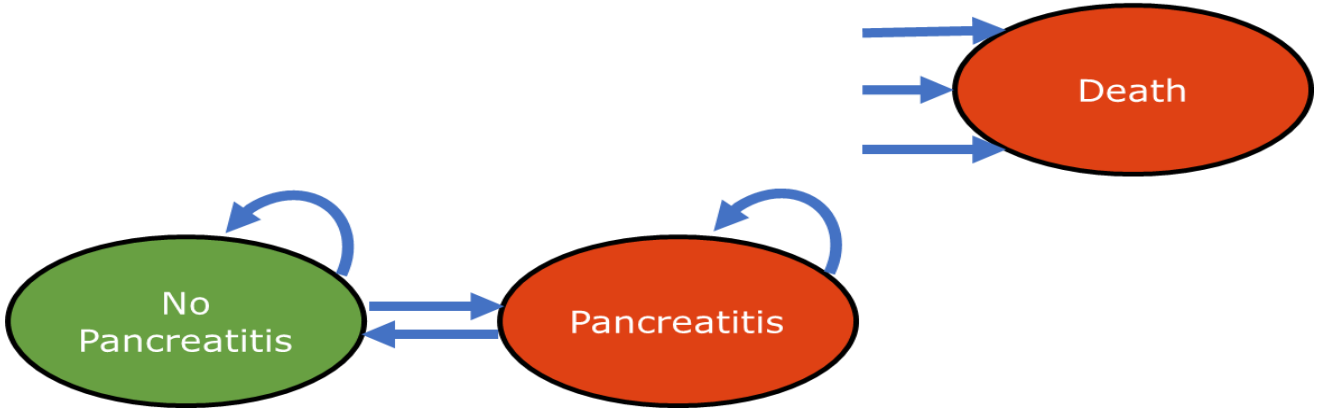
What is the committee's preferred ICER?

Does QALY weighting apply?

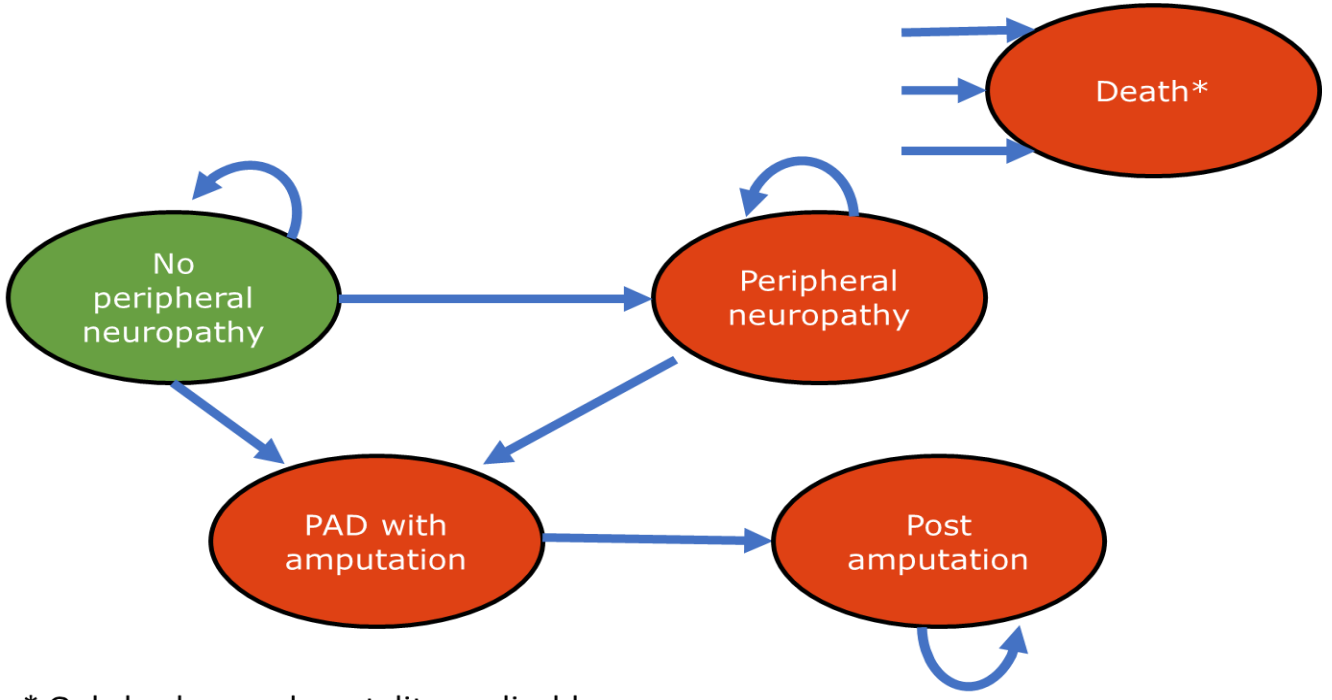
Population indicated for metreleptin include children, are there any additional considerations required?

Appendices

Pancreas sub-model structure



Neuropathy sub-model structure



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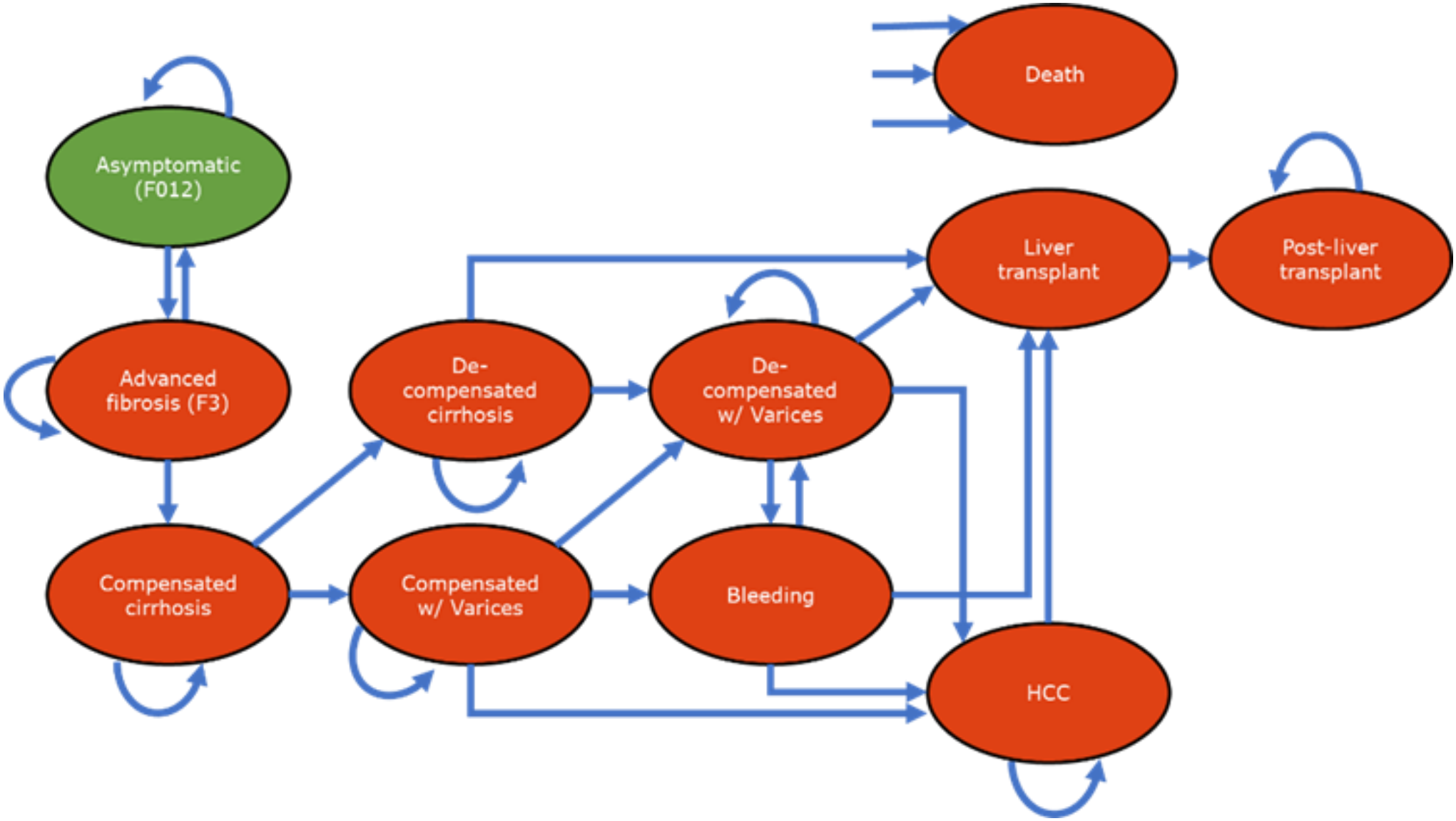
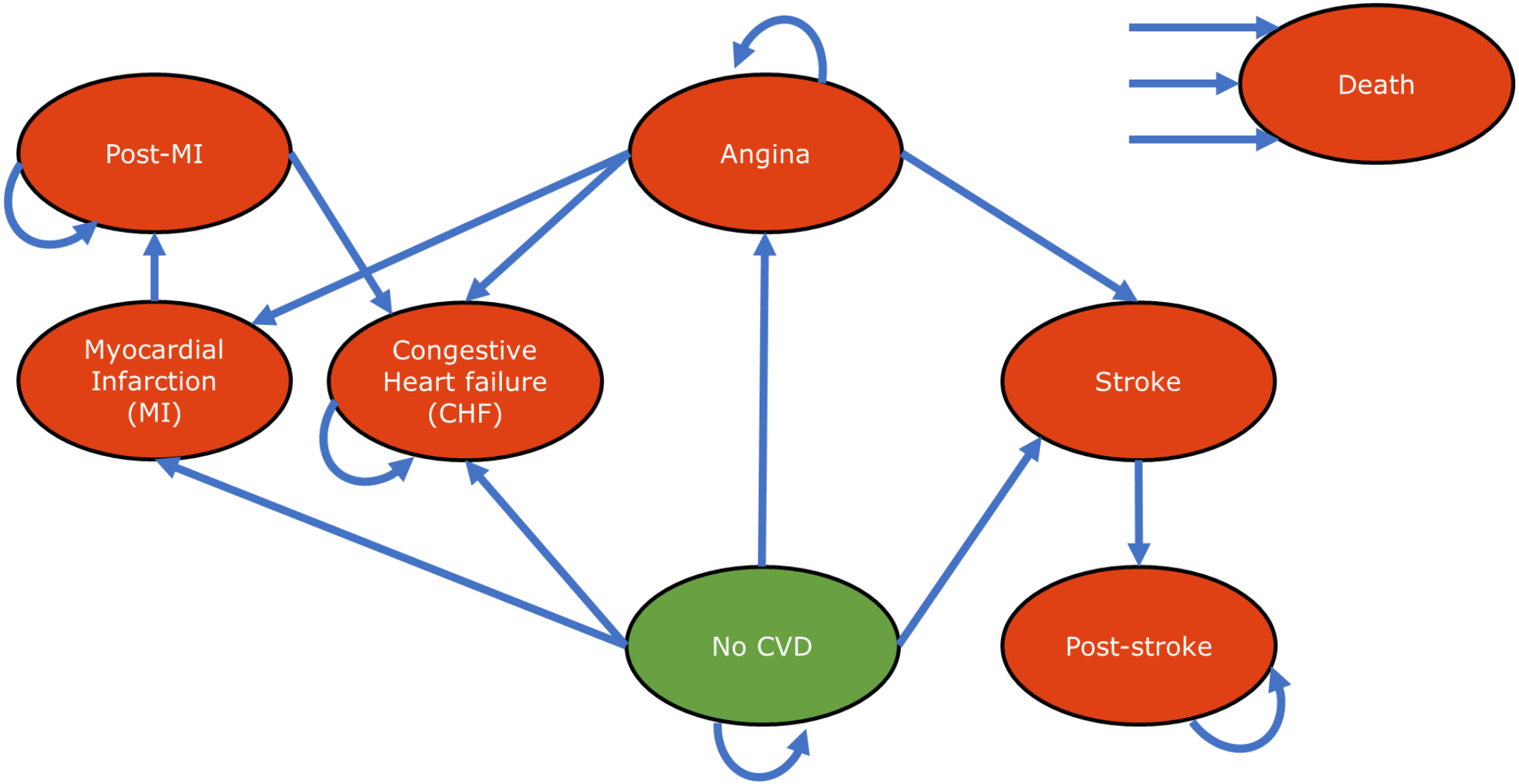
* Only background mortality applicable

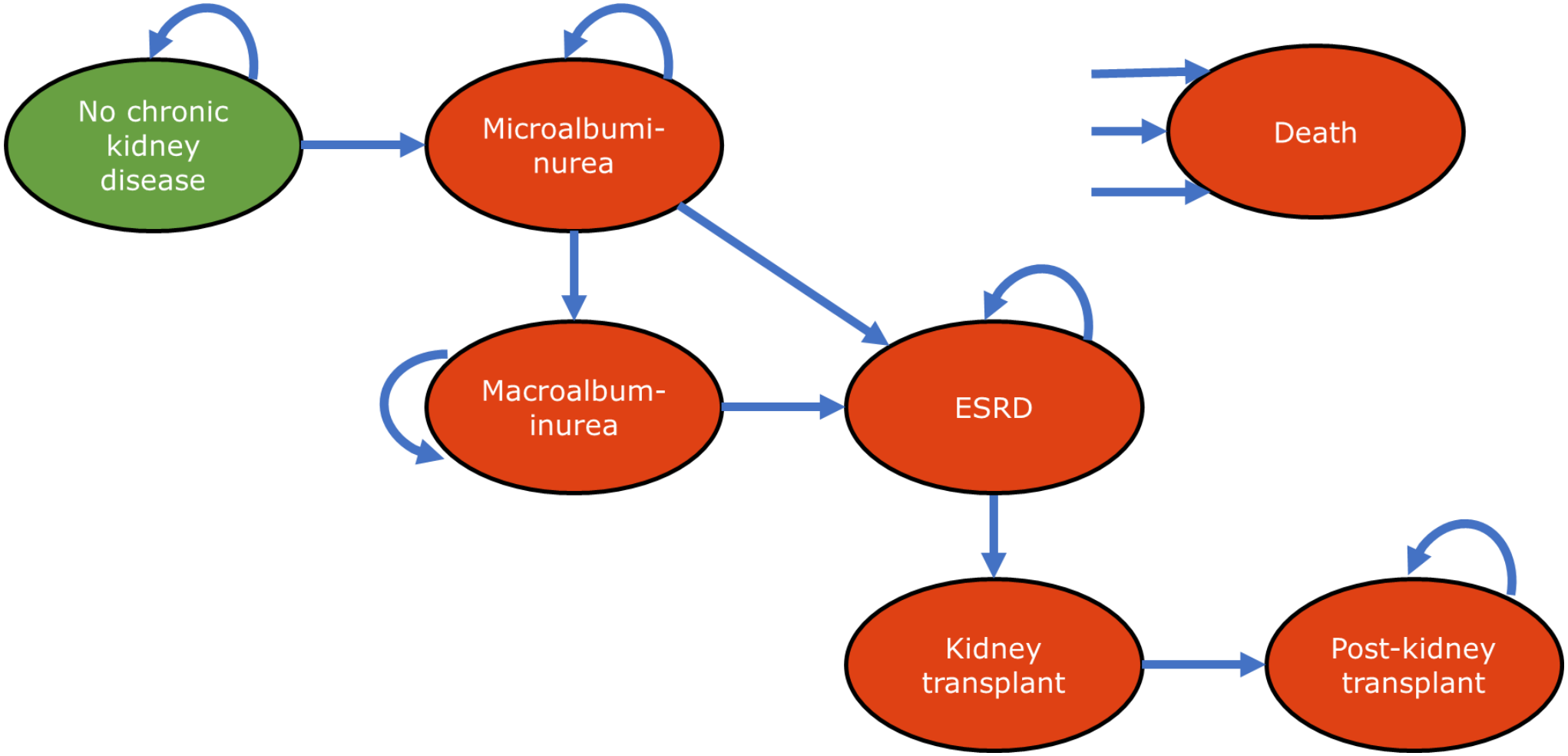
Liver sub-model structure



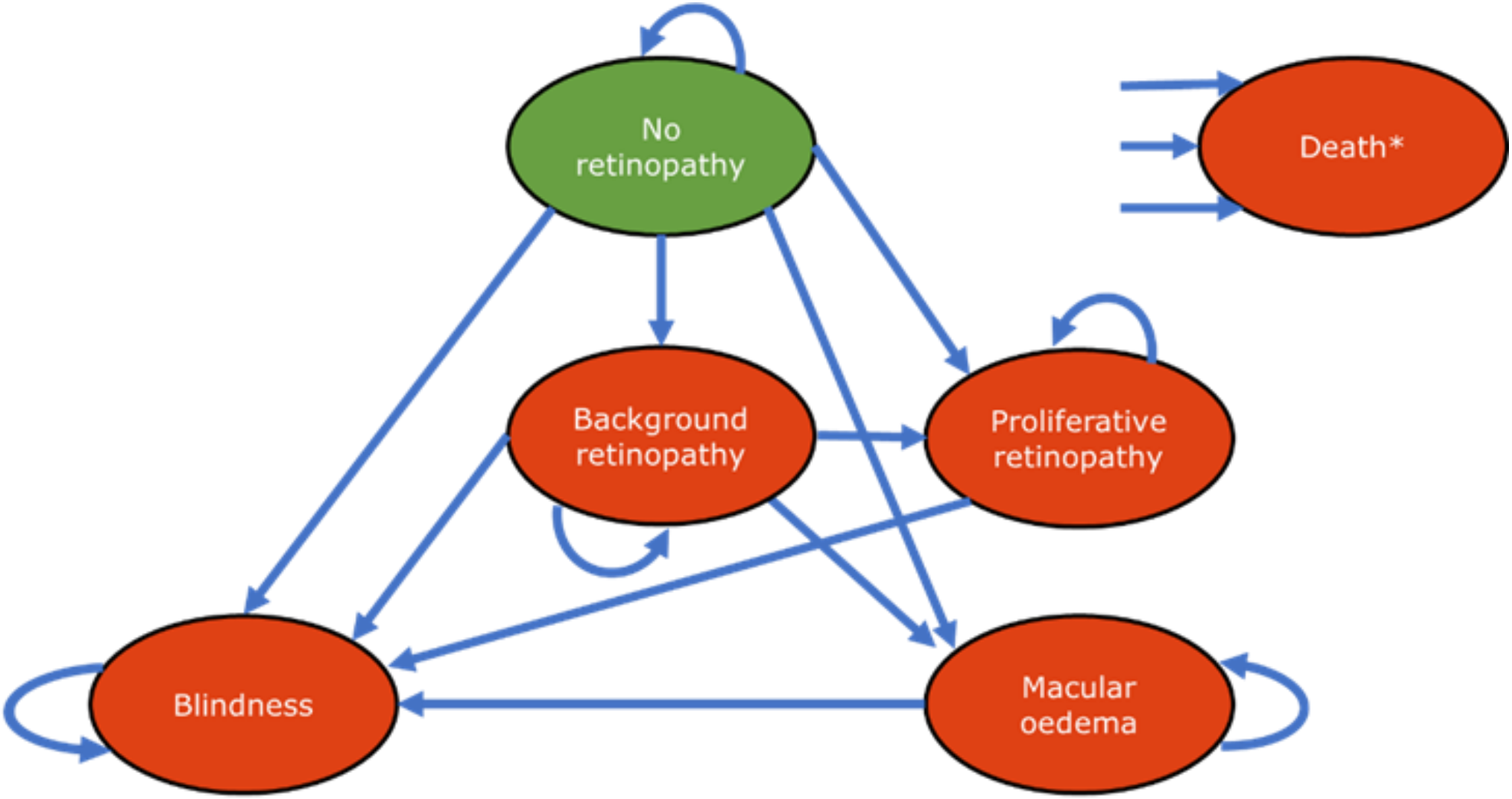
Cardiovascular sub-model structure



Kidney sub-model structure



Retinopathy sub-model structrue



* Only background mortality applicable

Undiscounted incremental QALYs

QALY weighting applied in 7 scenarios:

	Outcome	QALY gain
		Undiscounted
Company base case	GL patients	[redacted]
Company scenario analysis - HbA1c annual drift	0.1% annual increase	[redacted]
	0.05% annual increase	[redacted]
Company scenario analysis - Reversion of HbA1c to baseline level upon discontinuation **GL population only**		[redacted]
Company scenario analysis – maintenance liver benefit **GL population only**	1-year post-discontinuation	[redacted]
	5-year post-discontinuation	[redacted]
	9-year post-discontinuation	[redacted]