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Clinical Research

Lipid-lowering efficacy and safety of alirocumab in a real-life setting in France: Insights from the ODYSSEY APPRISE study☆

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HIGHLIGHTS

- Ancillary analysis of French patients enrolled in ODYSSEY APPRISE.
- Trial conducted to determine lipid-lowering efficacy and safety of alirocumab.
- Real-life setting: patients at high cardiovascular risk with hypercholesterolaemia.
- Statins and ezetimibe are the first and second-line therapies.
- These therapies are used even less in France than in other countries.
- Alirocumab was well tolerated, safe and highly effective at reducing LDL-C.
- This supports PCSK9 use to manage hypercholesterolaemia in high-risk CV patients.

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ABSTRACT

Background. – Recently, a multicentre, prospective, single-arm, phase 3b, open-label trial was conducted to determine the safety and efficacy of alirocumab, a proprotein convertase subtilisin/kexin type 9 inhibitor, in a real-life setting. This study enrolled patients at high cardiovascular risk, with heterozygous familial hypercholesterolaemia (HeFH) or non-familial hypercholesterolaemia (non-FH). Results showed that alirocumab was well tolerated and resulted in a clinically significant reduction in low-density lipoprotein cholesterol (LDL-C).
Aim. – This ancillary analysis aimed to describe the characteristics of the French patients enrolled in the study, the main results observed in this population according to their familial hypercholesterolaemia status, and adherence to treatment.
Methods. – French data were analysed separately from the original dataset of the study.
Results. – Among 215 French patients in the ODYSSEY APPRISE trial, 63.7% had non-FH, with a mean LDL-C concentration of 5.0 ± 1.8 mmol/L at baseline. The mean duration of alirocumab exposure was 72.4 ± 42.5 weeks, with only 48.4% of patients receiving statins concomitantly. At week 12, a mean reduction in LDL-C

Abbreviations: CAD, coronary artery disease
CVD, cardiovascular disease
HeFH, heterozygous familial hypercholesterolaemia
LDL-C, low-density lipoprotein cholesterol
LLT, lipid-lowering therapy
mITT, modified intention-to-treat
non-FH, non-familial hypercholesterolaemia
PCSK9, proprotein convertase subtilisin/kexin type 9
TEAE, treatment-emergent adverse event.

☆ Tweet: An ancillary analysis of the ODYSSEY-APPRISE survey conducted in French patients has shown that alirocumab was well tolerated, safe and highly effective at reducing LDL-C. These findings support the use of alirocumab in patients at high cardiovascular risk.

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of 56.5 ± 17.8% was observed: 51.2 ± 22.8% in HeFH; 59.5 ± 13.2% in non-FH. This improvement in LDL-C started from week 4 and remained stable and sustained until week 120 in both populations. The overall incidence of severe treatment-emergent adverse events (TEAEs) was 33.5%. The most frequent TEAEs were myalgia (15.8%) and asthenia (15.3%). No tolerance or efficacy differences were observed between patients with or without established coronary artery disease or other cardiovascular disease, whatever the age of these events or considering the concomitant use of other lipid-lowering therapies.
Conclusions. – In the French setting, alirocumab was well tolerated, safe and highly effective at reducing LDL-C. These findings support the use of alirocumab to manage hypercholesterolaemia in patients at high cardiovascular risk.

1. Background

Hypercholesterolaemia is a major risk factor for the development of atherosclerosis and coronary artery disease (CAD) [1,2]. Total low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol concentrations predict subsequent mortality, especially in people with pre-existing cardiovascular disease (CVD) [3]. In particular, an individual's risk of atherosclerotic disease is strongly determined by their cumulative lifelong exposure to LDL-C [4].

Some patients have heterozygous familial hypercholesterolaemia (HeFH), characterized by very high plasma concentrations of LDL-C, which is the primary vehicle for cholesterol transport in the circulation. However, the most common cause of elevated LDL-C is polygenic hypercholesterolaemia, which results from an interaction of unidentified genetic factors, compounded by a sedentary lifestyle and an increased intake of saturated and trans fatty acids [5].

To prevent atherosclerosis and its sequelae (myocardial infarction, ischaemic stroke and peripheral artery disease), current guidelines have set LDL-C goals according to cardiovascular risk. The management of hypercholesterolaemia involves the modification of behavioural factors and the use of lipid-lowering therapies (LLTs). Currently used drugs that reduce circulating concentrations of LDL-C include statins (which inhibit 3-hydroxy-3-methylglutaryl coenzyme A [HMG-CoA] reductase), ezetimibe (which inhibits Niemann-Pick C1-Like 1 [NPC_1L_1], a polytopic transmembrane protein involved in cholesterol absorption) and antiproprotein convertase subtilisin/kexin type 9 (PCSK9) monoclonal antibodies (which inhibit PCSK9, a liver-secreted protein that binds to the low-density lipoprotein receptor on hepatocytes and promotes their routing into lysosomes for proteolytic degradation) [6].

Because of their efficacy, safety and low cost, guidelines state that statins remain the main component of preventive strategies for atherosclerotic cardiovascular disease [7,8], but they are not necessarily adequate therapy for patients with elevated lipoprotein(a) and for patients with very high concentrations of LDL-C, such as those with HeFH [9]. Further, some patients are intolerant of statins, and might benefit from alternatives and/or combination therapies, such as ezetimibe and PCSK9 inhibitors (i.e. anti-PCSK9 human monoclonal antibodies). The Task Force for the Management of Dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS) [10] recommends considering the addition of a PCSK9 inhibitor for patients at very high cardiovascular risk who are not achieving their LDL-C goal (LDL-C ≥ 1.8 mmol/L [≥ 70 mg/dL]) while receiving statins and ezetimibe. Similarly, for adults with HeFH and LDL-C ≥ 2.6 mmol/L (≥ 100 mg/dL) while receiving statins and ezetimibe, the addition of a PCSK9 inhibitor is recommended. However, therapeutic indications may vary across countries for ezetimibe and PCSK9 inhibitors. In France, ezetimibe has received a favourable opinion for reimbursement in the treatment of HeFH and in the prevention of cardiovascular events in patients with CAD with a recent history of acute coronary syndrome, whose cholesterol levels are not controlled despite ongoing treatment with a statin at the maximum tolerated dose. Reimbursement of PCSK9 inhibitors was recently limited to adults with homozygous or heterozygous familial hypercholesterolaemia, at very high cardiovascular risk, insufficiently controlled by treatment combining a statin at the maximum tolerated dose and ezetimibe or cholestyramine, requiring low-density lipoprotein apheresis therapy in combination with these treatments, or in adult patients with established CAD (secondary prevention) with inadequately controlled hypercholesterolaemia (LDL-C ≥ 1.8 mmol/L [≥ 70 mg/dL]), despite ongoing treatment with a statin at the maximum tolerated dose and ezetimibe, again, in combination with this dual therapy [11,12].

Very few French data are available on the prevalence and management of hypercholesterolaemia at the population level. Prevalence of hypercholesterolaemia in France was estimated at 23.3% (27.8% in men, 19.0% in women) in a recent observational study, which also demonstrated that lipid-lowering prescriptions diverged greatly from current recommendations, with less than one-third of eligible patients being treated [13]. Prevalence of HeFH was assessed as 1 in 120 in a sample of French patients aged 35–74 years from three regions, using the Dutch Lipid Clinic Network Score, without genetic testing [14]. More recently, in two large international meta-analyses, the overall prevalence of FH was consistently found to be 1 in 310 [15,16].

It was therefore interesting to examine the data related to the French patients enrolled in the recently published ODYSSEY-APPRISE study from 2015 to 2019 [17]. This study was a single-arm, phase 3b, open-label study designed to obtain safety and efficacy data on alirocumab in a real-life setting among patients at high cardiovascular risk, with severe hypercholesterolaemia not adequately controlled by the maximum tolerated dose of statin, with or without other LLTs. The aim of this study was to describe the characteristics of the French patients, the main results observed in this population (according to their FH status) and adherence to treatment.

2. Methods

The methodology of the ODYSSEY APPRISE study was fully described in the main paper by Gaudet et al., presenting the overall study results [17].

In summary, this multicentre European/Canadian trial enrolled patients with a high cardiovascular risk and access to alirocumab in 16 countries. Patients were eligible for study participation if they were aged ≥ 18 years, with HeFH or with established CAD or a CAD risk equivalent, and with hypercholesterolaemia not adequately controlled with the maximum tolerated dose of statin, with or without other LLTs, distinguishing patients according to their cardiovascular risk: patients with HeFH with LDL-C ≥ 4.1 mmol/L (160 mg/dL), despite treatment; patients with HeFH with LDL-

C ≥ 3.4 mmol/L (130 mg/dL), despite treatment, and at least two cardiovascular risk factors; patients with HeFH with LDL-C ≥ 3.4 mmol/L (130 mg/dL), despite treatment, and established CAD or other CVD, diabetes or a family history of CAD; patients with non-familial hypercholesterolaemia (non-FH), with established CAD or other CVD, and with LDL-C ≥ 3.4 mmol/L (130 mg/dL); and patients with progressive CVD (CAD or peripheral artery occlusive disease or cerebrovascular disease, documented clinically or by imaging techniques, with a subsequent cardiovascular event, despite treatment) and LDL-C ≥ 2.6 mmol/L (100 mg/dL).

The first patient was enrolled on 23rd June 2015 and the last patient completed the study on 12 April 2019. Following a screening period of up to 3 weeks, patients received subcutaneous alirocumab 75 mg or 150 mg every 2 weeks. The starting dose was chosen by the investigator. The open-label treatment period with alirocumab lasted for a minimum of 12 weeks and a maximum of 30 months and featured an end-of-study visit at least 2 weeks after the last study treatment injection. During the study, the dose could be adjusted from 75 mg every 2 weeks to 150 mg every 2 weeks, or vice versa, at the investigator's discretion, based on treatment response. Alirocumab was administered on top of background stable maximum tolerated dose of statin, with or without other LLTs.

The primary endpoint of the study was to assess safety variables throughout the study, including adverse events of special interest. The main secondary efficacy endpoint was the percentage change in calculated LDL-C concentration from baseline to week 12. Key secondary efficacy endpoints assessed at week 12 included the proportion of patients achieving a calculated LDL-C concentration < 2.6 mmol/L (100 mg/dL), < 1.8 mmol/L (70 mg/dL) or < 1.8 mmol/L (70 mg/dL) and/or ≥ 50% reduction from baseline (if LDL-C ≥ 1.8 mmol/L [70 mg/dL]).

The safety population included patients who received at least one dose or a partial dose of alirocumab. The efficacy analysis was performed on the modified intention-to-treat (mITT) population, which included all patients who received at least one dose or a partial dose of alirocumab, had baseline LDL-C data available and had at least one LDL-C measurement within the analysis window associated with week 12. Adherence to treatment was defined as: (injections received/theoretical injections) × 100.

All analyses were descriptive and were conducted under the responsibility of the promotor of the study (Sanofi) by the Biostatistics Department of this company. French Data were analysed separately from the original dataset of the study, and overall data presented as reference were taken from the paper by Gaudet et al. [17]. Consequently, no statistical tests were used to compare the French results with the overall population (including France). Data sharing is not applicable to this article as no new data were created or analysed in this study. The data that support the findings of this study are available from the promotor, upon reasonable request.

3. Results

Among the 994 patients enrolled in the full ODYSSEY-APPRISE study, 217 were enrolled by the 49 French centres, corresponding to 215 individuals in the safety population and 194 in the mITT population.

3.1. Patient characteristics

The baseline characteristics of the French patients are presented in Table 1. Interestingly, the proportion of HeFH among French patients was much lower than that observed in the global population of the ODYSSEY APPRISE study. Among French patients, only 36.3% had HeFH versus 64.0% in the global study results. French patients were also treated less frequently with other LLTs versus PCSK9 inhibitors (statins and/or ezetimibe) compared with the global study.

Table 1
Patients' baseline characteristics.

Safety population	French patients	Overall ODYSSEY APPRISE population
	(*n* = 215)	(*n* = 994)
Age (years)	59.5 ± 11.4	56.6 ± 11.7
Male sex	149 (69.3)	625 (62.9)
Race		
White/Caucasian	208 (96.7)	969 (97.5)
Black	4 (1.9)	10 (1.0)
Asian/Oriental	2 (0.9)	6 (0.6)
Multiracial	0 (0.0)	1 (0.1)
Other	1 (0.5)	8 (0.8)
Body mass index (kg/m^2)	27.4 ± 4.3	28.0 ± 4.9
HbA1c (%)	5.9 ± 1.0	5.4 ± 1.2
Medical history of CAD or other CVD	174 (80.9)	631 (63.5)
Any cardiovascular risk factors	158 (73.5)	755 (76.0)
Type of hypercholesterolaemia		
HeFH	78 (36.3)	636 (64.0)
Non-FH	137 (63.7)	358 (36.0)
Lipids (mmol/L)		
Total cholesterol	7.1 ± 1.9	6.8 ± 1.6
LDL-C	5.0 ± 1.8	4.7 ± 1.6
HDL-C	1.2 ± 0.4	1.3 ± 0.4
Non-HDL-C	5.8 ± 2.1	5.4 ± 1.7
Triglycerides	1.5 (1.2: 2.3)	1.5 (1.1: 2.1)
Previous medication: LLTs		
Statins	105 (48.8)	758 (76.3)
Ezetimibe	98 (45.6)	589 (59.3)

CAD: coronary artery disease; CVD: cardiovascular disease; HbA1c: glycated haemoglobin; HDL-C: high-density lipoprotein cholesterol; HeFH: heterozygous familial hypercholesterolaemia; LDL-C: low-density lipoprotein cholesterol; LLT: lipid-lowering therapy; Non-FH: non-familial hypercholesterolaemia. Data are expressed as mean ± standard deviation, number (%) or median (Q1: Q3).

Overall, 64.2% of the French patients started with an initial dose of 75 mg of alirocumab every 2 weeks versus 69.1% in the global study. The mean duration of alirocumab exposure was 72.4 ± 42.5 weeks. At week 12, the alirocumab dose was adjusted from 75 mg every 2 weeks to 150 mg every 2 weeks in 29.0% (*n* = 40) of these patients.

During the study, 151/215 (70.2%) French patients were receiving concomitant LLTs (Table 2), compared with 873/994 (87.8%) of the overall population. Patients with HeFH were more likely than non-FH patients to be concomitantly taking any form of LLT (87.2% vs. 60.6%), statins (74.4% vs. 33.6%) or ezetimibe (70.5% vs. 35.8%). Concomitant use of statins (especially high-intensity statins) was therefore much lower in both HeFH and non-FH French patients than in the global study.

3.2. Efficacy

In the mITT population (*n* = 192), a mean 56.5 ± 17.8% decrease in LDL-C concentration from baseline was observed in French patients at week 12: 51.2 ± 22.8% in HeFH; 59.5 ± 13.2% in non-FH. This decrease was observed from week 4, and remained stable and sustained until week 120 in both HeFH and non-FH patients (Fig. 1). Overall, 141 patients (73.4%) (66.6% to 79.5%) reached the target defined by LDL-C < 70 mg/dL and/or ≥ 50% reduction from baseline in LDL-C at week 12: respectively, 42 (59.2%) (46.8% to 70.7%) in HeFH patients, and 99 (81.8%) (73.8% to 88.2%) in non-FH patients (Table 3).

A subgroup analysis was conducted among French patients with established CAD or other CVD (*n* = 154) or without any established CAD or other CVD (*n* = 38) (Fig. 2). A 58.5 ± 15.6% decrease in LDL-C concentration from baseline value was observed at week 12 in patients with established CVD versus a 48.2 ± 23.1% decrease in

Table 2
Concomitant medications: lipid-modifying therapies.

	French patients (n = 215)			Overall ODYSSEY APPRISE population (n = 994)		
	HeFH	Non-FH	Overall	HeFH	Non-FH	Overall
	(n = 78)	(n = 137)	(n = 215)	(n = 636)	(n = 358)	(n = 994)
PCSK9 inhibitors only	10 (12.8)	54 (39.4)	64 (29.8)	40 (6.3)	81 (22.6)	121 (12.2)
Any LLT (other than PCSK9)	68 (87.2)	83 (60.6)	151 (70.2)	596 (93.7)	277 (77.4)	873 (87.8)
Statins	58 (74.4)	46 (33.6)	104 (48.4)	555 (87.3)	203 (56.7)	758 (76.3)
Low intensity	28 (30.8)	17 (12.4)	43 (20.0)	119 (18.7)	59 (16.5)	178 (17.9)
High intensity[a]	30 (38.5)	31 (22.6)	61 (28.4)	436 (68.6)	144 (40.2)	580 (58.4)
Ezetimibe	55 (70.5)	49 (35.8)	104 (48.4)	441 (69.3)	148 (41.3)	589 (59.3)
LLT other than statins or ezetimibe (fibrates, omega-3)	6 (7.7)	13 (9.5)	19 (8.8)	33 (5.2)	35 (9.8)	68 (6.8)

HeFH: heterozygous familial hypercholesterolaemia; LLT: lipid-lowering therapy; Non-FH: non-familial hypercholesterolaemia; PCSK9: proprotein convertase subtilisin/kexin type 9. Data are expressed as number (%).

[a] Atorvastatin (40 or 80 mg), rosuvastatin (20 or 40 mg) or simvastatin (80 mg) daily.

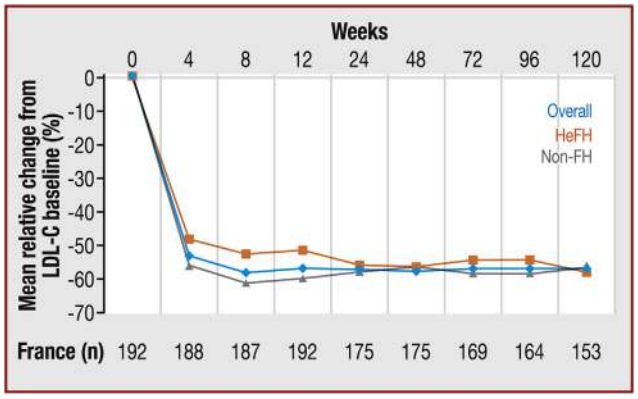


Fig. 1. Mean relative change in low-density lipoprotein cholesterol (LDL-C) from baseline in French patients. HeFH: heterozygous familial hypercholesterolaemia; non-FH: non-familial hypercholesterolaemia.

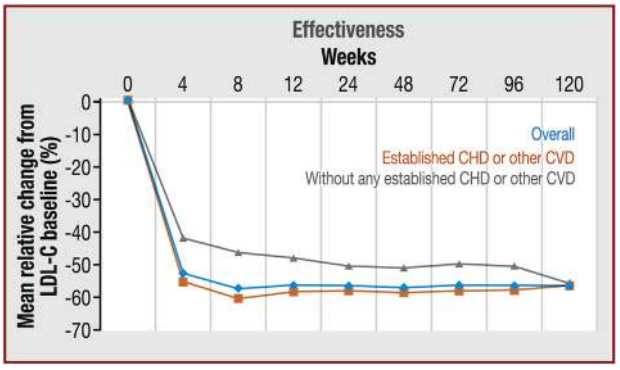


Fig. 2. Mean relative change in low-density lipoprotein cholesterol (LDL-C) from baseline in French patients according to their cardiovascular disease (CVD) history. CAD: coronary artery disease.

patients without any CVD, but similar relative changes were observed at week 24 and week 120, suggesting that the difference was only related to the low number of patients without any CVD.

Among the French patients with established CAD or other CVD (n = 154) in the mITT population, the time of the last established CAD or other CVD was ≤ 12 months in 38 patients (24.7%) and > 12 months in 116 patients (75.3%). Relative change in LDL-C concentration from baseline at week 12 was a reduction of 61.1 ± 11.9% and 57.7 ± 16.6%, respectively, with no significant difference between these two populations.

Table 3
Efficacy, adherence and treatment-emergent adverse events in French patients.

	French patients	Overall ODYSSEY APPRISE population [17,18]
mITT population	192 (100)	921 (100)
Patients achieving LDL-C goals at week 12		
LDL-C < 100 mg/dL	141 (73.4)	687 (74.6)
LDL-C < 70 mg/dL	99 (51.6)	462 (50.2)
LDL-C < 70 mg/dL and/or ≥ 50% reduction from baseline	141 (73.4)	636 (69.1)
Adherence ≥ 100%	84 (43.7)	593 (64.4)
Safety population	215 (100)	994 (100)
Any TEAE	208 (96.7)	712 (71.6)
Severe TEAE	72 (33.5)	161 (16.2)
TEAE leading to death	1 (0.5)	2 (0.2)
Most frequent TEAEs		
Occurring in ≥ 10% of patients		
Myalgia	34 (15.8)	
Asthenia	33 (15.3)	
Injection site haematoma	32 (14.9)	
Headache	28 (13.0)	
Muscle spasms	26 (12.1)	
Bronchitis	22 (10.2)	
Occurring in ≥ 5% of patients		
Nasopharyngitis		78 (7.8)
Myalgia		71 (7.1)
Headache		62 (6.2)
Influenza		53 (5.3)

LDL-C: low-density lipoprotein cholesterol; mITT: modified intention-to-treat; TEAE: treatment-emergent adverse event. Data are expressed as number (%).

Results were also similar according to concomitant statin use. Among patients with a high-intensity statin, 39/54 (72.2%) (58.4% to 83.5%) reached the target defined by LDL-C < 70 mg/dL and/or ≥ 50% reduction from baseline in LDL-C at week 12, and 30/40 (75.0%) (58.8% to 87.3%) and 72/98 (73.5%) (63.6% to 81.9%), respectively, among patients receiving a concomitant low/moderate-intensity statin or no statin. At week 48, results were 68.5%, 65% and 64.3% in these three groups of patients, respectively.

3.3. Tolerance

On raw data, the incidence of treatment-emergent adverse events (TEAEs) was higher in French patients compared with the overall population, for any TEAEs and severe TEAEs. The most frequent TEAEs were also different from the global results, with

twice the frequency of myalgia and headache in France than in the global analysis, and significant frequency of asthenia and injection site haematomas (Table 3).

Among the 215 treated patients, 85.1% completed the treatment period, and 14.9% of patients did not complete the study treatment period; the most common reason cited for discontinuation was adverse event, in 16 patients (7.4%).

Finally, the incidence of TEAEs was not different according to background statin therapy: $n = 60$ (98.4%) in patients treated with a high-intensity statin; $n = 41$ (93.2%) in patients receiving a low/moderate-intensity statin; and $n = 107$ (97.3%) in patients not treated with a statin. For severe TEAEs, the incidences were $n = 20$ (32.8%), $n = 9$ (20.5%) and $n = 43$ (39.1%), respectively.

3.4. Adherence

In the French mITT population, 43.7% patients were ≥ 100% adherent to alirocumab (e.g. possibly as a result of receiving an alirocumab dose earlier than the 14-day dosing window) compared with 64% in the overall study [18]. At week 12, the percentage of patients who achieved the objective of LDL-C concentration < 70 mg/dL and/or ≥ 50% reduction from baseline was 75.0% ($n = 63$) (64.4% to 83.8%) in patients ≥ 100% adherent versus 72.2% ($n = 78$) (62.8% to 80.4%) in patients < 100% adherent, showing no statistical difference. Unlike the global analysis, more patients achieved LDL-C < 70 mg/dL and/or ≥ 50% reduction from baseline in the ≥ 100% adherent subgroup versus the < 100% adherent subgroup. However, a similar tendency was observed at week 48 across the French subgroups defined by their adherence, with 63.0% (53.1% to 72.1%) of < 100% adherent patients versus 69.0% (58.0% to 78.7%) of ≥ 100% adherent patients achieving the LDL-C objective.

4. Discussion

Overall, the characteristics of the French patients were rather different from those of the global ODYSSEY APPRISE trial, with an almost inverse proportion of patients with HeFH and non-FH. In France, alirocumab was first reimbursed only in combination with optimized LLT in adult patients with HeFH who were inadequately controlled and required low-density lipoprotein apheresis therapy (from March 2017). Furthermore, from 2013 onwards, there was extensive media coverage and multiple public discussions and debates about the efficacy and safety of statins [19]. A study conducted in 2015 showed that lipid-lowering prescriptions diverged greatly in France from recommendations, with less than a third of eligible patients being treated [13].

In this context, participation in the ODYSSEY APPRISE trial was an opportunity for non-FH patients with high LDL-C concentration not treated with a maximal dose of statins to get access to alirocumab treatment, and to offer a preventive treatment to patients with a major risk factor for CVD. It was not surprising to observe a much lower use of statins (specifically high-intensity statins) in the French patients enrolled in the ODYSSEY APPRISE trial compared with the global population of this trial, and in both HeFH and non-FH patients, which could not be attributed to a higher rate of patients presenting a statin intolerance in France [20] compared with other countries [21].

Following the global results of the ODYSSEY APPRISE trial, the indication was then extended in France to “established atherosclerotic CVD”, in monotherapy or in combination with other LLTs in patients who are intolerant to statins or in whom statins are contraindicated, or with established atherosclerotic CVD other than a history of recent acute coronary syndrome, or not receiving optimized treatment with at least one statin at the maximum tolerated dose. Finally, this reimbursement was strictly regulated with a previous authorization scheme for prescriptions limiting the use of PCSK9 monoclonal antibodies in patients with HeFH or in adult patients with CAD (secondary prevention) with inadequately controlled hypercholesterolaemia (LDL-C ≥ 0.7 g/L), despite ongoing treatment with a statin at the maximum tolerated dose and ezetimibe, again, in combination with this dual therapy.

Limitations of this analysis include the relatively small size of the sample considered, and limits resulting from the ODYSSEY APPRISE trial itself: the lack of a comparative control; and biases resulting from the open-label design. Another limitation was the consequence of the fact that we had no clear data on adherence to concomitant LLTs during the observation period.

The main efficacy endpoint was fully in line with the global ODYSSEY APPRISE trial results. A significant $-56.5 \pm 17.8\%$ decrease in LDL-C concentration from baseline was observed in French patients at week 12 versus −54.8% in the global trial. In addition, as with the global results, the mean reduction in LDL-C from baseline was rather similar in the HeFH and non-FH groups: $-51.2 \pm 22.8\%$ in HeFH patients and $-59.5 \pm 13.2\%$ in non-FH patients versus −53.4% and −57.6%, respectively, in the global results.

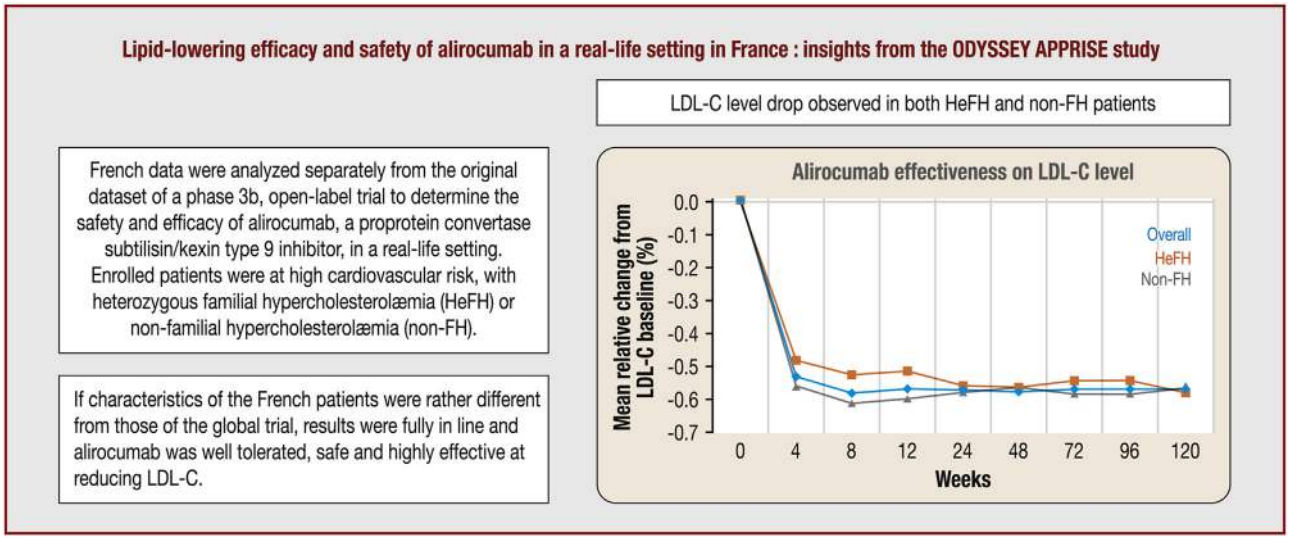
This improvement in LDL-C results was observed from week 4 and remained stable and sustained until week 120 in both HeFH and non-FH patients. Finally, the percentage of French patients reaching the target defined by LDL-C < 70 mg/dL and/or ≥ 50% reduction from baseline in LDL-C at week 12 was 59.2% in HeFH patients and 81.8% in non-FH patients versus 64.7% and 77.4%, respectively, in the global trial results.

The ODYSSEY APPRISE French data do not support any tolerance or efficacy differences between patients with or without established CAD or other CVD, or according to the age of these events. Furthermore, global results do not show differences in efficacy response according to the use of concomitant LLTs, with a relative change from baseline to week 12 in the mean calculated LDL-C concentration (mmol/L), with a $56.5 \pm 19.1\%$ reduction in patients with continuous statins and either ezetimibe or fenofibrate uptake, $50.3\% \pm 22.5\%$ in patients without statins and without ezetimibe or fenofibrate and $57.0 \pm 16.5\%$ in patients without statins but with either ezetimibe or fenofibrate. These results are important in France, where the percentage of patients not benefiting from statins because of intolerance or other reasons is high.

Finally, some TEAEs were identified much more frequently in France than in other countries (asthenia or injection site haematomas), with no clear explanation for this phenomenon and, notably, without difference regarding background statin therapy, as one could hypothesize poorer tolerability of LLTs in patients with statin intolerance. It remains possible that sociocultural aspects (diffuse suspicion with regard to LLTs in the French population, supported by widespread media coverage) may have had an impact on the safety results.

5. Conclusions

As indicated in the consensus statement from the European Atherosclerosis Society Consensus Panel, consistent evidence from numerous and multiple different types of clinical and genetic studies unequivocally establishes that LDL-C causes atherosclerotic CVD. Statins and ezetimibe are the first and second-line therapies, but are used even less frequently in France than in other countries. However, the use of PCSK9 inhibitors, with or without concomitant LLTs, may offer an opportunity for patients at high cardiovascular risk, with severe hypercholesterolaemia not controlled under these treatments or with statin intolerance, whatever the time of their last established CAD or other CVD (Central Illustration).



Central Illustration: Lipid-lowering efficacy and safety of alirocumab in a real-life setting in France: insights from the ODYSSEY-APPRISE study.

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Disclosure of interest

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