



# No evidence of neurocognitive adverse events associated with alirocumab treatment in 3340 patients from 14 randomized Phase 2 and 3 controlled trials: a meta-analysis of individual patient data

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## Aims

Despite patient reports of neurocognitive disorders with lipid-lowering treatments (LLTs), large clinical trials have found no significant association between neurocognitive disorders and LLTs. We assessed incidence of neurocognitive treatment-emergent adverse events (TEAEs) from 14 Phase 2 and 3 trials of the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor alirocumab.

## Methods and results

Patients (most on background maximally tolerated statin) received alirocumab 75/150 mg every 2 weeks ( $n = 3340$ ; 4029 patient-years of exposure), placebo ( $n = 1276$ ), or ezetimibe ( $n = 618$ ). Data were pooled by the control used. Neurocognitive TEAEs were reported by 22 (0.9%) alirocumab-treated patients vs. 9 (0.7%) with placebo in placebo-controlled trials [hazard ratio (HR) 1.24, 95% confidence interval (CI) 0.57–2.68] and 10 (1.2%) with alirocumab vs. 8 (1.3%) with ezetimibe in ezetimibe-controlled trials (HR 0.81, 95% CI 0.32–2.08). Rates of neurocognitive TEAEs were similar in patients receiving alirocumab with LDL cholesterol (LDL-C) levels  $<25$  mg/dL ( $<0.65$  mmol/L;  $n = 5/839$ ; 0.6%; 0.5/100 patient-years) vs.  $\geq 25$  mg/dL ( $n = 26/2501$ ; 1.0%; 0.8/100 patient-years). One patient (0.1%; ezetimibe-controlled pool) receiving alirocumab had a neurocognitive TEAE leading to discontinuation vs. two (0.2%) patients receiving placebo and three (0.4%) patients receiving ezetimibe. Neurocognitive TEAE incidence was also similar between alirocumab and controls when stratified by age.

## Conclusions

Neurocognitive TEAE incidences were low ( $\leq 1.2\%$ ), with no significant differences between alirocumab vs. controls up to 104 weeks. No association was found between neurocognitive TEAEs and LDL-C  $<25$  mg/dL based on the completed Phase 2 and 3 trials examined, although long-term effects of very low LDL-C levels induced by PCSK9 inhibitors are currently unknown.

## Keywords

Cholesterol-lowering drugs • Patient safety • Cognitive function • LDL • PCSK9

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## Introduction

Due to rare post-marketing reports of memory loss or confusion with statin treatment, the US Food and Drug Administration (FDA) changed the labelling of statins in 2012 to indicate that neurocognitive disorders had been associated with statin use.<sup>1</sup> However, the case reports of neurocognitive effects with statins have not been confirmed in large randomized controlled trials or meta-analyses, and no significant association between neurocognitive disorders and low levels of low-density lipoprotein cholesterol (LDL-C) have been shown.<sup>2–7</sup> Despite this, a potential association between lipid-lowering treatments (LLTs) and neurocognitive disorders remains an area of debate.

Alirocumab is a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor, a new class of LLT. In Phase 2 and 3 clinical trials, alirocumab demonstrated large reductions in LDL-C.<sup>8–20</sup> In 2014, the FDA directed companies developing PCSK9 inhibitors to monitor neurocognitive events and to consider neurocognitive testing during late-stage trials.<sup>21</sup> To assess the potential association between alirocumab and neurocognitive disorders, we examined safety data collected from 14 completed clinical trials of alirocumab.

## Methods

### Trial participants and study designs

This analysis included data from 14 double-blind trials (4 Phase 2 and 10 Phase 3). Methods and results of the trials have been reported previously.<sup>8–20</sup> Patients had either heterozygous familial hypercholesterolaemia (HeFH) or non-FH and were randomized to alirocumab 75 or 150 mg every 2 weeks vs. placebo or ezetimibe. Double-blind treatment periods were 8–12 weeks for Phase 2 and 24–104 weeks for Phase 3 trials. Most patients received study treatment as add-on to background maximally tolerated statin. Further details are provided in the

Supplementary material online, Tables S1 and S2. All study protocols were approved by the appropriate institutional review board, and all patients provided informed, written consent.

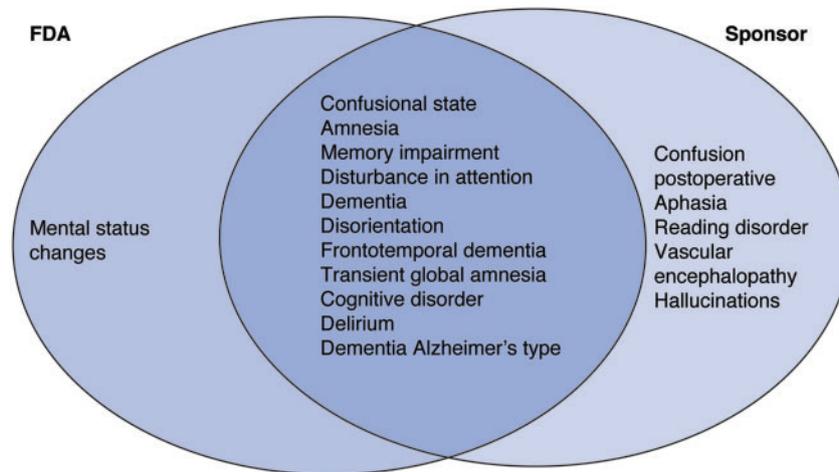
### Recording of safety data

This analysis focuses on treatment-emergent adverse events (TEAEs), defined as those events occurring from the first dose of study treatment up to 70 days after the last dose. All safety data were collected while patients and investigators were blinded to treatment allocations. TEAEs were categorized using standard Medical Dictionary of Regulatory Activities (MedDRA) preferred terms (lowest level term reviewed). Two different groupings or custom MedDRA queries (CMQs) were used to define neurocognitive TEAEs in this analysis (Figure 1), a broad set of terms defined by the study sponsors (sponsor CMQ) and a more focused set of terms which the FDA proposed (FDA CMQ).<sup>5</sup>

Neurocognitive events were self-reported by the patients and recorded by the investigators. No formal neurocognitive testing was included in trials. The trials included in the analysis did not employ a screening tool for evaluating cognitive impairment, and there were no selection criteria related to concomitant medications or cognitive status that may affect cognition. Patients who prematurely discontinued study treatment were followed up where possible for at least 10 weeks or until recovery or stabilization of any TEAEs. All TEAEs were recorded, regardless of their severity or potential relationship to alirocumab. Severity of neurocognitive events was determined by investigators.

### Statistical analysis

Data were analysed in two pools according to the control used in the trials (placebo or ezetimibe) and also in an overall pool of all studies. Event rates were calculated by dividing the number of patients by the duration of exposure (in 100 patient-years). To compare treatment groups in the placebo and in the ezetimibe pools, the hazard ratio (HR) and 95% confidence interval (CI) levels were calculated using a Cox model stratified in the study. Event rates were also calculated in patients treated with alirocumab who had two consecutive LDL-C levels <25 mg/dL (<0.65 mmol/L) separated by at least 21 days, with HR and 95% CI calculated using a Cox



**Figure 1** Individual preferred terms included in custom Medical Dictionary of Regulatory Activities (MedDRA) query groupings of neurocognitive events by the US Food and Drug Administration (FDA)<sup>5</sup> and alirocumab study sponsors. Adverse events were reported by patients in the trials and recorded by the trial investigators, then encoded according to standard MedDRA adverse event (preferred) terms. For the purposes of this analysis, two groupings of preferred terms were categorized as 'neurocognitive events', one defined by the FDA and the other defined by the alirocumab study sponsors.

model stratified on the propensity score to achieve LDL-C <25 mg/dL (quintile) and including the covariate for two consecutive LDL-C <25 mg/dL (yes/no) as fixed effect and study as random effect. Further details on the propensity score analysis are given in the [Supplementary material online](#). The Kaplan–Meier curves are presented for each pool to describe the cumulative incidence of neurocognitive events. An analysis was also performed by age group (<65, ≥65 to <75, and ≥75 years). Average percentage and absolute LDL-C reductions during treatment were determined for patients with and without neurocognitive TEAEs from the area under the curve and taking into account all LDL-C levels to the end of treatment period or occurrence of a neurocognitive TEAE, whichever came first. Previous reports have suggested an association between low HDL-C and memory decline,<sup>22,23</sup> hence, neurocognitive TEAEs were also analysed by baseline HDL-C levels (*post hoc* analysis). To examine the effects of alirocumab on neurocognitive TEAEs in studies of longer duration, a sensitivity analysis was also performed including only those patients treated for at least 52 weeks.

## Results

### Patient population

Safety data were available for a total of 5234 patients (alirocumab,  $n = 3340$ ; placebo,  $n = 1276$ ; and ezetimibe,  $n = 618$ ). Patients received alirocumab for a total of 4029 patient-years. Baseline characteristics were similar across alirocumab and control groups (see [Supplementary material online, Table S1](#)). The mean age of study participants was 58.5–62.1 years (range across the groups in the placebo-controlled and ezetimibe-controlled pools), with 59.8–67.2% males; the majority (86.2–90.1%) were White. Across the groups, 66.2–75.3% of patients had a history of clinical atherosclerotic cardiovascular disease and 5.8–8.6% had a history of ischaemic stroke. In the pool of placebo-controlled trials, which included four trials specifically recruiting patients with HeFH, 36.5% of patients receiving alirocumab and 36.4% receiving placebo had HeFH; corresponding figures were 4.6% for alirocumab and 7.0% for ezetimibe in the ezetimibe-controlled pool (see [Supplementary material online, Table S1](#)). Alirocumab produced significant and substantial reductions in LDL-C vs. control in all trials (see [Supplementary material online, Table S2](#)).

### Neurocognitive treatment-emergent adverse events

Results analysed using the sponsor CMQ definition of neurocognitive events are presented in the main article with analyses using the FDA CMQ definition in the [Supplementary material online](#) (except where stated). The majority of neurocognitive TEAEs identified in this analysis under the FDA definition were also present in the sponsor definition, except for 'mental status changes', which was not included in the sponsor definition; several terms included in the sponsor definition were not included in the FDA definition ([Figure 1](#)). Overall rates of neurocognitive TEAEs, including those classified as serious and those leading to treatment discontinuation, were low and similar between groups ([Figure 2A](#)). The most common individual events were confusional state, amnesia, and memory impairment, which were observed in six patients or fewer ( $\leq 0.5\%$ ) in each group (see [Supplementary material online, Tables S3 and S4](#)).

Neurocognitive TEAEs were reported by 22 (0.9%; 95% CI 0.6–1.3%) patients in the alirocumab group vs. 9 (0.7%; 95% CI 0.3–1.3%) patients in the placebo group in the placebo-controlled pool (HR 1.24; 95% CI 0.57–2.68; [Figure 2B](#)). In the ezetimibe-controlled pool, neurocognitive TEAEs were reported by 10 (1.2%; 95% CI 0.6–2.1%) patients in the alirocumab group vs. 8 (1.3%; 95% CI 0.6–2.4%) patients in the ezetimibe group (HR 0.81; 95% CI 0.32–2.08; [Figure 2B](#)). Although for the largest trial (LONG TERM, 1550 patients allocated to alirocumab in the safety population) neurocognitive TEAEs were observed for 18 (1.2%) alirocumab vs. 4 (0.5%) placebo-treated patients (HR 2.28; 95% CI 0.77–6.75), and no difference between alirocumab and control groups was observed in the pools, which include 1632 patients from the other Phase 3 trials in addition to those from LONG TERM ([Figure 2B](#)). Neurocognitive TEAEs as defined using the FDA CMQ were reported in 16 (1.0%) alirocumab-treated patients in LONG TERM, compared with 6 (0.8%) placebo-treated patients (HR 1.35; 95% CI 0.53–3.46; [Supplementary material online, Table S5](#)). Cumulative incidence curves for the time to first neurocognitive event were similar for alirocumab and control groups ([Figure 3](#); [Supplementary material online, Figure S1](#)).

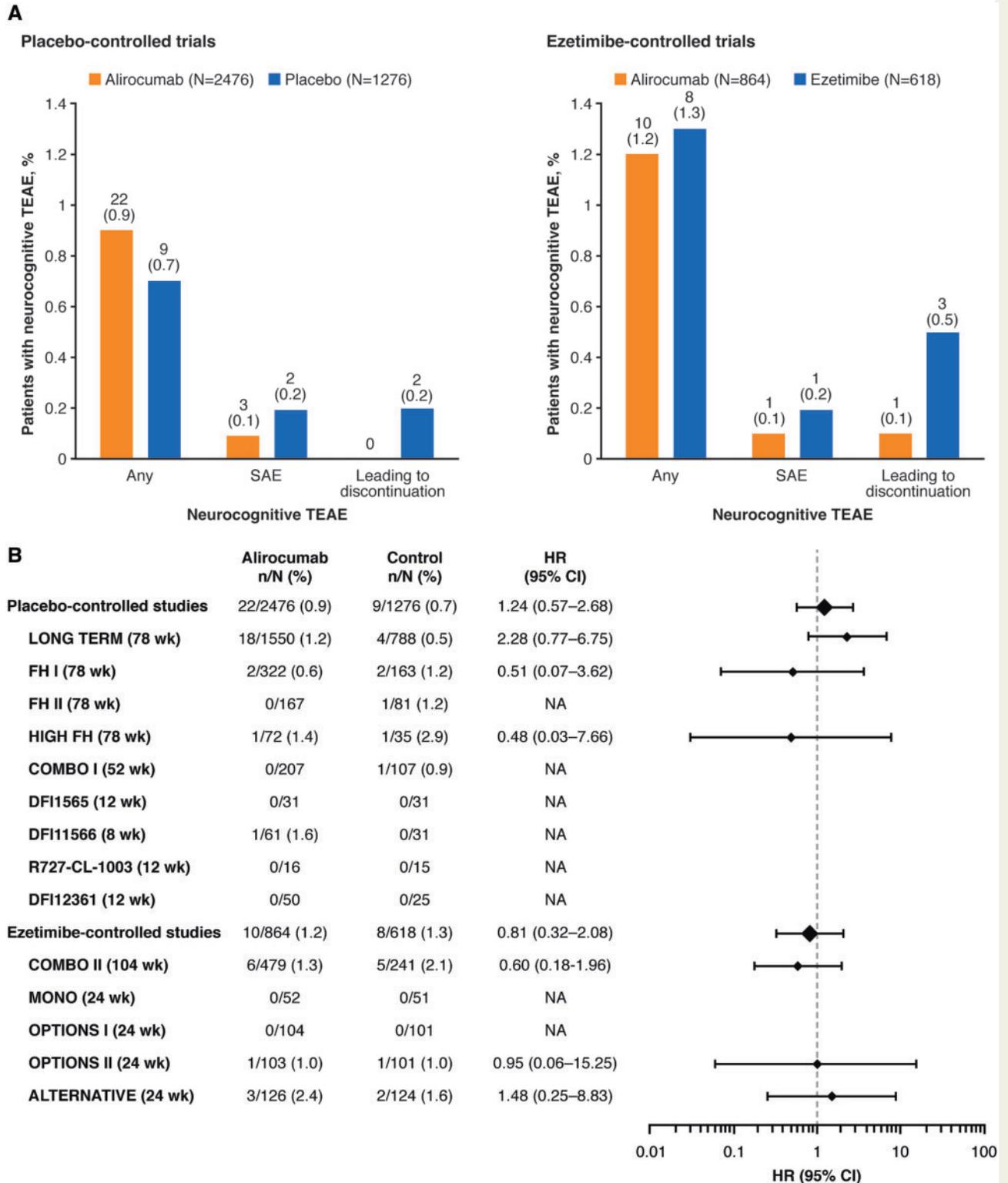
The majority of neurocognitive TEAEs were considered to be mild or moderate in severity ([Table 1](#) and [Supplementary material online, Table S6](#)). Neurocognitive events led to treatment discontinuation for no patients who received alirocumab and for two (0.2%) patients who received placebo in the placebo-controlled pool. One of the placebo-treated patients who discontinued had dementia of unknown origin (classified as moderate in severity), whereas the other had delirium (classified as moderate) and dementia (classified as severe and leading to death). In the ezetimibe-controlled pool, neurocognitive events led to discontinuation in one patient in the alirocumab group (0.1%; memory impairment, classified as mild) and three (0.5%) patients in the ezetimibe group (disturbance in attention, mild; transient global amnesia, moderate; and confusional state, moderate).

### Subanalysis by age group and concomitant medication

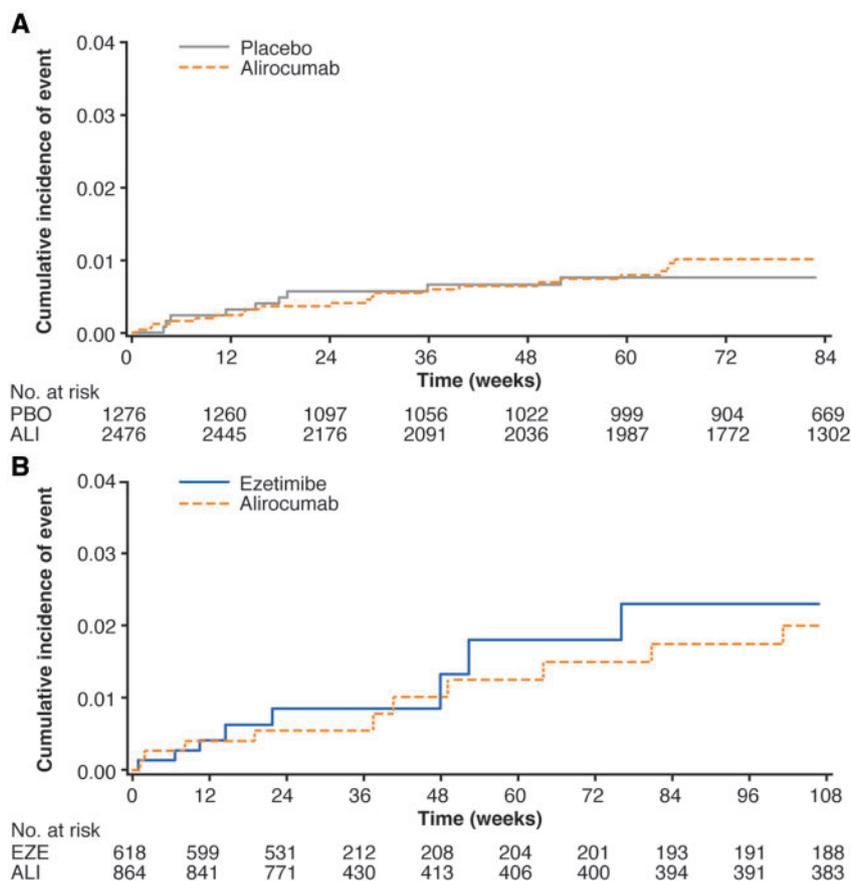
The percentages of patients with neurocognitive TEAEs were similar between alirocumab and control groups in each age category, although the percentage of neurocognitive TEAEs was higher in both alirocumab and control groups in patients ≥75 years of age vs. those <65 years of age and ≥65 to <75 years of age ([Figure 4](#) and [Supplementary material online, Table S7](#)). Results were similar when comparing patients <75 vs. ≥75 years of age (see [Supplementary material online, Table S8](#)). The percentage of patients with neurocognitive TEAEs was low, regardless of the receipt of medications with potential neurocognitive effects, and there were no statistically significant differences between the alirocumab and control groups (see [Supplementary material online, Table S9](#)).

### Lipid levels and neurocognitive treatment-emergent adverse events

In total, 839 (25.1%) patients who received alirocumab achieved two consecutive LDL-C values <25 mg/dL (<0.65 mmol/L). One patient in the control group achieved such LDL-C levels and was not considered for this analysis. Incidence of neurocognitive TEAEs was similar in alirocumab-treated patients with two consecutive LDL-C values



**Figure 2** Overall percentage rates of neurocognitive treatment-emergent adverse events (TEAEs) (A) and hazard ratios for incidence of neurocognitive TEAEs (B) in alirocumab-treated patients compared with the controls. Neurocognitive TEAEs categorized using the sponsor custom MedDRA query as illustrated in Figure 1. In (A), values on chart are n (%) = number and percentage of patients with at least one neurocognitive disorder TEAE. Hazard ratios (HR) were calculated using a Cox model in each study. CI, confidence interval.



**Figure 3** The Study-adjusted Kaplan–Meier cumulative incidence curve for the time to first neurocognitive event during the treatment in pools of (A) placebo-controlled studies and (B) ezetimibe-controlled studies. Neurocognitive treatment-emergent adverse events (TEAEs) categorized using the Sponsor custom MedDRA query. Patients are censored at the end of TEAE period (last injection of study treatment + 70 days).

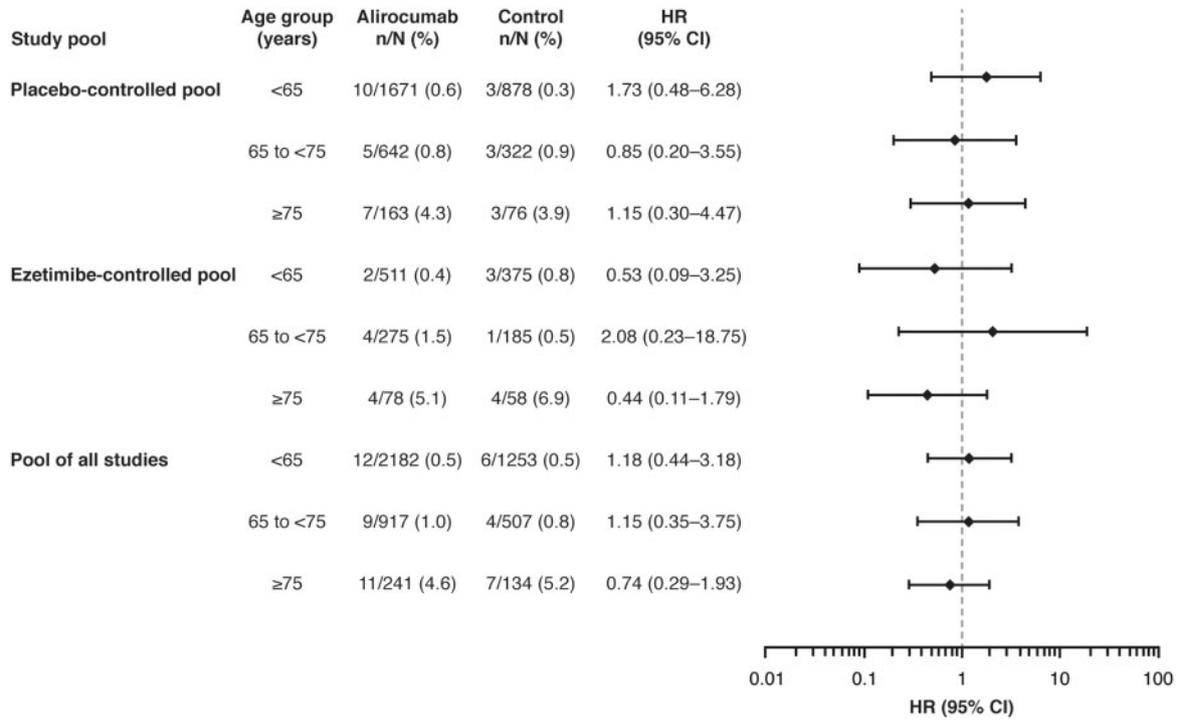
**Table 1** Severity of neurocognitive TEAEs

	Placebo-controlled pool		Ezetimibe-controlled pool		Pool of all studies	
	Alirocumab (n = 2476)	Placebo (n = 1276)	Alirocumab (n = 864)	Ezetimibe (n = 618)	Alirocumab (n = 3340)	Control (n = 1894)
Any neurocognitive TEAE, n (%)	22 (0.9)	9 (0.7)	10 (1.2)	8 (0.9)	32 (1.0)	17 (0.9)
Mild	14 (63.6)	4 (44.4)	9 (90.0)	4 (50.0)	23 (0.7)	8 (0.4)
Moderate	8 (36.4)	4 (44.4)	1 (10.0)	4 (50.0)	9 (0.3)	8 (0.4)
Severe	0	1 (11.1)	0	0	0	1 (0.1)

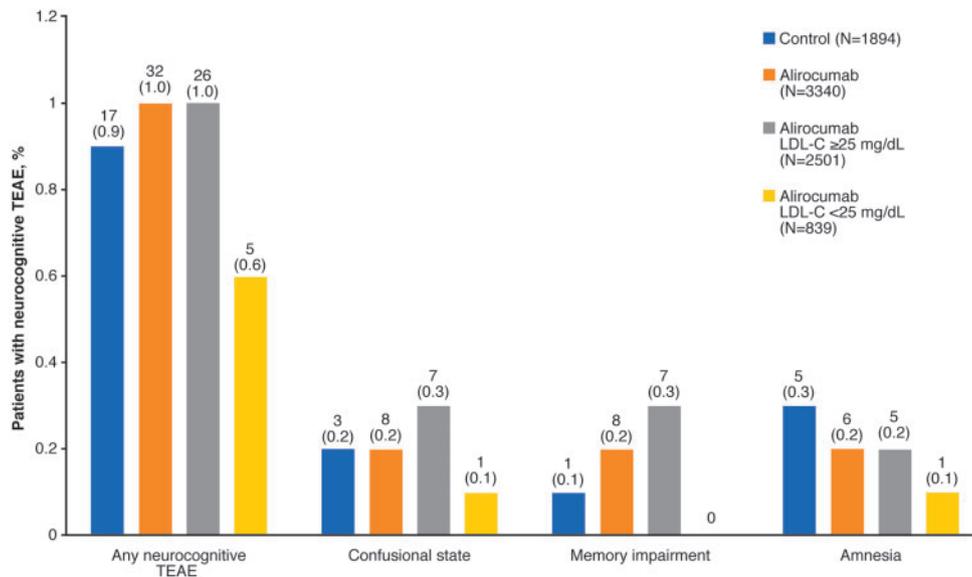
Neurocognitive TEAEs categorized using the Sponsor CMQ. CMQs, custom Medical Dictionary of Regulatory Activities queries; TEAEs, treatment-emergent adverse events.

<25 mg/dL vs. those with LDL-C levels ≥25 mg/dL (HR 0.39; 95% CI 0.14–1.10; Figure 5). Similarly, low rates of individual events were also observed across these subgroups (Figure 5; further details in Supplementary material online, Table S10). In those with two consecutive LDL-C levels <25 mg/dL, four events (confusional state, amnesia, dementia, and frontotemporal dementia) were considered to be of moderate severity and one event (aphasia) was considered to be mild. It is conceivable that the magnitude of LDL-C reduction rather

than the achieved level may have an association with adverse effects; however, mean LDL-C reductions during alirocumab treatment were somewhat smaller in patients with neurocognitive TEAEs than for patients without a neurocognitive TEAE (see Supplementary material online, Table S11). The incidence of neurocognitive TEAEs in those with HDL-C above and below the median level was similar in both men and women and across treatment groups (see Supplementary material online, Table S12).



**Figure 4** Neurocognitive treatment-emergent adverse events (TEAEs) based on age categories. Neurocognitive TEAEs categorized using the Sponsor custom MedDRA query. Interaction *P*-values between age groups: placebo-controlled pool, *P* = 0.7345; ezetimibe-controlled pool, *P* = 0.4964; pool of all studies, *P* = 0.9009.



**Figure 5** Neurocognitive treatment-emergent adverse events (TEAEs) in patients with two consecutive LDL cholesterol levels <25 mg/dL (<0.65 mmol/L). Neurocognitive TEAEs categorized using the Sponsor custom MedDRA query. Values on chart are *n* (%).

### Sensitivity analysis in patients treated $\geq 52$ weeks

This analysis included six trials with double-blind treatment periods of 52 weeks or more (five placebo-controlled trials and one ezetimibe-controlled; see [Supplementary material online, Table S2](#)). A large proportion of the pooled patient population were treated for 52 weeks or more: 1991 (80.4%) and 1000 (78.4%) patients who received alirocumab or placebo, respectively, in the placebo-controlled trials and 410 (47.5%) and 209 (33.8%) patients who received alirocumab or ezetimibe, respectively, in the ezetimibe-controlled trials. The occurrence of neurocognitive TEAEs in patients treated  $\geq 52$  weeks was similar to the overall analysis, with no apparent differences between the alirocumab and control groups (see [Supplementary material online, Tables S13 and S14](#)). Among patients treated  $\geq 52$  weeks, neurocognitive TEAEs were reported in 14 (0.7%) and 6 (0.6%) of patients treated with alirocumab and placebo, respectively (HR 1.17; 95% CI 0.45–3.06), and in 6 (1.5%) and 4 (1.9%) of patients treated with alirocumab and ezetimibe, respectively (HR 0.75; 95% CI 0.21–2.67; results using Sponsor CMQ; [Supplementary material online, Table S13](#)). Furthermore, among patients treated  $\geq 52$  weeks, incidence of neurocognitive TEAEs was similar in alirocumab-treated patients with two consecutive LDL-C values  $< 25$  mg/dL vs. those with LDL-C levels  $\geq 25$  mg/dL [4 (0.6%) vs. 15 (0.9%); HR 0.51; 95% CI 0.15–1.71].

## Discussion

In this large pooled analysis of completed Phase 2 and 3 trials, across 4029 patient-years of exposure to alirocumab, the overall rate of neurocognitive TEAEs was low, and there was no significant difference in the incidence of neurocognitive TEAEs between the alirocumab and control (placebo and ezetimibe) groups, including when stratified by age, nor between alirocumab-treated patients with LDL-C  $< 25$  mg/dL vs.  $\geq 25$  mg/dL. One patient receiving alirocumab discontinued due to a neurocognitive TEAE (mild memory impairment), compared with two placebo- and three ezetimibe-treated patients. Furthermore, in a sensitivity analysis including only patients treated for 52 weeks or more, we saw no evidence of an increase in neurocognitive TEAEs in the alirocumab-treated patients compared with the controls.

A recent meta-analysis by Khan *et al.*<sup>24</sup> of PCSK9 inhibitor trials found a higher rate of neurocognitive events with PCSK9 inhibitors vs. placebo in a pool of the two largest trials: the alirocumab ODYSSEY LONG TERM trial<sup>16</sup> and an open-label study of evolocumab.<sup>25</sup> There was no difference between PCSK9 inhibitor and control in a pool of 10 smaller Phase 3 studies.<sup>24</sup> The meta-analysis by Khan *et al.*<sup>24</sup> included a larger set of alirocumab trials (10 in total) compared with a previous similar analysis by Lipinski *et al.*<sup>26</sup> (which included 6 alirocumab trials); however, both analyses were limited by data the author groups did not have access to, such as severity of the events and rate of discontinuations. As we report here, the majority of neurocognitive events reported in the alirocumab Phase 2 and 3 trials were considered to be mild and the rate of discontinuation due to neurocognitive events was low. Furthermore, this analysis includes data up to the end of study for longer studies such as COMBO II (104 weeks), which were previously unavailable.

In this analysis of relatively short Phase 2 and 3 trials (compared with the forthcoming alirocumab outcomes trial), there was no difference in rates of neurocognitive TEAEs between those with two consecutive LDL-C levels  $< 25$  mg/dL and those without. Similarly, there appeared to be no relationship between LDL-C levels and incidence of neurocognitive TEAEs over  $\sim 1$ –2 years of treatment with evolocumab.<sup>25,27</sup> This is consistent with the results from statin studies, including the JUPITER trial that found no increase in the rate of memory impairment or nervous system disorders in patients who achieved LDL-C levels  $< 30$  mg/dL (0.78 mmol/L) with rosuvastatin treatment.<sup>3</sup> Furthermore, no increase in neurocognitive events was found over a period of 6 years in patients who achieved LDL-C  $< 30$  mg/dL (0.78 mmol/L) in the IMPROVE-IT trial (including patients treated with ezetimibe/simvastatin combination or simvastatin alone).<sup>28</sup> Additionally, a study examining a single nucleotide polymorphism in the PCSK9 gene associated with lower LDL-C levels found no association between this and neurocognitive function.<sup>29</sup> These observations remain to be analysed in larger and longer term studies.

An association between low HDL-C and memory decline in middle-aged adults has been reported previously<sup>22,23</sup> and may be a confounding factor when assessing neurocognitive function in patients with dyslipidaemia. However, in this analysis, there were no significant differences in neurocognitive TEAE rates in those above or below median HDL-C levels across all treatment groups and both genders.

Factors such as coronary heart disease and age are independent risk factors for Alzheimer's disease and many other age-related conditions associated with cognitive decline.<sup>30</sup> This makes analysis of the relationship between PCSK9 inhibitors, LDL-C levels, and cognitive decline a complex one since the population treated with these drugs is typically older, often with comorbidities and concomitant medication use. In this analysis, there was no significant effect of medications with potential neurocognitive effects on the rate of neurocognitive TEAEs. Furthermore, there was no difference in neurocognitive TEAEs between alirocumab and control groups when stratified by age ( $< 65$ ,  $\geq 65$  to  $< 75$ , and  $\geq 75$  years), although the incidence of neurocognitive TEAEs was overall higher in patients (both alirocumab- and control-treated) who were aged  $\geq 75$  years.

## Limitations

Although an association between alirocumab treatment and neurocognitive TEAEs was not found in these relatively short-term Phase 2 and 3 trials (longest follow-up was 2 years), the long-term effects of very low levels of LDL-C induced by PCSK9 inhibitors are unknown. Also, it is acknowledged that the overall number of neurocognitive events observed in alirocumab trials to date is too small to draw definitive conclusions. Due to the small number of neurocognitive events and the relatively small number of patients in this study, the CIs for the HRs are wide and do not exclude HRs  $> 2$ . A study of a greater dimension in terms of number of events and patients would permit more precise estimations of the HRs of neurocognitive events in alirocumab vs. control. Moreover, the statistical analysis did not explicitly take into consideration the competing risk of death. However, the incidence of death was low and similar between alirocumab and control arms (alirocumab vs. placebo: 15 (0.6%) vs.

9 (0.7%), alirocumab vs. ezetimibe: 6 (0.7%) vs. 6 (1.0%); number and percentage of patients who died prior to any neurocognitive event as per sponsor CMQ; results were similar with the FDA CMQ). The effect of alirocumab on neurocognitive events will require further investigation in the ongoing large cardiovascular outcomes trial of alirocumab (ODYSSEY OUTCOMES; NCT01663402). Results from a recent outcomes trial of a different PCSK9 inhibitor (>27 000 patients) showed no significant difference between evolocumab and placebo in terms of physician-reported neurocognitive events, although mean follow-up was limited (2.2 years).<sup>31</sup>

No dedicated tool was used to assess neurocognitive TEAEs; all were patient reported. However, although formal neuropsychological testing with well-validated tests have been shown to detect small differences in performance on a group-mean basis, in some instances, only fairly large changes in cognitive performance on the part of individual changes can be reliably detected. For example, Woods *et al.*<sup>32</sup> found that a minimum of 50% change in recall memory performance was required to meet the criteria for being a reliable change in an individual patient. Such a large change on the part of an individual seems unlikely to go undetected by clinical observation and would likely be noticed and self-reported by patients as in the current analysis.

No specific survey was used for assessment and severity was not assessed using a validated scale. The study designs did not capture or screen for neurocognitive deficits at entry; neurocognitive decline was not assessed during the studies and the use of concomitant medications that could influence neurocognitive state was not a prespecified analysis in any of the studies.

In ODYSSEY OUTCOMES, a Neurocognitive Expert Panel Charter has been established to review in a blinded manner all neurocognitive TEAEs and to explore possible aetiology. Furthermore, a dedicated study of neurocognitive events using formal testing and comparing alirocumab with placebo over 2 years is now under way (clinicaltrials.gov identifier: NCT02957682). In a substudy of the evolocumab outcomes trial (NCT02207634), which utilized tests of neurocognitive function, as well as a patient questionnaire, no difference was found between evolocumab or placebo in neurocognitive tests.<sup>27</sup>

Self-report in the controlled context of a clinical trial can also lead to a bias towards over-detection, with events reported which might not be noted as a problem or reported during real-world clinical use. However, randomization should reduce problems with this type of bias.

Ultimately, any potential risk of neurocognitive TEAEs associated with PCSK9 inhibition must be weighed against the potential benefits of therapy, including decreased risk of major adverse cardiovascular events.<sup>21</sup>

## Conclusion

Overall, this analysis of 4 Phase 2 and 10 Phase 3 trials of alirocumab found low rates of neurocognitive TEAEs distributed evenly across the alirocumab, placebo, and ezetimibe groups. There was no association found between neurocognitive TEAEs and LDL-C levels <25 mg/dL, reductions in LDL-C, or HDL-C levels. However, further monitoring in long-term outcomes studies is needed, with specific assessment of any effect on cognition over a longer period and consideration given to potential contributing factors such as

concomitant medication and comorbid conditions. A further study is now under way to specifically evaluate neurocognitive function and neurocognitive TEAEs occurring with longer term exposure to alirocumab, using formal testing.

## Supplementary material

Supplementary material is available at *European Heart Journal* online.

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