ORIGINAL ARTICLE

# A Multicenter Study in Malaysia to Determine the Efficacy and Safety of a Generic Atorvastatin

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**SUMMARY**

**A multicenter study was conducted to assess the efficacy of a generic form of Atorvastatin (Ranbaxy's Storvas®) in the treatment of Primary Hypercholesterolemia. One hundred and nineteen patients were given 10mg of Storvas® for four weeks and increased to 20mg if target LDL-Cholesterol was not achieved. LDL-Cholesterol was reduced by 36.6% at four weeks and 37.5% at eight weeks from baseline. Total cholesterol and triglycerides were significantly reduced. There were no drug-related serious adverse events. We conclude that the generic atorvastatin is safe and effective in the treatment of primary hypercholesterolaemia and the results are comparable to published data on innovator atorvastatin.**

**KEY WORDS:**
*Hypercholesterolaemia, Coronary Heart Disease (CHD), 3-hydroxy-3 methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, Generic Statins, Atorvastatin, Storvas*

## INTRODUCTION

Dyslipidaemia is an important risk factor for cardiovascular disease[1-5]. The risk increases progressively with increasing serum cholesterol levels particularly elevated LDL-cholesterol[6]. In Malaysia, the prevalence of hypercholesterolemia was found to be 20% among persons aged 30 years or older in the National Health Survey conducted in 1996[7]. Pharmacological treatment for dyslipidaemia is considered when therapeutic life-style changes which include diet modification, weight reduction and exercise, cessation of smoking and restriction of alcohol consumption fail to achieve the desired target.

3-hydroxy-3 methylglutaryl-coenzyme A reductase inhibitors (commonly referred to as Statins) inhibit the biosynthesis of cholesterol and also increase the density of LDL receptors. Atorvastatin is a potent statin. Previous controlled and uncontrolled studies showed that a mean reduction in LDL-cholesterol (LDL-C) of 25%-61% could be achieved in patients with primary hypercholesterolemia given atorvastatin 2.5-80 mg daily for at least six weeks [8-12]. The current recommended dose range for atorvastatin is from 10 to 80mg daily. While atorvastatin ranked first in Australia, it merely ranked 29th on our national drug use list[13]. This suggests that cost is still a significant barrier in access to the drug. The availability of a lower cost atorvastatin will be helpful in this regards.

A generic form of atorvastatin (Storvas®) has recently been introduced in Malaysia by Ranbaxy, (Malaysia) Sdn. Bhd. This product has been shown to be bioequivalent to the original atorvastatin, Lipitor®. A review of literature reveals that few trials have been conducted to demonstrate the therapeutic efficacy of generic drugs. It is assumed that bioequivalence of a generic drug compared with the original drug will translate into the same clinical effectiveness and safety. The purpose of this study was to establish the clinical efficacy and safety of a generic form of atorvastatin (Storvas®) in lowering serum cholesterol in Malaysian patients with primary hypercholesterolaemia. Also, to our knowledge, this would be the first ever documented study to prospectively evaluate the safety and effectiveness of atorvastatin in Malaysia.

## MATERIALS AND METHODS

The Ranbaxy Atorvastatin Trial was a multi-center, open label, single group trial to assess the efficacy of Storvas® (Atorvastatin calcium) over a period of eight weeks in patients with primary hypercholesterolemia. The study was conducted in compliance with Good Clinical Practice guidelines and was approved by Medical Research Ethics Committee of the Ministry of Health. Informed consent was obtained from all participants prior to the conduct of any study related procedure. Study monitoring was done to ensure the integrity of the data and compliance to the protocol.

Patients with primary hypercholesterolaemia above the age of 18 years and who did not benefit from 12 weeks of Therapeutic Life Style changes (TLC) were recruited. The LDL-cholesterol level for inclusion ranged from 2.6 to 7.5mmol/l depending on the 10-year risk of coronary heart disease (CHD) and the presence of CHD or CHD equivalent conditions. Patients with known hypersensitivity or muscle toxicity to statins, family history of hereditary muscle disorders, uncontrolled diabetes mellitus, treatment with lipid lowering drugs in the previous six weeks, elevated liver enzymes to more than 1.5 times above the upper limit of normal (ULN), elevated serum Creatine Phosphokinase (CPK) more than five times ULN, serum creatinine above 1.2 times ULN and serum triglycerides of more than 5.56mmol/L at baseline were excluded from the study.

After initial screening, patients underwent a baseline evaluation and all eligible patients were given Storvas® 10 mg Tablets once daily for four weeks. After four weeks of

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treatment, lipid measurements were repeated for all patients and patients who had attained their target level of LDL-C were continued on the same dose for another four weeks. For patients who failed to achieve the target LDL-C at Week 4, the dose of Storvas® was increased to 20mg for the next four weeks. The LDL-cholesterol targets were adopted from the "The National Cholesterol Education Program (NCEP-ATP III)" Guidelines[14]. The targets for patients with CHD or CHD risk equivalent, two or more major risk factors for CHD and 0-1 risk factor were < 2.6mmol/L, < 3.4mmol/L and < 4.1 mmol/L respectively. All laboratory measurements were performed by a central laboratory. Analysis included lipid profile, full blood count, fasting glucose, liver function test, renal profile and creatine phosphokinase (CPK).

Analysis was performed on the "Intention-to-treat" (ITT) population. The ITT population included all eligible subjects enrolled into the study and received at least one dose of study treatment and had at least one efficacy assessment done. The primary end-point was percentage reduction from baseline of LDL-C at four weeks and eight weeks.

## RESULTS

Of the 122 patients recruited from 14 participating centers, 119 completed four weeks of treatment with Storvas® and had their first efficacy assessment. The trial profile is shown in Figure 1.

*Compliance:*

Good compliance (defined as at least 80% of the prescribed tablets having been taken) was achieved throughout the study with 97% of the patients compliant at four weeks and 94% at eight weeks.

*Primary end-point*

The LDL-C at Baseline, Week 4 and Week 8 are shown in Table II.

The mean LDL-cholesterol was reduced from 4.35mmol/l at baseline to 2.72mmol/l at four weeks and to 2.67mmol/l at eight weeks. The mean percentage reduction of LDL-cholesterol from baseline was 36.6% at four weeks and 37.5% at eight weeks. The reductions were statistically significant.

Ninety seven patients (82%) achieved target LDL-cholesterol level at week 4 and week 8. Eighty-five patients who achieved LDL-cholesterol target at 4 weeks maintained the target at 8 weeks. Twelve patients, who did not achieve the LDL-cholesterol target at 4 weeks, achieved the target with 20mg of Storvas® at 8 weeks. Twelve other patients, who initially achieved the LDL-C target at four weeks, had an LDL-C of above target at 8 weeks (Table III).

*Secondary end-points*

The total cholesterol and triglyceride levels were significantly reduced. Total cholesterol was reduced by 28.2% at four weeks and 28.9% at eight weeks and triglycerides were reduced by 16% and 14% at four weeks and eight weeks respectively (Table IV). The HDL-cholesterol was marginally reduced at four weeks and eight weeks.

*Safety evaluation*

Safety evaluation was based on the predefined safety analysis set which included all patients who received at least one dose of study treatment. There were five serious adverse events reported during the study and none was assigned by investigators to be causally related to the study drug. Seventy-one adverse event episodes were reported in 51 patients, 15.5% of these were thought to be related to study drug. These adverse events were abdominal pain, diarrhoea, arthralgia, musculoskeletal pain, dizziness, headache and pruritus. CPK was increased above baseline in four patients. The maximum CPK recorded was 650U/L (2.2 times above the ULN) in one patient. The patient was asymptomatic and did not require any dose adjustment of the study drug. Alanine transaminase (ALT) was increased from baseline in two patients and the maximum elevation was 1.4 times above ULN. No patients had to withdraw the study drug due to adverse effects.

## DISCUSSION

Statins are widely used in Malaysia. The most recent data from the Malaysian Statistics on Medicine 2005 report[13] showed that the utilization of lipid lowering drugs in the Malaysian population was ranked third after anti-hypertensive and anti-diabetic medicines. The utilization rate was 18.9 Define Daily Dose (DDD) per 1000 population indicating that 1.9% of the population was treated with lipid lowering drugs (mostly statins). The cost of lipid lowering agents was RM108.5 million out of the estimated RM2.2 billion total expenditure on prescription drugs in 2005. The relative high ranking of lipid reducers in the league table of drug utilization and cost however belie the underutilization of this important class of drug considering its high prevalence in the population. In contrast, in Australia (the only country in the region with available medicine use statistics) [15] lipid reducers dominated its top-10 drug list in year 2000, with a

**Table I: Demographics and Baseline Characteristics of Trial Patients**

| Characteristics | |
|---|---|
| Age, years, median (range) | 54 (20-76) |
| Men>45 years or women >55 years, N (%) | 75 (61) |
| Male:Female, N (ratio) | 52:67 (1:1.3) |
| Malay:Chinese:Indian:Others (%) | 55:29:15:2 |
| Hypertension, N (%) | 84 (69) |
| Diabetes mellitus, N (%) | 43 (36) |
| Cigarette smoking, N (%) | 14 (11) |
| Low HDL cholesterol, N (%) | 17 (14) |
| Family history of premature CHD | 13 (11) |
| Haemoglobin, g/L (SD) | 138.0 ( 17.0) |
| TSH, mIU/L | 1.7 (1.0) |
| ALT, U/L | 24.1 (9.5) |
| AST, U/L | 23.7(6.1) |
| Creatinine, Ìmol/L | 76.8 (22.5) |
| CPK, U/L | 125.9 (79.7) |
| Total Cholesterol, mmol/L | 6.43 (1.02) |
| HDL Cholesterol, mmol/L | 1.31 (0.31) |
| LDL Cholesterol, mmol/L | 4.35 (0.88) |
| Triglycerides, mmol/L | 1.68(0.72) |
| Glucose (fasting), mmol/L | 6.0 (2.1) |

The baseline characteristics of the 119 patients who had at least 1 efficacy assessment (the ITT population) are shown in Table I.

**Table II: LDL-cholesterol by Study visit**

| LDL Cholesterol, mmol/L | Baseline | Week 4 | Week 8 |
|---|---|---|---|
| N | 119 | 119 | 119 |
| Mean | 4.35 | 2.72 | 2.67 |
| Median | 4.34 | 2.64 | 2.64 |
| SD | 0.88 | 0.67 | 0.60 |
| Mean of change from Baseline | | -1. 63 | -1.68 |
| Median of change from Baseline | | -1.66 | -1.73 |
| SD of change from Baseline | | 0.78 | 0.74 |
| Mean percentage change from Baseline | | -36.6 | -37.5 |
| SD percentage change from Baseline | | 14.2 | 13.0 |
| p-value compared to baseline | | <0.0001* | <0.0001* |

* Wilcoxon sign rank test
SD = standard deviation

**Table III: Distribution of patients achieving the NCEP ATP III goals by risk group (ITT population)**

| LDL-C Goal according to risk factor | Week 4 (N=119) Achieved the goal | | | Week 8 (N=119) Achieved the goal | | |
|---|---|---|---|---|---|---|
| | Total | No | % | Total | No | % |
| CHD or CHD risk equivalent: LDL <2.6 | 52 | 36 | 69 | 52 | 36 | 69 |
| Multiple (2+) risk factor: LDL<3.4 | 34 | 29 | 85 | 34 | 29 | 85 |
| 0-1 risk factor: LDL<4.2 | 33 | 32 | 97 | 33 | 32 | 97 |
| Total | 119 | 97 | 82 | 119 | 97 | 82 |

NCEP = National Cholesterol Education Program; Adult Treatment Panel III

**Table IV: Secondary end-points by study visit**

| | Baseline | Week4 | Week8 |
|---|---|---|---|
| Mean Total Cholesterol, mmol/L (SD) | 6.43(1.02) | 4.58 (0.82) | 4.53 (0.74) |
| Mean percentage reduction from Baseline (SD) | | 28.2 (11.7) | 28.9 (10.9) |
| p-value compared to baseline | | <0.0001* | <0.0001* |
| Mean Triglycerides, mmol/L (SD) | 1.68(0.72) | 1.32 (0.51) | 1.37 (0.58) |
| Mean percentage reduction from Baseline (SD) | | 16.0(27.2) | 14.2(26.4) |
| p-value compared to baseline | | <0.0001* | <0.0001* |
| Mean HDL Cholesterol, mmol/L (SD) | 1.31(0.31) | 1.25 (0.28) | 1.23 (0.31) |
| Mean percentage reduction from Baseline (SD) | | 3.1 (17.4) | 5.5 (18.0) |
| p-value compared to baseline | | 0.0020* | <0.0001* |

* Wilcoxon sign rank test
SD = standard deviation

utilization rate of at least 70 DDD/1000 population. It is hoped that with the cost saving of using a generic atorvastatin, there will be an increased in utilization of the drug to benefit a wider population of patients.

In our study, generic atorvastatin Storvas® significantly reduced the LDL-cholesterol by 36.6% at four weeks and 37.5% at eight weeks. The mean absolute reduction of LDL-cholesterol was 1.63 and 1.68mmol/l at 4 weeks and eight weeks respectively. Although we did not conduct a randomised comparative trial with innovator atorvastatin (Lipitor®), our results are comparable with the results published in the literature. In two studies, treatment with 10mg of Lipitor® for 6 weeks was associated with approximately 37% reduction in the LDL-cholesterol[16,17]. In the ASCOT-LLA study, 10mg of Lipitor® reduced the LDL-cholesterol by 35% (an absolute reduction of 1.2mmol/l) compared with placebo at one year [18]. The reduction in the total cholesterol and triglyceride were also consistent with the outcome reported in the literature where trials have been conducted largely on western populations. There are no previous published studies on atorvastatin in Malaysian patients. HDL-cholesterol was marginally reduced in our study.

Data on achieving National Cholesterol Education Program Adult Treatment Panel III (ATP III) goals in Asia are limited. The recently published REALITY-Asia Study (a retrospective cohort study) reported that across all cardiovascular risk categories, only 48% of patients attained ATP III targets for LDL-C, including 38% of those with CHD/diabetes and it recommended the need for more effective treatment to help Asian patients achieve their cholesterol treatment targets[19]. In the Korean Ten Centers' Study, the LDL-C goal attainment rate improved from 50% in 2004 to 76% in 2007 when the study was repeated using the same study protocol at the same ten hospitals[20]. This suggests that goal attainment rates have been improving in certain Asian countries possibly due to stricter treatment approaches and/or usage of more potent medications. In our Study, atorvastatin (Storvas®) therapy was able to achieve target goal attainment rates of 82% among all patients and 69% in the CHD/ CHD risk equivalent patients. This would indicate that better LDL-C target goal can be achieved using relatively new and high potency statins

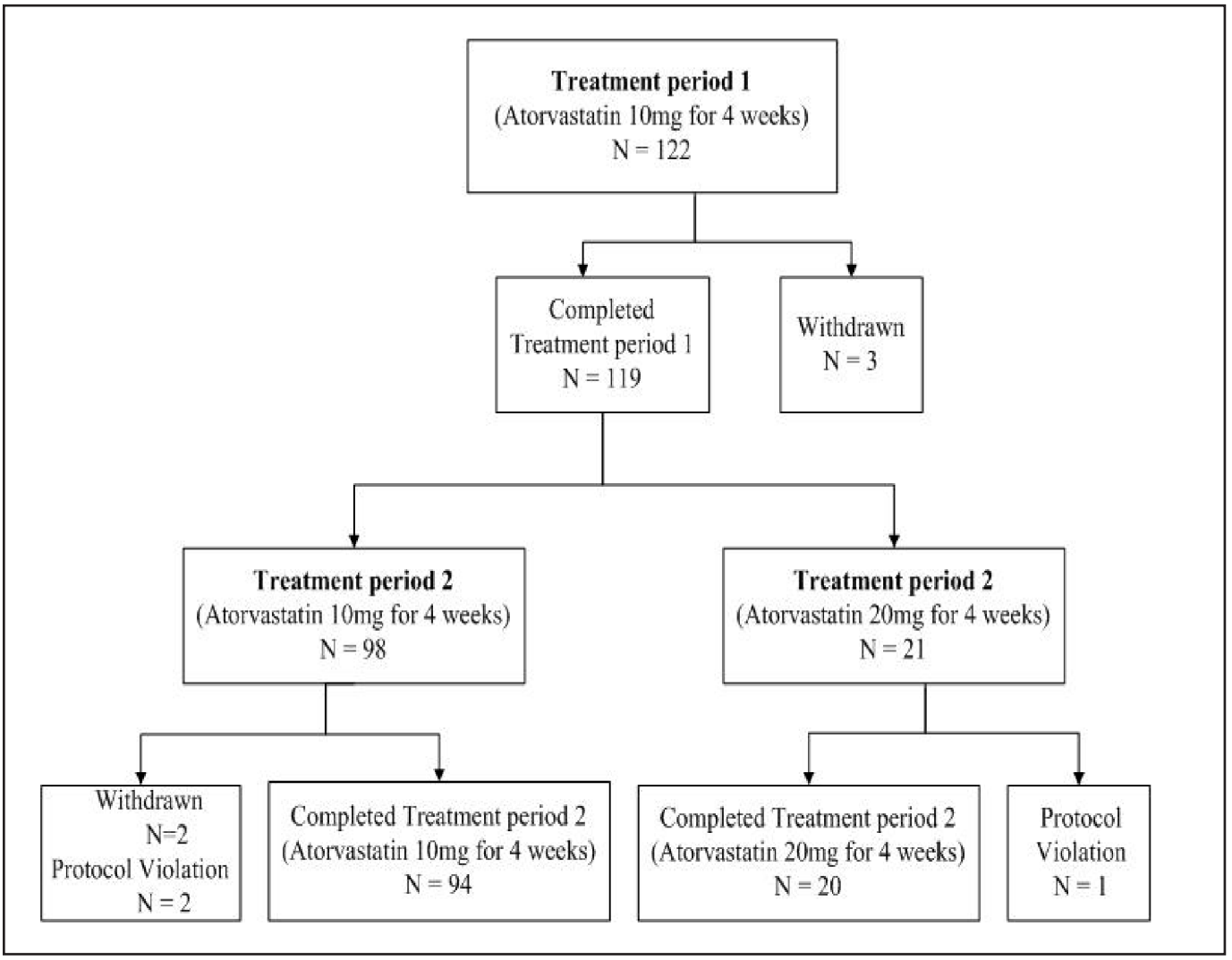


**Fig. 1:** Trial profile of study patients

like atorvastatin compared to the older statins such as lovastatin. In the REALITY-Asia Study, lovastatin was still commonly used in Malaysia with 23% of the sampled patients being on this drug. It would be expected that the availability of Storvas®, a low-cost generic form of a potent statin, atorvastatin can significantly increase the proportion of patients achieving their target LDL-C goals, as seen in this study.

Excellent compliance achieved throughout the study suggests the tolerability of the drug. In our study, mild myalgia and CPK elevation were reported in 3 and 10 patients respectively. None required withdrawal of study drug. Elevation of ALT was mild; the mean elevation was only 1.4 times the ULN.

As this is not a randomized active or placebo controlled study, the confounding effects of diet and exercise on the results could not be completely ruled out. However we attempted to minimize this by including only patients who had failed to achieve their target LDL-cholesterol after therapeutic life style changes (TLC) have been instituted for at least 12 weeks. The patients were also advised to continue TLC during the study. We believe that the changes in the lipid profile during the study were largely due to the study medication. The limitations of an open label single arm study with historical comparison to the innovator should also be considered in the interpretation of the results.

In conclusion, the data suggests that the generic atorvastatin (Storvas®) is efficacious and safe in the treatment of hypercholesterolaemia and the results are consistent with previous published data on innovator atorvastatin (Lipitor®).

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