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ADDENDUM TO THE FDA ADVISORY COMMITTEE BRIEFING DOCUMENT

PRALUENT™ (alirocumab)

BLA 125559

ENDOCRINOLOGIC AND METABOLIC DRUGS ADVISORY COMMITTEE

MEETING DATE: JUNE 9, 2015

AVAILABLE FOR PUBLIC RELEASE

Addendum: Safety data

This document is an addendum for the following sections of the briefing document:

- Section 9.9.4 – Adverse Events of Special Interest: Neurocognitive Events
- Section 9.11 – Cardiovascular Events Confirmed by Adjudication.

The original Advisory Committee briefing document includes data for neurocognitive events and CV events as of the data cut-off date of 31 December 2014. This was the cut-off date that we had used for the FDA 4-month safety update report (SUR). We chose this SUR data set so that the data provided in the briefing document would be consistent with the final LONG TERM study data published earlier this year in the *New England Journal of Medicine* by Robinson et al. However, the FDA has since informed us that they will restrict their presentation at the Advisory Committee meeting to the safety data initially submitted in the BLA application. To avoid confusion, we have decided to do the same. This addendum provides the neurocognitive event and CV event data as of 31 August 2014 as initially submitted in the BLA.

For reference, data as of 31 December 2014 provided in the original advisory committee briefing document are provided in this addendum along with the data as of 31 August 2014. As you will see, the differences are small and do not change any of the conclusions in the original briefing document.

Addendum: Indication

We are also providing a revision to the proposed indication based on the FDA's comment in their briefing book that alirocumab monotherapy could be used in patients who cannot tolerate statins (see Section 2.1 – Indication).

2.1 Proposed Indication

A revision to the proposed indication in the original briefing document is provided below. The change made is indicated by blue, strikethrough text.

> Therapy with lipid-altering agents should be only one component of multiple risk factor intervention in individuals at increased risk for atherosclerotic vascular disease due to hypercholesterolemia. Drug therapy is indicated as an adjunct to diet when the response to diet and other non-pharmacologic measures has been inadequate.
>
> Alirocumab (PRALUENT) is indicated for long-term treatment of adult patients with primary hypercholesterolemia (non-familial and heterozygous familial) or mixed dyslipidemia, including patients with type 2 diabetes mellitus, to reduce low-density lipoprotein cholesterol (LDL-C), total cholesterol (Total-C), non-high-density lipoprotein cholesterol (non-HDL-C), apolipoprotein B (Apo B), triglycerides (TGs), and lipoprotein (a) [Lp(a)], and to increase high-density lipoprotein cholesterol (HDL-C) and apolipoprotein A-1 (Apo A-1).
>
> Alirocumab is indicated in combination with a statin (HMG-CoA reductase inhibitor), with or without other lipid-modifying therapy (LMT).
>
> Alirocumab is indicated as monotherapy, or as add-on to other non-statin LMT, ~~**including**~~ in patients who cannot tolerate statins.
>
> **Limitations of Use**
>
> The effect of alirocumab on cardiovascular morbidity and mortality has not been determined.

9.9 Adverse Events of Special Interest (AESI)

9.9.4 Neurocognitive Events

Table 29 in the original advisory committee briefing document presented a summary of the neurocognitive events in the placebo- and ezetimibe-controlled pools as of 31 August 2014 and the final data from the LONG TERM study as of 31 December 2014.

This addendum provides the neurocognitive events in the LONG TERM study as of 31 August 2014 in addition to the pooled safety data provided in the original briefing book (see Table 29A).

Table 29 – SUR data (original in the briefing document):

Number (%) of Patients with Neurocognitive Disorder TEAE(s) in Placebo-controlled and Ezetimibe-controlled Pools (as of 31 August 2014 provided in the initial BLA) and in the LONG TERM Study (final data as of 31 December 2014)

	Placebo-controlled pool[a] (on top of statins)		Ezetimibe-controlled pool (+/- statin)		LONG TERM[a] (on top of statins)	
	Placebo (N=1276)	Alirocumab (N=2476)	Ezetimibe (N=618)	Alirocumab (N=864)	Placebo N=788	Alirocumab N=1550
Sponsor's CMQ						
TEAEs	9 (0.7%)	21 (0.8%)	6 (1.0%)	8 (0.9%)	4 (0.5%)[b]	18 (1.2%)[b]
Rate per 100 PY	0.6	0.7	1.3	1.1	0.3	0.8
HR (95% CI)	1.18 (0.54 to 2.58)		0.94 (0.32 to 2.74)		2.28 (0.77 to 6.75)	
SAEs, n (%)	2 (0.2%)	3 (0.1%)	1 (0.2%)	1 (0.1%)	1 (0.1%)	3 (0.2%)
Leading to discontinuation, n (%)	2 (0.2%)	0	2 (0.3%)	0	1 (0.1%)	0
FDA's CMQ						
TEAEs	11 (0.9%)	21 (0.8%)	6 (1.0%)	7 (0.8%)	6 (0.8%)	16 (1.0%)
Rate per 100 PY	0.8	0.7	1.3	1.0	0.5	0.7
HR (95% CI)	0.96 (0.46, 2.00)		0.80 (0.26, 2.40)		1.35 (0.53 to 3.46)	
SAEs, n (%)	4 (0.3%)	3 (0.1%)	1 (0.1%)	1 (0.1%)	3 (0.4%)	3 (0.2%)
Leading to discontinuation, n (%)	2 (0.2%)	0	2 (0.3%)	0	1 (0.1%)	0

[a] LONG TERM study is the largest of four 78-week studies included in the placebo-controlled pool.
[b] Robinson 2015.
PY = Patient Years at Risk

Table 29A – BLA data (Addendum):

Number (%) of Patients with Neurocognitive Disorder TEAE(s) in Placebo-controlled and Ezetimibe-controlled Pools (data as of 31 August 2014 provided in the initial BLA)

	Placebo-controlled pool[a] (on top of statins)		Ezetimibe-controlled pool (+/- statin)		LONG TERM[a] (on top of statins)	
	Placebo (N=1276)	Alirocumab (N=2476)	Ezetimibe (N=618)	Alirocumab (N=864)	Placebo N=788	Alirocumab N=1550
Sponsor's CMQ						
TEAEs	9 (0.7%)	21 (0.8%)	6 (1.0%)	8 (0.9%)	4 (0.5%)	18 (1.2%)
Rate per 100 PY	0.6	0.7	1.3	1.1	0.4	0.9
HR (95% CI)	1.18 (0.54 to 2.58)		0.94 (0.32 to 2.74)		2.29 (0.77 to 6.76)	
SAEs, n (%)	2 (0.2%)	3 (0.1%)	1 (0.2%)	1 (0.1%)	1 (0.1%)	3 (0.2%)
Leading to discontinuation, n (%)	2 (0.2%)	0	2 (0.3%)	0	1 (0.1%)	0
FDA's CMQ						
TEAEs	11 (0.9%)	21 (0.8%)	6 (1.0%)	7 (0.8%)	6 (0.8%)	17 (1.1%)[b]
Rate per 100 PY	0.8	0.7	1.3	1.0	0.6	0.9
HR (95% CI)	0.96 (0.46, 2.00)		0.80 (0.26, 2.40)		1.44 (0.57 to 3.64)	
SAEs, n (%)	4 (0.3%)	3 (0.1%)	1 (0.1%)	1 (0.1%)	3 (0.4%)	3 (0.2%)
Leading to discontinuation, n (%)	2 (0.2%)	0	2 (0.3%)	0	1 (0.1%)	0

[a] LONG TERM study is the largest of four 78-week studies included in the placebo-controlled pool.
[b] Note that one neurocognitive event that was reported as a TEAE in the interim data as of 31 August 2014 in the LONG TERM study was later identified as past medical history (see Table 29 in the original briefing book provided above).
PY = Patient Years at Risk

9.11 Cardiovascular Events Confirmed by Adjudication

Table 41 – SUR data (original in the briefing document):

Treatment-Emergent MACE Confirmed by Adjudication in Global Pool of Phase 3 Studies (data as of 31 December 2014 provided in the 4-month SUR)

Category of Adjudication	Control (N=1792)	Alirocumab (N=3182)
Any patients with treatment emergent MACE event		
n (%)	36 (2.0%)	58 (1.8%)
95% mid-p CI	1.4% to 2.7%	1.4% to 2.3%
Events per 100 patient-years	1.7	1.5
95% CI	1.2 to 2.4	1.1 to 1.9
Hazard ratio versus control (95% CI)	0.82 (0.54 to 1.25)	
Endpoint components		
CHD death (including undetermined cause)	10 (0.6%)	10 (0.3%)
Non-fatal MI	25 (1.4%)	33 (1.0%)
Fatal and non-fatal ischemic stroke[a]	3 (0.2%)	13 (0.4%)
Unstable angina requiring hospitalization	1 (<0.1%)	2 (<0.1%)

[a] Includes strokes not otherwise specified

Based on analyses of all data in the 4-month safety update, which include final data from the completed studies, LONG TERM and FH1.

Table 41A – BLA data (Addendum):

Treatment-Emergent MACE Confirmed by Adjudication in Global Pool of Phase 3 Studies (data as of 31 August 2014 provided in the initial BLA)

Category of Adjudication	Control (N=1792)	Alirocumab (N=3182)
Any patients with treatment emergent MACE event		
n (%)	33 (1.8%)	52 (1.6%)
95% mid-p CI	1.3 % to 2.5%	1.2% to 2.1%
Events per 100 patient-years	1.8	1.5
95% CI	1.2 to 2.5	1.1 to 1.9
Hazard ratio versus control (95% CI)	0.81 (0.52 to 1.25)	
Endpoint components		
CHD death (including undetermined cause)	9 (0.5%)	8 (0.3%)
Non-fatal MI	23 (1.3%)	30 (0.9%)
Fatal and non-fatal ischemic stroke[a]	3 (0.2%)	12 (0.4%)
Unstable angina requiring hospitalization	1 (<0.1%)	2 (<0.1%)

[a] Includes strokes not otherwise specified

Figure 33 – SUR data (original in the briefing document):

Forest Plot of Hazard Ratio for Treatment-Emergent MACE versus Control by Study in Phase 3 Placebo-controlled and Ezetimibe-controlled Studies (data as of 31 December 2014 provided in the 4-month SUR)

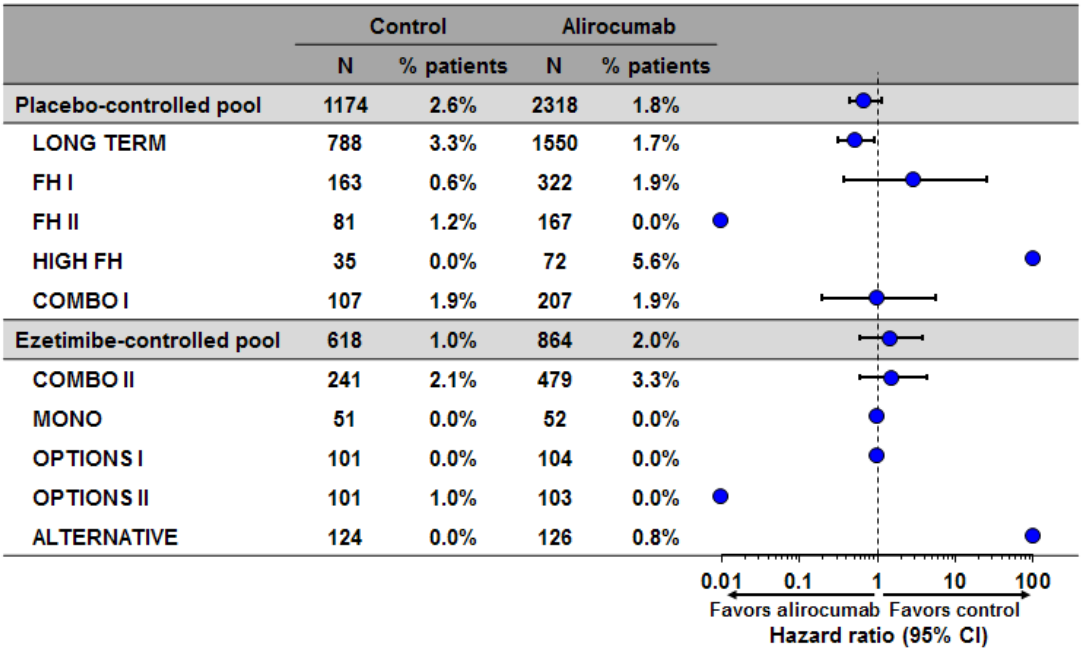

Figure 33A – BLA data (Addendum):

Forest Plot of Hazard Ratio for Treatment-Emergent MACE versus Control by Study in Phase 3 Placebo-controlled and Ezetimibe-controlled Studies (data as of 31 August 2014 provided in the initial BLA)

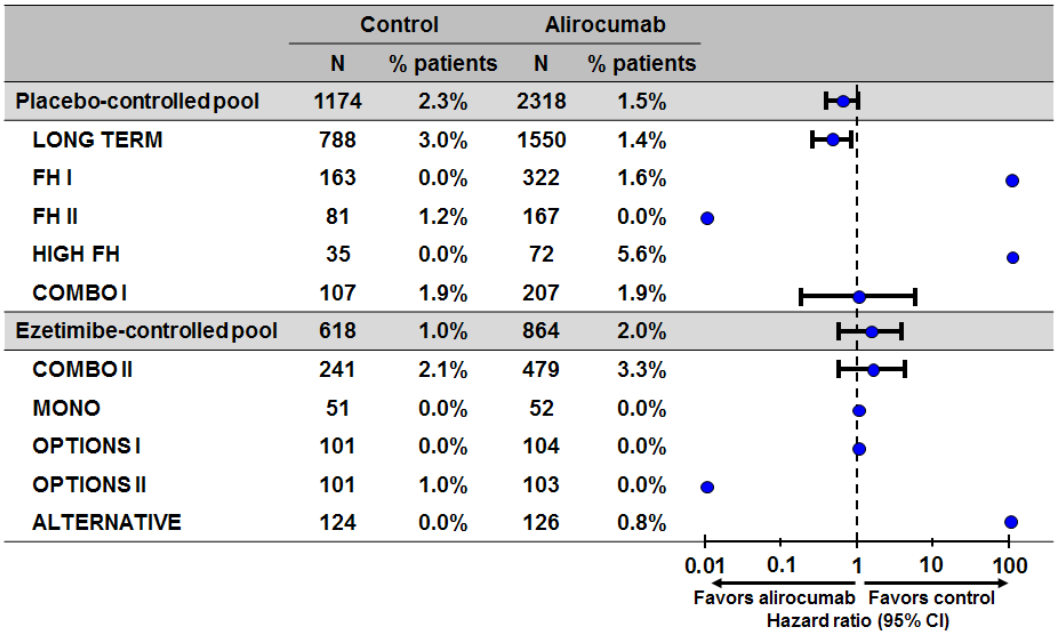

Table 42 – SUR data (original in the briefing document):

Treatment Emergent CV Events Confirmed by Adjudication in Global Pool of Phase 3 Studies (data as of 31 December 2014 provided in the 4-month SUR)

Category of Adjudication	Control (N=1792)	Alirocumab (N=3182)
Any patients with treatment emergent CV event confirmed by adjudication		
n (%)	59 (3.3%)	121 (3.8%)
95% mid-p CI	2.5% to 4.2%	3.2% to 4.5%
Events per 100 patient-years	2.8	3.1
95% CI	2.2 to 3.7	2.6 to 3.7
Hazard ratio versus control (95% CI)	1.07 (0.78 to 1.46)	
Endpoint components		
CHD death (including undetermined cause)	10 (0.6%)	10 (0.3%)
Non-fatal MI	25 (1.4%)	33 (1.0%)
Fatal and non-fatal ischemic stroke[a]	3 (0.2%)	13 (0.4%)
Unstable angina requiring hospitalization[b]	1 (<0.1%)	2 (<0.1%)
Congestive heart failure requiring hospitalization	6 (0.3%)	12 (0.4%)
Ischemia driven coronary revascularization procedure	35 (2.0%)	80 (2.5%)

[a] Includes strokes not otherwise specified

[b] With evidence of progressive ischemic condition

Based on analyses of all data in the 4-month safety update, which include final data from the completed studies, LONG TERM and FH1.

Table 42A – BLA data (Addendum):

Treatment Emergent CV Events Confirmed by Adjudication in Global Pool of Phase 3 Studies (data as of 31 August 2014 provided in the initial BLA)

Category of Adjudication	Control (N=1792)	Alirocumab (N=3182)
Any patients with treatment emergent CV event confirmed by adjudication		
n (%)	53 (3.0%)	110 (3.5%)
95% mid-p CI	2.2% to 3.8%	2.9% to 4.1%
Events per 100 patient-years	2.8	3.2
95% CI	2.1 to 3.7	2.6 to 3.8
Hazard ratio versus control (95% CI)	1.08 (0.78 to 1.50)	
Endpoint components		
CHD death (including undetermined cause)	9 (0.5%)	8 (0.3%)
Non-fatal MI	23 (1.3%)	30 (0.9%)
Fatal and non-fatal ischemic stroke[a]	3 (0.2%)	12 (0.4%)
Unstable angina requiring hospitalization[b]	1 (<0.1%)	2 (<0.1%)
Congestive heart failure requiring hospitalization	6 (0.3%)	12 (0.4%)
Ischemia driven coronary revascularization procedure	31 (1.7%)	73 (2.3%)

[a] Includes strokes not otherwise specified

[b] With evidence of progressive ischemic condition

Table 43 – SUR data (original in the briefing document):

CV Events Confirmed by Adjudication in LONG TERM Study (final data provided in the 4-month SUR)

Cardiovascular events of interest, n(%)	Placebo (N=788)	Alirocumab 150 Q2W (N=1550)
Death from coronary heart disease, including death from unknown cause	7 (0.9%)	4 (0.3%)
Non-fatal MI	18 (2.3%)	14 (0.9%)
Fatal and non-fatal ischemic stroke	2 (0.3%)	9 (0.6%)
Unstable angina requiring hospitalization[a]	1 (0.1%)	0
Congestive heart failure requiring hospitalization	3 (0.4%)	9 (0.6%)
Ischemia-driven coronary revascularization procedure	24 (3.0%)	48 (3.1%)
Positively adjudicated CV events, including all CV adverse events listed above	40 (5.1%)	72 (4.6%)
Any patients with treatment emergent cardiovascular events confirmed by adjudication (MACE event)[b]	26 (3.3%)	27 (1.7%)

[a] With evidence of progressive ischemic condition

[b] Post-hoc analysis not specified in the study protocol. MACE=CHD death, non-fatal MI, ischemic stroke, or unstable angina (hospitalized)

Robinson et al., NEJM 2015.

Table 43A – BLA data (Addendum):

CV Events Confirmed by Adjudication in LONG TERM Study (interim data as of 31 August 2014 provided in the initial BLA)

Cardiovascular events of interest, n(%)	Placebo (N=788)	Alirocumab 150 Q2W (N=1550)
Death from coronary heart disease, including death from unknown cause	6 (0.8%)	3 (0.2%)
Non-fatal MI	17 (2.2%)	11 (0.7%)
Fatal and non-fatal ischemic stroke	2 (0.3%)	8 (0.5%)
Unstable angina requiring hospitalization[a]	1 (0.1%)	0
Congestive heart failure requiring hospitalization	3 (0.4%)	9 (0.6%)
Ischemia-driven coronary revascularization procedure	20 (2.5%)	41 (2.6%)
Positively adjudicated CV events, including all CV adverse events listed above	35 (4.4%)	62 (4.0%)
Any patients with treatment emergent cardiovascular events confirmed by adjudication (MACE event)[b]	24 (3.0%)	22 (1.4%)

[a] With evidence of progressive ischemic condition

[b] Post-hoc analysis not specified in the study protocol. MACE=CHD death, non-fatal MI, ischemic stroke, or unstable angina (hospitalized)

Figure 34 – final data (correction to briefing document):

MACE Confirmed by Adjudication in LONG TERM Study (final data) – Kaplan-Meier Analysis (Post-hoc Analysis)

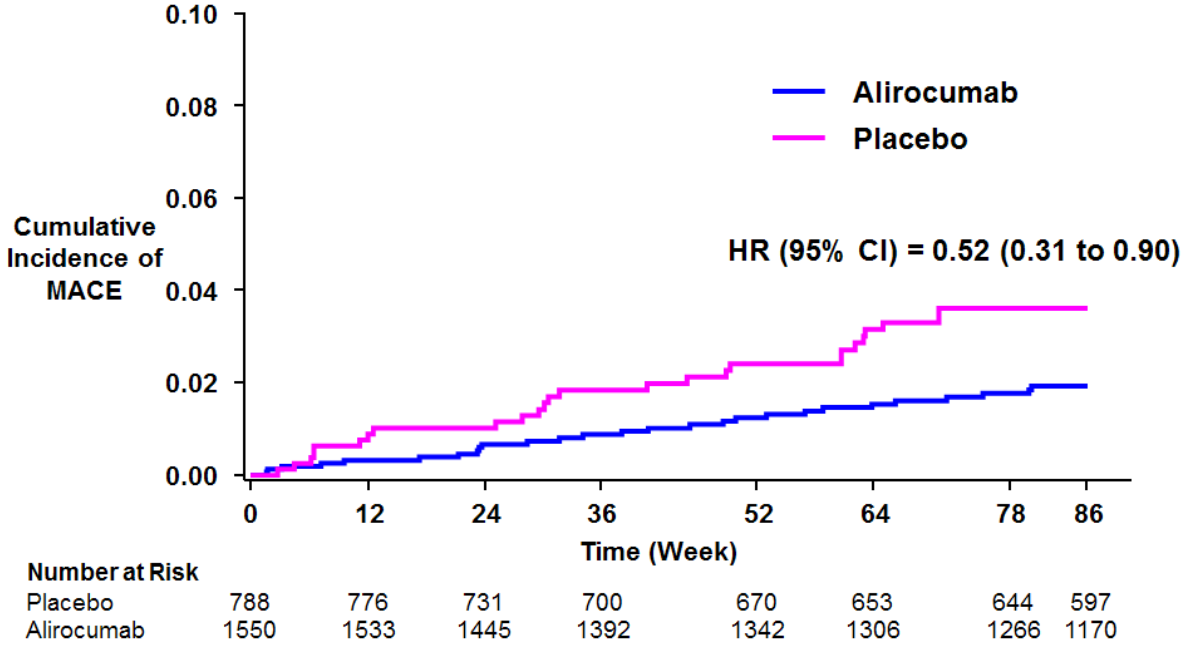

Figure 34A – BLA data (Addendum):

MACE Confirmed by Adjudication in LONG TERM Study – Kaplan-Meier Analysis (Post-hoc Analysis) (interim data as of 31 August 2014 provided in the initial BLA)