References

Indication and Clinical Use:

LEQVIO® (inclisiran injection) is indicated as an adjunct to lifestyle changes, including diet, to further reduce low-density lipoprotein cholesterol (LDL-C) level in adults with the following conditions who are on a maximally tolerated dose of a statin, with or without other LDL-C-lowering therapies:

- Heterozygous familial hypercholesterolemia (HeFH), or
- Non-familial hypercholesterolemia with atherosclerotic cardiovascular disease

The effect of LEQVIO® on cardiovascular morbidity and mortality has not been determined.

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

Geriatrics (≥65 years of age): Of the 1,833 patients treated with inclisiran in the Phase III program, 981 (54%) patients were 65 years of age and older, while 239 (13%) patients were 75 years of age and older. Elderly subjects with heterozygous familial hypercholesterolemia were however less represented (22% were aged ≥65 years). No overall differences in safety or efficacy were observed between patients aged ≥65 years and younger patients.

Contraindications:

- Hypersensitivity to LEQVIO® or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container.
- For lipid-lowering therapies such as statin or other lipid-lowering therapies used in combination with LEQVIO®, see the CONTRAINDICATIONS section of the product monographs for those medications.

Relevant Warnings and Precautions:

- **Endocrine and metabolism:** Disturbances in glucose metabolism homeostasis have been observed in patients treated with LEQVIO®. Periodic monitoring of patients at high risk of diabetes mellitus is recommended (e.g., metabolic syndrome).
- **Hepatic/Biliary/Pancreatic:** The safety and efficacy of LEQVIO® in patients with severe hepatic impairment have not been studied. Patients with active liver disease were excluded from the pivotal trials. Transaminase elevations have been observed in patients treated with LEQVIO®. Transaminase elevations generally occurred after 6 months following initiation of treatment. The effect was usually transient, although some patients experienced a sustained effect (i.e., for at least 2 consecutive visits). Patients with an active liver disease or unexplained elevations in ALT, AST, >3x the ULN, or total bilirubin >2x ULN, were excluded from the pivotal trials. Treatment should be discontinued for severe or clinically significant transaminase elevations. For resumption of dosing after interruption see DOSING AND ADMINISTRATION in the Product Monograph.
- **Injection-site reactions:** Injection-site reactions have been reported in approximately 8% of patients receiving LEQVIO® in the placebo-controlled trials. Symptoms included erythema, pain, pruritis, rash, bruising, or discolouration around the injection site. The severity of the reaction was predominantly mild. Monitor for reactions and manage clinically as needed.
- **Renal:** Due to limited data, the safety and efficacy of LEQVIO® in patients with severe renal impairment could not be established. The safety and efficacy of LEQVIO® in patients with end-stage renal disease with or without hemodialysis have not been studied. The pivotal trials only included patients with calculated glomerular filtration rate >30 mL/min and no current or planned renal dialysis or renal transplantation.
- **Pregnant or breastfeeding women:** There are no or limited amount of data from the use of inclisiran in pregnant women. Inclisiran should not be used during pregnancy. It is unknown if inclisiran is excreted in human milk; however, a risk to the suckling child cannot be excluded. A decision must be made whether to discontinue breastfeeding or to discontinue/abstain from inclisiran therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.
- **Fertility:** There are no data on the effect of LEQVIO® on human fertility. No effects on fertility were observed in female and male rats at doses equivalent to 20.4-fold and 44.1-fold based on area under the curve (AUC), compared to exposures observed at the maximum recommended human dose – MRHD.

For more information:

Consult the Product Monograph at https://www.ask.novartispharma.ca/download.htm?res=leqvio_scrip_e.pdf&resTitleId=1816 for important information relating to adverse drug reactions, drug interactions and dosing information which have not been discussed in this piece. The Product Monograph is also available by calling 1-800-363-8883 or emailing medinfo.canada@novartis.com.

Scan the QR code to access the LEQVIO® Product Monograph.

NEXT

References

As an adjunct to lifestyle changes and a maximally tolerated dose of statin with or without other LDL-C-lowering therapies[1]

CONSIDER PrLEQVIO®

The first-and-only siRNA PCSK9 inhibitor†‡

THE FIRST siRNA PCSK9 INHIBITOR THAT CAN HAVE A TWICE-ANNUAL DOSING REGIMEN†§

The recommended dose of LEQVIO® is 284 mg administered as a single subcutaneous injection: initially, again at 3 months, and then once every 6 months.§

LEQVIO® is a double-stranded siRNA that causes the degradation of PCSK9 mRNA.†

LDL-C = low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin kexin-9; siRNA = small interfering ribonucleic acid.
† Clinical significance is unknown.
‡ Comparative clinical significance has not been established.
§ Consult the LEQVIO® Product Monograph for complete dosing information.

LEQVIO®: A siRNA PCSK9 inhibitor that can have a twice-annual dosing regimen[1†‡§]

The recommended dose of LEQVIO® is 284 mg administered as a single subcutaneous injection: initially, again at 3 months, followed by a dose every 6 months[1‡§]

HCP administration of LEQVIO®[1]

Each pre-filled syringe contains 284 mg LEQVIO® in 1.5 mL of solution.[1]

- HCP-administered[1¶]
- Single-dose prefilled syringe[1††]
- Single subcutaneous injection[‡‡] per dose[1]

HCP = healthcare provider; PCSK9 = proprotein convertase subtilisin kexin-9; siRNA = small interfering ribonucleic acid.
† Comparative clinical significance is unknown.
‡ Clinical significance has not been established.
§ Consult the LEQVIO® Product Monograph for complete dosing schedule.
¶ LEQVIO® is intended for administration by a healthcare professional (doctor, nurse, or pharmacist).
†† Each 284 mg dose is administered using a single pre-filled syringe. Each pre-filled syringe is for single use only.
‡‡ LEQVIO® is for subcutaneous injection into the abdomen. Injections should not be given into areas of active skin disease or injury, such as sunburns, skin rashes, inflammation, or skin infections.

PRODUCT INFORMATION

LEQVIO® PRODUCT INFORMATION

- Store between 15°C and 25°C. Do not freeze.
- Discard after single use.
- Dispose of the syringe and needle in an approved sharps container.

LEQVIO® significantly reduced LDL-C vs. placebo in patients who have non-familial hypercholesterolemia with ASCVD

In the ORION-10 clinical trial, LEQVIO® demonstrated a:

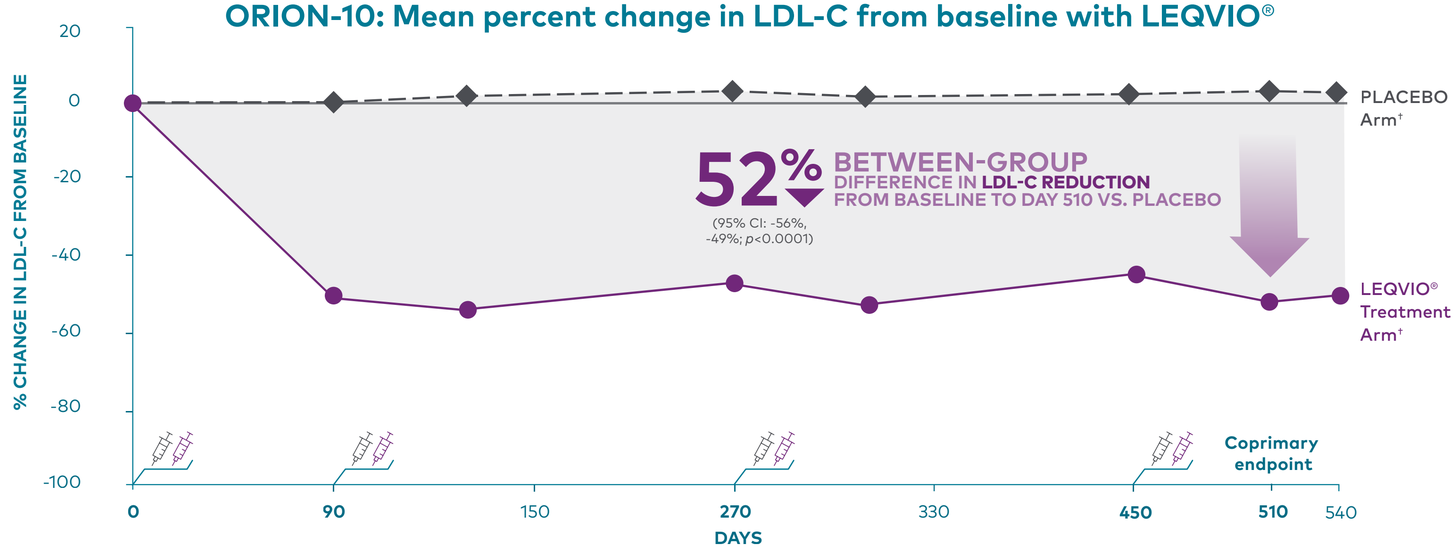
Coprimary Endpoint 1 | Coprimary Endpoint 2

Enlarge Graph

Patients treated with LEQVIO® experienced a greater mean percent-change reduction in LDL-C from baseline to Day 510 compared to placebo (-51% vs. 1%, respectively).

- Producing a between-group difference of -52% (95% CI: -56%, -49%; $p<0.0001$)

ORION-10: Mean percent change in LDL-C from baseline with LEQVIO®



Placebo Arm (n):	780	762	745	724	715	698	666	670
LEQVIO® Treatment Arm (n):	781	758	757	737	731	721	691	705

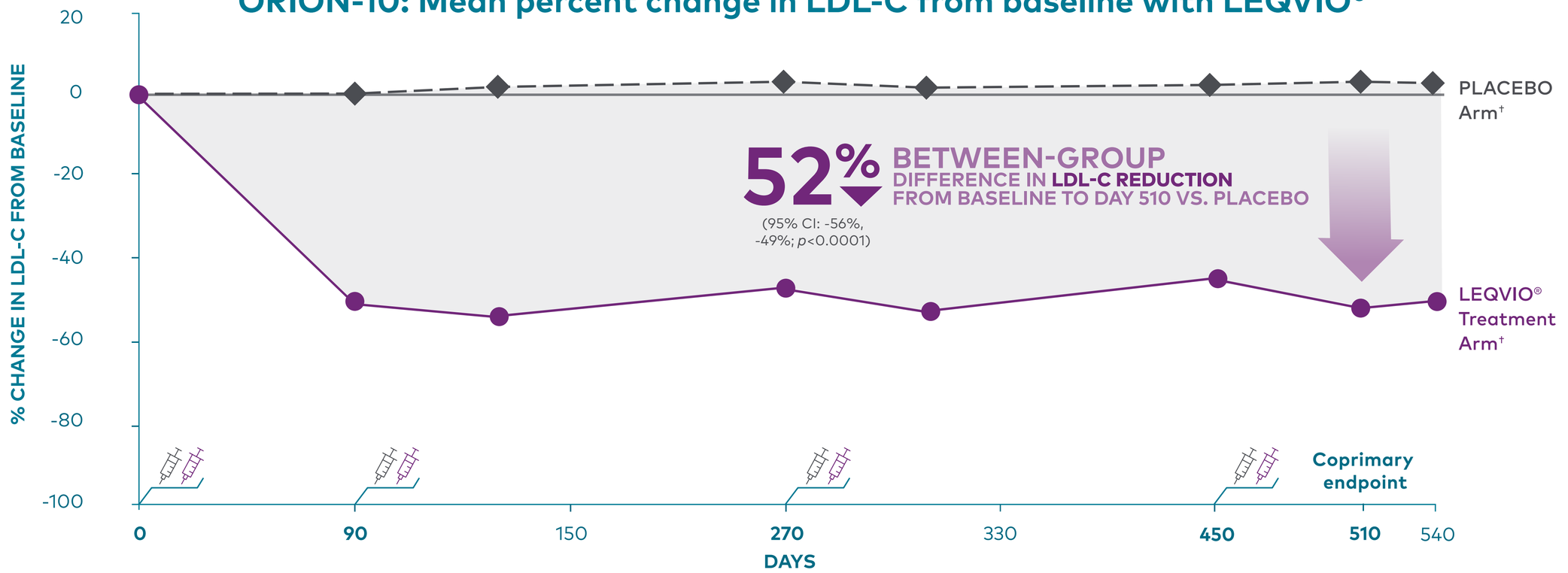
Adapted from the LEQVIO® Product Monograph.

ASCVD = atherosclerotic cardiovascular disease; CI = confidence interval; LDL-C = low-density lipoprotein cholesterol.
† Patients in each study arm in the ORION-10 clinical trial were receiving a maximally tolerated dose of statin, with or without other lipid-modifying therapy, such as ezetimibe.

Clinical Trial Designs | **Subgroup Analyses** | **Other Secondary Endpoints**

Home | Dosing | Efficacy Data ASCVD | Efficacy Data HeFH | Safety Data | MOA | LEQVIO® Assist PSP | Summary | Fair Balance

ORION-10: Mean percent change in LDL-C from baseline with LEQVIO®



Placebo Arm (n):	780	762	745	724	715	698	666	670
LEQVIO® Treatment Arm (n):	781	758	757	737	731	721	691	705

Adapted from the LEQVIO® Product Monograph.

CI = confidence interval; LDL-C = low-density lipoprotein cholesterol.
† Patients in each study arm in the ORION-10 clinical trial were receiving a maximally tolerated dose of statin, with or without other lipid-modifying therapy, such as ezetimibe.

LEQVIO® significantly reduced LDL-C vs. placebo in patients who have non-familial hypercholesterolemia with ASCVD

In the ORION-10 clinical trial, LEQVIO® demonstrated a:

Coprimary Endpoint 1 | **Coprimary Endpoint 2**

54%
(95% CI: -56%, -51%; $p<0.0001$)

BETWEEN-GROUP DIFFERENCE IN TIME-ADJUSTED PERCENT CHANGE IN LDL-C FROM BASELINE AFTER DAY 90 AND UP TO DAY 540 VS. PLACEBO

Patients treated with LEQVIO® experienced a greater time-adjusted percent change reduction in LDL-C from Day 90 to Day 540 (-51% vs. 3%, respectively).

- Producing a between-group difference of -54% (95% CI: -56%, -51%; $p<0.0001$)

LEQVIO® was also studied in the ORION-11 (N=1,617) clinical trial in a mixed population (patients who had non-familial hypercholesterolemia with ASCVD and/or ASCVD risk equivalent patients).[1]

Note: LEQVIO® is not indicated for the treatment of patients with ASCVD risk equivalents.

ASCVD = atherosclerotic cardiovascular disease; CI = confidence interval; LDL-C = low-density lipoprotein cholesterol.

Clinical Trial Designs | Subgroup Analyses | Other Secondary Endpoints

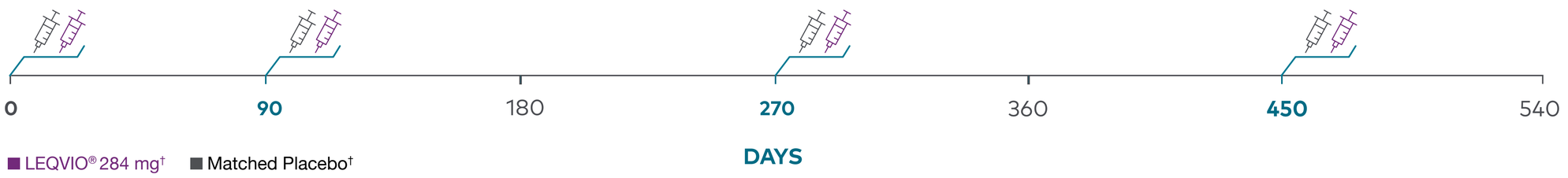
Home | Dosing | Efficacy Data ASCVD | Efficacy Data HeFH | Safety Data | MOA | LEQVIO® Assist PSP | Summary | Fair Balance

PrLEQVIO® inclisiran injection

ORION-10 CLINICAL TRIAL DESIGN[1]

ORION-10		
Features	Multicentre, double-blind, randomized (1:1), placebo-controlled	
Location	United States	
Population	• Non-familial hypercholesterolemia • With ASCVD	
Treatment Arms	LEQVIO® 284 mg SC (n=781)	Matched placebo (n=780)
Administration	Days 0, 90, 270, and 450	
Coprimary Endpoints	Percent change in LDL-C from baseline to Day 510 Time-adjusted percent change in LDL-C from Day 90 up to Day 540	

Patients were randomized (1:1) to receive SC injections of either:[1,2]



ASCVD = atherosclerotic cardiovascular disease; LDL-C = low-density lipoprotein cholesterol; SC = subcutaneous.
† Patients in each study arm in the ORION-10 clinical trial were receiving a maximally tolerated dose of statin, with or without other lipid-modifying therapy, such as ezetimibe.

ORION-10: PATIENT DEMOGRAPHICS AND BASELINE CHARACTERISTICS

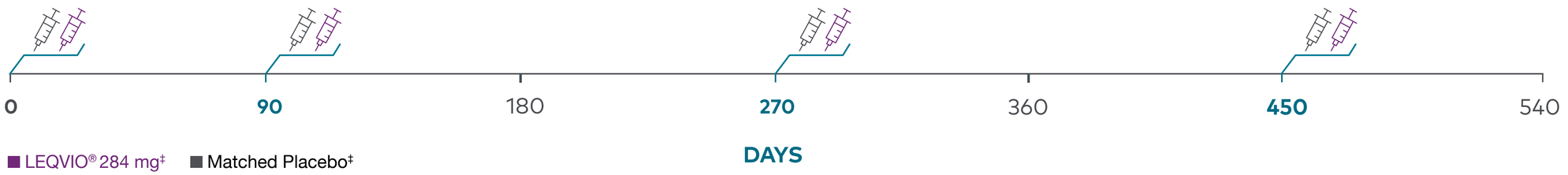
	ORION-10 (N=1,561)	
Characteristics†	**LEQVIO® (N=781)**	**Placebo (N=780)**
Age (years)	66.4 (8.9)	65.7 (8.9)
Males (%)	68.5	70.3
Caucasians (%)	83.6	87.8
Cardiovascular risk factors (%)		
ASCVD	100	100
Current smoker‡	15.7	14.2
Hypertension‡	91.4	89.9
Diabetes‡	47.5	42.4
HeFH‡	1.0	1.5
Concomitant LLT (%)		
Statin (%)	89.9	88.7
High-intensity statin (%)	67.2	68.8
Ezetimibe	10.2	9.5
Lipid measures (mmol/L)		
LDL-C	2.70 (1.02)	2.71 (0.96)
Non-HDL-C	3.47 (1.15)	3.48 (1.12)
ApoB	0.0018 (0.001)	0.0018 (0.001)

ApoB = apolipoprotein B; ASCVD = atherosclerotic cardiovascular disease; HDL-C = high-density lipoprotein cholesterol; HeFH = heterozygous familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol; LLT = lipid-lowering therapy.
† All data presented as mean (SD), unless specified otherwise.
‡ Percentages are reported as a proportion of the overall cohort.

ORION-11 CLINICAL TRIAL DESIGN[1]

ORION-11		
Features	Multicentre, double-blind, randomized (1:1), placebo-controlled	
Location	International (Europe and South Africa)	
Population	• Non-familial hypercholesterolemia • With ASCVD or ASCVD risk equivalents† **Note:** LEQVIO® is not indicated for the treatment of patients with ASCVD risk equivalents.	
Treatment Arms	LEQVIO® 284 mg SC (n=810)	Matched placebo (n=807)
Administration	Days 0, 90, 270, and 450	
Coprimary Endpoints	Percent change in LDL-C from baseline to Day 510 Time-adjusted percent change in LDL-C from Day 90 up to Day 540	

Patients were randomized (1:1) to receive SC injections of either:[1,2]



ASCVD = atherosclerotic cardiovascular disease; LDL-C = low-density lipoprotein cholesterol; SC = subcutaneous.
† In ORION-11, ASCVD risk equivalent was defined as the presence of type 2 diabetes, familial hypercholesterolemia, and including patients whose 10-year risk of a CV event assessed by the Framingham Risk Score or equivalent has a target LDL-C of ≥100 mg/dL (≥2.6 mmol/L). **Note:** LEQVIO® is not indicated for the treatment of patients with ASCVD risk equivalents.
‡ Patients in each study arm in the ORION-11 clinical trial were receiving a maximally tolerated dose of statin, with or without other lipid-modifying therapy, such as ezetimibe.

ORION-11: PATIENT DEMOGRAPHICS AND BASELINE CHARACTERISTICS

	ORION-11 (N=1,617)	
Characteristics‡	**LEQVIO® (N=810)**	**Placebo (N=807)**
Age (years)	64.8 (8.3)	64.8 (8.7)
Males (%)	71.5	72.0
Caucasians (%)	97.7	98.6
Cardiovascular risk factors (%)		
ASCVD	87.9	87
ASCVD risk equivalent†	12.1	13
Current smoker§	19.8	16.4
Hypertension§	79.0	81.9
Diabetes§	36.5	33.7
HeFH§	1.7	1.7
Concomitant LLT (%)		
Statin (%)	94.6	94.9
High-intensity statin (%)	79.0	78.2
Ezetimibe	6.3	7.7
Lipid measures (mmol/L)		
LDL-C	2.77 (1.08)	2.68 (0.94)
Non-HDL-C	3.54 (1.21)	3.46 (1.06)
ApoB	0.0019 (0.001)	0.0019 (0.0001)

ApoB = apolipoprotein B; ASCVD = atherosclerotic cardiovascular disease; HeFH = heterozygous familial hypercholesterolemia; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; LLT = lipid-lowering therapy.

† In ORION-11, ASCVD risk equivalent was defined as the presence of type 2 diabetes, familial hypercholesterolemia, and including patients whose 10-year risk of a CV event assessed by the Framingham Risk Score or equivalent has a target LDL-C of ≥100 mg/dL (≥2.6 mmol/L). **Note:** LEQVIO® is not indicated for the treatment of patients with ASCVD risk equivalents.

‡ All data presented as mean (SD), unless specified otherwise.

§ Percentages are reported as a proportion of the overall cohort, including patients in the risk-equivalent category.

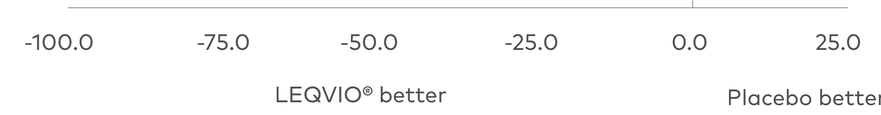
TREATMENT DIFFERENCES IN PERCENT CHANGE FROM BASELINE IN LDL-C AT DAY 510: POOLED ANALYSIS OF ORION-10 AND ORION-11[1]

In a pooled analysis of the two ASCVD studies (ORION-10 and ORION-11), consistent and statistically significant ($p<0.05$) percent change in LDL-C from baseline to Day 510 and time-adjusted percentage change in LDL-C from baseline after Day 90 up to Day 540 were observed.

- This was observed across all subgroups irrespective of baseline demographics, baseline disease characteristics, comorbidities, and geographic regions.

Demographic Characteristics | **Baseline Disease Characteristics** | **Additional Subgroups**

Subgroup	LEQVIO® N	Placebo N	LS Mean Percent Difference in LDL-C %	95% CI
Overall				
Overall	1,591	1,587	-54.8	-57.0 to -52.7
Sex				
Male	1,114	1,129	-54.0	-56.6 to -51.5
Female	477	458	-57.0	-61.2 to -52.8
Age				
<65 yr	664	699	-54.0	-59.0 to -51.8
≥65 yr	927	888	-57.0	-57.1 to -51.6
Age				
<75 yr	1,359	1,342	-54.9	-57.3 to -52.5
≥75 yr	232	245	-54.9	-59.7 to -50.0
Body mass index				
≤30	821	768	-53.0	-55.9 to -50.0
>30	770	817	-57.0	-60.2 to -53.8
Race				
White	1,444	1,481	-55.1	-57.4 to -52.9
Black	122	95	-52.7	-62.7 to -42.8
Other	25	11	-46.1	-79.9 to -12.3



ASCVD = atherosclerotic cardiovascular disease; CI = confidence interval; LDL-C = low-density lipoprotein cholesterol; LS = least-squares.

Adapted from the LEQVIO® Product Monograph.

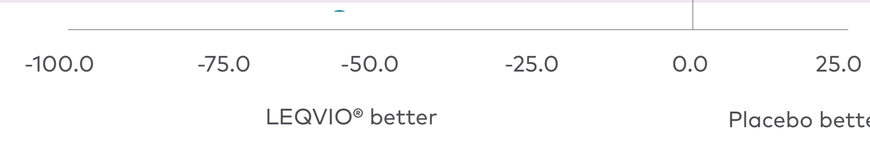
TREATMENT DIFFERENCES IN PERCENT CHANGE FROM BASELINE IN LDL-C AT DAY 510: POOLED ANALYSIS OF ORION-10 AND ORION-11[1]

In a pooled analysis of the two ASCVD studies (ORION-10 and ORION-11), consistent and statistically significant ($p<0.05$) percent change in LDL-C from baseline to Day 510 and time-adjusted percentage change in LDL-C from baseline after Day 90 up to Day 540 were observed.

- This was observed across all subgroups irrespective of baseline demographics, baseline disease characteristics, comorbidities, and geographic regions.

Demographic Characteristics | **Baseline Disease Characteristics** | **Additional Subgroups**

Subgroup	LEQVIO® N	Placebo N	LS Mean Percent Difference in LDL-C %	95% CI
Baseline statin treatment				
On statin	1,467	1,458	-55.2	-57.5 to -52.9
Not on statin	124	129	-50.2	-55.9 to -44.4
Intensity of statin treatment				
High-intensity statin	1,171	1,174	-55.2	-57.8 to -52.6
Not on a high-intensity statin	420	413	-54.1	-57.8 to -50.3
Lipid management treatment (LMT)				
Any statin	1,467	1,458	-55.2	-57.5 to -52.9
Other LMT but no statin†	65	53	-55.6	-64.1 to -47.2
No LMT†	59	76	-46.2	-54.3 to -38.3
Metabolic disease				
Diabetes	667	603	-55.8	-59.4 to -52.1
Metabolic syndrome	425	454	-57.2	-61.2 to -53.2
Neither	499	530	-51.9	-55.6 to -48.2
Risk category				
ASCVD	1,493	1,482	-55.3	-57.6 to -53.1
ASCVD equivalent†	98	105	-47.2	-56.1 to -38.3
Renal function (eGFR)				



†LEQVIO® is not indicated for these patient populations.
ASCVD = atherosclerotic cardiovascular disease; CI = confidence interval; eGFR = estimated glomerular filtration rate; LDL-C = low-density lipoprotein cholesterol; LMT = lipid management treatment; LS = least-squares.

Adapted from the LEQVIO® Product Monograph.

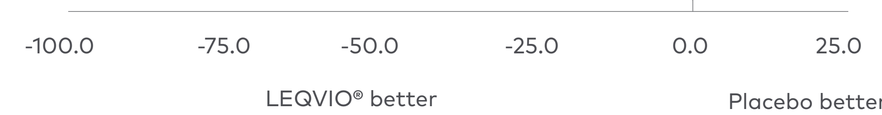
TREATMENT DIFFERENCES IN PERCENT CHANGE FROM BASELINE IN LDL-C AT DAY 510: POOLED ANALYSIS OF ORION-10 AND ORION-11[1]

In a pooled analysis of the two ASCVD studies (ORION-10 and ORION-11), consistent and statistically significant ($p<0.05$) percent change in LDL-C from baseline to Day 510 and time-adjusted percentage change in LDL-C from baseline after Day 90 up to Day 540 were observed.

- This was observed across all subgroups irrespective of baseline demographics, baseline disease characteristics, comorbidities, and geographic regions.

Demographic Characteristics | **Baseline Disease Characteristics** | **Additional Subgroups**

Subgroup	LEQVIO® N	Placebo N	LS Mean Percent Difference in LDL-C %	95% CI
Metabolic disease				
Diabetes	667	603	-55.8	-59.4 to -52.1
Metabolic syndrome	425	454	-57.2	-61.2 to -53.2
Neither	499	530	-51.9	-55.6 to -48.2
Risk category				
ASCVD	1,493	1,482	-55.3	-57.6 to -53.1
ASCVD equivalent†	98	105	-47.2	-56.1 to -38.3
Renal function (eGFR)				
Normal	823	854	-55.2	-58.2 to -52.2
Mild impairment	584	540	-53.5	-57.1 to -49.9
Moderate impairment	180	188	-57.7	-64.5 to -50.9
Baseline triglycerides (mmol/L)				
≤1.5	797	799	-53.6	-56.6 to -50.6
>1.5	794	788	-56.0	-59.2 to -52.9
Baseline LDL-C (mg/dL)				
≤2.48	819	807	-62.3	-67.2 to -57.4
>2.48	772	780	-53.1	-55.5 to -50.6



†LEQVIO® is not indicated for these patient populations.
ASCVD = atherosclerotic cardiovascular disease; CI = confidence interval;
eGFR = estimated glomerular filtration rate; LDL-C = low-density lipoprotein cholesterol;
LMT = lipid management treatment; LS = least-squares.

Adapted from the LEQVIO® Product Monograph.

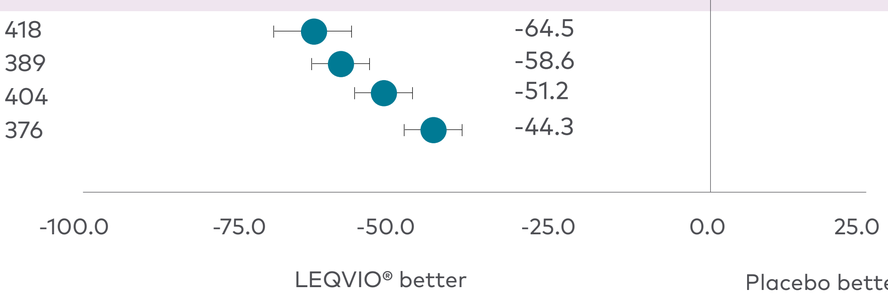
TREATMENT DIFFERENCES IN PERCENT CHANGE FROM BASELINE IN LDL-C AT DAY 510: POOLED ANALYSIS OF ORION-10 AND ORION-11[1]

In a pooled analysis of the two ASCVD studies (ORION-10 and ORION-11), consistent and statistically significant ($p<0.05$) percent change in LDL-C from baseline to Day 510 and time-adjusted percentage change in LDL-C from baseline after Day 90 up to Day 540 were observed.

- This was observed across all subgroups irrespective of baseline demographics, baseline disease characteristics, comorbidities, and geographic regions.

Demographic Characteristics | **Baseline Disease Characteristics** | **Additional Subgroups**

Subgroup	LEQVIO® N	Placebo N	LS Mean Percent Difference in LDL-C %	95% CI
Baseline LDL-C quartiles (mmol/L)				
≤2.1	402	418	-64.5	-69.6 to -59.4
>2.1 – ≤2.48	417	389	-58.6	-62.7 to -54.5
>2.48 – ≤3.1	370	404	-51.2	-55.0 to -47.3
>3.1	402	376	-44.3	-48.1 to -40.6



Adapted from the LEQVIO® Product Monograph.

ASCVD = atherosclerotic cardiovascular disease; CI = confidence interval; LDL-C = low-density lipoprotein cholesterol; LS = least-squares.

ORION-10 | ORION-11

ORION-10: OTHER SECONDARY ENDPOINTS

Proportion who achieved an LDL-C <1.8 mmol/L (70 mg/dL)

At Day 510

84% LEQVIO®-TREATED PATIENTS

vs.

18% PLACEBO-TREATED PATIENTS

WITH NON-FAMILIAL HYPERCHOLESTEROLEMIA WITH ASCVD ACHIEVED THE LDL-C TARGET OF <1.8 MMOL/L (70 MG/DL)

ASCVD = atherosclerotic cardiovascular disease; LDL-C = low-density lipoprotein cholesterol.

ORION-10 | ORION-11

ORION-11: OTHER SECONDARY ENDPOINTS

Proportion who achieved an LDL-C <1.8 mmol/L (70 mg/dL)

At Day 510

82% LEQVIO®-TREATED PATIENTS

vs.

16% PLACEBO-TREATED PATIENTS

WITH NON-FAMILIAL HYPERCHOLESTEROLEMIA WITH ASCVD ACHIEVED THE LDL-C TARGET OF <1.8 MMOL/L (70 MG/DL)

ASCVD = atherosclerotic cardiovascular disease; LDL-C = low-density lipoprotein cholesterol.

LEQVIO® significantly reduced LDL-C vs. placebo in patients with HeFH

In the ORION-9 clinical trial, LEQVIO® demonstrated:

Coprimary Endpoint 1 | Coprimary Endpoint 2

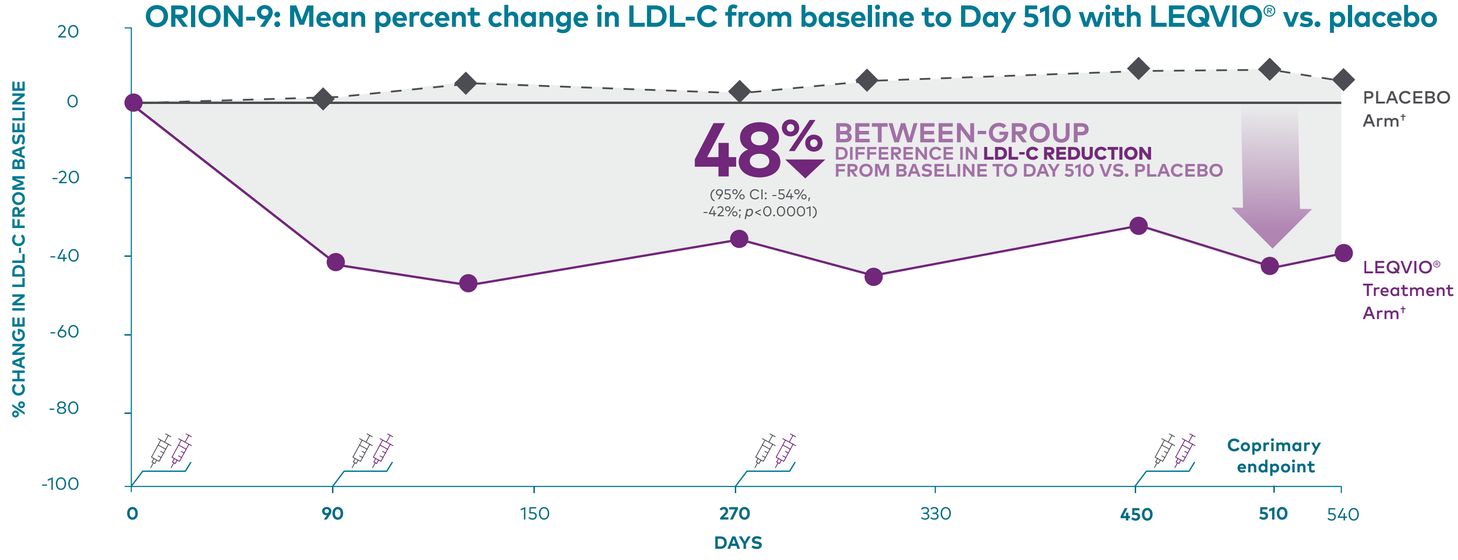
Patients treated with LEQVIO® experienced a greater mean percent-change reduction in LDL-C from baseline to Day 510 compared to placebo (-40% vs. 8%, respectively).

- Producing a between-group difference of -48% (95% CI: -54%, -42%; $p<0.0001$)

In the ORION-9 clinical trial, the maximally tolerated dose of statin was defined as the maximum dose of a statin that could be taken by the patient on a regular basis without unacceptable adverse events.

Enlarge Graph

ORION-9: Mean percent change in LDL-C from baseline to Day 510 with LEQVIO® vs. placebo



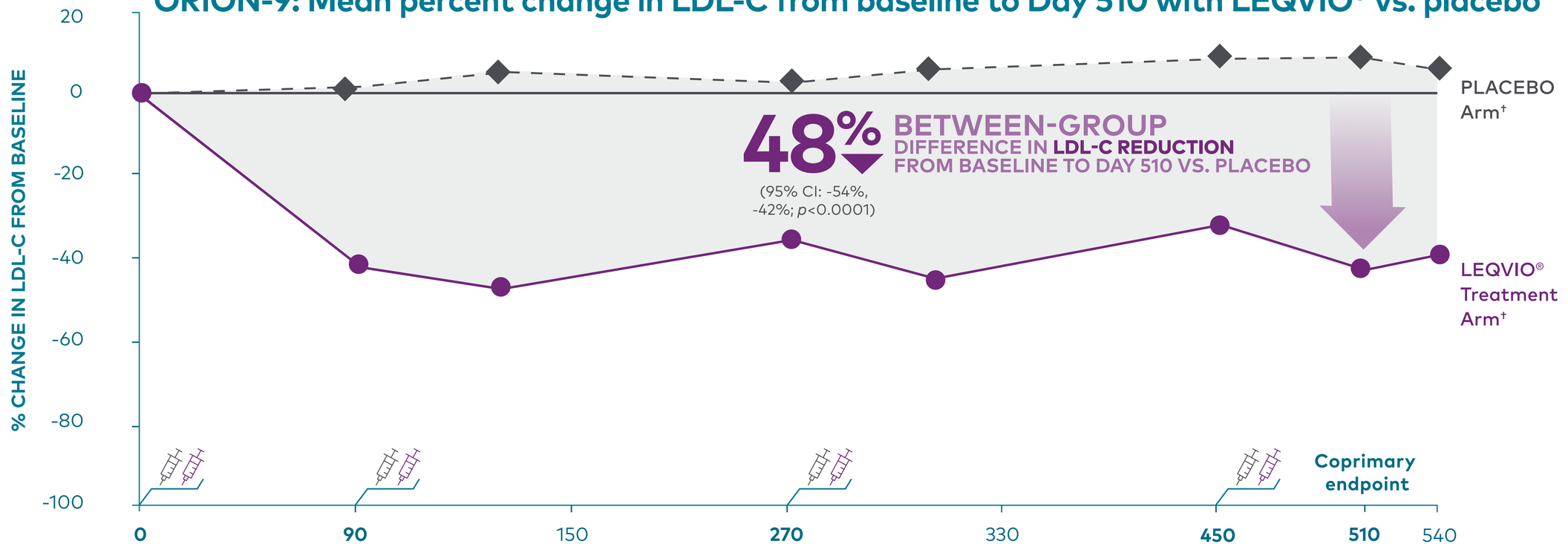
Placebo Arm (n):	240	237	238	235	233	233	229	232
LEQVIO® Treatment Arm (n):	242	240	239	240	237	237	231	232

Adapted from the LEQVIO® Product Monograph.

CI = confidence interval; HeFH = heterozygous familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol.
† Patients in the ORION-9 clinical trial were on a maximally tolerated dose of statin, with or without other lipid-lowering therapies, such as ezetimibe.[1,7]

ORION-9 Clinical Trial Design | **ORION-9 Other Secondary Outcomes**

ORION-9: Mean percent change in LDL-C from baseline to Day 510 with LEQVIO® vs. placebo



Placebo Arm (n):	240	237	238	235	233	233	229	232
LEQVIO® Treatment Arm (n):	242	240	239	240	237	237	231	232

Adapted from the LEQVIO® Product Monograph.

CI = confidence interval; LDL-C = low-density lipoprotein cholesterol.
† Patients in the ORION-9 clinical trial were on a maximally tolerated dose of statin, with or without other lipid-lowering therapies, such as ezetimibe.[1,7]

LEQVIO® significantly reduced LDL-C vs. placebo in patients with HeFH

In the ORION-9 clinical trial, LEQVIO® demonstrated a:

Coprimary Endpoint 1 | **Coprimary Endpoint 2**

44% (95% CI: -48%, -40%; *p*<0.0001)

BETWEEN-GROUP DIFFERENCE IN **TIME-ADJUSTED PERCENT CHANGE IN LDL-C REDUCTION** FROM BASELINE AFTER DAY 90 AND UP TO DAY 540 VS. PLACEBO

Patients treated with LEQVIO® experienced a greater time-adjusted percent change reduction in LDL-C from Day 90 to Day 540 (-38% vs. 6%, respectively).

- Producing a between-group difference of -44% (95% CI: -48%, -40%; *p*<0.0001)

CI = confidence interval; HeFH = heterozygous familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol.

ORION-9 Clinical Trial Design | ORION-9 Other Secondary Outcomes

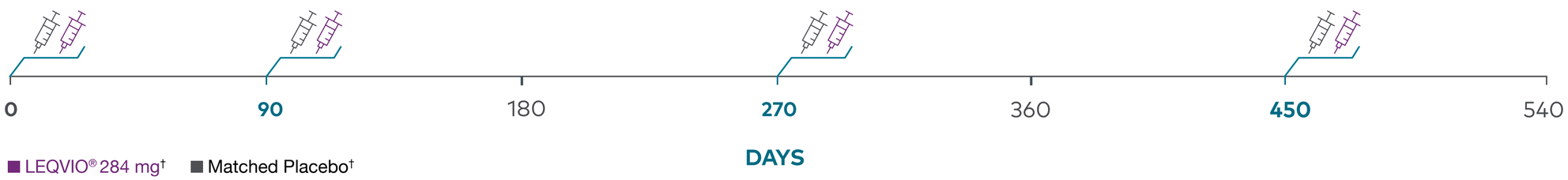
Home | Dosing | Efficacy Data ASCVD | Efficacy Data HeFH | Safety Data | MOA | LEQVIO® Assist PSP | Summary | Fair Balance

Pr LEQVIO® inclisiran injection

ORION-9 CLINICAL TRIAL DESIGN[1]

	ORION-9	
Features	Multicentre, double-blind, randomized (1:1), placebo-controlled	
Location	International	
Population	• HeFH • Diagnosis made via genotyping or clinical criteria (Simon Broome or WHO/Dutch Lipid Network criteria)	
Treatment Arms	• LEQVIO® 284 mg SC (n=242)	Matched placebo (n=240)
Administration	Days 0, 90, 270, and 450	
Coprimary Endpoints	Percent change in LDL-C from baseline to Day 510 Time-adjusted percent change in LDL-C after Day 90 up to Day 540	

Patients were randomized (1:1) to receive SC injections of either:[1,2]



HeFH = heterozygous familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol; SC = subcutaneous; WHO = World Health Organization.
† Patients in each study arm in the ORION-9 clinical trial were taking a maximally tolerated dose of statin, with or without other lipid-modifying therapy, such as ezetimibe.

ORION-9: PATIENT DEMOGRAPHICS AND BASELINE CHARACTERISTICS

	ORION-9 (N=482)	
Characteristics†	**LEQVIO® (N=242)**	**Placebo (N=240)**
Age, years (IQR)	56 (47 – 63)	56 (46 – 64)
Males (%)	46.3	47.9
Caucasians (%)	93.4	94.6
Cardiovascular risk factors (%)		
ASCVD	24.4	30.4
Current smoker	11.6	11.7
Hypertension	42.1	42.1
Diabetes	8.3	11.7
Concomitant LLT (%)		
Statin (%)	90.5	90.4
High-intensity statin (%)	76.4	71.2
Ezetimibe	55.8	50.0
Lipid measures (mg/dL)		
LDL-C	151.4 (50.4)	154.7 (58.0)
Non-HDL-C	178.5 (55.4)	181.5 (62.5)
ApoB	123.8 (33.2)	124.5 (34.8)

ApoB = apolipoprotein B; ASCVD = atherosclerotic cardiovascular disease; HDL-C = high-density lipoprotein cholesterol; IQR = interquartile range; LDL-C = low-density lipoprotein cholesterol; LLT = lipid-lowering therapy.
† All data presented as mean (SD), unless specified otherwise.

ORION-9: OTHER SECONDARY OUTCOMES

At Day 510,

53%
LEQVIO® -TREATED PATIENTS

vs.

1%
PLACEBO-TREATED PATIENTS

WHO HAD **HeFH WITH ASCVD**
ACHIEVED THE LDL-C TARGET OF <1.8 MMOL/L (70 MG/DL)

At Day 510,

67%
LEQVIO® -TREATED PATIENTS

vs.

9%
PLACEBO-TREATED PATIENTS

WHO HAD **HeFH WITHOUT ASCVD**
ACHIEVED THE LDL-C TARGET OF <2.6 MMOL/L (100 MG/DL)

ASCVD = atherosclerotic cardiovascular disease; HeFH = heterozygous familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol.

LEQVIO® demonstrated safety profile

The safety profile of LEQVIO® was evaluated in 3 pivotal Phase III trials in patients treated for up to 18 months

In the ORION Phase III clinical trials:

- 3,655 patients have been observed, with 1,833 patients exposed to 4 injections of LEQVIO® for up to 18 months (mean treatment duration of 526 days)[1,9]
- Most common adverse reactions were injection-site reactions (LEQVIO® 8.2% vs. placebo 1.8%), which were mild to moderate in severity and resolved without sequelae

Adverse Events | Renal/Hepatic Impairment | Immunogenicity | Injection-site AEs | Drug Interaction Potential

AE = adverse event.

ADVERSE EVENTS IN THE ORION-9, ORION-10, AND ORION-11 CLINICAL TRIALS

Treatment-Emergent Adverse Events

The most common TEAEs that occurred more frequently in the LEQVIO®-treated subjects were: diabetes mellitus (11.57%), nasopharyngitis (7.64%), arthralgia (4.96%), back pain (4.53%), urinary tract infection (4.42%), diarrhea (3.87%), bronchitis (4.26%), cough (3.33%), headache (3.22%), angina pectoris (3.16%), dizziness (3.22%), pain in extremity (3.27%), dyspnea (3.22%), and injection-site reaction (3.06%).

- There were 0.7% (12/1,833) discontinuations in inclisiran-treated subjects from the pivotal studies due to adverse events.

Adverse drug reactions reported in ≥1% of patients treated with LEQVIO® and more frequently than placebo (safety population)[1†]

Adverse Reactions n (%)	**LEQVIO® (n=1,833)**	**Placebo (n=1,822)**
Patients with ≥1 TEAE	1,430 (78.01)	1,409 (77.33)
Blood and lymphatic system disorders • Anemia	 38 (2.07)	 33 (1.81)
Cardiac disorders • Angina pectoris	 58 (3.16)	 57 (3.13)
Ear and labyrinth disorders • Vertigo	 21 (1.15)	 14 (0.77)
Eye disorders • Cataract	 22 (1.20)	 20 (1.10)
Gastrointestinal disorders • Abdominal pain • Diarrhea • Dyspepsia • Large intestine polyp • Nausea	 35 (1.91) 71 (3.87) 22 (1.20) 19 (1.04) 35 (1.91)	 31 (1.70) 63 (3.46) 18 (0.99) 13 (0.71) 26 (1.43)
General disorders and administration site conditions • Injection-site erythema • Injection-site pain • Injection-site reaction • Oedema peripheral	 30 (1.64) 41 (2.24) 56 (3.06) 38 (2.07)	 4 (0.22) 9 (0.49) 2 (0.11) 34 (1.87)

Adapted from the LEQVIO® Product Monograph.

TEAE = treatment-emergent adverse event.
† The safety data are derived from 3 placebo-controlled trials (ORION-9, ORION-10, and ORION-11).

ADVERSE EVENTS IN THE ORION-9, ORION-10, AND ORION-11 CLINICAL TRIALS

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Adverse drug reactions reported in ≥1% of patients treated with LEQVIO® and more frequently than placebo (safety population)[1†]

Adverse Reactions n (%)	LEQVIO® (n=1,833)	Placebo (n=1,822)
Infections and infestations		
• Bronchitis	78 (4.26)	50 (2.74)
• Cellulitis	21 (1.15)	14 (0.77)
• Gastroenteritis	30 (1.64)	19 (1.04)
• Lower respiratory tract infection	34 (1.85)	27 (1.48)
• Nasopharyngitis	140 (7.64)	134 (7.35)
• Pneumonia	46 (2.51)	36 (1.98)
• Respiratory tract infection	20 (1.09)	18 (0.99)
• Upper respiratory tract infection	105 (5.73)	103 (5.65)
• Urinary tract infection	81 (4.42)	66 (3.62)
Investigations		
• Blood pressure increased	22 (1.20)	14 (0.77)
Metabolism and nutrition disorders		
• Diabetes mellitus	212 (11.57)	207 (11.36)
• Hyperglycemia	25 (1.36)	14 (0.77)
Musculoskeletal and connective tissue disorders		
• Arthralgia	91 (4.96)	72 (3.95)
• Back pain	83 (4.53)	77 (4.23)
• Muscle spasms	28 (1.53)	25 (1.37)
• Pain in extremity	60 (3.27)	47 (2.58)
• Spinal osteoarthritis	21 (1.15)	15 (0.82)

Adapted from the LEQVIO® Product Monograph.

TEAE = treatment-emergent adverse event.
†The safety data are derived from 3 placebo-controlled trials (ORION-9, ORION-10, and ORION-11).

ADVERSE EVENTS IN THE ORION-9, ORION-10, AND ORION-11 CLINICAL TRIALS

Treatment-Emergent Adverse Events

The most common TEAEs that occurred more frequently in the LEQVIO®-treated subjects were: diabetes mellitus (11.57%), nasopharyngitis (7.64%), arthralgia (4.96%), back pain (4.53%), urinary tract infection (4.42%), diarrhea (3.87%), bronchitis (4.26%), cough (3.33%), headache (3.22%), angina pectoris (3.16%), dizziness (3.22%), pain in extremity (3.27%), dyspnea (3.22%), and injection-site reaction (3.06%).

- There were 0.7% (12/1,833) discontinuations in inclisiran-treated subjects from the pivotal studies due to adverse events.

Adverse drug reactions reported in ≥1% of patients treated with LEQVIO® and more frequently than placebo (safety population)[1†]

Adverse Reactions n (%)	**LEQVIO® (n=1,833)**	**Placebo (n=1,822)**
• Diabetes mellitus • Hyperglycemia	212 (11.57) 25 (1.36)	207 (11.36) 14 (0.77)
Musculoskeletal and connective tissue disorders • Arthralgia • Back pain • Muscle spasms • Pain in extremity • Spinal osteoarthritis	 91 (4.96) 83 (4.53) 28 (1.53) 60 (3.27) 21 (1.15)	 72 (3.95) 77 (4.23) 25 (1.37) 47 (2.58) 15 (0.82)
Nervous system disorders • Dizziness • Headache • Sciatica	 59 (3.22) 59 (3.22) 19 (1.04)	 55 (3.02) 56 (3.07) 18 (0.99)
Psychiatric disorders • Insomnia	 20 (1.09)	 19 (1.04)
Renal and urinary disorders • Acute kidney injury • Renal impairment	 19 (1.04) 23 (1.25)	 17 (0.93) 16 (0.88)
Respiratory, thoracic and mediastinal disorders • Asthma • Cough • Dyspnoea	 20 (1.09) 61 (3.33) 59 (3.22)	 15 (0.82) 54 (2.96) 47 (2.58)

Adapted from the LEQVIO® Product Monograph.

TEAE = treatment-emergent adverse event.
†The safety data are derived from 3 placebo-controlled trials (ORION-9, ORION-10, and ORION-11).

RENAL IMPAIRMENT

No dose adjustment is **necessary** for patients with **mild and moderate renal impairment** despite an increase in drug exposure.

- There is very limited efficacy and safety data in patients with severe renal impairment treated with LEQVIO® (n=11) in the pivotal trials; none of the patients received dose adjustment.
- The effect of end-stage renal disease (CrCL <15 mL/min) and of hemodialysis on the pharmacokinetics and pharmacodynamics of LEQVIO® has not been studied.

HEPATIC IMPAIRMENT

No dose adjustment is **necessary** for patients with **mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment** despite an increase in drug exposure.

- LEQVIO® should be used with caution in patients with moderate hepatic impairment due to very limited efficacy and safety data.
- Patients with severe hepatic impairment (Child-Pugh class C) have not been studied.

CrCL = creatinine clearance.

IMMUNOGENICITY

The immunogenicity of LEQVIO® has been evaluated using a semi-quantitative enzyme-linked immunosorbent assay for the detection of inclisiran-reactive IgG/IgM antibodies in human serum.†

In the pivotal trials, 1,830 patients were tested for anti-drug antibodies (ADA). Confirmed positivity was detected in 1.8% (33/1,830) of patients prior to dosing and in 4.9% (90/1,830) of patients during the 18 months of treatment with LEQVIO® .

- No clinically significant differences in the clinical efficacy, safety or pharmacodynamic profiles of LEQVIO® were observed in the patients who tested positive for anti-inclisiran antibodies.
- Long-term immunogenicity with subsequent injections is unknown since the observation period was limited to 18 months (4 injections) in the pivotal trials.

Ig = immunoglobulin.
† The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. In addition, the observed incidence of antibody positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to LEQVIO® in the studies described herein with the incidence of antibodies in other studies or to other products may be misleading.

INJECTION-SITE AEs IN THE ORION-9, ORION-10, AND ORION-11 CLINICAL TRIALS

Across the three pivotal clinical trials, injection-site AEs occurred in 8.2% of patients treated with LEQVIO® and 1.8% of patients who received placebo.

- Treatment discontinuation due to injection-site reactions occurred in 0.2% of patients treated with LEQVIO® and 0.0% of patients who received placebo.

All of these adverse drug reactions were mild or moderate in severity, transient and resolved without sequelae.

AE = adverse event.

DRUG INTERACTION POTENTIAL[1]

No clinical drug interaction studies have been performed. Inclisiran is not a substrate, inhibitor, or inducer of CYP450 enzymes or transporters and is not expected to cause drug-drug interactions or to be affected by inhibitors of CYP450 enzymes or transporter.

CYP450 = cytochrome P450.

The first-and-only siRNA PCSK9 inhibitor indicated in non-familial hypercholesterolemia with ASCVD and HeFH[1,6,8†‡]

LEQVIO® (inclisiran injection) is indicated as an adjunct to lifestyle changes, including diet, to further reduce low-density lipoprotein cholesterol (LDL-C) level in adults with the following conditions who are on a maximally tolerated dose of a statin, with or without other LDL-C-lowering therapies:

- Heterozygous familial hypercholesterolemia (HeFH), or
- Non-familial hypercholesterolemia with atherosclerotic cardiovascular disease (ASCVD)

The effect of LEQVIO® on cardiovascular morbidity and mortality has not been determined.

A mechanism of action that includes the cellular mechanism of RNA interference[†‡]

LEQVIO® is a **double-stranded siRNA** that **causes** the **degradation of PCSK9** mRNA to **increase** hepatocyte **LDL-C receptor recycling and expression**.

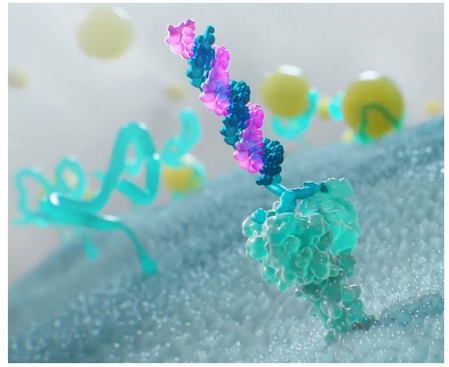
- The N-acetylgalactosamine (**GalNAc**) conjugated on the sense strand of LEQVIO® facilitates uptake at the liver and **selectively targets asialoglycoprotein receptors (ASGPR) in the liver.**
- LEQVIO® **works with** the **RNA interference** mechanism to direct the catalytic breakdown of mRNA for PCSK9.

LEQVIO®'s siRNA-directed catalytic breakdown of PCSK9 mRNA leads to:

- Increased LDL-C receptor recycling
- Increased LDL-C receptor expression on hepatocyte cell surface

Collectively, these mechanisms generally:

- **Increase hepatic LDL-C uptake** and
- **Lower LDL-C levels** in the circulation



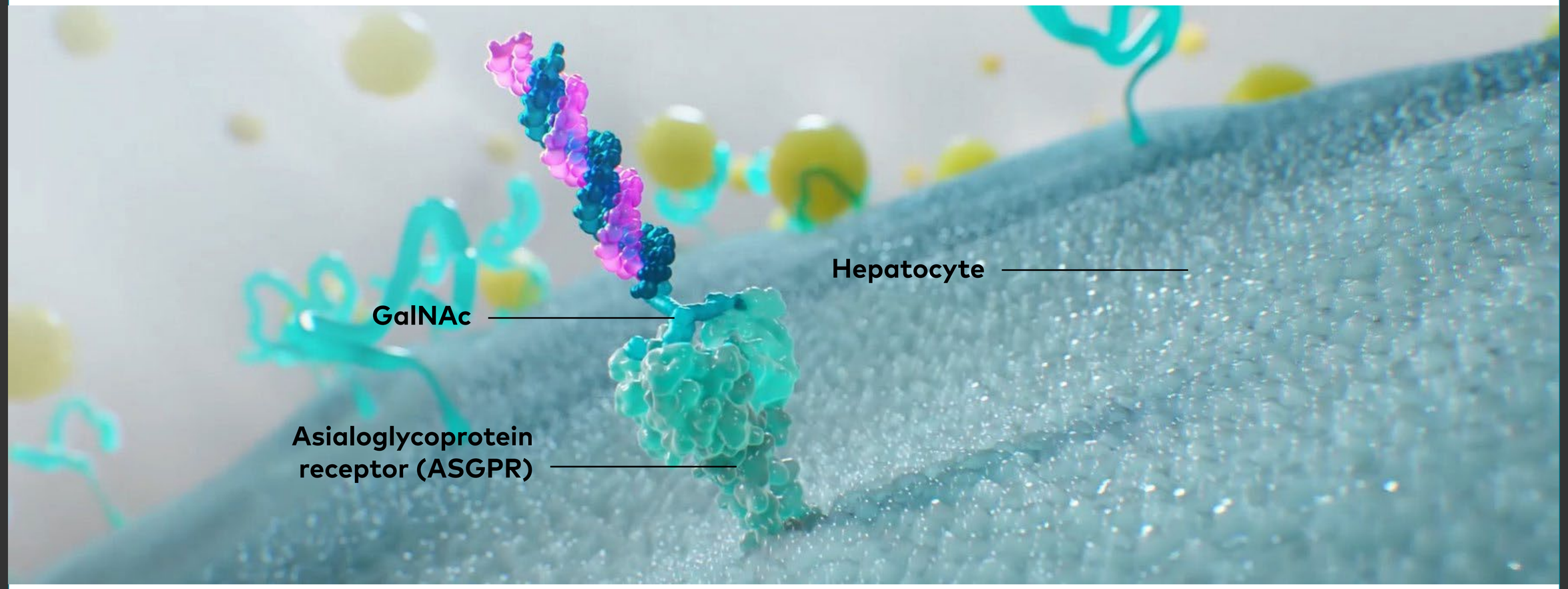
Mechanism of Action

After inclisiran is cleared from the plasma, its mechanism of action also includes long-term intracellular presence (>42 days in monkeys and >98 days in rats after a single administration), which contributes to its long duration of effect in lowering LDL-C.

PK/PD

ASGPR = asialoglycoprotein receptors; GalNAc = N-acetylgalactosamine; HeFH = heterozygous familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol; mRNA = messenger RNA; PCSK9 = proprotein convertase subtilisin/kexin type 9; RNA = ribonucleic acid; siRNA = small interfering RNA.
† Clinical significance is unknown.
‡ Comparative clinical significance has not been established.

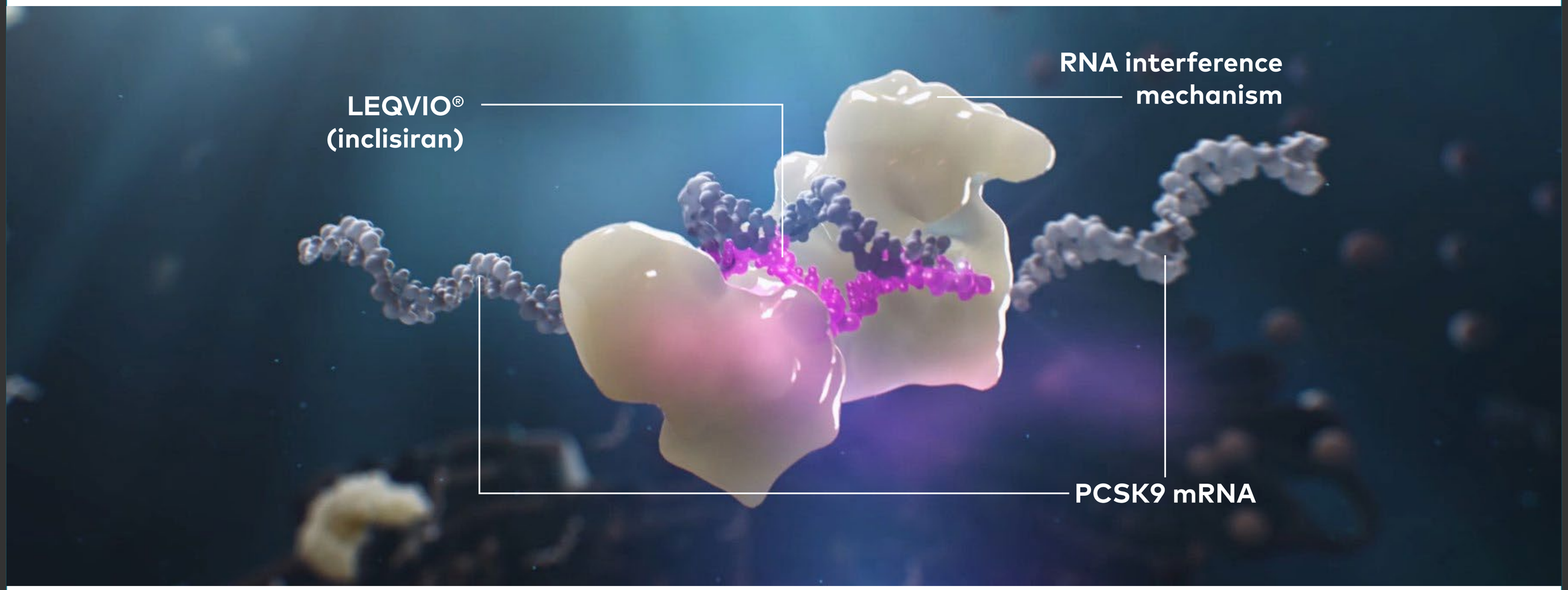
LEQVIO® (INCLISIRAN INJECTION) MECHANISM OF ACTION†‡



- The *N-acetylgalactosamine* (GalNAc) conjugated on the sense strand of LEQVIO® *facilitates uptake at the liver* and selectively targets hepatic ASGPR.

ASGPR = asialoglycoprotein receptor; GalNAc = N-acetylgalactosamine.
† Clinical significance is unknown.
‡ Comparative clinical significance has not been established.

LEQVIO® (INCLISIRAN INJECTION) MECHANISM OF ACTION†‡



- LEQVIO® works with the *RNA interference mechanism* to *direct the catalytic breakdown of mRNA for PCSK9.*

mRNA = messenger ribonucleic acid; PCSK9 = proprotein convertase subtilisin/kexin-9; RNA = ribonucleic acid.
† Clinical significance is unknown.
‡ Comparative clinical significance has not been established.

LEQVIO® (INCLISIRAN INJECTION) MECHANISM OF ACTION†‡

After inclisiran is cleared from the plasma, its mechanism of action also includes long-term intracellular presence (>42 days in monkeys and >98 days in rats after a single administration), which contributes to its long duration of effect in lowering LDL-C.

- The degradation of PCKS9 mRNA *increases LDL receptor recycling and expression* on the hepatocyte cell surface, which generally *increases LDL-C uptake and lowers LDL-C levels* in the circulation.

LDL-C = low-density lipoprotein cholesterol; mRNA = messenger ribonucleic acid; PCSK9 = proprotein convertase subtilisin/kexin-9.
† Clinical significance is unknown.
‡ Comparative clinical significance has not been established.

LEQVIO® ABSORPTION AND ELIMINATION†

In healthy subjects who received the recommended dosing regimen of 284 mg of inclisiran, plasma concentrations reached peak over a range of 0.5 to 12 hours post-dose with a mean C_{max} of 509 ng/mL with a CV % of 50.7%.

- Concentrations reached undetectable levels after 24 to 48 hours post-dosing.
- Minimal to no accumulation of inclisiran in plasma was observed after repeat dosing.

The mean terminal elimination half-life of inclisiran is approximately 9.6 hours, and no accumulation occurs with multiple dosing.

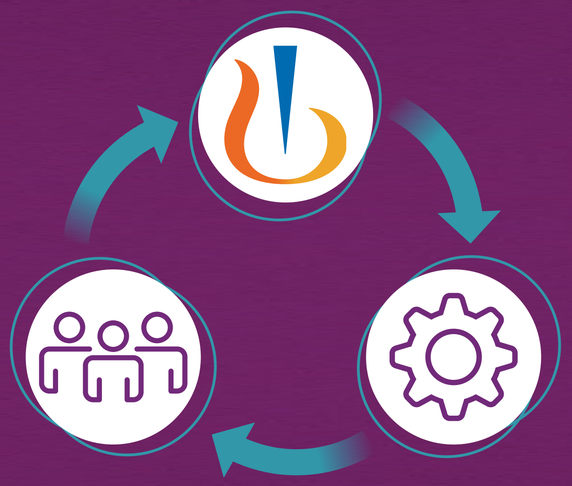
- On average, 16% of inclisiran is cleared through the kidney.
- Based on animal data, the remaining clearance is primarily due to tissue uptake, particularly the liver, the target organ for cholesterol-lowering, followed by the kidney, which is the major site of inclisiran elimination.
- Inclisiran exhibits a **slow elimination half-life** from liver based on animal studies (270 hours in rats; 1,980 hours in monkeys).

C_{max} = maximal concentration; CV = coefficient of variation.
† Clinical significance is unknown.

The LEQVIO® Assist Patient Support Program

From Novartis, for you

At Novartis, we are deeply invested in supporting patients. We aim to assist patients through their treatment with LEQVIO®, and, in turn, the healthcare professionals that support them.



As an internally managed PSP, we are a deeply devoted team with experience in patient support.

- Novartis values flow through LEQVIO® Assist, keeping patient support at the forefront of our thinking.
- We bring our expertise to the table, as a guiding hand and partner for both you and your patients.

By coordinating injection location and facilitating access to reimbursement, we **do our part to help with the administrative process.**

PSP = Patient Support Program.

Leqvio® ASSIST Patient Support Program

Supporting patients in partnership with you

Helping hands at the ready

Connected care

Our experienced team of Novartis associates is devoted to patient support throughout their treatment journey.

- **The Reimbursement Specialist is your dedicated point of contact.**
- In partnership with the **Clinical Coordinator**, they follow the patient from the start of their journey and through every step.
- Together, they are the dedicated **Assist Team** for you and your patient.

Coordinated support

We proactively manage communications – handling insurer requests, following up with patients, and liaising back with you.

- Through the Assist Team, we aim to keep the lines of communication open and active during periods between doses.
- The Assist Team proactively coordinates between the patient's care team on the one hand, and the HCPs and insurers on the other.

Customized services

We allow the patient to choose their injection location and then coordinate drug delivery for them.

- By offering customizable injection location services, we aim to provide flexibility to the patient.

Leqvio® ASSIST Patient Support Program

Ongoing Services

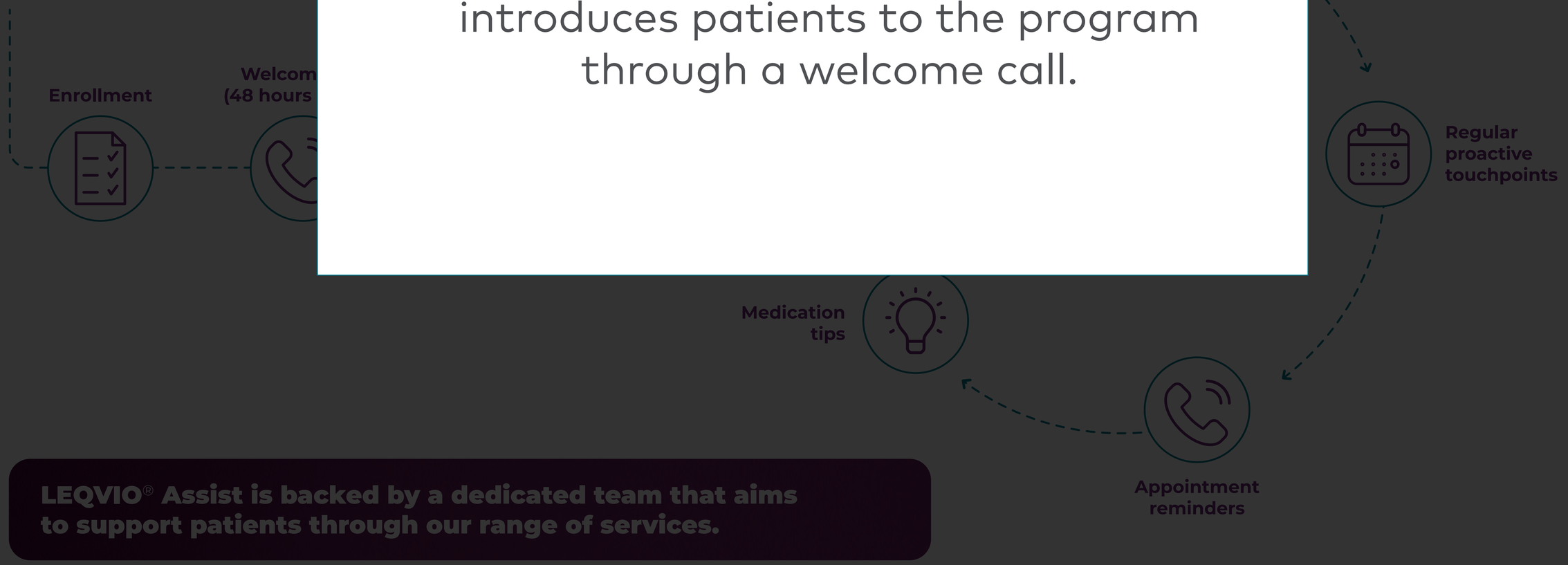
Our team is here to support your patients every step of the way

LEQVIO® Assist is backed by a dedicated team that aims to support patients through our range of services.

Leqvio® ASSIST Patient Support Program

Ongoing Services

Our team is here
every step of th



The **Reimbursement Specialist** introduces patients to the program through a welcome call.

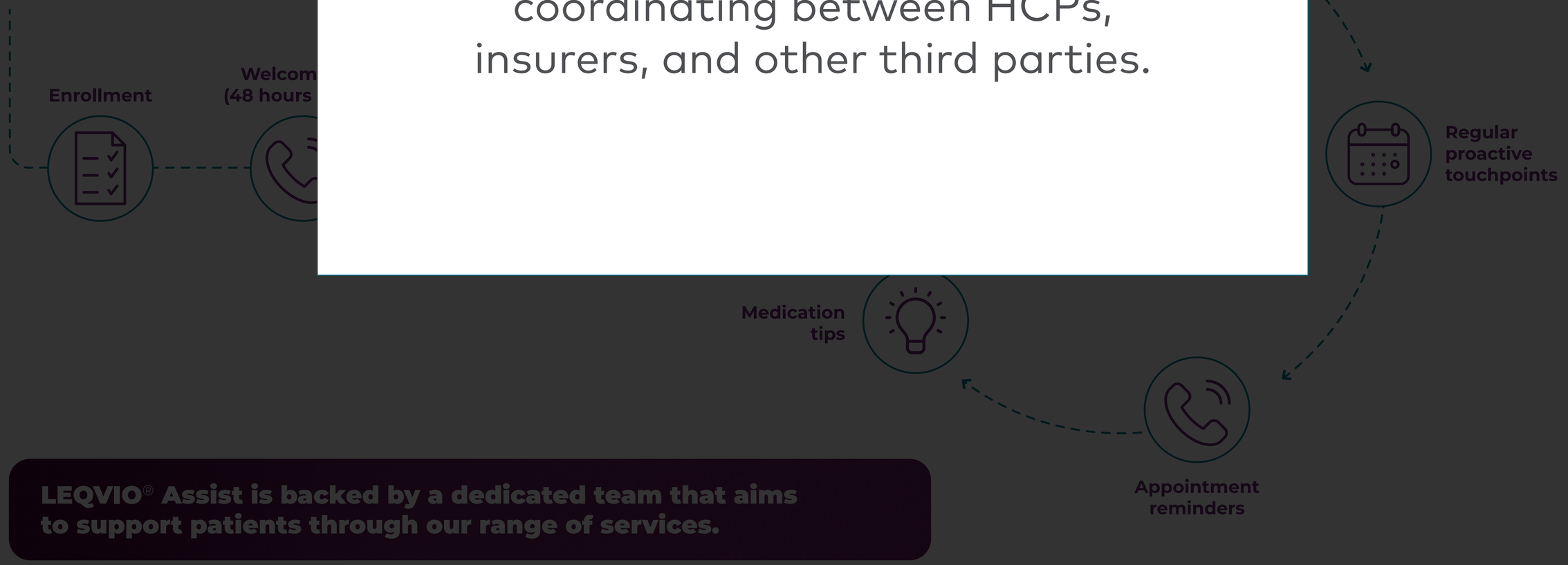
LEQVIO® Assist is backed by a dedicated team that aims to support patients through our range of services.

C_{max} = maximal concentration; CV = coefficient of variation.
† Clinical significance has not been established.

Leqvio® ASSIST Patient Support Program

Ongoing Services

Our team is here
every step of th



The **Reimbursement Specialist** provides reimbursement navigation, coordinating between HCPs, insurers, and other third parties.

LEQVIO® Assist is backed by a dedicated team that aims to support patients through our range of services.

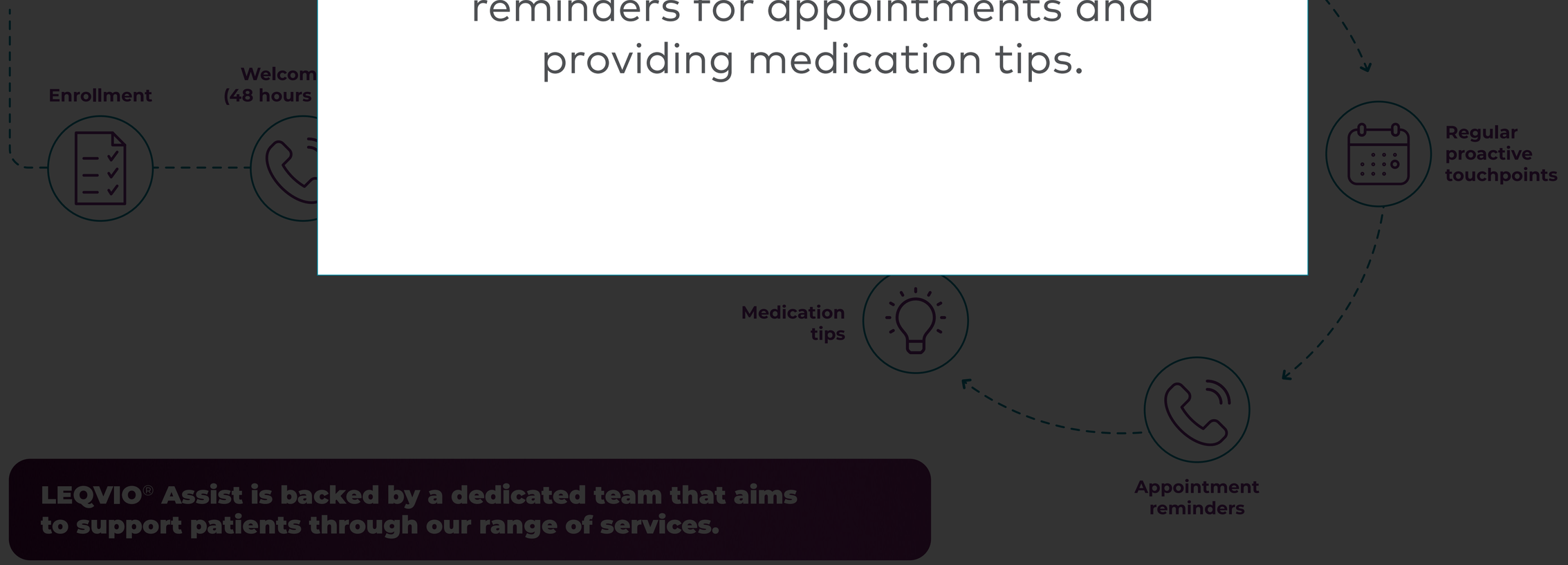
C_{max} = maximal concentration; CV = coefficient of variation.
† Clinical significance has not been established.

Leqvio® ASSIST Patient Support Program

Pr LEQVIO® inclisiran injection

Ongoing Services

Our team is here
every step of th



The **Clinical Coordinator** proactively follows up with the patient, sending reminders for appointments and providing medication tips.

LEQVIO® Assist is backed by a dedicated team that aims to support patients through our range of services.

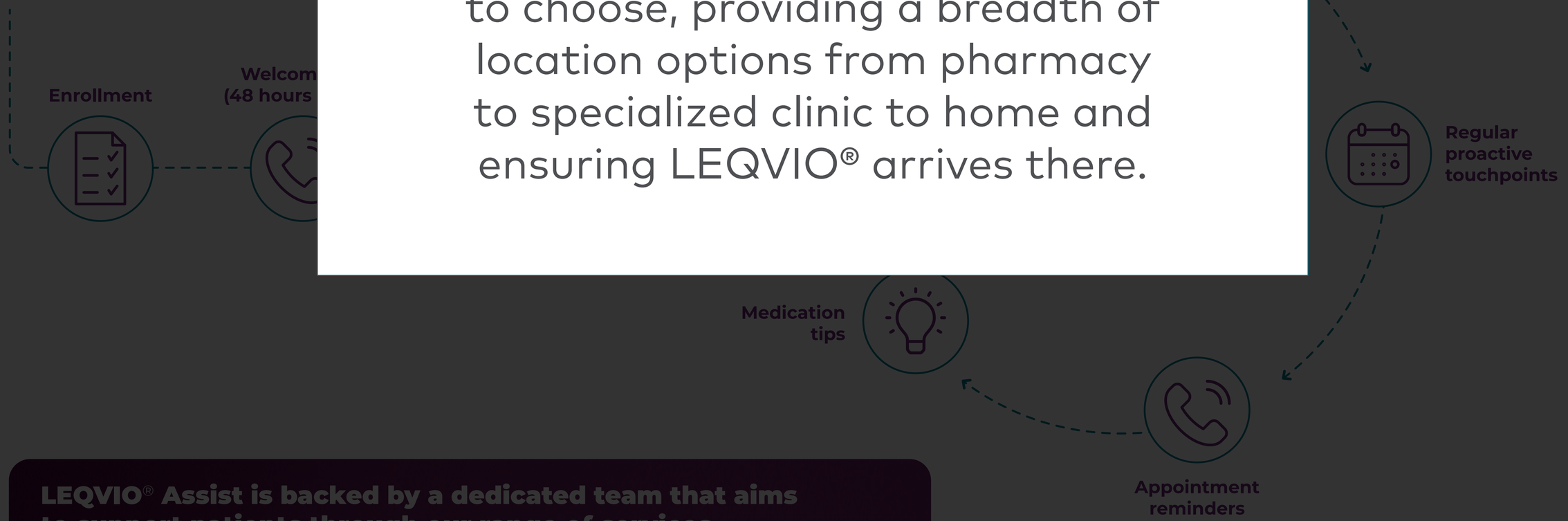
C_{max} = maximal concentration; CV = coefficient of variation.
† Clinical significance has not been established.

Leqvio® ASSIST Patient Support Program

Ongoing Services

Our team is here
every step of th

When it comes to injection services and medication delivery, the **Clinical Coordinator** allows the patient to choose, providing a breadth of location options from pharmacy to specialized clinic to home and ensuring LEQVIO® arrives there.



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Leqvio® ASSIST Patient Support Program

Ongoing Services

Our team is here every step of th

When it comes to injection services and medication delivery, the **Clinical Coordinator** allows the patient to choose, providing a breadth of location options from harmacy to specialized clinic to home and ensuring LEQVIO® arrives there.

Enrollment

Welcom (48 hours

The **Reimburse Specialist** introduces patients to the program through a welcome call.

Specialist provides reimbursement navigation, coordinating between HCPs, insurers, and other third parties.

Regular proactive touchpoints

The **Clinical Coordinator** proactively follows up with the patient, sending reminders for appointments and providing medication tips.

Medication tips

Appointment reminders

LEQVIO® Assist is backed by a dedicated team that aims to support patients through our range of services.

Scan the QR code to access the LEQVIO® Assist **PSP enrollment form.**

C_{max} = maximal concentration; CV = coefficient of variation.
† Clinical significance has not been established.

Leqvio® ASSIST Patient Support Program

CONSIDER LEQVIO®

LEQVIO®: THE FIRST siRNA PCSK9 INHIBITOR THAT CAN HAVE A TWICE-ANNUAL DOSING REGIMEN‡§

The recommended dose of LEQVIO® is 284 mg administered as a single subcutaneous injection: initially, again at 3 months, and then once every 6 months.§

LEQVIO® IS A DOUBLE-STRANDED siRNA THAT CAUSES THE DEGRADATION OF PCSK9 mRNA.†

DEMONSTRATED LDL-C REDUCTION[1¶¥]

In addition to a maximally tolerated dose of a statin, with or without other lipid-modifying therapy (such as ezetimibe):

In ORION-10, patients with non-familial hypercholesterolemia with ASCVD who were treated with LEQVIO® experienced a greater mean percent-change reduction in LDL-C from baseline to Day 510 compared to placebo (-51% vs. 1%, respectively).

- Producing a between-group difference of -52% (95% CI: -56%, -49%; *p*<0.001)

In ORION-9, patients with HeFH who were treated with LEQVIO® experienced a greater mean percent-change reduction in LDL-C from baseline to Day 510 compared to placebo (-40% vs. 8%, respectively).

- Producing a between-group difference of -48% (95% CI: -54%, -42%; *p*<0.0001)

Consider LEQVIO® to further reduce LDL-C in your patients with non-familial hypercholesterolemia with ASCVD or HeFH who are on a maximally tolerated dose of a statin, with or without other lipid-lowering therapies.

† Clinical significance is unknown.
‡ Comparative clinical significance has not been established.
§ Consult the LEQVIO® Product Monograph for complete dosing information.
¶ In the ORION-9 clinical trial (n=482), patients who received 284 mg of LEQVIO® (inclisiran injection) administered subcutaneously at baseline, 3 months, and every subsequent 6 months exhibited an average between-group difference in LDL-C reduction of 47.9% (95% CI: -53.5%, -42.3%; *p*<0.0001) when compared to placebo. The reduction in LDL-C was maintained across each 6-month dosing interval up to trial Day 510.[1,4]
¥ In the ORION-10 (n=1,561) and ORION-11 (n=1,617) clinical trials, patients who received 284 mg of LEQVIO® (inclisiran injection) administered subcutaneously at baseline, 3 months, and every subsequent 6 months exhibited an average between-group difference in LDL-C reduction of 52% (95% CI: -55.7%, -48.8; *p*<0.001) and -49.9% (95% CI: -53.1, -46.6; *p*<0.0001) when compared to placebo, respectively. The reduction in LDL-C was maintained across each 6-month dosing interval up to trial Day 510.[1,2]

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REFERENCES

1. LEQVIO® (inclisiran injection) Product Monograph. Novartis Pharmaceuticals Canada Inc. July 23rd, 2021.

2. Ray KK, Wright RS, Kallend D, *et al*. Two Phase 3 Trials of Inclisiran in Patients with Elevated LDL Cholesterol. *N Engl J Med*. 2020;382(16):1507-1519.

3. Ray KK, Wright RS, Kallend D, *et al*. Two Phase 3 Trials of Inclisiran in Patients with Elevated LDL Cholesterol. *N Engl J Med*. 2020;382(16_Suppl):1-32.

4. Pearson GJ, Thanassoulis G, Anderson TJ, *et al*. 2021 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult [published online ahead of print, 2021 Mar 26]. *Can J Cardiol*. 2021;S0828-282X(21)00165-3.

5. Chen G, Farris MS, Cowling T, *et al*. Treatment and Low-Density Lipoprotein Cholesterol Management in Patients Diagnosed With Clinical Atherosclerotic Cardiovascular Disease in Alberta. *Can J Cardiol*. 2019;35(7):884-891.

6. Lamb YN. Inclisiran: First Approval. *Drugs*. 2021;81:389-395.

7. Raal FJ, Kallend D, Ray KK, *et al*. Inclisiran for the Treatment of Heterozygous Familial Hypercholesterolemia. *N Engl J Med*. 2020;382(16):1520-1530.

8. Data on File. Novartis Pharmaceuticals, 2022.

9. Data on File. Novartis Pharmaceuticals, 2022.