PharmacoEconomics (2018) 36:115–126
https://doi.org/10.1007/s40273-017-0590-5

ORIGINAL RESEARCH ARTICLE

Budget Impact Analysis of PCSK9 Inhibitors for the Management of Adult Patients with Heterozygous Familial Hypercholesterolemia or Clinical Atherosclerotic Cardiovascular Disease

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Published online: 27 November 2017

Abstract

Objective The aim of this study was to assess the budget impact of introducing the proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i) alirocumab and evolocumab to market for the treatment of adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular (CV) disease requiring additional lowering of low-density lipoprotein cholesterol (LDL-C).

Methods A 3-year model estimated the costs of lipid-modifying therapy (LMT) and CV events to a hypothetical US health plan of 1 million members, comparing two scenarios—with and without the availability of PCSK9i as add-on therapy to statins. Proportions of patients with uncontrolled LDL-C despite receiving statins, and at risk of CV events, were estimated from real-world data. Total undiscounted annual LMT costs (2017 prices, including PCSK9i costs of $14,563.50), dispensing and healthcare costs, including the costs of CV events, were estimated for all prevalent patients in the target population, based on baseline risk factors. Maximum PCSK9i utilization of 1–5% over 3 years according to risk group (following the same pattern as current ezetimibe use), and 5–10% as a secondary scenario, were assumed.

Results Total healthcare budget impacts per target patient (and per member) per month for years 1, 2 and 3 were $3.62($0.10), $7.22($0.20) and $10.79($0.30), respectively, assuming 1–5% maximum PCSK9i utilization, and $15.81($0.44), $31.52($0.88) and $47.12($1.31), respectively, assuming 5–10% utilization. Results were sensitive to changes in model timeframe, years to maximum PCSK9i utilization and PCSK9i costs.

Conclusions The budget impact of PCSK9i as add-on therapy to statins for patients with hypercholesterolemia is relatively low compared with published estimates for other specialty biologics. Drug cost rebates and discounts are likely to further reduce budget impact.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s40273-017-0590-5) contains supplementary material, which is available to authorized users.

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Key Points for Decision Makers

Assuming utilization rates of 1–5 for the proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i) alirocumab and evolocumab in patients with clinical atherosclerotic cardiovascular disease or heterozygous familial hypercholesterolemia receiving statins and with uncontrolled LDL-C, the introduction of these treatments was estimated to increase total healthcare costs per target patient (and per member) per month by $3.62 ($0.10), $7.22 ($0.20) and $10.79 ($0.30) for years 1, 2 and 3, respectively.

These findings suggest that the PCSK9i alirocumab and evolocumab, at wholesale acquisition cost, are likely to have a smaller impact on US healthcare plans compared with prior estimates.

To the extent that the manufacturers offer rebates and discounts to the wholesale acquisition cost, the budget impact would be even lower than the results presented herein.

1 Introduction

Cardiovascular disease (CVD) is considered one of the leading causes of mortality in the US and worldwide [1]. The American Heart Association estimated that the combined direct and indirect costs of CVD and stroke in the US in 2012 was $316.6 billion [2]. Hypercholesterolemia, particularly elevated low-density lipoprotein cholesterol (LDL-C) levels, constitutes a major risk factor for the development of atherosclerotic CVD (ASCVD) and an increased risk of cardiovascular (CV) events [3, 4]. A positive relationship has been established between the lowering of blood cholesterol and LDL-C levels and the reduction of CV event rates [3, 5–10]. Statins are endorsed in current treatment guidelines to reduce LDL-C in both the primary and secondary prevention setting [4, 11–14]; however, as many as 8.1 million patients with clinical ASCVD in the US fail to achieve the recommended reduction of lipid levels necessary to optimally reduce the risk of CV events despite treatment with a statin [15–17].

Non-statin lipid-modification therapy (LMT) may be added to statin therapy for patients who continue to have high LDL-C despite treatment with maximally tolerated doses of statins or who are intolerant to statin therapy [4, 13]. Inhibitors of proprotein convertase subtilisin/kexin type 9 (PCSK9), which is involved in the control of LDL-C receptor degradation, represent a new class of non-statin LMT for use as an adjunct treatment with statins in patients with elevated LDL-C [18]. In phase II and III studies, treatment with the PCSK9 inhibitors (PCSK9i) alirocumab and evolocumab has been shown to be an efficacious and well-tolerated approach to lower LDL-C levels [19–36]. Both alirocumab and evolocumab were approved by the US FDA in 2015 as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical ASCVD who require additional lowering of LDL-C levels [18, 37], and the treatments are now included in European and US guidelines for these specific patient groups [38, 39].

The efficacy and long-term safety of PCSK9i for the treatment of individuals with hypercholesterolemia, clinical ASCVD, HeFH and/or homozygous familial hypercholesterolemia (HoFH) have been evaluated in the phase III ODYSSEY programme for alirocumab, and the PROFICIO programme for evolocumab. Data from the ODYSSEY and PROFICIO clinical programmes suggest sustained LDL-C reductions of up to 61% after 12 weeks associated with alirocumab [29] and evolocumab [34]. Despite endorsements of their clinical value, the perceived costs and budgetary concerns of treatment-eligible patients [40] are likely to have had a role in the limited uptake of PCSK9i in resource-constrained health systems [41]. Therefore, further evidence of their economic impact to healthcare budgets, with particular consideration of eligible patient groups, is warranted to support formulary adoption and treatment decision making [42]. This evaluation examined the pharmacy and total healthcare budget impacts of introducing alirocumab and evolocumab to a US health plan as a treatment modality for adult patients with HeFH or clinical ASCVD who are treated with statins and require additional LDL-C lowering.

2 Methods

2.1 Model Overview

The budget impact model estimated pharmacy (i.e. LMT) costs and total healthcare costs (i.e. costs of LMT and CV events) for a US health plan over a 3-year period. Two scenarios were evaluated with respect to the utilization of PCSK9i among patients with HeFH and ASVCD receiving statins and with uncontrolled LDL-C: (1) the reference case, in which PCSK9i was not an option for add-on LMT; and (2) the new case, with PCSK9i as an option for these patients, based on real-world data and modelling assumptions. The expected budget impact of PCSK9i was calculated as the difference in pharmacy and total healthcare

costs for the target population between these two scenarios (electronic supplementary Fig. 1).

For each scenario and each year of the 3-year projection period, total undiscounted annual LMT medication, dispensing and healthcare costs, including the costs of CV events, were estimated for all prevalent patients in the target population. The model was developed in Microsoft Excel 2007 (Microsoft Corporation, Redmond, WA, USA) and complied with recommendations of the Academy of Managed Care Pharmacy Format for Formulary Submissions [43] and the International Society for Pharmacoeconomics and Outcomes Research Principles of Good Practice for Budget Impact Analysis [42].

2.2 Target Population

The target population in the model included all adults ($\geq$ 18 years) with HeFH or clinical ASCVD who were treated with statins and had uncontrolled LDL-C, defined as LDL-C $>$ 70 mg/dL. Patients were stratified into two age groups: 18–64 and $\geq$ 65 years. Patients were then assigned to two mutually exclusive subgroups hierarchically ranked (highest first) by presumed CV risk [44] (electronic supplementary Tables 1a and b): (1) HeFH (with or without clinical ASCVD); or (2) clinical ASCVD (without HeFH). The clinical ASCVD subgroup included (a) acute coronary syndrome, (b) history of ischemic stroke, (c) history of myocardial infarction (MI), (d) history of other coronary heart disease, and (e) peripheral artery disease (Fig. 1).

The base-case estimates of the percentage of patients in each age and risk group, as well as the percentages of patients within each group with uncontrolled LDL-C, including those with uncontrolled LDL-C receiving statins (electronic supplementary Table 2), were estimated from real-world data derived from the Truven Health MarketScan® Research Databases of a large US commercial managed care database representing an employer-sponsored health plan population in 2013 (Truven Health Analytics, Ann Arbor, MI, USA; and data on file, Regeneron Pharmaceuticals, Inc., and Sanofi US). The prevalence of ASCVD, adjusted for age, sex and high CV risk conditions, was then extrapolated to the US population (electronic

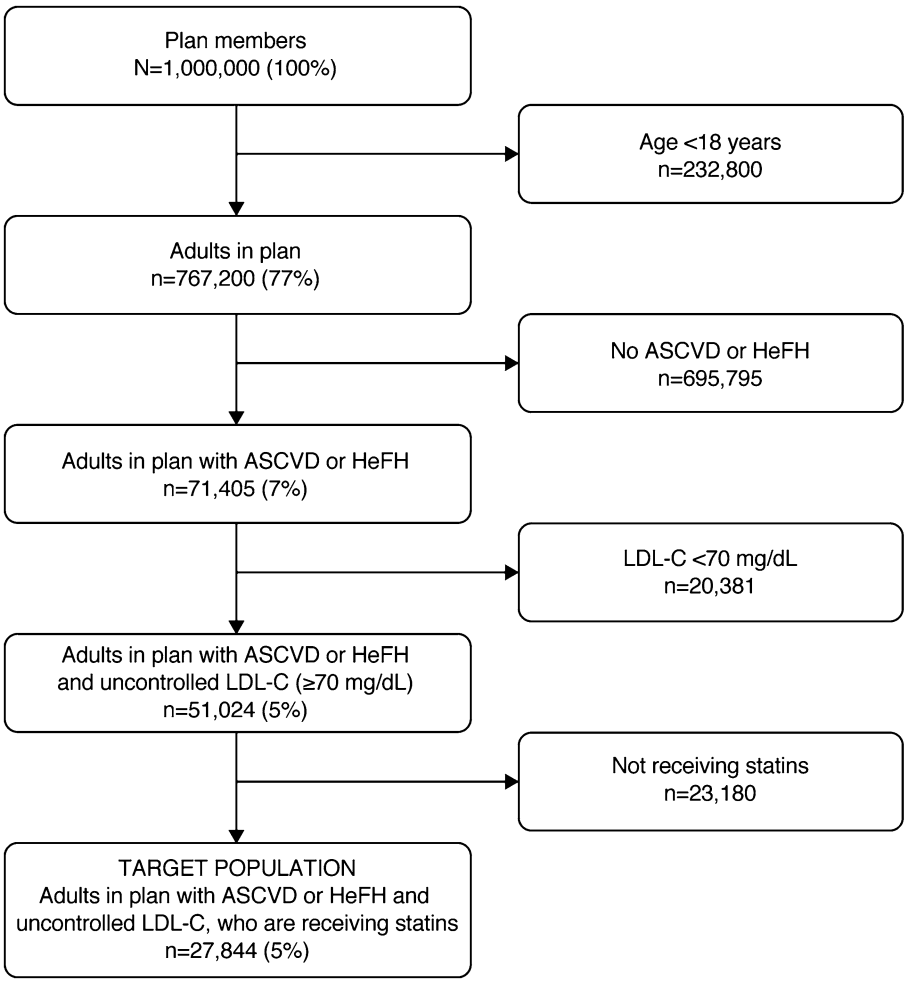

Fig. 1 Derivation of the target patient population. *ASCVD* atherosclerotic cardiovascular disease, *HeFH* heterozygous familial hypercholesterolemia, *LDL-C* low-density lipoprotein cholesterol

Table 1 Treatment mix in the reference scenario

Age group/treatment	Patients in the target population receiving each LMT in the reference scenario[a] by age and risk group					
	HeFH (%)	Clinical ASCVD				
		Recent ACS (%)	History of IS (%)	History of MI (%)	Other CHD (%)	PAD (%)
Age 18–64 years						
Statin monotherapy	88.9	86.0	89.2	80.9	81.3	86.2
Statin + ezetimibe	2.1	5.3	2.5	7.1	6.7	4.3
Statin + other LMT[b]	9.0	8.7	8.3	12.0	11.9	9.6
Total	100.0	100.0	100.0	100.0	100.0	100.0
Age ≥ 65 years						
Statin monotherapy	89.9	91.3	91.9	89.8	87.9	93.5
Statin + ezetimibe	3.9	2.9	3.3	4.3	4.6	2.2
Statin + other LMT[b]	6.3	5.8	4.8	5.9	7.5	4.3
Total	100.0	100.0	100.0	100.0	100.0	100.0

ACS acute coronary syndrome, *ASCVD* atherosclerotic cardiovascular disease, *CHD* coronary heart disease, *HeFH* heterozygous familial hypercholesterolemia, *IS* ischemic stroke, *LMT* lipid-modifying therapy, *MI* myocardial infarction, *PAD* peripheral artery disease, *PCSK9i* proprotein convertase subtilisin/kexin type 9 inhibitors

[a]In the reference scenario, patients receive therapy with a statin ± other LMT, excluding PCSK9i (i.e. 0% PCSK9i utilization)

[b]'Other' LMT includes niacin (nicotinic acid) and bile acid sequestrants (cholestyramine, colesevelam and colestipol)

supplementary Table 1b) [16, 45–47]. The proportion of these patients receiving LMT, and, of those receiving LMT, the proportion achieving LDL-C thresholds of < 100 and < 70 mg/dL [16, 45–47], was then estimated. The target patient population and growth trends in the hypothetical health plan assumed that the 1 million members followed the US Census Bureau general population age distribution and population growth rate (0.74%) [48].

2.3 Treatment Combination and Cost

Data on the combinations of LMTs received by the target population under the reference scenario were derived from the Truven MarketScan data and extrapolated to the US population as above (Table 1) (data on file, Regeneron Pharmaceuticals, Inc., and Sanofi US) [16, 45–49].

LMTs were classified into the following four categories: (1) statin monotherapy; (2) statin and ezetimibe; (3) statin and other LMT (including niacin and bile acid sequestrants); (4) statin and PCSK9i. The model did not consider any triple therapy in its calculation given the already low utilization rate of ezetimibe.

For PCSK9i, it was assumed that 3-year utilization would follow the same pattern as current ezetimibe use, although in a secondary analysis a higher rate was applied based on the uptake rates for statins after the first 5 years on the market [50, 51]. Therefore, the percentage of patients in the target population who would receive PCSK9i was assumed to increase linearly each year to maximum rates at year 3, while the use of statins and other

Table 2 Treatment utilization in the reference and new scenarios

Scenario	Statin and LMT utilization		
	Year 1	Year 2	Year 3
Reference scenario			
Receiving statin ± other LMT[a]	27,838	28,050	28,263
Receiving statin + PCSK9i	0	0	0
1–5% PCSK9i utilization			
Receiving statin ± other LMT[a,b]	27,727	27,825	27,923
Receiving statin + PCSK9i[c]	111	225	339
5–10% PCSK9i utilization			
Receiving statin ± other LMT[a,d]	27,351	27,068	26,779
Receiving statin + PCSK9i[e]	487	982	1484

HeFH heterozygous familial hypercholesterolemia, *LMT* lipid-modifying therapy, *PCSK9i* proprotein convertase subtilisin/kexin type 9 inhibitors

[a]'Other' LMT includes niacin (nicotinic acid) and bile acid sequestrants (cholestyramine, colesevelam and colestipol)

[b]Net of number receiving PCSK9i in the new scenario

[c]Based on percentage receiving PCSK9i: 1.67, 3.33 and 5.00% in HeFH risk group, and 0.33, 0.66 and 1.00% in all other risk groups in years 1, 2 and 3, respectively, of reference case statin ± other LMT users

[d]Net of number receiving PCSK9i in the secondary scenario

[e]Based on percentage receiving PCSK9i in the secondary scenario: 3.33, 6.67 and 10.00% in the HeFH risk group, and 1.67, 3.33 and 5.00% in all other risk groups in years 1, 2 and 3, respectively, of reference case statin ± other LMT users

Table 3 Annual cost of statin therapy with or without add-on LMT

Treatment	Average daily cost ($)	Compliance (%)	Annual cost ($)
Statin monotherapy	0.31	58	145.51
Statin + ezetimibe			
Fixed-dose combination[a]	2.78	58	667.91
Separate products			
Statin	0.44	58	172.54
Ezetimibe	1.90	58	481.62
Total			654.15
Average			660.62
Statin + other LMT[b]			
Fixed-dose combination[c]	6.47	58	1449.09
Separate products			
Statin	0.35	58	153.48
Other LMT[b]	3.40	58	799.17
Total			952.65
Average			987.40
Statin + PCSK9i			
Statin	0.44	78	232.03
PCSK9i	39.95	78	11,480.33
Total			11,712.36

LMT lipid-modifying therapy, *PCSK9i* proprotein convertase subtilisin/kexin type 9 inhibitors

[a]It was assumed that 47% of the utilization of a statin + ezetimibe was used as a fixed-dose combination (Truven MarketScan Database 2015; data on file)

[b]'Other' LMT includes niacin (nicotinic acid) and bile acid sequestrants (cholestyramine, colesevelam and colestipol)

[c]It was assumed that 7% of the utilization of a statin + other LMT was used as a fixed-dose combination (Truven MarketScan Database 2015; data on file)

LMT were proportionally reduced. In the base case, PCSK9i utilization started at 0.33% in year 1 and increased 0.33% each year, reaching a maximum of 1% for all risk groups, except HeFH, which started at 1.67% in year 1 and increased by 1.67% each year to a maximum of 5% (Table 2). The higher 5% utilization rate for HeFH was applied since treatments for this condition are limited and based on real-world uptake for alirocumab through September 2016 (data on file, Regeneron Pharmaceuticals, Inc., and Sanofi US). In the secondary analysis, the maximum PCSK9i utilization rate was increased to 5% for all risk groups, except HeFH, which reached 10% at year 3. Utilization rates across all risk groups were assumed to be equivalent between age groups.

The 2017 wholesale acquisition costs (WACs) were applied for alirocumab, evolocumab and all other LMTs (Truven Health Analytics, Ann Arbor, MI, USA) (Table 3). Alirocumab and evolocumab were both assumed to be self-administered as subcutaneous injection once every 2 weeks, with the cost of PCSK9i treatments based on their average ($558.58 per injection, $39.90 per day, or $14,563.50 per year), given that the present analysis evaluates the budgetary impact of the treatment class based on their equivalent efficacy [38]. The cost of dispensing for all drugs was estimated to be $10.50 per prescription, based on a study of the costs of dispensing drugs in community pharmacies in the US [52]. It was assumed that PCSK9i would be dispensed as a 1-month supply (two injections) every 4 weeks.

Because data on adherence with a combination of a statin and PCSK9i in a real-world setting are unavailable, estimates were based on median adherence to subcutaneous exenatide (78%) administered once every 7 days, which was the nearest analogue given its similar method of administration (subcutaneous injection) [53]. Adherence with other LMTs was assumed to equal 58%, as estimated in a retrospective claims-based study of statin utilization in high CV-risk patients [49]. The analyses assumed no discounts, rebates, co-payments, or co-insurances on the cost of medications. Estimates of total LMT costs for the reference case and for the scenario with PCSK9i, including its budget impact, were made in terms of per-patient per-month (PPPM) and per-member per-month (PMPM).

2.4 Costs of Cardiovascular Events

For the estimation of the total healthcare budget impact of introducing PCSK9i to a health plan, the model also considered the potential cost-offsets resulting from expected reductions in CV events associated with reductions in LDL-C. The estimated incremental mean percentage LDL-C reductions for PCSK9i + statin were 57.0% versus statin monotherapy [54], 36.10% versus statin + ezetimibe [54], and 36.10% versus statin + other LMT. Adherence to PCSK9i (78%) was also taken into account in the estimation of CV events.

CV events considered were MI, unstable angina, revascularization, ischemic stroke and CV death. As CV event data have only recently become available for evolocumab [55], with results for alirocumab expected in 2018, the annual CV event incidence was calculated using CV-risk functions derived from estimates of the relative risk reduction associated with lowering LDL-C. Relative risks were obtained from the Cholesterol Treatment Trialists' (CTT) Collaboration meta-analysis [11]; baseline risk estimates were derived from the Truven MarketScan Research Database in which patients were assigned to two mutually exclusive CV risk-based subgroups (Regeneron Pharmaceuticals, Inc., and Sanofi US) (electronic supplementary Table 1c) [44]. The CTT meta-analysis was based on statin trials and the data were assumed to be generalizable to other cholesterol-lowering therapies.

Costs of CV events were based on estimates from a study by O'Sullivan and colleagues [56] that used data from a variety of sources for event costs and costs in the first, second and third year after the event. Drug costs were based on WACs, and costs for CV events were based on administrative claims data from a large US health for enrolees aged ≥ 35 years making a claim for a CV event any time during 2003. Generalized linear models were fitted to develop cost prediction equations for selected CV events, including ischemic stroke, MI, unstable angina, revascularization procedures and CV-related death. Separate equations were used for patients with events and for their propensity score-matched controls. Acute costs were equal to the sum of event costs and first-year costs. Long-term costs were equal to the average of year 2 and year 3 costs. For patients in whom multiple events occurred simultaneously (e.g. hospitalization for MI in which revascularization took place), the event was included as a case for the procedure (e.g. revascularization) rather than the diagnosis (MI). Costs were adjusted to 2015 price levels using the Consumer Price Index (CPI) for medical care (Table 4). The per event, annual costs of CV events for the target population were assumed to be equivalent for risk and age groups, and for both scenarios.

Table 4 Acute and long-term cardiovascular event costs

Event	Acute costs ($)	Long-term costs ($)
Myocardial infarction	68,622	11,004
Unstable angina	32,147	6182
Revascularization	39,112	0
Ischemic stroke	22,627	1051
Cardiovascular death	17,620	0

Source: O'Sullivan et al. [56]

2.5 Sensitivity Analyses

Sensitivity analyses were conducted around PPPM total healthcare costs. Key parameters, including costs of CV events and percentages of plan members in different age and population groups, were varied between plausible ranges. The PCSK9i utilization rate and costs of alirocumab and evolocumab injections varied by $\pm 50\%$, while the percentage of plan members with uncontrolled LDL-C varied by $\pm 25\%$.

2.6 Payer Perspective Analysis

As a separate scenario, the budget impact of PCSK9i was calculated from the perspective of commercial and Medicare Advantage health plans. In these analyses, the age distribution of the population was set to match the age distribution of a typical health plan of each type, which was derived from data from the US Census Bureau and America's Health Insurance Plans [57–60].

3 Results

3.1 Target Population and Treatment Costs

For the hypothetical health plan of 1 million members, 62.6% were assumed to be between 18 and 64 years of age, and 14.1% were aged ≥ 65 years (23.3% were under 18 years of age). Depending on the age group, 0.1–0.2% of plan members were estimated to have HeFH, and 0.4–8.5% were estimated to have clinical ASCVD [16] (Table 1) [16]. All patients with HeFH were estimated to have uncontrolled LDL-C, and most (90.3–96.7%) received statin therapy. Similarly, most of the patients who had clinical ASCVD were estimated to have uncontrolled LDL-C (58.2–78.9%). Depending on the age and risk group, between 35.9 and 67.4% of these patients were estimated to have received a statin. The number of patients in the target population who would receive PCSK9i was projected to increase from 112 in year 1 to 340 in year 3 (Table 2), for a total of 676 person-years of treatment over years 1–3.

LMT costs for the reference scenario were estimated to increase from $6.66 million in year 1 to $6.76 million in year 3 due to population growth. With the introduction of PCSK9i, assuming 1–5% utilization in the base case, LMT costs in the target population were projected to be $7.94 million, $9.29 million and $10.66 million for years 1, 2 and 3, respectively (electronic supplementary Fig. 2a). This would result in a 3-year pharmacy budget increase of $7.76 million.

On the basis of PPPM (and PMPM), LMT costs were estimated to be $19.94 ($0.56) for each year of the reference scenario. With the introduction of PCSK9i, PPPM (PMPM) LMT costs were projected to increase to $23.78 ($0.66), $27.61 ($0.77) and $31.44 ($0.88) for years 1, 2 and 3, respectively (electronic supplementary Fig. 2b).

For the reference scenario, it was estimated that a total of 5667 CV events (1875, 1889 and 1903 for years 1, 2 and 3, respectively) would occur in the target population (i.e. adults in a plan with ASCVD or HeFH and uncontrolled LDL-C receiving statins). In the new scenario, the introduction of PCSK9i was projected to reduce the number of CV events by 10.2, to a total of 5656 events over 3 years. As a consequence of the CV events avoided with the introduction of PCSK9i, a cost offset of $0.46 million would be realized ($0.07, $0.15 and $0.24 million for years 1, 2 and 3, respectively) (electronic supplementary Fig. 2c).

By incorporating these cost offsets, the introduction of PCSK9i would yield a net total healthcare budget increase of $1.21 million, $2.43 million and $3.66 million for each of years 1, 2 and 3, respectively ($7.30 million over 3 years). On a PPPM (PMPM) basis, total healthcare costs would range from $1652 ($45.99), $1675 ($46.65) to $1699 ($47.30) for each of the years 1, 2 and 3, respectively, for the reference scenario, and from $1655 ($46.09), $1683 ($46.85) to $1709 ($47.60) for years 1, 2 and 3, respectively, after the introduction of PCSK9i (electronic supplementary Fig. 2d), resulting in a PPPM (PMPM) total healthcare budget impact of $7.23 ($0.20) for the 3-year period.

When PCSK9i utilization rates were increased to 5–10% over the 3 years, the number of patients receiving PCSK9i in the target population increased from 487 in year 1 to 1484 in year 3 (Table 2), for a total of 2953 person-years of treatment over the 3-year period. Compared with the reference scenario, 3-year LMT costs increased by $33.89 million (increments of $5.59 million in year 1 to $17.03 million in year 3) (electronic supplementary Fig. 2a). At higher utilization of PCSK9i, PPPM (PMPM) LMT costs were $36.68 ($1.02), $53.43 ($1.49) and $70.17 ($1.95) in years 1, 2 and 3, respectively (electronic supplementary Fig. 2b), resulting in a 3-year pharmacy budget impact of $33.56 ($0.93) and total healthcare budget impact of $31.56 ($0.88).

With the increased utilization of PCSK9i, compared with the reference scenario, a total of 45.5 fewer CV events for the new scenario were projected (decreasing by 7.5, 15.1 and 22.8 for years 1, 2 and 3, respectively) over 3 years. This would result in 3-year CV event-related cost savings of $2.02 million ($0.31, $0.66 and $1.05 million for years 1, 2 and 3, respectively) (electronic supplementary Fig. 2c). Total healthcare costs PPPM (PMPM) would range from $1668 ($46.43), $1707 ($47.52) to $1746 ($48.61) for years 1, 2 and 3, respectively (electronic supplementary Fig. 2d), resulting in a PPPM (PMPM) total healthcare budget impact of $31.56 ($0.88) for the 3-year period.

3.2 Sensitivity Analyses

Model results were most sensitive to model timeframe and years to maximum utilization of PCSK9i for ages 18–64 years (each varied from 1 to 5 years); low and high parameter values for these variables ranged from $3.62 to $8.62, and $9.32 to $5.53, respectively. Alirocumab and evolocumab injection costs, which varied from $280.00 to $840.00, and $279.29 to $837.87, respectively, produced PPPMs ranging from $5.70 to $8.75, and $5.70 to $8.74 (Fig. 2, electronic supplementary Table 3).

3.3 Payer Perspective

From the perspective of different healthcare payers (Table 5), assuming 1–5% utilization rates for PCSK9i, the projected number of eligible patients in the base case of 1 million members ranged from a 3-year total of 494 for a commercial health plan, to 1831 for a Medicare Advantage health plan. The incremental cost of LMT over the 3-year period was lower for a commercial health plan ($5.7 million higher than in the reference scenario) than for a typical Medicare Advantage health plan ($21.1 million higher than in the reference scenario). For a commercial health plan, 3-year PPPM (PMPM) total healthcare costs increased by $8.08 ($0.15) compared with the reference scenario, whereas for a Medicare Advantage health plan, PPPM (PMPM) total healthcare costs increased by $6.26 ($0.58). Similar trends were observed assuming 5–10% PCSK9i utilization rates (Table 5).

4 Discussion

This budget impact analysis demonstrated that, assuming the percentage of patients receiving PCSK9i would increase linearly over time to 1–5% of the eligible population in 3 years, adding PCSK9i to the formulary at the list price would result in incremental PPPM (PMPM) total healthcare costs of $3.62 ($0.10) in the first year, up to

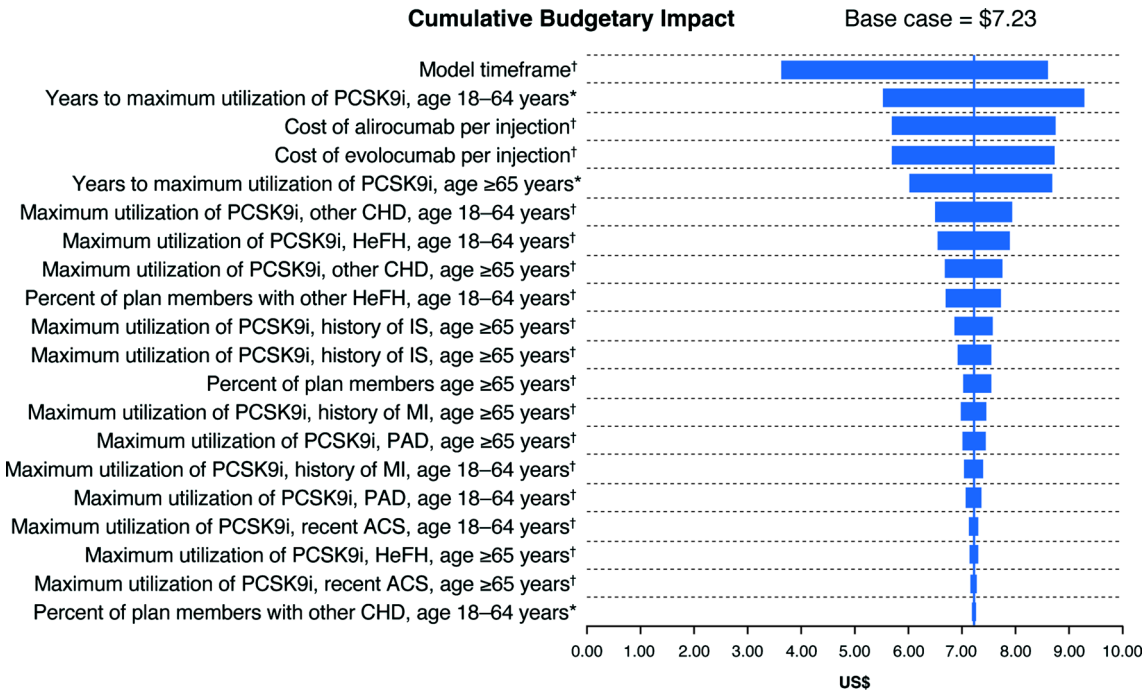

Fig. 2 Tornado diagram of sensitivity analysis (per-member per-month). *ACS* acute coronary syndrome, *ASCVD* atherosclerotic cardiovascular disease, *CHD* coronary heart disease, *HeFH* heterozygous familial hypercholesterolemia, *IS* ischemic stroke, *LDL-C* low-density lipoprotein cholesterol, *LMT* lipid-modifying therapy, *MI* myocardial infarction, *PAD* peripheral artery disease, *PCSK9i* proprotein convertase subtilisin/kexin type 9 inhibitors. †A parameter where the high value returned a larger budgetary impact. *A parameter where the low value returned a larger budgetary impact

Table 5 Payer perspective analysis

	Commercial	Medicare advantage
Assuming 1–5% PCSK9i utilization		
Total person-years of PCSK9i treatment at the end of 3 years	494	1831
Incremental costs of LMT[a], $ millions	5.65	21.05
Incremental costs of CV events avoided[a], $ millions	− 0.27	− 1.59
Incremental total costs[a], $ millions	5.39	19.46
PPPM total healthcare budget impact[a], $	8.08	6.26
PMPM total healthcare budget impact[a], $	0.15	0.58
Assuming 5–10% PCSK9i utilization		
Total person-years of PCSK9i treatment at the end of 3 years	2010	8777
Incremental costs of LMT[a], $ millions	23.01	100.89
Incremental costs of CV events avoided[a], $ millions	− 1.09	− 7.51
Incremental total costs[a], $ millions	21.94	93.38
PPPM total healthcare budget impact[a], $	32.88	30.06
PMPM total healthcare budget impact[a], $	0.60	2.57

LMT lipid-modifying therapy, *PPPM* per-patient per-month, *PMPM* per-member per-month, *PCSK9i* proprotein convertase subtilisin/kexin type 9 inhibitors

[a]New scenario with the introduction of PCSK9i versus reference scenario

$10.79 ($0.30) in the third year of the projection compared with the reference scenario without the availability of PCSK9i. However, the model did not include rebates or discounts that drug manufacturers may offer to payers. For example, the Medicaid Drug Rebate Program requires a drug manufacturer to have a national rebate agreement with the Secretary of the Department of Health and Human Services in exchange for state Medicaid coverage [61]. If the Medicaid rebate of at least 23.1% for innovator drugs was applied to PCSK9i for a health plan, the PPPM

(PMPM) total healthcare impact would be $2.74 ($0.08), $5.46 ($0.15) and $8.16 ($0.22) in years 1, 2 and 3, respectively, in the base case, and $11.98 ($0.33), $23.85 ($0.66) and $35.62 ($0.99) in years 1, 2 and 3, respectively, with 5–10% utilization.

In addition, the increase in PMPM LMT costs associated with the addition of PCSK9i compared with the reference scenario is substantially less than the PMPM costs reported for the most commonly used specialty therapy drugs. In year 3, the increased LMT cost with the addition of PCSK9i ($0.32 PMPM at a maximum utilization rate of 1–5% over 3 years) is lower than the year 1 PMPM cost (including discounts and rebates) for the top three specialty therapy drugs, which range from $2.80 for adalimumab to $1.78 for the ledipasvir and sofosbuvir combination [62]. With a maximum utilization rate of 5–10% over 3 years, the incremental LMT cost of adding PCSK9i ($0.93 PMPM) remains lower than the PMPM cost for other biologics such as adalimumab.

On a population level, our analysis estimated that the availability of PCSK9i will increase the cost of LMT therapy in a hypothetical plan of 1 million members by $7.76 million over 3 years, assuming a maximum utilization rate of 5% within 3 years. When adjusted to the US population, this reflects a cost increase of approximately $1.7 billion.

A comparison of our results with other recent economic evaluations of PCSK9i is warranted. Kazi et al. estimated the budget impact of alirocumab and evolocumab combined use in all eligible patients in the US, and obtained increased net healthcare costs of $120 billion over 5 years [63]. However, their estimate was likely to be driven by the substantially higher estimates of uptake of the anti-PCSK9 antibodies in the analysis compared with the estimates used in the analysis reported in this study. Their assumption that 61% of patients with familial hypercholesterolemia and 65% of patients with ASCVD would initiate therapy with the two currently available PCSK9i at 5 years (corresponding to an uptake of 37% and 39% after 3 years, respectively) appear to significantly exceed those reported for the current use of ezetimibe and other LMT (not including PCSK9i) [51], and for statins in the first 5 years on the market [50], whereas in the current analysis, it was presumed that PCSK9i would be utilized at a maximum rate of 1–5 or 5–10% in the third year of the projection.

Separately, a recent commentary by Schulman and colleagues projected that the addition of PCSK9i to the hyperlipidemia treatment armamentarium would increase costs across the insurance pool by $10.33 PMPM if 5% of adults aged 40–64 years who had elevated LDL-C levels were eligible for treatment with PCSK9i [64]. The time frame and analysis details are not specified in the commentary, making direct comparisons difficult. The increased cost after the addition of PCSK9i reported by Schulman et al. is greater than the estimates described in this study ($1.36 PMPM at 3 years, assuming a utilization rate of 5% after 3 years). This may in part be due to the pool of eligible patients considered in the commentary, which appears to be much more broadly defined and therefore larger than that used in the model described herein. The population utilized in the present analysis closely corresponds to the alirocumab and evolocumab product labelling (i.e. eligible patients had HeFH or clinical ASCVD and were receiving statin treatment and had uncontrolled LDL-C ($\geq$ 70 mg/dL)).

This study has several limitations. First, data on the actual utilization of PCSK9i were not available at the time this analysis was conducted and were therefore assumed to be either 1–5 or 5–10% of the target population, reflecting the historical uptake of ezetimibe and statins and the usage patterns of PCSK9i in the HeFH population. Furthermore, the alirocumab ODYSSEY OUTCOMES trial is still ongoing and the early results of the evolocumab FOURIER trial have only just become available [55]; these studies will indicate the effect of treatment with PCSK9i on long-term CV-related mortality and morbidity [65, 66]. Therefore, estimates of the potential savings associated with a potential reduction in CV morbidity and mortality resulting from the introduction of PCSK9i to the market were based on data on reductions in LDL-C with PCSK9i and information on the effect of changes in LDL-C on CV risk for statins. Analyses accounting for these potential benefits will be performed when the results and analyses of both these trials are available. The model also does not include the cost of treatment for adverse events, nor other related healthcare events that may be associated with the PCSK9i treatment. However, it appears unlikely that substantial costs related to adverse events will be incurred, given that pooled analysis of recently completed ODYSSEY and PROFICIO phase III programmes indicated that treatment-emergent adverse events were generally transient and similar between the alirocumab, evolocumab and control groups [67]. Additionally, the costs of CV events were based on resource use data published in 2011 (2007 values) [56]. Given that healthcare costs in the US increased by 3.6–4.0% yearly between 2010 and 2013 [68], it is possible that the costs may have been slightly underrepresented. However, comparisons of results based on costs in the MarketScan data were similar to those based on recently published WACs [50]. Finally, further extrapolation to non-commercial Medicare and Medicaid populations is warranted but would require additional data to account for factors that could predispose these cohorts to treatment, e.g. comorbid conditions and socioeconomic status, and other factors as likely predictors of PCSK9i use in these populations.

5 Conclusions

Assuming that the maximum utilization rate of PCSK9i among patients with clinical ASCVD or HeFH receiving statins and with uncontrolled LDL-C would be 1–5% after 3 years, the introduction of PCSK9i was estimated to increase total healthcare costs in a hypothetical US health plan by $3.62 PPPM ($0.10 PMPM) at year 1, to $10.79 PPPM ($0.30 PMPM) at year 3. If the manufacturers offer rebates and discounts to the list price, the budget impact would be lower than the results presented herein. The budget impact analysis of PCSK9i introduction will be updated when the mortality and morbidity data from both ongoing long-term outcomes trials and real-world data on alirocumab and evolocumab uptake are available.

Data Availability Statement The datasets generated and/or analysed during the current study are available upon reasonable request to the corresponding author.

Acknowledgements The authors would like to thank Sean Sullivan for contributing to the initial study concept and data analysis, and Emilie Duchesneau for her assistance conducting the analysis. Medical writing assistance and editorial support, under the direction of the authors, were respectively provided by Gauri Saal, MA Economics, and Elke Sims of Prime (Knutsford, UK), funded by Sanofi/Regeneron according to Good Publication Practice guidelines (http://annals.org/aim/article/2424869). The sponsor was involved in the study design, collection, analysis and interpretation of data, as well as data checking of information provided in the article. The authors had unrestricted access to study data, were responsible for all content and editorial decisions, and received no honoraria related to the development of this publication.

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