SYNOPSIS

Title of the study: A multicenter, double-blind, randomized, 12-month, placebo-controlled study to evaluate the lipid-lowering effect, safety and tolerability of AVE5530 25 mg/day and 50mg/day when added to ongoing stable statin therapy (HMG-CoA reductase inhibitors) in patients with primary hypercholesterolemia (EFC6910)

Investigator(s): [redacted]

Study center(s): The study was conducted at 130 centers in 17 countries (Australia, Belgium, Canada, Czech Republic, Denmark, France, Germany, Hungary, Israel, the Netherlands, New Zealand, Norway, Poland, Russia, Spain, Sweden, and the United States of America).

Publications (reference): Not applicable

Study period:

Date first patient enrolled: 07 August 2008

Date last patient completed: 17 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 statin on low-density lipoprotein cholesterol (LDL-C) levels over a period of 12-weeks in patients with hypercholesterolemia.

The secondary objectives of this study were to assess:

- the effects of AVE5530 25 mg and 50 mg on LDL-C over 6 months and 12 months
- the effects of AVE5530 25 mg and 50 mg on total cholesterol and apolipoprotein-B (Apo-B) over 12 weeks, 6 months, and 12 months
- 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 study was terminated prematurely after all 1015 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, parallel-group, 3-arm, placebo-controlled, multicenter and multinational study.

Number of patients:

Planned: 1000

Randomized: 1015

Treated: 1008

Efficacy: 1001

Safety : 1008

Diagnosis and criteria for inclusion: Adult patients of at least 18 years of age, with primary hypercholesterolemia and ongoing statin treatment at the same dose for at least 6 weeks, and LDL-C levels $\geq$100 mg/dL (2.59 mmol/L) at screening (considered insufficiently controlled) 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 creatinine 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 with treatment group as fixed effect, and baseline as covariate. In this model, each dose of AVE5530 was compared to placebo using appropriate contrast, and 95% confidence interval (CI) 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.

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 25 mg AVE5530 for 10 days ([redacted]). This patient is not counted in the safety population; no adverse events were reported for her ([redacted]).

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

		AVE5530		
	Placebo	**25 mg**	**50 mg**	**All**
Randomized population	202 (100%)	404 (100%)	409 (100%)	1015 (100%)
Efficacy population				
Modified Intent-to-Treat (mITT)	199 (98.5%)	402 (99.5%)	400 (97.8%)	1001 (98.6%)
Safety population	201	403	404	1008

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 1015 randomized patients, 1008 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 944 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=202)	**25 mg (N=404)**	**50 mg (N=409)**	**All (N=1015)**
Randomized and not treated	1 (0.5%)	1 (0.2%)	5 (1.2%)	7 (0.7%)
Randomized and treated	201 (99.5%)	403 (99.8%)	404 (98.8%)	1008 (99.3%)
Completed the overall study treatment period	0	0	0	0
Did not complete the overall study treatment period	201 (99.5%)	403 (99.8%)	404 (98.8%)	1008 (99.3%)
Reasons for permanent treatment discontinuation				
Adverse event	7 (3.5%)	11 (2.7%)	8 (2.0%)	26 (2.6%)
Lack of efficacy	0	0	0	0
Poor compliance with protocol	0	0	2 (0.5%)	2 (0.2%)
Lost to follow-up	0	1 (0.2%)	0	1 (<0.1%)
Other [a]	194 (96.0%)	391 (96.8%)	394 (96.3%)	979 (96.5%)
Withdrawal due to subject's request	11 (5.4%)	27 (6.7%)	21 (5.1%)	59 (5.8%)

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 1008 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

	Placebo (N=201)	AVE5530 25 mg (N=403)	AVE5530 50 mg (N=404)
Duration of study treatment exposure (days)			
Number	200	399	403
Mean (SD)	141.8 (35.3)	142.2 (35.0)	142.9 (36.4)
Median	141.0	142.0	143.0
Min : Max	8 : 254	5 : 266	4 : 267
Duration of study treatment exposure by category [n(%)]			
Number	200	399	403
≤ 42 days (6 weeks)	5 (2.5%)	7 (1.7%)	12 (3.0%)
]42-63] days (]6-9] weeks)	0	6 (1.5%)	2 (0.5%)
]63-84] days (]9-12] weeks)	5 (2.5%)	3 (0.7%)	1 (0.2%)
]84-183] days (12 weeks-6 months)	176 (87.6%)	352 (87.3%)	359 (88.9%)
]183-274] days (]6-9] months)	14 (7.0%)	31 (7.7%)	29 (7.2%)
Cumulative duration of study treatment exposure by category [n(%)]			
Number	200	399	403
≥ 1 day	200 (99.5%)	399 (99.0%)	403 (99.8%)
> 42 days (6 weeks)	195 (97.0%)	392 (97.3%)	391 (96.8%)
> 63 days (9 weeks)	195 (97.0%)	386 (95.8%)	389 (96.3%)
> 84 days (12 weeks)	190 (94.5%)	383 (95.0%)	388 (96.0%)
> 183 days (6 months)	14 (7.0%)	31 (7.7%)	29 (7.2%)

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

Demographics: Patient demographic characteristics are presented in Table 4. The majority of patients were taking either simvastatin (48.1%) or atorvastatin (34.1%) when they entered the study. The distribution of patients taking these statins was generally similar across the treatment groups ([redacted]).

Table 4 - Patient demographics and characteristics at baseline - randomized population

	Placebo (N=202)	AVE5530 25 mg (N=404)	AVE5530 50 mg (N=409)	All (N=1015)
Age (years)				
Number	202	404	409	1015
Mean (SD)	59.7 (9.4)	60.4 (9.1)	60.0 (9.4)	60.1 (9.3)
Median	60.5	61.5	61.0	61.0
Q1 : Q3	54.0 : 66.0	55.0 : 66.5	55.0 : 66.0	55.0 : 66.0
Min : Max	32 : 82	32 : 85	22 : 84	22 : 85

Age Group (years) [n(%)]				
Number	202	404	409	1015
<45	14 (6.9%)	22 (5.4%)	27 (6.6%)	63 (6.2%)
[45-65[	127 (62.9%)	244 (60.4%)	256 (62.6%)	627 (61.8%)
≥65	61 (30.2%)	138 (34.2%)	126 (30.8%)	325 (32.0%)
Sex [n(%)]				
Number	202	404	409	1015
Male	106 (52.5%)	225 (55.7%)	224 (54.8%)	555 (54.7%)
Female	96 (47.5%)	179 (44.3%)	185 (45.2%)	460 (45.3%)
Race [n(%)]				
Number	202	404	409	1015
Caucasian/White	190 (94.1%)	391 (96.8%)	388 (94.9%)	969 (95.5%)
Black	9 (4.5%)	9 (2.2%)	13 (3.2%)	31 (3.1%)
Asian/Oriental	2 (1.0%)	4 (1.0%)	8 (2.0%)	14 (1.4%)
Other	1 (0.5%)	0	0	1 (<0.1%)
Ethnicity [n(%)]				
Number	202	404	409	1015
Hispanic	6 (3.0%)	20 (5.0%)	19 (4.6%)	45 (4.4%)
Non Hispanic	196 (97.0%)	384 (95.0%)	390 (95.4%)	970 (95.6%)
Weight (kg)				
Number	201	404	408	1013
Mean (SD)	82.7 (15.4)	82.7 (15.9)	81.8 (15.2)	82.3 (15.5)
Median	82.6	81.3	79.8	80.5
Q1 : Q3	73.0 : 92.0	71.9 : 91.2	70.6 : 92.1	71.7 : 91.9
Min : Max	50 : 130	50 : 139	50 : 141	50 : 141
Height (cm)				
Number	201	404	408	1013
Mean (SD)	167.7 (10.2)	169.1 (9.9)	168.8 (9.5)	168.7 (9.8)
Median	167.0	169.0	169.0	168.0
Q1 : Q3	160.0 : 176.0	162.0 : 176.0	162.0 : 176.0	162.0 : 176.0
Min : Max	147 : 196	142 : 194	130 : 198	130 : 198
Framinghmam score				
Number	202	404	407	1013
<10%	67 (33.2%)	141 (34.9%)	148 (36.4%)	356 (35.1%)
10-20%	71 (35.1%)	140 (34.7%)	118 (29.0%)	329 (32.5%)
>20%	64 (31.7%)	123 (30.4%)	141 (34.6%)	328 (32.4%)

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 analysis of covariance model (Table 5).

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

LDL-C (mg/dL)	Placebo (N=199)	AVE5530 25 mg (N=402)	AVE5530 50 mg (N=400)
Baseline			
Number	199	400	398
Mean (SD)	130.5 (25.6)	131.5 (28.1)	130.4 (26.6)
Median	126.0	125.0	125.0
Min : Max	83 : 227	83 : 238	86 : 241
Week 12 Endpoint			
Number	199	400	398
Mean (SD)	124.8 (32.8)	112.3 (32.7)	109.6 (32.1)
Median	120.0	106.0	105.0
Min : Max	43 : 306	36 : 263	33 : 234
Percent change from baseline at Week 12 Endpoint			
Number	199	400	398
Mean (SD)	-3.7 (19.8)	-14.2 (19.2)	-15.5 (19.7)
Median	-4.5	-15.2	-16.2
Min : Max	-65 : 68	-61 : 93	-66 : 103
LS Mean (SE)	-3.77 (1.37)	-14.11 (0.97)	-15.55 (0.97)
LS Mean Difference (SE)		-10.35 (1.68)	-11.78 (1.68)
95% CI		(-13.65 to -7.04)	(-15.09 to -8.48)
p-value vs placebo		<.0001*	<.0001*

Note: p-values come from covariance analysis using baseline 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 similar, in the placebo group, 50.2% of patients, compared to the AVE5530 25 mg group (48.9%) and the AVE5530 50 mg group (50.7%). The incidences of serious TEAEs and TEAEs leading to discontinuation of investigational product were low overall, and slightly higher in the placebo group compared to the AVE5530 groups. 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=201)	25 mg (N=403)	50 mg (N=404)
Patients with any TEAE	101 (50.2%)	197 (48.9%)	205 (50.7%)
Patients with any serious TEAE	6 (3.0%)	7 (1.7%)	11 (2.7%)
Patients with any TEAE leading to death	0	0	0
Patients with any TEAE leading to permanent treatment discontinuation	7 (3.5%)	11 (2.7%)	8 (2.0%)

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 belonged to the infections and infestations system organ class (SOC) (20.8% and 20.5% versus 22.9% 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 increases in CPK were reported more frequently in the AVE5530 groups compared to the placebo group (Table 7). All TEAEs are presented by SOC, high level group term, high level term, 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=201)	25 mg (N=403)	50 mg (N=404)
Any class	101 (50.2%)	197 (48.9%)	205 (50.7%)
Infections and infestations	46 (22.9%)	84 (20.8%)	83 (20.5%)
Nasopharyngitis	16 (8.0%)	24 (6.0%)	21 (5.2%)
Upper respiratory tract infection	10 (5.0%)	6 (1.5%)	13 (3.2%)
Influenza	5 (2.5%)	6 (1.5%)	8 (2.0%)
Sinusitis	5 (2.5%)	6 (1.5%)	2 (0.5%)
Nervous system disorders	17 (8.5%)	29 (7.2%)	23 (5.7%)
Headache	14 (7.0%)	15 (3.7%)	10 (2.5%)
Vascular disorders	4 (2.0%)	9 (2.2%)	13 (3.2%)
Hypertension	4 (2.0%)	4 (1.0%)	10 (2.5%)
Respiratory, thoracic and mediastinal disorders	15 (7.5%)	22 (5.5%)	13 (3.2%)
Cough	5 (2.5%)	10 (2.5%)	5 (1.2%)

Gastrointestinal disorders	35 (17.4%)	67 (16.6%)	57 (14.1%)
Diarrhoea	8 (4.0%)	15 (3.7%)	13 (3.2%)
Flatulence	6 (3.0%)	16 (4.0%)	13 (3.2%)
Constipation	5 (2.5%)	11 (2.7%)	9 (2.2%)
Abdominal pain	5 (2.5%)	6 (1.5%)	2 (0.5%)
Musculoskeletal and connective tissue disorders	17 (8.5%)	50 (12.4%)	46 (11.4%)
Back pain	6 (3.0%)	12 (3.0%)	11 (2.7%)
Arthralgia	2 (1.0%)	12 (3.0%)	10 (2.5%)
Investigations	10 (5.0%)	19 (4.7%)	27 (6.7%)
Blood creatine phosphokinase increased	1 (0.5%)	6 (1.5%)	9 (2.2%)

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 $\geq$ 2% in at least one group are presented

- **Summary of serious adverse events**

The incidence of serious TEAEs was low in all treatment groups. Except for the SOC of cardiac disorders, serious TEAEs in the AVE5530 groups were not predominant in any particular SOC (Table 8). Please refer to [redacted] for the summary table of all serious TEAEs and [redacted] for details presented in the narratives. Of note, 1 patient in the AVE5530 25 mg group had a serious posttreatment adverse event of colon adenoma that was considered, by the Investigator, to be related to the investigational product and resulted in unblinding for regulatory purposes. The patient is not counted in Table 8 since the serious adverse event occurred in the posttreatment period.

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

		AVE5530	
Primary System Organ Class Preferred Term	**Placebo (N=201)**	**25 mg (N=403)**	**50 mg (N=404)**
Any class	6 (3.0%)	7 (1.7%)	11 (2.7%)
Infections and infestations	1 (0.5%)	1 (0.2%)	1 (0.2%)
Pyelonephritis acute	0	0	1 (0.2%)
Cellulitis	1 (0.5%)	0	0
Lower respiratory tract infection	0	1 (0.2%)	0
Parotitis	1 (0.5%)	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (0.2%)	0
Rectal cancer metastatic	0	1 (0.2%)	0
Metabolism and nutrition disorders	0	0	1 (0.2%)
Hyperglycaemia	0	0	1 (0.2%)
Ketoacidosis	0	0	1 (0.2%)

Psychiatric disorders	1 (0.5%)	0	0
Bipolar I disorder	1 (0.5%)	0	0
Nervous system disorders	0	1 (0.2%)	0
Vertebrobasilar insufficiency	0	1 (0.2%)	0
Ear and labyrinth disorders	0	0	1 (0.2%)
Vertigo	0	0	1 (0.2%)
Cardiac disorders	3 (1.5%)	2 (0.5%)	2 (0.5%)
Angina pectoris	0	1 (0.2%)	0
Angina unstable	0	1 (0.2%)	1 (0.2%)
Atrial fibrillation	1 (0.5%)	0	0
Coronary artery disease	0	0	1 (0.2%)
Palpitations	1 (0.5%)	0	0
Ventricular tachycardia	0	0	1 (0.2%)
Acute myocardial infarction	1 (0.5%)	0	0
Vascular disorders	0	0	2 (0.5%)
Hypotension	0	0	1 (0.2%)
Varicose vein	0	0	1 (0.2%)
Gastrointestinal disorders	2 (1.0%)	1 (0.2%)	0
Inguinal hernia	0	1 (0.2%)	0
Pancreatitis acute	1 (0.5%)	0	0
Volvulus	1 (0.5%)	0	0
Hepatobiliary disorders	0	0	1 (0.2%)
Cholelithiasis	0	0	1 (0.2%)
Reproductive system and breast disorders	0	1 (0.2%)	1 (0.2%)
Benign prostatic hyperplasia	0	1 (0.2%)	0
Ovarian cyst	0	0	1 (0.2%)
General disorders and administration site conditions	0	0	1 (0.2%)
Non-cardiac chest pain	0	0	1 (0.2%)
Investigations	0	0	1 (0.2%)
Blood creatine phosphokinase increased	0	0	1 (0.2%)

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 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.

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

Discontinuation due to TEAEs occurred more frequently in the placebo group (3.5%) compared with the AVE5530 groups (2.7% and 2.0%) (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=201)	AVE5530 25 mg (N=403)	AVE5530 50 mg (N=404)
Any class	7 (3.5%)	11 (2.7%)	8 (2.0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (0.2%)	0
Rectal cancer metastatic	0	1 (0.2%)	0
Psychiatric disorders	3 (1.5%)	1 (0.2%)	1 (0.2%)
Depression	0	0	1 (0.2%)
Bipolar I disorder	1 (0.5%)	0	0
Confusional state	1 (0.5%)	0	0
Mood altered	1 (0.5%)	0	0
Restlessness	0	1 (0.2%)	0
Nervous system disorders	1 (0.5%)	2 (0.5%)	2 (0.5%)
Headache	1 (0.5%)	1 (0.2%)	1 (0.2%)
Dizziness	1 (0.5%)	0	2 (0.5%)
Paraesthesia	0	1 (0.2%)	0
Lethargy	0	1 (0.2%)	0
Cardiac disorders	1 (0.5%)	0	2 (0.5%)
Coronary artery disease	1 (0.5%)	0	1 (0.2%)
Palpitations	0	0	1 (0.2%)
Ventricular tachycardia	0	0	1 (0.2%)
Vascular disorders	0	1 (0.2%)	0
Blood pressure fluctuation	0	1 (0.2%)	0
Gastrointestinal disorders	3 (1.5%)	4 (1.0%)	2 (0.5%)
Diarrhoea	0	1 (0.2%)	0
Flatulence	0	1 (0.2%)	0
Constipation	0	1 (0.2%)	0
Nausea	0	0	1 (0.2%)
Abdominal pain upper	0	1 (0.2%)	0
Abdominal distension	0	0	1 (0.2%)
Dyspepsia	1 (0.5%)	0	1 (0.2%)

Abdominal pain	1 (0.5%)	2 (0.5%)	0
Volvulus	1 (0.5%)	0	0
Skin and subcutaneous tissue disorders	0	2 (0.5%)	1 (0.2%)
Pruritus allergic	0	1 (0.2%)	0
Rash	0	0	1 (0.2%)
Angioedema	0	1 (0.2%)	0
Musculoskeletal and connective tissue disorders	0	2 (0.5%)	3 (0.7%)
Arthralgia	0	2 (0.5%)	1 (0.2%)
Pain in extremity	0	0	1 (0.2%)
Myalgia	0	0	1 (0.2%)
Muscle spasms	0	0	1 (0.2%)
Muscular weakness	0	1 (0.2%)	0
Reproductive system and breast disorders	0	0	1 (0.2%)
Atrophic vulvovaginitis	0	0	1 (0.2%)
General disorders and administration site conditions	0	0	2 (0.5%)
Fatigue	0	0	1 (0.2%)
Malaise	0	0	1 (0.2%)
Pyrexia	0	0	1 (0.2%)
Investigations	0	2 (0.5%)	1 (0.2%)
Blood creatine phosphokinase increased	0	1 (0.2%)	0
Hepatitis b surface antigen positive	0	0	1 (0.2%)
Weight increased	0	1 (0.2%)	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 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 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].

Conclusions: [redacted]

Date of report: 15-Oct-2009