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ORIGINAL RESEARCH ARTICLE

Lipid-Lowering Efficiency and Safety of Alirocumab 300 mg Using a 2-mL Autoinjector Device in Real-World Practice: The MARS Study

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Abstract

Background Alirocumab is a fully human monoclonal antibody to proprotein convertase subtilisin kexin type 9 used for the reduction of low-density lipoprotein cholesterol (LDL-C) in high-risk patients not reaching their LDL-C target. Recently, a 2-mL prefilled autoinjector has been developed to support the monthly 300-mg dosing regimen with a single-injection administration.

Methods and Objectives Monthly application of 300 mg AlirRocumab (Praluent®) using the 2-mL SYDNEY Device (MARS) is a non-interventional, open, prospective, multi-center cohort study conducted in Germany between 2021 and 2023 with an observational period of 12 weeks. Patients included had primary hypercholesterolemia (heterozygous familial or non-familial) or mixed dyslipidemia and confirmed vascular disease and other risk factors or confirmed familial heterozygous hypercholesterolemia. Primary objectives were to assess the effectiveness of the 2-mL SYDNEY autoinjector measured by the lipid-lowering effect of alirocumab and to document therapy satisfaction, patient adherence, and persistence. Secondary objectives were to assess safety (adverse events) and tolerability.

Results A total of 146 patients were analyzed: 110 (75.3%) patients were proprotein convertase subtilisin kexin type 9 inhibitor naïve and 36 (24.7%) were pre-treated with a proprotein convertase subtilisin kexin type 9 inhibitor. Patient mean age was 65.6 years with a preponderance of male gender (59.6%). At 12 weeks, the LDL-C value had decreased by a median of 59.5 mg/dL (1.5 mmol/L) in naïve patients (median relative decrease: − 52.0%). In the pre-treated group, the LDL-C value remained mainly unchanged (median slight numerical relative increase: 1.6%). Treatment satisfaction was rated similarly in both groups with most patients being satisfied/very satisfied and rating the injection as effective, safe, and easy to handle. Twenty-three adverse events in 13 patients (8.0%) were documented. Three patients experienced one serious adverse event each; for five patients, an adverse drug reaction was observed, although none was serious. The occurrence of adverse events was similar in both groups.

Conclusions Alirocumab 300 mg administered with the 2-mL SYDNEY autoinjector was safe and effective in lowering LDL-C after 12 weeks in a routine clinical setting in Germany. The treatment schedule was perceived to be beneficial with excellent device acceptance and satisfaction, potentially increasing patient adherence.

Clinical Trial Registration Clinicaltrials.gov: NCT05129241.

Key Points

This study demonstrated the effectiveness and safety of alirocumab 300 mg using the 2-mL SYDNEY autoinjector in a real-world setting in Germany.

The 2-mL SYDNEY device provides patients with a convenient option of injecting the alirocumab 300-mg dose as a single injection with good safety.

Patients were highly satisfied with the new autoinjector device, reporting it as effective and user friendly.

1 Introduction

The causal role of low-density lipoprotein cholesterol (LDL-C) in the development of atherosclerosis is well established and patients with elevated LDL-C levels remain at high risk for cardiovascular disease [1]. Current guidelines for the management of dyslipidemia from The European Society

Extended author information available on the last page of the article

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of Cardiology/European Atherosclerosis Society Task Force emphasize the importance of assessing the overall cardiovascular risk. Specific target values for LDL-C for each cardiovascular risk level have been proposed [2]. In patients at very high risk, a therapeutic regimen should aim for a LDL-C reduction of ≥ 50% from the baseline value and an LDL-C target value of < 55 mg/dL (1.4 mmol/L). For patients with atherosclerosis who experience a second vascular event within 2 years taking a maximally tolerated statin-based therapy, an LDL-C goal of < 40 mg/dL (< 1.0 mmol/L) may be considered. In patients at high risk, an LDL-C reduction of ≥ 50% from baseline and an LDL-C target value of < 70 mg/dL (1.8 mmol/L) are suggested. Finally, in patients at moderate or low risk, the LDL-C target values are < 100 mg/dL (2.6 mmol/L) and < 116 mg/dL (3.0 mmol/L), respectively [2].

Alirocumab, a fully human monoclonal antibody to proprotein convertase subtilisin/kexin type 9 (PCSK9), has been shown to significantly reduce LDL-C in patients receiving statin therapy compared with controls [3, 4]. In Germany, alirocumab is currently reimbursed in combination with a statin and/or other lipid-lowering therapies (LLTs) and in addition to dietary change for patients with primary hypercholesterolemia (heterozygous familial or non-familial) or mixed dyslipidemia and confirmed vascular disease (coronary artery disease, cerebrovascular manifestation, or peripheral arterial disease) and other risk factors, who demonstrate persistently elevated LDL-C levels despite receiving documented maximum dietary therapy and LLTs for more than 12 months and when lipid apheresis therapy is indicated.

Two non-interventional studies have investigated the use of alirocumab in Germany under real-life conditions [5, 6]. The PEARL study in patients with hypercholesterolemia treated with alirocumab 75 or 150 mg every 2 weeks demonstrated a reduction in LDL-C levels by 48.6% at week 24 compared with baseline [5]. Steffens et al. reported in the OPTIMIZE study that after 12 weeks of treatment with alirocumab (initial dose: 75 mg [61.3%] and 150 mg [38.7%] every 2 weeks), the LDL-C target value (< 70 mg/dL [< 1.8 mmol/L]) was reached in 57% of patients with atherosclerotic cardiovascular disease with high baseline LDL-C levels with or without statin intolerance [6]. The efficacy and safety results in these studies were consistent with the results observed in the ODYSSEY Phase III program [7].

The initially available alirocumab autoinjector had a volume of 1 mL, which contained 150 mg of active ingredient. Therefore, two injections were needed for a monthly dose administration of 300 mg. In order to reduce the application frequency to only one injection for the required monthly dose, the SYDNEY autoinjector with a volume of 2 mL, which contains 300 mg of the active ingredient, was developed. Frias et al. investigated user friendliness and therapy acceptance of the 2-mL SYDNEY device in a randomized open-label study of patients with or without supervision and calibrated the pharmacokinetic properties and efficacy and safety against the current standard [8]. The study confirmed the efficacy of the 2-mL SYDNEY device, as already a single injection of 2 mL containing alirocumab 300 mg via the SYDNEY autoinjector reduced the LDL-C values. Unexpected technical problems or new safety concerns were not observed when compared to 1-mL autoinjectors [8].

There are currently no data available on 2-mL SYDNEY autoinjector use in patients with hypercholesterolemia in routine clinical care in Germany. Hence, the MARS (Monthly Application of 300 mg AliRocumab (Praluent®) using the 2-mL SYDNEY Device) study was designed to evaluate the effectiveness, treatment acceptance, patient adherence and persistence, and safety of treatment with the 2-mL SYDNEY autoinjector in routine clinical care in Germany.

2 Methods

2.1 Study Design

MARS is a non-interventional, open, prospective, multicenter study in Germany between 2021 and 2023 with an observational period of approximately 12 weeks. The primary aim was to demonstrate the benefits for patients with higher than desired LDL-C levels and atherosclerotic cardiovascular disease after 12 weeks of treatment and to identify potential side effects when used in everyday practice in Germany. During the observational period of 12 weeks, a baseline visit, two intermediate visits at approximately 4 and 8 weeks, and a final visit 12 weeks after starting the use of the alirocumab 2-mL SYDNEY autoinjector were scheduled. The study was performed in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) including all subsequent amendments. Approval from the local institutional ethics committee was obtained at the Principal Investigator's site.

2.2 Patient Population

Patients treated with the alirocumab 2-mL SYDNEY autoinjector according to the summary of product characteristics were included. The inclusion criteria were as follows: (1) primary hypercholesterolemia (heterozygous familial or non-familial) or mixed dyslipidemia and confirmed vascular disease and other risk factors OR confirmed familial heterozygous hypercholesterolemia; (2) physician's therapeutic decision for the 2-mL SYDNEY autoinjector independent of patient's participation in the study; (3) documented

maximum dietary efforts and LLT over 12 months; (4) insufficient LDL-C reduction despite maximum dietary or LLT; (5) no prior therapy with a PCSK9 inhibitor OR prior treatment with a PCSK9 inhibitor every 2 weeks (Q2W) or monthly (Q4W) [switch patients]; (6) patient information was handed out; and (7) written and dated informed consent was provided. Exclusion criteria included concomitant participation in a clinical study, existing therapy with lipid apheresis, contraindications for a therapy with alirocumab in accordance with summary of product characteristics, age < 18 years, and planned or existing pregnancy, cancer, drug or alcohol abuse, dementia, or general inability to understand the content of the observational study.

2.3 Study Objectives

The primary objectives were to investigate:

- The effectiveness of the 2-mL SYDNEY autoinjector measured by the absolute and relative reduction of LDL-C after 12 weeks of alirocumab treatment.
- Therapy satisfaction as well as patient adherence and persistence after 12 weeks of treatment with the 2-mL SYDNEY autoinjector assessed with the questionnaire based on the validated Injection Treatment Acceptance Questionnaire (ITAQ) [8].

The secondary objective was to investigate the tolerability of the 2-mL SYDNEY autoinjector during 12 weeks of treatment measured by the incidence and number of adverse events (AEs) and product technical complaints.

2.4 Sample Size

As this is a non-interventional study without pre-defined hypotheses, no formal sample size or power calculation was conducted. However, a non-formal justification for the intended sample size is as follows: for 300 patients and an assumed standard deviation of 20%, the expected length of the two-sided 95% confidence interval (CI) for the mean percent change in LDL cholesterol reduction is 4.6%. Assuming a mean LDL-C reduction of 50% leads to a 95% CI of [47.7, 52.3]. Assuming 150 patients in each subsample (pre-treated with a PCSK9 inhibitor and treatment-naïve patients) and a standard deviation of 20%, the expected length of the two-sided 95% CI is 6.4%. Given 300 patients, at least one rare AE (single event probability: 1/100) will be detected with a probability of 95%.

2.5 Statistical Analysis

Continuous data were presented as mean ± standard deviation for normally distributed data or median and interquartile range for non-normally distributed data. Normality was checked using the Shapiro–Wilk test. Categorical data were presented by means of (absolute and relative) frequency; the calculation of percentages was based on the number of patients with valid data per parameter, i.e., excluding patients with missing values. Categorical data reported as "unknown" were treated as missing values. In addition, 95% CIs were calculated for the main evaluation variables. It was tested (one sided *t* test) if the decrease in LDL-C was above 50%.

All baseline and follow-up characteristics as well as the primary outcomes were analyzed for the full analysis set (FAS), which included all patients enrolled in the study who received at least one dose of alirocumab within this study, met the selection criteria, and for whom sufficient data for the analysis of the primary variables were documented. That is, either the change in LDL-C after approximately 12 weeks of treatment or at least one ITAQ item had to be available. Secondary outcomes were analyzed for the safety analysis set (SAS), which included all patients enrolled in the study who received at least one dose of alirocumab within this study. All statistical analyses were carried using the SAS® package (version 9.4).

3 Results

3.1 Patient Characteristics

In total, 165 patients were enrolled at 50 sites (Fig. 1). Two patients had no treatment with alirocumab documented and, therefore, were excluded from the SAS, which included 163 patients. A further 17 patients were excluded because of insufficient information for the primary variables available, resulting in 146 patients included in the FAS. A total of 110 (75.3%) FAS patients were not treated with a PCSK9 inhibitor before alirocumab initiation (naïve). The remaining 36 (24.7%) patients reported previous treatment with a PCSK9 inhibitor, including inclisiran (pre-treated).

The mean age in the total FAS population was 65.6 ± 10.3 years and the majority (59.6%) were male (Table 1). The median BMI was 27.3 (interquartile range 25.1, 29.7) kg/m^2 and 32 patients (22.2%) had type 2 diabetes mellitus. Most of the patients were at very high risk (82.3%) with a recommended LDL-C target of <55 mg/dL (< 1.4 mmol/L) and a ≥ 50% reduction in the baseline value. For four patients (2.8%), the recommended LDL-C target was < 40 mg/dL (< 1.0 mmol/L). Overall, patient characteristics were similar for PCSK9 inhibitor-naïve and pre-treated patients, except that naïve patients reported having a higher

mean systolic blood pressure (136.6 vs 126.7 mmHg) and a higher rate of type 2 diabetes (24.1% vs 16.7%).

About one third (31.1%) of the patients had a clinical familial hypercholesterolemia diagnosis and the percentage of patients with familial hypercholesterolemia was higher in PCSK9 inhibitor pre-treated patients (46.9%) than in naïve patients (26.0%; Fig. 2). About half of the patients had non-familial hypercholesterolemia (48.6%) or mixed dyslipidemia (50.0%), respectively. Coronary heart disease (CHD) was documented in 78.5% of patients and acute coronary syndrome in 25.6%, while in 25.2% both CHD and acute coronary syndrome were present. Hypertension was reported in 75.2% of patients and 23.3% had heart failure. In total, 10.4% of the patients reported a previous stroke, 3.5% had transient ischemic disease, and 11.6% had peripheral artery disease. Baseline values of total cholesterol, LDL-C, triglycerides, and lipoprotein a were on average higher in PCSK9 inhibitor-naïve than in pre-treated patients. Median values of high-density lipoprotein cholesterol were similar in both subgroups.

The percentage of patients with any LLT other than PCSK9 inhibitors in the previous 12 months before the initiation of alirocumab and/or during the study was higher in naïve patients (75.3%) than in pre-treated patients (54.5%). No information on previous LLT or LLT during the study was available for 20 patients.

A total of 61.4% of patients were statin intolerant: 57.8% of PCSK9 inhibitor-naïve patients and 72.2% of pre-treated patients. Among the patients with statin intolerance, 67.4% were completely statin intolerant and 32.6% were partially intolerant. In partially statin-intolerant patients, the majority had moderate symptoms (65.5%). The percentage of patients with complete intolerance was lower in naïve patients compared with the pre-treated patients (61.9% vs 80.8%).

3.2 LDL-C and Lipid Change

After 12 weeks of treatment (Visit 4 [V4] of treatment compared to Visit 1 [V1], i.e. baseline), LDL-C decreased on average by a median of 59.5 mg/dL (1.5 mmol/L) in PCSK9 inhibitor-naïve patients and remained rather unchanged in pre-treated patients (median absolute change: 2.5 mg/dL [0.1 mmol/L]). The median LDL-C values at V1 compared to V4 are displayed in Fig. 3. In PCSK9 inhibitor-naïve patients, a median relative decrease (V4–V1) of 52.0% was observed. The median relative change in pre-treated patients was 1.6%. Overall, the distribution of achieved LDL-C levels in naïve patients shifted towards lower values and a narrower range of values at 12 weeks compared with baseline (Fig. 4).

Baseline values of total cholesterol, triglycerides, were on average higher in naïve than in pre-treated patients (Table 1 of the Electronic Supplementary Material). Median values of high-density lipoprotein cholesterol were similar in both subgroups. During the course of the study, lipids remained rather unchanged in pre-treated patients. In contrast, averages of all lipids but high-density lipoprotein cholesterol were essentially lower already at V2 in comparison to V1 in naïve patients. While the mean value of triglycerides slightly decreased at V3 and V4 in comparison to V2, total cholesterol and LDL-C remained rather unchanged in naïve patients.

3.3 Therapy Satisfaction, Patient Adherence and Persistence

A total of 141 (96.6%) of the FAS patients answered at least one ITAQ question (Table 2). In general, therapy with the 2-mL SYDNEY autoinjector was rated similarly by naïve and pre-treated patients. The majority of the patients rated the injection as effective or very effective (75.7%) and safe

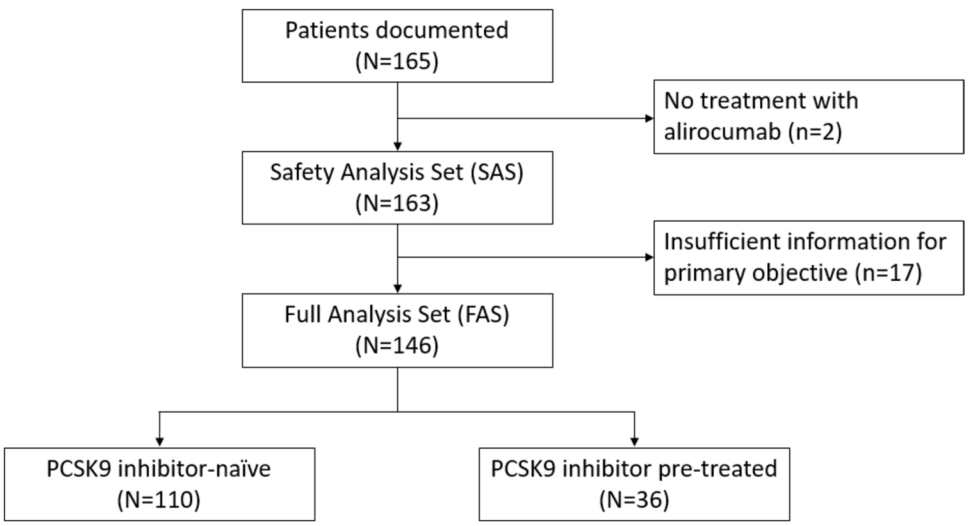

Fig. 1 Patient disposition. *PCSK9* proprotein convertase subtilisin/kexin type 9

Table 1 Patient characteristics at baseline (full analysis set)

n (%), mean ± SD or median (IQR)	PCSK9 inhibitor naïve (*N* = 110)	Pre-treated (*N* = 36)	Total (*N* = 146)
Age (years)	65.2 ± 10.2	66.9 ± 10.9	65.6 ± 10.3
Male	66 (60.0)	21 (58.3)	87 (59.6)
Height (cm)	172.1 ± 9.5	170.3 ± 9.4	171.6 ± 9.5
Weight (kg)	82.0 (71.5, 92.5)	78.0 (67.2, 90.0)	81.0 (70.3, 92.0)
BMI (kg/m^2)	27.5 (25.3, 30.1)	27.0 (24.0, 28.6)	27.3 (25.1, 29.7)
Systolic BP (mmHg)	136.6 ± 17.0	126.7 ± 13.4	134.1 ± 16.7
Diastolic BP (mmHg)	80.8 ± 8.3	77.4 ± 8.4	80.0 ± 8.4
LDL-C target			
< 40 mg/dL and ≥50% reduction[a]	2 (1.9)	2 (5.6)	4 (2.8)
< 55 mg/dL and ≥ 50% reduction[a]	88 (83.8)	28 (77.8)	116 (82.3)
< 70 mg/dL and ≥ 50% reduction[a]	12 (11.4)	6 (16.7)	18 (12.8)
< 100 mg/dL	3 (2.9)	0 (0.0)	3 (2.1)
< 116 mg/dL	0 (0.0)	0 (0.0)	0 (0.0)
Any LLT other than PCKS9 inhibitor[b]	70 (75.3)	18 (54.5)	88 (69.8)
Lipid profile			
Total cholesterol (mg/dL)	198.0 (158.0, 257.0)	149.0 (124.0, 205.0)	187.5 (147.5, 235.0)
LDL-C (mg/dL)	116.0 (91.2, 164.0)	76.5 (53.3, 112.0)	110.0 (79.5, 141.0)
HDL-C (mg/dL)	51.0 (42.0, 57.2)	53.0 (42.4, 63.3)	51.1 (42.0, 59.9)
Triglycerides (mg/dL)	161.0 (110.0, 224.8)	141.0 (92.0, 195.0)	157.7 (108.5, 224.8)
Lp(a) (mg/dL)	35.0 (8.3, 78.2)	11.5 (8.3, 42.0)	25.6 (8.3, 62.9)

BMI body mass index, *BP* blood pressure, *HDL-C* high-density lipoprotein cholesterol, *IQR* interquartile range, *LDL-C* low-density lipoprotein cholesterol, *LLT*, *Lp(a)* lipoprotein a, *PCSK9* proprotein convertase subtilisin kexin type 9, *SD* standard deviation

[a]Compared to baseline

[b]In the previous 12 months before the start of alirocumab treatment and/or during the study

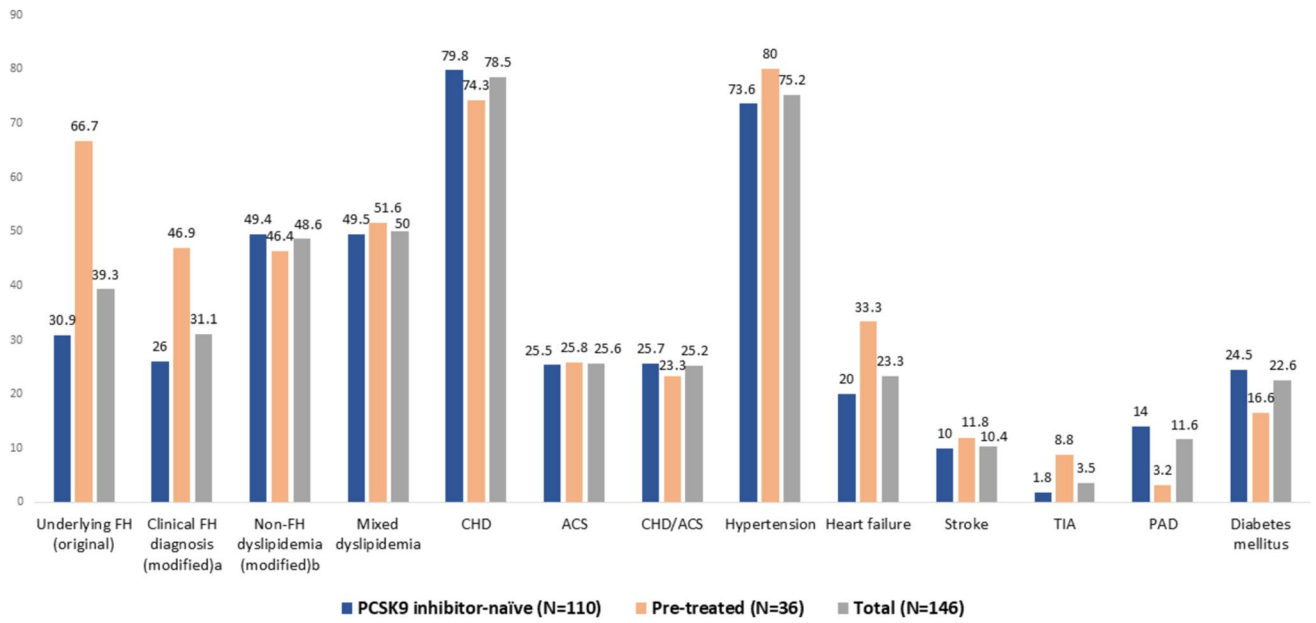

Fig. 2 Disease presentation at baseline (full analysis set). *ACS* acute coronary syndrome, *CHD* coronary heart disease, *FH* familial hypercholesterolemia, *PAD* peripheral artery disease, *PCSK9* proprotein convertase subtilisin/kexin type 9, *TIA* transient ischemic attack. [a]According to a procedure introduced by Klose et al. [15]. [b]If possible, initially unknown cases were replaced with "no" if FH = "yes"

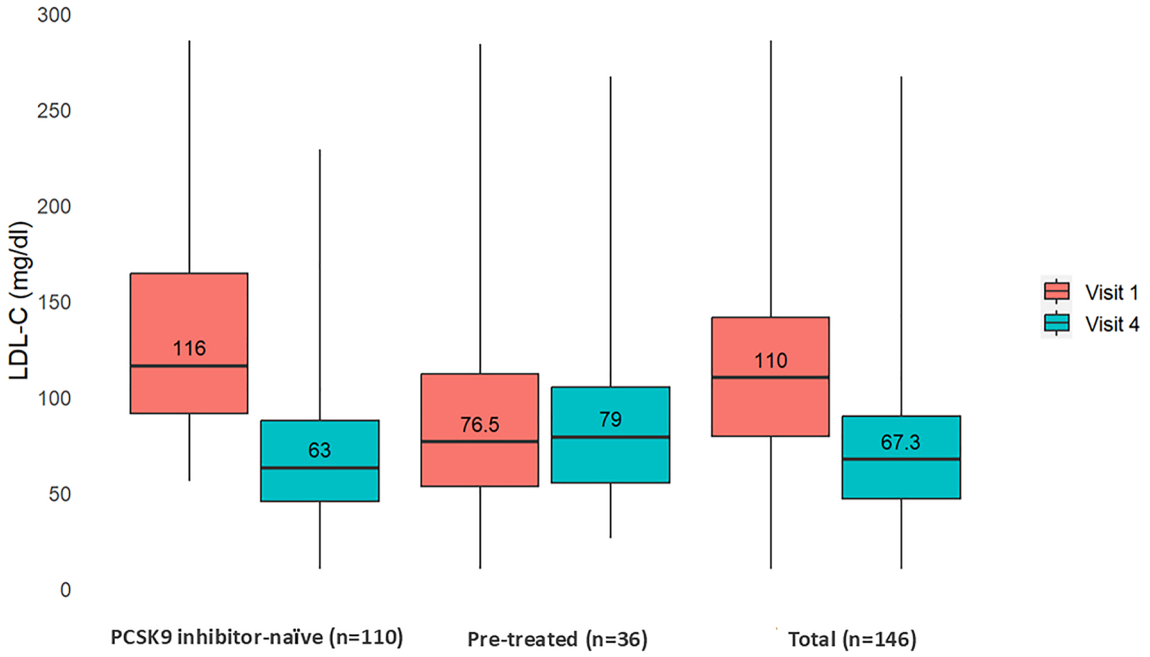

Fig. 3 Median low-density lipoprotein cholesterol (LDL-C) at 12 weeks (visit 4) compared to baseline (visit 1) [Full analysis set]

or very safe (91.6%). Five patients felt unsafe (3.8%) and 11 patients (8.5%) experienced a reaction at the injection site, of which four assessed the reaction as not disturbing and the remaining seven as at most a little disturbing.

Most patients (94.9%) rated the handling of the injection as easy or very easy. Patients rarely experienced pain when injecting (4.3%). For more than 90% of the patients, self-injections were acceptable/totally acceptable and practicable/very practicable.

Almost all patients planned to continue self-injections probably or for sure (97.1%) and were satisfied/very satisfied

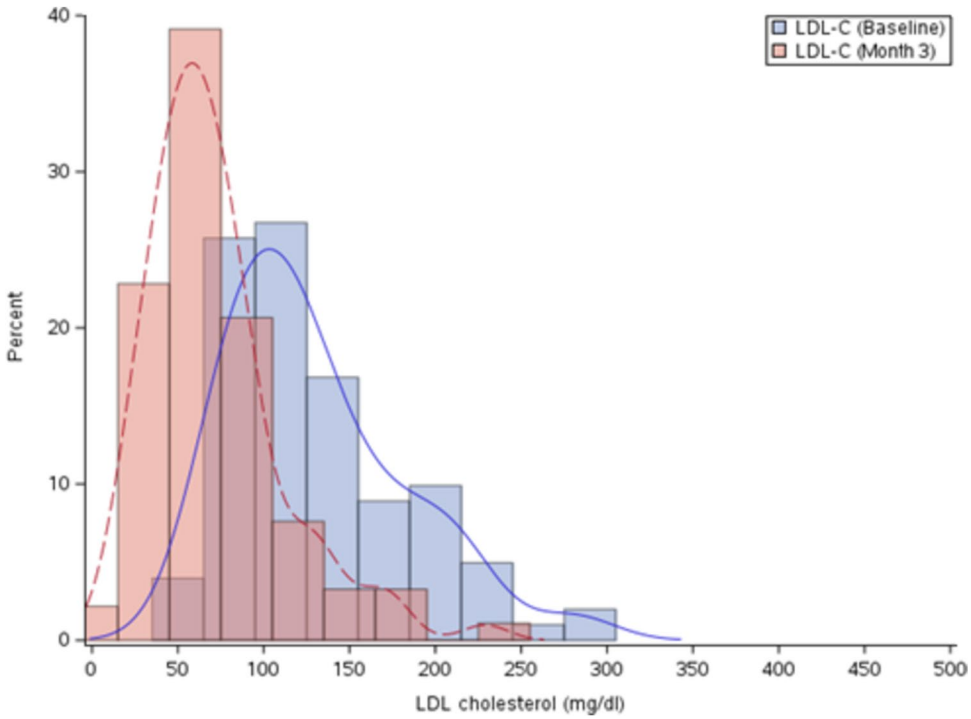

Fig. 4 Distribution of low-density lipoprotein cholesterol (LDL-C) values at baseline and 12 weeks in naïve patients (full analysis set)

with the treatment (97.2%). Compared to their previous treatment (only pre-treated patients, total $n = 36$), 77.4% of patients liked the treatment with the 2-mL SYDNEY autoinjector every 4 weeks better and 22.6% reported no difference.

3.4 Adverse Events (AEs)

In total, 23 AEs in 13 patients (8.0%) out of the 163 patients of the SAS population were reported with a similar occurrence in naïve and pre-treated patients (Table 3). Three patients (1.8%) experienced at least one SAE. In five patients (3.1%) at least one adverse drug reaction was observed, although none of them was serious. For two patients (1.2%), their SAE (no causal relationship with alirocumab) led to study drug withdrawal. There were no fatal cases. In total, for 13 (56.5%) of the 23 AEs, the patient recovered, one patient recovered with sequelae (4.3%), six AEs (26.1%) were not resolved, and for three AEs (13.0%) the outcome was unknown.

The most frequent *Medical Dictionary for Regulatory Activities* primary System Organ Classes were general disorders and administration site conditions ($n = 3$, 1.8%) and respiratory, thoracic and mediastinal disorders ($n = 3$, 1.8%; Table 4). Of the latter, the most frequent was rhinorrhea ($n = 3$, 1.8%).

4 Discussion

The results of the present study demonstrated the effectiveness of alirocumab 300 mg using the 2-mL SYDNEY autoinjector in reducing LDL-C levels. In addition, switch from 2- to 4-weekly dosing (6-month dosing to 4 weekly for one patient) was possible without any substantial LDL-C change. Patients were in general satisfied with the therapy and considered the treatment effective and user friendly.

The patient characteristics of the study cohort are largely in line with the known epidemiological data. Dyslipidemia is an established risk factor for CHD. Accordingly, the majority of enrolled patients (78.5%) reported having CHD. Furthermore, the expression of dyslipidemia is influenced by various factors, including obesity and diet. Many patients were overweight, with a median BMI of 27.3 kg/m^2. For 69.8% of the patients, it was reported that they had been treated with LLT in the previous 12 months before initiation of alirocumab and/or during the study (other than PCSK9 inhibitors and apheresis). However, 20 had no information on previous LLT or other LLT during the study. As per the recommendations by the Joint Federal Committee (G-BA), the patients should have been treated with other LLTs before starting with alirocumab. Therefore, it is possible that this therapy was not reported sufficiently and that a higher proportion of patients has indeed received LLTs other than PCSK9 inhibitors and apheresis beforehand. The naïve patients had higher baseline LDL-C values and reported higher systolic pressure and diabetes more than the pre-treated patients.

After 12 weeks of treatment, a median decrease of LDL-C by 52% was observed in PCSK9 inhibitor-naïve patients, confirming the benefit from treatment with alirocumab, which was also reported in previous randomized controlled trials. The ODYSSEY CHOICE I trial showed an LDL-C reduction after 12 weeks by 52.7% in patients receiving alirocumab 300 mg Q4W without concomitant treatment with statins and a LDL-C reduction by 58.8% in patients with concomitant statins [9]. The results of the OPTIMIZE study (75 mg or 150 mg Q2W) showed a 50.7% reduction [6]. For the pre-treated group who were switched from another PCSK9i therapy to the alirocumab Q4W regimen, our results indicate that the monthly dosage of alirocumab is just as effective as the Q2W regimen, yet offering the advantage of a monthly injection, including better consistency and a reduced burden with the treatment. With respect to other LLTs, alirocumab, along with evolocumab, appears to be a more effective agent in lowering LDL-C levels compared with inclisiran, bempedoic acid, and ezetimibe. The results of a recent meta-analysis of non-statin LLTs revealed that evolocumab (140 mg Q2W/420 mg Q4W) and alirocumab (75 mg Q2W, 150 mg Q2W, and 300 mg Q4W) resulted in a greater reduction of LDL-C at 12 weeks compared with inclisiran, the bempedoic acid/ezetimibe fixed-dose combination, and ezetimibe and bempedoic acid used as monotherapies [10].

PCSK9 inhibitor-naïve patients in the present study had on average lower LDL-C values at baseline (mean 130.2 mg/dL [3.37 mmol/L]) compared with patients in the OPTIMIZE (mean 150.5 mg/dL [3.89 mmol/L]) and PEARL (mean 180.5 mg/dL [4.7 mmol/L]) studies (Fig. 5). Similarly, the median LDL-C values in the PCSK9 inhibitor-naïve patients in the present analysis at baseline were lower (116.0 mg/dL [3.00 mmol/L]) compared with the reported baseline values in the German multi-center HYDRA-ACS study (median 166 mg/dL [4.29 mmol/L]) [11]. For this reason, the change in LDL-C in the present study has not been that prominent. Low baseline LDC-C values in patients in the current study may be explained by the fact that most patients had been treated by the cardiologists in the private practices, meaning the patient's therapy and the LDL-C values could have been followed up closely before the baseline visit. Furthermore, it can be observed that as a result of the various ongoing initiatives and increased awareness, there has been an improvement in the lipid management as

Table 2 Injection Treatment Acceptance Questionnaire (ITAQ) items over the past 12 weeks (full analysis set)

		n (%)
At least one ITAQ question answered	Yes	141 (96.6)
	No	5 (3.4)
Effectiveness and safety of injection		
How effective do you think the injection has been?	Not effective at all	2 (1.4)
	Close to ineffective	0 (0.0)
	Somewhat effective	7 (5.0)
	Effective	35 (25.0)
	Very effective	71 (50.7)
	I cannot estimate	25 (17.9)
Did you experience any reactions at the injection side (such as redness, bruising or swelling)	Yes	11 (8.5)
	No	119 (91.5)
How safe have you felt with self-injection?	Very unsafe	3 (2.3)
	Somewhat unsafe	2 (1.5)
	Partially safe	6 (4.6)
	Safe	65 (49.6)
	Very safe	55 (42.0)
Handling of injection		
How easy was it to give yourself the injection treatment?	Very difficult	0 (0.0)
	Difficult	2 (1.4)
	A little difficult	5 (3.6)
	Easy	72 (52.2)
	Very easy	59 (42.8)
Did you experience any pain when injecting your treatment?	Yes	6 (4.3)
	No	132 (95.7)
How acceptable did you find the time to give yourself the injection treatment?	Not acceptable at all	1 (0.7)
	Not acceptable	1 (0.7)
	Neither acceptable nor unacceptable	1 (0.7)
	Acceptable	45 (32.8)
	Totally acceptable	89 (65.0)
How acceptable did you find the number of times you had to give yourself the injection treatment?	Not acceptable at all	1 (0.7)
	Not acceptable	1 (0.7)
	Neither acceptable nor unacceptable	1 (0.7)
	Acceptable	62 (44.6)
	Totally acceptable	74 (53.2)
How easy was it to remember to give yourself the injection treatment?	Very difficult	2 (1.4)
	Difficult	1 (0.7)
	Neither difficult nor easy	15 (10.7)
	Easy	53 (37.9)
	Very easy	69 (49.3)
How easy was it to fit in taking the injection into your daily life?	Very difficult	1 (0.7)
	Difficult	0 (0.0)
	Neither difficult nor easy	14 (10.0)
	Easy	54 (38.6)
	Very easy	71 (50.7)
How practical has the self-injection been for you?	Very much impractical	0 (0.0)
	Impractical	1 (0.7)
	Neither practical nor impractical	4 (2.9)
	Practical	67 (48.2)
	Very practical	67 (48.2)

Table 2 (continued)

		n (%)
Overall evaluation of self-injections		
Would you continue self-injection?	For sure not	0 (0.0)
	Rather not	1 (0.7)
	I do not know	3 (2.1)
	Probably yes	23 (16.4)
	Yes sure	113 (80.7)
If you think about all aspects of your injection treatment in the last 12 weeks, how satisfying did you find the treatment?	Dissatisfied at all	0 (0.0)
	Not satisfied	1 (0.7)
	Neither satisfied nor dissatisfied	3 (2.1)
	Satisfied	42 (29.8)
	Very satisfied	95 (67.4)
How did you like the treatment with the Praluent® 2-mL SYDNEY autoinjector monthly compared to previous treatment every 2 weeks?[a]	Worse	0 (0.0)
	No difference	8 (24.2)
	Better	25 (75.8)

[a]Only pre-treated patients

Table 3 Number of patients with AEs (safety analysis set)

n (%)	PCSK9 inhibitor-naïve (*N* = 125)	Pre-treated (*N* = 38)	Total (*N* = 163)
No AE	114 (91.2)	36 (94.7)	150 (92.0)
Any AE	11 (8.8)	2 (5.3)	13 (8.0)
Any non-SAE	9 (7.2)	1 (2.6)	10 (6.1)
Any SAE	2 (1.6)	1 (2.6)	3 (1.8)
Any drug related AE	4 (3.2)	1 (2.6)	5 (3.1)
Any AE leading to study drug withdrawal	3 (2.4)	1 (2.6)	4 (2.5)
Any SAE leading to study drug withdrawal	2 (1.6)	0 (0.0)	2 (1.2)
Any fatal AE	0 (0.0)	0 (0.0)	0 (0.0)

AE adverse event, *PCSK9* proprotein convertase subtilisin kexin type 9, *SAE* serious adverse event

Table 4 Number of patients with AEs by SOC (SAS)

SAS patients with AEs by SOC, *n* (%)	PCSK9 inhibitor naïve (*N* = 125)	Pre-treated (*N* = 38)	Total (*N* = 163)
General disorders and administration site conditions	3 (2.4)	0 (0.0)	3 (1.8)
Respiratory, thoracic and mediastinal disorders	2 (1.6)	1 (2.6)	3 (1.8)
Injury, poisoning and procedural complications	2 (1.6)	0 (0.0)	2 (1.2)
Musculoskeletal and connective tissue disorders	2 (1.6)	0 (0.0)	2 (1.2)
Nervous system disorders	1 (0.8)	1 (2.6)	2 (1.2)
Eye disorders	1 (0.8)	0 (0.0)	1 (0.6)
Infections and infestations	0 (0.0)	1 (2.6)	1 (0.6)
Investigations	1 (0.8)	0 (0.0)	1 (0.6)
Metabolism and nutrition disorders	1 (0.8)	0 (0.0)	1 (0.6)
Reproductive system and breast disorders	1 (0.8)	0 (0.0)	1 (0.6)
Skin and subcutaneous tissue disorders	0 (0.0)	1 (2.6)	1 (0.6)
Vascular disorders	1 (0.8)	0 (0.0)	1 (0.6)

AE adverse event, *PCSK9* proprotein convertase subtilisin kexin type 9, *SAS* safety analysis set, *SOC* system organ class

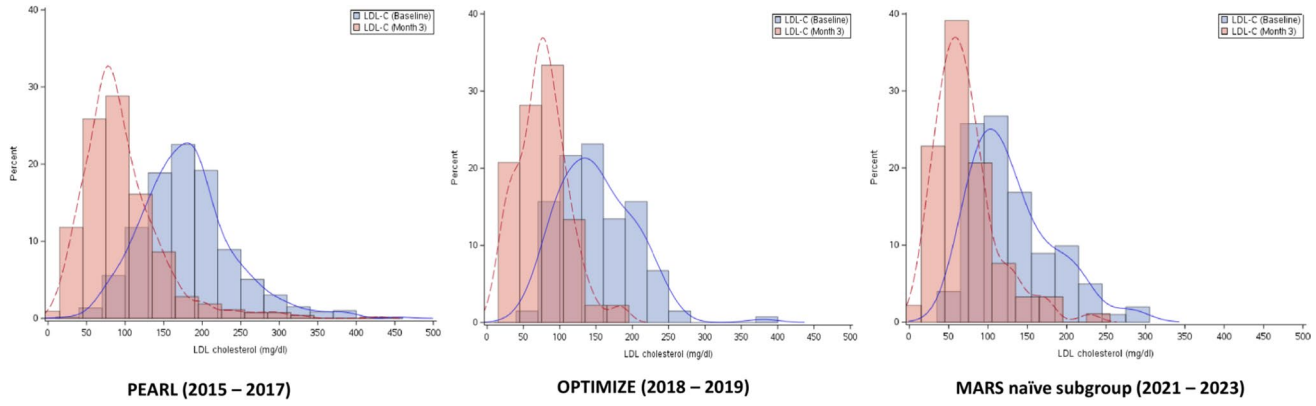

Fig. 5 Distribution of low-density lipoprotein cholesterol (LDL-C) values at baseline and 12 weeks in three German non-interventional studies

LLTs are better implemented and because of the lower target values, the use of PCSK9 inhibitors is also considered in patients with lower baseline values.

Despite the availability of effective LLTs, patient adherence and compliance are often poor for various reasons, which presents a major barrier to achieving LDL-C goals [12, 13]. A less frequent dosing regimen is one of the ways to improve patient acceptance and adherence [13]. In general, patients in our study were satisfied with the therapy using the 2-mL SYDNEY autoinjector and considered the treatment effective and user friendly. These real-world findings confirm the results reported in the randomized SYDNEY study, where the majority of patients were very satisfied in all assessments and very confident in using the 2-mL SYDNEY device [8]. The results of another alirocumab study also reported positive acceptance of the alirocumab prefilled pen and syringe devices by both patients and physicians, with most patients willing to use self-injection, particularly after training [14]. The high rating of overall ease of use of the device in our study is encouraging as simple self-administration could improve treatment adherence. Importantly, the treatment appeared to be well tolerated, with over 90% of patients experiencing no reactions at the injection site and no new safety signals being detected. The rates of injection-site reactions using 2 × 1-mL injections of alirocumab 300 mg Q4W were considerably higher in the ODYSSEY CHOICE I trial (18.5% in patients not receiving statins and 15.7% in patients receiving statins) [9]. In addition, most of the PCSK9 inhibitor pre-treated patients (75.8%) in our study preferred the treatment schedule of the 2-mL SYDNEY autoinjector (300 mg Q4W) over their previous treatment. This implies that a monthly dose provides patients with a less frequent dosing regimen compared with the Q2W dosing regimen, which may be more convenient for patients and may result in a better long-term adherence to treatment. The vast majority (97.1%) of the patients in our study planned to continue with the Q4W treatment (probably or for sure), suggesting a potential improvement in adherence. It is also worth mentioning that 96.6% of patients in our study answered at least one ITAQ question, which is high considering the non-interventional design.

5 Limitations

The present study was subject to several limitations. First, non-interventional observational studies have inherent limitations in validity, owing to lower data quality and higher susceptibility to various sources of bias than in a clinical trial. Additionally, the study was conducted only in Germany; therefore, the data from a single country may deviate from those of an international cohort. The majority of study centers were established institutions and physicians were mostly internists specialized in cardiology, which might have influenced the baseline characteristics or information on previous treatments. The observational time of 12 weeks was relatively short to assess and appreciate the results of a treatment with a monthly dosing regimen. Thus, the real-life long-term efficacy and safety of alirocumab could not be assessed in this study. Moreover, the number of patients included in this study (FAS: 165) was relatively small, particularly in the pre-treated subgroup ($n = 36$), and the results should be interpreted with caution. Additionally, there is a small number of patients from the FAS who responded to likability of the treatment with the Praluent® 2-mL SYDNEY autoinjector monthly compared to previous treatment every 2 weeks, which provides little information on comparison to an every 2-week regimen. Last, selection bias into treatment with alirocumab was present because of statin

intolerance as patients in this population had previously initiated and not responded to statin therapy.

6 Conclusions

This study demonstrated the effectiveness and safety of alirocumab 300 mg using the 2-mL SYDNEY autoinjector in patients with primary hypercholesterolemia or mixed dyslipidemia and existing atherosclerotic cardiovascular disease or in patients with confirmed heterozygous familial hypercholesterolemia, for whom the LDL-C values were not sufficiently controlled (despite maximum dietary control or LLT), and who fulfilled the other selection criteria in a routine clinical setting in Germany. Moreover, PCSK9 inhibitor-naïve patients benefited from optimization therapy with a PCSK9 inhibitor in addition to other LLTs. Overall, the new autoinjector device is easy to use with high degrees of treatment acceptance and satisfaction, which could potentially improve patient adherence.

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Declarations

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Conflicts of interest/competing interests Klaus G. Parhofer, Peter Bramlage, and Ursula Rauch-Kröhnert have received consultancy honoraria from Sanofi. The institution of Peter Bramlage has received an honorarium for drafting the study protocol and publication. Constanze Gries, Cornelia Harder, Christiane Look, and W. Dieter Paar are employees and shareholders of Sanofi.

Ethics approval Ethical approval was obtained from participating centers before enrollment with the approval number EA4/154/21.

Consent to participate Written and dated informed consent was obtained from every patient before enrollment in the study.

Consent for publication Not applicable.

Availability of data and material The dataset utilized in this article are not publicly available and can be shared upon reasonable request to the corresponding author.

Code availability Not applicable.

Authors' contributions Substantial contributions to the conception or design of the work: PB, CG, CL, WDP. Acquisition, analysis, or interpretation of data for the work: KGP, CH, URK. Drafting the work or reviewing: PB. Reviewing critically for important intellectual content: KGP, CH, CL, WDP, URK. Final approval of the version to be published: all authors. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: all authors.

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