

# Updates in Lipid Pharmacotherapy

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# AHA/ACC



High-intensity statin for patients with clinical ASCVD



Ezetimibe in patients with LDL >70 mg/dL on max statin



PCSK9 inhibitor in patients with LDL >70 mg/dL on max statin and ezetimibe

# ESC/EAS



High-intensity statin to reach LDL goals for set level of risk



Ezetimibe addition if goal is not achieved with high-intensity statin



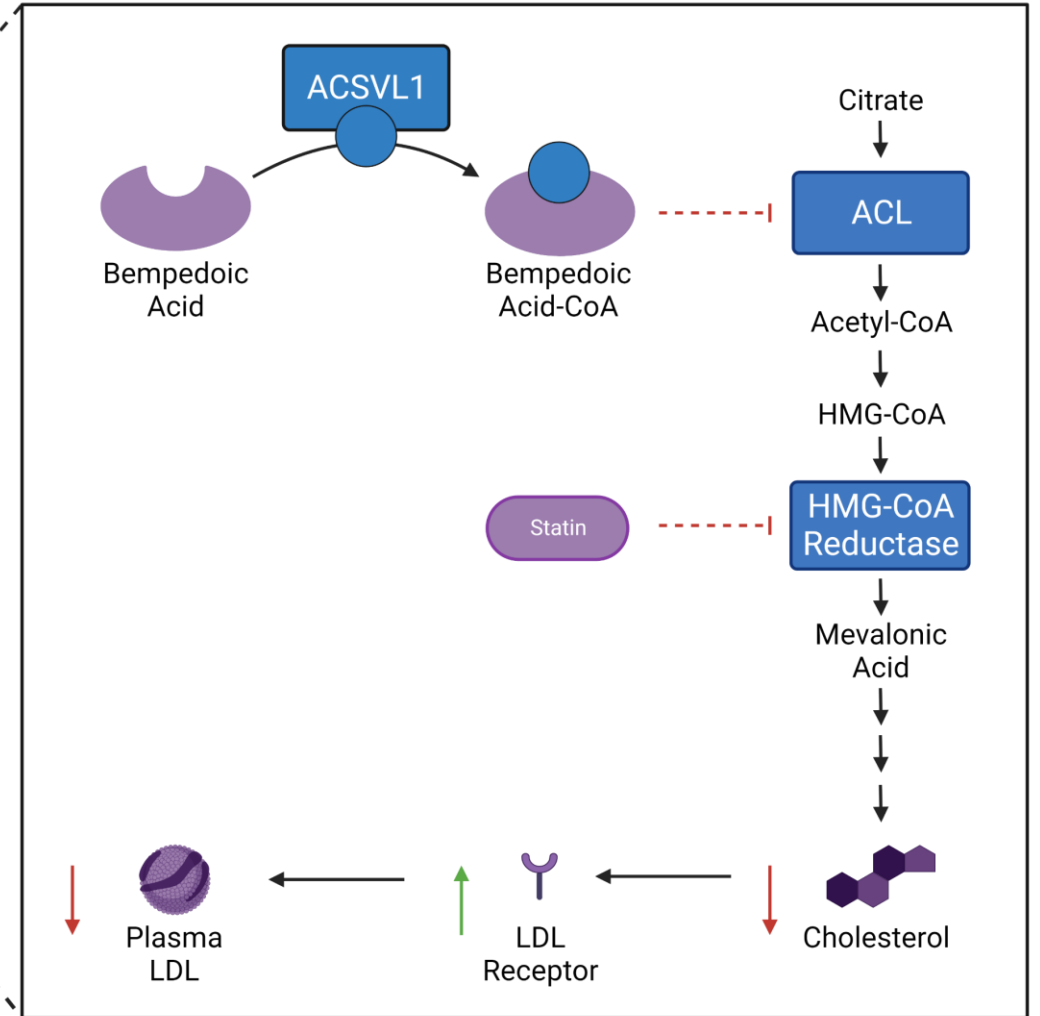
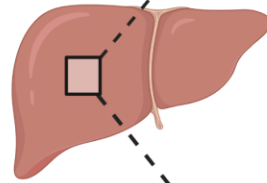
PCSK9 inhibitor for secondary prevention not at goal with statin and ezetimibe



Icosapent ethyl in those at high-risk with elevated TG levels on statin therapy

# Bempedoic Acid

- Prodrug
- Inhibits ACL
- Active only in liver



# CLEAR Harmony

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- ASCVD and/or HeFH
- Maximally tolerated lipid therapy
- LDL  $\geq$ 70 mg/dL
- Exclusion
  - Gemfibrozil use
  - Simvastatin >40 mg
  - PCSK9 inhibitors before week 24

# CLEAR Wisdom

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- ASCVD and/or HeFH
- Maximally tolerated lipid therapy
- LDL  $\geq$ 70 mg/dL
- Exclusion
  - Gemfibrozil
  - Simvastatin >40 mg

# CLEAR Harmony

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Bempedoic Acid  
180 mg once daily



Placebo  
once daily

## Primary Endpoint

Safety

## Secondary Endpoint

% change LDL-C from baseline to week 12  
% change in non-HDL-C, TC, apoB, hsCRP

# CLEAR Wisdom

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Bempedoic Acid  
180 mg once daily



Placebo  
once daily

## Primary Endpoint

% change in LDL-C from baseline to week 12

## Secondary Endpoints

% change in non-HDL-C, TC, apoB, hsCRP



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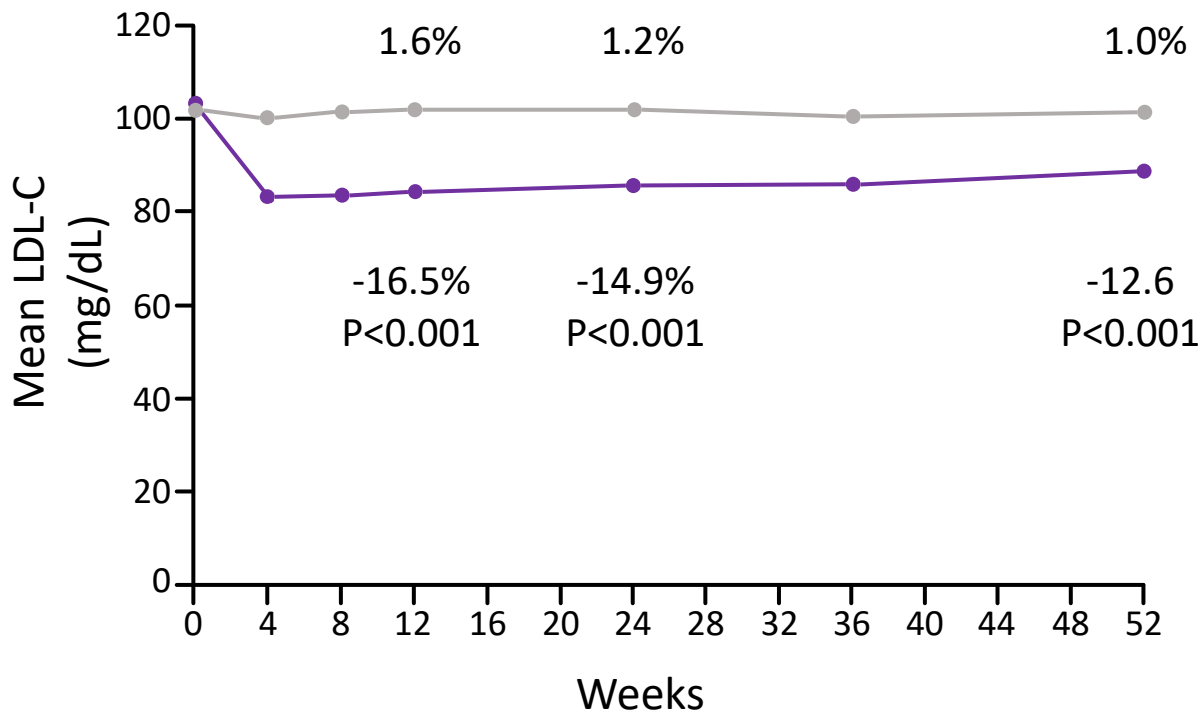
# CLEAR Harmony

	<b>Bempedoic Acid N=1488</b>	<b>Placebo N=742</b>
<b>Age (years)</b>	65.8	66.8
<b>Female (%)</b>	26.1	28.7
<b>White (%)</b>	95.6	96.5
<b>ASCVD (%)</b>	97.4	98.0
<b>Statin therapy (%)</b>	99.8	100
<b>LDL-C (mg/dL)</b>	103.6	102.3

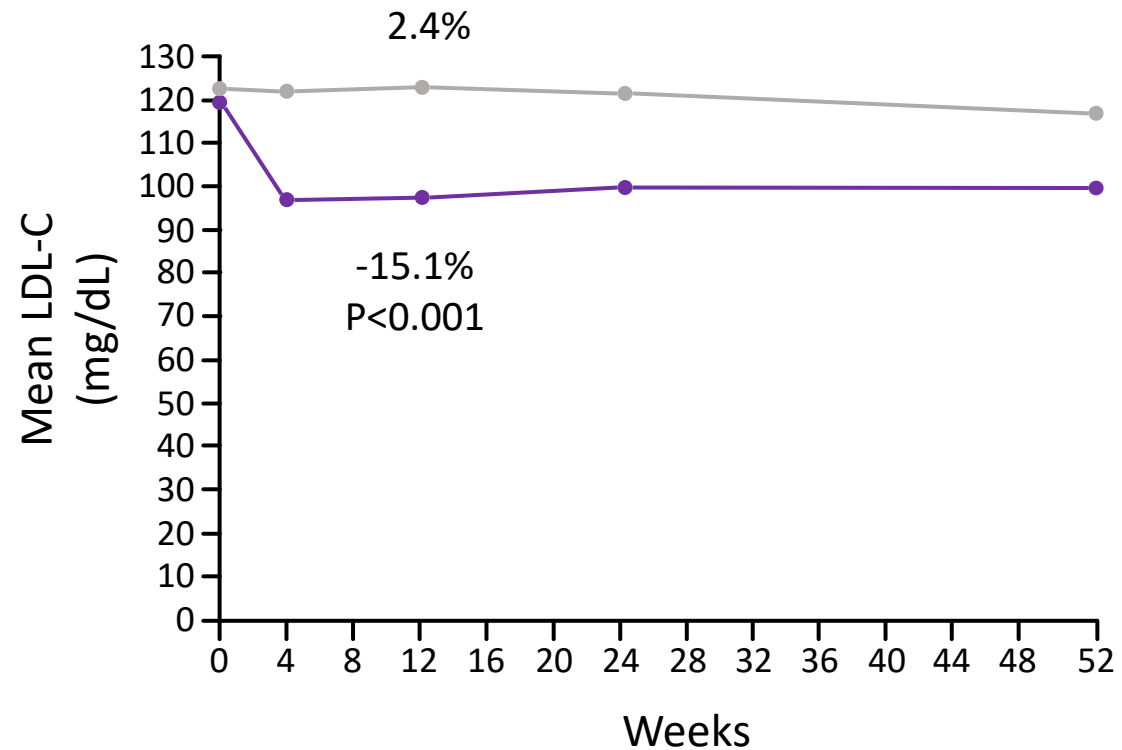
# CLEAR Wisdom

	<b>Bempedoic Acid N=522</b>	<b>Placebo N=257</b>
<b>Age (years)</b>	64.1	64.7
<b>Female (%)</b>	37.2	34.6
<b>White (%)</b>	94.1	94.9
<b>ASCVD only (%)</b>	94.8	93.8
<b>Statin only (%)</b>	79.7	76.3
<b>LDL-C (mg/dL)</b>	119.4	122.4

# CLEAR Harmony



# CLEAR Wisdom



# CLEAR Harmony

# CLEAR Wisdom

	<b>Bempedoic Acid N=1488</b>	<b>Placebo N=742</b>
<b>SAE (%)</b>	14.5	14.0
<b>Discontinuation from AE (%)</b>	10.9	7.1
<b>MACE (%)</b>	4.6	5.7
<b>Myalgia (%)</b>	6.0	6.1
<b>New-onset or worsening DM (%)</b>	3.3	5.4
<b>Gout (%)</b>	1.2	0.3

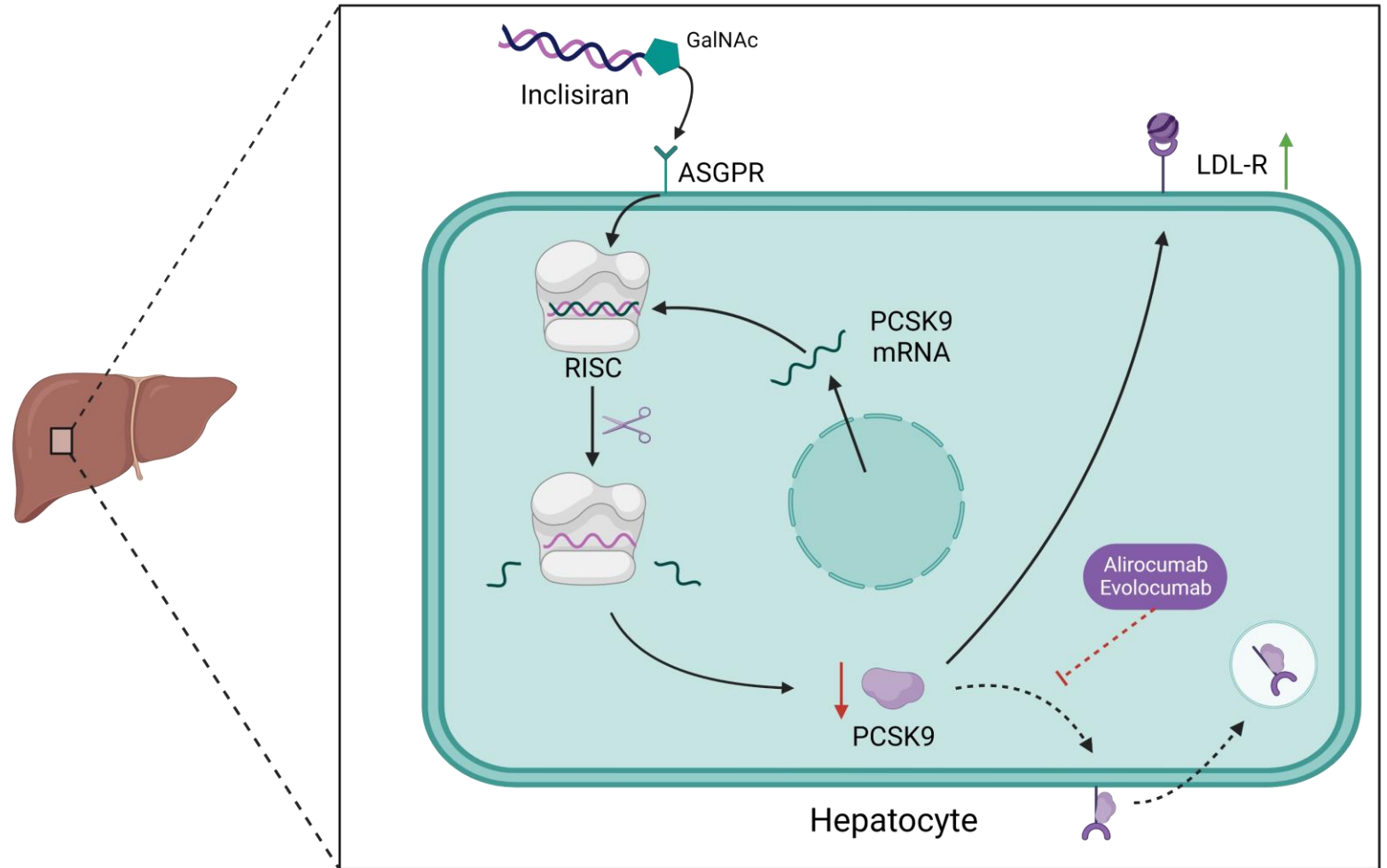
	<b>Bempedoic Acid N=522</b>	<b>Placebo N=257</b>
<b>SAE (%)</b>	20.3	18.7
<b>Discontinuation from AE (%)</b>	10.9	8.6
<b>UTI (%)</b>	5.0	1.9
<b>Myalgia (%)</b>	2.9	3.1
<b>New-onset or worsening DM (%)</b>	6.9	7.4
<b>Gout (%)</b>	2.1	0.8





# Inclisiran

- Small interfering RNA (siRNA)
- Enhanced uptake to liver by ASGPR
- Enhances breakdown of PCSK9 mRNA



# ORION 10

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- Adults with ASCVD in US
- LDL-C  $\geq$ 70 mg/dL
- Excluded patients on PCSK9 inhibitors within 90 days

# ORION 11

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- ASCVD or ASCVD risk equivalent
- LDL-C  $\geq$ 70 mg/dL
- LDL-C  $\geq$ 100 mg/dL in those with risk equivalent
- Excluded patients on PCSK9 inhibitors within 90 days



# ORION 10

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Inclisiran 284 mg subcutaneously  
Day 1, 90, 270, 450

# ORION 11

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Placebo 1.5 mL subcutaneously  
Day 1, 90, 270, 450

## Primary Endpoint

% change in LDL from baseline to day 510

## Secondary Endpoint

% change in TC, apoB, non-HDL-C



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# ORION 10

	<b>Inclisiran N=781</b>	<b>Placebo N=780</b>
<b>Age (years)</b>	66.4	65.7
<b>Female (%)</b>	31.5	29.7
<b>White (%)</b>	83.6	87.8
<b>ASCVD (%)</b>	100	100
<b>Statin therapy (%)</b>	89.8	88.7
<b>LDL-C (mg/dL)</b>	104.5	104.8

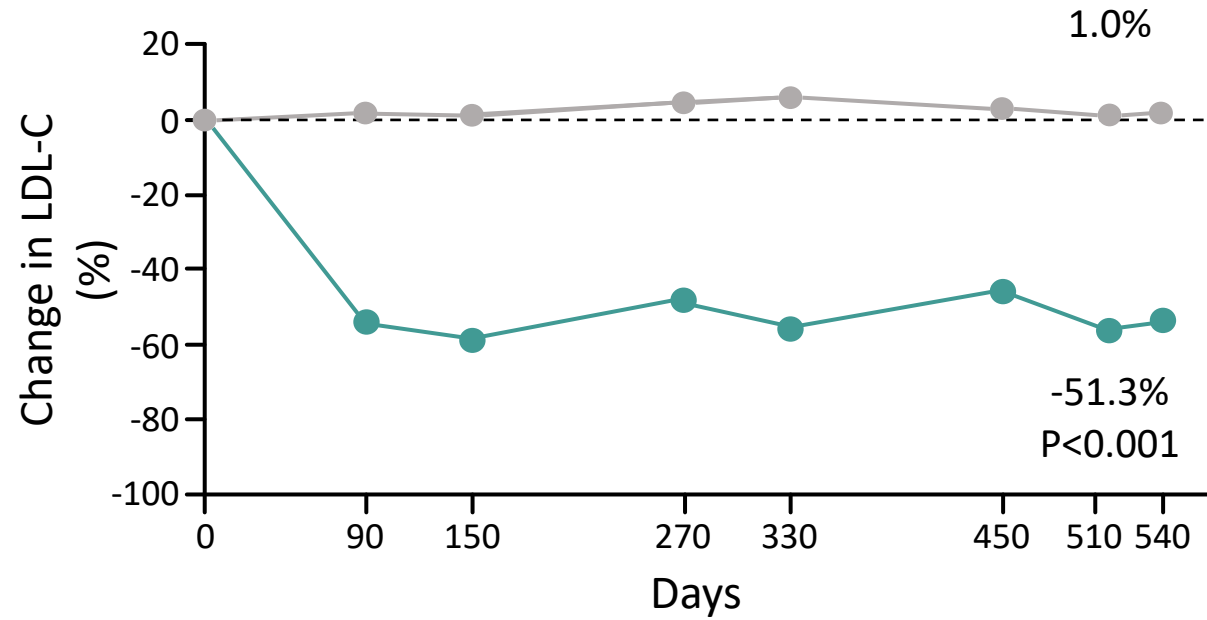
# ORION 11

	<b>Inclisiran N=810</b>	<b>Placebo N=807</b>
<b>Age (years)</b>	64.8	64.8
<b>Female (%)</b>	28.5	28.0
<b>White (%)</b>	97.7	98.6
<b>ASCVD (%)</b>	87.9	87.0
<b>Statin therapy (%)</b>	94.6	94.9
<b>LDL-C (mg/dL)</b>	107.2	103.7

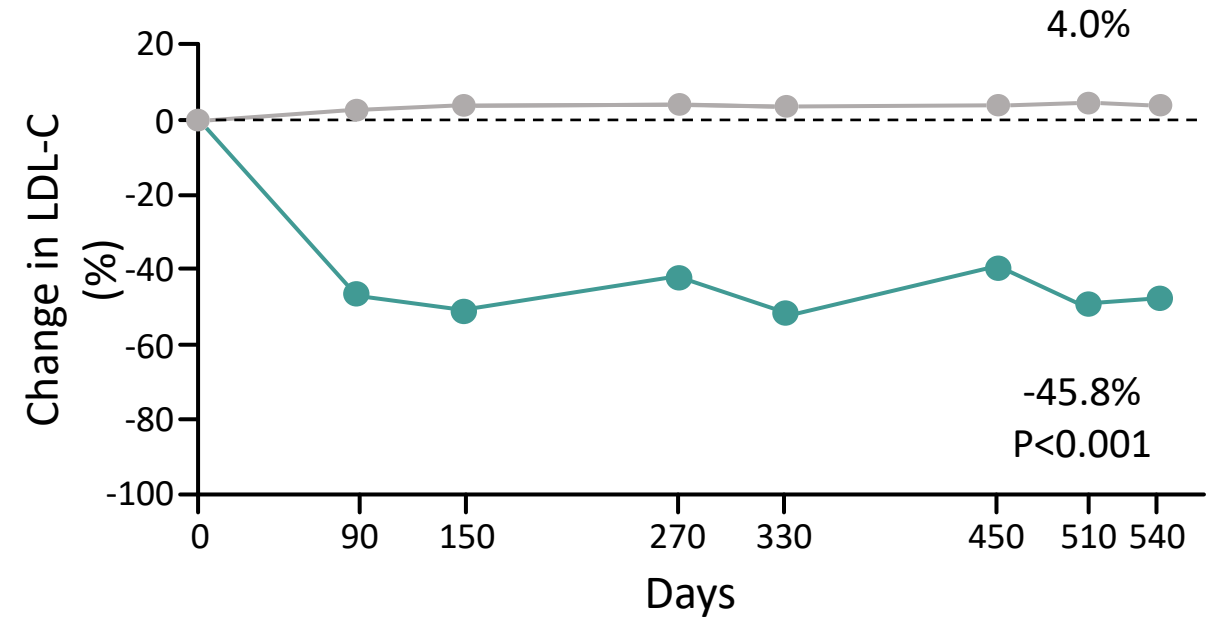


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# ORION 10

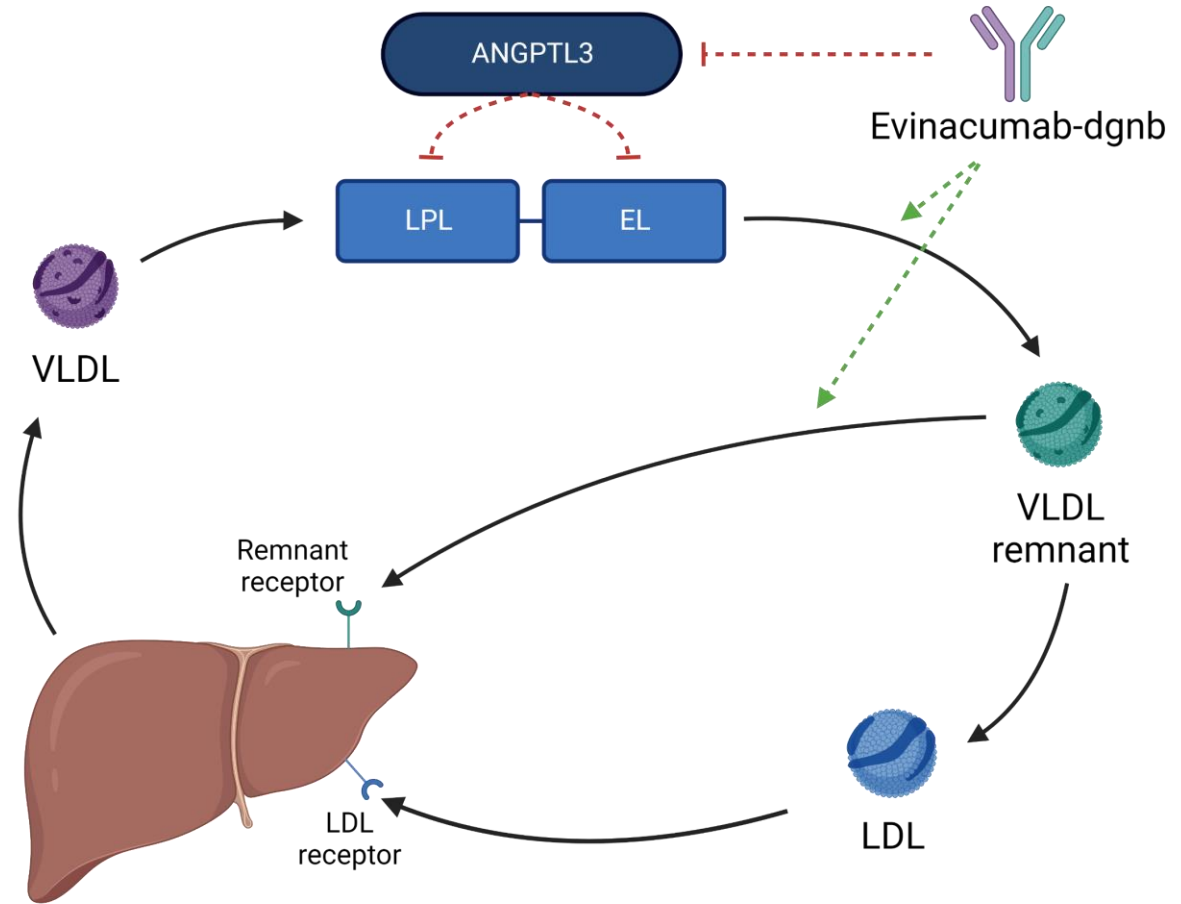


# ORION 11



# Evinacumab-dgnb

- Human monoclonal antibody
- Inhibits ANGPTL3
- Promotes VLDL remnant clearance



# ELIPSE HoFH

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## Inclusion Criteria

12+ years old

HoFH

Max tolerated lipid-lowering therapy

LDL >70 mg/dL



IV evinacumab 15 mg/kg  
Every 4 weeks

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IV placebo  
Every 4 weeks

## Primary Outcome

% change in LDL from  
baseline to week 24



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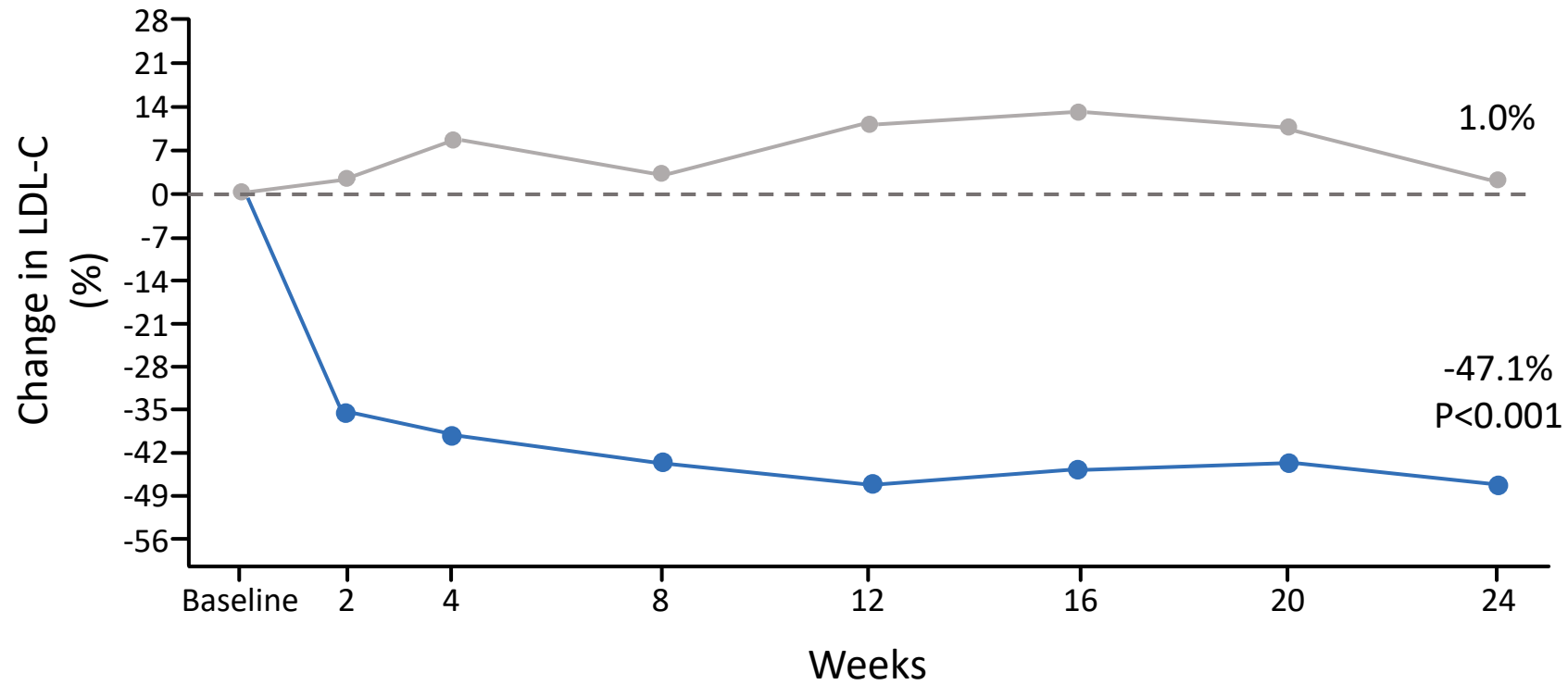
# ELIPSE HoFH

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	<b>Evinacumab N=43</b>	<b>Placebo N=22</b>
<b>Age (years)</b>	44.3	36.7
<b>Female (%)</b>	56	50
<b>White (%)</b>	72	77
<b>Genotype HoFH diagnosis (%)</b>	67	68
<b>LDL-C (mg/dL)</b>	259.5	246.5



# ELIPSE HoFH



# ELIPSE HoFH

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- No discontinuations from treatment
- Most common:
  - Influenza-like illness
  - Nasopharyngitis

# Lipid Lowering Potency

	LDL-C	TC	HDL	Non-HDL-C	apoB	TG
High-intensity Statins	>50%	---	1%	---	---	-15%
Ezetimibe	-24%	-13%	1%	-20%	-13%	-12%
PCSK9 inhibitors	59%	-36%	8%	-51%	-49%	-15%
Bempedoic Acid	-18%	-11%	-6%	-13%	-12%	2%
Inclisiran	-60-70%	-34%	7.5%	-47%	-45%	-15%
Icosapent ethyl	-5%	---	-1%	-10%	-5%	-32%
Evinacumab	-49%	-48%	-30%	-52%	-37%	-50%

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 Raal et al. N Engl J Med 2020;383:711-20  
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Sabatine et al. N Engl J Med 2017;376:1713-22  
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