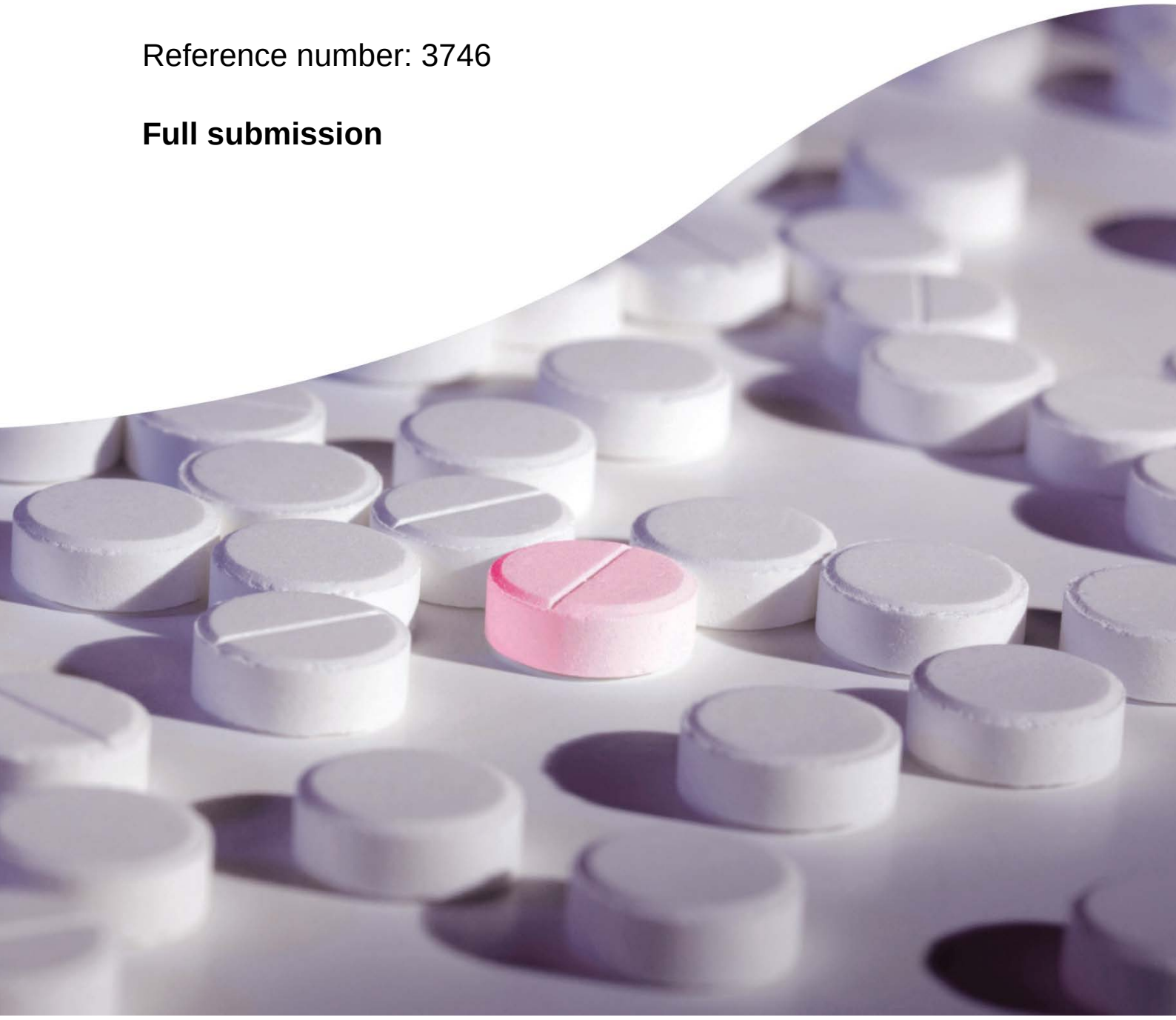
AWTTC
All Wales Therapeutics & Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG Secretariat Assessment Report

Inclisiran (Leqvio®▼)
284 mg solution for injection in pre-filled syringe

Reference number: 3746

Full submission



PAMS
Patient Access to Medicines Service
Mynediad Claf at Wasanaeth Meddyginiaethau

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This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

AWMSG Secretariat Assessment Report
Inclisiran (Leqvio®▼) 284 mg solution for injection in pre-filled syringe

1.0 KEY FACTS

Assessment details	Inclisiran (Leqvio®▼) for adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet: • in combination with a statin or statin with other lipid lowering therapies in patients who are unable to reach low-density lipoprotein cholesterol (LDL-C) goals with the maximum tolerated dose of a statin, or • alone or in combination with other lipid lowering therapies in patients who are statin intolerant, or for whom a statin is contraindicated. ▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. The applicant company has submitted evidence for a subpopulation of the licensed indication and request that AWMSG consider inclisiran for use only in a subpopulation of the licensed indication who are at high risk of further CV events: • patients with high risk due to previous cardiovascular (CV) events and LDL-C ≥4.0 mmol/L, or • patients with recurrent/polyvascular disease and LDL-C ≥3.5 mmol/L, or • patients with heterozygous familial hypercholesterolaemia (HeFH) and LDL-C ≥3.5 mmol/L, for secondary prevention of CV events, or • patients with HeFH and LDL-C ≥5.0 mmol/L, for primary prevention of CV events.
Current clinical practice	Initial management of hypercholesterolaemia involves dietary and lifestyle changes including smoking cessation, weight loss and increased physical activity. Statins are the treatment of choice for patients with hypercholesterolaemia. However, a proportion of patients fail to achieve adequate LDL-C control despite maximum tolerated doses of statins and require additional lipid-lowering therapy. In addition, a further proportion of patients have contra-indications to or are unable to tolerate statins, and therefore require alternative lipid

	lowering therapy to reduce LDL-C. For these groups of patients, current treatment options include ezetimibe and, for a smaller number of higher risk patients, the PCSK9 inhibitors alirocumab and evolocumab.
Clinical effectiveness	The company submission included three double-blind, placebo-controlled, phase III studies: ORION-9 recruited 482 patients with HeFH and LDL-C ≥2.6 mmol/L; ORION-10 recruited 1,561 patients with atherosclerotic cardiovascular disease (ASCVD) and LDL-C ≥1.8 mmol/L and ORION-11 included 1,617 patients with ASCVD and LDL-C ≥1.8 mmol/L or an ASCVD risk equivalent and LDL-C ≥2.6 mmol/L. Patients in all studies were aged ≥18 year and were receiving a statin at maximally tolerated dose or were intolerant to all doses of at least two different statins. The three trials had similar designs to facilitate data pooling. Eligible patients were randomised equally to receive inclisiran 284 mg or placebo by subcutaneous injection on days 1, 90, 270 and 450. All three studies met their co-primary endpoints; inclisiran significantly reduced both the mean percentage change in LDL-C from baseline to day 510 and the time-adjusted percentage change in LDL-C from day 90 to day 540, compared with placebo. Efficacy was supported by the key secondary outcomes. Clinical benefits were achieved with minimal side effects. Unpublished interim results from the open-label extension study, ORION-8, demonstrates inclisiran maintains its efficacy in lowering LDL-C levels at 116 weeks of treatment with an overall safety profile comparative to inclisiran treated-patients in the phase III studies. In the absence of head-to-head trials comparing inclisiran with PCSK9 inhibitors in the population of interest, the company conducted network meta-analyses (NMAs). Company-reported results demonstrated no statistically significant differences in treatment efficacy between either alirocumab or evolocumab and inclisiran. However, the NMAs are subject to limitations.
Cost-effectiveness	A cost-utility analysis compares inclisiran (Leqvio®) 284 mg solution for injection pre-filled syringes in combination with standard of care (SoC), where SoC consists of maximally tolerated statins with or without ezetimibe, with three comparator regimens: SoC, alirocumab with SoC, and evolocumab with SoC. AWTTC-sought clinical experts identify the PCSK9 inhibitors as the main comparators. The CUA focuses on the following patient populations:

	• patients with high risk due to previous CV events and LDL-C ≥4.0 mmol/L • patients with recurrent/polyvascular disease and LDL-C ≥3.5 mmol/L • patients with HeFH and LDL-C ≥3.5 mmol/L, for secondary prevention of CV events • patients with HeFH and LDL-C ≥5.0 mmol/L, for primary prevention of CV events. The company base case, which includes a Welsh Patient Access Scheme (WPAS) discount for inclisiran, suggests that when inclisiran with SoC is compared with SoC it offers a cost-effective treatment option in all targeted populations, except the primary prevention HeFH population. When compared with alirocumab with SoC and evolocumab with SoC, the base case suggests that inclisiran is both less costly and less effective. However, when cost-effectiveness thresholds are applied, inclisiran can potentially deliver a net health benefit at a population level while providing an additional treatment option for patients. The lack of outcome data for inclisiran and the efficacy assumptions applied in the model introduce notable uncertainty in the cost-effectiveness estimates produced by the model. Also, the base case results do not include the Patient Access Scheme (PAS) discounts associated with the PCSK9 inhibitor comparators. However, AWTTC analyses incorporating the confidential comparator PAS discounts are available to AWMSG committees for decision-making purposes.
Budget impact	The company estimates that [commercial in confidence figure removed] patients are likely to receive treatment with inclisiran in Wales in Year 1, increasing to [commercial in confidence figure removed] patients in Year 5. The company base case suggests cost savings of [commercial in confidence figure removed] in Year 1, increasing to [commercial in confidence figure removed] in Year 5. However, this analysis uses list price for the PCSK9 inhibitor comparators. AWTTC analyses incorporating the confidential comparator PAS discounts are therefore available to AWMSG committees for decision-making purposes. The base case also predicts additional NHS resource use costs valued at [commercial in confidence figure removed] in Year 1, increasing to [commercial in confidence figure removed] in Year 5. resulting from the administration costs associated with inclisiran.

	The budget impact considerations are limited to acquisition and administration costs only; other resource use is not included (e.g. costs/cost savings associated with CV events).
Additional factors to consider	Inclisiran (Leqvio®) is the first and only cholesterol-lowering siRNA, representing a step-change in the management of LDL-C levels and is already available for patients in England and Scotland through published guidance from the National Institute for Health and Care Excellence and the Scottish Medicines Consortium respectively.

This assessment report is based on evidence submitted by Novartis Pharmaceuticals UK Ltd. and an evidence search conducted by AWTTC on 26 October 2021[1].

2.0 BACKGROUND

2.1 Condition and clinical practice

Hypercholesterolaemia is defined as the presence of increased levels of low-density lipoprotein cholesterol (LDL-C)[2], while the term "mixed dyslipidaemia" is used to describe a combination of increased levels of LDL-C and triglycerides, and decreased high-density lipoprotein (HDL-C)[3]. About 50% of UK adults live with cholesterol levels exceeding national guideline recommendations (total cholesterol >5 mmol/L)[3]. Excessive levels of LDL-C can lead to a build-up of fatty material (plaques or atheroma) on the walls of arteries, a process called atherosclerosis or atherosclerotic cardiovascular disease (ASCVD)[4,5]. There is a "dose-dependent" association between increased duration of exposure to LDL-C and the increased risk of developing ASCVD[5]. There is also a strong relationship between elevated LDL-C levels and other clinical manifestations such as cerebrovascular disease (e.g. ischaemic stroke) and peripheral vascular disease[6]. Ischaemic heart disease is the leading cause of death worldwide and is responsible for 25% (approximately 9,300) of all deaths in Wales each year[3,7]

Hypercholesterolaemia can be broadly divided into familial and non-familial disease. Familial hypercholesterolaemia (FH) is an inherited condition characterised by high cholesterol concentration in the blood which can lead to early-onset myocardial infarctions (MI), even as early as the third decade of life[8]. Non-familial hypercholesterolaemia (non-FH) has no specific genetic cause and is usually multifactorial[9]. Initial management of hypercholesterolaemia involves dietary and lifestyle changes including smoking cessation, weight loss and increased physical activity. Statins are the treatment of choice for patients with hypercholesterolaemia[10]. Typically, standard-of-care includes maximally tolerated statins with or without ezetimibe; however, there is considerable variability in individual responses to statins and many individuals at risk for CVD fail to achieve LDL-C goals. Some patients demonstrate intolerance to statins, mostly due to myalgias and weakness and require alternative lipid lowering therapy to reduce LDL-C[11,12].

As listed in section 2.4, the National Institute for Health and Care Excellence (NICE) has issued guidance for a number of newer therapies for hypercholesterolaemia including guidance for the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors alirocumab and evolocumab as well as for bempedoic acid[13-15]. NICE has also recently published guidance for inclisiran for the indication under consideration[16]. This recommendation does not apply within Wales as the commercial access arrangement agreed between the marketing authorisation holder and NHS England is not applicable to NHS Wales. Therefore, inclisiran meets the criteria for appraisal by AWMSG.

2.2 Medicine

Inclisiran (ALN-PCSSC) is a chemically modified double-stranded 21-23mer small interfering RNA (siRNA). Inclisiran inhibits the translation of PCSK9 in the liver cell thus preventing the degradation of the LDL-receptor (LDLR) on the cell surface, which leads to a reduction of LDL-C[6].

Inclisiran (Leqvio®) was granted marketing authorisation by the Medicines and Healthcare products Regulatory Agency (MHRA) in January 2021 for adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet:

- in combination with a statin or statin with other lipid-lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin, or
- alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.

The recommended dosage of inclisiran is 284 mg (in a pre-filled syringe) administered as a single subcutaneous injection: initially, again at 3 months and then every 6 months[17].

The applicant company has submitted evidence for a subpopulation of the licensed indication and request that AWMSG consider inclisiran for use only in a subpopulation of the licensed indication who are at high risk of further CV events:

- patients with high risk due to previous cardiovascular (CV) events and LDL-C ≥4.0 mmol/L, or
- patients with recurrent/polyvascular disease and LDL-C ≥3.5 mmol/L, or
- patients with heterozygous familial hypercholesterolaemia (HeFH) and LDL-C ≥3.5 mmol/L, for secondary prevention of CV events, or
- patients with HeFH and LDL-C ≥5.0 mmol/L, for primary prevention of CV events.

2.3 Comparators

The comparators included in the company submission are standard of care (SoC) alone, where SoC consists of maximally tolerated statins with or without ezetimibe, and SoC with the addition of PCSK9 inhibitors, either alirocumab or evolocumab[1].

2.4 Guidance and related advice

- NICE technology appraisal guidance (TA733). Inclisiran for treating primary hypercholesterolaemia or mixed dyslipidaemia. October 2021[16].

- Scottish Medicines Consortium Advice No. SMC2358. August 2021[18].
- NICE clinical guideline (CG71). Familial hypercholesterolaemia: identification and management. October 2019[10].
- NICE clinical guideline (CG181). Lipid modification to prevent cardiovascular disease. September 2016[19].
- NICE technology appraisal guidance (TA394). Evolocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia. June 2016[14].
- NICE technology appraisal guidance (TA393). Alirocumab for treating primary hypercholesterolaemia and mixed dyslipidaemia. June 2016[13].
- NICE technology appraisal guidance (TA385). Ezetimibe for treating primary heterozygous-familial and non-familial hypercholesterolaemia. February 2016[20].
- NICE quality standard guideline (QS100). Cardiovascular risk assessment and lipid modification. September 2015[21].
- NICE quality standard guideline (QS41). Familial hypercholesterolaemia. August 2013[22].

The All Wales Medicines Strategy Group (AWMSG) has recommended the use of atorvastatin (Lipitor®)[23] and evolocumab (Repatha®)[24] for hypercholesterolaemia.

2.5 Prescribing and supply

AWTTC is of the opinion that, if recommended, inclisiran (Leqvio®) is appropriate for specialist only prescribing within NHS Wales for the indication under consideration.

3.0 CLINICAL EFFECTIVENESS

The company submission includes evidence from three randomised controlled trials; ORION-9, ORION-10 and ORION-11[25,26]. All three trials had similar design to facilitate data pooling, including objectives, endpoints, placebo control, medication dosage, the schedule and sequence of study procedures[6]. The objectives of the ORION trials were to assess the efficacy, safety and adverse-event profile of inclisiran over a period of 18 months in patients at high risk for CVD whose LDL cholesterol levels were elevated despite receiving statin therapy at the maximum tolerated dose with or without additional lipid-lowering therapy.

3.1 ORION-9, ORION-10 and ORION-11 trials

The three ORION trials in the company submission (ORION-9, ORION-10 and ORION-11) randomised an overall total of 3,660 patients in a 1:1 ratio to either 300 mg inclisiran sodium subcutaneously (equivalent to 284 mg inclisiran) or matching placebo. Each trial was a randomised, double-blind, parallel group, multicentre study to evaluate the efficacy and safety of inclisiran over a duration of 540 days.

The primary endpoints across the ORION trials were:

- Percentage change in LDL-C from baseline to day 510
- Time-adjusted percentage change in LDL-C from baseline after day 90 and up to day 540

The key inclusion criteria for each trial included:

- ORION-9: history or family history of HeFH confirmed via genetic testing and serum LDL-C level of ≥2.6 mmol/L[25]
- ORION-10: history of ASCVD and serum LDL-C level of ≥1.8 mmol/L[26]
- ORION-11: history of ASCVD and serum LDL-C level of ≥1.8 mmol/L or ASCVD- risk equivalent at screening and LDL-C level of ≥2.6 mmol/L

The majority of participants in each trial were receiving background lipid modifying therapy (LMT)[25,26]. Selected patient characteristics are given in Table 1.

Table 1. Characteristics of participants in the studies across treatment groups (intention-to-treat [ITT] population)[1,6,16,25,26]

	ORION-9		ORION-10		ORION-11	
	Inclisiran (n=242)	Placebo (n=240)	Inclisiran (n=781)	Placebo (n=780)	Inclisiran (n=810)	Placebo (n=807)
Age (years)						
Mean ± SD	54.4 ±12.48	55.0 ±11.81	66.4 ±8.90	65.7 ±8.89	64.8 ±8.29	64.8 ±8.68
Sex						
Male, n (%)	112 (46.3)	115 (47.9)	535 (68.5)	112 (46.3)	535 (68.5)	579 (71.5)
Race						
White, n (%)	226 (93.4)	227 (94.6)	653 (83.6)	685 (87.8)	791 (97.7)	796 (98.6)
Cardiovascular risk factors, n (%)						
ASCVD	59 (24.4)	73 (30.4)	781 (100)	780 (100)	712 (87.9)	702 (87.0)
ASCVD risk equivalent†	183 (75.6)	167 (69.6)	0 (0)	0 (0)	98 (12.1)	105 (13.0)
Lipid lowering therapy, n (%)						
Any	229 (94.6)	226 (94.2)	748 (95.8)	730 (93.6)	784 (96.8)	781 (96.8)
Statin	219 (90.5)	217 (90.4)	701 (89.8)	692 (88.7)	766 (94.6)	766 (94.9)
High-intensity statin	185 (76.4)	171 (71.2)	525 (67.2)	537 (68.8)	640 (79.0)	631 (78.2)
Ezetimibe	135 (55.8)	120 (50.0)	80 (10.2)	74 (9.5)	52 (6.3)	62 (7.7)

†Patients in this category had type 2 diabetes, familial hypercholesterolemia, or a 10-year risk of a cardiovascular event of 20% or greater as assessed by the Framingham Risk Score for Cardiovascular Disease or equivalent[27].

3.2 Results of the ORION-9, ORION-10 and ORION-11 studies

All ORION phase III clinical trials met their co-primary endpoints, demonstrating that after two starter doses, twice-yearly subcutaneous dosing with inclisiran resulted in sustained and effective LDL-C reductions vs placebo[16]. Results for each trial are presented separately in Table 2.

Table 2. Results for the two primary and key secondary outcomes of the ORION-9, ORION-10 and ORION-11 studies (intention-to-treat [ITT] population)[1,6,25,26]

	ORION-9		ORION-10		ORION-11	
	Inclisiran (n=242)	Placebo (n=240)	Inclisiran (n=781)	Placebo (n=780)	Inclisiran (n=810)	Placebo (n=807)
% patients completing study	97%	96%	92%	89%	95%	95%
Mean baseline LDL-C (mmol/L)	3.9	4.0	2.7	2.7	2.8	2.7
Primary outcomes						
% change in LDL-C from baseline to day 510	-40%	8.2%	-51%	1.0%	-46%	4.0%
Between-group difference (95% CI) p-value	-48% (-54 to -42) p<0.001		-52% (-56 to -49) p<0.001		-50% (-53 to -47) p<0.001	
Time-adjusted % change in LDL-C between day 90 and day 540	-38%	6.2%	-51%	2.5%	-46%	3.4%
Between-group difference (95% CI) p-value	-44% (-49 to -40) p<0.001		-54% (-56 to -51) p<0.001		-49% (-52 to -47) p<0.001	
Key secondary outcomes						
Absolute change from baseline in LDL-C (mmol/L) to day 510	-1.5	0.26	-1.5	-0.05	-1.3	0.03
Between-group difference (mmol/L) (95% CI), p-value	-1.8 (-2.0 to -1.6), p<0.001		-1.4 (-1.5 to -1.3), p<0.001		-1.3 (-1.4 to -1.3), p<0.001	
Time-adjusted absolute change from baseline in LDL-C (mmol/L) between day 90 and day 540	-1.5	0.10	-1.4	-0.01	- 1.3	0.01
Between-group difference (mmol/L) (95% CI), p-value	-1.6 (-1.4 to -1.3), p<0.001		-1.4 (-1.4 to -1.3), p<0.001		-1.3 (-1.3 to -1.2), p<0.001	
% change in PCSK9 from baseline to day 510	-61%	18%	-70%	14%	-64%	16%
% difference from placebo (95% CI), p-value	-78% (-84 to -73), p<0.0001		-83% (-89 to -77), p<0.0001		-79% (-82 to -77), p <0.0001	
% change in total cholesterol from baseline to day 510	-25%	6.7%	-34%	-0.4%	-28%	1.8%
% difference from placebo (95% CI), p-value	-32% (-36 to -28), p<0.0001		-33% (-35 to -31), p<0.0001		-30% (-32 to -28), p<0.0001	

% change in apolipoprotein B from baseline to day 510	-33%	2.9%	-45%	-1.7%	-38%	0.8%
% difference from placebo (95% CI), p-value	-36% (-40 to -32), p<0.0001		-43% (-46 to -41), p<0.0001		-39% (-41 to -37), p<0.0001	
% change in non-HDL-C from baseline to day 510	-35%	7.4%	-47%	-0.1%	-41%	2.2%
% difference from placebo (95% CI), p-value	-42% (-47 to -37), p<0.0001		-47% (-50 to -44), p<0.0001		-43% (-46 to -41), p<0.0001	
CI: confidence interval; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; PCSK9: proprotein convertase subtilisin-kexin type 9						

3.3 Interim results from ORION-8

The long-term efficacy and safety of inclisiran is being investigated in ORION-8, an open-label extension study for patients who completed one of the phase III studies (ORION-9, -10, or -11). ORION-8 will provide safety assessments with a follow-up of up to 3 years (approximately 4.5 years when combined with the pivotal phase III feeder studies).

The company provided interim unpublished efficacy data from ORION-8 which analysed [commercial in confidence figure removed] patients (see Table 3). Inclisiran treatment demonstrated long-term efficacy with no evidence of attenuation of the LDL-C-lowering effect. The longest on-treatment duration was seen in [commercial in confidence figure removed] patients who had completed the Day 1,080 visit. The mean LDL-C percentage reduction observed in these patients at Day 1,080 (Day 1,620 from the start of the feeder study) was [commercial in confidence figure removed][28].

Table 1. Long-term efficacy of inclisiran (ORION-8)[28]

Endpoint	Timepoint	Statistics	Inclisiran (n=2,990)
% change from baseline* in LDL-C	Day 90 (Day 630 (90 weeks) from the feeder study)	N	¶¶
		Mean ± SD	¶¶
		Median	¶¶
	Day 270 (Day 810 (116 weeks) from the feeder study)	N	¶¶
		Mean ± SD	¶¶
		Median	¶¶
* Baseline is defined as Day 1 in the ORION-9, ORION-10, and ORION-11 studies; all subsequent time-points are counted from the start of the extension LDL-C, low-density lipoprotein cholesterol; SD, standard deviation. ¶¶ commercial in confidence figure removed.			

3.4 Summary of the network meta-analysis (NMA)

To address the lack of direct comparative evidence, the company submitted Bayesian network meta-analyses (NMAs) to estimate the efficacy and safety of inclisiran compared to existing treatments, including alirocumab and evolocumab[1].

The eligible populations for the NMAs included patients with ASCVD or risk equivalent who were receiving maximum tolerated doses of statins; patients with ASCVD or risk equivalent who were statin intolerant and patients with HeFH who were receiving maximum tolerated doses of statins. Due to a lack of relevant comparator studies, the company noted that it was not possible to perform an NMA in patients with HeFH who were statin intolerant[1].

[commercial in confidence text removed][1,16].

Findings from the NMAs demonstrated no statistically significant differences between inclisiran and alirocumab or evolocumab across the hypercholesteremia patient populations[1].

3.5 Comparative safety

The most frequently reported treatment-emergent adverse events of any grade in the pooled inclisiran and placebo groups included diabetes mellitus, nasopharyngitis, upper respiratory tract infection, hypertension and arthralgia. Pooled safety analysis of the three ORION studies reported that 78% (1,430/1,833) of inclisiran and 77% (1,409/1,822) of placebo patients had at least one treatment-emergent adverse event. However, overall, the type and incidence of common adverse events were comparable between the inclisiran and placebo groups with the exception of injection site reactions. Treatment emergent adverse events considered related to inclisiran included injection site pain (2.0%; 37/1,833), and injection site erythema (1.5%; 27/1,833)[6]. These were mainly mild in severity, transient and resolved without sequelae and were not associated with a higher dropout rate or a lower compliance[6].

Interim results from ORION-8, the open-label extension study, report a similar overall safety profile to that observed for inclisiran treated-patients in the phase III studies. In the ORION-9 -10 and -11 safety pool analysis, [commercial in confidence figure removed] of inclisiran-treated patients (150/1,833) experienced adverse reactions at the injection site, compared with [commercial in confidence figure removed] of patients in ORION-8 ([commercial in confidence figure removed]). These were localised, predominantly mild or occasionally moderate, and transient in nature[29].

Overall, the most common treatment emergent adverse events and serious adverse events were similar to those previously reported in the pivotal studies[29].

3.6 Ongoing studies

In addition to the ongoing extension study ORION-8, a clinical outcome study, ORION-4, is recruiting over 15,000 patients to assess the effect of inclisiran on major adverse cardiovascular events (MACE). Results from ORION-4 are expected in December 2026[30].

3.7 AWTTC critique

- Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of death worldwide. Cardiovascular events are often acute but prolonged periods of recovery and recurrent events are common, impacting on quality of life and placing a substantial burden on the healthcare system. Elevated levels of LDL-C increase the risk of developing ASCVD and national guidelines emphasise the importance of targeting cholesterol. As these recommendations recognise that the LDL-C goals are not always achievable by maximum tolerated statin therapy, an unmet need remains and additional LDL-C lowering therapies are necessary. With NICE advice for inclisiran not implementable within NHS Wales, there is currently inequity of access to and a lack of advice for inclisiran for Welsh patients.
- Data from the ORION-9, -10 and -11 trials showed that significantly more patients reached LDL-C targets on inclisiran than on placebo (by

48% to 52%) demonstrating the clinical effectiveness of inclisiran therapy. Efficacy was supported by significant reductions in other relevant parameters of the cholesterol profile[6]. Interim unpublished data from the open label extension study, ORION-8, suggests that efficacy is maintained over the longer term and that inclisiran is well-tolerated[28]. Although LDL-C levels are an approved surrogate marker for CVD risk there is currently a lack of cardiovascular outcomes for inclisiran[6] unlike for the comparators. The clinical outcome study, ORION-4, is designed to address this issue.

- The company has suggested AWMSG considers inclisiran for a restricted population (see section 2.2), narrower than most of those eligible for inclusion in the ORION studies. However, this restriction is in line with the restricted recommendation for the PCSK9 inhibitors alirocumab and evolocumab (NICE guidance), which the company has included as comparators in their submission; Welsh clinical experts confirm these are the most appropriate comparators. Bempedoic acid was not considered a comparator as it has only recently been recommended by NICE and is not yet part of established practice in Wales.
- There is a lack of comparative evidence to alirocumab and evolocumab. The NMA presented by the company has a number of limitations including heterogeneity across the studies, patient populations, background treatment and timing of assessment of percentage change in LDL-C. In addition, the NMA were performed in a broader patient population than those suggested by the company should be eligible for treatment with inclisiran in NHS Wales.
- The introduction of inclisiran would offer an additional injectable lipid lowering treatment and it appears to be well tolerated. After two initial doses, inclisiran is administered by subcutaneous injection at a maintenance dose of once every six months by a healthcare professional. This may improve treatment compliance in patients which is an important factor. Alirocumab and evolocumab require subcutaneous injection every 2 to 4 weeks; although this can be administered by the patient at home they need to be willing and trained to do so. AWTTC-sought clinical expert opinion considered use of inclisiran a therapeutic advancement, however they highlight there is still an unmet need for those patients who fall outside the restricted population suggested by the company.

4.0 COST-EFFECTIVENESS

4.1 Context

The company submission includes a cost-utility analysis (CUA) comparing inclisiran (Leqvio®) 284 mg (in a pre-filled syringe) in combination with standard of care (SoC), where SoC consists of maximally tolerated statins with or without ezetimibe, with three comparator regimens: SoC, alirocumab with SoC, and evolocumab with SoC. The CUA focuses on the following patient populations:

- patients with high risk due to previous CV events and LDL-C ≥4.0 mmol/L

- patients with recurrent/polyvascular disease and LDL-C ≥3.5 mmol/L
- patients with HeFH and LDL-C ≥3.5 mmol/L, for secondary prevention of CV events
- patients with HeFH and LDL-C ≥5.0 mmol/L, for primary prevention of CV events.

Choice of comparators is guided by NICE recommendations[10,13,14,19,20]. The targeted populations are narrower than the full licensed indication, as they specify a ≥ 3.5mmol/L LDL-C threshold or higher.

The CUA takes the form of a cohort Markov model, comprising 1-year cycles. The model adopts a 40-year time horizon and an NHS Wales/Personal and Social Services perspective. Costs and outcomes are discounted at 3.5%. The submission incorporates a Wales Patient Access Scheme (WPAS) discount for inclisiran. The comparators, alirocumab and evolocumab, also have associated confidential Patient Access Scheme (PAS) discounts.

The model structure is based on models submitted to SMC and NICE for the appraisal of inclisiran[16,18], and has been validated by the company through discussions with clinical experts. It is characterised by 15 health states; three initial health states, ten post-event states and two absorbing health states (CV death and non-CV death). Patients enter the model in one of the three initial states, and transition between states based on the predicted risks of cardiovascular (CV) events (fatal and non-fatal) and the risk of death from non-CV causes. Time dependency has been built into the model to capture the increased risk of a secondary event in the first year post recent cardiac event. Following movement to a post non-fatal event state, patients remain at risk of subsequent events (fatal and non-fatal). However, patients only transition when a worse health state occurs, to avoid illogical model outputs.

Baseline characteristics, including age, sex, prevalence of diabetes and average LDL-C at baseline are taken from the ORION clinical trials[25,26]. Baseline CV risks are sourced from retrospective descriptive analysis of real-world data from the Clinical Practice Research Datalink (CPRD)[31]. Given the current lack of outcomes data for inclisiran, the model uses reductions in LDL-C as an intermediate outcome which is then linked to reductions in CV events. The efficacy data used in the model are derived from a network meta-analysis. The outcome selected for efficacy in the NMAs was the percent change in LDL-C at 24 weeks in all populations. Treatment efficacy is estimated separately for patients with ASCVD and HeFH and is assumed to be constant across all baseline LDL-C categories, in accordance with company sought clinical expert opinion. It is assumed that patients in the SoC arm do not experience any change in LDL-C. Rate ratios for CV events are obtained from the Cholesterol Treatment Trialists (CTT) meta-analyses, based on large-scale RCTs of statin therapy with a treatment duration of ≥2 years[32,33]. Neither discontinuation of active therapy or statins, nor adverse events are incorporated in the base case. Rates of non-CV mortality are taken from lifetables for Wales[34], and have been adjusted to remove the proportion of deaths due to CV causes using cause-specific mortality data[35].

The model includes medicine acquisition and administration costs, and health state costs. The company base case uses the WPAS price for inclisiran and the list price for all comparator medicines. The medicine composition of SoC used in the analysis is guided by the ORION-11 clinical trial. The unit costs for statins, ezetimibe and the comparator PCSK9 inhibitors are taken from the BNF[36,37]. Administration costs are apportioned to the use of inclisiran only. It is assumed that administration requires 10 minutes of nurse time; which is costed using PSSRU unit costs[38]. This is considered a conservative approach by the company, as the other PCSK9 inhibitors incur either a one-off training cost for self-injection instruction or regular administration costs (neither of which are included in the model). Acute costs for CV events are informed by NHS reference costs[39] and post-event costs are sourced from NICE TA393 and CG181[13,19]. Costs are inflated to 2018/19 values using the HCHS pay and prices index[40].

Health outcomes are accrued in the initial and post-event health states. Baseline utility values are informed by a study which estimates age- and gender-adjusted utilities for people with no history of CV disease from the Health Survey for England[41]. These values are combined with cohort-specific and post-event utility multipliers, taken from TA393[13]. The one-off QALY loss applied to patients experiencing an acute event in a more severe health state are calculated as the difference in utilities between Year 1 post-event and the stable post-stroke utility, regardless of the baseline health state.

Deterministic and probabilistic sensitivity analyses were conducted to test the influence of the uncertainty of individual parameters on the model results for each of the sub-population base cases. Model parameters were varied over a range determined either by the 95% CI or ±15%. The company also tested the impact of alternative levels of PAS discount on comparators, varying the discount on alirocumab and evolocumab between 5% and 95%, in 5% increments. Scenario analyses further explores: inclusion of discontinuation (all therapies); statin intolerant patients for the ASCVD population; direct use of clinical trials data for inclisiran efficacy; alternative CV event rate ratios applied in year 1; an assumption of equal efficacy for inclisiran and PCSK9 inhibitors; delaying inclisiran impact until day 90; and the use of alternative sources to estimate CV event rates.

4.2 Results

The results of the base case pair-wise comparisons are detailed in Table 4. When compared with SoC, the incremental cost-effectiveness ratios (ICERs) generated range between [commercial in confidence figure removed] and [commercial in confidence figure removed] per QALY gained for the high risk ASCVD, very high-risk CVD and secondary prevention HeFH populations; and is estimated at [commercial in confidence figure removed] per QALY gained for the primary prevention HeFH population. The main cost differences can be attributed to medicine acquisitions costs.

When compared with alirocumab with SoC, and evolocumab with SoC, in all populations the point estimate for the ICER falls within the south west quadrant of the cost-effectiveness plane (i.e. inclisiran is less costly and less effective than the comparators), producing ICERs ranging between [commercial in

confidence figure removed] and [commercial in confidence figure removed] saved per QALY forgone. In the south west quadrant, an ICER > £20,000 saved per QALY forgone can be considered cost-effective; delivering a net health benefit at a population level and providing additional treatment options for patients. The main cost differences can be attributed to medicine acquisition costs. The base case results do not include the discounts available on the comparators.

The results of the univariate sensitivity analysis show that the ICERs for the high risk ASCVD and very-high risk CVD populations are most sensitive to the risk ratio per mmol/L reduction in LDL-C for CV death and stroke, and efficacy of inclisiran, alirocumab and evolocumab. For the primary prevention HeFH population, the ICERs are most sensitive to efficacy of inclisiran, alirocumab and evolocumab, and CV death event rates. For the secondary prevention HeFH population, ICERs are most sensitive to efficacy of inclisiran, alirocumab, and evolocumab, the risk ratio per mmol/L reduction in LDL-C for CV death and CV events.

The company conducted analyses exploring PAS on comparators reveal that when compared with alirocumab with SoC for the ASCVD, primary prevention HeFH and very high-risk populations inclisiran still has the potential to deliver a net health benefit at a population level when discounts on alirocumab range between [commercial in confidence figure removed]. For the secondary prevention HeFH population this remains the case when the discount on alirocumab ranges between [commercial in confidence figure removed]. When compared with evolocumab with SoC for the ASCVD, secondary prevention HeFH and very high-risk populations inclisiran still has the potential to deliver a net health benefit at a population level when discounts on evolocumab range between [commercial in confidence figure removed]. For the primary prevention HeFH population this remains the case when the discount on evolocumab ranges between [commercial in confidence figure removed].

Table 5 includes a selection of the extensive scenario analyses undertaken by the company, assessed in order of plausibility. The results of the probabilistic sensitivity analyses are included in Table 4.

Table 4. Results of the base case pair-wise comparisons of inclisiran versus comparator (at list price) for each patient population

Medicines	Total costs	Total life-years	Total QALYs	ICER (£/QALY) *	Probability of inclisiran being a cost-effective treatment at thresholds of	
					£20,000	£30,000
High Risk ASCVD with LDL-C ≥ 4.0mml/L						
Inclisiran + SoC	¶¶	11.36	7.94	-	-	-
SoC	£7,312	9.47	6.53	¶¶	¶¶	¶¶
Alirocumab + SoC	£54,324	11.39	7.96	¶¶	¶¶	¶¶
Evolocumab + SoC	£55,570	11.59	8.11	¶¶	¶¶	¶¶
Primary prevention HeFH with LDL-C ≥ 5.0mml/L						
Inclisiran + SoC	¶¶	18.56	15.07	-	-	-
SoC	£3,329	17.64	14.27	¶¶	¶¶	¶¶
Alirocumab + SoC	£82,667	18.60	15.11	¶¶	¶¶	¶¶
Evolocumab + SoC	£83,786	18.64	15.14	¶¶	¶¶	¶¶
Secondary prevention HeFH with LDL-C ≥ 3.5mml/L						
Inclisiran + SoC	¶¶	15.35	11.22	-	-	-
SoC	£9,161	13.66	9.91	¶¶	¶¶	¶¶
Alirocumab + SoC	£73,170	15.46	11.31	¶¶	¶¶	¶¶
Evolocumab + SoC	£74,249	15.56	11.39	¶¶	¶¶	¶¶
Very high-risk CVD with LDL-C ≥ 3.5mml/L						
Inclisiran + SoC	¶¶	11.05	8.54	-	-	-
SoC	£5,009	9.30	7.11	¶¶	¶¶	¶¶
Alirocumab + SoC	£51,687	11.08	8.56	¶¶	¶¶	¶¶
Evolocumab + SoC	£52,979	11.27	8.72	¶¶	¶¶	¶¶

ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year
† point estimate in south west quadrant of the cost-effectiveness plane. In the south west quadrant ICERs ≥ £20,000 - £30,000 per QALY forgone can deliver a net health benefit at a population level and provide additional treatment options for patients – these medicines can therefore be considered a worthwhile treatment option.
*may not compute due to rounding
¶¶ commercial in confidence figure removed.

Table 5. Results of scenario and sensitivity analyses

Scenarios/Populations	ICER	Plausibility
Including discontinuation of inclisiran and PCSK9 inhibitors, assuming patients discontinue inclisiran and the PCKS9 inhibitors at the same rate		
High risk ASCVD with LDL-C ≥ 4.0 mml/L a) Inclisiran + SoC vs SoC b) Inclisiran + SoC vs alirocumab + SoC c) Inclisiran + SoC vs evolocumab + SoC	 **a)** ¶¶ **b)** ¶¶† **c)** ¶¶†	The base case assumes no discontinuation, which is not reflective of the pivotal trials. The NMA results suggest no statistical difference in discontinuation. These scenarios offer insight into the inclusion of discontinuation rates and offer a plausible alternative to the base case.
Primary prevention HeFH with LDL-C ≥ 5.0 mml/L a) Inclisiran + SoC vs SoC b) Inclisiran + SoC vs alirocumab + SoC c) Inclisiran + SoC vs evolocumab + SoC	 **a)** ¶¶ **b)** ¶¶† **c)** ¶¶†	
Secondary prevention HeFH with LDL-C ≥ 3.5 mml/L a) Inclisiran + SoC vs SoC b) Inclisiran + SoC vs alirocumab + SoC c) Inclisiran + SoC vs evolocumab + SoC	 **a)** ¶¶ **b)** ¶¶† **c)** ¶¶†	
Very high-risk CVD with LDL-C ≥ 3.5 mml/L a) Inclisiran + SoC vs SoC b) Inclisiran + SoC vs alirocumab + SoC c) Inclisiran + SoC vs evolocumab + SoC	 **a)** ¶¶ **b)** ¶¶† **c)** ¶¶†	

Scenarios/Populations	ICER	Plausibility
Including discontinuation of inclisiran and PCSK9 inhibitors, with discontinuation taken from the pivotal trials (ORION, ODDYSEY and FOURIER)		
High risk ASCVD with LDL-C ≥ 4.0 mml/L a) Inclisiran + SoC vs SoC b) Inclisiran + SoC vs alirocumab + SoC c) Inclisiran + SoC vs evolocumab + SoC	 **a)** ¶¶ **b)** ¶¶ **c)** ¶¶	The base case assumes no discontinuation. These scenarios explore the impact of the inclusion of the discontinuation rates from the pivotal trials, and offer plausible alternatives to the base case.
Primary prevention HeFH with LDL-C ≥ 5.0 mml/L a) Inclisiran + SoC vs SoC b) Inclisiran + SoC vs alirocumab + SoC c) Inclisiran + SoC vs evolocumab + SoC	 **a)** ¶¶ **b)** ¶¶ **c)** ¶¶	
Secondary prevention HeFH with LDL-C ≥ 3.5 mml/L a) Inclisiran + SoC vs SoC b) Inclisiran + SoC vs alirocumab + SoC c) Inclisiran + SoC vs evolocumab + SoC	 **a)** ¶¶ **b)** ¶¶ **c)** ¶¶	
Very high-risk CVD with LDL-C ≥ 3.5 mml/L a) Inclisiran + SoC vs SoC b) Inclisiran + SoC vs alirocumab + SoC c) Inclisiran + SoC vs evolocumab + SoC	 **a)** ¶¶ **b)** ¶¶ **c)** ¶¶	

Efficacy for inclisiran taken from the clinical trials		
Primary prevention HeFH with LDL-C ≥ 5.0 mml/L a) Inclisiran + SoC vs SoC b) Inclisiran + SoC vs alirocumab + SoC c) Inclisiran + SoC vs evolocumab + SoC	 **a)** ¶¶ **b)** ¶¶† **c)** ¶¶†	Given the uncertainties associated with the NMAs, and the favourable results produced from the analyses for inclisiran, these scenarios provide useful insight into the application of trial data.
Secondary prevention HeFH with LDL-C ≥ 3.5 mml/L a) Inclisiran + SoC vs SoC b) Inclisiran + SoC vs alirocumab + SoC c) Inclisiran + SoC vs evolocumab + SoC	 **a)** ¶¶ **b)** ¶¶† **c)** ¶¶†	
Adjusting rate ratios for CV events according to Collins et al		
Primary prevention HeFH with LDL-C ≥ 5.0 mml/L a) Inclisiran + SoC vs SoC b) Inclisiran + SoC vs alirocumab + SoC c) Inclisiran + SoC vs evolocumab + SoC	 **a)** ¶¶ **b)** ¶¶† **c)** ¶¶†	Research suggests that the impact of LDL-C lowering therapies is smaller in the first year of treatment[42]. This scenario therefore provides an exploration of the impact of applying a smaller rate ratio (RR) in the first year, with a larger RR each year thereafter.
Using CPRD data for the secondary prevention HeFH with LDL-C ≥ 3.5mmol/L population		
Secondary prevention HeFH with LDL-C ≥ 3.5 mml/L a) Inclisiran + SoC vs SoC b) Inclisiran + SoC vs alirocumab + SoC c) Inclisiran + SoC vs evolocumab + SoC	 **a)** ¶¶ **b)** ¶¶† **c)** ¶¶†	Company-sought clinical expert opinion suggests that in the UK patients are often incorrectly coded with FH in CPRD databases, which has the potential to skew event rates. Use of this alternative data source useful in addressing the uncertainty surrounding this phenomenon.
Equal efficacy for inclisiran and PCSK9 inhibitors		
All 4 patient populations a) Inclisiran + SoC vs alirocumab + SoC b) Inclisiran + SoC vs evolocumab + SoC	¶¶	This scenario explores the results of applying a cost minimisation approach to analysis. Given the different mechanism of action of the medicines and the lack of efficacy evidence, it is not appropriate to assume equivalence. This scenario does not offer a plausible alternative to the base case.

† point estimate in south west quadrant of the cost-effectiveness plane. In the south west quadrant ICERs ≥ £20,000 - £30,000 per QALY forgone are considered cost-effective and can deliver a net health benefit at a population level and provide additional treatment options for patients – these medicines can therefore be considered a worthwhile treatment option.
¶¶ commercial in confidence figure removed.

4.3 AWTTC critique

The submission is characterised by both strengths and limitations:

- The submission gives a detailed, transparent account of the methods and data sources used in the analysis.
- Reasonable justifications are provided for the assumptions applied in the model. Clinical expert opinion has also been sought to validate the major assumptions underlying the model.
- Extensive sensitivity and scenario analyses have been conducted.
- The analysis identifies SoC as a comparator. However, AWTTC-sought clinical expert opinion suggests that the PCSK9 will be the treatments displaced in practice. SoC is only considered a comparator in patients unable to tolerate PCSK9 inhibitors.
- Efficacy is based on a surrogate marker, namely LDL-C. The rate ratios used in the model (i.e. the rate at which the risk of a cardiovascular event declines with the absolute reduction in LDL-C levels) are based on the CTTC meta-analysis which measures the effects of statins[32]. The use of this surrogate marker and the application of the findings of the CTTC analysis has been an approach accepted in previous appraisals of PCSK9 inhibitor. This approach may be considered acceptable, however there remains uncertainty relating to the direct application of statin-related CV risk reductions to inclisiran, given the differences in mechanisms of action between the two groups of medicine.
- The model assumes maintained efficacy over the entire time horizon. Even though interim unpublished data from the open label extension study, ORION-8, suggests that efficacy is maintained, the assumption that it is maintained over the entire time horizon is associated with uncertainty.
- The company acknowledge that outcomes trials for alirocumab and evolocumab exist, which estimate a direct effect of treatment on the rate of CV events. The modelling reflects CV event rate based on statin data. It may have been useful if the company had explored how the modelled events compare to these new data.
- The base case also does not include discontinuation of treatment. However, the company have explored discontinuation in scenario analyses (see Table 5).
- There is notable heterogeneity between the studies included in the NMAs. This, in addition to the use of 24-week outcomes to inform long-term outcomes, introduces uncertainty in the efficacy estimates.
- The CPRD analysis used data from the Aurum primary care dataset, which does not contain Welsh patients. The company acknowledge this limitation. However, it is also suggested that application of English data possibly produces conservative analysis, as higher deprivation in Wales may be associated with higher event rates than those identified in the English data.

4.4 Review of published evidence on cost-effectiveness

A literature review conducted by All Wales Therapeutics and Toxicology Centre (AWTTC) identified economic evaluations which include inclisiran as one of the medicines analysed; however, these studies did not focus on the patient sub-populations of interest in this submission.

5.0 BUDGET IMPACT

5.1 Context and methods

The company has estimated that there will be [commercial in confidence figure removed] people with ASCVD or HeFH requiring primary prevention who are eligible for treatment in Wales in Year 1, increasing to [commercial in confidence figure removed] in Year 5. This estimate is based on CPRD prevalence and treatment data, using Welsh practices. It is assumed that the CPRD prevalence data account for mortality and incidence. The estimates for inclisiran uptake have been guided by data relating to PCSK9 inhibitors. An anticipated market share of [commercial in confidence figure removed] in Year 1, increasing to [commercial in confidence figure removed] in Year 5 is further applied to estimate the number of people likely to be prescribed inclisiran in Wales for the indications covered in the submission. The company provides a breakdown of how comparator medicines are likely to be displaced as a result. The base case assumes that all patients treated with inclisiran would otherwise have received alirocumab or evolocumab. The WPAS discount is applied to inclisiran. All other medicines acquisition costs reflect list prices.

Sensitivity and scenario analyses have been performed to explore the impact of: varying market share (±15%), different levels of PAS discounts for alirocumab and evolocumab; and an assumption that the entire inclisiran market share comes from the displacement of SoC.

5.2 Results

The budget impact is presented in Table 6. The company estimates that introducing inclisiran would lead to an overall cost saving of [commercial in confidence figure removed] in Year 1, increasing to a saving of [commercial in confidence figure removed] in Year 5. This estimate incorporates cost differences resulting from the displacement of alirocumab and evolocumab only.

Sensitivity analysis exploring alternative market share assumptions, whereby inclisiran displaces ±15% evolocumab and alirocumab, resulted in projected savings ranging between a minimum of [commercial in confidence figure removed] in Year 1 and a maximum of [commercial in confidence figure removed]. An alternative assumption that all market share for inclisiran comes from the displacement of SoC results in a projected additional cost of [commercial in confidence figure removed] in Year 1, increasing to [commercial in confidence figure removed] in Year 5. The sensitivity analyses exploring PAS on the comparators project budget impacts ranging from an annual savings of [commercial in confidence figure removed] to an additional annual cost of [commercial in confidence figure removed], when discounts ranging from 5% to 95% are applied to each of the PCSK9 inhibitors (evolocumab and alirocumab) individually. Further analyses exploring an equal PAS discount for both PCSK9 inhibitors simultaneously, applied in 5% increments, results in budget impacts ranging from an annual saving of [commercial in confidence figure removed] to an additional annual cost of [commercial in confidence figure removed].

Table 6. Company-reported savings associated with use of inclisiran for people with ASCVD or HeFH requiring primary prevention (based on list price for comparators)

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of eligible patients	¶¶	¶¶	¶¶	¶¶	¶¶
Uptake of new medicine (%)	¶¶	¶¶	¶¶	¶¶	¶¶
Number of patients receiving new medicine allowing for discontinuations	¶¶	¶¶	¶¶	¶¶	¶¶
Medicine acquisition costs in a market without new medicine	¶¶	¶¶	¶¶	¶¶	¶¶
Medicine acquisition costs in a market with new medicine	¶¶	¶¶	¶¶	¶¶	¶¶
Net medicine acquisition costs	¶¶	¶¶	¶¶	¶¶	¶¶
Net supportive medicines costs	£0	£0	£0	£0	£0
Net medicine acquisition cost savings (including supportive medicines)	¶¶	¶¶	¶¶	¶¶	¶¶

¶¶ commercial in confidence figure removed.

The company estimated that net resource implications arising from the introduction of inclisiran will lead to a cost of [commercial in confidence figure removed] in Year 1, increasing to [commercial in confidence figure removed] in Year 5. This is a consequence of the administration costs associated with inclisiran, and the costs associated with CV events. These resource type costs are included for potential planning purposes.

5.3 AWTTC critique

- The submission gives a detailed, transparent account of the methods and data sources used to estimate budget impact.
- The assumption that only evolocumab and alirocumab are displaced by inclisiran is at odds with the inclusion of SoC as a comparator in the CUA.
  However, AWTTC-sought clinical opinion suggests that this assumption is plausible, except in instances where patients are unable to tolerate PCSK9 inhibitors. Sensitivity analyses explore the impact of displacing SOC only. This is useful in terms of gaining insight into the impact of varying displacement assumptions.
- It was not possible to verify the company's annual figures for the number of eligible patients. However, AWTTC sought clinical expert opinion suggest the estimated numbers are plausible.

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