Drug Substance(s)/ NA Study Code NIS-SA-CRE-2009/01 NIS-GU-CRE-2009/01 Date 03-April-2011	**SYNOPSIS**	(For national authority use only)

Centralized Pan-Middle East Survey on the Undertreatment of Hypercholesterolemia (CEPHEUS)

Study dates		**Phase of development**
First subject enrolled	22 November 2009	NA
Last subject completed	07 July 2010	

Objectives

Primary

- To establish the proportion of patients on lipid-lowering pharmacological treatment reaching the LDL-C goals according to the NCEP ATP III / updated 2004 NCEP ATP III, overall and by country.

Secondary

- To establish the proportion of patients on lipid-lowering pharmacological treatment reaching the LDL-C goals according to the NCEP ATP III / updated 2004 NCEP ATP III in the following sub-populations:
  - Primary/secondary prevention patients,
  - Patients with metabolic syndrome (according to NCEP III definition).
- To establish the proportion of patients on lipid-lowering pharmacological treatment reaching the non HDL-C goals according to the NCEP ATP III / updated 2004 NCEP ATP III (<130 mg/dL), in the sub-population patients with fasting triglycerides >200 mg/dL.
- To identify determinants (e.g. patient and physician characteristics, or recommendations) for undertreatment of hypercholesterolemia. Undertreatment is defined as receiving lipid-lowering pharmacological treatment and not reaching the LDL-C goals according to the NCEP ATP III/ updated 2004 NCEP ATP III / Third Joint European Task Force guidelines.
- To explore physician characteristics associated with the allocation of treatment regimen.

Study design
This was a multi-centre survey of patients who were on lipid-lowering pharmacological treatment in 6 Middle East countries, including Saudi Arabia, United Arab Emirates, Kuwait, Qatar, Bahrain and Oman**.**

Target subject population and sample size
A total number of 5457 subjects were recruited.

Investigational product and comparators: dosage, mode of administration and batch Numbers.
Not applicable.

Duration of treatment
Not applicable. A single visit for every subject.

Variables

- Pharmacokinetic
Not applicable.

- Safety
This was not a therapeutic or a safety study. Only serious adverse events were to be registered throughout the study. No serious adverse event was experienced by any of the included subjects.From the day the informed consent has been signed until the blood sample has been taken, all SAEs had to be reported. All SAEs will be recorded on a SAE reporting form in accordance with local requirements and AstraZeneca procedures for global pharmacovigilance purposes.
Investigators and other site personnel must inform appropriate AstraZeneca representatives of any SAE that occurs in the course of the study within 1 day (i.e. immediately but no later than the end of the next business day) of when he or she becomes aware of it.
The AstraZeneca representative will work with the investigator to compile all the necessary information and ensure that the appropriate AstraZeneca Drug Safety Department receives a report by day one for all fatal and life-threatening cases and by day five for all other SAEs.
The investigator is responsible for informing the Ethics Committee and/or the Regulatory Authority of the SAE as per local requirements. In countries implementing the EU Clinical Trials Directive, this will be taken care of by AstraZeneca.

Statistical methods

Primary variable

The number and percentage of subjects achieving the LDL-C goals, according to the NCEP ATP III / updated 2004 NCEP ATP III guidelines.

Secondary variables

The number and percentage of subjects achieving the LDL-C goals, according to the NCEP ATP III / updated 2004 NCEP ATP III guidelines for several subject subsets.
The number and percentage of subjects achieving LDL-C goals according to the Third Joint European Task Force guidelines, overall and for several subject subsets.
The number and percentage of subjects achieving the non HDL-C goals according to the NCEP ATP III / updated 2004 NCEP ATP III (<130 mg/dL), in the following sub-population: patients with fasting triglycerides >200 mg/dL.
The association between achievement of LDL-C goals, according to the NCEP ATP III / 2004 updated NCEP ATP III / Third Joint European Task Force guidelines, and patient and physician variables, assessed by multivariate logistic regression models.
The approach to the statistical analyses in this project was descriptive in nature. Continuous data have been described by their mean, standard deviation, minimum and maximum. All summaries have been presented on all available data. Categorical data have been described by the number and percentage of subjects in each category. The calculations of proportions have not included the missing category.

Determination of sample size

The primary objective of this survey was to determine the proportion of patients achieving the LDL-C goals, according to the NCEP ATP III / updated 2004 NCEP ATP III guidelines. This outcome measure is described overall and by country. One of the secondary objectives of this survey was to determine the proportion of patients achieving the LDL-C goals, according to the NCEP ATP III / updated 2004 NCEP ATP III guidelines in subgroups of patients within each country: Primary prevention patients, secondary prevention patients, patients with and without metabolic syndrome.
Sample size calculations were based on the need to ensure that the proportion of subjects reporting on the primary and secondary endpoints could be estimated with sufficient precision, overall and on a by-country basis, to represent the heterogeneity of this population. Hence, sample size determination per country was not based on test power considerations but on the confidence limit approach to ensure adequate precision estimates.
The following table 6 provides an overview about the sample sizes needed to achieve a certain precision of estimates given that the expected achieving percentage is 50%.

Table 6- Overview of the width of observed two-sided 95% confidence interval for various sample sizes

Width of the observed two-sided 95% confidence interval	Expected percentage of patients achieving European LDL-C goals	Approximate sample size
+/- 4%	50%	600
+/- 3%	50%	1,067
+/- 2%	50%	2,300

A reasonable requirement on the precision is that the incidence should be determined within +/-2% points, i.e. the length of the two-sided 95% confidence should not exceed 2 percentage points in each direction from the point estimate. Based on these calculations, a sample size of about 2,300 patients was considered sufficient to meet the primary objective of this protocol.
We also wished to estimate the endpoints within +/-2% points for the following subgroups: Primary prevention patients and secondary prevention patients, Patients with and without the metabolic syndrome.
IMS data in Saudi Arabia show that currently 1,128,000 patients are treated with statins, of which 940,000 (80%) in primary prevention and 188,000 (20%) in secondary prevention. The prevalence of metabolic syndrome in patients on lipid-lowering treatment in Saudi Arabia is estimated to be 40% and above. In absence of data for the other Middle East countries participating in this survey, (United Arab Emirates, Kuwait, Oman and Qatar), and not expecting any significant differences, the percentages for Saudi Arabia were applied to all 6 countries.
For a precision of +/-2% points, 2300 patients were needed in the smallest subgroup (e.g. secondary prevention and patients with the metabolic syndrome).
Assuming that, in the Middle East countries participating in this survey, including Saudi Arabia, United Arab Emirates, Bahrain, Kuwait, Oman and Qatar, the proportion of metabolic syndrome patients is similar to the proportion of secondary prevention patients at around 35%, and then a total sample size of about 5000 patients was required.

Subject population
A total number of 5457 subjects were recruited by 177 specialists and primary care physicians located in 6 Middle East countries, including Saudi Arabia, United Arab Emirates, Kuwait, Qatar, Bahrain & Oman.

The subjects were selected and invited to participate into the survey as follows:

- consecutive patients who come in for a regularly scheduled visit to the clinic
- Subjects who drop out of the survey was not replaced.

Subjects fulfilled all of the following criteria:

- Subject must be 18 years of age or older of either gender or race.
- Subject must provide informed consent and comply with the survey procedures.
- Subject is on lipid lowering drug treatment for at least 3 months, with no dose change for a minimum of 6 weeks.

- Subjects who were, unwilling or unable to provide informed consent, were excluded from the study.

Summary of pharmacokinetic results

Not applicable.

Summary of pharmacodynamic results (not applicable)
Not applicable.

Summary of pharmacokinetic/pharmacodynamic correlations
Not applicable

Summary of results
The analysis of the primary and secondary variables as well as baseline assessments and analysis of patient questionnaire data were based on the FAS population. Analysis of the investigator questionnaire was based on the returned questionnaires. The mean age of subjects was 55.56years (SD: 11.29). Subjects were 2201 (41.84 %) female and 3060 (58.16 %) male. The reasons for being pharmacologically treated were primary prevention (n=3773; 71.54%), secondary prevention (n=1438; 27.27%) and familial hypercholesterolemia (n=63; 1.19%). Among the lipid-lowering drugs used, statins (n=5260; 94.43%) and fibrates (n=174; 3.12%) were the most frequent drugs.
Patient questionnaire
Of the 5276 patients with lab data available, (5270; 99.88%) of patients filled at least one question of the patient questionnaire. According to patients:
Only 37.97 %(n=2001) of patients had heard or had been told about LDL-C cholesterol and only 39.75% (n=2095) about the HDL-C cholesterol.
43.91% (n=2304) of patients had been informed about their cholesterol levels.
The physician had given a target cholesterol level to 1992(40.79%) of them.
Since patients first being prescribed a lipid-lowering drug (LLD), most patients (n=4032; 76.96%) were still taking the same drug, 10.94% (n=573) had changed the drug once or twice, 10.35% (n=542) had increased the dose and 1.76% (n=92) had changed the drug several times.(n=3593; 78.18%) of patients were satisfied, (n=1951; 49.94. %) were motivated and (n= 963; 25.20%) were concerned about the way their high cholesterol was being treated.
When asked about the frequency with which the patient was seen by the physician for a check-up of their cholesterol, 10.64% (n=558) indicated to have more than one check up every three months, 39.88% (n=2091) every three months, 29.72% (n=1558) every six months, 10.99% (n=576) once every year, 4.01% (n=210) less than once a year and 1.91% (n=100) had no check-ups.
When asked about how often they forget to take their treatment, 43.32% (n=970) of responders said no more often than once a month, 24.12% (n=540) once every two weeks, 13.80% (n=309) once a week and 18.76% (n=420) more than once a week.
58.46% (n=2983) thought that missing a tablet no more often than once a month would not jeopardise the cholesterol levels, 17.66% (n=901) thought no more often than once every two weeks, 6.27% (n=320) no more than once a week, and 17.62% (n=899) more than once a week.

Investigator questionnaire

All 177(100%) questionnaires sent to investigators, were filled out and collected. Most investigators were male (n=124; 70.86%), they had a mean age of 43.91(SD:8.77), GP or PCP physicians comprised the largest (n=71; 42.01%), followed by cardiologists (31.36; n=53).

According to investigators:

Most investigators (n=155; 87.57%) use guidelines to establish individual target cholesterol levels.

The guidelines used are: the Joint European guideline (SCORE) (14.58%; n=21), NCEP ATP III guidelines (FRAMINGHAM) (n=67; 46.53%), National guidelines (n=27; 18.75%), individual practice guidelines (n=9; 6.25%), and local healthcare authority guidelines (n=13; 9.03%).

44.52 %(n=69) of investigators reported scheduling a visit for cholesterol review every three months, 40 %(n=62) of them for once every six months and 11.61 % (n=18) for once per year.

The mean proportion of LLD most frequently recommended to patients is statins 0.83 (SD: 0.20) of patients, followed by fibrates 0.10 (SD: 0.10).

The mean proportion of 0.50 (SD: 0.23) of patients achieve their target level and stay at this concentration, 0.20 (SD: 0.13) generally stay at their target level but sometimes their cholesterol concentration gets too high, 0.15 (SD: 0.14) never reach their target level and 0.15(SD: 0.12) reached their target level in the past but have since relapsed.

When asked if they feel that a sufficient number of patients reach their target level, 3.39% (n=6) of investigators disagreed strongly, 10.17% (n=18) disagreed, 26.55% (n=47) had a neutral opinion, 46.33% (n=82) agreed and 12.43% (n=22) strongly agreed.

Patients achieving the LDL-C goals recommended by the different guidelines

The percentages of survey patients reaching the LDL-C goal according to the NCEP ATP III, 2004 updated NCEP ATP III, and Third Joint European Task Force (TJETF) guidelines and the main characteristics of patients achieving the LDL-C goal are presented in the table below.

Table I-Patients attaining the LDL-C goal recommended by the different guidelines

		NCEP ATP III		**2004 NCEP ATP III**		**TJETF**	
		N	**%**	**N**	**%**	**N**	**%**
Overall survey		3413	64.69%	2745	52.03%	3148	59.67%
Age	<40	246	66.13%	226	60.75%	191	51.34%
	40-54	1399	63.71%	1200	54.64%	1281	58.33%
	55-70	1401	65.04%	1051	48.79%	1324	61.47%
	>70	362	66.30%	263	48.17%	347	63.55%
Gender	Male	2029	66.31%	1504	49.15%	1877	61.34%
	Female	1374	62.43%	1232	55.97%	1262	57.34%
BMI	Normal weight	487	68.50%	363	51.05%	456	64.14%
	Overweight	1169	66.01%	908	51.27%	1061	59.91%
	Obese	1750	62.99%	1469	52.88%	1623	58.42%
CHD	Yes	1106	68.44%	540	33.42%	1147	70.98%
	No	2306	63.07%	2204	60.28%	2000	54.70%
PAD	Yes	85	57.05%	37	24.83%	89	59.73%
	No	3327	64.94%	2707	52.84%	3058	59.69%

Cerebrovascular Disease	Yes	118	61.46%	53	27.60%	118	61.46%
	No	3294	64.84%	2691	52.97%	3029	59.63%
Current smoker	Yes	370	59.01%	288	45.93%	329	52.47%
	No	3043	65.45%	2457	52.85%	2819	60.64%
Diabetes	Yes	1972	58.87%	1589	47.43%	1972	58.87%
	No	1441	74.82%	1156	60.02%	1176	61.06%
Hypertension	Yes	2275	65.11%	1751	50.11%	2166	61.99%
	No	1138	63.86%	994	55.78%	982	55.11%
Family history of Premature CVD	Yes	694	63.90%	526	48.43%	653	60.13%
	No	2719	64.89%	2219	52.96%	2495	59.55%
Type of prevention	1ary prevention	2393	63.42%	2242	59.42%	2095	55.53%
	2ary prevention	990	68.85%	473	32.89%	1028	71.49%
	Familial hypercholesterolemia	29	46.03%	29	46.03%	24	38.10%
Metabolic syndrome (NCEP III)	Yes	1106	56.86%	891	45.81%	1057	54.34%
	No	2286	69.29%	1838	55.71%	2070	62.75%
Type of therapy	Statin monotherapy	3131	64.57%	2512	51.80%	2950	59.89%
	Fibrates monotherapy	21	47.73%	20	45.45%	16	34.78%
	Others	16	59.26%	9	33.33%	16	59.26%
		NCEP ATP III		**2004 NCEP ATP III**		**TJETF**	
Type of therapy single or multiple	mono	3168	64.39%	2541	51.65%	2982	59.65%
	Combination therapy	174	64.44%	133	49.26%	162	59.56%
Risk category	High/Very high/ High (1)	2396	58.88%	553	31.95%	2014	58.31%
	Medium/High but/High (2)/	581	91.07%	1233	52.74%	400	73.39%
	Low/Medium high/High (3)	436	76.63%	57	32.76%	44	13.13%
	Medium low/Other			321	81.27%	690	73.25%
	Low			581	91.07%		

In general, the proportion of patients reaching the target LDL-C levels according to 2004 updated ATP III guideline across all categories is less than the two other guidelines.

Only 33.42%(n=540) of CHD patients, 24.83%(n=37) of PAD patients, and 27.60%(n=53) of cerebro-vascular disease patients achieved the target based on this guideline.

And only 32.89 %(n=473) of secondary prevention patients have reached the target of the latter guideline.

<u>Predictors of achieving the LDL-C goals recommended by the different guidelines:</u>

The main multivariate significant predictors ($p<0.05$) of attaining the LDL-C goal were:

- According to the NCEP ATP III guidelines:
  - Female gender (OR: 1.061; [0.928, 1.212])
  - Age group: <40 Years (OR: 1.047; [0.968, 1.134])
  - BMI: Being Obese (OR: 1.114;[1.009,1.229]

- High waist circumference (OR: 1.123; [0.959, 1.314])
- Being diabetic (OR: 1.032; [0.911, 1.169])
- Being smoker (OR: 1.091;[0.903,1.319])
- Patients agreeing for taking prescribed tablets when the cholesterol level returned to normal (OR: 3.680; [1.093, 12.386]) and were advised lifestyle change alongwith prescribed tablet (OR: 3.492;[1.044,11.673])
- Patients agreeing on "still on the same tablet but the dose has increased" (OR:1.367; [0.851,2.196])
- Patients agreeing on feeling satisfied with the way their high cholesterol has been treated (OR: 1.035; [0.867, 1.234])
- Patients agreeing on every three months they see their doctor for checkup cholesterol level.(OR: 1.240; [0.883,1.740])
- Physicians agreeing on doctors mostly recommended statins for pharmacological treatment for hypercholesterolemia(OR:1.011;[0.0.857,1.847])
- Physicians agreeing on the use of guideline of "Framingham" (OR: 1.586; [1.230, 2.494])
- Physicians agreeing on often seeing patients once in every three months (OR: 1.721; [1.278, 3.872])

- Physicians agreeing on "I feel pressured to get patients to their target cholesterol levels" (OR: 1.013; [0.946, 1.085])
- Physicians agreeing on "A sufficient number of patients reach their target cholesterol level" (OR: 1.027; [0.965, 1.092])
- Physicians agreeing on "I am frustrated that the guidelines instruct me to prescribe a low dose of lipid lowering drug to all patients and titrate upwards" (OR: 1.061; [0.996, 1.130])
- Physicians agreeing on "I feel constrained to use less effective lipid lowering drugs first line" (OR:1.036; [0.987,1.088])
- Physicians agreeing on "Patients become concerned that their condition is more severe if their lipid lowering drug is titrated up" (OR: 1.016; [0.956, 1.081])

- According to the 2004 updated NCEP ATP III guidelines:

- Female gender (OR:1.252 ;[1.1509,1.3633])
- Age < 40 Years(OR:1.734; [1.307,2.300])
- BMI: Being Obese (OR:1.034;[1.0238,1.1276]
- Being smoker (OR:1.456;[1.217,1.741])
- Being diabetes (OR:1.623;[1.441,1.828])
- Having CVD family history (OR:1.252; [1.089,1.440])
- Patients disagreeing for stopped taking tablets when the cholesterol level returned to normal (OR:1.533;[1.141,2.059])
- Patients disagreeing for forget to take cholesterol-lowering tablets(OR:1.272;[0.901,1.796])
- Patients agreeing once in three month see their doctor for a check-up of their cholesterol level (OR:1.658;[1.182,2.326])

- Patients agreeing , doctors mostly recommended statins for pharmacological treatment for hypercholesterolemia (OR:1.0357;[0.7683,1.1283]
- Physicians agreeing the use of individual practice guidelines than others (OR:1.267;[0.939,1.709])
- Physicians agreeing to review their patient cholesterol level once in every three months (OR:1.0340;[0.9562,1.1181])
- Physicians feel constrained to use less effective lipid lowering drugs first line(OR:1.081;[1.032,1.132])
- Physicians agreeing Patients become concerned that their condition is more severe if their lipid lowering drug is titrated up (OR:1.120;[1.056,1.189])

- According to the TJETF guidelines:

- Female gender (OR: 1.1.650; [01.361,2.002])
- Age group: <40 Years(OR:0.438,[0.284,0.674]) & Age group (40-55)Years (OR: 0.505; [0.383,0.666])
- Being diabetic (OR: 1.311; [1.099,1.562])
- Patients agreeing on they have stopped taking tablets when their cholesterol return to normal (OR: 2.527; [1.458, 4.380])
- Patients agreeing on once a week missing a tablets without affecting their cholesterol levels (OR: 1.408; [1.270, 2.617])
- Patients agreeing on satisfactorily feel the way their high cholesterol has been treated (OR: 2.701; [2.136,3.415])
- Patients agreeing on seeing doctor less than once a year for a cholesterol checkup (OR:12.429; [4.859, 31.788])
- Physicians agreeing on the use of guideline on “National guidelines” (OR: 0.707; [0.532,0.938])and local health authority guidelines (OR: 0.339; [0.239,0.481])
- Physicians ageing on “I feel frustrated that I am not always able to effectively able to treatment my patients with CV disorders” (OR:0.544; [0.492,602])
- Physicians agreeing on “I find stressful trying to get my patients to their cholesterol targets” (OR: 2.305; [1.955, 2.717])
- Physicians agreeing on “I feel pressured to get patients to their target cholesterol levels” (OR: 0.721; [0.624, 0.834])
- Physicians agreeing on “A sufficient number of patients reach their target cholesterol level” (OR: 2.077; [1.775, 2.432])
- Physicians agreeing on “I am frustrated that the guidelines instruct me to advise lifestyle changes alone as first line therapy in all aspects.” (OR: 1.303; [1.173, 1.447])
- Physicians agreeing on “I tend to prescribe a lipid lowering drug only to patients who have proved they can adhere to diet and exercise change” (oR:1.179; [1.042, 1.315])
- Physicians agreeing on “Patients compliance decreases if lipid lowering drugs take too long to have an effect” (OR:0.629; [0.551,0.719])
- Physicians agreeing on “I feel constrained to use less effective lipid lowering drugs first line” (OR:1.385; 1.260, 1.522])
- Physicians agreeing on “Patients become concerned that their condition is more severe if their lipid lowering drug is titrated up” (OR:1.156,[1.010,1.323])
- Physicians agreeing on “Patients become concerned that their condition is more severe if their lipid lowering drug is frequently changed” (OR:0.599; [0.526, 0.682])