

CKJX839A1DE01 Study Results Synopsis for Public Disclosure

Title

A non-interventional implementation study to evaluate treatment with Inclisiran (Leqvio®) and other lipid lowering treatments in a real-world setting (VICTORION-Implement)

Keywords

1) Non-interventional study; 2) Lipid-lowering treatment; 3) Cardiovascular prevention; 4) Inclisiran

Rationale and background

For many years, cardiovascular disease (CVD) has consistently been reported as the leading cause of death in Germany, accounting for 33.7% of all deaths, which corresponds to a total number of more than 339.000 deaths in 2024 (Statistisches Bundesamt 2026). There are 5 major risk factors contributing to the development of CVD: hypertension, hyperlipidemia, overweight or obesity, diabetes, and smoking (Magnussen *et al.* 2025). In order to reduce the cardiovascular (CV) risk, the 2019 European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) guideline for the management of dyslipidemia recommends patient-level CV risk classification based on those factors, followed by the definition of individual treatment goals (Mach *et al.* 2020). Treatment recommendations in the dimension hyperlipidemia include a low-density lipoprotein cholesterol (LDL-C) reduction of $\geq 50\%$ from baseline and a LDL-C treatment goal of < 55 mg/dL (< 1.4 mmol/L) in very high-risk patients, while high risk patients should achieve a goal of < 70 mg/dL (< 1.8 mmol/L). Although many treatment options for the reduction of LDL-C levels are available, the DA VINCI study, a European Union (EU)-wide cross-sectional observational study, demonstrated a gap between the recommended treatment goals and clinical practice in Europe (Ray *et al.* 2021). Only 33% of patients in this cohort study attained their respective treatment goal, with only 18% of very high-risk patients achieving an LDL-C level < 1.4 mmol/L.

Inclisiran is a first-in-class, small interfering ribonucleic acid (siRNA) developed for long-term lowering of LDL-C. After subcutaneous administration, inclisiran is selectively taken up by hepatocytes, where it activates the endogenous ribonucleic acid (RNA) interference pathway by binding to the RNA-induced silencing complex (RISC). Inclisiran targets the RISC to bind specifically proprotein convertase subtilisin kexin type 9 (PCSK9) messenger RNA (mRNA), leading to its degradation, thereby reducing the synthesis of PCSK9 protein in the liver. The resulting reduction in circulating PCSK9 increases the availability of low-density lipoprotein (LDL) receptors on the hepatocyte surface, as PCSK9-bound LDL receptors are degraded after vesicular uptake, while unbound LDL receptors are recycled to the cell membrane (DeWeerd *et al.* 2019, Kosmas *et al.* 2018, Wiciński *et al.* 2017). The increased availability of LDL receptors on hepatocytes enhances LDL-C clearance from the bloodstream, leading to sustained LDL-C reduction.

The results of the pivotal Phase 3 inclisiran clinical development program consistently demonstrated sustained reductions in LDL-C of approximately 50% (placebo-adjusted), thereby providing the efficacy evidence for regulatory approval (Ray *et al.* 2020). In Germany, inclisiran is available under a reimbursement restriction (GBA 2021). As a result, inclisiran is used in a restricted patient population significantly smaller than the pivotal study population and European Medicines Agency (EMA) label. Evidence for this population is limited, as the restrictive patient characteristics imposed by the German label are only reflected in a small proportion of the study population of previously conducted clinical trials. Therefore, this non-interventional study (NIS) aimed to collect data for the specific population in which inclisiran is reimbursed in Germany. As a reference population for the different stages of lipid lowering treatment (LLT) in CV risk reduction, patients receiving oral lipid lowering treatments (oLLTs) and patients currently undergoing lipid apheresis were observed.

Research question and objectives

The purpose of the NIS was to characterize patients treated with inclisiran and other LLTs in order to improve understanding of disease burden, quality of life (QoL), treatment paradigms and safety outcomes in routine practice. All procedures, treatment adaptations, and laboratory assessments were performed following the investigators' judgement as part of routine care and were conducted independently of study participation.

Study design

The study was designed as a multicenter, non-randomized, non-interventional, 3-cohort study with prospective collection of primary data from routine clinical care. The decision to start, interrupt, adapt or switch any treatment was at the discretion of the treating physician and patient and was independent of enrollment into this study.

Patients were allocated to 1 of 3 treatment cohorts following the investigator's routine treatment decision at baseline. Cohort A comprised patients newly initiated on an oLLT on top of a statin, or new oLLT alone in case of statin intolerance or contraindication. Patients newly initiated on inclisiran in compliance with the restricted reimbursement criteria (either in cohort B1 with PCSK9i-naïve patients or in cohort B2 with patients that were previously treated with a PCSK9 monoclonal antibody [mAb]) were allocated to cohort B. Patients treated with inclisiran on top of lipid apheresis were allocated to cohort C.

Setting

137 sites contributed data to this study, including office-based cardiologists, nephrologists, endocrinologists, angiologists, lipidologists, and apheresis centers. In cohort B, only patients fulfilling the restricted reimbursement criteria for inclisiran were to be enrolled.

The treating physician was allowed to adapt the LLT during the follow-up phase of the study according to his/her decision. Patients were to be followed for up to 21 months after enrollment during their routine visits, regardless of whether they remained on their initial therapy or later switched to another LLT.

Subjects and study size, including dropouts

The target population was planned to include approximately 1,000 patients in cohort A, 1,000 patients in cohort B, and 30 patients in cohort C. Patients could be enrolled directly at LLT initiation or up to 7 days thereafter.

Overall, 1,873 patients were enrolled. Of these, 5 patients were screen-failed before being entered into the trial master file (TMF). Among the remaining 1,868 patients, 908 patients (48.5%) were included in the safety analysis set (SAF), defined as patients who received inclisiran at least once during the study, and 1,618 patients (86.4%) were included in the full analysis set (FAS).

Cohort A: Patients with documented atherosclerotic cardiovascular disease (ASCVD) not at individual LDL-C goal and newly initiated on an oLLT (e.g., ezetimibe, bempedoic acid [BA], cholestyramine) on top of a statin; alone or in combination with other LLTs in patients who were statin-intolerant, or for whom a statin was contraindicated.

Cohort B: Patients newly initiated on inclisiran fulfilling the restricted reimbursement criteria or individual access requirements who were not at their individual LDL-C goal as per their CV risk, as recommended in the 2019 EAS/ESC guidelines.

Cohort C: Patients with inclisiran on top of regular weekly or biweekly lipid apheresis (LDL-C or lipoprotein a [Lp(a)]).

Variables and data sources

The primary endpoint was to collect descriptive data on patient characteristics in terms of demographics, medical history, comorbidity burden, and previous CV events:

- **Demography:** Age, gender, ethnicity, postal code, status of health insurance, participation in disease management programs (DMPs), smoking status, school education, education / vocational training, academic education, and working status.
- **Medical history and previous CV events:** Occurrence of CV event before baseline, type of CV event before baseline, date of first ASCVD diagnosis, treatment with medication due to CV event, presence of abdominal aortic aneurysm, presence of peripheral artery disease (PAD), presence of any additional or other CV events, vital signs, height, body weight, presence of heterogenous FH (heFH), presence of statin intolerance, and presence of statin contraindication.
- **Comorbidity burden:** Diabetes mellitus, medication for diabetes mellitus, date of first diagnosis of diabetes mellitus, other comorbidities, medication for comorbidities, and number of lipid aphereses in the last 12 months (cohort C only).

Secondary variables/endpoints included:

- **Laboratory status:** LDL-C, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), non-HDL-C, triglycerides (TG), Lp(a), C-reactive protein (CRP), high sensitivity CRP (hsCRP), creatinine, glycated hemoglobin (HbA1c), and estimated glomerular filtration rate (eGFR)
- **Healthcare resource utilization:** Inpatient and outpatient visits, examinations, treatments, and consultations; for cohorts B1 and B2: Number and percentage of patients progressing to lipid apheresis after initiation of inclisiran therapy over time.
- **Adherence:** Proportion of days covered (PDC) by at least 1 LLT, percentage of patients with PDC of $\geq 80\%$ (sensitivity: 90%/100%) in subgroups by LLT, time to discontinuation of inclisiran/any LLT, percentage of patients discontinuing inclisiran/any LLT.
- **Effectiveness:** Changes over time in LDL-C, TC, HDL-C, non-HDL-C, TGs, Lp(a), CRP, hsCRP, creatinine, HbA1c, and eGFR; proportion of patients achieving prespecified LDL-C targets based on 2019 ESC/EAS guideline for the management of dyslipidemia; percentage of patients achieving $\geq 50\%$ LDL-C reduction over time, Changes over time in SMART-Risk Scores.
- **Treatment modifications:** Descriptive data on dose and strength of medication(s) received at baseline, dose changes, switching of LLT at different visits, and initiation of lipid apheresis for LDL-C.
- **Patient reported outcomes:** Changes over time in World Health Organization-Quality of Life (WHO-QoL) questionnaire, Treatment Satisfaction Questionnaire for Medication (TSQM, modified), evaluation of nutritional factors via questionnaire, evaluation of health data from patients (e.g., physical activity).
- **Safety and tolerability:** Number and percentage of adverse events (AEs), serious adverse events (SAEs), and (S)AEs leading to discontinuation of therapy.

Two endpoints pre-defined specifically for apheresis patients in cohort C (change in frequency of lipid apheresis and changes in inflammatory markers) could not be appropriately evaluated due to low recruitment numbers in this cohort ($n=5$ in FAS). Formally, 1 of the 5 patients in Cohort C switched from weekly to 2-weekly aphereses during the study.

Statistical methods

Only descriptive data analyses were carried out, supported by calculation of confidence intervals (CIs). All statistical analyses were performed in an explorative way.

ResultsPatient disposition

Among all 1,873 patients, the study documentation was completed as planned in 774 patients (80.7%) in cohort A and in 728 patients (80.3%) in cohort B. Due to the pre-defined last patient last visit (LPLV) date 12 months after last patient first visit (LPFV), patients entering late into the study were only able to complete the 9 months or the 15 months visit. Among the 1,618 patients in the FAS, a total of 491 patients (59.1%) in cohort A, 438 patients (56.0%) in cohort B, 389 patients (56.6%) in cohort B1, 49 patients (51.6%) in cohort B2, and 1 patient (20.0%) in cohort C were observed for the maximum period of 21 months.

LLT before study entry

Prior use of LLTs (i.e., LLTs administered at day -30 before baseline) was reported for 1,386 FAS patients (85.7%). A total of 783 patients (94.2%) in cohort A and 600 patients (76.7%) in cohort B were on at least one active LLT 30 days before baseline. The most common ($\geq 10.0\%$ of patients) LLTs in the oLLT cohort A were atorvastatin (478 patients, 57.5%), rosuvastatin (177 patients, 21.3%), simvastatin (101 patients, 12.2%), and ezetimibe (89 patients, 10.7%); bempedoic acid (BA) was used in 3 patients (0.4%). The most common LLTs in the inclisiran cohort B were ezetimibe (447 patients, 57.2%), BA (292 patients, 37.3%), rosuvastatin (241 patients, 30.8%), and atorvastatin (140 patients, 17.9%).

Overall, 773 patients (93.0%) in cohort A vs. 409 patients (52.3%) in cohort B were on active statin therapy at day -30 before study start. Statin use in cohort B was higher in patients newly initiated on a PCSK9 targeted therapy (cohort B1, 384 patients [55.9%]) than in patients switching from PCSK9 mAb to inclisiran (cohort B2, 25 patients [26.3%]).

No washout periods for patients switching from PCSK9 mAb to inclisiran were defined in the protocol. Exact dates for the discontinuation of PCSK9 mAb therapy before entering the study were available for 77.9% of FAS patients in cohort B2 (n=74). In those patients, the mean time between discontinuation of the PCSK9 mAb and first inclisiran intake was 183.7 ± 371.7 days (median: 25.5 days, range: 0–1,872 days). Reasons for the discontinuation of previous treatment with the PCSK9 mAb were "adverse effects or intolerance" (33 patients, 34.7%), "no achievement of LDL-C target" (26 patients, 27.4%), "patient wish" (19 patients, 20.0%), "different dose interval" (13 patients, 13.7%), "lack of response to prior therapy" (10 patients, 10.5%), and "application mode" (1 patient, 1.1%; multiple specifications per patient were possible).

LLT regimens at baseline (following start of new LLT)

At baseline, the proportion of patients with high-intensity statin (HIS) in cohort A increased from prior 58.5% (n=486) to 72.6% (n=603) at baseline, the proportion of patients treated with ezetimibe increased from 10.7% (n=89) to 98.3% (n=817), and the proportion of patients treated with BA increased from 0.4% (n=3) to 15.6% (n=130). In contrast, the inclisiran cohort was characterized by patients with intolerances to oLLTs: In cohort B (i.e., the patients starting inclisiran), the use of oLLTs before baseline was low and remained stable across the population, with the fraction of patients receiving statins changing from 52.3% (n=409) prior compared to 50.9% (n=398) of patients at baseline, high intensity statin from prior 40.0% (n=313) to 39.3% (n=307) at baseline, ezetimibe from 57.2% (n=447) prior to 55.8% (n=436) at baseline and BA from 37.3% (n=292) prior to 33.6% (n=263) at baseline. In the PCSK9 switcher sub-cohort B2, only 26.3% (n=25) of patients received any statin, 40.0% (n=38) ezetimibe and 16.8% (n=16) BA at baseline.

Primary objective: Baseline characteristics

The mean ($\pm$ standard deviation [SD]) age across cohorts was slightly higher in cohort A (68.5 ± 10.0 years) than in cohort B (64.5 ± 10.2 years). In addition, the proportion of males was numerically higher in cohort A (604 patients, 72.7%) compared with cohort B (481 patients, 61.5%). Consequently, patients initiating inclisiran in cohort B appeared to be on average younger and were more frequently female than patients escalating oLLT in cohort A.

Almost all study patients in either cohort were of Caucasian ethnicity (717 patients [86.3%] in cohort A and 721 patients [92.2%] in cohort B).

The prevalence of a history of CV events was higher in cohort A than in cohort B (733 patients [88.2%] in cohort A compared to 549 patients [70.2%] in cohort B). The prevailing type in both cohorts were events related to coronary heart disease (CHD), which occurred in 606 patients (82.7%) in cohort A and in 486 patients (88.5%) in cohort B. Cerebrovascular events were reported in 166 patients (22.6%) in cohort A and in 88 patients (16.0%) in cohort B. Of note, the median time since the patients' first CV event at study start (i.e., the current LLT escalation) was 62.0 months in cohort A (i.e., about 5.2 years) and 74 months in cohort B (i.e., about 6.2 years).

All patients were assigned to an individual CV risk category at baseline according to the criteria defined in the 2019 ESC/EAS Guidelines (Mach *et al.* 2020). All patients in Cohort A (100.0%) were classified as being at very high CV risk. In Cohort B, 718 patients (91.8%) were also categorized as "very high risk", while the remaining 64 patients (8.2%) were classified as "high risk".

Familial hypercholesterolemia (FH) status was known for 21.3% (165/776) of patients in cohort A and 40.8% (296/726) of patients in cohort B. For those tested, a higher proportion of patients with heterozygous FH was observed in cohort B (76 patients, 10.5% of all patients, 25.7% of tested patients) compared with cohort A (13 patients, 1.7% of all patients, 7.9% of tested patients). The proportion of patients who did not tolerate or could not be treated with a statin was clearly higher in cohort B than in cohort A (cohort A: 25 patients [3.0%], cohort B: 384 patients [49.1%]).

The proportion of patients with diabetes mellitus or other comorbidities were slightly higher in cohort A than in cohort B (diabetes mellitus: 254 patients [30.6%] in cohort A vs. 184 patients [23.5%] in cohort B; other comorbidities: 772 patients [92.9%] in cohort A vs. 686 patients [87.7%] in cohort B). At the preferred term (PT) level, CV risk factors such as arterial hypertension, obesity, atrial fibrillation (AF), obstructive sleep apnea (OSA), and renal failure occurred more frequently in cohort A than in cohort B (80.9% [n=672] vs. 69.6% [n=544] for arterial hypertension, 12.5% [n=104] vs. 7.0% [n=55] for obesity, 11.9% [n=99] vs. 6.0% [n=47] for AF, 7.6% [n=63] vs. 2.9% [n=23] for OSA, and 6.7% [n=56] vs. 3.3% [n=26] for renal failure).

In terms of baseline laboratory values, numerical differences between cohort A and cohort B in the lipid panel were seen for TC (median: 160.8 mg/dL in cohort A vs. 185.6 mg/dL in cohort B), non-HDL-C

(median: 106.0 mg/dL in cohort A vs. 134.9 mg/dL in cohort B), Lp(a) (median: 13.2 mg/dL in cohort A vs. 46.8 mg/dL in cohort B), and LDL-C (median: 84.9 mg/dL [Q1/Q3: 73.0 / 106.2] in cohort A vs. 108.1 mg/dL [82.2 / 147.0] in cohort B).

Adherence and persistence

Main variables to assess adherence and persistence were the proportion of days covered (PDC) by the newly started treatment and persistence of newly started LLT treatment at each visit. Patients were regarded as "adherent" for as long as no therapy interruption or deviation from treatment regimen was documented by the treating physician.

In cohort A, the mean PDC was $85.8 \pm 29.3\%$ for newly started atorvastatin (n=203), $89.4 \pm 26.9\%$ for newly started rosuvastatin (n=130), $79.9 \pm 36.5\%$ for newly started BA (n=129), and $87.1 \pm 30.1\%$ for newly started ezetimibe (n=777). In cohort B, the mean PDC for newly started inclisiran (n=782) was $98.9 \pm 7.2\%$.

Proportions of patients with PDC $\geq 80\%$ in cohort A were 78.3% (n=159) for atorvastatin, 85.4% (n=111) for rosuvastatin, 76.0% (n=98) for BA, and 83.4% (n=648) for ezetimibe. For inclisiran in cohort B, the proportion of patients with PDC $\geq 80\%$ was 98.1% (n=767).

The persistence with newly initiated therapy at month 21 in cohort A was 71.7% (203 of 283 participants for which persistence was assessable) with statins, 72.5% (427/589) with ezetimibe, and 62.0% (57/92) with BA. The persistence with inclisiran therapy was 85.5% (407/476) in cohort B1 and 70.4% (50/71) in cohort B2.

Changes in LDL-C over time

The median LDL-C value at baseline was 84.9 mg/dL (Q1/Q3: 73.0 / 106.2, n=745) in patients with escalation of oLLT (cohort A) and thus lower than in patients initiating inclisiran (108.1 mg/dL, [82.2 / 147.0], n=690). LLT escalation resulted in absolute median changes in LDL-C from baseline at month 3 of -28.6 mg/dL (-43.0 / -16.6, n=513) in cohort A and -42.0 mg/dL (-61.0 / -18.5, n=582) in cohort B. LDL-C lowering benchmarks remained stable over the course of the study until month 21 (cohort A: median change of -28.0 mg/dL [-46.0 / -15.0], n=377; cohort B: median change of -38.2 mg/dL [-60.0 / -17.0], n=335).

The cohort of PCSK9i-naïve patients newly initiating inclisiran (cohort B1) showed a relative median LDL-C lowering of -42.6 % (-56.2 / -22.4, n=510) at month 3 and -38.5 % (-53.4 / -20.1, n=295) at month 21, while LDL-C values remained largely stable in the population switching from PCSK9 mAbs (cohort B2; median change of -6.8 % [-41.6 / 33.9, n=72] at month 3 and -18.1 % [-37.5 / 12.2, n=40] at month 21). Overall, high variances in the extent of LDL-C lowering responses were observed in all cohorts.

At month 3, the LDL-C target value of ≤ 55 mg/dL was achieved in 250 of 553 patients (45.2%) in cohort A, 227 of 572 patients (39.7%) in cohort B1, and 8 of 84 patients (9.5%) in cohort B2. A $\geq 50\%$ -reduction from baseline was seen in 88 of 513 patients (17.2%) in cohort A, 172 of 510 patients (33.7%) in cohort B1, and 10 of 72 patients (13.9%) in cohort B2.

Changes in other laboratory variables of the lipid panel

Besides LDL-C, numerical changes in other variables of the lipid panel were observed between baseline and month 21. Observed median changes were as follows: Total cholesterol: -30.5 mg/dL (Q1/Q3: -50.7 / -13.1, n=358) in cohort A and -38.7 mg/dL (-65.0 / -12.4, n=319) in cohort B; non-HDL-C: -26.4 mg/dL (-51.0 / -11.6, n=66) in cohort A and -44.0 mg/dL (-67.0 / -17.8, n=82) in cohort B; and triglycerides: -17.6 mg/dL (-51.3 / 15.0, n=330) in cohort A and -10.0 mg/dL (-46.0 / 19.0, n=291) in cohort B.

Baseline Lp(a) values were available for 49.0% (407 patients) of patients in cohort A and 46.4% (363 patients) of patients in cohort B. Lp(a) levels were considerably higher in cohort B1 (median: 55.1 mg/dL [10.9 / 118.4], n=320) than in cohort B2 (median: 27.0 mg/dL [10.9 / 102.0], n=43) and cohort A (median: 13.2 mg/dL [6.5 / 67.8]). In line with the current guideline recommendation to measure Lp(a) once in a lifetime, the number of patients with repeated Lp(a) measurements available was negligible.

Health resource utilization

Proportions of patients with reported in-patient hospitalizations in-between visits (including the period of 6 months prior to baseline) until month 21 ranged from 2.2% (11/490, month 15-21) to 15.7% (130/830, within 6 months prior to baseline) in cohort A and from 2.3% (10/428, month 15-21) to 7.6% (59/780, within 6 months prior to baseline) in cohort B.

Proportions of patients with reported professional consultations between 2 visits (including the period of 6 months prior to baseline) until month 21 ranged from 27.3% (133/487, month 15-21) to 53.3% (439/823, within 6 months prior to baseline) in cohort A and from 30.6% (210/686, baseline-month3) to 44.3% (334/420, within 6 months prior to baseline) in cohort B.

Only 3 patients (0.4%) overall in cohort B (2 patients in cohort B1 and 1 patient in cohort B2) progressed to lipid apheresis during the study after initiation of inclisiran.

Changes in SMART scores over time

No relevant changes from baseline over time were observed in the analyses of the SMART score.

Patient-reported outcomes

- WHO-QoL: The results on self-reported quality of life using the WHO-QoL questionnaire were similar across cohorts at baseline and suggested largely stable QoL scores over time in both cohorts. Patients scored lowest in the domain physical health at baseline (average of 64.1 ± 17.5 points in the total population [$n=1190$]), but a positive trend was observed in patients receiving inclisiran in cohort B (mean difference to baseline +1 point, 95% CI [-0.63; 2.73]). In cohort A, stable values for physical health were reported over the course of the observation period (mean difference to baseline ± 0 points, 95% CI [-1.98; 1.94]). Interpretation of these findings should, however, consider the lower number of available responses at month 21 (454/929 patients, 48.8%) compared to baseline.
- TSQM-9: From baseline to month 21, mean global treatment satisfaction scores and effectiveness scores increased slightly in both cohort A and in cohort B. Observed increases in treatment satisfaction over time were consistently more pronounced in the population initiating inclisiran compared to patients initiating oLLT. In the dimension assessing the treatment convenience, mean scores in cohort A remained stable (mean change of -0.7 ± 17.8 points at Month 21), whereas an improvement was observed in cohort B (mean change of 4.0 ± 20.6 points).
- Nutrition questionnaire: Due to the high proportion of missing data across items and time points, the low number of valid observations in several response categories, and the small sample size in some subgroups, the nutritional questionnaire data should be interpreted with caution. There was a slight trend towards a more nutrition-conscious profile in cohort B patients compared to cohort A at baseline. Within-cohort changes from baseline were mainly observed in cohort A and predominantly reflected an increase over time in the reported purchase of selected food groups as organic products, while in cohort B the responses were comparatively stable over time, with no significant changes or trends observed in any item.

Adverse events in patients treated with inclisiran

The pattern of documented AEs in the 908 patients treated with inclisiran was consistent with the population of patients with ASCVD and a mostly "very high risk" of CV events. Most of the documented AEs had a mild or moderate intensity. 358 patients (39.4%) reported at least one AE, any SAE was reported in 158 patients (17.4%), study-drug related, non-serious AEs (nsADRs) in 103 patients (11.3%), and study-drug related SAEs (SADRs) in 6 patients (0.7%). Overall, the analyses of adverse events reported in the population of patients exposed to inclisiran in this study did not point to any new or unexpected safety issues that might impact the established safety profile of inclisiran as documented in the current Summary of Product Characteristics (SmPC).

Discussion

The treatment cohorts represented different patient populations in terms of demography and medical characteristics. Patients initiating inclisiran in cohort B showed a trend towards being younger, still working, better educated, more health-conscious, more often with private insurance status, and women seemed to be overrepresented when compared to patients escalating their oLLT. The proportions of patients with statin intolerance/contraindication (cohort A: 3.0%; cohort B: 49.1%) and presence of heFH (cohort A: 1.7%; cohort B: 10.5%) were higher in cohort B than in cohort A. Those trends were even more pronounced in the population switching from PCSK9 mAbs to inclisiran (B2) compared to the PCSK9 naïve population (B1). German registry studies (Stürzebecher *et al.* 2024, Stürzebecher *et al.* 2025) have reported on this patient population that is characterized by therapy intolerances and requires special attention when defining a treatment strategy to achieve target levels.

An important inclusion criterion for this study was that the patients must not have reached their individual LDL-C target value at the time of enrollment into this study. As a result, a selection of patients took place who still had an increased LDL-C value with maximum tolerable statin therapy. Native LDL-C values were not documented. In both treatment cohorts, an early and significant reduction in LDL-C levels was

observed following LLT intensification at baseline (median -34.9 % at month 3 in cohort A, -42.6 % in cohort B1). Patients switching from PCSK9 mAbs to inclisiran showed stabilization of their LDL-C level (median -6.8 % in cohort B2). After 3 months, 45.2% of patients in cohort A, 39.7% of patients in cohort B1 and 9.5% of patients in cohort B2 were brought to the LDL-C target of ≤ 55 mg/dL. Rates of target achievement did not improve significantly over the observation period, although many patients in cohort A had not yet exhausted all LLT options. This reflects known data from European cohort studies that have been showing for years that target achievement in very high-risk ASCVD patients remains unsatisfactory (Arif *et al.* 2026). The median population LDL-C value at the end of observation in cohort A was 55.0 mg/dL (Q1/Q3: 43.6 / 70.0). While this suggests that 75 % were below the target of 70 mg/dL LDL-C, it also shows that most patients could be brought below the target of < 55 mg/dL by further intensification of LLT, a treatment strategy that is recommended for this very high risk population by the ESC/EAS guideline and has been shown to be superior to a target strategy aiming for < 70 mg/dL LDL-C in a recent open-label trial (Lee *et al.* 2026).

The FH status was reported as "unknown" in more than two-thirds of the study patients (1,042 of 1,504 patients, 69.3%), which indicates that screening for genetic predisposition for hyperlipidemia does not play a major role in clinical routine.

The LDL-C baseline values showed that the majority of patients with very high risk of CV events enrolled in this study were not at their individual LDL-C goal 5–6 years after an initial CV event.

The cornerstones of the treatment regimen following the dose escalation at baseline in cohort A were statins (97.0% [n=806] of patients, 72.6% with HIS) and ezetimibe (98.3% of patients). In cohort B, combination partners in addition to inclisiran were statins (50.9% [n=398] of patients, 39.3% with HIS), ezetimibe (55.8%), and BA (33.6%). Inclisiran as monotherapy was used at baseline in 25.2% (n=173) of patients in cohort B1 and 46.3% (n=44) of patients in cohort B2, meaning that a quarter of patients in cohort B1 and almost half of the patients in cohort B2 had a contraindication for, or did not tolerate combination treatment with oLLTs.

A total of 95 patients in cohort B had received PCSK9i prior to treatment with inclisiran, thus representing cohort B2. Reasons for the switch from prior PCSK9i to inclisiran were "adverse effects or intolerance" (34.7%), "no achievement of LDL-C target" (27.4%), "patient wish" (20.0%), "different dose interval" (17.3%), "lack of response to prior therapy" (10.5%), and "application mode" (1.1%). Thus, inclisiran was initiated in a substantial proportion of patients despite prior intolerance and/or inadequate response to PCSK9 inhibitor therapy. This needs to be considered when interpreting the effectiveness data in cohort B2. Although the presence of heFH was an exclusion criterion in this observational study, a genetic reason for complete non-response to PCSK9 inhibition cannot be excluded regarding the low genetic screening rates in these patients (Tandirerung 2025).

In patients initiating inclisiran after discontinuation of previous PCSK9 mAb therapy (cohort B2), the incidence of AEs leading to discontinuation of inclisiran was higher (17/116 patients, 14.7%) than in patients who initiated inclisiran as first PCSK9 targeted therapy (cohort B1, 52/765 patients, 8.8%). This difference between cohort B1 and cohort B2 again suggested that the latter cohort represented a difficult-to-treat patient population that was particularly prone to side effects (German-Cardiac-Society 2026, Makhmudova *et al.* 2023, Raal *et al.* 2024, Stürzebecher *et al.* 2025).

The treatment cohort initiating inclisiran achieved the lowest median LDL-C value at month 3, while the population median LDL-C value slightly increased towards the 9 months and 15 months visit, before decreasing again towards the 21 months visit. The ORION-11 study has shown that the LDL-C lowering effect of inclisiran remains constant over a period of at least 510 days. At the same time, it is known that patients who initiate a long-acting PCSK9 antibody therapy are more likely to discontinue their oLLT (Engebretsen *et al.* 2025, LaFratte *et al.* 2023). The same effect might be true for some patients initiating inclisiran in this study, which could explain the observed increase in median LDL-C levels. Post-hoc adherence analyses on individual patient level might provide insights on this hypothesis.

The safety profile of inclisiran documented in this study was consistent with the reference safety information provided in the current SmPC, and no new or otherwise relevant safety findings were observed.

Conclusion

The results of this observational study supported those of the preceding pivotal trials on inclisiran and suggest that inclisiran is a well-tolerated and effective adjunct therapy for patients who are unable to achieve their LDL-C goals with statins in routine clinical practice. This appears particularly relevant for patients who are unable to achieve adequate lipid control due to multiple therapy intolerances and who

are not suitable for standard treatment with statins or other oLLTs. Treatment satisfaction reports and very low discontinuation rates suggest that the mode of administration and prolonged dosing intervals may support long-term adherence to and persistence with LLT, which are critical for treatment success in chronic disease management. Nevertheless, these real-world data from multiple specialized sites in Germany also indicate that, despite frequent consultations of different specialists and a wide range of available LLT options, a considerable proportion of patients at very high CV risk remain inadequately controlled. These findings highlight an ongoing unmet medical need for closer patient monitoring and education, as well as for additional effective treatment strategies to further reduce the risk of potentially life-threatening CV events in patients with ASCVD at very high risk.

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