The SYDNEY Device Study: A Multicenter, Randomized, Open-label Usability Study of a 2-mL Alirocumab Autoinjector Device

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ABSTRACT

Purpose: The proprotein convertase subtilisin/kexin type 9 inhibitor alirocumab has produced significant reductions in LDL-C at a dose of 300 mg q4w administered as 2 separate 150-mg injections via a 1-mL autoinjector (AI). A recently developed 2-mL device (SYDNEY) permits the administration of a single 300mg dose of alirocumab.

Methods: We assessed the usability and product technical complaints (PTCs) reported by patients using the 2-mL SYDNEY device in unsupervised settings, adverse events, and effects on LDL-C, in a multicenter, randomized, open-label, 16-week study conducted in the United States. For their first dose, 69 patients with hypercholesterolemia despite receiving statin with or without other lipid-lowering therapy randomly received supervised, self-administered alirocumab 300 mg via 1 × 300 mg injection with the SYDNEY device (n = 35) or 2 × 150-mg injections with the currently approved AI (n = 34). All continuing patients subsequently received unsupervised, self-administered alirocumab 300 mg q4w using the SYDNEY device at weeks 4, 8, and 12. The primary end point was the proportion of SYDNEY device–associated PTCs related to the use of the unsupervised injections.

Findings: Baseline characteristics between the study arms varied only in a higher percentage of males being randomized to the study arm using the SYDNEY device (74.3%) compared with the AI arm (44.1%). A single PTC was reported during the unsupervised injections (0.5%; 1 of 196 injections; 95% CI, 0.0%–3.2%). This event was classified as patient related as opposed to device related. No PTCs occurred during supervised injections. Mean LDL-C reductions from baseline at week 4 were 66.2% with SYDNEY and 51.2% with the AI; after adjustment for sex differences between groups, mean LDL-C reductions were 63.5% and 53.9%, respectively. LDL-C reductions persisted for 16 weeks. The most common adverse event was upper respiratory tract infection (3 with SYDNEY and 0 with the AI during weeks 0–4).

Implications: The SYDNEY device allowed for a single 2-mL injection of alirocumab 300 mg, providing substantial LDL-C reductions with no new product technical issues or no new safety concerns compared with the currently marketed 1-mL AI device. In conclusion, the 2-mL SYDNEY device provides patients with the possibility of injecting the 300-mg alirocumab dose as a single injection. ClinicalTrials.gov identifier: NCT03415178. (*Clin Ther*. 2020;42:94–107) © 2019 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Key words: alirocumab, autoinjector, device usability, PCSK9 inhibitor, self-administration, SYDNEY device.

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INTRODUCTION

Alirocumab is a fully human monoclonal antibody to proprotein convertase subtilisin/kexin type 9 (PCSK9) that significantly reduces LDL-C and cardiovascular events versus controls.[1,2] Alirocumab is dosed using various regimens, including 75 mg (every 2 weeks) q2w, 150 mg q2w, and 300 mg every 4 weeks (q4w).[3]

The alirocumab 300 mg q4w dosing regimen (300 mg q4w with possible dose adjustment to 150 mg q2w at week 12) significantly reduced LDL-C versus placebo and was well tolerated in the Phase III ODYSSEY CHOICE I (Study to Evaluate the Efficacy and Safety of an Every Four Weeks Treatment Regimen of Alirocumab (REGN727/SAR236553) in Patients With Primary Hypercholesterolemia) study.[4] At week 24, the least-squares (LS) mean change from baseline in LDL-C levels was −58.8% with alirocumab 300 mg q4w and −51.6% with alirocumab 75 mg q2w (0.1% reduction with placebo) in patients receiving background statin (both $p < 0.0001$ vs placebo).[4]

Monoclonal antibodies, such as alirocumab, have solubility constraints at high concentrations[5]; the maximum possible concentration of alirocumab for therapeutic use is approximately 150 mg/mL. Therefore, because the currently marketed autoinjector (AI) has a 1-mL volume, administration of 300 mg of alirocumab requires 2 separate injections of 150 mg. To facilitate the 300-mg q4w dosing regimen, the 2-mL SYDNEY device was developed that permits a single injection of 300 mg of alirocumab.

The current report presents the results of an assessment of the ease of use and acceptability of the large-volume 2-mL SYDNEY device when used by patients in supervised and unsupervised settings. We compared the SYDNEY device with the currently marketed 1-mL AI to calibrate the pharmacokinetic properties, efficacy, and safety against the current standard.

METHODS

This study was a multicenter, randomized, open-label, 16-week study, with 2 parallel arms for the first 4 weeks and then a single arm for the subsequent visits through week 12. A 1-month follow-up assessment was performed at week 16. The study was conducted in the United States between March 29 and August 10, 2018. The study design is shown in Figure 1.

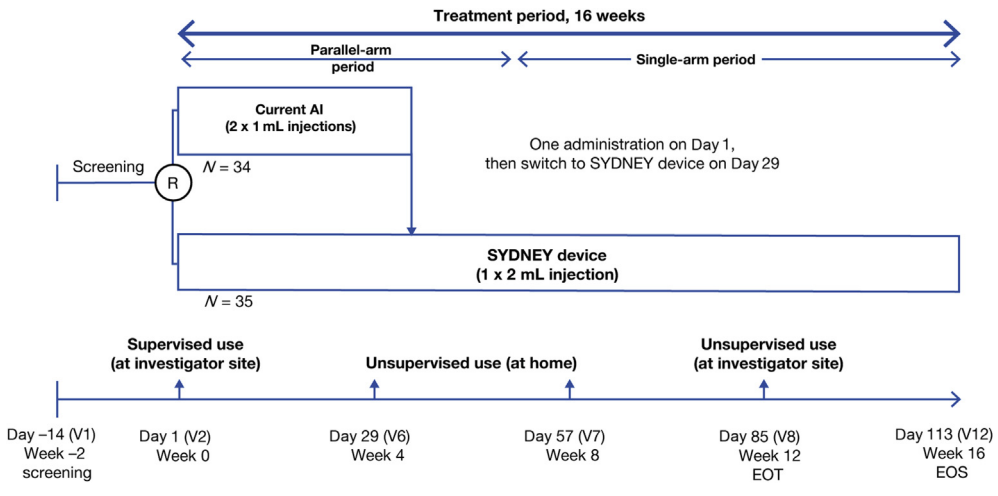

Figure 1. Study design. Blue arrow indicates alirocumab 300-mg SC administration. All administrations were self-injected, and training was given before day 1 self-injection. Supervised was defined as guidance provided, unsupervised as no guidance provided and patient was alone, and observed as no guidance provided and patient was on site. AI = autoinjector; EOS = end of study; EOT = end of treatment; R = randomization; V = visit.

Study Participants

Patients (≥18 years of age) had heterozygous familial hypercholesterolemia or hypercholesterolemia with high or very high cardiovascular risk, defined as coronary heart disease, non-coronary heart disease cardiovascular disease, and other risk factors (Supplemental Table I).

The study included randomized patients with hypercholesterolemia not controlled despite a stable daily dose of statin (atorvastatin [20 or 40 mg] or rosuvastatin [10 or 20 mg]) for at least 4 weeks before the screening visit (week −2), with or without other lipid-lowering therapy. Eligible patients had LDL-C levels ≥70 mg/dL (≥1.81 mmol/L) at the screening visit and were receiving a stable dose of lipid-lowering therapy (including statin) for at least 4 weeks before screening and from screening to randomization. The previous use of any device for PCSK9 inhibitor administration, participation in any clinical trial for a PCSK9 inhibitor, and levels of fasting serum triglycerides >400 mg/dL (>4.52 mmol/L) at screening excluded patients from this study. All patients provided written informed consent. The study protocol received approval from the appropriate local US health authority ethics committee (independent ethics committees and/or institutional review boards). Supplemental Table I lists the full inclusion and exclusion criteria.

The study included randomized patients who received supervised, self-administered alirocumab 300 mg via 1 injection with the SYDNEY device (Figure 2A) or 2 injections with the approved AI (Figure 2B) for the first dose at week 0. All patients then self-administered unsupervised alirocumab 300 mg q4w using SYDNEY at weeks 4, 8, and 12.

Before randomization, all patients received instructions in self-injection using both devices at the investigational site. Randomization occurred after the satisfactory completion of injection training (as determined by investigator or designee). The first injection (week 0), using the AI or SYDNEY, occurred at the investigational site by the patient under direct supervision by site staff; patients were monitored for at least 30 min after their first injection.

The currently marketed device, the 1-mL AI, delivers 2 separate 1-mL injections of 150 mg/mL alirocumab for the 300-mg q4w dosing regimen. The SYDNEY device is a 2-step disposable device

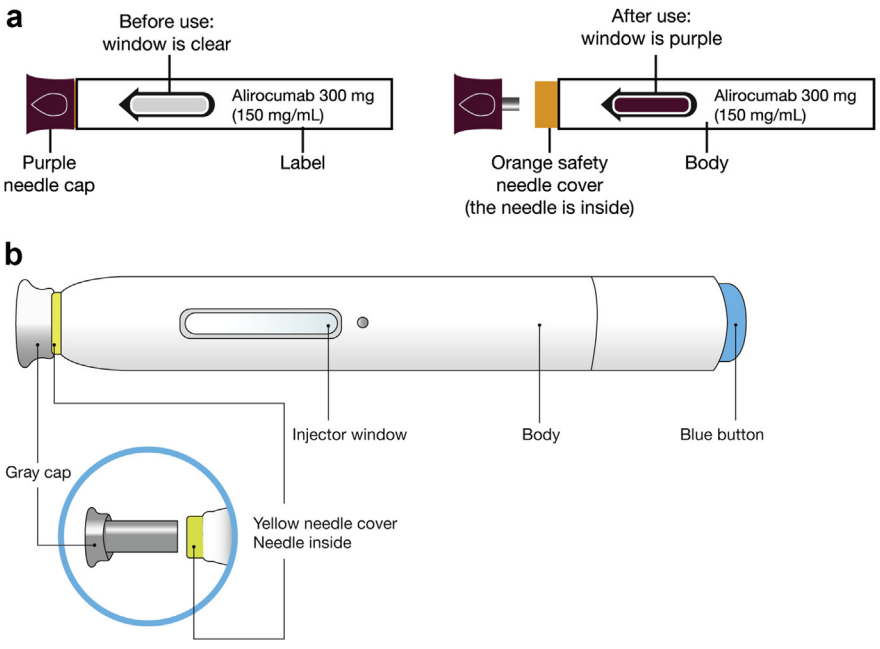

Figure 2. The 2-mL SYDNEY study device (A) and the autoinjector device (B).

designed to deliver 2 mL of 150 mg/mL of alirocumab subcutaneously in ≤20 s. The main functional difference, other than the injected volume between the new SYDNEY device and the current AI device, is that there is 1 fewer step for preparation of the injection with SYDNEY because there is no longer the need to depress a button to initiate the injection.

Primary Objective and Study End Points

The primary study objective was the collection of 12 weeks of real-use (usability) data in the unsupervised setting. The primary study end point was the proportion of product technical complaints (PTCs) related to the unsupervised injections on weeks 4, 8, and 12. The supplementary material provides further details on the definition and identification of PTCs.

Secondary end points included the proportion of PTCs from the supervised injections (week 0, day 1) for each device (AI and SYDNEY); alirocumab pharmacokinetic parameters; free and total PCSK9 levels measured using pharmacokinetic serum samples (as previously described[6]); antidrug antibodies (ADAs), including neutralizing antibodies assessed throughout the study (as previously described[7]); percentage and absolute change from baseline in LDL-C at weeks 4, 8, 12, and 16; and safety, including treatment-emergent adverse events (AEs), serious AEs, and AEs of special interest (including injection-site reactions), assessed throughout the study.

In this study, the LDL-C levels were estimated using Friedewald formula unless triglyceride values were >400 mg/dL (4.52 mmol/L), in which case LDL-C levels were measured via beta quantification. Specific validated ELISAs were used to determine free and total PCSK9 levels and total alirocumab levels (Regeneron Pharmaceuticals, Inc., Tarrytown, NY). The lower limits of detection were 31.2 ng/mL for free PCSK9, 156 ng/mL for total PCSK9, and 78 ng/mL for alirocumab; values below these levels are set to 0 for presentation of results.

Treatment acceptability was assessed with 3 patient questionnaires. The injection experience questionnaire included questions about specific aspects of using the device at weeks 0, 4, 8, and 12. The patient perspective questionnaire aimed to provide understanding of the patient experience and satisfaction associated with the use of the SYDNEY device at week 12 (after the last study drug injection). The 22-item validated patient-reported Injection-Treatment Acceptance Questionnaire assessed patient acceptance of self-injection treatments at week 12 and included 5 domain sources (perceived efficacy, acceptance of side effects, injection self-efficacy, injection convenience, and overall acceptance) as well as a total score.[8,9] The sponsor of the SYDNEY study developed the injection experience questionnaire and patient perspective questionnaire to assess patient experience and perspective on some more specific characteristics of AI devices that are not included in the Injection-Treatment Acceptance Questionnaire. Both the injection experience questionnaire and patient perspective questionnaire have been validated in a separate content validation study (conducted by ICON Clinical Research Ltd, Dublin, Ireland).

Statistical Analysis

Sample size was based on empirical considerations. Considering a dropout rate of 10%, we planned to randomize 66 patients (ratio 1:1) to ensure 60 evaluable patients overall: a group of 33 patients to use SYDNEY through the entire study and a group of 33 patients to use the AI for the first injection (supervised) then switch to SYDNEY for the subsequent 3 unsupervised injections. Between the 2 groups, 180 unsupervised injections were expected to occur.

The primary end point was analyzed in the safety population for the single-arm period, which included all randomized patients who received at least 1 dose or part of a dose of study treatment. Expecting a maximum of 3 PTCs for the 180 injections (observed PTC rate of 1.67%) with SYDNEY, the upper bound of the 2-sided 95% CI calculated with the Wilson score method was estimated to be no higher than 5.2%.

All secondary device-related end points were analyzed in the safety population using descriptive statistics. In addition, 95% CIs for the number of PTCs and the number and percentage of patients with any PTCs are provided using the Wilson score method.

The LDL-C percentage change calculation at week 4 included the modified intention-to-treat (mITT) population of the parallel-arm period with an ANCOVA model. In this model, the treatment group was assigned as the fixed effects and the baseline value as the continuous covariate. The mITT

population of the parallel-arm period included all randomized patients who received at least 1 dose or part of a dose, and who had an evaluable LDL-C value at baseline and an on-treatment LDL-C value within the week 4 analysis window. The LS means and 95% CIs were provided for the SYDNEY and AI groups and for the difference between them. Percentage and absolute change from baseline in LDL-C levels at weeks 8, 12, and 16 were summarized descriptively on the mITT population of the single-arm period (defined as for the parallel-arm period but for analysis windows from week 8 to week 16).

Safety data were presented on the safety populations of the parallel-arm and single-arm periods and were analyzed by descriptive statistics. Further details on the safety population, the treatment-emergent AE parallel-arm and single-arm periods, the pharmacokinetic population, and the patient questionnaires are provided in the supplementary material. In a post hoc analysis, LDL-C was analyzed in the mITT population of the parallel-arm period using an ANCOVA model with fixed categorical effect of the treatment group (SYDNEY or the AI) and sex, as well as the continuous fixed covariate of corresponding baseline value.

RESULTS

A total of 69 patients were randomized: 34 to the AI arm and 35 to the SYDNEY arm. Figure 3 shows the patient disposition in a CONSORT diagram. Baseline characteristics were similar between arms, except for a higher percentage of males in the SYDNEY (74.3%) versus the AI arm (44.1%) (Table I). At

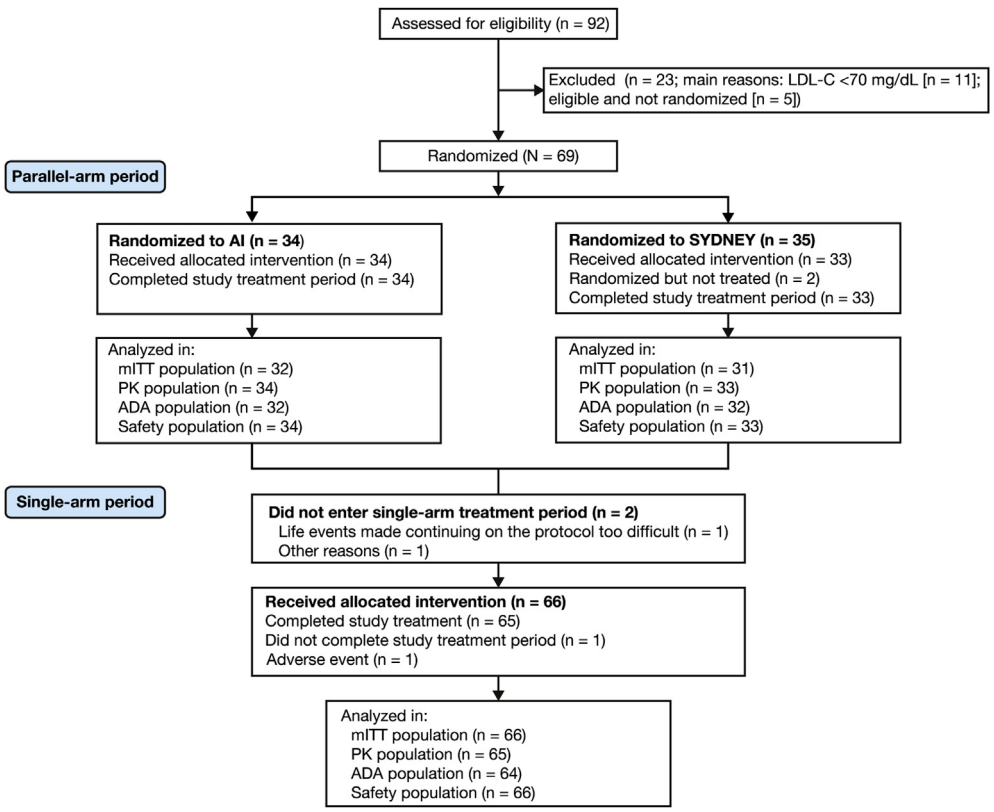

Figure 3. Patient disposition. AI, autoinjector; ADA, antidrug antibody; mITT = modified intention to treat; PK = pharmacokinetic.

Table I. Baseline characteristics (randomized population).

	AI (N = 34)	**SYDNEY** (N = 35)
Age, mean (SD)	65.1 (8.6)	65.4 (8.1)
Sex, male, n (%)	15 (44.1)	26 (74.3)
Race, white, n (%)	24 (70.6)	31 (88.6)
BMI, kg/m^2, mean (SD)	32.2 (6.2)	31.9 (5.6)
HeFH, n (%)	1 (2.9)	1 (2.9)
Statin, n (%)	34 (100)	34 (97.1)
Atorvastatin	29 (85.3)	27 (77.1)
Rosuvastatin	5 (14.7)	7 (20.0)
Any LLT other than statin, n (%)	7 (20.6)	9 (25.7)
CHD, n (%)	18 (52.9)	19 (54.3)
Acute MI	4 (11.8)	9 (25.7)
Silent MI	3 (8.8)	1 (2.9)
Unstable angina	1 (2.9)	3 (8.6)
Coronary revascularization procedure	15 (44.1)	16 (45.7)
Stable angina pectoris	4 (11.8)	3 (8.6)
Clinically significant asymptomatic coronary heart disease	11 (32.4)	13 (37.1)
Non-CHD CVD	10 (29.4)	9 (25.7)
Ischemic stroke	2 (5.9)	5 (14.3)
Peripheral arterial disease	4 (11.8)	4 (11.4)
Abdominal aortic aneurysm	3 (8.8)	0
Atherosclerotic renal artery stenosis	0	1 (2.9)
Carotid artery disease	5 (14.7)	6 (17.1)
Other risk factors	22 (64.7)	18 (51.4)
Moderate chronic kidney disease	3 (8.8)	1 (2.9)
Type 2 diabetes mellitus	20 (58.8)	16 (45.7)
10-year fatal CVD risk SCORE ≥5%	2 (5.9)	3 (8.6)
Patients having received the first injection, n (%)	34 (100)	33 (94.3)*
Location of alirocumab injection, n (%)		
Abdomen	14 (41.2)	12 (34.3)
Thigh	20 (58.8)	21 (60.0)
Lipids, mean (SD), mg/dL [mmol/L]		
LDL-C	98.6 (24.3) [2.56 (0.63)]	91.0 (15.0) [2.36 (0.39)]
<70 mg/dL [<1.81 mmol/L], n/N (%)	3/34 (8.8)	1/34 (2.9)
≥70 to <100 mg/dL [≥1.81 to <2.59 mmol/L], n/N (%)	16/34 (47.1)	25/34 (73.5)
≥100 to <130 mg/dL [≥2.59 to <3.37 mmol/L], n/N (%)	11/34 (32.4)	7/34 (20.6)
≥130 to <160 mg/dL [≥3.37 to <4.14 mmol/L], n/N (%)	4/34 (11.8)	1/34 (2.9)

(*continued on next page*)

Table I. (*Continued*)

	AI (N = 34)	**SYDNEY** (N = 35)
Total cholesterol	175.4 (30.3) [4.54 (0.79)]	167.8 (21.9) [4.35 (0.57)]
HDL-C	51.4 (11.0) [1.33 (0.29)]	48.9 (11.6) [1.27 (0.30)]
Fasting TGs, median (Q1:Q3)	108.5 (90.0:143.0) [1.23 (1.02:1.62)]	129.0 (87.0:182.0) [1.46 (0.98:2.06)]

AI, autoinjector; BMI, body mass index; CHD, coronary heart disease; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; HeFH, heterozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; MI, myocardial infarction; SCORE, systematic coronary risk evaluation; SD, standard deviation; TG, triglyceride.

* In the SYDNEY study, 1 patient received no injection (withdrew from study before Day 1) and was considered not treated, and another patient received 1 injection in error using a training AI kit and was considered not treated for the parallel-arm period and treated for the single arm period.

baseline, the mean (SD) LDL-C level was 98.6 (24.3) mg/dL (2.56 [0.63] mmol/L) in the AI group and 91.0 (15.0) mg/dL (2.36 [0.39] mmol/L) in the SYDNEY group; the proportion of patients with baseline LDL-C levels ≥70 to <100 mg/dL (≥1.81 to <2.59 mmol/L) was higher in the SYDNEY group (73.5%) than in the AI group (47.1%) (Table I). Other baseline lipid parameters were generally similar between the treatment groups.

During the parallel-arm period, all randomized patients in the AI group received 2 alirocumab 150-mg injections at week 0, and 33 randomized patients (94.3%) in the SYDNEY group received 1 alirocumab 300-mg injection at week 0 (Figure 3). Two patients randomized to the SYDNEY arm did not receive treatment in the parallel-arm period; 1 patient withdrew consent before day 1, and 1 patient received the AI training kit in error (Table I). Two patients (1 each from the SYDNEY and AI arm) did not enter the single-arm period because of life events and other reasons (Figure 3). In the single-arm period, 66 patients received 300-mg injections with the SYDNEY device, resulting in 196 unsupervised SYDNEY injections. The treatment compliance as assessed by mean (SD) injection frequency during the single-arm period was 28.1 (0.6) days.

Efficacy Evaluation

A single PTC was reported from the unsupervised injections at week 4 (0.5%; 1 of 196 injections; 95% CI, 0.0%−3.2%) and classified as patient related as opposed to device related (Table II). For this PTC, the patient reported leaking of medication during the injection; however, subsequent investigation of the submitted device revealed no defect; therefore, the complaint was characterized as related to the patient's use of the device. Leaking during self-injection with an AI device sometimes happens in cases of premature removal of the device before the injection is complete. No PTCs were reported associated with the supervised injections at week 0 in either treatment group (Table II).

The LS mean LDL-C reductions from baseline at week 4 were 66.2% with SYDNEY and 51.2% with AI; these reductions persisted for 16 weeks (Table II and Figure 4). The LS mean LDL-C reductions were 63.5% and 53.9%, respectively, after adjustment for sex differences between the groups (Table II).

Safety Evaluation

A total of 17 patients experienced treatment-emergent AEs during the parallel-arm period, including 5 patients (14.7%) in the AI group and 12 (36.4%) in the SYDNEY group (Table III). Only 1 patient reported a treatment-emergent AE that led to treatment discontinuation in the parallel-arm period; this was a case of alanine aminotransferase >5 times the upper limit of normal (1 patient [1.3%] in the SYDNEY arm). From baseline to week 4, the most common AE was upper respiratory tract infection (3 with SYDNEY and 0 with the AI). A single event of mild injection−site reaction occurred in 1 patient in the SYDNEY arm during the parallel period (Table III). The investigator considered this mild

Table II. Primary endpoint and key secondary endpoints.

		SYDNEY
Single-arm period		
Primary end point		
Number of unsupervised injections at Weeks 4, 8, and 12 (safety population)		196
SYDNEY-associated PTCs, n (%) [95% CI]	1 (0.5) [0.0%–3.2%]	
Device-related, n (%)	0	
Patient-related, n (%)	1 (0.5)	
Key secondary end points	**AI**	**SYDNEY**
Parallel-arm period		
mITT population, n	32	31
Absolute change from baseline in LDL-C at Week 4, LS mean (SE), mg/dL [mmol/L]	−50.2 (3.9) [−1.30 (0.10)]	−62.1 (4.0) [−1.61 (0.10)]
Difference vs AI, LS mean (SE)	−12.0 (5.7) [−0.31 (0.15)]	
Adjustment for sex	−52.3 (4.0) [−1.35 (0.10)]	−60.0 (4.0) [−1.55 (0.10)]
Difference vs AI, LS mean (SE)	−7.7 (5.9) [−0.20 (0.15)]	
Change from baseline in LDL-C at Week 4, LS mean (SE), %	−51.2 (4.4)	−66.2 (4.4)
Difference vs AI, LS mean (SE)	−15.0 (6.3)	
Adjustment for sex	−53.9 (4.4)	−63.5 (4.4)
Difference vs AI, LS mean, (SE)	−9.6 (6.5)	
Safety population, n	34	33
Number of PTCs at supervised injections at Week 0, n (%)	0	0

AI, autoinjector; CI, confidence interval; LDL-C, low-density lipoprotein cholesterol; LS, least squares; mITT, modified intention-to-treat; PTC, product technical complaint; SD, standard deviation; SE, standard error.

injection–site reaction as related to alirocumab injection (swelling).

In the single-arm period, 23 patients (34.8%) reported treatment-emergent AEs. Besides urinary tract infections (4 patients [6.1%]), no other treatment-emergent AEs occurred in >5% of patients. No deaths were reported in this study. Investigators considered treatment-emergent AEs of 3 patients (4.5%) as related to alirocumab injection (musculoskeletal pain, alanine aminotransferase increased, blood creatine kinase increased, and contusion).

Overall, 1 patient in the SYDNEY group had preexisting positive ADA status at baseline. During the parallel-arm period, treatment-emergent positive ADA assay responses for binding antibodies were observed in 2 patients (6.3%) in the AI group and in 1 patient (3.1%) in the SYDNEY group. During the single-arm period, 2 treatment-emergent positive ADA assay responses (3.3%) were observed. All ADA-positive samples exhibited low titers. None of the ADA-positive samples were positive in the neutralizing ADA assay. In all patients with positive ADA status (parallel- and single-arm periods), no AE trends were identified.

Pharmacokinetic Evaluation

Mean baseline free and total PCSK9 concentrations were similar across the 2 device groups (Figure 5). After single-dose administration using the AI or

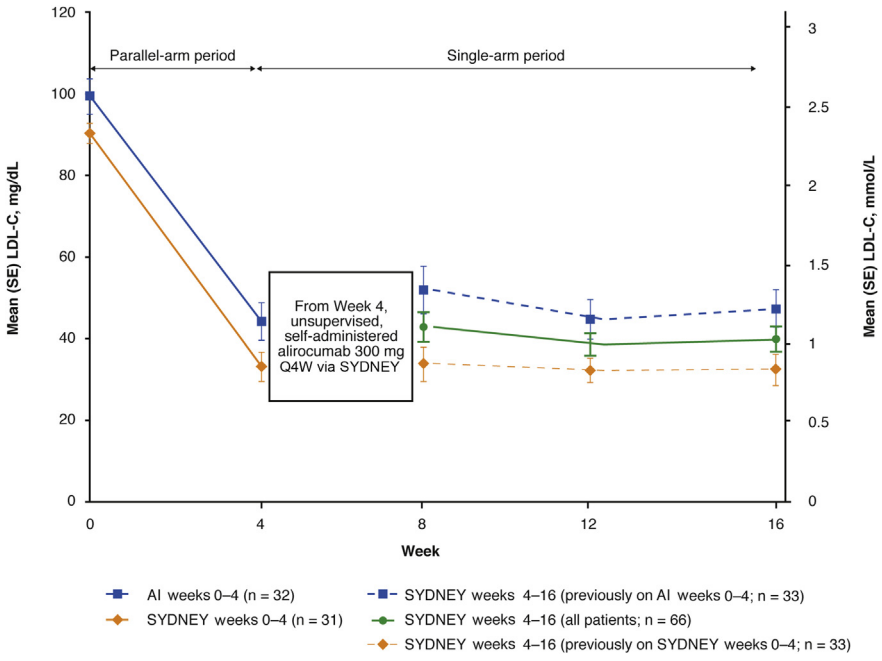

Figure 4. Mean (SE) LDL-C over time (modified intention-to-treat population). AI = autoinjector.

SYDNEY, mean free PCSK9 concentrations decreased to undetectable levels at week 1, whereas total PCSK9 levels increased. The time courses of mean alirocumab concentrations obtained after administration of both devices (AI and SYDNEY) were similar (Figure 6A). Steady state appeared to be reached from week 4 for the SYDNEY device (Figure 6B).

Evaluation of Patient Questionnaires

During the parallel-arm period, most patients found the AI and SYDNEY devices "very easy" to use, with mean patient experience scores ≥9.8 for both devices (score ranged from 1 [very difficult] to 10 [very easy]) (Supplemental Table II). At weeks 4, 8, and 12, the SYDNEY device continued to receive high patient experience scores during the single-arm period (Supplemental Table II). The mean patient perspective score was ≥9.7 in all assessments ("very satisfied"), and most patients were "very confident" in using the SYDNEY device (mean [SD] patient confidence score, 9.9 [0.4]) (Supplemental Table III). For the SYDNEY device, the mean (SD) overall acceptance score was 93.08 (9.94) at week 12 (score ranged from 0 to 100) (Supplemental Table IV).

DISCUSSION

This study found that, in a clinical setting, the new 2-mL SYDNEY device was overall well tolerated, without any significant technical issues compared with the current AI. The primary end point measured by the proportion of PTCs on the SYDNEY device for 196 unsupervised injections during the single-arm period (weeks 4–12) was 0.5% (1/196; 95% CI, 0.0%–3.2%; patient related), and no PTCs were reported during the supervised injection on day 1. Similarly, in other clinical studies across different therapy areas, AI devices were associated with few PTCs.[10–12]

We observed a difference in percentage reduction in LDL-C from baseline at week 4 with a 15% (12.0 mg/dL [0.31 mmol/L]) greater decrease with the SYDNEY device (–66.2%) compared with the AI (–51.2%). A difference in the distribution of the sexes between the 2 arms, with a higher proportion of men in the SYDNEY arm, may partially have contributed to this difference because women may not respond as well as men to alirocumab treatment. Previously, mild heterogeneity of treatment effect according to sex was observed in the ODYSSEY LONG TERM study,

Table III. Safety overview of the parallel-arm and single-arm periods (safety population).

Parallel-arm period, n (%)	**AI** (N = 34)	**SYDNEY** (N = 33)
TEAEs	5 (14.7)	12 (36.4)
Treatment-emergent SAEs	1 (2.9)	1 (3.0)
TEAE leading to discontinuation	0	1 (3.0)
Injection-site reactions	0	1 (3.0)
AEs of special interest		
Pregnancy of female patient/female partner of male patient	0	0
Symptomatic overdose (serious or non-serious) with study treatment/non-study treatment	0	0
Increase in alanine aminotransferase*	0	1 (3.0)
General allergic events†	0	1 (3.0)
Local injection site reactions (requiring consultation with another physician for evaluation of hypersensitivity/allergy)	0	1 (3.0)
Neurological events requiring additional examination/ procedures and/or referral to a specialist	0	0
Neurocognitive events	0	0
TEAEs occurring in ≥ 5**% of patients, preferred term**		
Upper respiratory tract infection	0	3 (9.1)
Arthralgia	0	2 (6.1)
Contusion	2 (5.9)	1 (3.0)

Single-arm period, n (%)	**SYDNEY (N = 66)**
TEAEs	23 (34.8)
Treatment-emergent SAEs	2 (3.0)
TEAE leading to discontinuation	0
Injection site reactions	0
AEs of special interest	
Pregnancy of female patient/female partner of male patient	0
Symptomatic overdose (serious or non-serious) with study treatment/non-study treatment	0
Increase in alanine aminotransferase*	3 (4.5)
General allergic events†	1 (1.5)
Local injection site reactions (requiring consultation with another physician for evaluation of hypersensitivity/allergy)	0
Neurological events requiring additional examination/ procedures and/or referral to a specialist	0
Neurocognitive events	0
TEAEs occurring in ≥ 5% of patients, preferred term	
Urinary tract infection	4 (6.1)

AE, adverse event; ALT, alanine aminotransferase; SAE, serious adverse event; TEAE, treatment-emergent adverse event; ULT, upper limit of normal. TEAEs were those events that developed or worsened or became serious during the TEAE period. TEAE period of the parallel-arm period: defined as the time from the first injection to the day before the second injection for patients entering into the single-arm period or to 70 days after the first injection for patients not entering into the single-arm period. TEAE period of the single-arm period: defined as the time from the second injection up to the day of last injection + 70 days. Serious adverse events were defined as any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, or is a medically important event. Adverse events of special were prespecified in the study protocol, as listed in the Table above.

* Increase in ALT defined as: ALT ≥3 times ULT (if baseline ALT <ULN) or ALT ≥2 times the baseline value (if baseline ALT>ULN).

† The selection of preferred terms for general allergic events is based on Standardized MedDRA Queries (SMQs): hypersensitivity (broad + narrow) excluding the following preferred terms: infusion site dermatitis, infusion site hypersensitivity, infusion site rash, infusion site urticaria, injection site dermatitis, injection site hypersensitivity, injection site rash, injection site urticaria and injection site vasculitis.

which assessed the alirocumab 150-mg q2w dosing regimen.[2] After adjustment for sex, the difference in percentage reduction in LDL-C from baseline at week 4 was less pronounced (9.6%), with a decrease of −63.5% for SYDNEY and −53.9% for the AI. The percentage changes in LDL-C from baseline throughout this study showed a consistent difference between the 2 groups despite the fact that all patients received alirocumab with the SYDNEY device from week 4 to the study end. Therefore, the difference observed in percentage reduction in LDL-C between the SYDNEY and AI arms was likely not related to the device and was probably a chance finding. Background statin treatment was comparable

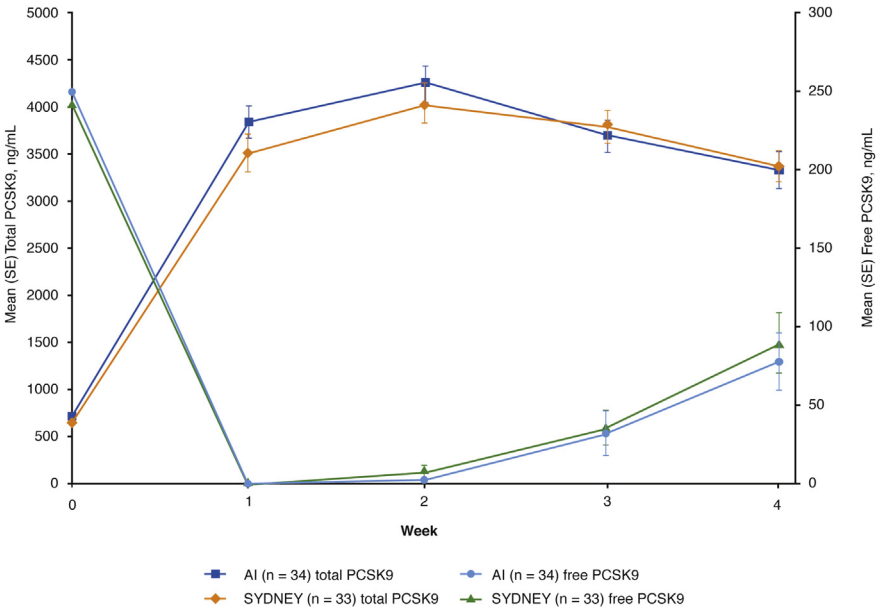

Figure 5. Total and free PCSK9 concentrations over time during treatment period in the parallel-arm period (pharmacokinetic population). Total and free PCSK9 concentrations below the lower limit of quantification (equal to 156 ng/mL for total PCSK9 and 31.2 ng/mL for free PCSK9) are set to zero. PCSK9 = proprotein convertase subtilisin/kexin type 9.

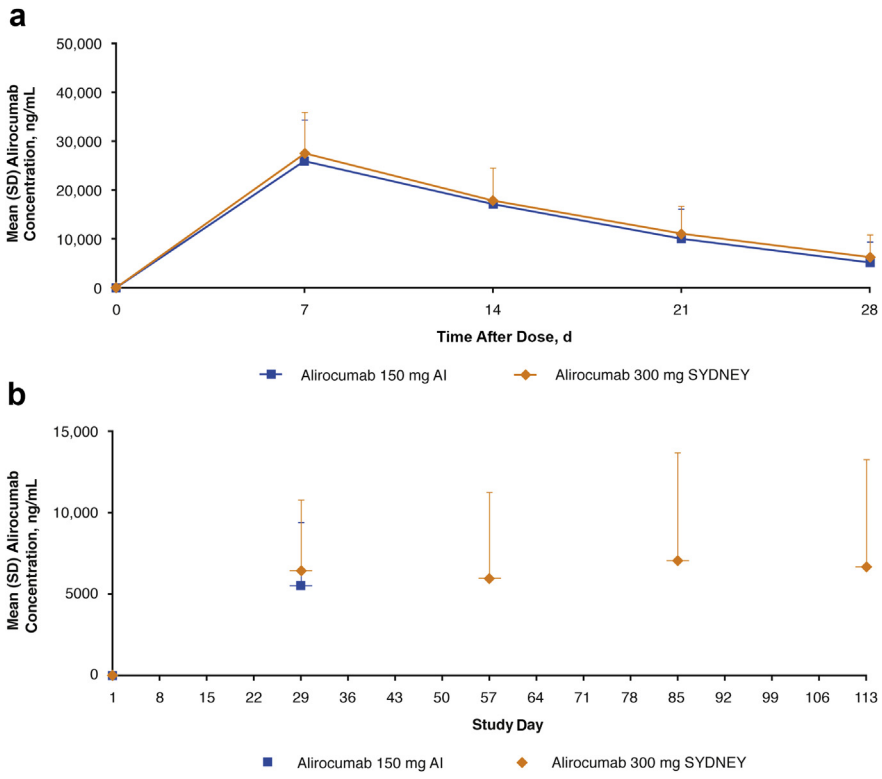

Figure 6. Mean (SD) alirocumab concentration after administration using the AI or SYDNEY. Time profile of patients (A) after a single dose on day 1 and (B) after multiple doses on days 1 to 113 (pharmacokinetic population).

between the 2 groups at baseline; however, medication adherence data are not available to rule out potential confounding factors related to lipid-lowering therapy. A substantial and clinically meaningful decrease in LDL-C with the SYDNEY device was maintained at weeks 8, 12, and 16.

Compared with the AI, alirocumab pharmacokinetic parameters observed with the SYDNEY device were similar. After administration, free PCSK9 levels, representing unbound PCSK9 available to interact with the low-density lipoprotein receptor, were reduced to undetectable levels as expected at 7 days with both AI and SYDNEY. Levels gradually increased in subsequent weeks until the next dose. Total PCSK9 concentrations, representing all circulating PCSK9, including inactive alirocumab-bound PCSK9, increased from baseline after the first alirocumab dose. Reductions in free PCSK9 were consistent with the observed reductions in LDL-C.[6] Furthermore, the free PCSK9 reductions were similar to those observed between weeks 21 and 24 in patients on background statin who received alirocumab 300-mg q4w throughout CHOICE I.[4]

In this study, the generation of ADAs was low, and none of the ADA-positive samples were positive in the neutralizing ADA assay. This finding is consistent with ADA data reported for CHOICE I and a pooled analysis of 10 Phase III ODYSSEY studies that used the 75- and 150-mg q2w dosing regimens.[4,7] Overall, the SYDNEY device was well tolerated, with no new relevant tolerability findings. The safety profile was similar to the alirocumab 300-mg q4w dosing regimen used in the CHOICE I study.[4]

Patient acceptance of the SYDNEY device was good based on the results of patient questionnaires on injection experience, patient perspective, and

injection-treatment acceptance. These results, as well as the excellent treatment adherence during the single-arm period (mean injection frequency of 28.1 days), suggest that, in clinical practice, the SYDNEY device would not deter most patients from self-administering alirocumab. Similar results were previously reported in an alirocumab study that assessed patient and physician perceptions of the ease of use and acceptance of the AI device and the prefilled syringe.[13]

A limitation of this study is the relatively short 16-week study duration for LONG TERM usability and acceptability assessment of alirocumab administration via the SYDNEY device. Despite this short duration, the 196 unsupervised SYDNEY injections administered during the study were considered an adequate amount to assess the potential utility and patient acceptability of this new device. In addition, the unblinded nature of the study (ie, the use of the AI or SYDNEY devices were visible to the participants and investigators) might have introduced a bias in terms of safety reporting.

In this study, the SYDNEY device allowed for a single 2-mL injection of alirocumab 300 mg, providing a similar pharmacokinetic profile and significant LDL-C reductions with no product technical issues or safety concerns compared with the current 1-mL AI device. In conclusion, the SYDNEY 2-mL device provides patients with a safe and convenient option to inject the 300-mg dose of alirocumab as a single injection.

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APPENDIX A. SUPPLEMENTARY DATA

Methods

Product technical complaints (PTCs) were defined as complaints reported on the patient complaint form that triggered an investigation by the Device Department, and were categorized as either device-related, patient-related, or undetermined. If the event was considered relating to an issue with the device such as a fault or malfunction, it was considered device-related. If the event was considered not related to the function of the device, but for instance to how the patient used the device (e.g. an issue with injection technique) it was considered patient-related. Complaints categorized as not related to the device or the patient were not considered as PTCs. This definition was used for both primary and secondary endpoints.

A possible complaint identified by the investigator following the patient diary review and the patient interview triggered the completion of the patient complaint form by the investigator. The completed patient complaint form and the corresponding device (both elements referred to as the "complaint sample") were sent to the Research & Development complaint office, where the type of complaint was determined. All complaint samples which were potentially due to device issue or patient use were sent to Site Frankfurt Devices/PTC Center where, after an investigation, the complaint was classified as device-related, patient-related, undetermined, or not related to device or patient.

The safety population consisted of all randomized patients who received at least 1 dose or part of a dose. The treatment-emergent adverse event (TEAE) parallel-arm period was defined as the time from the first injection to the day before the second injection for patients entering into the single arm period, or to 70 days after the first injection, whichever came first. The TEAE single-arm period was defined as the time from the second injection up to the day of last injection +70 days.

The pharmacokinetics (PK) population consisted of all randomized patients who received at least 1 dose or part of a dose and had at least 1 evaluable blood sample for PK that was used for analysis of alirocumab and proprotein convertase subtilisin/kexin type 9 concentrations.

The patient questionnaires were analyzed with descriptive statistics. Raw values were summarized quantitatively and qualitatively by visit. Moreover, for the Injection-Treatment Acceptance Questionnaire, the 5 domain scores and the total score were summarized quantitatively.

Supplementary Table 1. SYDNEY study patient inclusion and exclusion criteria.

Inclusion criteria

I 01. Patients were in either category A or B (below) and were not adequately controlled with a stable daily dose of atorvastatin (20 mg or 40 mg) or rosuvastatin (10 mg or 20 mg) for ≥4 weeks prior to the screening visit (Week −2), with or without other LLT.

- Patients with HeFH*

OR

- Non-FH patients with high and very-high cardiovascular risk, including patients with coronary heart disease (CHD), non-CHD CVD, and other risk factors:
  - Very high CV risk was defined as a history of documented CHD, ischemic stroke, transient ischemic attack, carotid artery occlusion >50% without symptoms, carotid endarterectomy or carotid artery stent procedure, peripheral arterial disease, abdominal aortic aneurysm, renal artery stenosis, renal artery stent procedure, type 1 or type 2 diabetes mellitus with target organ damage.
  - High CV risk was defined as a calculated 10-year fatal CVD risk SCORE ≥5% (1), moderate chronic kidney disease, type 1 or type 2 diabetes mellitus without target organ damage, or HeFH.
  - Documented CHD included 1 or more of the following:
    - Acute myocardial infarction.
    - Silent myocardial infarction.
    - Unstable angina.

Supplementary Table 1. (*Continued*)

- Coronary revascularization procedure (eg, percutaneous coronary intervention or coronary artery bypass graft surgery).
- Clinically significant CHD diagnosed by invasive or non-invasive testing (such as coronary angiography, stress test using treadmill, stress echocardiography or nuclear imaging).

○ Non-CHD CVD included 1 or more of the following:

- Documented previous ischemic stroke with a focal ischemic neurological deficit that persisted more than 24 h, considered as being of atherothrombotic origin. CT or MRI had to be performed to rule out hemorrhage and non-ischemic neurological disease.
- Peripheral arterial disease.
- Abdominal aortic aneurysm.
- Atherosclerotic renal artery stenosis.
- Carotid artery disease (transient ischemic attacks or >50% obstruction of a carotid artery).

○ Other risk factors:

- Documented moderate chronic kidney disease as defined by 30 $\leq$ eGFR <60 mL/min/1.73 m^2 for $\geq$3 months, including the screening visit.
- Type 1 or type 2 diabetes mellitus.
- A calculated 10-year fatal CVD risk SCORE $\geq$5% (ESC/EAS guidelines for the management of dyslipidemias).[1]

I 02. Patient willing and able to self-inject for the duration of the study.

I 03. Signed written informed consent form.

Exclusion criteria

E 01. LDL-C <70 mg/dL (<1.81 mmol/L) at the screening visit.

E 02. Currently taking a daily dose of statin that is not atorvastatin 20 mg or 40 mg, or rosuvastatin 10 mg or 20 mg.

E 03. Not on a stable dose of LLT (including statin) for $\geq$4 weeks prior to the screening visit and from screening to randomization.

E 04. Use of fibrates other than fenofibrate within 4 weeks of the screening visit or between screening and randomization visits.

E 05. Use of red yeast rice products within 4 weeks of the screening visit or between screening and randomization visits.

E 06. Plasmapheresis treatment within 2 months prior to the screening visit, or patients who had plans to receive it.

E 07. Patients who were planned to undergo scheduled PCI, CABG, carotid or peripheral revascularization during the study.

E 08. History of New York Heart Association Class III or IV heart failure within the past 12 months.

E 09. Age <18 years or legal age of majority at the screening visit, whichever is greater.

E 10. Known history of homozygous FH.

E 11. Previous use of any device for PCSK9 inhibitor administration, or participation in any clinical trial for a PCSK9 inhibitor.

E 12. Conditions/situations such as:

- Any clinically significant abnormality identified at the time of screening that in the judgment of the investigator or any sub-investigator would preclude safe completion of the study or constrain endpoints assessment, eg, major systemic diseases, patients with short life expectancy.
- Investigator or any sub-investigator considered patients as inappropriate for this study for any reason, eg:
  - ○ Those deemed unable to meet specific protocol requirements, eg, scheduled visits,
  - ○ Those deemed unable to administer or tolerate LONG TERM injections as per the patient or the investigator,

(*continued on next page*)

Supplementary Table 1. (*Continued*)

- ○ Investigator or any sub-investigator, pharmacist, study coordinator, other study staff, or relative thereof directly involved in the conduct of the protocol, etc,
- ○ Presence of any other conditions (eg, geographic, social ….), actual or anticipated, that the investigator felt would restrict or limit the patient's participation for the duration of the study.

E 13. Patients who had taken any investigational drugs within 1 month or 5 half-lives, whichever is longer.

E 14. Patients who withdrew consent during the screening period (patient who was not willing to continue or fails to return).

E 15. Laboratory findings during the screening period (not including randomization labs) with the following values:

- TGs >400 mg/dL (>4.52 mmol/L) at the screening visit (Week –2). Note: 1 repeat lab was allowed.
- Positive serum pregnancy test in women of childbearing potential.
- eGFR <30 mL/min/1.73 m^2 according to 4-variable modification of diet in renal disease equation.
- ALT or AST >3 *x* ULN (1 repeat lab was allowed).
- CK > 3 *x* ULN (1 repeat lab was allowed).

E 16. All contraindications to the background therapies or warning/precaution of use (when appropriate) as displayed in the respective national product labeling.

E 17. History of a serious hypersensitivity reaction to alirocumab (including hypersensitivity vasculitis and hypersensitivity reactions requiring hospitalization).

E 18. Pregnant or breast-feeding women.

E 19. Women of childbearing potential not protected by highly-effective method(s) of birth control (as defined in the informed consent form and/or in a local protocol addendum) and/or who are unwilling or unable to be tested for pregnancy.

ALT, alanine transaminase; AST, aspartate aminotransferase; CABG, coronary artery bypass graft; CHD, coronary heart disease; CK, creatinine kinase; CT, computed tomography; CVD, cardiovascular disease; EAS, European Atherosclerosis Society; eGFR, estimated glomerular filtration rate; ESC, European Society of Cardiology; FH, familial hypercholesterolemia; HeFH, heterozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; LLT, lipid-lowering therapy; MI, myocardial infarction; MRI, magnetic resonance imaging; PCI, percutaneous coronary intervention; PCSK9, proprotein convertase subtilisin/kexin type 9; SCORE, systematic coronary risk evaluation; TG, triglycerides; ULN, upper limit of normal; WHO, World Health Organization.

*Diagnosis of HeFH had to be made either by genotyping or by clinical criteria. For those patients not genotyped, the clinical diagnosis was based on either the WHO criteria/Dutch Lipid Clinical Network criteria with a score >8 points or the Simon Broome register diagnostic criteria with a criterion for definite FH.

[1]Perk J, De Backer G, Gohlke H, et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). *Eur Heart J*. 2012; 33:1635–1701.

Supplementary Table 2. Summary of injection experience questionnaire for the parallel-arm period (Week 0) and single arm period (Weeks 4, 8 and 12; safety population).

Mean score* (SD) [n respondents]	Parallel-arm period		Single-arm period		
	Week 0		Week 4	Week 8	Week 12
	AI (N = 34)	SYDNEY (N = 33)	SYDNEY (N = 66)	SYDNEY (N = 66)	SYDNEY (N = 66)
Inspect the medication label on the AI to make sure you have the right product and dose	9.9 (0.2) [34]	9.9 (0.2) [33]	9.9 (0.4) [66]	9.9 (0.3) [65]	9.8 (0.8) [64]
Look through the AI window to check the appearance of the medication	10.0 (0.2) [34]	9.9 (0.5) [33]	10.0 (0.3) [66]	9.9 (0.3) [65]	9.9 (0.3) [64]
Pull off the cap	9.9 (0.5) [34]	9.8 (0.4) [33]	9.9 (0.4) [66]	10.0 (0.2) [65]	9.9 (0.4) [64]
Press the yellow (orange) safety needle cover down against the skin	9.9 (0.4) [34]	9.9 (0.2) [33]	9.7 (0.9) [66]	9.8 (1.2) [65]	9.8 (0.4) [64]
Push the button to start the injection	9.9 (0.4) [34]	N/A	N/A	N/A	N/A
Watch the window to check the progress of the injection	9.9 (0.5) [34]	9.9 (0.4) [33]	9.8 (0.5) [66]	9.8 (0.7) [64]	9.8 (0.6) [64]
Hold the AI in place at the injection site for the entire injection	9.8 (0.6) [34]	9.8 (0.6) [33]	9.8 (0.6) [66]	9.9 (0.4) [64]	9.9 (0.3) [64]
Determine when the injection is completed	9.8 (0.7) [34]	9.8 (0.6) [33]	9.8 (0.7) [66]	9.9 (0.4) [64]	9.9 (0.3) [64]
Overall ease of use	9.9 (0.2) [34]	9.8 (0.5) [33]	9.9 (0.5) [66]	9.9 (0.3) [64]	9.8 (0.5) [64]

*Possible answers ranged from 1 ("very difficult") to 10 ("very easy"). AI, autoinjector; SD, standard deviation.

Supplementary Table 3. Summary of patient perspective questionnaire in the single-arm period.

Mean score (SD) [n respondents]	SYDNEY (N = 66)
The size of the AI*	9.7 (0.8) [65]
The ease of holding the AI in your hand*	9.8 (0.6) [65]
The 2-step operation: remove the cap, press the AI against your skin to start the injection*	9.9 (0.4) [65]
Length of time it took to complete the injection*	9.9 (0.3) [65]
The fact that the needle is hidden before and after the injection*	10.0 (0.3) [65]
Once monthly injection*	10.0 (0.1) [65]
Have you previously used another AI or pen injector to deliver a different medication? n (%)	*n* = 65
I don't remember	1 (1.5)
Yes	11 (16.9)
No	53 (81.5)
How confident are you that you used the SYDNEY device correctly in this study?†	9.9 (0.4) [65]

AI, autoinjector; SD, standard deviation.
*Possible answers ranged from 1 ("very dissatisfied") to 10 ("very satisfied").
†Possible answers ranged from 1 ("not confident at all") to 10 ("very confident").

Supplementary Table 4. Summary of I-TAQ in the single-arm period.

Mean score (SD) [n respondents]	SYDNEY (N = 66)
Perceived efficacy*	91.4 (14.5) [65]
Acceptance of side effects*	6.5 (23.1) [65]
Injection self-efficacy*	96.0 (8.5) [65]
Injection convenience*	90.4 (13.1) [65]
Total score*	71.1 (8.2)
Overall acceptance	93.1 (9.9)

I-TAQ, Injection-Treatment Acceptance Questionnaire; SD, standard deviation.
*Each score is converted to a 0–100 scale, with higher scores indicating more satisfaction.
†Calculated as follows (perceived efficacy + acceptance of side effects + injection self-efficacy + injection convenience)/4.