Inclisiran – clinical data
Inclisiran is a siRNA that mimics the body’s process of RNA interference, thus increasing LDLRs on the liver.

Small interfering double-stranded RNA\textsuperscript{1,2}

- Acts in the hepatocyte at the level of the cytoplasm, not the nucleus\textsuperscript{1}
- Mimics the RNA interference pathway to prevent production of PCSK9 protein by degradation of its mRNA\textsuperscript{2}
- Has nucleotides which are modified for durability\textsuperscript{2}
- Conjugated with GalNAc for targeted delivery to the liver\textsuperscript{2}
**December 2020: Novartis receives EU approval for Inclisiran, a first-in-class siRNA to lower cholesterol with two doses a year**

Inclisiran is approved for the treatment of adults with primary hypercholesterolemia (heterozygous familial and non-familial) or mixed dyslipidemia, as an adjunct to diet:

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

**After an initial dose and one at 3 months**
### 2019 ESC/EAS guideline treatment goals for LDL-C according to risk categories

<table>
<thead>
<tr>
<th>CV Risk</th>
<th>Treatment goal for LDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>3.0 mmol/L (116 mg/dL)</td>
</tr>
<tr>
<td>Moderate</td>
<td>2.6 mmol/L (100 mg/dL)</td>
</tr>
<tr>
<td>High</td>
<td>1.8 mmol/L (70 mg/dL)</td>
</tr>
<tr>
<td>Very High</td>
<td>1.4 mmol/L (55 mg/dL)</td>
</tr>
</tbody>
</table>

#### Treatment goals

- **Low Risk**
  - SCORE* <1%
- **Moderate Risk**
  - SCORE* ≥1% and <5%
  - Young patients (T1DM <35 years; T2DM <50 years) with DM duration <10 years without other risk factors
- **High Risk**
  - SCORE* ≥5% and <10%
  - Markedly elevated single risk factors, in particular TC >8 mmol/L (310 mg/dL) or LDL-C >4.9 mmol/L (190 mg/dL) or BP ≥180/110 mmHg
  - FH without other major risk factors
  - Moderate CKD (eGFR 30–59 mL/min)
  - DM without target organ damage, with DM duration ≥10 years or other additional risk factor
- **Very High Risk**
  - ASCVD (clinical/imaging)
  - SCORE* ≥10%
  - FH with ASCVD or with another major risk factor
  - Severe CKD (eGFR <30 mL/min)
  - DM & target organ damage: ≥3 major risk factors; or early onset of T1DM of long duration (>20 years)

---

* Systematic Coronary Risk Estimation (SCORE) for 10-year risk of fatal CVD

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*Mach F et al. Eur Heart J. 2020; 41:111-88*
DA VINCI study demonstrates current gaps in reaching 2016 and 2019 ESC/EAS LDL-C goals

Overall, **54%** attainment overall risk-based **2016 goal**
- low risk: 63%
- moderate risk: 75%
- high risk: 63%
- very high risk: 39%

Only **33%** attained overall **2019 goal**

In patients with established ASCVD, 2019 goal attainment was approximately **half** that of **2016**

A comprehensive clinical trial program profiles the efficacy and safety of inclisiran

1. Lipid biomarkers

- ORION-6\(^{1,2}\) (Impaired hepatic function)
- ORION-7\(^3\) (Patients with renal impairment)
- ORION-12\(^{1,2}\) (T-QT)
- ALN-PCSSC-001\(^4\) (Hypercholesterolemia; SAD/MD*)

2. Cardiovascular outcomes

- ORION-1\(^5\) (ASCVD)
- ORION-2\(^6\) (HoFH Pilot)
- ORION-3\(^7\) (Long-term effect ORION-1 extension)

3. Pediatrics

- ORION-3\(^{15}\) (ASCVD & risk equivalents)

4. Plaque burden

- ORION-5\(^8\) (HoFH)
- ORION-6\(^9\) (ASCVD)
- ORION-11\(^{13}\) (ASCVD & risk equivalents)
- ORION-9\(^{11}\) (HeFH)
- ORION-10\(^{12}\) (ASCVD)
- ORION-18\(^{16}\) (ASCVD & risk equivalents)

- ORION-4\(^8\) (CVOT and LDL-C extension)
- ORION-10\(^{12}\) (ASCVD)
- ORION-11\(^{13}\) (ASCVD & risk equivalents)

- ORION-13\(^{14}\) (HoFH)
- ORION-16\(^{15}\) (HeFH)

*SAD/MD=single ascending dose/multiple dose.

A comprehensive clinical trial program profiles the efficacy and safety of inclisiran.

**Phase 1**
- ORION-6\(^{1,2}\) (Impaired hepatic function)
- ORION-7\(^3\) (Patients with renal impairment)
- ORION-12\(^{1,2}\) (T-QT)
- ALN-PCSSC-001\(^4\) (Hypercholesterolemia; SAD/MD*)

**Phase 2**
- ORION-1\(^5\) (ASCVD)
- ORION-2\(^6\) (HoFH Pilot)
- ORION-3\(^7\) (Long-term effect ORION-1 extension)

**Phase 3**
- ORION-4\(^8\) (CVOT and LDL-C extension)
- ORION-5\(^9\) (HoFH)
- ORION-10\(^{12}\) (ASCVD)
- ORION-8\(^{10}\) (Long-term effect ORION-9, -10, -11 extension)
- ORION-9\(^{11}\) (HeFH)
- ORION-11\(^{13}\) (ASCVD & risk equivalents)

**Secondary Prevention**
- ORION-13\(^{14}\) (HoFH)
- ORION-16\(^{15}\) (HeFH)

**Primary Prevention**
- ORION-12\(^{1}\),\(^{2}\) (T-QT)
- ORION-10,\(^{11}\),\(^{12}\) (ASCVD & risk equivalents)

**In planning**
- ORION-13\(^{14}\) (ASCVD)
- ORION-15\(^{16}\) (HeFH)

---

* SAD/MD = single ascending dose/multiple dose.

3. NCT03159416.
4. NCT02314442.
5. NCT02597127.
6. NCT02963311.
7. NCT03060577.
8. NCT03705234.
9. NCT03851705.
10. NCT03814187.
11. NCT03397121.
12. NCT0399370.
13. NCT0399370.
14. NCT04659863.
15. NCT04652726.
16. NCT04765657

---

[Novartis Logo]

Reimagining Medicine
### Phase 3 ORION-9, -10, and -11

Study inclusion/exclusion criteria

<table>
<thead>
<tr>
<th>Trial Specific Inclusion Criteria</th>
<th>ORION-9&lt;sup&gt;1,2&lt;/sup&gt; (n=482)</th>
<th>ORION-10&lt;sup&gt;3,4&lt;/sup&gt; (n=1561)</th>
<th>ORION-11&lt;sup&gt;3,4&lt;/sup&gt; (n=1617)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HeFH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stable on a low-fat diet</td>
<td>-</td>
<td>-</td>
<td>ASCVD risk equivalents</td>
</tr>
<tr>
<td>LDL-C ≥2.6 mmol/L (100 mg/dL)</td>
<td>LDL-C ≥1.8 mmol/L (70 mg/dL)</td>
<td>ASCVD (CHD, CVD, PAD)</td>
<td></td>
</tr>
</tbody>
</table>

### Common key inclusion criteria:

- ≥18 years of age; fasting triglyceride <4.52 mmol/L (<400 mg/dL) at screening; had received statin treatment at the maximally tolerated dose or demonstrated documented intolerance. Ezetimibe therapy was allowed.

### Common key exclusion criteria:

- Prior or planned use of a PCSK9 mAb; MACE within 3 months of randomization; had prior/planned use of other investigational drugs; NYHA class IV heart failure or LVEF <25%; uncontrolled severe hypertension; severe concomitant non CV disease; fasting TG ≥4.52 mmol/L (400 mg/dL).

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Phase 3 ORION-9, -10, and -11
Study design and endpoints1-4

18-month, double-blind, randomized, placebo-controlled

Randomized 1:1 inclisiran 300 mg* vs placebo – on top of maximal tolerated statin dose

Screening
Day -14 to -1

Study assessments

V1 Day 1 V2 Day 30 V3 Day 90 V4 Day 150 V5 Day 270 V6 Day 330 V7 Day 450 V8 Day 510

End of study
Day 540 (V9)
90 days post last dose

Key primary endpoints

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

Key secondary endpoints

- Absolute change in LDL-C from baseline to Day 510
- Time-adjusted absolute change in LDL-C from baseline between Day 90 and up to Day 540
- Percentage change from baseline to Day 510 in PCSK9, TC, ApoB, and non-HDL-C
- Safety and tolerability profile of inclisiran, measured by AEs, SAEs, vital signs, and clinical laboratory values

*300 mg inclisiran sodium salt, equivalent to 284 mg of inclisiran.

### Phase 3 ORION-9, -10, and -11
Baseline demographics (overall study population)\(^1,2\)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ORION-9(^1)</th>
<th>ORION-10(^2)</th>
<th>ORION-11(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>HeFH (n=482)</td>
<td>ASCVD (n=1561)</td>
<td>ASCVD/risk equivalent (n=1617)</td>
</tr>
<tr>
<td>ASCVD status (%)</td>
<td>27.4%</td>
<td>100%</td>
<td>87.4% (ASCVD) 12.6% (risk equivalents)</td>
</tr>
<tr>
<td>Average age (yr)</td>
<td>56</td>
<td>66</td>
<td>65</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>47.1%</td>
<td>69.4%</td>
<td>71.7%</td>
</tr>
<tr>
<td>LDL-C</td>
<td>4.0 mmol/L (153.1 mg/dL)</td>
<td>2.71 mmol/L (104.7 mg/dL)</td>
<td>2.73 mmol/L (105.5 mg/dL)</td>
</tr>
<tr>
<td>Statin use (%)</td>
<td>90.5%</td>
<td>89.2%</td>
<td>94.7%</td>
</tr>
<tr>
<td>High intensity statin use (%)</td>
<td>73.9%</td>
<td>68%</td>
<td>78.6%</td>
</tr>
<tr>
<td>Ezetimibe use</td>
<td>52.9%</td>
<td>9.9%</td>
<td>7.1%</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>10%</td>
<td>44.9%</td>
<td>35.1%</td>
</tr>
</tbody>
</table>

Phase 3 ORION-9, -10, and -11
Primary endpoint: differential LDL-C percentage change Day 510

Significant reductions in LDL-C percent change with inclisiran vs placebo on top of maximally tolerated statin dose at Day 510 (range, -47.9% – 52.3%)

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient Population</th>
<th>Between group difference</th>
<th>% change in LDL-C from baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORION-9</td>
<td>(HeFH) N=482</td>
<td>-47.9% (P&lt;0.001)</td>
<td>-39.7%</td>
</tr>
<tr>
<td>ORION-10</td>
<td>(ASCVD) N=1561</td>
<td>-52.3% (P&lt;0.001)</td>
<td>-51.3%</td>
</tr>
<tr>
<td>ORION-11</td>
<td>(ASCVD, ASCVD risk equivalents) N=1617</td>
<td>-49.9% (P&lt;0.001)</td>
<td>-45.8%</td>
</tr>
</tbody>
</table>

Phase 3 ORION-9, -10, and -11
Inclisiran provides effective and sustained LDL-C lowering over 18 months

![Percent change in LDL-C over time](image)

Phase 3 ORION-9, -10, and -11
Primary endpoint: differential time-adjusted LDL-C percentage change after Day 90 and up to Day 540

Significant reductions in LDL-C percent change with inclisiran vs placebo on top of maximally tolerated statin dose after Day 90 and up to Day 540 (range, -44.3% – -53.8%)

<table>
<thead>
<tr>
<th>Study</th>
<th>LDL-C Percent Change</th>
<th>Between Group Difference</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORION-9 (HeFH)</td>
<td>-38.1</td>
<td>6.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ORION-10 (ASCVD)</td>
<td>-51.3</td>
<td>2.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ORION-11 (ASCVD, ASCVD risk equivalents)</td>
<td>-45.8</td>
<td>3.4</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Phase 3 ORION-9, -10, and -11
Secondary endpoint: differential absolute reduction in LDL-C Day 510

**Significant absolute reduction in LDL-C with inclisiran vs placebo on top of maximally tolerated statin dose at Day 510 (range, 51.9 mg/dL [1.34 mmol/L] – 68.9 mg/dL [1.8 mmol/L])**

<table>
<thead>
<tr>
<th>Study</th>
<th>Baseline LDL-C</th>
<th>Inclisiran LDL-C</th>
<th>Placebo LDL-C</th>
<th>Between group difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORION-9</td>
<td>51.9 mg/dL</td>
<td>50.9 mg/dL</td>
<td>56.2 mg/dL</td>
<td>-5.3 mg/dL [-0.15 mmol/L]</td>
</tr>
<tr>
<td>ORION-10</td>
<td>54.1 mg/dL</td>
<td>53.9 mg/dL</td>
<td>56.2 mg/dL</td>
<td>-2.3 mg/dL [-0.15 mmol/L]</td>
</tr>
<tr>
<td>ORION-11</td>
<td>68.9 mg/dL</td>
<td>50.9 mg/dL</td>
<td>68.9 mg/dL</td>
<td>-19.0 mg/dL [-0.27 mmol/L]</td>
</tr>
</tbody>
</table>

**Note:** LDL-C values are given in mg/dL and mmol/L.

Phase 3 ORION-9, -10, and -11
Secondary endpoint: Percentage of patients with ≥50% reduction in LDL-C from baseline at Day 510

Inclisiran reduced LDL-C by ≥50% in clinical studies involving patients with HeFH, ASCVD, and ASCVD risk equivalents

<table>
<thead>
<tr>
<th>Study</th>
<th>% of patients with ≥50% reduction in LDL-C from baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORION-9 (HeFH) N=482</td>
<td>38</td>
</tr>
<tr>
<td>ORION-10 (ASCVD) N=1561</td>
<td>72.8</td>
</tr>
<tr>
<td>ORION-11 (ASCVD, ASCVD risk equivalents) N=1617</td>
<td>57.7</td>
</tr>
</tbody>
</table>

Phase 3 ORION-9, -10, and -11
Percentage of patients achieving indicated LDL-C thresholds at Day 510*

<table>
<thead>
<tr>
<th>THRESHOLD³</th>
<th>Placebo (%)</th>
<th>Inclisiran (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2.6 mmol/L (100 mg/dL)</td>
<td>8.8</td>
<td>65.3</td>
</tr>
<tr>
<td>&lt;1.8 mmol/L (70 mg/dL)</td>
<td>1.3</td>
<td>40.9</td>
</tr>
<tr>
<td>&lt;1.3 mmol/L (50 mg/dL)</td>
<td>0.8</td>
<td>19.0</td>
</tr>
<tr>
<td>&lt;0.65 mmol/L (25 mg/dL)</td>
<td>0</td>
<td>0.8</td>
</tr>
</tbody>
</table>

Up to 74% of patients from ORION-10 and ORION-11 were able to achieve guideline recommended LDL-C levels <70 mg/dL (<1.8 mmol/L) with inclisiran

---

*Subjects can be represented in more than one category.

Phase 3 ORION-9, -10, and -11
Inclisiran lowers plasma PCSK9 levels and other lipids

<table>
<thead>
<tr>
<th>Percent change at Day 510</th>
<th>ORION-9¹,² (HeFH) N=482</th>
<th>ORION-10³,⁴ (ASCVD) N=1561</th>
<th>ORION-11³,⁴ (ASCVD, ASCVD risk equivalents) N=1617</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Inclisiran</td>
<td>Placebo</td>
<td>Inclisiran</td>
</tr>
<tr>
<td>PCSK9</td>
<td>-60.7%</td>
<td>+17.7%</td>
<td>-69.8%</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>-26.1%</td>
<td>+6.8%</td>
<td>-33.6%</td>
</tr>
<tr>
<td>Non-HDL cholesterol</td>
<td>-36.1%</td>
<td>+7.5%</td>
<td>-47.4%</td>
</tr>
<tr>
<td>ApoB</td>
<td>-34.0%</td>
<td>+2.9%</td>
<td>-44.8%</td>
</tr>
<tr>
<td>Lp(a)* (median)</td>
<td>-13.5%</td>
<td>+3.7%</td>
<td>-21.9%</td>
</tr>
<tr>
<td>HDL-C</td>
<td>+8.6%</td>
<td>+6.0%</td>
<td>+7.5%</td>
</tr>
</tbody>
</table>

¹Day 540 sampling.

Phase 3 ORION-9, -10, and -11
Decrease in LDL-C observed across pre-specified sub-populations

ORION-10 and ORION-11: Subgroup analysis of placebo-corrected percentage change in LDL-C from baseline to Day 510 (ITT population)

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>male or female</th>
<th>&lt;65 or ≥65</th>
<th>On statin or not on statin</th>
<th>High intensity statin or not on high intensity statin</th>
<th>Diabetes, metabolic syndrome, or neither</th>
<th>ASCVD or ASCVD equivalent</th>
<th>Normal, mild impairment, moderate impairment</th>
</tr>
</thead>
</table>

ORION-9: Subgroup analysis according to genotype* showed robust reductions in LDL-C in all genotypes

*Presence or absence of a monogenic familial hypercholesterolemia variant and according to the presence or absence of variants in LDLR, APOB, and PCSK9.

What is the efficacy of inclisiran?

Two doses of the 300 mg inclisiran* regimen at Day 0 and Day 90 showed the greatest efficacy over the dosing interval of 6 months compared to one dose only in a phase 2 trial1

Inclisiran provides effective and sustained lowering of LDL-C2,3

The decrease in LDL-C was observed across pre-specified sub-populations, including patients with metabolic disease (diabetes, metabolic syndrome) and/or impaired renal function2,3

*300 mg inclisiran sodium salt, equivalent to 284 mg of inclisiran.
What is the safety profile of inclisiran?

Inclisiran has a safety profile generally similar to placebo.
Phase 3 ORION-9
AEs and SAEs were generally similar between the inclisiran and placebo groups

### Adverse Events and Serious Adverse Events – Safety Population*

<table>
<thead>
<tr>
<th>Event</th>
<th>Inclisiran</th>
<th>Placebo</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1 AE</td>
<td>185 (76.8)</td>
<td>172 (71.7)</td>
<td>1.1 (1.0–1.2)</td>
</tr>
<tr>
<td>≥1 SAE</td>
<td>18 (7.5)</td>
<td>33 (13.8)</td>
<td>0.5 (0.3–0.9)</td>
</tr>
<tr>
<td>≥1 AE leading to discontinuation</td>
<td>3 (1.2)</td>
<td>0</td>
<td>NA</td>
</tr>
</tbody>
</table>

### Frequent adverse events

<table>
<thead>
<tr>
<th>Event</th>
<th>Inclisiran</th>
<th>Placebo</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasopharyngitis</td>
<td>28 (11.6)</td>
<td>20 (8.3)</td>
<td>1.4 (0.8–2.4)</td>
</tr>
<tr>
<td>Influenza</td>
<td>13 (5.4)</td>
<td>21 (8.8)</td>
<td>0.6 (0.3–1.2)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>16 (6.6)</td>
<td>16 (6.7)</td>
<td>1.0 (0.5–1.9)</td>
</tr>
<tr>
<td>Back pain</td>
<td>17 (7.1)</td>
<td>10 (4.2)</td>
<td>1.7 (0.8–3.6)</td>
</tr>
<tr>
<td>Injection site reaction</td>
<td>22 (9.1)</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>11 (4.6)</td>
<td>6 (2.5)</td>
<td>1.8 (0.7–4.9)</td>
</tr>
</tbody>
</table>

### Protocol defined injection site reactions

<table>
<thead>
<tr>
<th>Event</th>
<th>Inclisiran</th>
<th>Placebo</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>(most events were mild and transient)</td>
<td>41 (17.0)</td>
<td>4 (1.7)</td>
<td>10.2 (3.7–28.1)</td>
</tr>
</tbody>
</table>

*Shown are events occurring with a frequency of 5% or more in either the inclisiran group or the placebo group in each trial. The safety population included all the patients who received at least 1 dose of inclisiran or placebo.

Adverse events were recorded over the trial period of 540 days.

- More participants experienced TEAEs at the injection site reaction in the inclisiran group
- They were predominantly mild; none were severe or persistent

Phase 3 ORION-10
AEs and SAEs were generally similar between the inclisiran and placebo groups

<table>
<thead>
<tr>
<th>Adverse Events and Serious Adverse Events – Safety Population*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclisiran</td>
</tr>
<tr>
<td>N=781 No. of patients (%)</td>
</tr>
<tr>
<td>≥1 AE</td>
</tr>
<tr>
<td>≥1 SAE</td>
</tr>
<tr>
<td>≥1 AE leading to discontinuation</td>
</tr>
</tbody>
</table>

Frequent adverse events
- Diabetes mellitus | 120 (15.4) | 108 (13.9) | 1.1 (0.9–1.4) |
- Bronchitis | 46 (5.9) | 30 (3.9) | 1.5 (1.0–2.4) |
- Hypertension | 42 (5.4) | 42 (5.4) | 1.0 (0.7–1.5) |
- Back pain | 39 (5.0) | 39 (5.0) | 1.0 (0.6–1.5) |
- Upper respiratory tract infection | 39 (5.0) | 33 (4.2) | 1.2 (0.7–1.9) |
- Dyspnoea | 39 (5.0) | 33 (4.2) | 1.2 (0.7–1.9) |

Protocol defined injection site reactions (most events were mild and transient) | 20 (2.6) | 7 (0.9) | 2.9 (1.2–6.7) |

*Shown are events occurring with a frequency of 5% or more in either the inclisiran group or the placebo group in each trial. The safety population included all the patients who received at least 1 dose of inclisiran or placebo. Adverse events were recorded over the trial period of 540 days.

• More participants experienced TEAEs at the injection site reaction in the inclisiran group
• They were predominantly mild; none were severe or persistent
## Adverse Events and Serious Adverse Events – Safety Population*

<table>
<thead>
<tr>
<th></th>
<th>Inclisiran</th>
<th>Placebo</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=811 No. of patients (%)</td>
<td>N=804 No. of patients (%)</td>
<td></td>
</tr>
<tr>
<td>≥1 AE</td>
<td>671 (82.7)</td>
<td>655 (81.5)</td>
<td>1.0 (0.9–1.1)</td>
</tr>
<tr>
<td>≥1 SAE</td>
<td>181 (22.3)</td>
<td>181 (22.5)</td>
<td>1.0 (0.8–1.2)</td>
</tr>
<tr>
<td>≥1 AE leading to discontinuation</td>
<td>23 (2.8)</td>
<td>18 (2.2)</td>
<td>1.3 (0.7–2.3)</td>
</tr>
<tr>
<td>Frequent adverse events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>91 (11.2)</td>
<td>90 (11.2)</td>
<td>1.0 (0.8–1.3)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>88 (10.9)</td>
<td>94 (11.7)</td>
<td>0.9 (0.7–1.2)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>53 (6.5)</td>
<td>54 (6.7)</td>
<td>1.0 (0.7–1.4)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>52 (6.4)</td>
<td>49 (6.1)</td>
<td>1.1 (0.7–1.5)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>47 (5.8)</td>
<td>32 (4.0)</td>
<td>1.5 (0.9–2.3)</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>32 (3.9)</td>
<td>40 (5.0)</td>
<td>0.8 (0.5–1.2)</td>
</tr>
<tr>
<td>Protocol defined injection site reactions (most events were mild and transient)</td>
<td>38 (4.7)</td>
<td>4 (0.5)</td>
<td>9.4 (3.4–26.3)</td>
</tr>
</tbody>
</table>

*Shown are events occurring with a frequency of 5% or more in either the inclisiran group or the placebo group in each trial. The safety population included all the patients who received at least 1 dose of inclisiran or placebo. Adverse events were recorded over the trial period of 540 days.


- More participants experienced TEAEs at the injection site reaction in the inclisiran group
- They were predominantly mild; none were severe or persistent
Studies are ongoing to evaluate inclisiran long-term outcomes ~48 months

**ORION-3**
- Patients ≥18 years of age
- Completion of ORION-1
- N=490

**ORION-8**
- Patients ≥18 years of age
- Completion of ORION-9, -10, -11, or -5
- N=2991

**ORION-4**
- Patients ≥55 years with ASCVD (prior MI, prior stroke or PAD)
- N=15,000*

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*Please see most recent information available at clinicaltrials.gov for estimated primary completion date.
What is the safety profile of inclisiran?

Inclisiran was well-tolerated with a safety profile similar to placebo in the current evidence at hand\(^1,2\)

The safety profile of inclisiran has been informed in more than 3500 patients by a comprehensive clinical development program including 3 confirmatory phase 3 studies: ORION-9, -10, and -11\(^1,2\)

Treatment-related AEs were similar in both groups with the exception of injection site reactions that were more frequent in the inclisiran group. Those were predominantly mild; none were severe or persistent\(^1,2\)

SAEs and AEs leading to discontinuation were also balanced among both arms\(^1,2\)

The ongoing cardiovascular outcomes trial (ORION-4, approx. 15,000 patients) and data from open-label extension trials of the phase 3 program (ORION-3 and ORION-8) will provide additional information on the long-term safety profile\(^3-5\)

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How is inclisiran administered?

Inclisiran provides effective and sustained LDL-C lowering with 2 maintenance doses per year.
Inclisiran provides effective and sustained LDL-C lowering with 2 maintenance doses per year

**Inclisiran dosing 2 doses per year**

**Administration**¹⁻³

- Inclisiran 300 mg† administered on:
  - **Day 1**, at **3 months** then **2 maintenance doses per year every 6 months** thereafter
- Subcutaneous injection administered by a healthcare provider
- No dose adjustments for renal impairment

**Safety**²⁻³

- Local skin reactions; majority were mild and transient

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¹In the maintenance phase.
²300 mg inclisiran sodium salt, equivalent to 284 mg of inclisiran.
³In the maintenance phase.

Medication burden impairs adherence and average LDL-C reduction over time

Therapeutic advances reducing the burden of long-term adherence and exposure to risk factors could improve population health

This material is dedicated to health care professionals in Romania.

For more information on product characteristics please see:

Inclisiran  Summary of Product Characteristics (europa.eu)

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Inclisiran – clinical data