Long-term safety, tolerability and efficacy of alirocumab versus placebo in high cardiovascular risk patients: first results from the ODYSSEY LONG TERM study in 2,341 patients

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ODYSSEY

Industry Relationships and Institutional Affiliations

Author	Disclosure
Jennifer G. Robinson	Research Grant; Significant; Amarin, Amgen, AstraZeneca, Daiichi-Sankyo, Genentech/Hoffman La Roche, Glaxo-Smith Kline, Merck, Regeneron/Sanofi, Zinfandel/Takeda. Consultant/Advisory Board; Modest; Amgen, Hoffman LaRoche, Merck, Pfizer, Sanofi.
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Michel Krempf	Grants, consulting fees and/or honoraria and delivering lectures for Abbott, Amgen, Astra Zeneca, BMS, Merck and Co, Novartis, Pfizer, Roche, Sanofi-Aventis
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Gérald Luc	Honoraria; Modest; Regeneron, Sanofi.
Maurizio Averna	Research Grant; Significant; MSD. Speakers Bureau; Modest; Aegerion, Sanofi, Amgen, MSD, Chiesi, Mediolanum, AstraZeneca. Consultant/Advisory Board; Modest; Aegerion, Sanofi, Amgen, MSD, Chiesi, Mediolanum, AZ, Kowa, Roche.
Erik Stroes	Consultant/Advisory Board; Modest; MSD, Amgen, Sanofi, Regeneron, Torrent.
Gisle Langslet	Consultant/Advisory Board; Modest; Amgen, Sanofi-Aventis, Janssen Pharmaceuticals.
Frederick J. Raal	Research Grant; Modest; Amgen, Sanofi/Regeneron. Speakers Bureau; Modest; Amgen, Sanofi/Regeneron, Pfizer, AstraZeneca. Honoraria; Modest; Amgen, Sanofi/Regeneron, Pfizer, Astra Zeneca. Consultant/Advisory Board; Modest; Amgen, Sanofi/Regeneron, Pfizer, AstraZeneca.
Mahfouz El Shahawy	None.
Michael J. Koren	Research Grant; Significant; Regeneron/Sanofi. Consultant/Advisory Board; Significant; Regeneron/Sanofi.
Norman Lepor	Other Research Support; Significant; Clinical Trial Investigator. Consultant/Advisory Board; Modest; Sanofi.
Christelle Lorenzato	Employee of Sanofi.
Robert Pordy	Employee of Regeneron Pharmaceuticals, Inc.
Umesh Chaudhari	Employee of Sanofi.
John J.P. Kastelein	Honoraria; Modest; Dezima Pharmaceuticals, Regeneron, Sanofi, Eli Lilly, Pfizer, Amgen, Genzyme, Aegerion, Esperion. Honoraria; Significant; Isis. Consultant/Advisory Board; Modest; Dezima Pharmaceuticals, Regeneron, Sanofi, Eli Lilly, Pfizer, Amgen, Genzyme, Aegerion, Esperion. Consultant/Advisory Board; Significant; Isis.

Overview of the ODYSSEY Phase 3 Programme

Fourteen global Phase 3 trials including >23 500 patients across >2000 study centres

HeFH population	HC in high CV-risk population	Additional populations
Add-on to max tolerated statin (± other LLT)	**Add-on to max tolerated statin (± other LLT)**	
ODYSSEY FH I (NCT01623115; EFC12492) LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL n=486; 18 months	ODYSSEY COMBO I (NCT01644175; EFC11568) LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL n=316; 12 months	ODYSSEY MONO (NCT01644474; EFC11716) Patients on no background LLTs LDL-C ≥100 mg/dL n=103; 6 months
ODYSSEY FH II (NCT01709500; CL1112) LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL n=249; 18 months	*ODYSSEY COMBO II (NCT01644188; EFC11569) LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL n=720; 24 months	ODYSSEY ALTERNATIVE (NCT01709513; CL1119) Patients with defined statin intolerance LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL n=314; 6 months
ODYSSEY HIGH FH (NCT01617655; EFC12732) LDL-C ≥160 mg/dL n=107; 18 months	ODYSSEY CHOICE I (NCT01926782; CL1308) LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL n=700; 12 months	
ODYSSEY OLE (NCT01954394; LTS 13463) Open-label study for FH from EFC 12492, CL 1112, EFC 12732 or LTS 11717 n≥1000; 30 months		ODYSSEY CHOICE II (NCT02023879; EFC13786) Patients not treated with a statin LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dl n=200; 6 months
ODYSSEY LONG TERM (NCT01507831; LTS11717) LDL-C ≥70 mg/dL n=2,341; 18 months		ODYSSEY OPTIONS I (NCT01730040; CL1110) Patients not at goal on moderate-dose atorvastatin LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL n=355; 6 months
	ODYSSEY OUTCOMES (NCT01663402; EFC11570) LDL-C ≥70 mg/dL n=18,000; 64 months	ODYSSEY OPTIONS II (NCT01730053; CL1118) Patients not at goal on moderate-dose rosuvastatin LDL-C ≥70 mg/dL OR LDL-C ≥100 mg/dL n=305; 6 months

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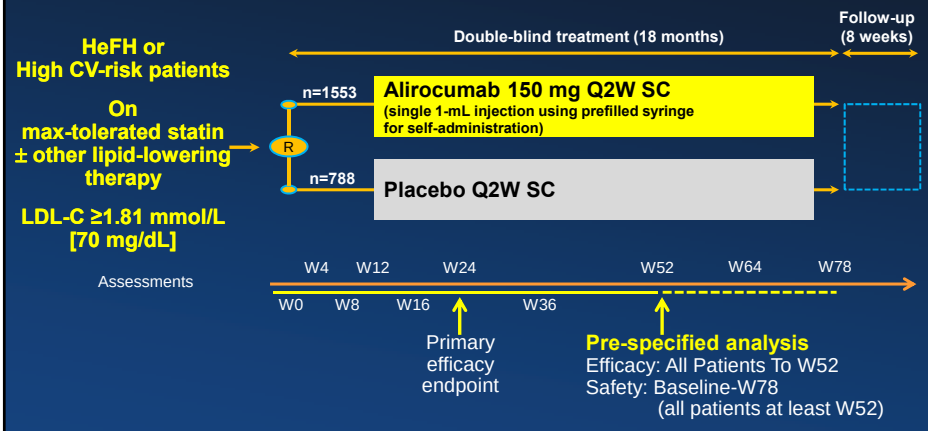
*For ODYSSEY COMBO II other LLT not allowed at entry.

ODYSSEY LONG TERM Study Design



86% (2011/2341) completed 52 weeks (both treatment arms)
26.1% (405/1553 alirocumab) and 25.6% (202/788 placebo) had completed 78 weeks by time of this analysis
Mean treatment duration: 65 weeks (both treatment arms)

ClinicalTrials.gov identifier: NCT01507831.

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Baseline Characteristics

All patients on background of max-tolerated statin ± other lipid-lowering therapy	Alirocumab (n=1553)	Placebo (n=788)
Age, years, mean (*SD*)	**60.4** (*10.4*)	**60.6** (*10.4*)
Male, % (n)	**63.3%** (983)	**60.2%** (474)
Race, White	**92.8%** (1441)	**92.6%** (730)
BMI, kg/m², mean (*SD*)	**30.2** (*5.7*)	**30.5** (*5.5*)
HeFH, % (n)	**17.8%** (276)	**17.6%** (139)
CHD history, % (n)	**67.9%** (1055)	**70.1%** (552)
Type 2 diabetes, % (n)	**34.9%** (542)	**33.9%** (267)
Any statin†, % (n)	**99.9%** (1552)	**99.9%** (787)
High-intensity statin‡, % (n)	**44.4%** (690)	**43.4%** (342)
Any LLT other than statins, % (n)	**28.1%** (437)	**27.9%** (220)
Ezetimibe, % (n)	**13.9%** (216)	**15.0%** (118)
LDL-C, calculated mean (*SD*)**, mmol/L [mg/dL]**	**3.2** (*1.1*) **[122.7** (*42.6*)**]**	**3.2** (*1.1*) **[121.9** (*41.4*)**]**

†Patients should receive either rosuvastatin 20-40 mg, atorvastatin 40-80 mg daily, or simvastatin 80 mg daily unless not tolerated and/or appropriate other dose given according to the judgement of the investigator

‡High-intensity statin: atorvastatin 40-80 mg or rosuvastatin 20-40 mg daily.

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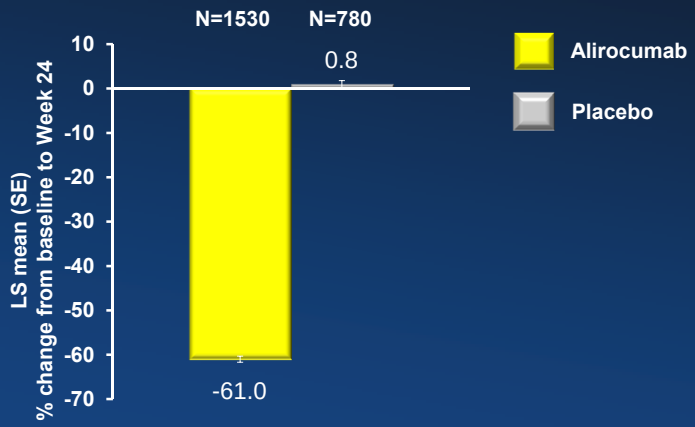
ODYSSEY

Alirocumab Significantly Reduced LDL-C from Baseline to Week 24 versus Placebo

Primary Endpoint: Percent Change from Baseline to Week 24 in LDL-C

All patients on background of maximally-tolerated statin ± other lipid-lowering therapy



LS mean difference (SE) versus placebo: −61.9% (1.3); *P*<0.0001

Intent-to-treat (ITT) analysis

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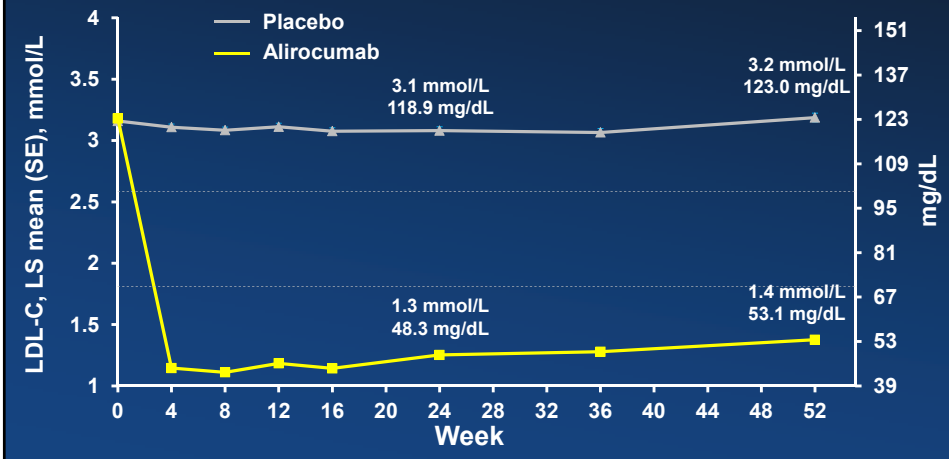
ODYSSEY

Alirocumab Maintained Consistent LDL-C Reductions over 52 Weeks

Achieved LDL-C Over Time

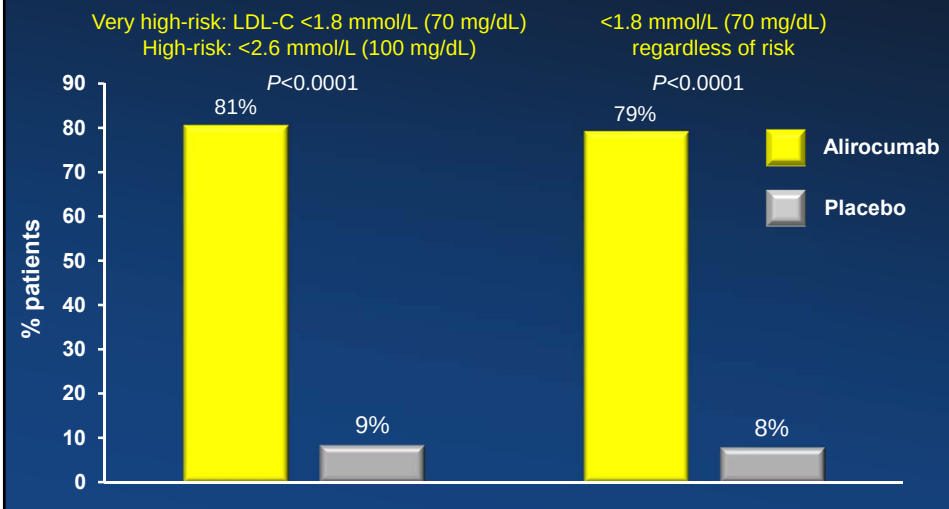
All patients on background of maximally-tolerated statin ±other lipid-lowering therapy



Intent-to-treat (ITT) analysis

Most Patients Receiving Alirocumab on Background Statin ± Other LLT Achieved LDL-C Goals

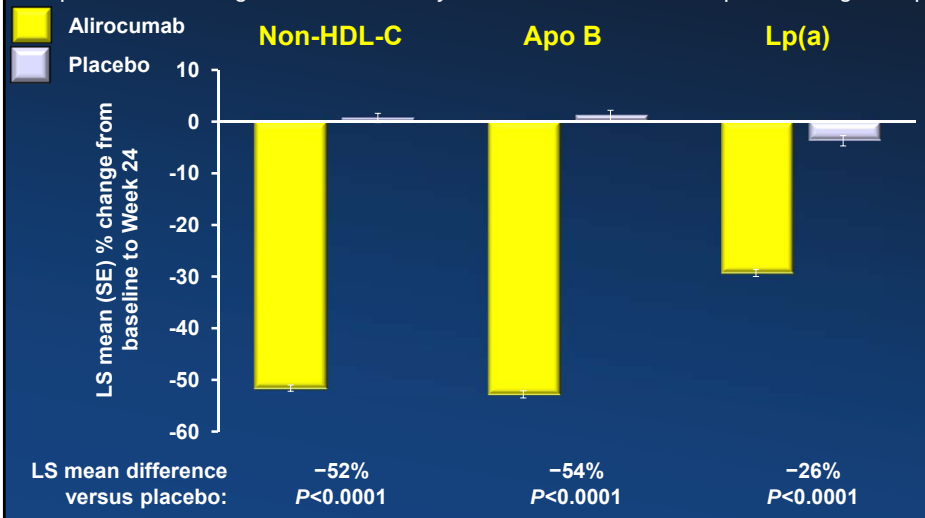
Proportion of patients reaching LDL-C goal at Week 24



Intent-to-treat (ITT) analysis; LLT = lipid-lowering therapy

Significant Reductions in Secondary Lipid Parameters at Week 24

All patients on background of maximally-tolerated statin ± other lipid-lowering therapy



LS mean difference versus placebo:	−52% *P*<0.0001	−54% *P*<0.0001	−26% *P*<0.0001

Adjusted mean (SE) shown for Lp(a).

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Treatment-Emergent Adverse Events

Safety Analysis (at least 52 weeks for all patients continuing treatment, including 607 patients who completed W78 visit)

% (n) of patients All patients on background of max-tolerated statin ± other lipid-lowering therapy	**Alirocumab (n=1550)**	**Placebo (n=788)**
TEAEs	**78.6%** (1218)	**80.6%** (635)
Treatment-emergent SAEs	**16.5%** (255)	**17.6%** (139)
TEAE leading to death	**0.5%** (7)	**1.0%** (8)
TEAEs leading to treatment discontinuation	**6.2%** (96)	**5.5%** (43)

- **Mean treatment duration: 65 weeks (both treatment arms)**
- **26.1% (405/1553 alirocumab) and 25.6% (202/788 placebo) completed 78 weeks**

Statistical analyses have not been performed.

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ODYSSEY

TEAEs by System-Organ-Class (≥2%) in any Group

Safety Analysis (at least 52 weeks for all patients continuing treatment, including 607 patients who completed W78 visit)

% (n) of patients All patients on background of max-tolerated statin ± other LLT	**Alirocumab (n=1550)**	**Placebo (n=788)**
Infections and infestations	**45.5%** (705)	**46.1%** (363)
Musculoskeletal and connective tissue disorders	**27.2%** (422)	**28.6%** (225)
Gastrointestinal disorders	**18.6%** (288)	**18.8%** (148)
Nervous system disorders	**17.0%** (264)	**17.8%** (140)
General disorders and administration site conditions	**15.4%** (238)	**17.0%** (134)
Injury, poisoning, and procedural complications	**13.4%** (207)	**14.2%** (112)
Respiratory, thoracic, and mediastinal disorders	**11.0%** (171)	**10.9%** (86)
Cardiac disorders	**9.1%** (141)	**11.8%** (93)
Skin and subcutaneous tissue disorders	**9.1%** (141)	**8.5%** (67)
Metabolism and nutrition disorders	**9.1%** (141)	**8.4%** (66)
Vascular disorders	**7.9%** (122)	**8.9%** (70)
Eye disorders	**6.5%** (100)	**6.1%** (48)
Investigations (lab parameters)	**6.1%** (95)	**5.2%** (41)
Psychiatric disorders	**5.9%** (91)	**8.0%** (63)
Renal and urinary disorders	**4.6%** (72)	**6.0%** (47)
Neoplasms, benign, malignant (incl cysts/polyps)	**2.5%** (38)	**3.4%** (27)
Reproductive system and breast disorders	**2.5%** (38)	**3.2%** (25)
Blood and lymphatic system disorders	**2.4%** (37)	**3.0%** (24)
Ear and labyrinth disorders	**2.0%** (31)	**2.9%** (23)

Adverse Events of Special Interest

Safety Analysis (at least 52 weeks for all patients continuing treatment, including 607 patients who completed W78 visit)

% (n) of patients All patients on background of max tolerated statin ± other lipid-lowering therapy	**Alirocumab (n=1550)**	**Placebo (n=788)**
Treatment-emergent local injection site reactions	**5.8%** (90)	**4.3%** (34)
General allergic reaction events	**9.0%** (140)	**9.0%** (71)
All cardiovascular events†	**4.0%** (62)	**4.4%** (35)
Neurological events‡	**4.2%** (65)	**3.9%** (31)
Neurocognitive disorders‡	**1.2%** (18)	**0.5%** (4)
Ophthalmological events‡	**2.5%** (38)	**1.9%** (15)
Haemolytic anaemia	**0**	**0**

† Confirmed by adjudication. Adjudicated CV events include all CV AEs positively adjudicated. The adjudication categories are the following: CHD death, non-fatal MI, fatal and non-fatal ischemic stroke, unstable angina requiring hospitalisation, congestive heart failure requiring hospitalisation, ischemia driven coronary revascularisation procedure [PCI, CABG].

‡Company MedDRA Queries (CMQ).

Statistical analyses have not been performed.

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ODYSSEY

Neurocognitive Adverse Events

Safety Analysis (at least 52 weeks for all patients continuing treatment, including 607 patients who completed W78 visit)

% (n) of patients All patients on background of max tolerated statin ± other lipid-lowering therapy	**Alirocumab (n=1550)**	**Placebo (n=788)**
Any neurocognitive disorder†	**1.2%** (18)	**0.5%** (4)
Amnesia	**0.3%** (5)	**0%** (0)
Memory impairment	**0.3%** (5)	**0.1%** (1)
Confusional state	**0.3%** (4)	**0.1%** (1)
Confusion postoperative	**<0.1%** (1)	**0%** (0)
Dementia	**<0.1%** (1)	**0.1%** (1)
Disorientation	**<0.1%** (1)	**0%** (0)
Disturbance in attention	**<0.1%** (1)	**0.1%** (1)
Frontotemporal dementia	**<0.1%** (1)	**0%** (0)
Transient global amnesia	**<0.1%** (1)	**0%** (0)

†Company MedDRA Queries (CMQ).
Statistical analyses have not been performed.

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ODYSSEY

Post-hoc Adjudicated Cardiovascular TEAEs†

Safety Analysis (at least 52 weeks for all patients in ongoing study)

Safety Analysis (at least 52 weeks for all patients continuing treatment, including 607 patients who completed W78 visit)

% (n) of patients All patients on background of max tolerated statin ± other lipid-lowering therapy	**Alirocumab (n=1550)**	**Placebo (n=788)**
CV events confirmed by adjudication	**1.4%** (22)	**3.0%** (24)
CHD death	**0.2%** (3)	**0.8%** (6)
Non-fatal MI	**0.7%** (11)	**2.2%** (17)
Fatal + non-fatal ischaemic stroke	**0.5%** (8)	**0.3%** (2)
Unstable angina requiring hospitalisation	0	**0.1%** (1)

Patients are censored at the end of TEAE period (last injection of study treatment + 70 days).

†Primary endpoint for the ODYSSEY OUTCOMES trial: CHD death, Non-fatal MI, Fatal and non-fatal ischemic stroke, Unstable angina requiring hospitalisation. "Unstable angina requiring hospitalisation" is limited to the UA events with definite evidence of progression of the ischemic condition (strict criteria).

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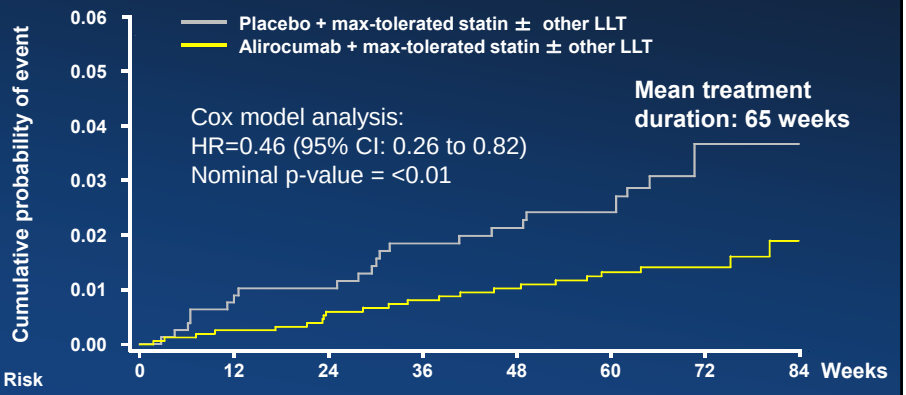
ODYSSEY

Post-hoc Adjudicated Cardiovascular TEAEs†

Safety Analysis (at least 52 weeks for all patients in ongoing study)

Kaplan-Meier Estimates for Time to First Adjudicated Major CV Event

Safety Analysis (at least 52 weeks for all patients continuing treatment, including 607 patients who completed W78 visit)



No. at Risk								
Placebo	788	776	731	703	682	667	321	127
Alirocumab	1550	1534	1446	1393	1352	1335	642	252

†Primary endpoint for the ODYSSEY OUTCOMES trial: CHD death, Non-fatal MI, Fatal and non-fatal ischemic stroke, Unstable angina requiring hospitalisation. LLT, lipid-lowering therapy

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Conclusions

- **Largest and longest double-blind study of a PCSK9 inhibitor**
  - **Current analysis provides ~1900 patient-years of double-blind patient exposure to alirocumab 150 mg Q2W**
- **In high CV-risk patients on max-tolerated statin ± other LLT:**
  - **Self-administered alirocumab produced significantly greater LDL-C ↓ vs. placebo at W24 (LS mean difference –61.9%)**
  - **79% of alirocumab pts achieved LDL-C goal of <1.81 mmol/L (70 mg/dL) at W24**
  - **Mean achieved LDL-C levels of 1.4 mmol/L (53.1 mg/dL) at W52 with alirocumab**
  - **TEAEs generally comparable in alirocumab and placebo arms**
- **A *post-hoc* safety analysis showed a lower rate of adjudicated major CV events**

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ODYSSEY


Thank you to all principal investigators and national coordinators!
Europe: 154 sites
Belgium: 4 sites; Bulgaria: 9 sites; Czech Rep.: 3 sites;
Denmark: 5 sites; Finland: 4 sites; France: 12 sites;
Germany: 15 sites; Hungary: 10 sites; Italy: 8 sites;
Netherlands: 12 sites; Norway: 5 sites; Poland: 9 sites;
Portugal: 4 sites; Romania: 4 sites; Russia: 7 sites; Spain: 8 sites;
Sweden: 5 sites; Ukraine: 11 sites; UK: 19 sites
Canada: 14 sites
USA: 115 sites
Israel: 4 sites
Central/South America: 22 sites
Argentina: 6 sites
Chile: 4 sites
Colombia: 5 sites
Mexico: 7 sites
South Africa: 11 sites
320 sites worldwide
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