Icosapent ethyl with statin therapy for reducing the risk of cardiovascular events in people with raised triglycerides

For public observers – redacted

Technology appraisal committee C - 4 May 2022

Chair: Steve O'Brien

Evidence assessment group: Kleijnen Systematic Reviews

Technical team: Kirsty Pitt, Charlie Hewitt, Ross Dent

Company: Amarin

NICE

Key issues

Table 1 Key issues

Issue	ICER impact
Mineral oil placebo – Is the company's additional evidence sufficient to justify lowering the reduction in treatment effect to account for the potential negative effect of the mineral oil placebo? (7% reduction currently preferred by committee)	Large
Loss of treatment effect after stopping treatment (waning) – Is there reason for committee to change its conclusion that people stopping icosapent ethyl would lose treatment effect after 10 years?	Large
REDUCE-IT generalisability – Does the company's advisory board feedback reduce the uncertainty around the generalisability of REDUCE-IT to the NHS in England?	Unknown

Key:

- Large impact
- Small impact
- Unknown impact

Icosapent ethyl (Vazkepa, Amarin)

Table 2 Technology details

Marketing authorisation (MHRA)	Indicated to reduce the risk of cardiovascular events in adult statin-treated patients at high cardiovascular risk with elevated triglycerides (≥150 mg/dL [≥ 1.7 mmol/L]) and • established cardiovascular disease, or • diabetes, and at least one other cardiovascular risk factor
Mechanism of action	• Highly purified and stable ethyl ester of the omega-3 fatty acid eicosapentaenoic acid (EPA) • Mechanism of action of pure EPA in reducing cardiovascular events not fully understood, but appears to modulate atherosclerosis pathway by lipid and non-lipid effects
Administration	Oral; daily dose of 4 capsules, taken as 2 capsules twice daily
Price	Proposed **new** list price [redacted] per pack of 120 capsules ([redacted] per year). No Patient Access Scheme. Previous proposed list price at second committee meeting was [redacted]

Abbreviations: MHRA, Medicines and Healthcare products Regulatory Authority

Summary

Table 3 Summary of appraisal

Comparators	Best supportive care = stable dose of statins with or without ezetimibe
Clinical setting	Primary care
Subgroups	• **Secondary prevention** (CV1): Adults with established cardiovascular disease • **Primary prevention** (CV2): Adults with diabetes and at least 1 other risk factor
REDUCE-IT clinical trial	Randomised controlled trial comparing icosapent ethyl with placebo (mineral oil)
Model	Partitioned survival approach with 8 health states

Analyses after first committee meeting only provided for **secondary prevention population**

Equality and equity considerations

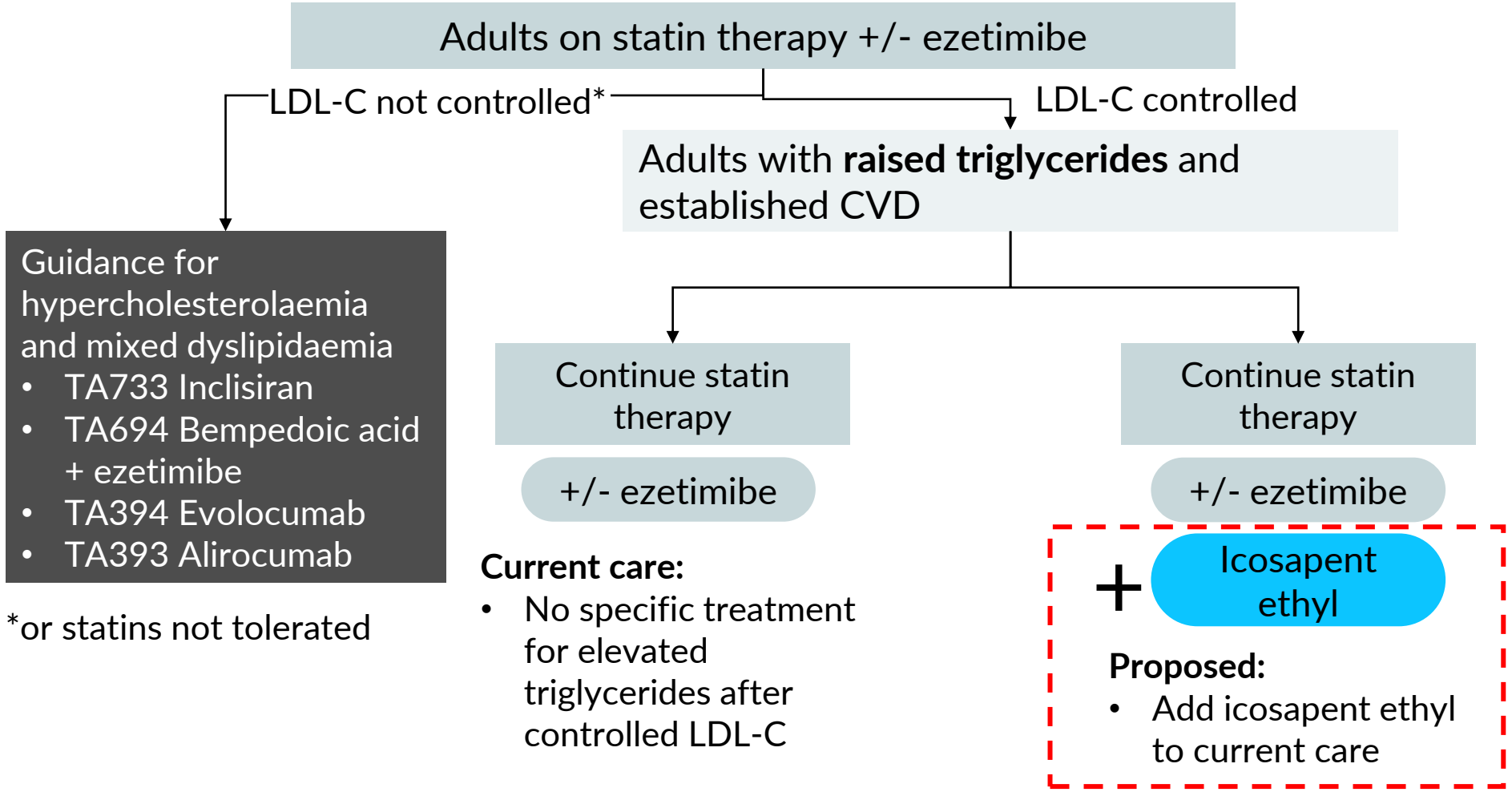
No additional equality considerations raised in second consultation

- People with Black, Asian and minority ethnic family backgrounds have higher triglyceride levels and increased CVD risk factors
- People in England's most deprived areas are almost 4 times more likely to die prematurely from CVD than people in the least deprived areas
- Variation in access to secondary and tertiary care
- People with severe mental illness are more likely to develop and die from preventable conditions like CVD
- People with learning disabilities are at increased risk of developing CVD
- Some faiths and ethical beliefs may restrict use of fish products
- Pregnancy and breast-feeding

CVD, cardiovascular disease

RECAP

Treatment pathway & proposed position



- Controlled LDL-C levels (REDUCE-IT): > 1.04 mmol/L and ≤ 2.60 mmol/L
  - *ACD: committee concluded acceptable to use these levels*
- Raised triglycerides (marketing authorisation): ≥ 1.70 mmol/L

CVD, cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; mmol/L, millimoles per litre

Second ACD – committee conclusions [1]

Table 4 Committee's previous conclusions

Issue	Committee conclusion
Comparator	Statins with or without ezetimibe is an appropriate comparator
Setting	Icosapent ethyl is likely to be used mostly in primary care
Population	• The population in the company's submission is narrower than the marketing authorisation in terms of LDL-C levels and is acceptable • It is appropriate to consider the effects of icosapent ethyl for the secondary prevention subgroup
Clinical evidence	• The population in REDUCE-IT may not be generalisable to the NHS in England • Current management of cardiovascular disease and diabetes is not fully reflected in REDUCE-IT • Icosapent ethyl's mechanism of action is not fully understood, which adds uncertainty • The treatment effect of icosapent ethyl is uncertain because of the mineral oil placebo in REDUCE-IT • It is appropriate to consider scenarios for an estimated reduction in treatment effect from 3% to 10% (considered 7% in preferred analysis)

Abbreviations: LDL-C, low-density lipoprotein cholesterol

Second ACD – committee conclusions [2]

Issue	Committee conclusion
Economic model	• The results from the company's model are uncertain because of the model structure and the discrepancy between model and trial outcomes • Using the composite 5-point MACE outcome in the model increases uncertainty • The company's updated time to event modelling is acceptable • It is plausible that the treatment effect may be lost after 10 years if treatment is discontinued • The treatment-independent non-cardiovascular-related death hazard ratios are acceptable • The company's model has uncertainties so the comparison with the validation model is also uncertain
Cost-effectiveness estimates	Because of the uncertainty an acceptable ICER is below £20,000 per QALY gained

Committee-preferred ICER = £34,067 per QALY gained → Icosapent ethyl is not recommended

Abbreviations: MACE, major adverse cardiac events; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

ACD2 committee-preferred model assumptions

Reduction in treatment effect to account for mineral oil placebo	Loss of treatment effect on discontinuation: None	At 10 years	At 5 years
	ICERs icosapent ethyl vs placebo (£/QALY gained)		
None			
1.5%			
3%			
7%		Committee's preferred ICER	

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

Consultation comments

NICE

Consultation responses

Comments received from:

- Amarin (company)
- HEART UK
- 30 members of the public

Public and patient organisation consultation comments summary

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- Interpretation of evidence regarding mineral oil is not reasonable
  - Systematic review showed no negative effects
  - FDA concluded 'no strong evidence for biological activity of the mineral oil placebo was found by the REDUCE-IT cardiovascular outcomes trial'
  - Benefits of icosapent consistent with benefits of EPA in JELIS study, which did not include placebo in trial
- Large economic and health burden of cardiovascular disease in the UK, unmet need
  - Availability of icosapent would help with Direct Enhanced Services contract in primary care, which includes cardiovascular disease diagnosis and prevention for 2021/22
- Triglycerides should be considered in cardiovascular risk assessment
- Further consideration could be made to most appropriate patient subgroup, e.g., narrowing eligibility using non-HDL cholesterol levels or higher triglyceride level
- Trial results are robust and promising in reduction of cardiovascular events
- Other treatments have been recommended when trials did not completely match clinical practice e.g., SGLT2 inhibitors in heart failure, when use of angiotensin-neprolysin inhibitors was low in clinical trials

Abbreviations: EPA, eicosapentaenoic acid; non-HDL, non-high density lipoprotein; SGLT, sodium-glucose cotransporter-2

Key issue: Mineral oil placebo [1]

Unclear whether mineral oil placebo impacts trial outcomes

Background

- Small increases in some biomarkers known to be associated with CV risk seen in placebo arm of REDUCE-IT
  - Triglycerides, non-HDL-C, LDL-C, apoB and hs-CRP
- Doi 2021 paper compared REDUCE-IT with similar trial, STRENGTH, which used corn oil placebo, and found an unexplained 13% benefit in REDUCE-IT
- European public assessment report (EPAR) notes that negative effect of mineral oil would not be more than 10%
- Committee preferred to consider scenarios with treatment effect reduction of 3% to 10% (7% preferred)

Company

- No evidence that mineral oil is not neutral - REDUCE-IT and STRENGTH investigated different active treatments (EPA in REDUCE-IT compared with mixed EPA and DHA preparation in STRENGTH)
- Studies have shown that DHA can counteract the benefits of EPA
- Significant differences in baseline characteristics between REDUCE-IT and Doi cohort
- Some biological parameters changed in the placebo arm of REDUCE-IT are correlated with CV risk, but may be related e.g., changes in LDL-C are accounted for in changes in non-HDL-C or apoB
- Changes in biological parameters in REDUCE-IT are consistent with placebo changes in 79% of CV outcomes trials (2003-2019, not using mineral oil as placebo), including trials of other NICE-appraised treatments
- JELIS trial (EPA) also showed statistically significant benefits in reducing CV events – no mineral oil placebo
- EPAR: putative negative effect 0.3-3% of major adverse cardiac events or less – based on analysis by FDA

Abbreviations: CV, cardiovascular; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; apoB, apolipoprotein B; non-HDL-C, non-high-density lipoprotein cholesterol

Key issue: Mineral oil placebo [2]

Company recreated FDA analysis and did propensity score matched approach

Company

- **Replicated FDA Cox regression model** to examine effects of hs-CRP and LDL-C on relative benefit of icosapent ethyl

- **New propensity score matched approach to Cox regression analysis**, accounting for overlapping effects of LDL-C, hs-CRP and apoB

- Explored relationship between on-treatment serum active drug concentration (EPA) and cardiovascular outcomes
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  -
- **Updated base case includes a 1.5% reduced treatment effect**

Abbreviations: hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; apoB, apolipoprotein B

Key issue: Mineral oil placebo [3]

ERG considers harmful placebo effect plausible but uncertain

ERG comments

- EPAR concludes maximum negative effect of mineral oil placebo would be 3%
- FDA indicated that LDL-C increase may occur due to reduction in absorption of statins
- FDA also stated that 0.65 mg/L difference in hs-CRP between arms of REDUCE-IT from baseline would increase the risk of cardiovascular outcomes by less than 0.3% in placebo arm
  - Maximum effect (combination of all identified mechanism including LDL-C and CRP) would be 3%
- Doi paper found a difference of 0.5 mg/L, corresponding to a 4% increase in risk
  - Maximum effect would be 7%
- Discrepancy is 10-fold difference in effect of CRP on cardiovascular disease (0.3% vs 4%)
- Highlighted a systematic review of reviews that did not find any evidence for effect of CRP on CV risk
- Considers it is plausible there was a harmful placebo effect in REDUCE-IT but size of effect is very uncertain
- Base case has no treatment effect reduction

Is the company's additional evidence sufficient to justify lowering the reduction in treatment effect to account for the potential negative effect of the mineral oil placebo?

Abbreviations: hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; EPAR, European Public Assessment Report

Key issue: Loss of treatment effect (waning) [1]

Loss of treatment effect not included in company model

Background

- Company's model assumed icosapent ethyl treatment effect in REDUCE-IT would not wane beyond the trial data collection period
- Committee concerned that treatment discontinuation was not linked to treatment effect. Uncertain if treatment effect in REDUCE-IT would continue over model time horizon as more people stop treatment
- Committee accepted ERG base case assumption where people stopping icosapent would have same clinical efficacy as placebo group after 10 years

Company

- No evidence to support loss of treatment effect – no loss of treatment effect assumed in updated base case
- Clinical experts at technical engagement and in the first meeting suggested no waning was likely reasonable
- Reiterated previous arguments:
  - Waning already accounted for because people stopping icosapent ethyl in REDUCE-IT were included in the extrapolations
  - REDUCE-IT showed sustained efficacy in people who stopped icosapent ethyl
- No loss of effect included in alirocumab appraisal (TA393) – although more people discontinued treatment in REDUCE-IT trial, follow-up was longer so this is to be expected

Is there reason for committee to change its conclusion that people stopping icosapent ethyl would lose treatment effect after 10 years?

Key issue: Loss of treatment effect (waning) [2]

Around [redacted]% of people had stopped treatment by the end of the trial

Figure 1 Time to discontinuation: observed KM curve vs. extrapolations for secondary prevention population

[redacted]

Figure 2 Hazard ratios over time for secondary prevention population

[redacted]

Key issue: Generalisability of REDUCE-IT trial

Company considers trial is generalisable to UK practice

Background

- Company previously presented comparison of baseline characteristics between REDUCE-IT and Steen et al., a retrospective study of 183,565 people with or without atherosclerotic cardiovascular disease from The Health Improvement Network database in the UK
- Committee noted potential differences between REDUCE-IT and Steen et al. in proportion of people that had recent acute coronary syndrome, diabetes, hypertension and ischaemic stroke
- Committee also concluded the current management of cardiovascular disease and diabetes is not fully reflected in REDUCE-IT in terms of PCSK9 inhibitor, SGLT2 inhibitor and GLP-1 agonist usage

Company

- Advisory board of 9 UK clinical experts conducted March 22
  - Concluded trial data would be generalisable to UK population
- Highlight that use of SGLT2 inhibitors and GLP-1 agonists in the trial was consistent with clinical practice at time of trial. PCSK9 inhibitor use not relevant as recommended for a different population.

ERG comments

- Agree PCSK9 inhibitor use (e.g. alirocumab) not relevant to this appraisal as different eligible populations

Does the company's advisory board feedback reduce the uncertainty around the generalisability of REDUCE-IT to the NHS in England?

Abbreviations: SGLT2, Sodium-glucose co-transporter-2; GLP-1, Glucagon-like peptide-1; PCSK9, Proprotein convertase subtilisin/kexin type 9

Company's comments on remaining areas of uncertainty

Committee: Icosapent ethyl's mechanism of action not fully understood, which adds uncertainty

- **Company:** Advisory board of clinical experts considers that a well-understood mechanism of action (MoA) is not required for clinical use e.g. metformin, SGLT2 inhibitors and GLP1 agonists have uncertain MoAs
- Highlighted paper on potential atheroprotective mechanisms
- CV risk reduction being larger than expected from triglyceride reduction (as in REDUCE-IT) is consistent with what is known about icosapent ethyl – no interaction between triglyceride levels and treatment effect

Committee: Using the composite 5-point MACE outcome in the model increases uncertainty

- **Company:** Outcome of death modelled separately to other events
- Cross-validation model uses individual cardiovascular outcomes and produces similar clinical and economic outcomes to the company's model using composite MACE outcome

Committee: The results from the company's model are uncertain

- **Company:** Model validation using a different model structure (Markov) and 6-month cycle length produced very similar results to company's model
- 3 UK clinical experts consulted considered survival estimates from model similar to expected survival in UK clinical practice and any discrepancies likely due to controlled environment of clinical trial setting

Committee: Because of the uncertainty an acceptable ICER is below £20,000 per QALY gained

- **Company:** Applying further assumptions in the model to test uncertainty (e.g., reducing treatment effect, waning) as well as only accepting ICER below £20,000 is double counting of uncertainty

Abbreviations: SGLT, sodium-glucose cotransporter-2; GLP-1, glucagon-like peptide-1; MACE, major adverse cardiac events

ERG's comments on remaining areas of uncertainty

Committee: Icosapent ethyl's mechanism of action not fully understood, which adds uncertainty

- **ERG:** Agree that uncertainty in mechanism of action has little bearing on results of a randomised controlled trial in general
- Uncertainty is because of size of treatment effect in REDUCE-IT compared to that in STRENGTH

Committee: The results from the company's model are uncertain

- **ERG:** Company's updated cross-validation comparison is likely appropriate

Summary of company and ERG base case assumptions

Table 5 Assumptions in company and ERG base case

Assumption	Previous committee preference	Company base case	ERG base case
Loss of treatment effect after discontinuation	Loss of treatment effect after discontinuation after 10 years	Not included	Loss of treatment effect after discontinuation after 10 years
Reduction in treatment effect to account for mineral oil placebo	7% relative reduction	Maximum 1.5% relative reduction	No reduction in treatment effect
Updated list price	N/A	List price reduced	List price reduced

Base case results

Company

Table 6 Company's deterministic incremental base case results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Placebo	[redacted]	[redacted]	-	-	-
Icosapent ethyl	[redacted]	[redacted]	[redacted]	[redacted]	£20,000

ERG

Table 7 ERG's deterministic incremental base case results

Technology	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Placebo	[redacted]	[redacted]	-	-	-
Icosapent ethyl	[redacted]	[redacted]	[redacted]	[redacted]	£21,062

Abbreviations: QALY, quality-adjusted life year; ICER, incremental-cost effectiveness ratio

ERG deterministic scenario analysis

Table 8 ERG scenario analyses (deterministic)

Scenario (icosapent vs placebo)	Inc. costs (£)	Inc. QALYs	ICER (£)
Company base case*	[redacted]	[redacted]	**£19,999**
ERG base case (loss of treatment effect upon discontinuation at 10y, no effect reduction)	[redacted]	[redacted]	**£21,062**
1) Loss of treatment effect at 5y, no effect reduction	[redacted]	[redacted]	£24,484
2) No loss of treatment effect, 3% treatment effect reduction	[redacted]	[redacted]	£21,750
3) Loss of treatment effect at 10y, 3% treatment effect reduction	[redacted]	[redacted]	£24,821
4) Loss of treatment effect at 10y, 7% treatment effect reduction**	[redacted]	[redacted]	£31,893
5) Loss of treatment effect at 5y, 7% treatment effect reduction	[redacted]	[redacted]	£37,019
6) Loss of treatment effect at 10y, 1.5% treatment effect reduction	[redacted]	[redacted]	£22,817
7) Loss of treatment effect at 5y, 1.5% treatment effect reduction	[redacted]	[redacted]	£26,503
8) Loss of treatment effect at 5y, 3% treatment effect reduction	[redacted]	[redacted]	£28,816
9) No loss of treatment effect, 7% treatment effect reduction	[redacted]	[redacted]	£27,900

*small discrepancy from company's presented results due to rounding of updated list price

**committee-preferred scenario at second meeting

Abbreviations: QALY, quality-adjusted life year; ICER, incremental-cost effectiveness ratio; inc, incremental

Summary of results and scenarios

Reduction in treatment effect to account for mineral oil placebo	ICERs icosapent ethyl vs placebo (£/QALY gained)	Loss of treatment effect on discontinuation: None	Loss of treatment effect on discontinuation: At 10 years	Loss of treatment effect on discontinuation: At 5 years
	None	£18,464	£21,062 ERG base case	£24,484
	1.5%	£19,999 Company base case	£22,817	£26,503
	3%	£21,750	£24,821	£28,816
	7%	£27,900	£31,893 Previous committee-preferred*	£37,019

*Committee-preferred ICER at previous list price was £34,067