ACC.15
TCT@ACC-i2 | innovation in intervention

A1350
JACC March 17, 2015
Volume 65, Issue 10S

Prevention

ADVERSE EVENTS IN PATIENTS WITH LOW-DENSITY LIPOPROTEIN CHOLESTEROL LEVELS <25 OR <15 MG/DL ON AT LEAST TWO CONSECUTIVE VISITS IN FOURTEEN RANDOMIZED, CONTROLLED, CLINICAL TRIALS OF ALIROCUMAB

Moderated Poster Contributions
Prevention Moderated Poster Theater, Poster Hall B1
Saturday, March 14, 2015, 4:00 p.m.-4:10 p.m.

Session Title: Therapeutic Horizons: Novel Therapies in Lipid Management
Abstract Category: 21. Prevention: Clinical
Presentation Number: 1164M-05

Authors: *Jennifer Robinson, Michel Farnier, Umesh Chaudhari, Bill Sasiela, Christelle Lorenzato, Kathryn Miller, John J P Kastelein, Sanofi, Paris, France, Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA*

Background: Alirocumab added to statin therapy has shown robust reductions in low-density lipoprotein cholesterol (LDL-C) and can also reduce it to very low levels. Consequences of very low LDL-C levels are not well understood. Therefore, AE rates were examined in patients (pts) who achieved 2 consecutive calculated LDL-C <25 or <15 mg/dL on alirocumab (ALI).

Methods: 14 trials were analyzed; 4 Phase 2 (8-12 weeks and completed) and 10 from the ODYSSEY program (6-24 months with double-blind safety assessment still ongoing in some). The pooled group comprises 5234 pts (3340 ALI and 1894 control). TEAEs were analyzed. LONG TERM (LTT), in which 2338 pts received ALI 150 mg or control every 2 weeks for up to 78 weeks, included laboratory tests for parameters that might be related to very low LDL-C.

Results: In the pooled ALI group, 796 (23.8%) pts, including 562 (36.3%) pts from LTT achieved LDL-C <25 mg/dL on ≥2 consecutive visits, and 288 (8.6%) from the pooled ALI group, including 223 (14.3%) from LTT, achieved LDL-C <15 mg/dL. TEAEs were generally similar across all groups. There were no cases of hemolytic anemia. In LTT, no clinically meaningful effect was observed in changes to cortisol levels or fat soluble vitamins.

Conclusion: In one of the largest evaluations of patients with pharmacologically-induced LDL-C <25 or <15 mg/dL, no safety signals were observed. Evaluations of the ongoing cardiovascular outcomes trial will extend these findings.

TABLE Select TEAEs ≥2% incidence in any group by primary system organ class and preferred term in the pooled group[†] and ODYSSEY LONG TERM

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)[†]	LONG TERM alirocumab 2 LDL-C <25 mg/dL (N=562)
Infections and infestations	36.3 (687)	38.5 (1286)	34.0 (271)	35.4 (102)	39.0 (219)
Nasopharyngitis	9.3 (176)	9.8 (326)	8.3 (66)	10.1 (29)	10.0 (56)
Upper respiratory tract infection	6.7 (126)	6.1 (203)	4.5 (36)	5.2 (15)	5.7 (32)
Urinary tract infection	4.1 (77)	4.1 (137)	4.6 (37)	4.9 (14)	5.5 (31)
Influenza	3.9 (73)	5.2 (173)	3.6 (29)	4.2 (12)	4.1 (23)
Bronchitis	3.3 (63)	3.8 (126)	4.4 (35)	3.1 (9)	5.2 (29)
Sinusitis	2.7 (51)	2.6 (87)	2.6 (21)	3.1 (9)	3.0 (17)
Lower respiratory tract infection	1.4 (26)	1.6 (53)	2.0 (16)	2.1 (6)	2.8 (16)
Gastroenteritis	2.3 (43)	1.9 (62)	0.6 (5)	1.0 (3)	0.7 (4)
Cellulitis	0.6 (11)	0.9 (30)	1.1 (9)	0 (0)	1.6 (9)
Rhinitis	1.2 (22)	0.9 (29)	0.9 (7)	0.7 (2)	1.2 (7)
Musculoskeletal and connective tissue disorders	25.2 (478)	24.2 (808)	21.1 (168)	20.1 (58)	22.6 (127)
Back pain	4.3 (82)	4.0 (133)	4.3 (34)	4.2 (12)	5.0 (28)
Arthralgia	5.0 (95)	4.0 (134)	3.1 (25)	2.1 (6)	3.2 (18)
Myalgia	4.8 (91)	4.9 (162)	3.1 (25)	3.8 (11)	3.0 (17)
Muscle spasms	2.4 (45)	2.8 (94)	2.5 (20)	3.5 (10)	2.8 (16)
Pain in extremity	3.4 (64)	2.4 (81)	2.1 (17)	1.4 (4)	2.1 (12)
Osteoarthritis	2.2 (42)	2.1 (69)	1.8 (14)	1.0 (3)	2.1 (12)
Musculoskeletal pain	1.4 (27)	1.9 (65)	1.0 (8)	1.0 (3)	1.4 (8)
Gastrointestinal disorders	16.8 (318)	17.0 (567)	12.7 (101)	10.1 (29)	13.7 (77)
Diarrhea	3.9 (74)	4.3 (142)	3.0 (24)	1.4 (4)	3.9 (22)
Nausea	2.5 (47)	2.2 (74)	0.9 (7)	1.0 (3)	0.9 (5)
Constipation	1.4 (27)	1.7 (58)	1.1 (9)	1.4 (4)	1.6 (9)
General disorders and administration site conditions	14.9 (282)	15.1 (504)	10.2 (81)	6.9 (20)	11.0 (62)
Injection site reaction	3.9 (73)	5.7 (191)	3.0 (24)	3.5 (10)	3.6 (20)
Fatigue	2.5 (48)	2.8 (93)	2.6 (21)	2.4 (7)	3.0 (17)
Non-cardiac chest pain	1.8 (35)	1.6 (54)	1.8 (14)	0.3 (1)	2.0 (11)
Nervous system disorders	14.9 (283)	14.9 (497)	10.3 (82)	9.0 (26)	11.2 (63)
Dizziness	3.6 (69)	3.0 (100)	1.8 (14)	1.4 (4)	1.4 (8)
Headache	4.6 (87)	4.6 (153)	1.8 (14)	1.4 (4)	1.8 (10)
Metabolism and nutrition disorders	6.3 (120)	6.9 (232)	7.0 (56)	7.3 (21)	8.0 (45)
Type 2 diabetes mellitus	0.7 (14)	1.1 (36)	1.8 (14)	1.4 (4)	2.5 (14)
Diabetes mellitus	1.3 (24)	1.2 (39)	1.5 (12)	2.4 (7)	1.4 (8)
Eye disorders	3.7 (71)	4.6 (152)	5.3 (42)	6.9 (20)	6.4 (36)
Cataract	0.9 (17)	0.8 (26)	1.5 (12)	2.4 (7)	1.8 (10)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	2.5 (48)	2.5 (85)	2.8 (22)	2.4 (7)	3.0 (17)

Additional parameters possibly related to low LDL-C, as measured in LTT

Laboratory parameter, % (n/N1)	Placebo (N=788)	Alirocumab (N=1550)
Cortisol		
<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)
Fat soluble vitamins		
Vitamin E <LLN regardless of baseline status	0.1 (1/738)	2.1 (31/1461)
Vitamin A <LLN regardless of baseline status	0.3 (2/762)	0.1 (2/1494)
Vitamin D <LLN regardless of baseline status	86.8 (659/759)	85.1 (1270/1493)
Vitamin K <LLN regardless of baseline status	5.5 (42/762)	8.4 (125/1496)

ACTH, adrenocorticotropic hormone; AE, adverse event; LLN, lower limit of normal; TEAE, treatment-emergent adverse event; ULN, upper limit of normal
[†]Phase 3 (ODYSSEY LONG TERM, FH I, FH II, HIGH FH, COMBO I, COMBO II, MONO, OPTIONS I, OPTIONS II, ALTERNATIVE; NCT01507831, 01623115, 01709500, 01617655, 01644175, 01644188, 01644474, 01730040, 01730053, 01709513) ; Phase 2 (DFI11565, DFI11566, CL-1003, DFI12361; NCT01288443, 01288469, 01266876, 01812707)
[‡]Abnormal ACTH stimulation test is defined as cortisol value <18 μg/dL (<497 nmol/L) at both 30 and 60 minutes after ACTH administration