Adverse Events in Patients with Low-Density Lipoprotein Cholesterol Levels <25 or <15 mg/dL (<0.65 or <0.39 mmol/L) on at Least 2 Consecutive Visits in 14 Randomized, Controlled, Clinical Trials of Alirocumab

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Industry Relationships and Institutional Affiliations

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Jennifer Robinson	Research grants to institution from Amarin, Amgen, AstraZeneca, Daiichi-Sankyo, Eisai, Glaxo-Smith Kline, Pfizer, Regeneron/Sanofi, and Takeda, and consultant/ advisory board fees from Amgen, Eli Lilly, Merck, Pfizer, and Regeneron/Sanofi.
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Umesh Chaudhari	Employee of and stockholder in Sanofi.
William Sasiela	Employee of and stockholder in Regeneron.
Christelle Lorenzato	Employee of and stockholder in Sanofi.
Kathryn Miller	Employee of and stockholder in Regeneron.
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Alirocumab Can Reduce LDL-C to Levels <25 mg/dL

- Alirocumab is a fully human monoclonal antibody to PCSK9
- When added to statins and other lipid-lowering therapies, alirocumab has shown robust reductions in low-density lipoprotein cholesterol (LDL-C) levels,[1–7] which can result in LDL-C levels <25 mg/dL in some patients
- In the ODYSSEY LONG TERM Phase 3 trial, alirocumab 150 mg every 2 weeks treatment reduced mean LDL-C from baseline by 61% versus placebo at Week 24[6]

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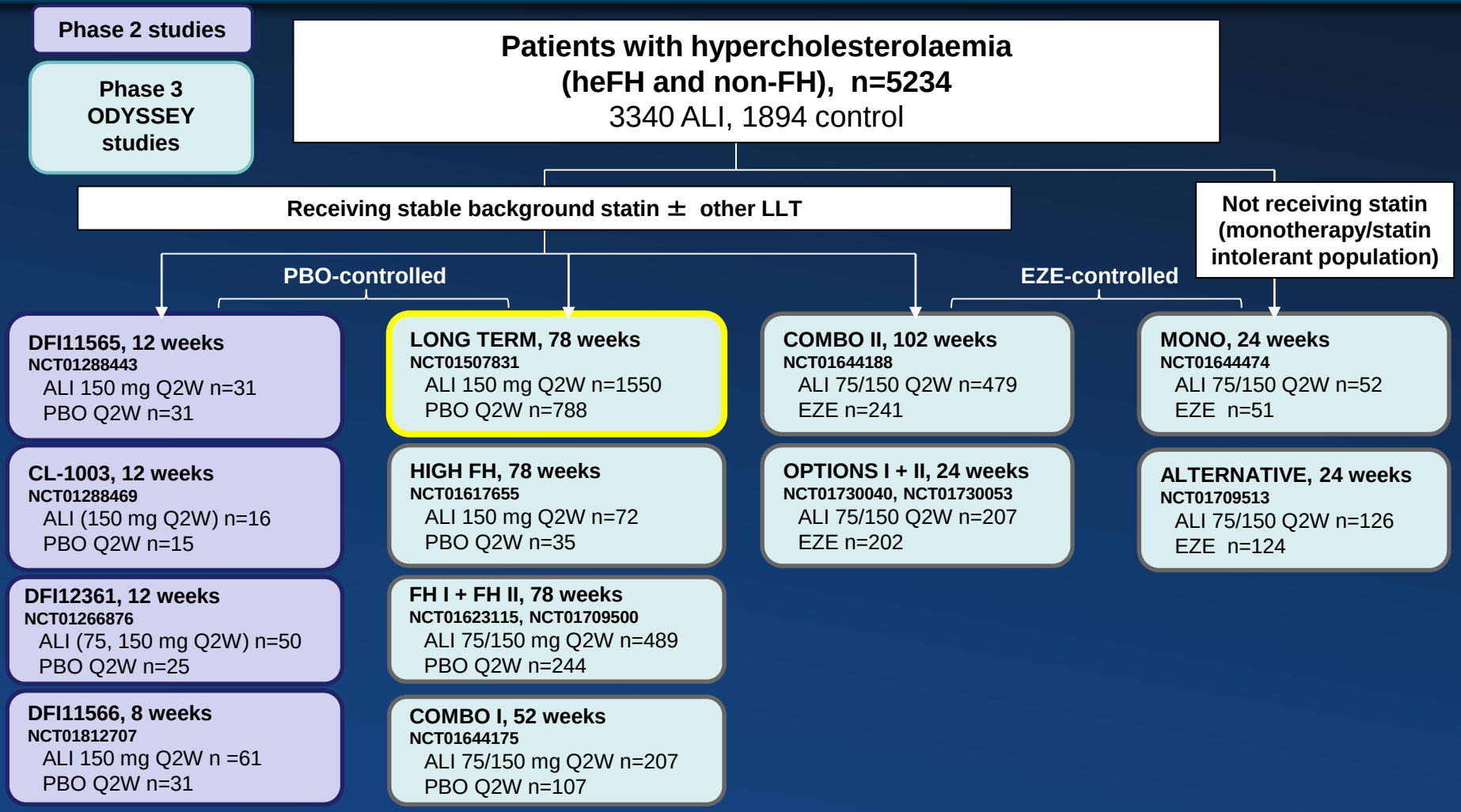
Aims

- Consequences of LDL-C levels <25 mg/dL are not well understood
- We investigated theoretical areas of concern for LDL-C levels <25 mg/dL
  - Peripheral nervous system, hemolytic anemia, gonadal hormones, fat-soluble vitamins
- Data pooled from 14 trials in the alirocumab clinical program to examine treatment-emergent adverse event (TEAE) rates in patients who achieved two consecutive calculated LDL-C values of <25 or <15 mg/dL on alirocumab
- In ODYSSEY LONG TERM:
  - Levels of gonadal hormones and adrenal function, were measured
  - Fat-soluble vitamins were also assessed, since these (particularly vitamin E) can rely on LDL for transport, and LDL-C levels <25 mg/dL could impact levels of fat-soluble vitamins

Studies Included in this Pooled Safety Analysis



ALI, alirocumab; EZE, ezetimibe; LLT, lipid-lowering therapy; PBO, placebo; Q2W, every 2 weeks. N values are for the safety populations. ALI 75/150 mg Q2W = alirocumab regimen adjusted from 75 to 150 mg Q2W at Week 12 if LDL-C was ≥70 mg/dL at Wk 8 (or, in OPTIONS + ALTERNATIVE, ≥70 mg/dL for patients with prior CHD or ≥100 mg/dL with CHD risk equivalents). Statin control arms from OPTIONS + ALTERNATIVE not included. Other LLT not allowed in COMBO II.

Monitoring of low LDL-C during the ODYSSEY studies

- Dedicated data monitoring committee (DMC) member and independent physician were provided access to unblinded LDL-C data to monitor patients who achieved two consecutive calculated LDL-C values <25 mg/dL (0.65 mmol/L)
  - At their discretion, an alert was sent to the site
  - Sham alerts also used to preserve the blind
  - The investigator would call the patient about occurrences of adverse events and decide whether the patient should be requested to rapidly have an unscheduled site visit, or assessment could be done at the next scheduled visit
  - At the site visit, the investigator assessed whether the patient needed additional work-up, should see a specialist and whether the study treatment should be temporarily or permanently discontinued

Patient Disposition (Safety Population)

- **In the pooled analysis:**
  - **796 (23.8%) alirocumab patients achieved LDL-C <25 mg/dL on ≥2 consecutive visits (approximately 70% came from LONG TERM on alirocumab 150 mg Q2W)**
  - **288 (8.6%) alirocumab patients achieved LDL-C <15 mg/dL on ≥2 consecutive visits**
- **Mean exposure to study treatment**
  - **58 weeks in both alirocumab and placebo groups in placebo-controlled trials; 80% of patients were exposed for at least 52 weeks.**
  - **42 weeks in the alirocumab group and 36 weeks in the ezetimibe group in ezetimibe-controlled trials; 47% of the alirocumab group and 40% of the ezetimibe group were exposed for at least 52 weeks.**

	Pooled control (n=1894)	Pooled alirocumab (n=3340)	Pooled alirocumab ≥2 LDL-C <25 mg/dL (n=796)	Pooled alirocumab ≥2 LDL-C <15 mg/dL (n=288)
Completed study period and/or continuing treatment, % (n)*	81.9% (1552)	82.3% (2750)	87.3% (695)	88.2% (254)

*Includes all studies whether complete or not.

Patient Baseline Characteristics (Safety Population)

% (n)	Pooled control (n=1894)	Pooled alirocumab (n=3340)	Pooled alirocumab ≥2 LDL-C <25 mg/dL (n=796)	Pooled alirocumab ≥2 LDL-C <15 mg/dL (n=288)
Age, yrs, mean ±SD	**59.7** ±10.8	**59.5** ±11.1	**62.1** ±9.7	**62.2** ±10.0
Males	**60.7** (1150)	**61.8** (2063)	**74.7** (595)	**75.3** (217)
Prior CHD	**60.9** (1154)	**61.7** (2061)	**74.1** (590)	**69.4** (200)
CHD risk equivalents	**29.7** (563)	**31.0** (1036)	**39.6** (315)	**44.8** (129)
Diabetes	**29.4** (557)	**29.7** (992)	**36.8** (293)	**41.7** (120)
HeFH	**25.1** (476)	**26.7** (893)	**9.5** (76)	**9.4** (27)
High-dose statin*	**42.1** (798)	**47.6** (1590)	**46.1** (367)	**43.8** (126)
Other LLT	**29.5** (559)	**29.0** (969)	**24.5** (195)	**22.9** (66)
Baseline LDL-C, mg/dL, mean ±SD	**126.3** ±48.5	**125.7** ±47.0	**100.2** ±28.5	**95.7** ±27.8

*High-dose statin = atorvastatin 40–80 mg, rosuvastatin 20–40 mg, or simvastatin 80 mg per day.
CHD, coronary heart disease; HeFH, heterozygous familial hypercholesterolaemia; LLT, lipid-lowering therapy.

Overview of Safety in Any Pooled Group

Primary system organ class, % (n) Preferred term, % (n)	Pooled control (n=1894)	Pooled alirocumab (n=3340)	Pooled alirocumab ≥2 LDL-C <25 mg/dL (n=796)	Pooled alirocumab ≥2 LDL-C <15 mg/dL (n=288)
Patients with any TEAE	**73.7** (1396)	**74.3** (2483)	**68.2** (543)	**67.0** (193)
Patients with any treatment emergent SAE	**13.3** (251)	**13.6** (453)	**13.1** (104)	**9.7** (28)
Patients with any TEAE leading to death	**1.0** (18)	**0.4** (15)	**0.4** (3)	**0** (0)
Patients with any TEAE leading to permanent treatment discontinuation	**6.6** (125)	**6.2** (207)	**3.5** (28)	**4.9** (14)

Select TEAEs ≥2% Incidence in Any Pooled Group (1)

Primary system organ class, % (n) Preferred term, % (n)	Pooled control (n=1894)	Pooled alirocumab (n=3340)	Pooled alirocumab ≥2 LDL-C <25 mg/dL (n=796)	Pooled alirocumab ≥2 LDL-C <15 mg/dL (n=288)
Infections and infestations	**36.3** (687)	**38.5** (1286)	**34.0** (271)	**35.4** (102)
Nasopharyngitis	**9.3** (176)	**9.8** (326)	**8.3** (66)	**10.1** (29)
Upper respiratory tract infection	**6.7** (126)	**6.1** (203)	**4.5** (36)	**5.2** (15)
Urinary tract infection	**4.1** (77)	**4.1** (137)	**4.6** (37)	**4.9** (14)
Influenza	**3.9** (73)	**5.2** (173)	**3.6** (29)	**4.2** (12)
Bronchitis	**3.3** (63)	**3.8** (126)	**4.4** (35)	**3.1** (9)
Sinusitis	**2.7** (51)	**2.6** (87)	**2.6** (21)	**3.1** (9)
Lower respiratory tract infection	**1.4** (26)	**1.6** (53)	**2.0** (16)	**2.1** (6)
Gastroenteritis	**2.3** (43)	**1.9** (62)	**0.6** (5)	**1.0** (3)

Select TEAEs ≥2% Incidence in Any Pooled Group (2)

Primary system organ class, % (n) Preferred term, % (n)	Pooled control (n=1894)	Pooled alirocumab (n=3340)	Pooled alirocumab ≥2 LDL-C <25 mg/dL (n=796)	Pooled alirocumab ≥2 LDL-C <15 mg/dL (n=288)
Musculoskeletal and connective tissue disorders	**25.2** (478)	**24.2** (808)	**21.1** (168)	**20.1** (58)
Back pain	**4.3** (82)	**4.0** (133)	**4.3** (34)	**4.2** (12)
Arthralgia	**5.0** (95)	**4.0** (134)	**3.1** (25)	**2.1** (6)
Myalgia	**4.8** (91)	**4.9** (162)	**3.1** (25)	**3.8** (11)
Muscle spasms	**2.4** (45)	**2.8** (94)	**2.5** (20)	**3.5** (10)
Pain in extremity	**3.4** (64)	**2.4** (81)	**2.1** (17)	**1.4** (4)
Osteoarthritis	**2.2** (42)	**2.1** (69)	**1.8** (14)	**1.0** (3)
Musculoskeletal pain	**1.4** (27)	**1.9** (65)	**1.0** (8)	**1.0** (3)

Select TEAEs ≥2% Incidence in Any Pooled Group (3)

Primary system organ class, % (n) Preferred term, % (n)	Pooled control (n=1894)	Pooled alirocumab (n=3340)	Pooled alirocumab ≥2 LDL-C <25 mg/dL (n=796)	Pooled alirocumab ≥2 LDL-C <15 mg/dL (n=288)
Gastrointestinal disorders	**16.8** (318)	**17.0** (567)	**12.7** (101)	**10.1** (29)
Diarrhea	**3.9** (74)	**4.3** (142)	**3.0** (24)	**1.4** (4)
Nausea	**2.5** (47)	**2.2** (74)	**0.9** (7)	**1.0** (3)
General disorders and administration-site conditions	**14.9** (282)	**15.1** (504)	**10.2** (81)	**6.9** (20)
Injection-site reaction	**3.9** (73)	**5.7** (191)	**3.0** (24)	**3.5** (10)
Fatigue	**2.5** (48)	**2.8** (93)	**2.6** (21)	**2.4** (7)
Non-cardiac chest pain	**1.8** (35)	**1.6** (54)	**1.8** (14)	**0.3** (1)

Select TEAEs ≥2% Incidence in Any Pooled Group (4)

Primary system organ class, % (n) Preferred term, % (n)	Pooled control (n=1894)	Pooled alirocumab (n=3340)	Pooled alirocumab ≥2 LDL-C <25 mg/dL (n=796)	Pooled alirocumab ≥2 LDL-C <15 mg/dL (n=288)
Nervous system disorders	**14.9** (283)	**14.9** (497)	**10.3** (82)	**9.0** (26)
Dizziness	**3.6** (69)	**3.0** (100)	**1.8** (14)	**1.4** (4)
Headache	**4.6** (87)	**4.6** (153)	**1.8** (14)	**1.4** (4)
Haemorrhagic stroke	**0.1** (1)	**0.1** (2)	**0**	**0**
Metabolism and nutrition disorders	**6.3** (120)	**6.9** (232)	**7.0** (56)	**7.3** (21)
Type 2 diabetes mellitus	**0.7** (14)	**1.1** (36)	**1.8** (14)	**1.4** (4)
Diabetes mellitus	**1.3** (24)	**1.2** (39)	**1.5** (12)	**2.4** (7)
Eye disorders	**3.7** (71)	**4.6** (152)	**5.3** (42)	**6.9** (20)
Cataract	**0.9** (17)	**0.8** (26)	**1.5** (12)	**2.4** (7)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	**2.5** (48)	**2.5** (85)	**2.8** (22)	**2.4** (7)

Summary of General Allergic TEAEs*

	Placebo-controlled pool		Ezetimibe-controlled pool	
% (n)	Placebo (N=1276)	Alirocumab (N=2476)	Ezetimibe (N=618)	Alirocumab (N=864)
Patients with any general allergic TEAE	**7.8** (99)	**8.6** (213)	**5.3** (33)	6.8 (59)
Patients with any general allergic treatment emergent SAE	**0.4** (5)	**0.4** (9)	**0.3** (2)	**0.1** (1)
Patients with any general allergic TEAE leading to death	**0**	**0**	**0**	**0**
Patients with any general allergic TEAE leading to permanent treatment discontinuation	**0.2** (2)	**0.6** (14)	**0.3** (2)	**0.8** (7)

Preferred term, % (n)	Pooled control (n=1894)	Pooled alirocumab (n=3340)	Pooled alirocumab ≥2 LDL-C <25 mg/dL (n=796)	Pooled alirocumab ≥2 LDL-C <15 mg/dL (n=288)
Pruritus	**0.4** (8)	**1.0** (35)	**1.3** (32)	**0.3** (2)

*Category of General allergic TEAEs based on preferred terms with Standardized MedDRA Queries "hypersensitivity" (broad + narrow) excluding the following preferred terms: "infusion site dermatitis", "infusion site hypersensitivity", "infusion site rash", "infusion site urticaria", "injection site dermatitis", "injection site hypersensitivity", "injection site rash", "injection site urticaria" and "injection site vasculitis".

Impact on Hormone Levels, as Measured in ODYSSEY LONG TERM

Cortisol, % (n/N)	Placebo (n=788)	Alirocumab (n=1550)
<LLN	**20.1** (154/767)	**19.6** (295/1506)
<LLN and ACTH >ULN	**0.6** (1/154)	**0.7** (2/295)
<LLN and ACTH >ULN and normal ACTH stimulation test	**100** (1/1)	**50.0** (1/2)
<LLN and ACTH >ULN and abnormal ACTH stimulation test	**0/1**	**50.0** (1/2)

- For confirmation, ACTH was measured in patients with abnormal cortisol levels

Gonadal hormones (men only), % (n/N)	Placebo (n=788)	Alirocumab (n=1550)
Total testosterone <LLN regardless of baseline status	**16.9** (74/439)	**20.8** (189/910)
Luteinizing hormone >ULN regardless of baseline status	**10.9** (62/571)	**10.6** (120/1127)
Follicle-stimulating hormone >ULN regardless of baseline status	**6.3** (36/571)	**5.9** (66/1128)

ACTH, adrenocorticotropic hormone; LLN, lower limit of normal; ULN, upper limit of normal.

Impact on Vitamin Levels, as Measured in ODYSSEY LONG TERM

Laboratory parameter, % (n/N)	Placebo (n=788)	Alirocumab (n=1550)
Fat-soluble vitamins		
Vitamin E <LLN regardless of baseline status	**0.1** (1/738)	**2.1** (31/1461)
Vitamin E/calculated LDL-C ratio: baseline, mean ±SD	**11.9** ±4.0	**12.0** ±4.1
Week 12 change from baseline	**–1.2** ±3.2	**15.9** ±20.9
Week 24 change from baseline	**0.3** ±4.2	**27.9** ±113.9
Week 52 change from baseline	**–0.2** ±4.2	**21.4** ±41.7
Vitamin A <LLN regardless of baseline status	**2.1** (16/762)	**2.3** (35/1494)
Vitamin D <LLN regardless of baseline status	**87.2** (662/759)	**85.7** (1279/1493)
Vitamin K <LLN regardless of baseline status	**5.5** (42/762)	**8.4** (125/1496)

LLN, lower limit of normal.

Correlation Between LDL-C Levels Measured by Beta Quantification and LDL-C Calculated by Friedewald Equation

- **Absolute and % difference between calculated and measured LDL-C according to measured LDL-C level**

	All (N=5222)	
	Absolute difference	**% difference**
Measured LDL-C <15 mg/dL (n=210)		
Median	**–3.0**	**–25.0**
Interquartile range	**–6.0 : 1.0**	**–56.5 : 9.1**
Measured LDL-C ≥15 mg/dL to <25 mg/dL (n=819)		
Median	**–3.5**	**–17.0**
Interquartile range	**–7.0 : 0.4**	**–35.5 : 1.6**

Summary

- In one of the largest evaluations of patients with pharmacologically induced LDL-C <25 mg/dL (N=796) or <15 mg/dL (N=288), who were treated with alirocumab for 8–52 weeks, no specific adverse events were identified with assessments performed 2–16 weeks apart:
  - There were no meaningful imbalances in TEAEs between groups, including musculoskeletal and neurologic conditions
  - In the laboratory analyses performed in LONG TERM, no clinically meaningful effect was observed in changes to levels of cortisol, gonadal hormones, or fat-soluble vitamins A,D, and K or vitamin E/LDL-C ratio
- Alirocumab is being evaluated in the ongoing ODYSSEY OUTCOMES trial (NCT01663402), in which approximately 18,000 patients will be treated with alirocumab or placebo for at least 2 years

Q&A

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