

Increased systemic exposure to rosuvastatin in Asian subjects residing in the United States compared with Caucasian subjects

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background

- Rosuvastatin is effective in reducing low-density lipoprotein cholesterol in patients with hypercholesterolaemia from diverse ethnic backgrounds, including those of South Asian, Hispanic American and African American origin.^{1,2}
- Rosuvastatin clearance is decreased by ~50% in Japanese subjects compared with Caucasian subjects.³
- An ~2-fold increase in systemic rosuvastatin exposure has been observed in Japanese subjects resident in Japan compared with Caucasian subjects resident in Western countries.^{4,5}
- An open-label study in healthy Caucasian, Chinese, Malay and Asian-Indian volunteers all residing in Singapore demonstrated increases in rosuvastatin plasma exposure; area under the plasma concentration-time curve from zero to time of the last quantifiable concentration (AUC_(0-t)) of 2.3-, 1.9- and 1.6-fold in Chinese, Malay and Asian-Indian volunteers, respectively, compared with Caucasians.⁶

objective

- To determine if differences in systemic exposure to rosuvastatin exist between the most populous Asian population sub-groups⁷ and Caucasian subjects living in the United States (US).

methods

- Prospective, open-label, single dose, single-centre pharmacokinetic study in healthy adults (18–65 years) with a body mass index (BMI) of 18–29 kg/m².
- Participants were of Caucasian origin (reference group) or of Chinese, Filipino, Asian-Indian, Korean, Vietnamese or Japanese heritage (self-reported), resident in the US for ≥12 continuous months prior to the study.
- Eligible subjects fasted for 8 h prior to receiving a single oral dose of rosuvastatin 20 mg and blood samples were collected for pharmacokinetic analysis pre-dose and for up to 72 h post-dose.
- Plasma concentrations of rosuvastatin, N-desmethyl rosuvastatin and rosuvastatin lactone were determined using a validated liquid chromatographic tandem mass spectrometric method.
- Dietary intake was recorded for 3 days during the screening period and evaluated using validated nutrition analysis software.
- Safety assessments (adverse events [AEs], medical examinations and clinical laboratory tests) were performed throughout the study.

Pharmacokinetic and statistical analyses

- Analyses were based either on the safety population, i.e. subjects who received ≥1 dose of rosuvastatin, or the evaluable population, i.e. subjects who completed all study procedures.
- Differences in diet (total daily caloric intake; daily cholesterol intake; and total fat, saturated fat, carbohydrate and protein as a % of total calories) between each Asian ethnic group and the Caucasian group were analysed by ANOVA.
- Pharmacokinetic parameters were estimated by non-compartmental analysis. AUC_(0-t), maximum plasma drug concentration (C_{max}) and terminal elimination half-life (t_{1/2z}) were log-transformed and analysed by ANOVA.
- Analysis of the time to reach peak concentration (t_{max}) was performed on untransformed data.
- An ANOVA model for log-transformed AUC_(0-t) was fitted for ethnic groups. Least squares means (LSMs) and 95% confidence intervals (CIs), and LSMs of the differences between each Asian ethnic group and the Caucasian group and their 90% CIs, were calculated.
- LSMs and CIs were anti-log transformed to derive least squares geometric means and 95% CIs, and least squares geometric mean ratios along with their 90% CIs. AUC, C_{max} and t_{1/2z} measures were treated similarly.
- LSMs and 95% CIs for N-desmethyl rosuvastatin AUC_(0-t) and C_{max} were derived as described above for rosuvastatin.

results

- In total, 184 subjects received single dose rosuvastatin 20 mg; of these 183 were evaluable for the pharmacokinetic analyses.
- Baseline characteristics are shown in Table 1. BMI was similar across all groups, although Caucasians were heavier (~7%) and taller than Asians.
- Dietary assessment revealed no significant differences in total daily caloric intake; daily cholesterol intake; and total fat, saturated fat, carbohydrate and protein as a % of total calories between the ethnic groups.
- Rosuvastatin pharmacokinetic parameters and statistical comparisons for each Asian group relative to the Caucasian group are shown in Table 2.
- Plasma rosuvastatin concentration-time profiles for each ethnic group are shown in Figure 1. Rosuvastatin AUC_(0-t) and C_{max} were consistently higher in all ethnic groups compared with Caucasians (Table 2).

Table 1. Baseline characteristics (safety population)

| | Chinese n=26 | Filipino n=27 | Asian-Indian n=26 | Korean n=26 | Vietnamese n=26 | Japanese n=27 | Caucasian n=26 |
|----------------------------------|-----------------|------------------|----------------------|----------------|--------------------|------------------|-------------------|
| Mean age, years (SD) | 25.9 (7.1) | 30.3 (8.5) | 24.5 (7.6) | 21.7 (1.9) | 33.5 (17.1) | 35.8 (13.1) | 32.6 (13.1) |
| Males, n (%) | 20 (77) | 18 (67) | 17 (65) | 12 (46) | 19 (73) | 17 (63) | 19 (73) |
| Mean body weight, kg (SD) | 69.7 (10.2) | 63.6 (10.4) | 68.3 (12.8) | 66.3 (10.8) | 66.4 (12.6) | 69.4 (11.1) | 74.9 (16.1) |
| Mean height, cm (SD) | 173 (8.2) | 164 (6.9) | 171 (8.5) | 168 (8.2) | 168 (8.9) | 168 (8.8) | 177 (11.4) |
| Mean BMI, kg/m ² (SD) | 23.4 (2.7) | 23.5 (2.8) | 23.3 (2.9) | 23.5 (3.3) | 23.4 (3.3) | 24.5 (2.7) | 23.8 (3.0) |

SD=standard deviation

Table 2. Pharmacokinetic parameters following a single oral dose of rosuvastatin 20 mg (evaluable population)

| | Pooled Asian† n=131 | Chinese n=26 | Filipino n=27 | Asian-Indian n=26 | Korean n=26 | Vietnamese n=26 | Japanese n=27 | Caucasian n=26 |
|---|------------------------|---------------------|---------------------|----------------------|---------------------|---------------------|---------------------|--------------------|
| AUC_(0-t) (ng.h/mL) | | | | | | | | |
| Gmean (95% CI) | 202 (186–218) | 207 (174–247) | 213 (180–254) | 146 (122–174) | 191 (160–227) | 205 (171–245) | 193 (162–229) | 116 (97–138) |
| Ratio (90% CI) [‡] | 1.74 (1.48–2.04) | 1.79 (1.45–2.20) | 1.84 (1.49–2.26) | 1.26 (1.02–1.55) | 1.64 (1.33–2.02) | 1.76 (1.43–2.17) | 1.66 (1.35–2.04) | – |
| C_{max} (ng/mL) | | | | | | | | |
| Gmean (95% CI) | 22.0 (20.1–24.1) | 22.4 (18.3–27.5) | 23.3 (19.1–28.5) | 15.3 (12.5–18.7) | 20.5 (16.7–25.1) | 20.2 (16.4–24.9) | 23.6 (19.3–28.8) | 11.9 (9.7–14.6) |
| Ratio (90% CI) [‡] | 1.85 (1.54–2.23) | 1.89 (1.48–2.40) | 1.97 (1.55–2.49) | 1.29 (1.01–1.64) | 1.72 (1.35–2.19) | 1.70 (1.33–2.17) | 1.98 (1.56–2.52) | – |
| t_{1/2z} (h)[§] | | | | | | | | |
| Gmean (95% CI) | 11.0 (10.4–11.7) | 11.9 (8.3–20.5) | 10.7 (5.5–17.5) | 11.4 (7.3–19.9) | 10.8 (7.1–15.6) | 11.6 (6.7–22.0) | 10.1 (5.0–21.0) | 14.5 (8.4–22.5) |
| Ratio (90% CI) [‡] | 0.76 (0.66–0.87) | 0.82 (0.70–0.96) | 0.74 (0.62–0.87) | 0.79 (0.67–0.93) | 0.75 (0.63–0.88) | 0.80 (0.68–0.94) | 0.70 (0.59–0.82) | – |
| t_{max} (h) | | | | | | | | |
| Mean (SD) | 3.86 (1.36) | 3.89 (1.24) | 3.55 (1.43) | 4.16 (1.38) | 3.52 (1.61) | 4.18 (1.34) | 4.19 (1.08) | 4.35 (1.24) |
| Median (range) | 4.00 (0.5–6.0) | 4.00 (1.0–6.0) | 3.00 (1.0–6.0) | 5.00 (1.0–6.0) | 3.54 (0.5–6.0) | 5.00 (0.5–6.0) | 5.00 (2.0–6.0) | 4.50 (2.0–6.1) |

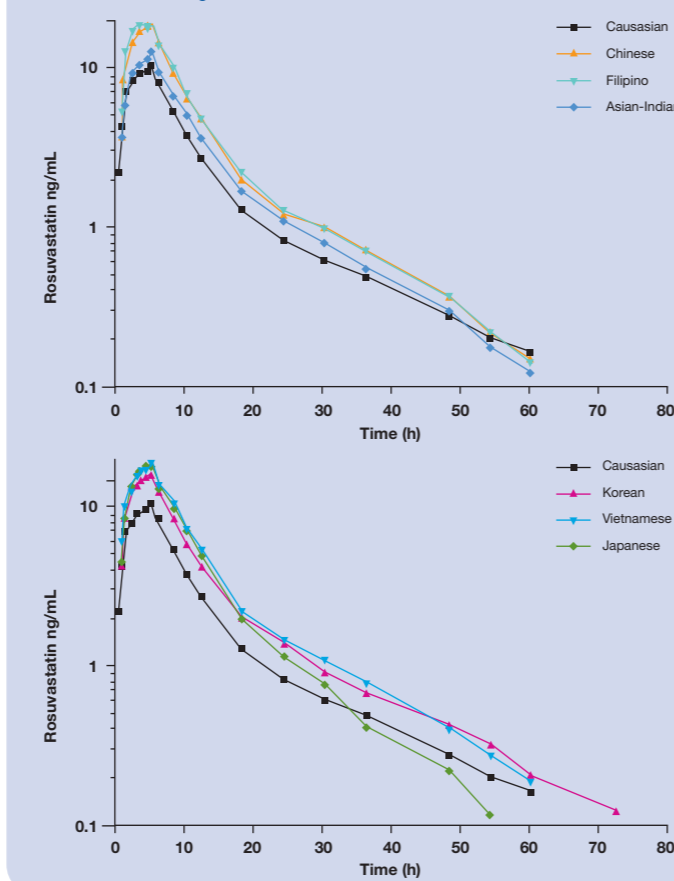
Gmean=geometric mean

†Includes: Chinese, Filipino, Korean, Vietnamese and Japanese groups

‡Ratio of Asian subgroup to Caucasian group (based on Gmean data)

§t_{1/2z} was not measured in all subjects: Pooled Asian (n=93); Chinese (n=21), Filipino (n=17), Asian-Indian (n=19); Korean (n=17); Vietnamese (n=19); Japanese (n=19) and Caucasian (n=14)

Figure 1. Gmean plasma concentrations following a single oral dose of rosuvastatin 20 mg



- Rosuvastatin plasma exposure was homogeneous among five of the Asian groups: Chinese, Filipino, Korean, Vietnamese and Japanese; these groups were pooled for comparison with the Caucasian control group (Table 2).
- Normalising AUC_(0-t) and C_{max} for body weight did not substantially change observed differences in exposure between the ethnic groups.
- No clinically significant difference in t_{1/2z} or t_{max} was observed between the ethnic groups, although each parameter tended to be shorter in each Asian subgroup compared with Caucasians.
- N-desmethyl rosuvastatin AUC_(0-t) and C_{max} were also consistently higher in Chinese, Japanese, Vietnamese, Korean and Filipino subjects compared with Caucasians. Exposure to N-desmethyl rosuvastatin in Asian-Indians was only slightly higher than in Caucasians (Table 3 and Figure 2). Similar trends were seen for rosuvastatin lactone.

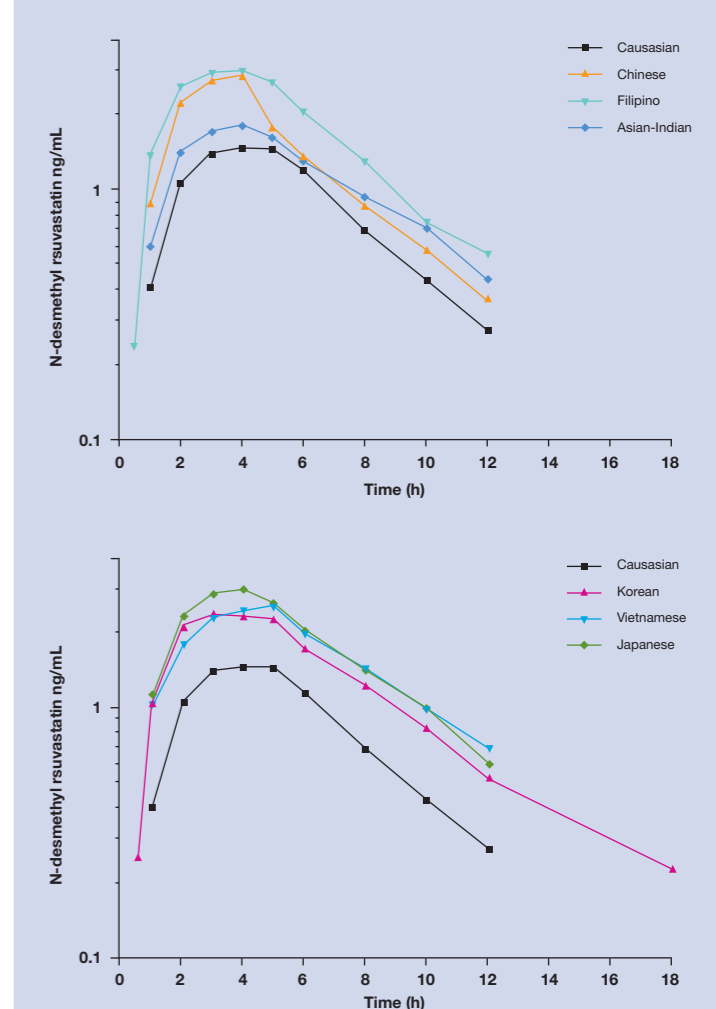
Table 3. N-desmethyl rosuvastatin AUC_(0-t) and C_{max}

| Group | n | AUC _(0-t) (ng.h/mL) Gmean (95% CI) | C _{max} (ng/mL) Gmean (95% CI) |
|---------------|-----|--|--|
| Pooled Asian† | 131 | 22.4 (20.2–24.8) | 3.2 (2.9–3.5) |
| Chinese | 26 | 23.3 (18.5–29.3) | 3.2 (2.6–4.0) |
| Filipino | 27 | 22.7 (18.1–28.4) | 3.4 (2.8–4.2) |
| Asian-Indian | 26 | 14.9 (11.8–18.7) | 2.1 (1.7–2.6) |
| Korean | 26 | 20.7 (16.5–26.1) | 2.9 (2.4–3.6) |
| Vietnamese | 25 | 21.5 (17.0–27.2) | 2.8 (2.3–3.5) |
| Japanese | 27 | 23.8 (19.0–29.8) | 3.5 (2.8–4.2) |
| Caucasian | 26 | 10.8 (8.6–13.6) | 1.7 (1.4–2.1) |

†Includes: Chinese, Filipino, Korean, Vietnamese and Japanese groups

- Metabolite to parent ratios were similar across the groups: N-desmethyl rosuvastatin AUC_(0-t) 0.09–0.12 ng.h/mL, C_{max} 0.14–0.15 ng/mL; rosuvastatin lactone AUC_(0-t) 0.21–0.29 ng.h/mL, C_{max} 0.12–0.13 ng/mL.
- Single-dose rosuvastatin 20 mg was well tolerated, with a similar safety profile across all the ethnic groups, and no safety concerns were identified.
- The most commonly occurring AEs were headache (7.6%), myalgia (3.3%), syncope (1.6%), allergic rhinitis (1.6%), viral upper respiratory tract infection (1.1%), and dysmenorrhea (1.1%).

Figure 2. Gmean plasma concentrations of N-desmethyl rosuvastatin following a single 20 mg oral dose of rosuvastatin



conclusions

- Plasma exposure to a single dose of rosuvastatin 20 mg was increased in the pooled Asian populations compared with Caucasians living in the US.
- The difference in rosuvastatin exposure between the pooled Asian group and the Caucasian group could not be attributed to diet, body weight or differences in the rate of metabolism of rosuvastatin.
- Pharmacokinetic differences between the pooled Asian and Caucasian groups do not appear to be caused by factor(s) unique to the local or regional environment, suggesting that rosuvastatin exposure is likely to be influenced more by intrinsic than extrinsic factors.
- Exposure in Asian-Indians was higher than in Caucasians but lower than in the pooled Asian group.
- The potential mechanism(s) underlying differences in rosuvastatin exposure between these populations remains to be elucidated.
- The influence of ethnic background on plasma exposure levels should be considered when making statin dosing decisions in Asian patients.

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