SUPPLEMENTAL MATERIAL

A Pooled Safety Analysis of Evolocumab in Over 6000 Patients from Double-blind and Open-label Extension Studies

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Table 1. Reasons for Non-enrollment in Open-label Extension Studies

Reason	Any Control (N=588)	Any Evolocumab (N=973)	Total (N=1561)
	n (%)		
Ended study drug early	**110 (18.7)**	**192 (19.7)**	**302 (19.3)**
Administrative decision	1 (0.2)	7 (0.7)	8 (0.5)
Adverse event	35 (6.0)	57 (5.9)	92 (5.9)
Death	0	2 (0.2)	2 (0.1)
Full consent withdrawn	10 (1.7)	12 (1.2)	22 (1.4)
Lost to follow-up	8 (1.4)	17 (1.7)	25 (1.6)
Other	14 (2.4)	29 (3.0)	43 (2.8)
Physician decision	4 (0.7)	3 (0.3)	7 (0.4)
Pregnancy	0	1 (0.1)	1 (0.1)
Subject request	38 (6.5)	64 (6.6)	102 (6.5)
Completed study drug	**478 (81.3)**	**781 (80.3)**	**1259 (80.6)**
Ended study early	**2 (0.3)**	**7 (0.7)**	**9 (0.6)**
Death	0	1 (0.1)	1 (0.1)
Full consent withdrawn	2 (0.3)	0	2 (0.1)
Lost to follow-up	0	6 (0.6)	6 (0.4)
Did not end study early, and reported intention to roll-over but did not roll over	**121 (20.6)**	**227 (23.3)**	**348 (22.3)**
Did not end study early, and reported intention to not roll over	**351 (59.7)**	**531 (54.6)**	**882 (56.5)**
Due to level of commitment	95 (16.2)	169 (17.4)	264 (16.9)
Due to parent experience	31 (5.3)	30 (3.1)	61 (3.9)
Due to personal reasons	225 (38.3)	332 (34.1)	557 (35.7)
Did not end study early, and unknown intention to roll over	**4 (0.7)**	**16 (1.6)**	**20 (1.3)**

Table 2. Baseline Characteristics According to Lowest LDL-C Level Achieved

Characteristic		Lowest LDL-C Achieved and Treatment Group				
		<25 mg/dL	**≥25 mg/dL and <40 mg/dL**	**All Patients With <40 mg/dL**	**≥40 mg/dL**	
	Initial Parent Trials*	**Any Evolocumab N = 1609**	**Any Evolocumab N = 956**	**Any Evolocumab N = 2565**	**Any Evolocumab N = 1339**	**Any Control† N = 2038**
	OLE‡	**Evolocumab + SoC N = 773**	**Evolocumab + SoC N = 759**	**Evolocumab + SoC N = 1532**	**Evolocumab + SoC N = 1426**	**SoC N = 1459**
Age, yr, mean (SD)	Initial parent trials	58.5 (10.3)	57.8 (11.6)	58.2 (10.8)	56.7 (12.1)	57.3 (11.1)
	OLE	58.9 (10.4)	58.5 (10.1)	58.7 (10.3)	57.0 (11.7)	58.2 (10.9)
Male sex, n (%)	Initial parent trials	953 (59.2)	455 (47.6)	1408 (54.9)	549 (41.0)	972 (47.7)
	OLE	500 (64.7)	394 (51.9)	894 (58.4)	583 (40.9)	749 (51.3)
Race or ethnicity, n (%)						
White	Initial parent trials	1344 (83.5)	779 (81.5)	2123 (82.8)	1113 (83.1)	1716 (84.2)
	OLE	646 (83.6)	644 (84.8)	1290 (84.2)	1252 (87.8)	1238 (84.9)
Asian	Initial parent trials	167 (10.4)	97 (10.1)	264 (10.3)	90 (6.7)	184 (9.0)
	OLE	90 (11.6)	76 (10.0)	166 (10.8)	65 (4.6)	122 (8.4)

Black or African American	Initial parent trials	66 (4.1)	65 (6.8)	131 (5.1)	111 (8.3)	105 (5.2)
	OLE	24 (3.1)	25 (3.3)	49 (3.2)	85 (6.0)	72 (4.9)
Other race	Initial parent trials	32 (2.0)	15 (1.6)	47 (1.8)	25 (1.9)	33 (1.6)
	OLE	13 (1.7)	14 (1.8)	27 (1.8)	24 (1.7)	27 (1.9)
Hispanic	Initial parent trials	75 (4.7)	52 (5.4)	127 (5.0)	71 (5.3)	118 (5.8)
	OLE	36 (4.7)	32 (4.2)	68 (4.4)	77 (5.4)	66 (4.5)
Lipids, mean (SD)						
LDL-C (mg/dL)	Initial parent trials	103.4 (27.0)	122.5 (29.1)	110.5 (29.3)	159.4 (50.1)	126.9 (42.5)
	OLE	108.1 (29.0)	118.2 (30.5)	113.1 (30.1)	143.6 (51.9)	129.1 (45.6)
PCSK9 (ng/mL)	Initial parent trials	415.0 (150.3)	379.1 (139.4)	401.7 (147.3)	356.5 (134.6)	378.4 (141.6)
	OLE	397.8 (137.1)	399.2 (139.0)	398.5 (138.0)	379.3 (145.8)	381.8 (143.6)
Cardiovascular risk factors, n (%)						
NCEP risk category high	Initial parent trials	631 (39.2)	320 (33.5)	951 (37.1)	425 (31.7)	623 (30.6)
	OLE	328 (42.4)	292 (38.5)	620 (40.5)	410 (28.8)	526 (36.1)

Coronary artery disease	Initial parent trials	365 (22.7)	182 (19.0)	547 (21.3)	237 (17.7)	343 (16.8)
	OLE	193 (25.0)	164 (21.6)	357 (23.3)	231 (16.2)	297 (20.4)
Cerebrovascular or peripheral arterial disease	Initial parent trials	149 (9.3)	82 (8.6)	231 (9.0)	122 (9.1)	150 (7.4)
	OLE	86 (11.1)	74 (9.7)	160 (10.4)	103 (7.2)	138 (9.5)

*Median study exposure: 3 months

†Control placebo and/or ezetimibe

‡Year 1 standard of care-controlled period of open-label extension studies; median study exposure: 11 months

OLE, open-label extension; SoC, standard of care

Table 3. Adverse Events According to Lowest LDL-C Level Achieved

AE		Lowest LDL-C Achieved and Treatment Group				
		<25 mg/dL	≥25 mg/dL and <40 mg/dL	All Patients With <40 mg/dL	≥40 mg/dL	
	Initial Parent Trials*	Any Evolocumab N = 1609	Any Evolocumab N = 956	Any Evolocumab N = 2565	Any Evolocumab N = 1339	Any Control† N = 2038
	OLE‡	Evolocumab + SoC N = 773	Evolocumab + SoC N = 759	Evolocumab + SoC N = 1532	Evolocumab + SoC N = 1426	SoC N = 1459
Any AE, %	Initial parent trials	51.4	50.4	51.0	52.1	50.0
	OLE	70.2	69.2	69.7	71.1	66.6
AEs leading to discontinuation of IP	Initial parent trials	1.2	1.0	1.2	3.1	0
	OLE	1.0	1.8	1.4	3.7	N/A§
SAEs	Initial parent trials	2.9	2.4	2.7	2.6	2.0
	OLE	7.8	7.1	7.4	8.2	7.8
Muscle-related AEs, %	Initial parent trials	4.5	3.9	4.2	6.6	4.8
	OLE	5.2	7.1	6.1	6.9	6.2
Neurocognitive AEs, %	Initial parent trials	0.06	0	0.04	0.3	0.3
	OLE	0.5	1.2	0.8	1.0	0.3

*Median study exposure: 3 months

†Control placebo and/or ezetimibe

‡Year 1 standard of care-controlled period of open-label extension studies; median study exposure: 11 months

§Not applicable; standard of care group did not receive investigational drug

AE, adverse event; N/A, not applicable; OLE, open-label extension; SAE, serious AE; SoC, standard of care; IP, investigational product

Table 4. Laboratory Parameters According to Lowest LDL-C Level Achieved

Laboratory Parameter		Lowest LDL-C Achieved and Treatment Group				
		<25 mg/dL	≥25 mg/dL and <40 mg/dL	All Patients With <40 mg/dL	≥40 mg/dL	
	Initial Parent Trials*	Any Evolocumab N = 1609	Any Evolocumab N = 956	Any Evolocumab N = 2565	Any Evolocumab N = 1339	Any Control† N = 2038
	OLE‡	Evolocumab + SoC N = 773	Evolocumab + SoC N = 759	Evolocumab + SoC N = 1532	Evolocumab + SoC N = 1426	SoC N = 1459
CK >5 x ULN, %	Initial parent trials	0.6	0.4	0.5	1.0	0.7
	OLE	0.4	0.9	0.7	0.5	1.1
CK >10 x ULN, %	Initial parent trials	0.2	0.1	0.2	0.3	0.2
	OLE	0.1	0.4	0.3	0.2	0.5
ALT or AST >3 x ULN, %	Initial parent trials	0.4	0.3	0.4	0.5	0.9
	OLE	0.9	0.8	0.8	1.3	1.2
Total bilirubin >2 x ULN, %	Initial parent trials	0.3	0.1	0.2	0	0.1
	OLE	0.4	0.3	0.3	0.1	0.1

*Median study exposure: 3 months

†Control placebo and/or ezetimibe

‡Year 1 standard of care-controlled period of open-label extension studies; median study exposure: 11 months

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; OLE, open-label extension; SoC, standard of care; ULN, upper limit of normal