This report may include approved and non-approved uses, formulations, or treatment regimens. The results reported may not reflect the overall profile of a product. Before prescribing any product mentioned in this report, healthcare professionals should consult local prescribing information for the product approved in their country.

2. Synopsis

MERCK RESEARCH LABORATORIES MK-6213 L-001662326, Tablet Hypercholesterolemia	**CLINICAL STUDY REPORT SYNOPSIS**

PROTOCOL TITLE/NO.: A Multicenter, Randomized, Double-Blind, Placebo- and Active-Controlled Study to Assess the Efficacy and Tolerability of MK-6213 Co-Administered with Atorvastatin in Patients with Primary Hypercholesterolemia #006

PROTECTION OF HUMAN SUBJECTS: This study was conducted in conformance with applicable country or local requirements regarding ethical committee review, informed consent, and other statutes or regulations regarding the protection of the rights and welfare of human subjects participating in biomedical research. Study audit information can be found in [redacted]

INVESTIGATOR(S)/STUDY CENTER(S): Multi-center (41 Investigators, 8 international, 9 countries) A list of Primary Investigators can be found in [redacted] and [redacted] and this includes only sites that received drug. Principal Authors Signature page can be found in [redacted]

PRIMARY THERAPY PERIOD: 24-Jul-08 to 08-Jan-09 | **CLINICAL PHASE:** IIa

DURATION OF TREATMENT: Patients were entered into a 2-week single-blind placebo run-in period, during which they received placebo for MK-6213 and placebo for atorvastatin. In the 4-week treatment period, patients received: MK6213 160 mg monotherapy, MK6213 160 mg and atorvastatin 20 mg, atorvastatin 20 mg monotherapy or placebo.

OBJECTIVE(S): **Primary:** In patients with primary hypercholesterolemia treated for 4 weeks, to evaluate the efficacy of MK6213 160 mg co-administered with atorvastatin 20 mg compared to atorvastatin 20 mg monotherapy in lowering LDL-CHYPOTHESES: Co-administration of MK-6213 160 mg with atorvastatin 20 mg results in a greater reduction in LDL-C compared to atorvastatin 20 mg alone after 4 weeks of treatment. **Secondary:** In patients with primary hypercholesterolemia treated for 4 weeks, OBJECTIVES: 1) To evaluate the safety and tolerability of MK-6213 160 mg treatment. 2) To evaluate the efficacy of MK-6213 160 mg monotherapy compared to placebo in lowering LDL-C, non-HDL-C, Apo B, TC and TG and raising HDL-C. 3) To evaluate the efficacy of MK-6213 160 mg co-administered with atorvastatin 20 mg compared to atorvastatin 20 mg monotherapy in lowering non-HDL-C, Apo B, TC and TG and raising HDL-C HYPOTHESES: 1) MK-6213 160 mg is well-tolerated. 2) MK-6213 160 mg monotherapy produces greater LDL-C reduction compared to placebo after 4 weeks of treatment.

STUDY DESIGN: This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study to assess the LDL-C lowering efficacy of MK-6213 160 mg co-administered with atorvastatin 20 mg compared to atorvastatin 20 mg alone. The study was 8-12 weeks, depending on the length of the washout period. Patients were randomized to 1 of 4 arms in a 2:2:2:1 fashion in the following order: MK-160 mg alone, MK-160 mg + atorvastatin 20 mg, atorvastatin 20 mg alone or placebo. Eligible patients had LDL-C values between 100-190 mg/dL, depending on their risk group. The protocol can be found in [redacted], informed consent in [redacted] and sample case report form in [redacted]. The study patient allocation schedule can be found in [redacted].

SUBJECT/PATIENT DISPOSITION:

	MK-6213 160mg + Atorvastatin 20mg		PBO MK-6213 160mg + Atorvastatin 20mg		MK-6213 160mg + PBO Atorvastatin 20mg		PBO MK-6213 160mg + PBO Atorvastatin 20mg		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Not Randomized									214	
Patients in population	94		96		96		48		334	
Study Disposition										
COMPLETED	91	(96.8)	90	(93.8)	91	(94.8)	48	(100.0)	320	(95.8)
DISCONTINUED	3	(3.2)	6	(6.3)	5	(5.2)	0	(0.0)	14	(4.2)
ADVERSE EVENT	1	(1.1)	3	(3.1)	1	(1.0)	0	(0.0)	5	(1.5)
LOST TO FOLLOW-UP	0	(0.0)	1	(1.0)	0	(0.0)	0	(0.0)	1	(0.3)
PROTOCOL VIOLATION	2	(2.1)	1	(1.0)	1	(1.0)	0	(0.0)	4	(1.2)
WITHDRAWAL BY SUBJECT	0	(0.0)	1	(1.0)	3	(3.1)	0	(0.0)	4	(1.2)

Each patient is counted once for Study Disposition based on the latest corresponding disposition record.
Atorva = Atorvastatin

DOSAGE/FORMULATION NOS.: Patients were entered into a 2-week single-blind placebo run-in period, during which patients received placebo for MK-6213 and placebo for atorvastatin. In the treatment period, patients received 1 of the following 4 treatments:

- MK6213 160 mg
- MK6213 160 mg + atorvastatin 20 mg
- Atorvastatin 20 mg
- Placebo

Additional information on study drug compliance can be found in Appendix [redacted]

DIAGNOSIS/INCLUSION CRITERIA: Men and women, 18-75 years of age, with LDL-C (off lipid-lowering medications) values ranging from 100 to 190 mg/dL (2.6–4.9 mmol/L), depending on CV risk category. The study population will include patients who, by NCEP/ATP III criteria and measured LDL-C values, fall into one of the following categories:

(1) "low risk" (0-1 risk factors) with off-treatment LDL-C 100-190 mg/dL (2.6–4.9 mmol/L)
(2) "moderate risk" (2 or more risk factors and 10-year CHD risk<10%) with off-treatment LDL-C 100-160 mg/dL (2.6–4.1 mmol/L)
(3) "moderate-high risk" (2 or more risk factors and 10-yr. CHD risk 10-20%) with:
    - off-treatment LDL-C 100-145 mg/dL (2.6–3.6 mmol/L)
    - or, 100-130 mg/dL (2.6–3.4 mmol/L) if the patient was taking lipid therapy more potent than atorvastatin 20 mg at screening. (See Appendix 6.3 Lipid Lowering Agents with Greater Potency than Atorvastatin 20 mg)
(4) Diabetic patients NOT taking lipid-lowering medication, with LDL-C 100-130 mg/dL (2.6–3.4 mmol/L), with < 2 other cardiovascular risk factors, without microalbuminuria, and who meet all other entry criteria are eligible.

Visit 1

Patients were eligible to continue to Visit 2 if they met the following criteria:

a) Patient is male or female and 18 to 75 years of age on day of signing informed consent.
b) A female patient who is not of reproductive potential without requiring the use of contraception. A female patient who is not of reproductive potential is defined as: one who has either 1) reached natural menopause (defined as 6 months of spontaneous amenorrhea with serum FSH levels in the postmenopausal range as determined by the laboratory, or 12 months of spontaneous amenorrhea), 2) 6 weeks post surgical bilateral oophorectomy with or without hysterectomy, or 3) bilateral tubal ligation.
c) A female of reproductive potential who agrees to take **acceptable contraceptive** precautions for the duration of the study.

Visit 2

Patients were eligible to continue to Visit 3 if they met the following criteria:

d) Patient is classified as "low risk" (0-1 risk factors) according to NCEP/ATPIII cardiovascular risk categories and Framingham risk score with an off-treatment LDL-C value of 100-190 mg/dL (2.6–4.9 mmol/L)

-or-

e) Patient is classified as "moderate risk" (2 or more risk factors and 10 year CHD risk<10%) according to NCEP/ATPIII cardiovascular risk categories and Framingham risk score with an off-treatment LDL-C value of 100-160 mg/dL (2.6–4.1 mmol/L)

-or-

f) Patient is classified as "moderate-high risk" (10-yr CHD risk 10-20%) according to NCEP/ATPIII cardiovascular risk categories and Framingham risk score with
   - an off-treatment LDL-C value of 100-145 mg/dL (2.6–3.6 mmol/L)
   - **or,** off-treatment LDL-C 100-130 mg/dL (2.6–3.4 mmol/L) if patient was taking lipid therapy more potent than atorvastatin 20 mg at the time of screening (See Appendix 6.3)

-or-

g) Diabetic patients **NOT** taking lipid-lowering medication, with LDL-C 100-130 mg/dL (2.6–3.4 mmol/L), with ≤ 2 other cardiovascular risk factors, and without microalbuminuria who meet all other entry criteria are eligible (see Section 2.3 Patient Exclusion Criteria (h).
h) Patient has serum triglycerides <350 mg/dL (4.0 mmol/L)
i) Patient has creatine phosphokinase (CK) ≤2 x upper limit of normal (ULN) [per central laboratory reference ranges].
j) Patient has alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤1.5 x upper limit of normal (ULN) [per central laboratory reference ranges].
k) Patient agrees to maintain a stable diet that is consistent with the NCEP/ATP III TLC diet for the duration of the study.

Visit 3

Patients were eligible for enrollment if they met the following criteria:

l) Patient has >75% compliance with study medication during the single-blind placebo run-in phase (determined by pill count) or in the opinion of the investigator, compliance will improve following additional counsel.
m) Patient is judged to be in generally good health and suitable for a study of lipid-lowering therapy based on medical history and physical exam.

EVALUATION CRITERIA:

Efficacy measurement: Fasting blood (at least 12 hours from the last meal) will be drawn for efficacy variables The *primary* efficacy endpoint is percent change from baseline in LDL-C at Week 4. The following *secondary* efficacy endpoints are also of interest, percent change from baseline at Week 4 in non-HDL-C, Apo B, TC, TG, and HDL-C. The baseline is defined as the value from Visit 3 (randomization visit). If the randomization value is not available, the last available pre-randomization measurement will be used as the baseline value.

Safety measurement: Safety and tolerability endpoints such as blood chemistry, hematology, vital signs, and ECG will be monitored. Clinical adverse experiences, selected safety endpoints of interest, and laboratory values exceeding predefined limits of change (PDLC) will be evaluated.

Tier 1 safety parameters include (1) ALT and/or AST consecutive elevations ≥3xULN, (2) CK elevations ≥ 5xULN and ≥10xULN, (3) CK elevations ≥10xULN with muscle symptoms, and (4) specific AEs of interest (myalgia, myopathy, and rhabdomyolysis). Specific AEs of myalgia, myopathy, and rhabdomyolysis will be grouped together.

Tier 2 adverse experiences include overall clinical adverse experiences, overall serious clinical adverse experiences, overall drug-related clinical adverse experiences, and clinical adverse experiences by body system (Note: the latter will include only adverse experiences occurring with an incidence of 4 or more in any of the 4 treatment groups). Other (more rare) adverse experiences by body system and other clinical and laboratory adverse experiences will be summarized as Tier 3.

STATISTICAL PLANNING AND ANALYSIS:

Efficacy: For the primary efficacy endpoint, percent change from baseline in LDL-C, a longitudinal data analysis (LDA) model proposed by Liang and Zeger was be used to assess the response across the time points of the study. This LDA model included both baseline value and post-baseline observed percentage change from baseline at Week 2 and Week 4 as response variables. The repeated measures model included factors for time (as categorical variable), treatment, baseline TG category (< median, ≥ median), and time-by-treatment interactions. An unstructured covariance was used for the within-subject correlation. The primary time point for this analysis was at Week 4. Comparisons of MK-6213 160 mg co-administration with atorvastatin 20 mg versus atorvastatin 20 mg and MK-6213 160 mg versus placebo were performed. These analyses addressed the primary and secondary hypotheses. In addition, the secondary lipid endpoints of non-HDL, Apo B, TC, and HDL-C also utilized this model. The secondary endpoint of percent change from baseline in TG was analyzed by non-parametric methods.

The closed ordered testing procedure (in the order of testing: the primary hypothesis and the secondary efficacy hypothesis) was applied to control the type I error across the primary and secondary hypotheses at 0.05 level. The primary hypothesis was tested at 2-tailed α=0.05 level first. If the statistical significance was achieved for the primary hypothesis, the secondary efficacy hypothesis was tested at 2-tailed α=0.05 level. However, if the statistical significance was not achieved for the primary hypothesis, the statistical test of the secondary efficacy hypothesis would be performed and nominal p-values will be reported as a measure of the strength of the effect without declaring statistical significance.

Safety: Safety and tolerability assessment followed a multi-tiered approach by clinical and / or statistical review of all safety parameters, including adverse experiences, laboratory values, and vital signs. For Tier 1 safety parameters, including ALT and/or AST consecutive elevations ≥3xULN, CK elevations ≥5xULN and ≥10xULN, CK elevations ≥10xULN with muscle symptoms, and specific AEs of interest (myopathy, myalgia, and rhabdomyolysis), formal inferential testing and 95% confidence intervals was performed for pair-wise comparisons of MK-6213 160 mg co-administered with atorvastatin 20 mg versus atorvastatin 20 mg, MK-6213 160 mg co-administered with atorvastatin 20 mg versus MK-6213 160 mg, MK-6213 160 mg versus placebo, and atorvastatin 20 mg versus placebo. For Tier 2 adverse experiences which included overall clinical adverse experiences, overall serious clinical adverse experiences, overall drug-related clinical adverse experiences, and clinical adverse experiences by body system (Note: the latter will include only adverse experiences occurring with an incidence of 4 or more in any of the 4 treatment groups), 95% confidence intervals for the between group differences were provided for the same pair-wise comparisons defined above. Other adverse experiences (Tier 3) were summarized by frequency of occurrence.

Sample Size and Power: Based upon a sample size of n=80, 80, 80, 40 in co-administration of MK-6213 160 mg with atorvastatin 20 mg, MK-6213 160 mg, atorvastatin 20 mg, and placebo, respectively, the following differences between treatments may be detected for the primary endpoint of the percent change from baseline (Table 2-1).

Table 2-1

Endpoint Percent Change from Baseline Detectable Treatment Difference

Parameter	N_1	N_2	Detectable Difference Power 90% (80%)	S.D. Estimate[†]
LDL-C % Δ from baseline	80	80	7.7% (6.9%)	S.D. LDL-C % Δ= 15%
	80	40	9.5% (8.2%)	
[†]Based on between-subject standard deviation of LDL-C percent change from baseline from the JV program PN038.				

Additional Statistical Analysis tables can be found in [redacted] and [redacted].

RESULTS:

EFFICACY:

Primary endpoint: The difference between co-administration of MK-6213 160 mg with atorvastatin 20 mg and atorvastatin 20 mg monotherapy in least square (LS) mean percent change from baseline in LDL-C at Week 4 was -10.0% (-50.7% vs. -40.6%; P<0.001) with 95% CI -14.6% to -5.5% based on the longitudinal data analysis (LDA) model in FAS.

Secondary Endpoint:

1. The difference between MK-6213 160 mg monotherapy and placebo in LS mean percent change from baseline in LDL-C at Week 4 was -17.9% (-13.3% vs. 4.6%; P<0.001) with 95% CI: -23.4% to -12.5% based on the longitudinal data analysis (LDA) model in FAS.
2. Co-administration of MK-6213 160 mg with atorvastatin 20 mg was more efficacious than atorvastatin 20 mg monotherapy in lowering non-HDL-C, Apo B, and TC at Week 4. There was no evidence that co-administration of MK-6213 160 mg with atorvastatin 20 mg was more efficacious than atorvastatin 20 mg monotherapy in lowering TG and raising HDL-C at Week 4.
3. MK-6213 160 mg monotherapy was more efficacious than placebo in lowering non-HDL-C, Apo B, and TC at Week 4. There was no evidence that MK-6213 160 mg monotherapy was more efficacious than placebo in lowering TG and raising HDL-C at Week 4.

A summary for the magnitude of treatment effect expressed in LS means (or medians) for the primary and secondary lipid endpoints are provided in Table 2-2.

Table 2-2

Summary of LS Mean (95% CI) for Percent Change from Baseline at Week 4 in the Primary and Secondary Lipid Endpoints
Full-Analysis-Set

Lipid endpoint	MK-6213 + Atorvastatin (n=92)	Atorvastatin (n=89)	MK-6213 (n=92)	Placebo (n=47)	(MK-6213 + Atorvastatin) vs. Atorvastatin	MK-6213 vs. Placebo
LDL-C	-50.7 (-53.8, -47.5)	-40.6 (-43.8, -37.4)	-13.3 (-16.5, -0.1)	4.6 (0.2, 9.1)	-10.0 (-14.6, -5.5)	-17.9 (-23.4, -12.5)
Non-HDL-C	-46.6 (-49.5, -43.6)	-38.0 (-41.0, -35.0)	-11.4 (-14.3, -8.5)	2.5 (-1.6, 6.6)	-8.6 (-12.7, -4.4)	-13.9 (-18.9, -8.9)
Apo-B	-40.4 (-43.1, -37.7)	-32.7 (-35.4, -30.0)	-8.8 (-11.5, -6.1)	3.5 (-0.3, 7.2)	-7.7 (-11.5, -3.9)	-12.2 (-16.8, -7.6)
Total Cholesterol	-35.1 (-37.4, -32.7)	-27.6 (-30.0, -25.2)	-8.5 (-10.9, -6.2)	2.5 (-0.8, 5.8)	-7.4 (-10.8, -4.1)	-11.0 (-15.1, -7.0)
Triglycerides (median)	-24.2 (-29.6, -18.9)	-25.9 (-32.1, -19.7)	1.6 (-6.9, 10.1)	-7.1 (-17.2, 3.0)	-1.0 (-7.7 , 5.9)	5.5 (-4.6 , 16.9)
HDL-C	3.8 (0.9, 6.8)	6.2 (3.2, 9.2)	1.4 (-1.6, 4.3)	2.1 (-2.1, 6.2)	-2.4 (-6.6, 1.8)	-0.7 (-5.8, 4.4)
Between-treatment comparisons were statistically significant at 0.05 level except for the comparisons on TG and HDL-C.						

SAFETY:

For Tier 1 AEs of myopathy, myalgia, and rhabdomyolysis, there were a total of 4 patients with myalgia AE (2 in the atorvastatin 20 mg group, 1 in the MK-6213 160 mg group, and 1 in the placebo group). No myopathy and rhabdomyolysis were reported in this study. For Tier 1 AEs of elevation of ALT and/or AST, and CK, there was no patient with ALT and/or AST consecutive elevations ≥3xULN in this study; there were 2 patients (1 on atorvastatin 20 mg and 1 on MK-6213 160 mg) with CK elevations ≥5xULN; there was no patient with CK elevations ≥10xULN with/without muscle symptoms in this study.

Adverse experience summary is provided in Table 2-3.

Table 2-3

Adverse Event Summary
All Patients as Treated

	MK-6213 160mg + Atorvastatin 20mg		PBO MK-6213 160mg + Atorvastatin 20mg		MK-6213 160mg + PBO Atorvastatin 20mg		PBO MK-6213 160mg + PBO Atorvastatin 20mg		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Patients in population	94		95		96		48		333	
with one or more adverse events	31	(33.0)	36	(37.9)	28	(29.2)	20	(41.7)	115	(34.5)
with no adverse event	63	(67.0)	59	(62.1)	68	(70.8)	28	(58.3)	218	(65.5)
with drug-related[†] adverse events	4	(4.3)	10	(10.5)	4	(4.2)	5	(10.4)	23	(6.9)
with serious adverse events	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
with serious drug-related adverse events	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued[‡] due to an adverse event	1	(1.1)	3	(3.2)	1	(1.0)	0	(0.0)	5	(1.5)
discontinued due to a drug-related adverse event	0	(0.0)	2	(2.1)	1	(1.0)	0	(0.0)	3	(0.9)
discontinued due to a serious adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to a serious drug-related adverse event	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

[†] Determined by the investigator to be related to the drug.

[‡] Study medication withdrawn.

Atorva = Atorvastatin

Additional Efficacy and Safety Tables can be found in [redacted], [redacted] and [redacted].

CONCLUSIONS:

In patients with primary hypercholesterolemia treated for 4 weeks,

1. Compared to atorvastatin 20 mg monotherapy, co-administration of MK-6213 160 mg with atorvastatin 20 mg produced a greater reduction in LDL-C, non-HDL-C, Apo B, and TC.
2. Compared to atorvastatin 20 mg monotherapy, co-administration of MK-6213 160 mg with atorvastatin 20 mg produced neither a greater reduction in TG nor a greater increase in HDL-C.
3. Compared to placebo, MK-6213 160 mg monotherapy produced a greater reduction in LDL-C, non-HDL-C, Apo B, and TC.
4. Compared to placebo, MK-6213 160 mg monotherapy produced neither a greater reduction in TG nor a greater increase in HDL-C.
5. MK-6213 160 mg was well-tolerated.

[redacted]

AUTHORS: [redacted]