SYNOPSIS

Title of the study: A multicenter, double-blind, randomized, placebo-controlled study to evaluate the efficacy, safety and tolerability of AVE5530 when added to ongoing stable statin therapy at high doses in patients with severe primary hypercholesterolemia (EFC10841)

Investigator(s): [redacted]

Study center(s): The study was conducted at 98 centers in 13 countries (Australia, Belgium, Bulgaria, Canada, Czech Republic, France, Israel, the Netherlands, Russia, Slovakia, South Africa, Ukraine, and USA).

Publications (reference): Not applicable

Study period:

Date first patient enrolled: 07 October 2008

Date last patient completed: 11 June 2009

Phase of development: 3

Objectives: The primary objective of this study was to assess the efficacy of AVE5530 25 mg and 50 mg as an add-on to ongoing stable high dose statin therapy on calculated low-density lipoprotein cholesterol (LDL-C) levels in comparison with placebo (ie statin alone) over a period of 12-weeks in patients with primary severe hypercholesterolemia. In addition, the following evaluations were to be performed at Week 12:

- the percent change from baseline in LDL-C measured by ultracentrifugation
- the proportion of patients achieving National Cholesterol Education Program – Adult Treatment Panel (NCEP-ATP) III target goals for calculated LDL-C.

The secondary objectives of this study were to assess:

- the effects of AVE5530 25 mg and 50 mg in comparison with placebo as an add-on to ongoing stable high dose statin therapy on total cholesterol and apolipoprotein-B (Apo-B) levels over 12 weeks
- the safety and tolerability of AVE5530 25 mg and 50 mg over a period of 12 weeks, 6 months, and 12 months, including liposoluble vitamin levels in all patients in selected centers (approximately 30% of the study population) over 12 weeks and 12 months.

The other objectives of this study were to assess:

- the effects of AVE5530 25 mg and 50 mg on calculated LDL-C, total cholesterol, and Apo-B levels over a period of 6 months and 12 months
- the effects of AVE5530 25 mg and 50 mg on high density lipoprotein cholesterol (HDL-C), triglycerides, apolipoprotein-A1 (Apo-A1), high sensitive C-reactive protein (hs CRP), and lipoprotein (a) (Lp[a]) levels over 12 weeks, 6 months, and 12 months
- the AVE5530 plasma concentrations in a subset of the patients.

The study was terminated prematurely after all 643 patients were randomized, following the Sponsor's decision to discontinue the AVE5530 program based on the efficacy results from a separate study. The monitoring therefore focused on the safety profile, based on the reporting of adverse events, and on the primary efficacy criterion. As a result, the analysis (as defined in the statistical analysis plan) focused on these data and the results are presented in this synopsis-style report. Appendices attached to this synopsis-style report were chosen to provide relevant information.

Methodology: This was a randomized, double-blind, fixed-dose, placebo-controlled, unbalanced parallel group (1:2:1, AVE5530 25 mg and AVE5530 50 mg to placebo) stratified by type of statin used (atorvastatin, simvastatin, and rosuvastatin), and multinational study.

Number of patients:	Planned: 600
	Randomized: 643
	Treated: 642
	Efficacy: 633
	Safety : 642
	Pharmacokinetics : 16
Diagnosis and criteria for inclusion: Adult patients of at least 18 years of age, with severe primary hypercholesterolemia and confirmed insufficient control with ongoing statin treatment at the highest doses (atorvastatin 80 mg, simvastatin 80 mg, or rosuvastatin 40 mg) were included in the study.	
Investigational product: AVE5530	
Dose: 25 mg or 50 mg	
Administration: Oral, in the evening with dinner	
Batch number(s): [redacted]	
Duration of treatment: 50 to 54 weeks of investigational product (AVE5530 or placebo) **Duration of observation:** up to 18 months	
Reference therapy: Placebo	
Dose: Not applicable	
Administration: Oral, in the evening with dinner	
Batch number(s): [redacted]	
Criteria for evaluation: The current report is a synopsis-style report, and as such, only the results of the primary analysis of the primary efficacy variable were assessed and are presented. Adverse events and potentially clinically significant abnormalities for renal function, liver function, and creatine phosphokinase (CPK) data were evaluated and analyzed using descriptive statistics.	

Statistical methods:

Efficacy: The primary efficacy variable was the percent change from baseline in calculated LDL-C at Week 12 Endpoint. The Week 12 Endpoint value was defined as the on-treatment Week 12 evaluation or if missing, the last, prior to Week 12, postbaseline, on-treatment evaluation carried forward.

The primary analysis model was an analysis of covariance (ANCOVA) with AVE5530 treatment (3 levels: placebo, AVE5530 25 mg, and AVE5530 50 mg) and type of statin (3 levels: atorvastatin 80 mg, simvastatin 80 mg, and rosuvastatin 40 mg) as fixed factors, and baseline LDL-C as covariate. In this model, each dose of AVE5530 was compared to placebo using appropriate contrast, and 95% confidence interval of the difference versus placebo (not adjusted for multiple comparisons). The Hochberg procedure was used in order to control the overall type-I error rate at the 5% level when testing the effect of AVE5530 versus placebo.

The primary efficacy population was the modified intent-to-treat (mITT) population. For the purpose of this synopsis-style report, where only the primary efficacy parameter was analyzed, it is defined as all randomized patients who received at least 1 dose of investigational product, and had a baseline and at least 1 postbaseline assessment during the first 12-week phase for the primary efficacy parameter. In this population, the treatment groups are as randomized.

Safety: Adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 12 and summarized by treatment group, using descriptive statistics. Potentially clinically significant abnormalities for creatinine, liver function, and CPK were summarized by treatment group, using descriptive statistics. The safety population consisted of all patients who were randomized and exposed to at least 1 dose of the investigational product. In this population, the treatment groups are based on investigational product actually received.

Pharmacokinetics: Individual patient AVE5530 plasma concentrations were analyzed, but no statistical analyses were performed.

Summary:

A summary of the study design and a study flow chart is provided after the synopsis.

Summary of populations: Table 1 summarizes the randomized, efficacy, and safety populations. One patient was considered to be not randomized but received 50 mg AVE5530 for 34 days ([redacted]). This patient is not counted in the safety population; however, the patient's adverse events are listed in [redacted].

Table 1 - Summary of analysis populations - n(%)

		AVE5530		
	Placebo	**25 mg**	**50 mg**	**All**
Randomized population	160 (100%)	160 (100%)	323 (100%)	643 (100%)
Efficacy population				
Modified Intent-to-Treat (mITT)	157 (98.1%)	157 (98.1%)	319 (98.8%)	633 (98.4%)
Safety population	160	160	322	642

Note: The safety population patients are tabulated according to the treatment actually received (as treated)
For the other populations, patients are tabulated according to their randomized treatment

Of the 643 randomized patients, 642 were exposed to at least 1 dose of investigational product. None of the randomized and treated patients completed the study as planned. A total of 620 patients discontinued treatment as of 29 April 2009, the date on which the program was terminated ([redacted]). The majority of these patients discontinued due to termination of the program and were counted in the category "other reason" (Table 2).

Table 2 - Summary of patient disposition – end of treatment - n(%) - randomized population

		AVE5530		
	Placebo (N=160)	**25 mg (N=160)**	**50 mg (N=323)**	**All (N=643)**
Randomized and not treated	1 (0.6%)	0	0	1 (0.2%)
Randomized and treated	159 (99.4%)	160 (100%)	323 (100%)	642 (99.8%)
Completed the overall study treatment period	0	0	0	0
Did not complete the overall study treatment period	159 (99.4%)	160 (100%)	323 (100%)	642 (99.8%)
Reasons for permanent treatment discontinuation				
Adverse event	1 (0.6%)	4 (2.5%)	5 (1.5%)	10 (1.6%)
Lack of efficacy	0	0	0	0
Poor compliance with protocol	1 (0.6%)	0	1 (0.3%)	2 (0.3%)
Lost to follow-up	0	0	0	0
Other [a]	157 (98.1%)	156 (97.5%)	317 (98.1%)	630 (98.0%)
Withdrawal due to subject's request	1 (0.6%)	2 (1.3%)	5 (1.5%)	8 (1.2%)

Note: Percentages are calculated using the number of randomized patients as denominator
[a] Includes treatment discontinuation due to program discontinuation by sponsor

Exposure: The safety population in this study included 642 patients randomized and exposed to at least 1 dose of the investigational product. The mean number of days patients were exposed to the investigational product was similar between treatment groups. Patient exposure, based on the safety population, is presented in Table 3.

Table 3 - Exposure to study drug - safety population

		AVE5530	
	Placebo (N=160)	**25 mg (N=160)**	**50 mg (N=322)**
Duration of study treatment exposure (days)			
Number	160	160	322
Mean (SD)	63.3 (39.5)	62.0 (37.8)	62.1 (37.5)
Median	55.0	55.0	55.0
Min : Max	10 : 196	5 : 196	2 : 205
Duration of study treatment exposure by category [n(%)]			
Number	160	160	322
≤ 42 days (6 weeks)	61 (38.1%)	53 (33.1%)	117 (36.3%)
]42-63] days (]6-9] weeks)	47 (29.4%)	54 (33.8%)	102 (31.7%)
]63-84] days (]9-12] weeks)	22 (13.8%)	24 (15.0%)	47 (14.6%)
]84-183] days (12 weeks-6 months)	26 (16.3%)	25 (15.6%)	51 (15.8%)
]183-274] days (]6-9] months)	4 (2.5%)	4 (2.5%)	5 (1.6%)
Cumulative duration of study treatment exposure by category [n(%)]			
Number	160	160	322
≥ 1 day	160 (100%)	160 (100%)	322 (100%)
> 42 days (6 weeks)	99 (61.9%)	107 (66.9%)	205 (63.7%)
> 63 days (9 weeks)	52 (32.5%)	53 (33.1%)	103 (32.0%)
> 84 days (12 weeks)	30 (18.8%)	29 (18.1%)	56 (17.4%)
> 183 days (6 months)	4 (2.5%)	4 (2.5%)	5 (1.6%)

Note: Patients are considered in the group of treatment they actually received

Demographics: Patient demographic characteristics are presented in Table 4.

Table 4 Patient demographics and characteristics at baseline - randomized population

		AVE5530		
	Placebo (N=160)	**25 mg (N=160)**	**50 mg (N=323)**	**All (N=643)**
Age (years)				
Number	160	160	323	643
Mean (SD)	56.9 (11.4)	55.7 (12.3)	56.0 (12.1)	56.1 (12.0)
Median	58.0	57.0	57.0	57.0
Q1 : Q3	51.0 : 65.0	48.0 : 64.0	48.0 : 65.0	49.0 : 65.0
Min : Max	20 : 85	23 : 81	21 : 82	20 : 85
Age group (years) [n(%)]				
Number	160	160	323	643

<45	24 (15.0%)	31 (19.4%)	51 (15.8%)	106 (16.5%)
[45-65[	93 (58.1%)	90 (56.3%)	184 (57.0%)	367 (57.1%)
≥65	43 (26.9%)	39 (24.4%)	88 (27.2%)	170 (26.4%)
Sex [n(%)]				
Number	160	160	323	643
Male	77 (48.1%)	77 (48.1%)	159 (49.2%)	313 (48.7%)
Female	83 (51.9%)	83 (51.9%)	164 (50.8%)	330 (51.3%)
Race [n(%)]				
Number	160	160	323	643
Caucasian/White	149 (93.1%)	148 (92.5%)	303 (93.8%)	600 (93.3%)
Black	6 (3.8%)	5 (3.1%)	6 (1.9%)	17 (2.6%)
Asian/Oriental	0	0	4 (1.2%)	4 (0.6%)
Other	5 (3.1%)	7 (4.4%)	10 (3.1%)	22 (3.4%)
Ethnicity [n(%)]				
Number	160	160	323	643
Hispanic	8 (5.0%)	6 (3.8%)	9 (2.8%)	23 (3.6%)
Non Hispanic	152 (95.0%)	154 (96.3%)	314 (97.2%)	620 (96.4%)
Weight (kg)				
Number	160	160	323	643
Mean (SD)	83.7 (15.1)	84.0 (17.5)	82.8 (17.1)	83.3 (16.7)
Median	82.1	83.1	81.5	82.2
Q1 : Q3	73.8 : 93.4	71.1 : 94.2	70.6 : 94.0	72.0 : 94.0
Min : Max	43 : 122	46 : 132	44 : 159	43 : 159
Height (cm)				
Number	159	160	322	641
Mean (SD)	168.2 (8.9)	169.3 (11.1)	168.8 (10.0)	168.8 (10.0)
Median	168.0	167.5	168.0	168.0
Q1 : Q3	162.0 : 174.0	162.0 : 178.0	161.0 : 177.0	162.0 : 176.0
Min : Max	150 : 191	146 : 198	148 : 193	146 : 198
Framingham score				
Number	160	160	323	643
<10%	51 (31.9%)	60 (37.5%)	129 (39.9%)	240 (37.3%)
10-20%	40 (25.0%)	42 (26.3%)	76 (23.5%)	158 (24.6%)
>20%	69 (43.1%)	58 (36.3%)	118 (36.5%)	245 (38.1%)
Actual background statin therapy (before randomization)				
Number	160	160	323	643

Atorvastatin 80mg	56 (35.0%)	55 (34.4%)	113 (35.0%)	224 (34.8%)
Simvastatin 80mg	48 (30.0%)	48 (30.0%)	97 (30.0%)	193 (30.0%)
Rosuvastatin 40mg	56 (35.0%)	57 (35.6%)	113 (35.0%)	226 (35.1%)

Efficacy results: The means and least squares means in percent changes from baseline at the Week 12 endpoint showed decreases in LDL-C in all groups. The decreases in both AVE5530 groups were greater than in the placebo group and these decreases were statistically significant using the ANCOVA model (Table 5).

Table 5 - Calculated low-density lipoprotein cholesterol percentage change from baseline at Week 12 Endpoint – modified intent-to-treat population

		AVE5530	
LDL-C (mg/dL)	**Placebo (N=157)**	**25 mg (N=157)**	**50 mg (N=319)**
Baseline			
Number	150	148	302
Mean (SD)	138.5 (32.3)	139.7 (34.4)	138.6 (33.2)
Median	130.8	132.8	130.3
Min : Max	85 : 225	89 : 262	80 : 265
Week 12 Endpoint			
Number	150	148	302
Mean (SD)	130.4 (38.5)	118.2 (38.6)	113.8 (35.7)
Median	126.0	114.0	108.5
Min : Max	51 : 324	37 : 220	40 : 294
Percent change from baseline at Week 12 Endpoint			
Number	150	148	302
Mean (SD)	-5.4 (19.4)	-14.7 (22.0)	-16.9 (21.7)
Median	-6.1	-14.1	-16.9
Min : Max	-61 : 107	-66 : 76	-69 : 128
LS Mean (SE)	-5.31 (1.72)	-14.52 (1.73)	-16.81 (1.21)
LS Mean Difference (SE)		-9.21 (2.43)	-11.50 (2.10)
95% CI		(-13.99 to -4.43)	(-15.62 to -7.38)
p-value vs placebo		0.0002*	<.0001*

Note: p-values are based on covariance analysis model with AVE5530 treatment group and type of statin as fixed effects and baseline LDL-C value as covariate.
A * indicates a statistically significant p-value according to Hochberg procedure
Only patients with a baseline and a post-baseline value are included

Safety results:

- **Overview of adverse events**

The incidence of treatment-emergent adverse events (TEAEs) was higher in the AVE5530 25 mg group (31.3%) and the AVE5530 50 mg group (29.5%) compared to the placebo group (24.4%). The incidences of serious TEAEs and TEAEs leading to discontinuation of investigational product were low, and higher in the AVE5530 groups compared to the placebo group. There were no deaths due to TEAEs in this study. An overview of the number of patients with at least 1 TEAE is presented in Table 6.

Table 6 - Overview of treatment-emergent adverse events - safety population

		AVE5530	
	Placebo (N=160)	25 mg (N=160)	50 mg (N=322)
Patients with any TEAE	39 (24.4%)	50 (31.3%)	95 (29.5%)
Patients with any serious TEAE	0	1 (0.6%)	4 (1.2%)
Patients with any TEAE leading to death	0	0	0
Patients with any TEAE leading to permanent treatment discontinuation	1 (0.6%)	4 (2.5%)	5 (1.6%)

n (%) = number and percentage of patients with at least one Treatment Emergent Adverse Event
TEAE : Treatment Emergent Adverse Event

- **Summary of treatment-emergent adverse events**

The most commonly reported TEAEs in the AVE5530 groups and the placebo group belonged to the infections and infestations system organ class (SOC) (6.3% and 9.6% versus 6.9% in the placebo group). There were no notable differences between the AVE5530 groups and the placebo group in TEAEs of gastrointestinal disorders. Treatment-emergent adverse events of myalgia were higher in the AVE5530 groups compared with the placebo group; however a similar trend was not observed for TEAEs of increase in CPK. Treatment-emergent adverse events of increases in alanine aminotransferase occurred more frequently in the AVE5530 25 mg group compared to the AVE5530 50 mg and placebo groups (Table 7). However, there was no imbalance in the number of reports of abnormal liver function tests when all preferred terms were considered. All TEAEs are presented by SOC, high-level group term (HLGT), high-level term (HLT), and preferred term (PT) in [redacted].

Table 7 - Number (%) of patients experiencing at least 1 treatment-emergent adverse event (cut-off: incidence of at least 2% in any treatment group): safety population

		AVE5530	
Primary System Organ Class Preferred Term	Placebo (N=160)	25 mg (N=160)	50 mg (N=322)
Any class	39 (24.4%)	50 (31.3%)	95 (29.5%)
Infections and infestations	11 (6.9%)	10 (6.3%)	31 (9.6%)
Nasopharyngitis	2 (1.3%)	1 (0.6%)	8 (2.5%)
Musculoskeletal and connective tissue disorders	7 (4.4%)	11 (6.9%)	25 (7.8%)
Myalgia	0	4 (2.5%)	6 (1.9%)
Back pain	5 (3.1%)	2 (1.3%)	2 (0.6%)
Investigations	8 (5.0%)	12 (7.5%)	10 (3.1%)
Alanine aminotransferase increased	2 (1.3%)	5 (3.1%)	4 (1.2%)

TEAE: Treatment Emergent Adverse Event, SOC: System Organ Class, PT: Preferred Term
MedDRA version: 12.0
n (%) = number and percentage of patients with at least one TEAE
Note: Table sorted by SOC internationally agreed order and PT sorted by decreasing frequency according to all TEAE summary table
Only SOC with at least one PT with a frequency ≥ 2% in at least one group are presented

- **Summary of serious adverse events**

There were serious TEAEs in the AVE5530 groups and none in the placebo group. One patient had a serious adverse event of abnormal liver function test that was considered, by the investigator, to be related to the investigational product and resulted in unblinding for regulatory purposes. Please refer to [redacted] for the summary table of all serious TEAEs and [redacted] for details presented in the narratives.

Table 8 - Number (%) of patients experiencing at least 1 serious treatment-emergent adverse event – safety population

Primary System Organ Class Preferred Term	Placebo (N=160)	AVE5530 25 mg (N=160)	AVE5530 50 mg (N=322)
Any class	0	1 (0.6%)	4 (1.2%)
Nervous system disorders	0	0	1 (0.3%)
Cerebrovascular accident	0	0	1 (0.3%)
Vascular disorders	0	0	1 (0.3%)
Aortic aneurysm	0	0	1 (0.3%)
Musculoskeletal and connective tissue disorders	0	0	1 (0.3%)
Neck pain	0	0	1 (0.3%)
General disorders and administration site conditions	0	0	1 (0.3%)
Non-cardiac chest pain	0	0	1 (0.3%)
Investigations	0	0	1 (0.3%)
Liver function test abnormal	0	0	1 (0.3%)
Injury, poisoning and procedural complications	0	1 (0.6%)	0
Femur fracture	0	1 (0.6%)	0

TEAE: Treatment Emergent Adverse Event, SOC: System Organ Class, PT: Preferred Term
MedDRA version: 12.0
n (%) = number and percentage of patients with at least one serious TEAE
Note: Table sorted by SOC internationally agreed order and PT sorted by decreasing frequency according to all TEAE summary table

- **Summary of deaths**

There were no treatment-emergent deaths. One patient died during the screening phase ([redacted]).

- **Summary of treatment-emergent adverse events leading to treatment discontinuation**

Discontinuation due to TEAEs occurred more frequently in the AVE5530 groups (2.5% and 1.6%) compared with the placebo group (0.6%) (Table 9). Please refer to [redacted] for details presented in the narratives.

Table 9 - Number (%) of patients experiencing at least 1 treatment-emergent adverse event resulting in permanent treatment discontinuation – safety population

Primary System Organ Class Preferred Term	Placebo (N=160)	AVE5530 25 mg (N=160)	AVE5530 50 mg (N=322)
Any class	1 (0.6%)	4 (2.5%)	5 (1.6%)
Infections and infestations	0	0	1 (0.3%)
Urinary tract infection	0	0	1 (0.3%)

Immune system disorders	0	1 (0.6%)	0
Drug hypersensitivity	0	1 (0.6%)	0
Nervous system disorders	0	0	1 (0.3%)
Lethargy	0	0	1 (0.3%)
Cardiac disorders	0	1 (0.6%)	0
Palpitations	0	1 (0.6%)	0
Gastrointestinal disorders	1 (0.6%)	1 (0.6%)	3 (0.9%)
Constipation	1 (0.6%)	0	1 (0.3%)
Flatulence	0	0	1 (0.3%)
Diarrhoea	0	1 (0.6%)	0
Dyspepsia	0	0	1 (0.3%)
Abdominal distension	0	0	1 (0.3%)
Change of bowel habit	0	0	1 (0.3%)
Skin and subcutaneous tissue disorders	0	1 (0.6%)	1 (0.3%)
Rash generalised	0	0	1 (0.3%)
Skin lesion	0	1 (0.6%)	0
Musculoskeletal and connective tissue disorders	0	2 (1.3%)	1 (0.3%)
Myalgia	0	2 (1.3%)	0
Back pain	0	0	1 (0.3%)
General disorders and administration site conditions	0	0	1 (0.3%)
Fatigue	0	0	1 (0.3%)
Investigations	0	0	1 (0.3%)
Blood creatine increased	0	0	1 (0.3%)
Blood phosphorus increased	0	0	1 (0.3%)
Blood urea increased	0	0	1 (0.3%)
Electrocardiogram qt prolonged	0	0	1 (0.3%)
Protein total increased	0	0	1 (0.3%)

TEAE: Treatment Emergent Adverse Event, SOC: System Organ Class, PT: Preferred Term
MedDRA version: 12.0
n (%) = number and percentage of patients with at least one TEAE leading to treatment discontinuation
Note: Table sorted by SOC internationally agreed order and PT sorted by decreasing frequency accroding to all TEAE summary table

- **Potentially clinically significant abnormalities**

There were few patients in the AVE5530 groups and the placebo group who had laboratory values for creatinine, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and CPK that met the criteria for a potentially clinically significant abnormality. Summary tables are provided in [redacted] and details about cases of interest are provided in the narratives in [redacted].

Pharmacokinetic results: Information regarding AVE5530 plasma concentrations is provided in [redacted].

Conclusions: [redacted]
Date of report: 16-Oct-2009