Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia

ADDENDUM to the ERG report

ERG's critique of the company's additional PAS ICERs and additional sensitivity analyses on potential non-PAS prescribing in primary care

Produced by Aberdeen HTA Group

Authors Graham Scotland[1,2]
Mehdi Javanbakht[1]
Aileen Neilson[1]
Miriam Brazzelli[2]

1 Health Economics Research Unit, University of Aberdeen
2 Health Services Research Unit, University of Aberdeen

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Contains CIC/AIC

This addendum to the ERG evaluation report provides:

i) the ERG's commentary on an updated PAS submission that was received on 03/12/15 (ID779 Alirocumab Sanofi PAS submisson v0.3 011215 JE [CIC]) after submission of the ERG report. The results of these further analyses are discussed in section A of this addendum;

ii) a critique of the additional sensitivity analyses provided by the company in response to NICE's request, which address the uncertainty relating to the availability of the agreed PAS discount for patients prescribed alirocumab using an FP10 form in a primary care setting. The results of these further sensitivity analyses are presented in section B of this addendum.

SECTION A: Additional PAS analyses submitted by the company

The ERG has checked all the additional PAS analyses submitted by the company and noted that most of these had already been provided by the company or replicated in the original ERG report. However, for completeness, all the company's PAS ICERs are reproduced in this addendum.

Company base case analyses with PAS

First of all, the company presented their updated base case results, for alicorumab as an add-on to maximally tolerated lipid lowering therapy. These are reproduced in Table 1 below. The ERG was able to replicate all of these results. The analysis for the HeFH secondary prevention cohort, using the THIN data to inform baseline risks, was the only ICER that was not presented in the original PAS submission. This shows the ICER to be somewhat higher (£19,060 per QALY) as compared with the ICER using the alternative source of baseline risk data reported by Mohrschladt et al. (ICER = £16,896 per QALY). This is as expected, as the baselines risks are substantially higher when using the Mohrschladt et al. data. This has been commented on the ERG's original report.

Secondly, the company provided updated base case ICERs for alirocumab as an add-on to statin compared directly with ezetimibe as an add-on to statin. These were not provided in the company's original PAS submission, and are reproduced in Table 2. The ERG can also replicate all these analyses. They show that when alirocumab is considered for patients inadequately controlled on statin alone, with ezetimibe as the active comparator, the ICERs are somewhat less favorable - ranging from £20,352 per QALY (HEFH secondary prevention) to £48,193 per QALY (HeFH primary prevention). Note, the company has only presented the HeFH secondary prevention ICER using the baseline risk data from Morschladt et al. The ICER is £23,234 using the THIN data for the baseline CV risks (Table 2b).

Table 3 shows the results of the company analyses for alirocumab as an add-on to ezetimibe, and versus ezetimibe, for those above the respective LDL-C thresholds who are intolerant to statins. Applying the company's inputs for the recurrent CVD/polyvascular disease population intolerant to statins (i.e. mean LDL-C = 4 mmol/L), the ERG get an ICER of £15,853 (Table 3b) rather than the £13,669 reported by the company (Table 3). The ERG believe the company may have inadvertently set the baseline LDL-C to 4.55 mmol/L for this

comparison, which does not match the value for the recurrent CVD/polyvascular disease population with an LDL-C ≥ 2.59 mmol/L in their submission. The ERG was able to replicate the alirocumab monotherapy versus ezetimibe monotherapy comparisons for the high risk CVD and the recurrent CVD/polyvascular disease populations, applying baseline LDL-C levels of 4.95 mmol/L and 4.94 mmol/L respectively. The company's submission indicates that the baseline LDL-C level following the washout period in the ALTERNATIVE trial (i.e. off-treatment) can be used for these head-to-head comparisons. This is stated to be ~4.95 mmol/L.

Table 1 Company's incremental cost-effectiveness results (versus background LLT) – Base cases with Patient Access Scheme

Patient population	Technology (and comparators)	Total costs	Total life years	Total QALYs	Incremental costs	Incremental life years	Incremental QALYs	ICER versus baseline
HeFH primary prevention (LDL-C ≥2.59 mmol/L)	Alirocumab + current maximal therapy (statins + ezetimibe)	[redacted]	[redacted]	[redacted]	52,256	1.62	1.42	36,793
	Current maximal therapy (statins + ezetimibe)	[redacted]	[redacted]	[redacted]				
HeFH secondary prevention (LDL-C ≥2.59 mmol/L) *Baseline risk data from Mohrschladt et al*	Alirocumab + current maximal therapy (statins + ezetimibe)	[redacted]	[redacted]	[redacted]	39,306	3.04	2.33	16,896
	Current maximal therapy (statins + ezetimibe)	[redacted]	[redacted]	[redacted]				
HeFH secondary prevention (LDL-C ≥2.59 mmol/L) *Baseline risk data from THIN*	Alirocumab + current maximal therapy (statins + ezetimibe)	[redacted]	[redacted]	[redacted]	40,733	2.85	2.14	19,060
	Current maximal therapy (statins + ezetimibe)	[redacted]	[redacted]	[redacted]				
High risk CVD (LDL-C ≥3.36 mmol/L)	Alirocumab + current maximal therapy (statins)	[redacted]	[redacted]	[redacted]	34,684	2.38	1.76	19,751
	Current maximal therapy (statins)	[redacted]	[redacted]	[redacted]				
Recurrent events/ polyvascular disease (LDL-C ≥2.59 mmol/L)	Alirocumab + current maximal therapy (statins)	[redacted]	[redacted]	[redacted]	31,953	2.42	1.64	19,447
	Current maximal therapy (statins)	[redacted]	[redacted]	[redacted]				

LLT: lipid lowering therapy; CVD: cardiovascular disease; HeFH: heterozygous familial hypercholesterolaemia; ICER: incremental cost-effectiveness ratio; LDL-C: low density lipoprotein cholesterol; QALY: quality-adjusted life-year

Table 2 Company's incremental cost-effectiveness results (versus ezetimibe) – Base cases with Patient Access Scheme

Patient population	Technology (and comparators)	Total costs	Total life years	Total QALYs	Incremental costs	Incremental life years	Incremental QALYs	ICER versus baseline
HeFH primary prevention (baseline LDL-C ≥2.59 mmol/L)	Alirocumab + statins	[redacted]	[redacted]	[redacted]	45,962	1.07	0.95	48,193
	Ezetimibe + statins	[redacted]	[redacted]	[redacted]				
HeFH secondary prevention (baseline LDL-C ≥2.59 mmol/L) *Baseline risk data from Mohrschladt et al*	Alirocumab + statins	[redacted]	[redacted]	[redacted]	34,632	2.21	1.70	20,352
	Ezetimibe + statins	[redacted]	[redacted]	[redacted]				
High-risk CVD (baseline LDL-C ≥3.36 mmol/L)	Alirocumab + statins	[redacted]	[redacted]	[redacted]	31,195	1.75	1.29	24,175
	Ezetimibe + statins	[redacted]	[redacted]	[redacted]				
Recurrent events/ Polyvascular Disease (baseline LDL-C ≥2.59 mmol/L)	Alirocumab + statins	[redacted]	[redacted]	[redacted]	28,781	1.83	1.25	23,078
	Ezetimibe + statins	[redacted]	[redacted]	[redacted]				

CVD: cardiovascular disease; HeFH: heterozygous familial hypercholesterolaemia; ICER: incremental cost-effectiveness ratio; LDL-C: low density lipoprotein cholesterol; QALY: quality-adjusted life-year

Table 2b Incremental cost-effectiveness results (versus ezetimibe) for the HeFH secondary prevention cohort (baseline LDL-C ≥2.59 mmol/L) using the THIN data to inform baseline CV risks – Base case with Patient Access Scheme (results produced by the ERG using the company's base case assumptions)

Sub Ref	Patient population	Technology (and comparators)	Total costs	Total life years	Total QALYs	Incremental costs	Incremental life years	Incremental QALYs	ICER versus baseline
	HeFH primary prevention (baseline LDL-C ≥2.59 mmol/L) *Baseline risk data from THIN*	Alirocumab + statins	[redacted]	[redacted]	[redacted]	35,806	2.05	1.54	23,234
		Ezetimibe + statins	[redacted]	[redacted]	[redacted]				

Table 3 Company's incremental cost-effectiveness results (versus background LLT) - Base cases with Patient Access Scheme

Patient population	Technology (and comparators)	Total costs	Total life years	Total QALYs	Incremental costs	Incremental life years	Incremental QALYs	ICER versus baseline
STATIN INTOLERANT								
High-risk CVD (baseline LDL-C ≥3.36mmol/L)	Alirocumab + ezetimibe	[redacted]	[redacted]	[redacted]	35,146	2.76	2.04	17,256
	Ezetimibe	[redacted]	[redacted]	[redacted]				
Recurrent events/ Polyvascular Disease (baseline LDL-C ≥2.59 mmol/L)	Alirocumab + ezetimibe	[redacted]	[redacted]	[redacted]	32,798	3.52	2.40	13,669
	Ezetimibe	[redacted]	[redacted]	[redacted]				
High-risk CVD (baseline LDL-C ≥3.36 mmol/L)	Alirocumab	[redacted]	[redacted]	[redacted]	30,829	2.40	1.78	17,295
	Ezetimibe	[redacted]	[redacted]	[redacted]				
Recurrent events/ Polyvascular Disease (baseline LDL-C ≥2.59 mmol/L)	Alirocumab	[redacted]	[redacted]	[redacted]	28,820	3.12	2.14	13,469
	Ezetimibe	[redacted]	[redacted]	[redacted]				

CVD: cardiovascular disease; HeFH: heterozygous familial hypercholesterolaemia; ICER: incremental cost-effectiveness ratio; LDL-C: low density lipoprotein cholesterol; QALY: quality-adjusted life-year

Table 3b Incremental cost-effectiveness results for the recurrent events/polyvascular disease population (baseline LDL-C ≥2.59 mmol/L) - Base cases with Patient Access Scheme (ERG's re-analysis)

Patient population	Technology (and comparators)	Total costs	Total life years	Total QALYs	Incremental costs	Incremental life years	Incremental QALYs	ICER versus baseline
STATIN INTOLERANT								
Recurrent events/ Polyvascular Disease (baseline LDL-C ≥2.59 mmol/L)	Alirocumab + ezetimibe	[redacted]	[redacted]	[redacted]	32,719	3.03	2.06	15,853
	Ezetimibe	[redacted]	[redacted]	[redacted]				

CVD: cardiovascular disease; HeF H: heterozygous familial hypercholesterolaemia; ICER: incremental cost-effectiveness ratio; LDL-C: low density lipoprotein cholesterol; QALY: quality-adjusted life-year

Company subgroup analysis with agreed PAS

The company provided subgroup analyses with the agreed PAS by baseline LDL-C level, and these are presented in Table 4 below. The ERG had already replicated and commented on these analyses in their original report (Table 40), and all the ICERs are matched exactly. They are presented below for completeness.

Table 4 Subgroup analyses by LDL-C levels with PAS

Patient population	Baseline LDL-C threshold (mmol/L)	Incremental costs £	Incremental QALY	ICER
HeFH primary prevention	2.59	52,256	1.42	36,793
	3.36	52,005	1.64	31,750
	4.13	51,804	1.79	28,923
HeFH secondary prevention	2.59	39,306	2.33	16,896
	3.36	39,224	2.48	15,838
	4.13	39,023	2.74	14,242
High Risk CVD	2.59	34,701	1.37	25,287
	3.36	34,684	1.76	19,751
	4.13	34,493	2.15	16,043
Recurrent events / Polyvascular disease	2.59	31,953	1.64	19,447
	3.36	32,085	2.09	15,332
	4.13	32,013	2.54	12,606

HeFH, heterozygous familial hypercholesterolaemia; ICER, incremental cost-effectiveness ratio; LDL-C, low-density lipoprotein cholesterol; QALY, quality-adjusted life-year

Company sensitivity analyses with agreed PAS

The company had already provided the following tables (Tables 5-8) in their original PAS submission, which the ERG had access during the course of this technology appraisal. These tables have already been considered and reproduced in the original ERG's report (Tables 42-45). They are reproduced below for completeness.

Table 5 HeFH primary prevention, alirocumab + statins + ezetimibe versus statins + ezetimibe deterministic sensitivity analysis with PAS

Parameter	Variation	ICER (£/QALY)
Base case with PAS		**36,793**
Annual CV risk	–20%	47,504
Annual CV risk	+20%	30,047
Adjustment of CV risk by age	–20%	37,023
Adjustment of CV risk by age	+20%	36,428
CV costs	–20%	37,094
CV costs	+20%	36,492
CV event costs	Doubled	35,287
Alirocumab efficacy (LDL-C lowering)	Lower CI	38,146
Alirocumab efficacy (LDL-C lowering)	Upper CI	35,659
Rate ratio per 1 mmol/L for calculation of baseline CV risk	Lower CI	33,828
Rate ratio per 1 mmol/L for calculation of baseline CV risk	Upper CI	39,413
Rate ratio per 1 mmol/L for treatment effect	Lower CI	29,787
Rate ratio per 1 mmol/L for treatment effect	Upper CI	Dominated
Acute CV disutilities	Lower CI	36,448
Acute CV disutilities	Upper CI	37,144
Baseline utilities	Lower CI	36,793
Baseline utilities	Upper CI	36,793
Chronic CV disutilities	Lower CI	35,751
Chronic CV disutilities	Upper CI	37,897

CI, confidence interval; CV, cardiovascular; HeFH, heterozygous familial hypercholesterolaemia; ICER, incremental cost-effectiveness ratio

Table 6 HeFH secondary prevention, alirocumab + statins + ezetimibe versus statins + ezetimibe - deterministic sensitivity analysis with PAS

Parameter	Variation	ICER (£/QALY)
Base case – with PAS		**16,896**
Annual CV risk	–20%	20,018
Annual CV risk	+20%	14,806
Adjustment of CV risk by age	–20%	16,932
Adjustment of CV risk by age	+20%	16,919
CV costs	–20%	17,192
CV costs	+20%	16,600
CV event costs	Doubled	15,416
Alirocumab efficacy (LDL-C lowering)	Lower CI	17,690
Alirocumab efficacy (LDL-C lowering)	Upper CI	16,222
Rate ratio per 1 mmol/L for calculation of baseline CV risk	Lower CI	16,020
Rate ratio per 1 mmol/L for calculation of baseline CV risk	Upper CI	17,622
Rate ratio per 1 mmol/L for treatment effect	Lower CI	12,477
Rate ratio per 1 mmol/L for treatment effect	Upper CI	Dominated
Acute CV disutilities	Lower CI	16,756
Acute CV disutilities	Upper CI	17,038
Baseline utilities	Lower CI	17,574
Baseline utilities	Upper CI	16,268
Chronic CV disutilities	Lower CI	16,722
Chronic CV disutilities	Upper CI	17,074

CI, confidence interval; CV, cardiovascular; HeFH, heterozygous familial hypercholesterolaemia;

ICER, incremental cost-effectiveness ratio;

Table 7 High risk CVD, alirocumab + statins versus statins - deterministic sensitivity analysis with PAS

Parameter	Variation	ICER (£/QALY)
Base case – with PAS		**19,751**
Annual CV risk	–20%	23,910
Annual CV risk	+20%	17,009
Adjustment of CV risk by age	–20%	19,710
Adjustment of CV risk by age	+20%	19,784
CV costs	–20%	19,979
CV costs	+20%	19,522
CV event costs (doubled)		18,608
Alirocumab efficacy (LDL-C lowering)	Lower CI	20,600
Alirocumab efficacy (LDL-C lowering)	Upper CI	19,021
Rate ratio per 1 mmol/L for calculation of baseline CV risk	Lower CI	18,650
Rate ratio per 1 mmol/L for calculation of baseline CV risk	Upper CI	20,689
Rate ratio per 1 mmol/L for treatment effect	Lower CI	14,518
Rate ratio per 1 mmol/L for treatment effect	Upper CI	Dominated
Acute CV disutilities	Lower CI	19,621
Acute CV disutilities	Upper CI	19,882
Baseline utilities	Lower CI	20,549
Baseline utilities	Upper CI	19,012
Chronic CV disutilities	Lower CI	19,578
Chronic CV disutilities	Upper CI	19,926

CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease; ICER, incremental cost-effectiveness ratio

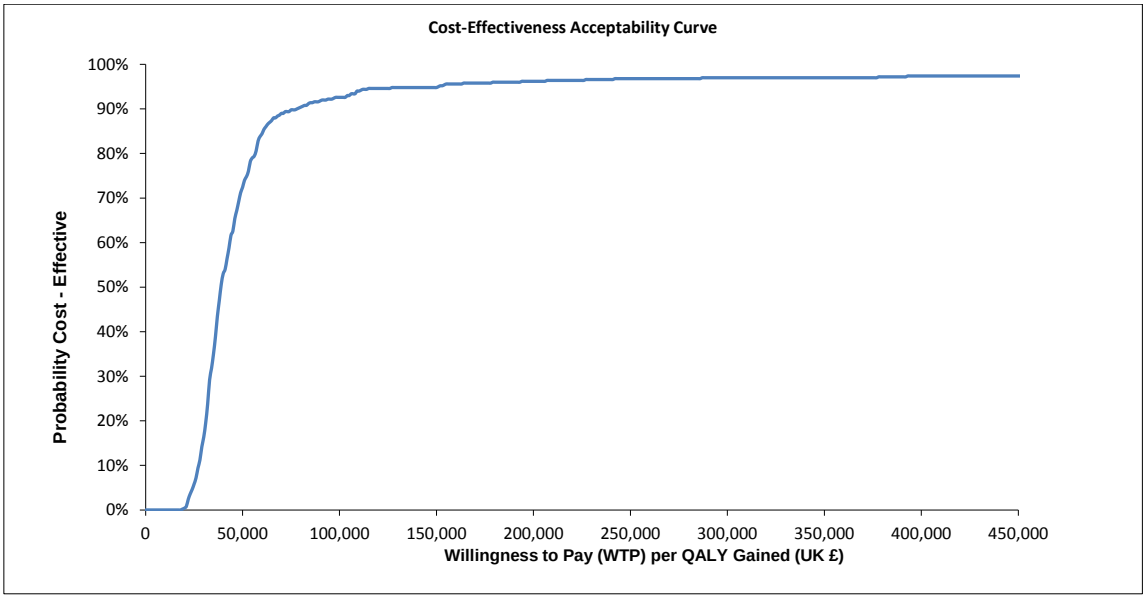
Table 8 Recurrent events/ polyvascular, alirocumab + statins versus statins - deterministic sensitivity analysis with PAS

Parameter	Variation	ICER (£/QALY)
Base case – with PAS		**19,447**
Annual CV risk	–20%	22,901
Annual CV risk	+20%	17,153
Adjustment of CV risk by age	–20%	18,799
Adjustment of CV risk by age	+20%	20,096
CV costs	–20%	19,649
CV costs	+20%	19,245
CV event costs	Doubled	18,435
Alirocumab efficacy (LDL-C lowering)	Lower CI	20,623
Alirocumab efficacy (LDL-C lowering)	Upper CI	18,460
Rate ratio per 1 mmol/L for calculation of baseline CV risk	Lower CI	18,919
Rate ratio per 1 mmol/L for calculation of baseline CV risk	Upper CI	19,872
Rate ratio per 1 mmol/L for treatment effect	Lower CI	13,268
Rate ratio per 1 mmol/L for treatment effect	Upper CI	Domniated
Acute CV disutilities	Lower CI	19,331
Acute CV disutilities	Upper CI	19,564
Baseline utilities	Lower CI	20,585
Baseline utilities	Upper CI	18,429
Chronic CV disutilities	Lower CI	19,358
Chronic CV disutilities	Upper CI	19,537

CI, confidence interval; CV, cardiovascular; ICER, incremental cost-effectiveness ratio

Company probabilistic sensitivity analysis with agreed PAS

In their original PAS submission, the company had already provided scatter plots and acceptability curves summarising the results of their base case probabilistic analyses with the agreed PAS. These analyses have already been reproduced and commented on as Figures 4-7 in the original ERG's report. They are reproduced below for completeness. Table 9 shows the corresponding probabilities of cost-effectiveness for the respective patient populations at different levels of willingness-to-pay per QALY gained (£20, £30 and £40k). These were not provided in the original PAS submission.



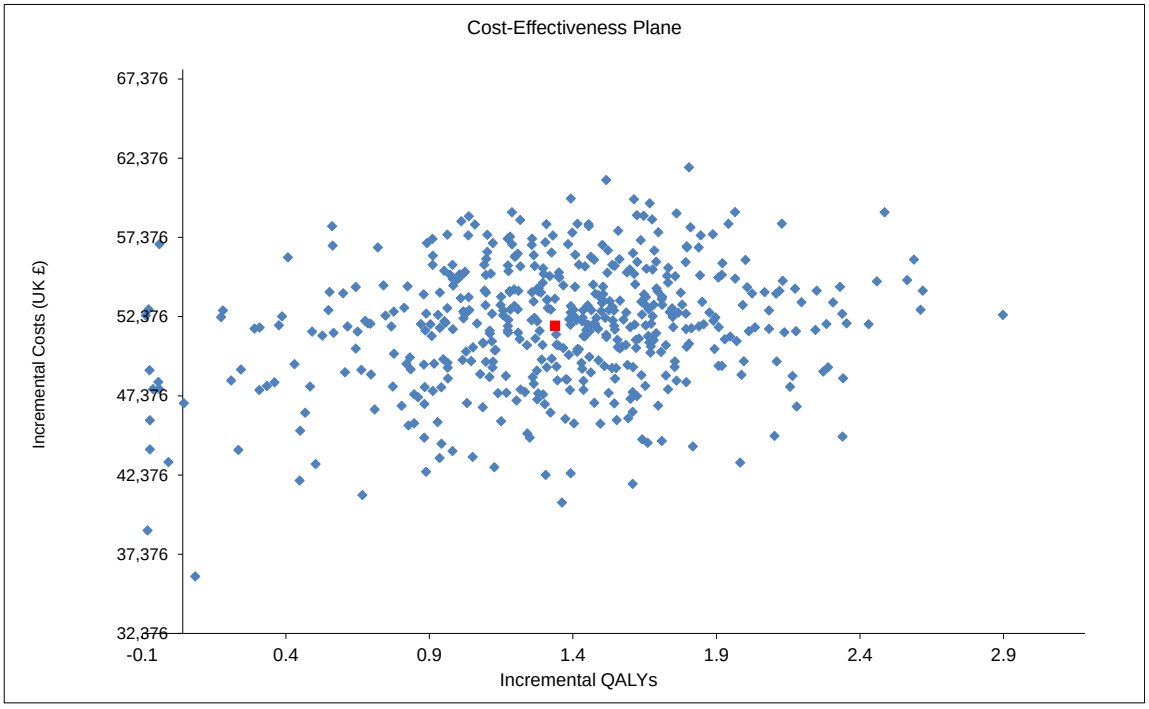


Figure 1 HeFH primary prevention, alirocumab + statins + ezetimibe versus statins + ezetimibe - scatter plot and CEAC

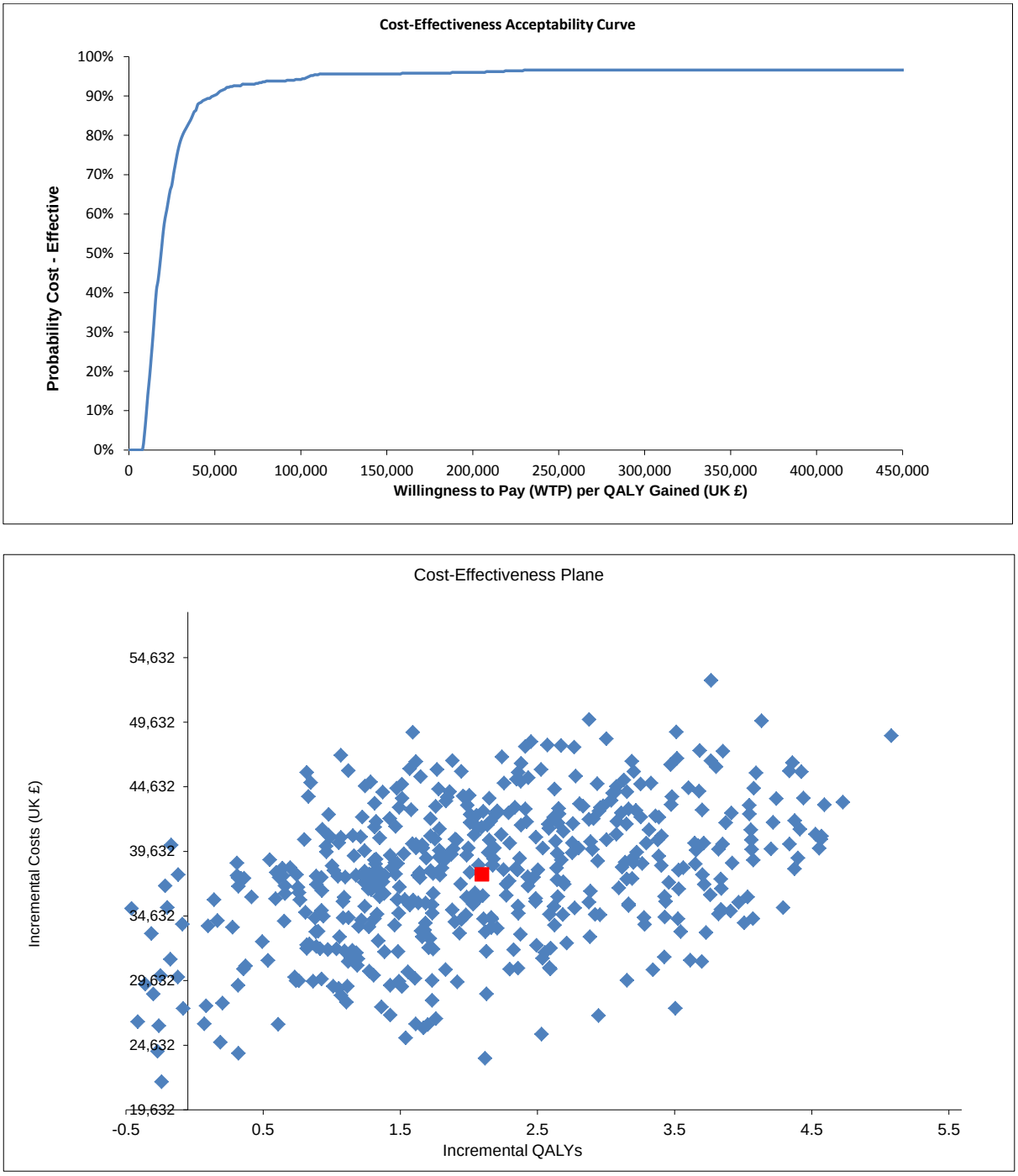
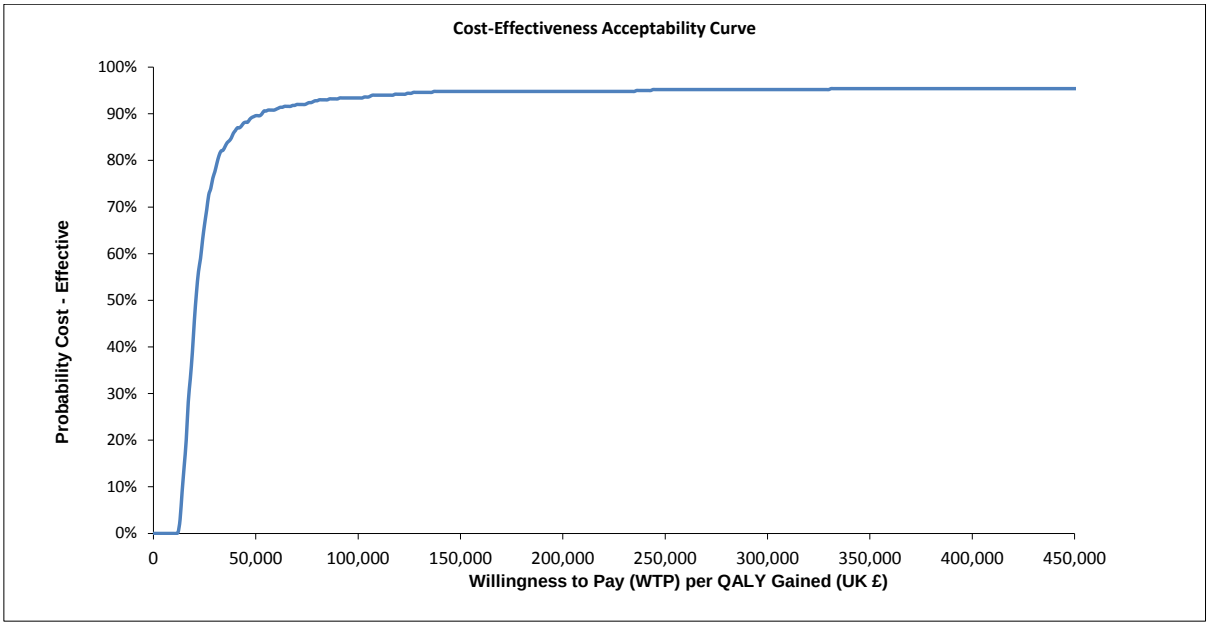


Figure 2 HeFH secondary prevention, alirocumab + statins + ezetimibe versus statins + ezetimibe - scatter plot and CEAC



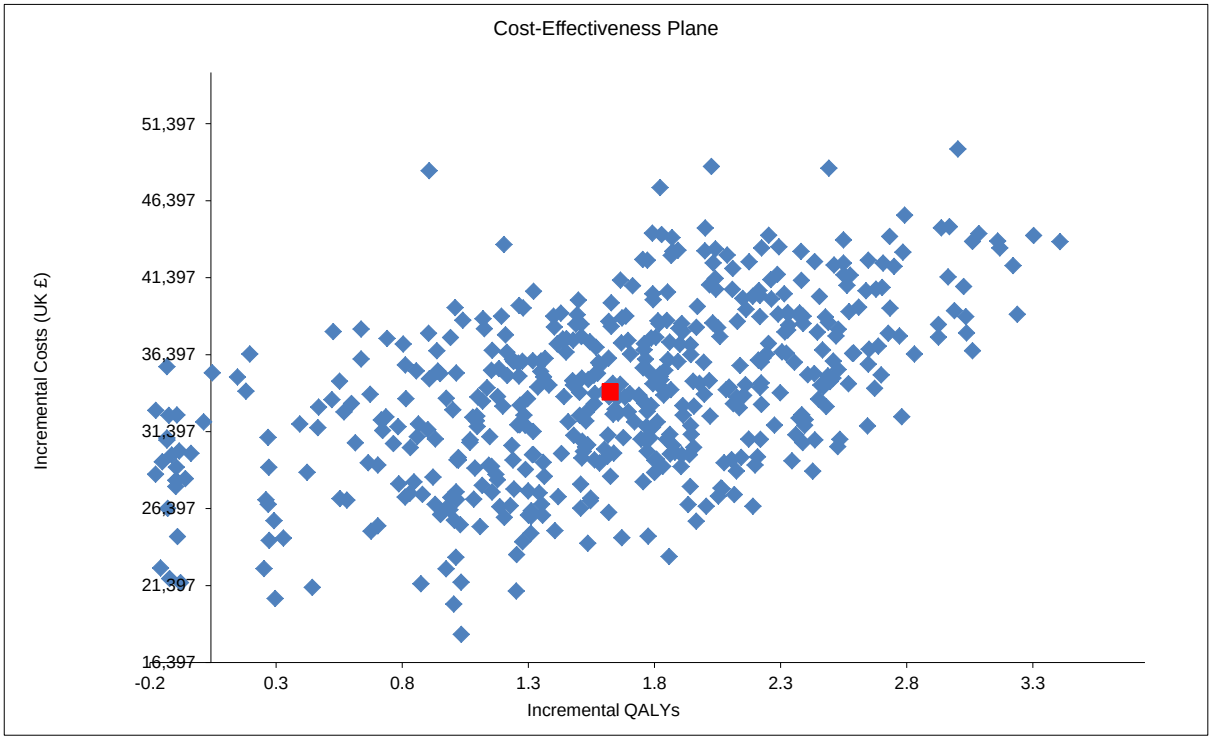
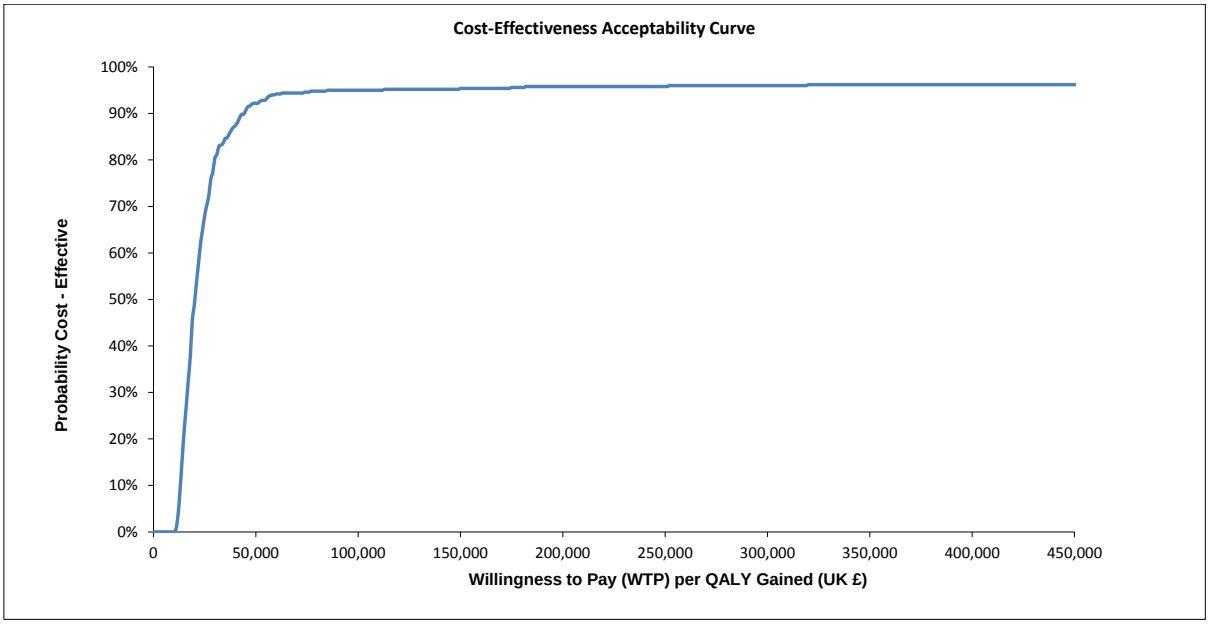


Figure 3 High Risk CVD, alirocumab + statins versus statins - scatter plot and CEAC



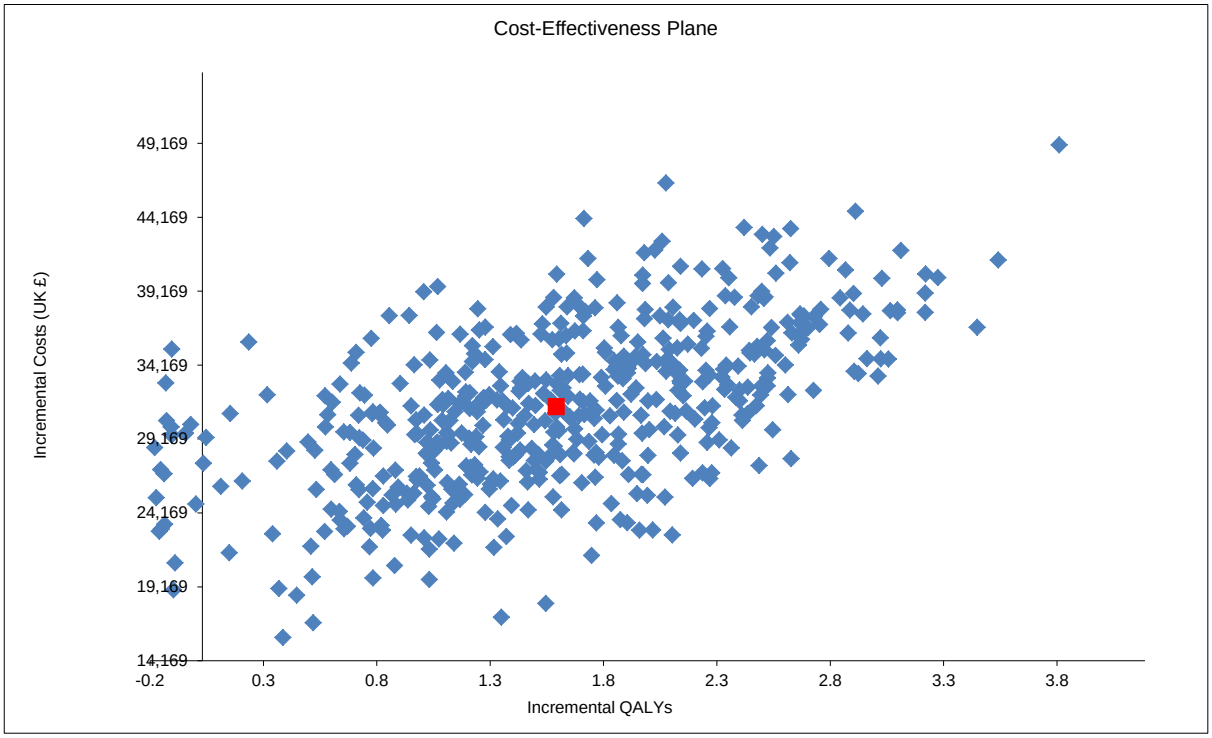


Figure 4 Recurrent events/ Polyvascular disease, alirocumab + statins versus statins - scatter plot and CEAC

Table 9 Probability of cost-effectiveness by Willingness to Pay for key patient groups – with Patient Access Scheme

	HeFH primary prevention (baseline LDL-C ≥2.59 mmol/L) – alirocumab + statins + ezetimibe versus statins + ezetimibe	HeFH secondary prevention (baseline LDL-C ≥2.59 mmol/L) – alirocumab + statins + ezetimibe versus statins + ezetimibe	High-risk CVD (baseline LDL-C ≥3.36 mmol/L) – alirocumab + statins versus statins	Recurrent events/ polyvascular disease (baseline LDL-C ≥2.59 mmol/L) – alirocumab + statins versus statins
Willingness to pay	**Probability of cost-effectiveness**			
20,000/QALY	15%	56%	46%	49%
30,000/QALY	36%	79%	78%	80%
40,000/QALY	51%	88%	86%	87%

CVD, cardiovascular disease; HeFH, heterozygous familial hypercholesterolaemia; QALY, quality-adjusted life-year

Company scenario analysis with agreed PAS

The company had already provided the following tables (Table 1-4), which summarise the results of scenario analyses in their original PAS submission. These analyses have already been reproduced and commented on as Tables 46-49 in the original ERG's report. They are reproduced below for completeness.

Table 10 HeFH primary prevention, alirocumab + statins + ezetimibe versus statins + ezetimibe - scenario analyses

Assumption	Base case	Scenarios	ICER (£/QALY)
***Base case* – with PAS**			**36,793**
Discontinuation rate	0%	3%	38,168
		8%	41,852
Cost and benefit discount rates	3.50%	0%	24,821
		5%	43,533
Treatment duration	Lifetime	1 year	50,197
		5 years	47,326
Model time horizon	Lifetime	5 years	398,895
		10 years	197,133
The relative risk for LDL-C reduction for alirocumab cohort	Navarese 2015 meta-analysis	CTT meta-analysis	60,736
		LONG TERM study	40,929
		Pooled phase III vs placebo	52,476
Adjustment of baseline CV risk by LDL-C calculation	CTT main equation	CTT Cox model 2 (approximately 0.84)	37,592
Utility	Age-adjusted, according to Ara 2010 publication	ODYSSEY	28,679
Treatment strategy	Up-titration as per ODYSSEY	100% use of 75 mg	39,235
		100% use of 150 mg	35,954

ACS, acute coronary syndrome; CTT, Cholesterol Treatment Trialists' Collaboration; CV, cardiovascular; HeFH, heterozygous familial hypercholesterolaemia; ICER, incremental cost-effectiveness ratio; LDL-C, low-density lipoprotein cholesterol; N/A, not available; NF, non-fatal; P-NF, post-non fatal; QALY, quality-adjusted life-year

Table 8 HeFH secondary prevention, alirocumab + statins + ezetimibe versus statins + ezetimibe - scenario analyses

Assumption	Base case	Scenarios	ICER (£/QALY)
Base case – with PAS			**16,896**
Baseline risk data	As per Mohrschladt 2004	As per THIN	19,060
Discontinuation rate	0%	3%	17,264
		8%	17,949
Cost and benefit discount rates	3.5%	0%	13,984
		5%	18,306
Treatment duration	Lifetime	1 year	18,863
		5 years	18,102
Model time horizon	Lifetime	5 years	64,199
		10 years	36,856
The relative risk for LDL-C reduction for alirocumab cohort	Navarese 2015 meta-analysis	CTT meta-analysis	32,937
		LONG TERM study	19,294
		Pooled phase III vs placebo	25,741
Adjustment of baseline CV risk by LDL-C calculation	CTT main equation	CTT Cox model 2 (approximately 0.84)	16,734
Utility	Age-adjusted, according to Ara 2010 publication	ODYSSEY	13,347
Treatment strategy	Up-titration as per ODYSSEY	100% use of 75 mg	18,259
		100% use of 150 mg	16,348

ACS, acute coronary syndrome; CTT, Cholesterol Treatment Trialists' Collaboration; CV, cardiovascular; HeFH, heterozygous familial hypercholesterolaemia; HSE; Health and Safety Executive; ICER, incremental cost-effectiveness ratio; LDL-C, low-density lipoprotein cholesterol; N/A, not available; NF, non-fatal; P-NF, post-non-fatal

Table 9 High Risk CVD, alirocumab + statins versus statins – scenario analyses

Assumption	Base case	Scenarios	ICER (£/QALY)
Base case – with PAS			19,751
Discontinuation rate	0%	3%	19,979
		8%	20,601
Cost and benefit discount rates	3.5%	0%	16,181
		5%	21,472
Treatment duration	Lifetime	1 year	20,148
		5 years	20,660
Model time horizon	Lifetime	5 years	85,694
		10 years	44,495
The relative risk for LDL-C reduction for alirocumab cohort	Navarese 2015 meta-analysis	CTT meta-analysis	41,431
		LONG TERM study	22,578
		Pooled phase III vs placebo	30,218
Adjustment of baseline CV risk by LDL-C calculation	CTT main equation	CTT Cox model 2 (approximately 0.84)	19,654
Utility	Age-adjusted, according to Ara 2010 publication	ODYSSEY	15,761
Treatment strategy	Up-titration as per ODYSSEY	100% use of 75 mg	21,571
		100% use of 150 mg	18,781

ACS, acute coronary syndrome; CTT, Cholesterol Treatment Trialists' Collaboration; CV, cardiovascular; CVD, cardiovascular disease; HSE, Health and Safety Executive; ICER, incremental cost-effectiveness ratio; LDL-C, low-density lipoprotein cholesterol; NF, non-fatal; P-NF, post-non-fatal

Table 10 Recurrent events/ polyvascular disease, alirocumab + statins versus statins – scenario analyses

Assumption	Base case	Scenarios	ICER (£/QALY)
Base case – with PAS			**19,447**
Discontinuation rate	0%	3%	19,738
		8%	20,353
Cost and benefit discount rates	3.5%	0%	16,317
		5%	20,931
Treatment duration	Lifetime	1 year	20,869
		5 years	20,222
Model time horizon	Lifetime	5 years	72,896
		10 years	38,468
The relative risk for LDL-C reduction for alirocumab cohort	Navarese 2015 meta-analysis	CTT meta-analysis	44,154
		LONG TERM study	22,651
		Pooled phase III vs placebo	31,181
Adjustment of baseline CV risk by LDL-C calculation	CTT main equation	CTT Cox model 2 (approximately 0.84)	19,336
Utility	Age-adjusted, according to Ara 2010 publication	ODYSSEY	15,968
Treatment strategy	Up-titration as per ODYSSEY	100% use of 75 mg	20,969
		100% use of 150 mg	17,915

ACS, acute coronary syndrome; CTT, Cholesterol Treatment Trialists' Collaboration; CV, cardiovascular; HSE, Health and Safety Executive; ICER, incremental cost-effectiveness ratio; LDL-C, low-density lipoprotein cholesterol; NF, non-fatal; P -NF, post-non-fatal

How the agreed PAS affects the ICERs

Finally, the company provided a table in their PAS submission illustrating how the agreed PAS affects the ICERs for the key base case analyses - for alirocumab as add on to maximally tolerated statin (+/- ezetimibe). This is reproduced as Table 11 below. Please note that the PAS was agreed prior to the ERG's report submission. Therefore, all analyses presented and discussed in the ERG's original report are based on the agreed PAS price for alirocumab.

In brief, the ERG was able to replicate all of the company's PAS ICERs using the stated parameter inputs, apart from one minor discrepancy for those with recurrent

CVD/polyvascular (LDL-C ≥ 2.59 mmol/L) disease who are statin intolerant (Alirocumab+ezetimibe versus ezetimibe). This appears to be explained by a simple input error for the baseline LDL-C value (4.55 mmol/L instead of 4 mmol/L) in the company's analysis (see Table 3 and Table3b above).

Table 11 Results showing the impact of patient access scheme on ICERs

	ICERs							
	HeFH Primary Prevention Alirocumab + statins + ezetimibe versus statins + ezetimibe		HeFH Secondary Prevention Alirocumab + statins + ezetimibe versus statins + ezetimibe		High Risk CVD Alirocumab + statins + versus statins + ezetimibe		Recurrent events/ polyvascular disease Alirocumab + statins + versus statins + ezetimibe	
	Without PAS	With PAS	Without PAS	With PAS	Without PAS	With PAS	Without PAS	With PAS
Basecases	[redacted]	£36,793	[redacted]	£16,896	[redacted]	£19,751	[redacted]	£19,447

PAS: patient access scheme

SECTION B: Additional requested sensitivity analyses surrounding the PAS

NICE request for additional sensitivity analysis

Following submission of the ERG's original report, NICE invited the company to submit additional sensitivity analyses to assess the potential impact of the PAS discount for alirocumab not being available when prescribed by a general practitioner using and FP10 form. The Department of Health's PAS approval letter, in fact, stated that: '*…alirocumab will initially be used in specialist secondary care clinics. However, as routine lipid management is an area of standard GP practice, it was noted that there may be a potential transition of patients from secondary to primary care after 2 to 3 years. This has potential implications for the proposed simple discount patient access scheme. As simple discounts cannot be realised when drugs are prescribed through FP10 prescriptions, the actual discount received by the NHS may be less than the percentage discount offered in the scheme.*'

In the company's PAS submission, all patients were assumed to remain under specialist secondary care management, with a sponsored home care service used to deliver medication to patients. Consequently, in the economic model the simple discount PAS was applied to all patients prescribed alirocumab. NICE invited the company to submit additional sensitivity analyses to vary:

i) the proportion of patients who transition from secondary care to primary care and'

ii) the time spent in secondary care before patients move to primary care

NICE specified that the PAS price should only be applied to patients who are prescribed alirocumab through secondary care, that sensitivity analyses should be undertaken for each of the populations in the model, and that justification should be provided for the inputs used.

Company's response to the request for additional sensitivity analysis

In response to NICE's request, the company maintained that FP10 prescribing is very unlikely for alirocumab and offered the following justifications:

1) The populations for which approval is being sought are those with HeFH and high risk CVD (i.e. secondary prevention and/or recurrent events), including

those with statin intolerance, who cannot achieve optimal LDL-C levels on current maximally tolerated routine lipid management therapies (LMTs). These are patients that require specialist support beyond the routine lipid management services provided by their primary care team.

2) Such high risk patients should be referred by GPs to expert lipid specialists, based in hospitals or in specialist lipid clinics, as indicated by the NICE's FH Guideline and Commissioning recommendations.
3) Alirocumab is listed on the high cost drugs exclusion list proposed for 2016/17 and is expected to be funded outside the national tariff. Hospitals will be able to prescribe alirocumab as part of CCG commissioned services and will recover the cost via the high cost drugs
4) The company understands, from their ongoing meetings with CCGs that Commissioners are seeking to limit the use of alirocumab within primary care, aligning their pathways to the most effective care for patients and most efficient funding mechanism, namely commissioned services from speciality care/hospitals only.
5) The majority of a sample of GPs, when surveyed by Adelphi Research in July 2015 (survey sponsored by the company), stated that they were '*extremely unlikely*' to prescribe a self-injected sub-cutaneous treatment for hypercholesteremia, even if a pre-filled pen device was available.
6) The company has in place arrangements for the supply of alirocumab to the NHS in England via two routes:
    a) directly to hospital pharmacies, and
    b) via approved homecare companies.

The company went on to note that this specialty care supply model is already operating effectively for alirocumab in several EU countries and in the US and it is their view that "*it is the most appropriate specialty care supply model for England*". For this reason, the company has no arrangements in place for the supply of alirocumab into primary care pharmacies in England.

The company, however, do also state that they *"…recognise that a situation could exist - however unlikely for alirocumab - in circumstances where FP10 prescriptions*

are written, CCGs may not want to buy a medicine at a net price equivalent to the PAS discounted price, for example via a primary care rebate scheme." They, therefore, provided the requested sensitivity analyses for the committee's consideration.

Company's implementation of the requested sensitivity analyses

The company made a number of simple adjustments to the economic model, which allows the user to specify and vary three additional input parameters: i) the minimum number of years following initiation of alirocumab treatment before any switching to primary care takes place; ii) the maximum percentage of patients who will move from secondary to primary care; and iii) the time in years by which the maximum percentage of patients will have transitioned to primary care. Simple linear interpolation is used to model growth in the percentage of patients transferred to primary care (on non-PAS prescribing) up to the defined maximum level, at the defined time point by which the maximum is reached. Alirocumab treatment costs in the model then become a weighted average of the PAS and non-PAS prices based on the modelled proportions in secondary and primary care.

The company provided results for five different scenarios, where the maximum percentage of patients transiting to primary care was varied between [redacted] and [redacted] and the time by which the maximum percentage is reached was set to 5 years. All patients were assumed to remain in secondary care for the first two years for all scenarios.

To inform the maximum percentage of patients that may transit to primary care, the company reviewed IMS sales data for a selection of 'analogue' medicines. These included monoclonal antibodies used in rheumatoid arthritis (RA), omalizumab (Xolair™), and denosumab (Prolia™). The company noted that these are *"NICE-approved medicines - subject to various PAS arrangements - used in conditions that until severity determines that specialist referral and management is needed, are typically managed in primary care."* The company estimated primary care (retail) and secondary care (hospital) sales volume using data from the combined IMS XBPI/HPAI datasets, held by IMS Health (http://www.imshealth.com/). They note that this is a national sales audit produced monthly by IMS, derived from reported

sales via hospital pharmacies and retail pharmacies. Hospital data is defined as the volume sales reported through the HPAI dataset. Retail data is defined as the volume sales reported through the XBPI dataset. All volume data is at unit level e.g. pack level. The data were reported annually for calendar years from 2011 to 2015 (comprising all 2015 data available at the time of analysis (YTD Oct15)). The company's summary of the data is reproduced in Table 12. A detailed breakdown of sales volume was provided for each individual RA monoclonal antibody as an appendix to the company response. This showed all the RA monoclonal antibodies to have similarly very low primary care prescribing levels. The company stated that they consider these medicines to be the closest analogues for the intended model of introducing the supply of alirocumab to the NHS. They noted that: "*They are initiated and managed from a secondary care setting, by specialists, in specialist clinics, usually with homecare and patient support services providing ongoing support of patients in the community.*"

Table 12 Hospital and retail sales split for several mono-clonal antibodies

BPIHPA_UK_M_IMS_001		2011	2012	2013	2014	2015
RA Mabs						
	Total Hospital	99.23%	99.26%	99.10%	99.25%	99.73%
	Total Retail	0.77%	0.74%	0.90%	0.75%	0.27%
Xolair ™						
	Total Hospital	99.68%	99.18%	99.37%	99.48%	99.73%
	Total Retail	0.32%	0.82%	0.63%	0.52%	0.27%
Prolia ™						
	Total Hospital	85.33%	72.47%	63.26%	57.04%	51.75%
	Total Retail	14.67%	27.53%	36.74%	42.96%	48.25%

For the purposes of the additional sensitivity analyses, the company noted that they used the [redacted] data to represent the upper limit of monoclonal antibody prescribing within primary care. They further noted that they did not consider it an appropriate analogue itself for alirocumab, being 'in tariff', not exclusively managed in secondary care, and not supplied via a homecare route. It consequently shows a

different pattern of delivery with increasing prescriptions in primary care; presently in the order of [redacted]. This was used to inform the upper limit of primary care prescribing reached by 5 years for alirocumab in the scenario analyses. The company's estimated ICERs from these additional scenario analyses are reproduced in Table 13 (deterministic) and 14 (probabilistic) below. A breakdown of the total and incremental costs and QALYs for each scenario was provided as an appendix to the company's response letter. This confirmed that it is only an increasing treatment cost in the alirocumab arm of the model (associated with increased non-PAS prescribing) that drives the observed increases in the ICERs.

The results indicate, as expected, that the ICER increases for each population as the the percentage of non-PAS uptake increases. By scenario 5, reflecting [redacted] non-PAS prescribing by year 5, the ICERs have increased by around £4000-£10,000. All subgroups, except the HeFH primary prevention (LDL-C ≥2.59 mmol/L) subgroup, have ICERs that remain below £25,000/QALY.

The probabilistic ICERs were found to be similar to the deterministic ICERs (Table 14). For scenario 5, alirocumab has a probability between [redacted] and [redacted] of being cost-effective at a WTP threshold of £30,000/QALY - excluding the HeFH primary prevention (LDL-C ≥2.59 mmol/L) population.

Table 13 Cost-effectiveness results for each scenario, by patient subgroup (breakdown provided in Appendix 2)

Patient population	Technology (and comparators)	Base case	Scenario 1 [redacted] by year 5 [start year 2)	Scenario 2 [redacted] by year 5 [start year 2)	Scenario 3 [redacted] by year 5 [start year 2)	Scenario 4 [redacted] by year 5 [start year 2)	Scenario 5 [redacted] by year 5 [start year 2)
HeFH primary prevention (LDL-C ≥2.59 mmol/L)	Alirocumab + current maximal therapy (statins + ezetimibe)	£36,793	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Current maximal therapy (statins + ezetimibe)						
HeFH secondary prevention (LDL-C ≥2.59 mmol/L) *Baseline risk data from Mohrschladt et al*	Alirocumab + current maximal therapy (statins + ezetimibe)	£16,896	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Current maximal therapy (statins + ezetimibe)						
High risk CVD (LDL-C ≥3.36 mmol/L)	Alirocumab + current maximal therapy (statins)	£19,751	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Current maximal therapy (statins)						
Recurrent events/ polyvascular disease (LDL-C ≥2.59 mmol/L)	Alirocumab + current maximal therapy (statins)	£19,447	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Current maximal therapy (statins)						

Table 14 Probabilistic cost-effectiveness results and estimated probability of being cost-effective at three WTP thresholds - Scenario 1 and Scenario 5

Patient population	Scenario 1 [redacted] by year 5 [start year 2) PSA ICER	Scenario 1 [redacted] by year 5 [start year 2) p(C/E @ 20K/Q)	Scenario 1 [redacted] by year 5 [start year 2) p(C/E @ 30K/Q)	Scenario 1 [redacted] by year 5 [start year 2) p(C/E @ 40K/Q)		Scenario 5 [redacted] by year 5 [start year 2) PSA ICER	Scenario 5 [redacted] by year 5 [start year 2) p(C/E @ 20K/Q)	Scenario 5 [redacted] by year 5 [start year 2) p(C/E @ 30K/Q)	Scenario 5 [redacted] by year 5 [start year 2) p(C/E @ 40K/Q)
HeFH primary prevention (LDL-C ≥2.59 mmol/L)	[redacted]	10.2%	33.0%	51.2%		[redacted]	0.00%	19.4%	36.6%
HeFH secondary prevention (LDL-C ≥2.59 mmol/L) *Baseline risk data from Mohrschladt et al*	[redacted]	56.6%	79.2%	88.2%		[redacted]	39.6%	69.0%	83.0%
High risk CVD (LDL-C ≥3.36 mmol/L)	[redacted]	45.6%	78.6%	86.4%		[redacted]	21.8%	64.0%	78.6%
Recurrent events/ polyvascular disease (LDL-C ≥2.59 mmol/L)	[redacted]	49.6%	77.0%	86.4%		[redacted]	25.8%	63.4%	82.2%

ERG's critique of the company's additional sensitivity analysis

The ERG reviewed the company's additional scenarios, and implemented the same changes to its modified version of the company's model. Thus the ERG can confirm that the described scenarios have been implemented as described, and the results have been exactly replicated.

In terms of justification for the scenarios explored, the ERG cannot suggest any better data sources to inform the input parameters. The company maintain that RA monoclonal antibodies provide the closest analogues for the proposed secondary/home care delivery model for alirocumab. However, they may not be necessarily the closest analogues in terms of the underlying nature of the condition being treated. For primary hypercholesterolemia patients who are being managed in secondary care because they are poorly controlled on statins alone, it might not be unreasonable to assume that similar rates of primary care prescribing (as observed for denosumab) could in theory be seen over time for alirocumab patients who do achieve control. However, if the counterfactual is that patients would otherwise remain uncontrolled without alirocumab, there might be a follow-up cost reduction (in terms of less frequent outpatient monitoring) which could partly counter the higher drug costs associated with the switch to primary care.

The ERG note that a similar discussion arose with respect to the proposed PAS for evolocumab during its recent NICE appraisal (http://www.nice.org.uk/guidance/indevelopment/gid-tag498), and the draft ACD states that *"The Committee agreed that up to 90% of people may have evolocumab through FP10 prescriptions in primary care after 2 years."* However, the company (Sanofi) provided a comment from a clinical expert stating: *"I would disagree with the statement that 'up to 90% of people' will be followed up in primary care. The reasons for this is that patients with FH are treated and followed up in lipid clinics in secondary care as referred to in NICE QS41 and CG71. Patients who have well documented intolerance to statins as referred to in NICE CG181 recommend specialist referral and these patients are subsequently managed in secondary care. Both these groups will be managed in secondary care because of the complexity of their lipid management and requirements for specialist risk assessment and intervention. These cohorts will potentially benefit from PCSK9 inhibition therapy."*

The ERG's clinical advisor is of the opinion that the proportion who will transit to primary care prescribing remains unknown. However, he suspects that, at least for the HeFH secondary prevention and recurrent CVD/polyvascular disease populations, the majority of patients would remain in secondary care, at least for the next few years. He also points out a potential reluctance of GPs to take on prescribing of these drugs (Dr William Simpson, NHS Grampian, personal communication; 07/12/2015).

In summary, the ERG accepts that there is potential for patients who achieve good control with alirocumab to be managed in primary care with FP10 prescribing. However, the proportion of patients who will make this transition is unknown and may vary between the modelled cohorts. It could perhaps be more likely for the HeFH primary prevention and high risk CVD cohorts who achieve target on alirocumab, and less likely for the HeFH secondary prevention and recurrent CVD/polyvascular disease cohorts who may require closer ongoing secondary care follow-up for other reasons.

Additional scenario analysis explored by the ERG

In light of the uncertainty surrounding the proportion of patients who might transit to primary care in each population, and the committee's stated position in the recent evolocumab appraisal, the ERG has extended the company's scenario analysis up to a maximum of [redacted] transiting to primary care by 5 years - otherwise applying the company's base case assumptions (Table 15). For completeness, the ERG also offer the same set of prescribing scenarios using their modified version of the company's model: i) retaining the scaled hazard ratios from Naverese et al. (Table 16); and ii) using the CTT meta-analysis to model all the effects of alirocumab (Table 17). Finally, to explore the impact of combining other scenario changes with the FP10 prescribing scenario, the ERG has reproduced the scenario analysis tables from the company's main submission with the company's maximum [redacted] transiting to primary care scenario (Tables 18-21).

Table 15 The ERG's extension of the company's non-PAS prescribing scenarios by patient population, up to 90% non-PAS primary care prescribing (otherwise applying the company's base case assumptions)

Patient population	Technology (and comparators)	Base case	Scenario 1 [redacted] by year 5 [start year 2)	Scenario 2 [redacted] by year 5 [start year 2)	Scenario 3 [redacted] by year 5 [start year 2)	Scenario 4 [redacted] by year 5 [start year 2)	Scenario 5 [redacted] by year 5 [start year 2)	Scenario 6 [redacted] by year 5 [start year 2)	Scenario 7 [redacted] by year 5 [start year 2)	Scenario 8 [redacted] by year 5 [start year 2)
HeFH primary prevention (LDL-C ≥2.59 mmol/L)	Alirocumab + current maximal therapy (statins + ezetimibe)	£36,793	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Current maximal therapy (statins + ezetimibe)									
HeFH secondary prevention (LDL-C ≥2.59 mmol/L) *Baseline risk data from Mohrschladt et al*	Alirocumab + current maximal therapy (statins + ezetimibe)	£16,896	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Current maximal therapy (statins + ezetimibe)									
High risk CVD (LDL-C ≥3.36 mmol/L)	Alirocumab + current maximal therapy (statins)	£19,751	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Current maximal therapy (statins)									
Recurrent events/ polyvascular disease (LDL-C ≥2.59 mmol/L)	Alirocumab + current maximal therapy (statins)	£19,447	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Current maximal therapy (statins)									

Table 16 Cost-effectiveness results for non-PAS prescribing scenarios using the ERG's base case assumptions (with the rate ratios per 1.0 mmol/L reduction in LDL-C for PCSK9-inhibitors from Navarese et al. meta-analysis)-with different PAS scenarios

Patient population	Technology (and comparators)	Base case	Scenario 1 [redacted] by year 5 [start year 2)	Scenario 2 [redacted] by year 5 [start year 2)	Scenario 3 [redacted] by year 5 [start year 2)	Scenario 4 [redacted] by year 5 [start year 2)	Scenario 5 [redacted] by year 5 [start year 2)	Scenario 6 [redacted] by year 5 [start year 2)	Scenario 7 [redacted] by year 5 [start year 2)	Scenario 8 [redacted] by year 5 [start year 2)
HeFH primary prevention (LDL-C ≥2.59 mmol/L)	Alirocumab + current maximal therapy (statins + ezetimibe)	41,243	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Current maximal therapy (statins + ezetimibe)									
HeFH secondary prevention (LDL-C ≥2.59 mmol/L) *Baseline risk data from Mohrschladt et al*	Alirocumab + current maximal therapy (statins + ezetimibe)	16,933	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Current maximal therapy (statins + ezetimibe)									
High risk CVD (LDL-C ≥3.36 mmol/L)	Alirocumab + current maximal therapy (statins)	19,432	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Current maximal therapy (statins)									
Recurrent events/ polyvascular disease (LDL-C ≥2.59 mmol/L)	Alirocumab + current maximal therapy (statins)	19,021	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Current maximal therapy (statins)									

Table 17 Cost-effectiveness results for non-PAS prescribing scenarios using the ERG's assumptions (with rate ratios per 1.0 mmol/L reduction in LDL-C from CTT meta-analysis)-with different PAS scenarios

Patient population	Technology (and comparators)	Base case	Scenario 1 [redacted] by year 5 [start year 2)	Scenario 2 [redacted] by year 5 [start year 2)	Scenario 3 [redacted] by year 5 [start year 2)	Scenario 4 [redacted] by year 5 [start year 2)	Scenario 5 [redacted] by year 5 [start year 2)	Scenario 6 [redacted] by year 5 [start year 2)	Scenario 7 [redacted] by year 5 [start year 2)	Scenario 8 [redacted] by year 5 [start year 2)
HeFH primary prevention (LDL-C ≥2.59 mmol/L)	Alirocumab + current maximal therapy (statins + ezetimibe)	67,215	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Current maximal therapy (statins + ezetimibe)									
HeFH secondary prevention (LDL-C ≥2.59 mmol/L) *Baseline risk data from Mohrschladt et al*	Alirocumab + current maximal therapy (statins + ezetimibe)	33,339	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Current maximal therapy (statins + ezetimibe)									
High risk CVD (LDL-C ≥3.36 mmol/L)	Alirocumab + current maximal therapy (statins)	42,131	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Current maximal therapy (statins)									
Recurrent events/ polyvascular disease (LDL-C ≥2.59 mmol/L)	Alirocumab + current maximal therapy (statins)	44,759	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Current maximal therapy (statins)									

Table 18 HeFH primary prevention (LDL-C ≥ 2.59 mmol/L), alirocumab plus statins plus ezetimibe versus statins plus ezetimibe) - scenario analyses

Assumption	Base case	Scenarios	ICER (£/QALY)
***Base case* – with new PAS policy**			[redacted]
Discontinuation rate	0%	3%	[redacted]
		8%	[redacted]
Cost and benefit discount rates	3.50%	0%	[redacted]
		5%	[redacted]
Treatment duration	Lifetime	1 year	[redacted]
		5 years	[redacted]
Model time horizon	Lifetime	5 years	[redacted]
		10 years	[redacted]
The relative risk for LDL-C reduction for alirocumab cohort	Navarese 2015 meta-analysis	CTT meta-analysis	[redacted]
		LONG TERM study	[redacted]
		Pooled phase III vs placebo	[redacted]
Adjustment of baseline CV risk by LDL-C calculation	CTT main equation	CTT Cox model 2 (approximately 0.84)	[redacted]
Utility	Age-adjusted, according to Ara 2010 publication	ODYSSEY	[redacted]
Treatment strategy	Up-titration as per ODYSSEY	100% use of 75 mg	[redacted]
		100% use of 150 mg	[redacted]

ACS, acute coronary syndrome; CTT, Cholesterol Treatment Trialists' Collaboration; CV, cardiovascular; HeFH, heterozygous familial hypercholesterolaemia; ICER, incremental cost-effectiveness ratio; LDL-C, low-density lipoprotein cholesterol; N/A, not available; NF, non-fatal; P-NF, post-non fatal; QALY, quality-adjusted life-year

Table 19 HeFH secondary prevention (LDL-C ≥ 2.59 mmol/L), alirocumab plus statins plus ezetimibe versus statins plus ezetimibe – scenario analyses

Assumption	Base case	Scenarios	ICER (£/QALY)
***Base case* – with new PAS policy**			[redacted]
Baseline risk data	As per Mohrschladt 2004	As per THIN	[redacted]
Discontinuation rate	0%	3%	[redacted]
		8%	[redacted]
Cost and benefit discount rates	3.5%	0%	[redacted]
		5%	[redacted]
Treatment duration	Lifetime	1 year	[redacted]
		5 years	[redacted]
Model time horizon	Lifetime	5 years	[redacted]
		10 years	[redacted]
The relative risk for LDL-C reduction for alirocumab cohort	Navarese 2015 meta-analysis	CTT meta-analysis	[redacted]
		LONG TERM study	[redacted]
		Pooled phase III vs placebo	[redacted]
Adjustment of baseline CV risk by LDL-C calculation	CTT main equation	CTT Cox model 2 (approximately 0.84)	[redacted]
Utility	Age-adjusted, according to Ara 2010 publication	ODYSSEY	[redacted]
Treatment strategy	Up-titration as per ODYSSEY	100% use of 75 mg	[redacted]
		100% use of 150 mg	[redacted]

ACS, acute coronary syndrome; CTT, Cholesterol Treatment Trialists' Collaboration; CV, cardiovascular; HeFH, heterozygous familial hypercholesterolaemia; HSE; Health and Safety Executive; ICER, incremental cost-effectiveness ratio; LDL-C, low-density lipoprotein cholesterol; N/A, not available; NF, non-fatal; P-NF, post-non-fatal

Table 20 High Risk CVD (LDL-C ≥ 3.36 mmol/L), alirocumab plus statins versus statins) - scenario analyses

Assumption	Base case	Scenarios	ICER (£/QALY)
***Base case* – with new PAS policy**			[redacted]
Discontinuation rate	0%	3%	[redacted]
		8%	[redacted]
Cost and benefit discount rates	3.5%	0%	[redacted]
		5%	[redacted]
Treatment duration	Lifetime	1 year	[redacted]
		5 years	[redacted]
Model time horizon	Lifetime	5 years	[redacted]
		10 years	[redacted]
The relative risk for LDL-C reduction for alirocumab cohort	Navarese 2015 meta-analysis	CTT meta-analysis	[redacted]
		LONG TERM study	[redacted]
		Pooled phase III vs placebo	[redacted]
Adjustment of baseline CV risk by LDL-C calculation	CTT main equation	CTT Cox model 2 (approximately 0.84)	[redacted]
Utility	Age-adjusted, according to Ara 2010 publication	ODYSSEY	[redacted]
Treatment strategy	Up-titration as per ODYSSEY	100% use of 75 mg	[redacted]
		100% use of 150 mg	[redacted]

ACS, acute coronary syndrome; CTT, Cholesterol Treatment Trialists' Collaboration; CV, cardiovascular; CVD, cardiovascular disease; HSE, Health and Safety Executive; ICER, incremental cost-effectiveness ratio; LDL-C, low-density lipoprotein cholesterol; NF, non-fatal; P-NF, post-non-fatal

Table 21 Recurrent events/polyvascular disease (LDL-C ≥ 2.59 mmol/L), alirocumab plus statins versus statins – scenario analyses

Assumption	Base case	Scenarios	ICER (£/QALY)
***Base case* – with new PAS policy**			[redacted]
Discontinuation rate	0%	3%	[redacted]
		8%	[redacted]
Cost and benefit discount rates	3.5%	0%	[redacted]
		5%	[redacted]
Treatment duration	Lifetime	1 year	[redacted]
		5 years	[redacted]
Model time horizon	Lifetime	5 years	[redacted]
		10 years	[redacted]
The relative risk for LDL-C reduction for alirocumab cohort	Navarese 2015 meta-analysis	CTT meta-analysis	[redacted]
		LONG TERM study	[redacted]
		Pooled phase III vs placebo	[redacted]
Adjustment of baseline CV risk by LDL-C calculation	CTT main equation	CTT Cox model 2 (approximately 0.84)	[redacted]
Utility	Age-adjusted, according to Ara 2010 publication	ODYSSEY	[redacted]
Treatment strategy	Up-titration as per ODYSSEY	100% use of 75 mg	[redacted]
		100% use of 150 mg	[redacted]

ACS, acute coronary syndrome; CTT, Cholesterol Treatment Trialists' Collaboration; CV, cardiovascular; HSE, Health and Safety Executive; ICER, incremental cost-effectiveness ratio; LDL-C, low-density lipoprotein cholesterol; NF, non-fatal; P -NF, post-non-fatal

Impact on the ICERs the non-PAS primary care prescribing

- The company's scenarios (up to [redacted] non-PAS prescribing by 5 years) indicate that when modelling the effects of alirocumab through the scaled hazard ratios of Navarese et al., the ICERs for alirocumab remain below £25,000 in all but the HeFH primary prevention cohort.
- Applying the same scenarios using the ERG modified base case assumptions, and continuing to model the effects of alirocumab on ACS events and CV deaths using the scaled hazard ratios from Navarese et al., the findings are similar. Further extending the proportion of patients

transitioning to primary care to [redacted] by 5 years raises the ICERs further. However, they remain below £30,000 – in all but the HeFH primary prevention population.

- Applying the non-PAS prescribing scenarios with the effects of alirocumab modelled through the CTT meta-analysis, the ICERs as expected increase further above base levels above £30,000.
- Combining the company's [redacted] non-PAS prescribing scenario with other uncertain scenarios, shows that from this alternative reference point; the ICERs remain reasonably robust (in terms of crossing thresholds) to changes assessed – apart from the source of hazard ratios per unit reduction in LDL-C

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