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Original Article

Cognitive function with evolocumab in pediatric heterozygous familial hypercholesterolemia

Daniel Gaudet, MD, PhD*, Andrea Ruzza, MD, PhD, Ian Bridges, MSc, Paul Maruff, PhD[1], Adrian Schembri, DPsych[2], Andrew Hamer, MD[3], François Mach, MD, Jean Bergeron, MD, Isabelle Gaudet, DPsy, PhD, Julie St Pierre, MD, PhD, John J.P. Kastelein, MD, PhD, G. Kees Hovingh, MD, PhD, Albert Wiegman, MD, PhD, Frederick J. Raal, MD, PhD, Raul D. Santos, MD, PhD, for the HAUSER-RCT Investigators†

The Clinical Lipidology and Rare Lipid Disorders Unit, Community Genomic Medicine Centre and ECOGENE-21, Department of Medicine, Université de Montréal, Chicoutimi, QC, Canada (Dr Daniel Gaudet); Global Development, Amgen, Thousand Oaks, CA, United States (Drs Ruzza and Hamer); Biostatistics Department, Amgen, Cambridge, United Kingdom (Mr Bridges); Cogstate Ltd., Melbourne, VIC, Australia (Drs Maruff and Schembri); Cardiology Department, Geneva University Hospital, Geneva, Switzerland (Dr Mach); Lipid Clinic, Department of Medicine, Centre Hospitalier Universitaire de Québec–Université Laval, QC, Canada (Dr Bergeron); Department of Psychology, Université de Montréal, and Laboratoire d'imagerie optique en neurodéveloppement (LIONLAB), Sainte-Justine University Hospital Research Center, Montréal, Chicoutimi, QC, Canada (Dr Isabelle Gaudet); Department of Pediatrics, Faculty of Medicine, McGill University, Montréal, QC, Canada (Dr Pierre); Department of Vascular Medicine, Amsterdam UMC, Amsterdam, Netherlands (Drs Kastelein and Hovingh); Department of Pediatrics, Amsterdam UMC, Amsterdam, Netherlands (Dr Wiegman); Division of Endocrinology and Metabolism, Department of Medicine Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa (Dr Raal); Lipid Clinic at the Heart Institute (InCor), University of São Paulo Medical School Hospital, São Paulo, Brazil (Dr Santos); Hospital Israelita Albert Einstein, São Paulo, Brazil (Dr Santos)

* Corresponding author.
E-mail addresses: daniel.gaudet@umontreal.ca (D. Gaudet), andrearuzza04@gmail.com (A. Ruzza), ibridges@amgen.com (I. Bridges), pmaruff@cogstate.com (P. Maruff), adrian.j.schembri@gmail.com (A. Schembri), azhnn@me.com (A. Hamer), Francois.Mach@hcuge.ch (F. Mach), jeanbergeron@cmlq.net (J. Bergeron), isabelle.gaudet.3@umontreal.ca (I. Gaudet), julie.st-pierre2@mcgill.ca (J.S. Pierre), j.j.kastelein@amsterdamumc.nl (J.J.P. Kastelein), g.k.hovingh@amsterdamumc.nl (G.K. Hovingh), a.wiegman@amsterdamumc.nl (A. Wiegman), Frederick.Raal@wits.ac.za (F.J. Raal), rdsf@uol.com.br (R.D. Santos).
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[1] The Turner Institute for Brain and Mental Health, School of Psychological Sciences, Monash University, Clayton, VIC, Australia
[2] pod, Richmond, VIC, Australia
[3] Cardiol Therapeutics, Oakville, ON, Canada
† HAUSER-RCT investigators are listed in Appendix A in the Supplement.

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KEYWORDS
Cholesterol;
LDL;
Evolocumab;
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Cognitive dysfunction;
PCSK9;
FH;
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Child

Background: Evolocumab is a fully human monoclonal antibody inhibitor of PCSK9 approved for lowering low-density lipoprotein cholesterol in adults and pediatric patients with familial hypercholesterolemia (FH). The cognitive safety of evolocumab has been established in adults but has not yet been described in pediatric patients.

Objective: To determine the effects of evolocumab on cognitive function in pediatric heterozygous FH.

Methods: Cognitive function was assessed during a 24-week, randomized, double-blind, placebo-controlled study (HAUSER-RCT) evaluating the efficacy, safety, and tolerability of 24 weeks of monthly subcutaneous injections of evolocumab in pediatric patients with FH. Cognitive safety endpoints included changes from baseline to week 24 in test scores in domains of psychomotor function, attention, visual learning, and executive function. Between-group differences in age-standardized mean test score changes were analyzed using analysis of covariance models and point estimates with 95% confidence interval (CI). Magnitudes of difference between treatment groups (Cohen's d) and reliable change indices were calculated for each cognitive function test.

Results: At week 24, changes from baseline in age-standardized cognitive test scores were similar between the treatment groups. Differences (95% CI) between the evolocumab and placebo groups in mean test score changes for the Groton Maze Learning, One-Card Learning, Identification, and Detection tests were 0.1 (–0.2, 0.4), –0.1 (–0.5, 0.4), 0.3 (0.0, 0.7), 0.3 (–0.1, 0.8), respectively. For all tests, abnormal and clinically important cognitive decline occurred with lesser frequency in the evolocumab group.

Conclusion: In pediatric patients with FH, 24-week treatment with evolocumab did not negatively influence cognition.

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Introduction

Cholesterol is an integral component of the cell membrane and of myelin in the central nervous system (CNS) and plays a crucial role in normal brain development and function.[1] As the brain contains approximately 25% of the body's cholesterol,[2] there is a hypothetical risk of CNS adverse events, such as cognitive dysfunction, with lipid-lowering therapies including statins, ezetimibe, and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors.[3,4] Initial support for this hypothesis arose from observations of associations between statin treatment and impaired cognitive function in postmarketing reports and clinical studies.[5,6] In 2012, the United States Food and Drug Administration (FDA) issued a safety label update for statins to include warnings of potential nonserious and reversible cognitive effects.[7] However, subsequent meta-analyses and systematic reviews of clinical studies using objective and validated assessments of cognitive function found no associations between the use of these lipid-lowering therapies, or the resultant reduction of low-density lipoprotein cholesterol (LDL-C), and cognitive dysfunction.[8–10] In 2014, the FDA requested developers of PCSK9 inhibitors to assess potential cognitive adverse events in their ongoing and future trials.[11-14]

Placebo-controlled randomized studies conducted in adult patients showed no evidence of cognitive dysfunction arising from PCSK9 inhibitors.[10,13] However, relationships between treatment with PCSK9 inhibitors and cognitive function have not been described in pediatric patients. The HAUSER-RCT study assessed cognitive function in pediatric patients with familial hypercholesterolemia (FH) who were on stable lipid-lowering therapy and randomized to evolocumab or placebo for 24 weeks.[15] Four domains of cognitive function were measured: psychomotor function, attention, visual learning, and executive function. These were chosen because their normal developmental trajectories are well understood, they are often impaired in neurodevelopmental diseases, and their measurement has been used previously to support medical and regulatory decisions about the cognitive safety of CNS-active drugs in children.[16]

Patients and methods

Trial design and oversight

HAUSER-RCT (ClinicalTrials.gov identifier, **NCT02392559**) was a phase 3, randomized, parallel-group, placebo-controlled, double-blind study that aimed to evaluate the efficacy, safety, and tolerability of 24 weeks of evolocumab, as an adjunct to stable lipid-lowering therapy and a low-fat diet, in pediatric patients with heterozygous FH. The study was sponsored by Amgen and the design has been described previously.[15,17] The study protocol and the informed consent form were reviewed and approved by institutional review boards and/or authorized bodies at each site. Study oversight was conducted in accordance with relevant regulatory requirements including the Code of Ethics of the World Medical Association (Declaration

of Helsinki), International Conference on Harmonisation, and Good Clinical Practice guidelines. Regular oversight of data pertaining to safety and efficacy was performed by an independent data monitoring committee and an independent biostatistical group. An Amgen medical writer and P.M. wrote the first draft of this report with input and oversight from D.G., A.R., I.B., A.S., and R.D.S. Data interpretation and development of later drafts were done by all coauthors who attest to the accuracy and integrity of the work.

Patients and randomization

Pediatric patients with heterozygous FH aged 10 to 17 years were screened if they were on stable lipid-lowering therapy for a minimum of 4 weeks before screening, on a low-fat diet, had LDL-C levels of 130 mg/dL (3.4 mmol per liter) or greater, and had triglyceride levels of 400 mg/dL (4.5 mmol per liter) or less. The eligibility criteria have been described previously[15,17] (Table S1 in the Supplement). Patients were assigned randomly using an interactive voice response system in a 2:1 ratio to receive subcutaneous injections of evolocumab (420 mg monthly) or placebo and stratified according to screening LDL-C (<160 vs ≥ 160 mg per deciliter [4.1 mmol per liter]) and age at baseline (<14 vs ≥ 14 years).

Assessment of cognitive function and endpoints

Cognition was assessed at screening, baseline (day 1), and week 24 visits using tests from the Cogstate computerized test battery. Executive function was assessed with the Groton Maze Learning Test, which is based on the hidden pathway maze learning paradigm. Visual learning was assessed with the One-Card Learning Test based on the pattern separation memory paradigm. Visual attention was assessed using the Identification test based on the choice reaction time paradigm. Psychomotor function was assessed with the Detection test based on the simple reaction time paradigm. The design and administration of each of these tests have been described in detail,[16] and description and function of these tests are included in the Supplemental Appendix. Each test provided a single performance measure. For the Groton Maze Learning Test, this was number of errors made in finding the pathway over five trials. For the One-Card Learning Test, this was the proportion of correct responses, and for the Identification and Detection tests, this was the average reaction time for correct responses. Cognitive safety endpoints included change from baseline to week 24 in raw and age-standardized test scores in total errors made in the Groton Maze Learning Test, accuracy of performance in the One-Card Learning Test, and speed of performance in the Identification and Detection tests.

Statistical analysis

A sample size of 150 patients randomized 2:1 to evolocumab or placebo was calculated to be adequate to test for evolocumab superiority for the primary endpoint (percent change in LDL-C level from baseline to week 24) with 99% power. Data analyses proceeded in six stages (steps 2–6 were post hoc). First, rates of missing or incomplete data for patients were computed for each test at each visit and the data summarized. Second, as normative data show that performance on each test improves with increasing chronological age,[16] each test score was standardized using an age-based mean and standard deviation (SD) from normative data. Third, age-standardized scores for each test were analyzed using analysis of covariance with change from baseline as the response variable, and baseline score and stratification factors as covariates. Least squares mean differences between the treatment groups in change from baseline to week 24 were estimated along with their 95% confidence intervals (CIs). Fourth, effect sizes (Cohen's d)[18] were used to express the magnitude of differences between the treatment groups. Fifth, reliable change indices were computed for each test for each patient by expressing the change from baseline to week 24 in test scores relative to expected variation over repeated measurements (within patient SD from normative data). Reliable change indices were adjusted so that positive values reflected an improvement in performance from baseline and negative values indicated a decline in performance. Abnormal change from baseline was defined for a test when the relative change index score was ≤ -1.65. Sixth, the number of patients with an abnormal change from baseline to week 24 was computed for each cognitive test. Patients with two or more abnormal changes from baseline scores (ie, two or more reliable change index (RCI) scores ≤ -1.65) were classified as showing clinically important cognitive decline at the week 24 assessment. Inferences about treatment effects were based on the 95% CIs associated with point estimates of treatment effects as well as effect sizes. Effect sizes less than 0.2 were classified as trivial and not interpreted. Effect sizes between 0.2 and 0.5 were considered small, between 0.5 and 0.8, moderate, and greater than 0.8, large.[18] All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

Patients

A total of 157 of 158 randomized patients were included in the full analysis set and received evolocumab or placebo (104 and 53 patients, respectively) from March 2016 through May 2019 (Figure S1 in the Supplement). Demographic and clinical characteristics of patients were similar between the two groups and have been described previously[15] (Table S2 in the Supplement). The mean (SD) age of patients was 13.7 (2.4) years, and the majority (56%) were female. At baseline, 11 patients (7%) had a medical history of or were taking medications for attention-deficit hyperactivity disorder (ADHD). Ten of these patients (evolocumab, $n = 7$; placebo, $n = 3$) provided cognitive test data at week 24. Mean (SD)

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Table 1 Age-standardized cognitive test scores.

Cognitive Domain	Test	Evolocumab ($n = 104$)	Placebo ($n = 53$)
Executive function	Groton Maze Learning Test— total errors, median (Q1, Q3)		
		Baseline	
		$n = 103$	$n = 53$
		0.23 (–0.47, 0.59)	0.28 (–0.40, 0.80)
		Week 24	
		$n = 96$	$n = 45$
		0.45 (–0.09, 1.21)	0.77 (0.23, 1.22)
Visual learning	One-Card Learning Test— Accuracy of Performance (arcsine square root proportion correct), median (Q1, Q3)		
		Baseline	
		$n = 104$	$n = 53$
		0.51 (–0.87, 1.69)	0.46 (–0.65, 1.52)
		Week 24	
		$n = 96$	$n = 45$
		0.49 (–0.72, 1.97)	0.78 (–0.91, 2.09)
Attention	Identification Test, Speed of Performance—$\log_{10}$ms, median (Q1, Q3)		
		Baseline	
		$n = 104$	$n = 53$
		–0.55 (–1.54, 0.30)	0.04 (–1.15, 0.91)
		Week 24	
		$n = 95$	$n = 45$
		–0.08 (–1.28, 0.84)	–0.15 (–1.26, 0.80)
Psychomotor function	Detection Test, Speed of Performance— $\log_{10}$ms, median (Q1, Q3)		
		Baseline	
		$n = 104$	$n = 53$
		–0.16 (–1.39, 0.77)	0.47 (–0.69, 1.22)
		Week 24	
		$n = 95$	$n = 45$
		0.36 (–1.56, 1.06)	0.25 (–0.93, 1.31)

Cognitive test scores were standardized relative to age-matched normative data. A higher score is indicative of better performance.

baseline level of LDL-C was 184.3 (45.6) mg per deciliter (4.8 [1.2] mmol per liter).

Outcomes

At week 24, data were missing for nine patients (9%) in the evolocumab group and eight patients (15%) in the placebo group. No data interpolation processes were applied. In sensitivity analyses, which included data captured after the week 24 assessment window, less than 2% of patients in each treatment group were missing a week 24 assessment. Group median (interquartile range) age-standardized and raw scores for each cognitive test at baseline and week 24 for the treatment groups are summarized in Table 1 and Table S3 (sensitivity analyses, Tables S4 and S5 in the Supplement).

Baseline-adjusted performance at week 24 was similar between the treatment groups for the Groton Maze Learning (between-group difference of 0.1; 95% CI, –0.2 to 0.4) and the One-Card Learning (between-group difference of –0.1; 95% CI, –0.5 to 0.4) tests, but numerically favored the evolocumab group for the Identification (between-group difference of 0.3; 95% CI, 0.0 to 0.7) and Detection (between-group difference of 0.3; 95% CI, –0.1 to 0.8) tests. Effect sizes expressing the magnitude of the difference in baseline-adjusted age-standardized scores at week 24 between the treatment groups indicated small benefits with evolocumab on the Identification ($d = 0.5$) and Detection ($d = 0.3$) tests but trivial differences between treatment groups on the Groton Maze Learning ($d = 0.1$) and One-Card Learning ($d = –0.1$) tests (Fig. 1).

Analyses of the relative change indices for individual cognitive tests at the 24-week assessment indicated that the percentage of patients with abnormal change from baseline scores (ie, reliable change index $\leq –1.65$) was greater in the placebo group than in the evolocumab group on each cognitive test (Table 2). When considered at the level of individual patients, clinically important cognitive decline (ie, RCI $\leq –1.65$ on two or more cognitive tests) occurred in 1 of 96 patients (1%) in the evolocumab group and 5 of 45 patients (11%) in the placebo group (Table 2). There were no apparent differences in baseline-adjusted age-standardized cognitive test results according to achieved LDL-C levels at week 24 due to evolocumab therapy (Table 3). Results of cognitive tests for pediatric patients with ADHD were consistent with that observed for the whole cohort (Fig. 2).

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Table 2 Clinically important cognitive decline at week 24.

		Evolocumab ($n = 104$)	Placebo ($n = 53$)
Cognitive domain	**Test**		
	Number of patients with RCI ≤ −1.65		
		n′= 96	n′ = 45
Executive function	Groton Maze Learning Test— no. (%)	1 (1)	1 (2)
Visual learning	One-Card Learning Test— no. (%)	n′ = 96 1 (1)	n′ = 45 1 (2)
Attention	Identification Test—no. (%)	n′ = 95 3 (3)	n′ = 45 6 (13)
Psychomotor function	Detection Test—no. (%)	n′ = 95 7 (7)	n′ = 45 9 (20)
	Number of tests with RCI ≤ −1.65		
0— no. (%)		85 (82)	35 (66)
1— no. (%)		10 (10)	5 (9)
2— no. (%)		1 (1)	4 (8)
3— no. (%)		0 (0)	0 (0)
4— no. (%)		0 (0)	1 (2)
No value— no. (%)		8 (8)	8 (15)

RCI scores ≤ −1.65 are considered significant at a 90% confidence level. n = number of patients randomized and dosed in the full analysis set; n′ = number of patients with a value at week 24. RCI, reliable change index.

Table 3 Results of cognitive safety endpoints in the evolocumab group by achieved LDL-C levels at week 24.

		Evolocumab ($n = 104$)
Change in age-standardized cognitive test scores from baseline to week 24		
Cognitive test		
Groton Maze Learning Test—Total Errors, median (Q1, Q3)		
	<70 mg/dL ($n = 23$)	0.45 (−0.06, 0.96)
	70 to <100 mg/dL ($n = 35$)	0.38 (−0.11, 0.87)
	100 to <130 mg/dL ($n = 11$)	0.16 (−0.19, 0.63)
	≥130 mg/dL ($n = 25$)	0.44 (−0.07, 1.13)
One-Card Learning Test—Accuracy of Performance (arcsine square root proportion correct), median (Q1, Q3)		
	<70 mg/dL ($n = 23$)	0.00 (−0.50, 0.95)
	70 to <100 mg/dL ($n = 35$)	0.04 (−0.75, 0.78)
	100 to <130 mg/dL ($n = 11$)	−0.02 (−0.99, 1.27)
	≥130 mg/dL ($n = 25$)	0.21 (−0.33, 0.98)
Identification Test, Speed of Performance—$\log_{10}$ms, median (Q1, Q3)		
	<70 mg/dL ($n = 23$)	0.09 (−0.31, 0.71)
	70 to <100 mg/dL ($n = 35$)	0.53 (−0.07, 1.16)
	100 to <130 mg/dL ($n = 10$)	0.24 (−0.99, 0.93)
	≥130 mg/dL ($n = 25$)	0.03 (−0.54, 0.57)
Detection Test, Speed of Performance—$\log_{10}$ms, median (Q1, Q3)		
	<70 mg/dL ($n = 23$)	0.22 (−0.27, 0.69)
	70 to <100 mg/dL ($n = 35$)	0.19 (−0.32, 1.04)
	100 to <130 mg/dL ($n = 10$)	0.08 (−0.79, 0.93)
	≥130 mg/dL ($n = 25$)	0.27 (−0.16, 0.83)

To convert LDL-C units to mmol/L, multiply values by 0.02586. LDL-C, low-density lipoprotein cholesterol; Q1, first quartile; Q3, third quartile.

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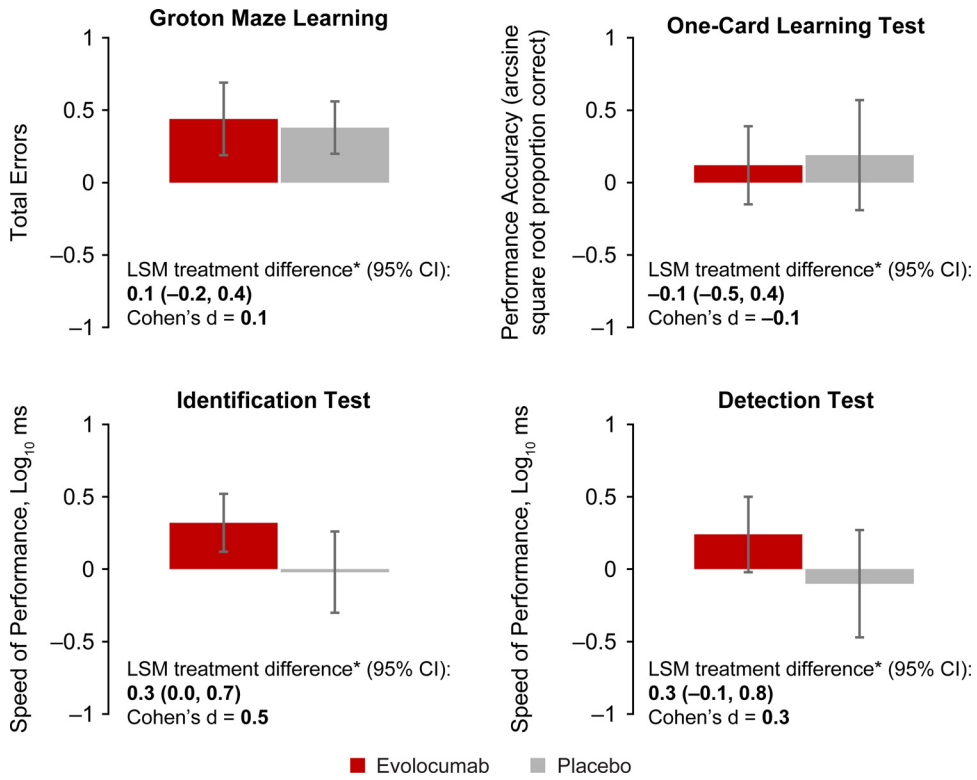

Fig. 1 Results of cognitive safety endpoints.

Change in age-standardized cognitive test scores from baseline to week 24. Higher scores are indicative of better performance. A positive change in LSM and Cohen's d indicates a more beneficial result with evolocumab vs placebo. *Least squares mean is from the analysis of covariance with change in age-standardized cognitive test score from baseline to week 24 as response and treatment group, baseline cognitive test score, and randomization stratification factors as covariates. LSM treatment difference is the value in the evolocumab group minus the value in the placebo group. Error bars indicate 95% CIs. CI, confidence interval; LSM, least squares mean.

Discussion

Cognitive function was assessed in 157 patients aged 10 to 17 years with heterozygous FH from the double-blind, placebo-controlled HAUSER-RCT study. Change from baseline, defined using either raw or age-standardized scores, on tests of psychomotor function, attention, visual learning, and executive function was similar in the evolocumab and placebo groups. The results of our study demonstrate that 24 weeks of monthly dosing of evolocumab had no impact on psychomotor function, attention, visual learning, or executive function in pediatric patients when considered either at the level of treatment groups or in terms of the proportion of individuals who showed clinically important change in cognitive function. Though an exploratory finding, evolocumab-treated patients had modestly superior performance in psychomotor function and attention as compared with patients in the placebo group.

Taken together, these data indicate that in pediatric patients with heterozygous FH, treatment with evolocumab does not give rise to impairment in cognitive function. Further, analyses of data at both group and individual level did not suggest any subgroup of children or adolescents to be more vulnerable to negative cognitive effects with evolocumab.

Small imbalances in cognitive adverse events favoring placebo had initially been observed in pooled lipid-lowering studies in both evolocumab and alirocumab programs.[12,13] However, no such association was observed in larger studies with dedicated cognitive assessments, including in the approximately 27,000 adult patients who participated in the double-blind, placebo-controlled, cardiovascular outcome FOURIER study, as well as in the EBBINGHAUS study, which studied a subgroup of FOURIER participants using a battery of objective neuropsychological tests (Cambridge Neuropsychological Test Automated Battery).[10,19] Furthermore, in the open-label OSLER-1 study evaluating the long-term effects of evolocumab treatment for up to 5 years in adult patients with hypercholesterolemia, cognitive adverse events were low compared with 1-year standard of care (0.4% vs 0%), and no evidence of an increase in cognitive adverse events was reported despite maintaining low LDL-C levels.[20] The data from the current study are consistent with and add to this corpus of evidence for the CNS safety of evolocumab; notably, this data further indicate that this safety extends to the developing brain in pediatric patients with FH. Of note, elevated cholesterol levels during childhood have recently been shown to be negatively associated with cognitive performance and associative learning in midlife,[21,22] which suggests an additional possible benefit of early

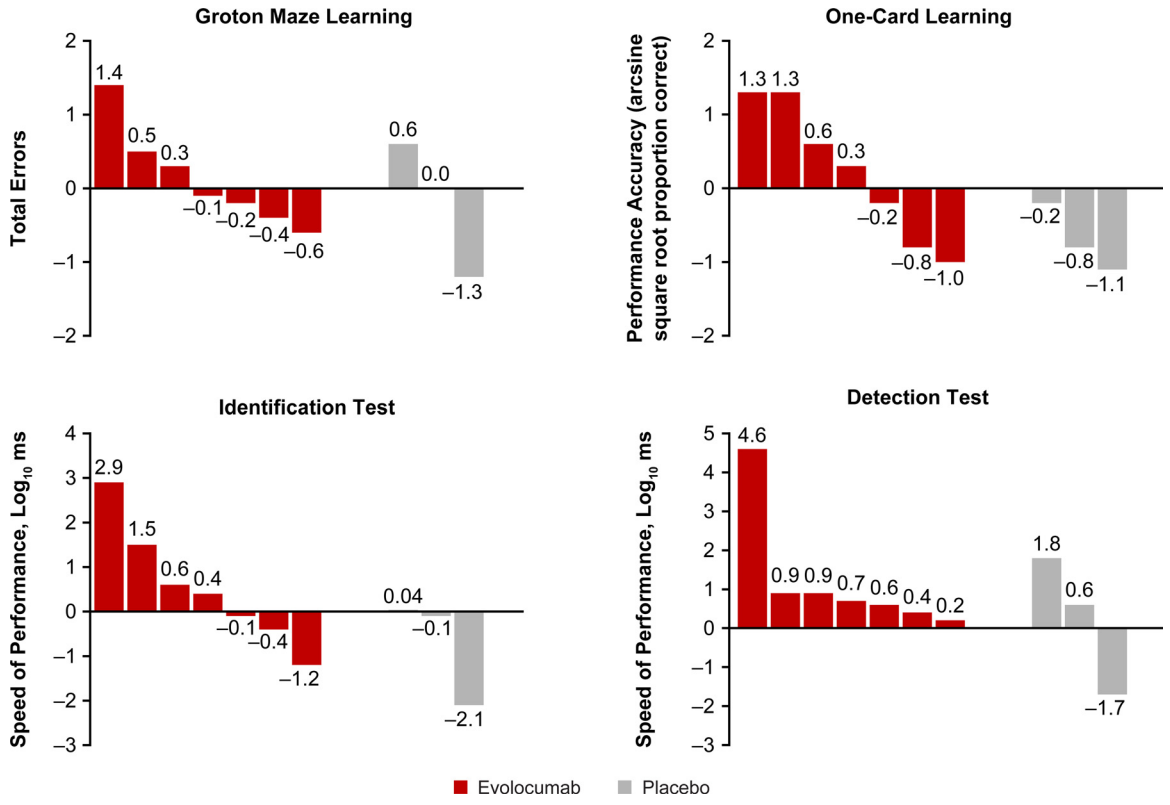

Fig. 2 Results of cognitive safety endpoints for patients with ADHD.
Change in age-standardized cognitive test scores from baseline to week 24 in individual patients with ADHD. Higher scores are indicative of better performance. ADHD, attention-deficit hyperactivity disorder.

treatment with PCSK9 inhibitors during childhood in patients with FH.

The main limitation of this study is that the effects of evolocumab were studied over a relatively short time period of 24 weeks. An open-label extension of this study (HAUSER-OLE) is currently ongoing for patients who completed HAUSER-RCT and will provide longer-term data on the safety and efficacy, including cognitive function, of evolocumab in pediatric patients with FH. Another limitation of this study is that it included some patients who met the clinical criteria for ADHD or depression. Although the small number of these patients precluded proper assessment of the effects of evolocumab on cognitive function, the cases of ADHD were distributed evenly between the treatment groups making it unlikely that they resulted in bias of the study outcomes.

Conclusions

In summary, monthly administration of evolocumab in pediatric patients with FH over 24 weeks did not negatively influence cognition. Longer-term data are needed to improve understanding of the safety and efficacy of evolocumab in this population. However, given the beneficial effects of early LDL-C lowering in pediatric patients with FH, evolocumab may be useful in the treatment of these patients.

Data sharing

Qualified researchers may request data from Amgen clinical studies; complete details are available at http://www.amgen.com/datasharing.

Author contributions

Dr D Gaudet had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Ruzza

Acquisition, analysis, or interpretation of data: All authors

Drafting of the manuscript: Gaudet, Ruzza, Bridges, Maruff, Schembri, Santos

Critical revision of the manuscript for important intellectual content: All authors

Statistical analysis: Bridges

Administrative, technical, or material support: Gaudet, Ruzza, Bridges, Santos

Supervision: Gaudet, Ruzza, Santos

Declaration of Competing Interest

Dr D Gaudet reports receiving consulting fees from HDL Therapeutics, Regeneron Pharmaceuticals, and Sanofi; and

grant support from Esperion, Gemphire Therapeutics, HDL Therapeutics, Pfizer, Regeneron Pharmaceuticals, Sanofi, and The Medicines Company. **Dr Ruzza** reports employment with and holding stock in Amgen; and holding pending patent 63/032451 on PCSK9 inhibitors and methods of use thereof to treat cholesterol-related disorders. **Mr Bridges** reports employment with and holding stock in Amgen. **Dr Maruff** and **Dr Schembri** are employees of Cogstate Ltd., the company that provided the cognitive tests in this study. **Dr Hamer** reports employment with Cardiol Therapeutics Inc. and holding stock in Amgen. **Dr Bergeron** reports receiving lecture fees from Amgen and HLS Therapeutics Inc.; grant support from Akcea Therapeutics–Ionis Pharmaceuticals, Amgen, Kowa, Novartis, Regeneron Pharmaceuticals, Sanofi, and The Medicines Company; and serving on the advisory boards for Amgen and Novartis. **Dr St Pierre**–Takeda, Novo Nordisk, and Bausch Health. **Dr Kastelein** reports consulting fees from AstraZeneca, CiVi Biopharma, CSL Behring, Draupnir Bio, Esperion, Gemphire Therapeutics, Madrigal Pharmaceuticals, Matinas BioPharma, NorthSea Therapeutics, Novo Nordisk, Novartis, Regeneron Pharmaceuticals, REGENXBIO, Staten Biotechnology, 89bio, OMEICOS Therapeutics, Serometrix. **Dr Hovingh** reports the following: employment with Novo Nordisk; consulting and speakers bureau fees from Aegerion Pharmaceuticals, Amgen, Regeneron Pharmaceuticals, and Sanofi; grant support from Aegerion Pharmaceuticals, Amgen, AstraZeneca, Eli Lilly, Genzyme, Ionis Pharmaceuticals, Kowa, Pfizer, Regeneron Pharmaceuticals, Roche, Sanofi, The Medicines Company; and serving on advisory boards for Aegerion Pharmaceuticals, Amgen, Regeneron Pharmaceuticals, Sanofi. **Dr Wiegman** reports research support for pharmaceutical trials of lipid-lowering agents from Amgen, Regeneron and Novartis. **Dr Raal** has received research grants, honoraria, or consulting fees for professional input and/or lectures from Sanofi, Regeneron, Amgen, and Novartis. **Dr Santos** reports receiving the following: consulting fees and lecture fees from Abbott, Amgen, AstraZeneca, Aché, EMS, Getz Pharma, Libbs, Merck, Merck Sharp & Dohme, PTC Therapeutics, Novo Nordisk, Novartis, Sanofi-Regeneron Pharmaceuticals; grant support from Amgen, Kowa, Esperion, Novartis, Sanofi-Regeneron Pharmaceuticals. The remaining authors have nothing to disclose.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jacl.2022.07.005.

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