Novel Antihyperlipidemics

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I have no relevant disclosures for this presentation.

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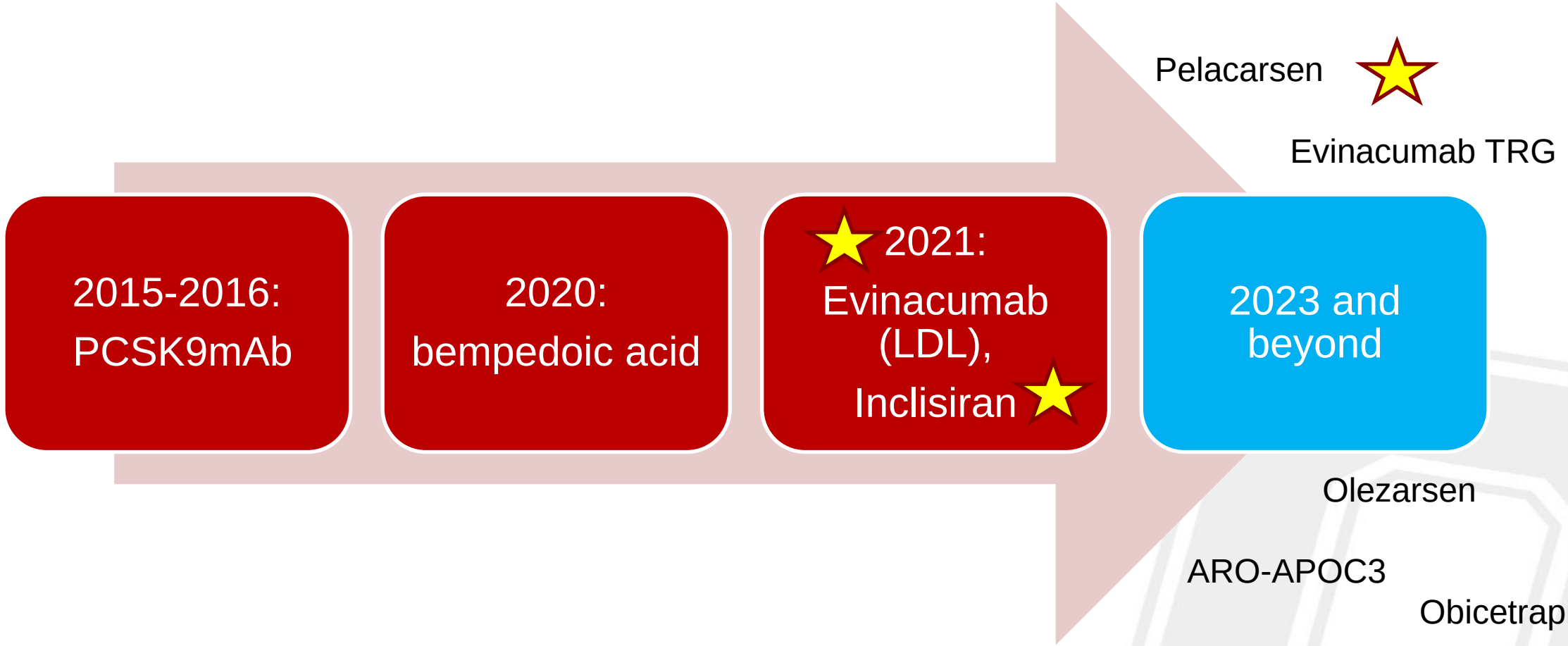
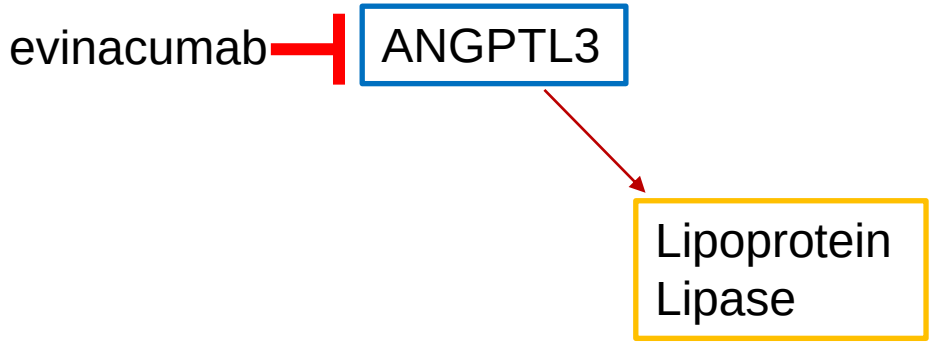
Novel Antihyperlipidemics



Evinacumab



- Human Monoclonal Antibody
  - Inhibits Angiopoietin Like 3 (ANGPTL3)
  - Results in decreased TRG, LDL-C, and HDL-C
- FDA approved for homozygous familial hypercholesterolemia (HoFH)
  - Approval: February 2021
  - ELIPSE trial
    - N = 65
    - 15 mg/kg IV Q4 weeks v placebo
    - Results after 24 weeks:

	LDL-C		
	Evinacumab	Placebo	*p*
% LDL-c reduction	-47.1	1.9	<0.001
% with ≥50% LDL-c reduction	56	5	<0.003
LDL-C <100 mg/dL (%)	47	23	----

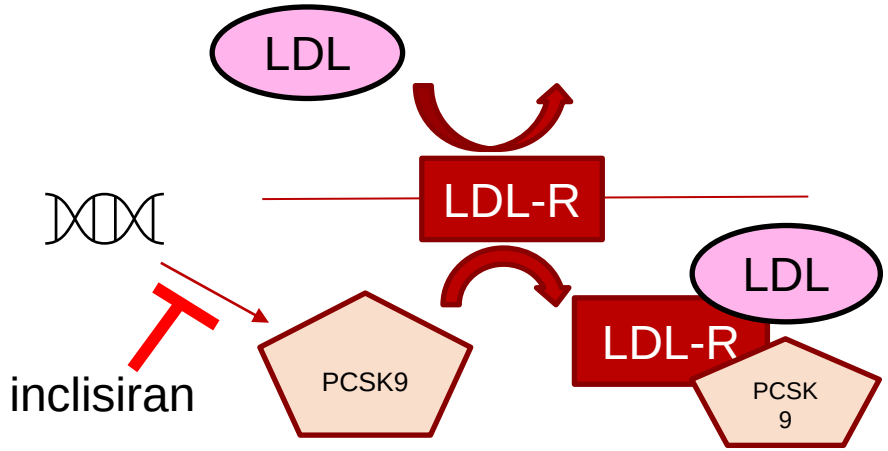
Evkeeza package insert. 2020
Raal et al. NEJM 2020.

Evinacumab

- Dosing / Administration (adults and children ≥12yo)
  - 15mg/kg IV every 4 weeks
  - Administered over 60 minutes
  - Can be given without regard for lipoprotein apheresis timing
- Common Side Effects (>5%)
  - Nasopharyngitis
  - Flu-like illness
  - Dizziness
  - Nausea
  - Infusion reactions (pruritus, fever, myasthenia)
- Pregnancy: contraindicated during and for 5 months following infusions
- Monitoring: LDL-c can be checked as soon as 2 weeks after first infusion

Evkeeza package insert. 2020

Inclisiran



- siRNA agent
  - Conjugated with triantennary N-acetylgalactosamine to facilitate hepatic uptake
  - In the hepatocyte, directs catalytic breakdown of mRNA for PCSK9
- FDA approved for Heterozygous familial hypercholesterolemia (HeFH) and secondary prevention of ASCVD
  - Approval: December 2021
  - ORION trials (9, 10, and 11)
    - Across studies, patients on PCSK9mAb were excluded

Leqvio package insert. 2020
Raal et al. NEJM 2020.
Ray et al. NEJM 2020.

ORION trials

	ORION-9	ORION-10	ORION-11
Indications	HeFH	ASCVD	
Duration	18 months		
N	482	1561	1414
Mean age	55	66	65
% women	53	31	25
% White	94	86	98
Mean baseline LDL	153 mg/dL	105 mg/dL	101 mg/dL
1o efficacy outcome	% LDL reduction baseline to day 510		
1o result	-48% (p <0.0001)	-52% (p <0.0001)	-51% (p <0.0001)

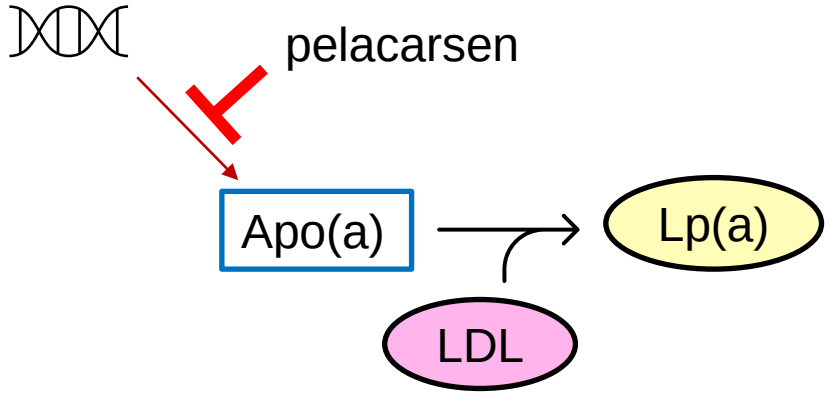
Raal et al. NEJM 2020.
Ray et al. NEJM 2020.

Inclisiran

- Dosing / Administration
  - 284mg on day 1, day 90, and then Q6 months ongoing
  - SubQ injection into the abdomen, upper arm, or thigh. Must be given by a healthcare provider.
  - If dose is missed by <3 months from due, give ASAP and resume prior schedule. If dose is missed by >3 months, restart with a new dosing schedule (including load)
- Common Side Effects (>5%)
  - Injection site reactions
  - Arthralgia
  - Antibody development
- Pregnancy: contraindicated during pregnancy
- Monitoring: lipid panel 4-12 weeks after starting therapy, and then ongoing Q3-12 months without regard to timing of dose

Leqvio package insert. 2020

Pelacarsen



- *Not* FDA approved
- Antisense medication to reduce lipoprotein(a)
- Current trial status:
  - Phase IIb – 286 patients with ASCVD and Lp(a) ≥60mg/dL, dose ranging trial
    - Primary endpoint: % change in Lp(a) from baseline to month 6
    - Yeang, et al: used direct measure Lp(a) to 'correct' LDL and better assess impact of pelacarsen on Lp(a) and on LDL
    - Lp(a) least-squared mean % change across groups: -35% to -80% (all statistically significant v placebo)
    - % of patients achieving Lp(a) <50mg/dL: 23% (20mg Q4 weeks) to 98% (20mg weekly) with similar efficacy for equivalent doses (for example, 20mg Q2 week v 40mg Qmonth)
  - HORIZON (NCT04023552) - ongoing
    - Lp(a) ≥70 mg/dL (≥175 nmol/L)
    - History of prior MI, stroke, or significant symptomatic peripheral arterial disease
    - Pelacarsen 80mg once monthly v placebo
    - Enrollment completed 7/2022 – 8325 patients. Results expected 2025.

Tsimaikas et al. NEJM 2020.
Yeang, et al. JACC 2022.

Pelacarsen

- Dosing / administration
  - HORIZON is testing 80mg Qmonth
  - SubQ injection
- Adverse events in phase IIb (higher incidence v placebo in 2b trial)
  - Injection site reactions
  - UTI
  - Myalgia
  - Headache
  - Slightly higher discontinuation rate for ADE (5% v 4%) with most common reasons being myalgia / arthralgia or malaise

Tsimaikas et al. NEJM 2020.

Other Phase 3 Medications

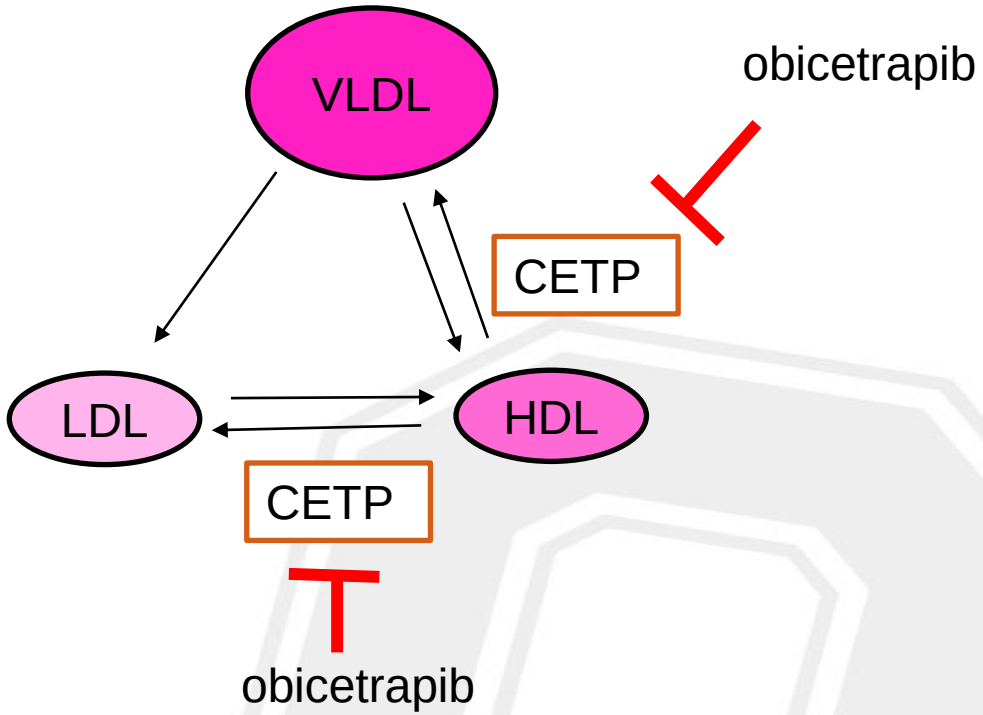
	Medication Type	Current Trials
ARO-APOC3	RNAi	PALISADE – FCS (phase 3) SHASTA-2 – severe hyperTRG (phase 2b) MUIR – mixed dyslipidemia (phase 2)
Olezarsen	LICA antisense	CORE – severe hyperTRG (phase 3) BALANCE – FCS (phase 3)
Obicetrapib	CETPi	BROADWAY – HeFH and/or ASCVD (phase 3)

ClinicalTrials.gov

Other Phase 3 Medications – Target LDL

	Medication Type	Current Trials
Obicetrapib	CETPi	BROADWAY – HeFH and/or ASCVD (phase 3)

- *Not* FDA approved
- Daily oral medication
- Phase 2 trials: ROSE, TULIP

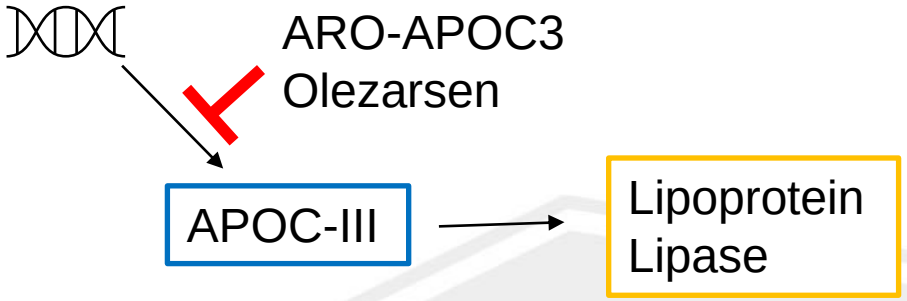


S Nicholls et al. Nature Medicine 2022.

Other Phase 3 Medications – Target TRG

	Medication Type	Current Trials
ARO-APOC3	RNAi	PALISADE – FCS
Olezarsen	LICA antisense	CORE – severe hyperTRG BALANCE – FCS

- *Not* FDA approved
- SubQ injections
- Phase 2 trials:
  - ARO-APOC3: SHASTA-2, MUIR
  - Olezarsen: Tardif et al



M-R Taskinen, C Packard, J Boren. Curr Atheroscler Rep. 2019

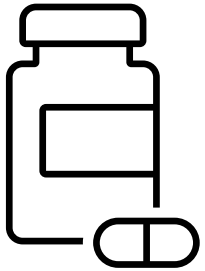
Evinacumab - TRG

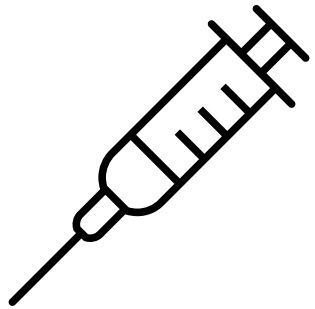
- *Not* FDA approved for this indication
- Current trial status:
  - Phase 2 (completed) – evinacumab for severe hypertriglyceridemia at risk for acute pancreatitis
    - 51 patients with hypertriglyceridemia and a history of acute pancreatitis, without HoFH
    - Patients were genotyped for lipoprotein lipase mutations
      - No LOF mutations: -81.7% (v +80.9%) during double blind period
      - One LOF mutation: -64.8% (v +9.4%) during double blind period
      - Two LOF mutations (FCS): no reduction in TRG
  - Phase 2b (NCT04863014 - ongoing) – evinacumab for reduction of acute pancreatitis episodes in patients with severe hypertriglyceridemia without FCS
    - As of 10/2022 status is now "active, not recruiting"

Rosenson et all. ACC 2021.

What's Next?

- MK-0616 – oral PCSK9i peptide
- Verve-101 – gene therapy
- Olpasiran – Lp(a) siRNA
- Ongericimab – recombinant human PCSK9i
- TBD!





Thank You!

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