OBJECTIVES
The primary objective of this study was to determine the pharmacokinetics of single oral doses of 10, 40, and 80 mg rosuvastatin and the pharmacokinetics of multiple doses of 80 mg rosuvastatin given over a 7-day period.
The secondary objective was to assess the safety and tolerability of single 10-, 40-, and 80-mg doses and of repeat 80-mg doses for 7 days.

METHODS
Design: This was an open-label, nonrandomized, parallel group trial conducted at a single center. Serial blood samples and a 24-hour urine specimen were obtained after ascending single-dose administrations of rosuvastatin 10, 40, and 80 mg in 3 groups of subjects. Subjects receiving the 80-mg dose then received rosuvastatin 80 mg once daily for 7 days after a 4 to 10 day wash-out period; serial blood samples and a 24-hour urine specimen were obtained on Day 7.
Population: 18 pediatric subjects.
Key inclusion criteria: pediatric subjects aged 10 to 17 years inclusive weighing at least 35 kilograms with a serum level of low-density lipoprotein cholesterol (LDL-C) at least
190 mg/dL, or LDL-C at least 160 mg/dL and at least 1 first-degree family member or grandparent with a history of premature coronary artery disease.

**Key exclusion criteria:** acute illness within 2 weeks prior to taking trial treatment; clinically significant abnormalities in clinical chemistry, hematology, or urine parameters; history or presence of gastrointestinal, hepatic, or renal condition known to interfere with absorption, distribution, metabolism, or excretion of drugs; history of Gilberts syndrome; treatment within 3 months of trial treatment with any drug known to have a well-defined potential for hepatotoxicity; treatment with any lipid lowering medications within 2 weeks before the first day of the administration of trial treatment; cigarette smoking.

**Dosage:** The first group of subjects received rosvastatin 10 mg once daily orally (F12672, lot number 2000022306) with 240 mL of water under fasting conditions on the morning of Day 1. If the trial treatment was well tolerated in 6 evaluable subjects, the second group received rosvastatin 40 mg (F12674, lot number 2000022306) in like fashion. If the trial treatment was well tolerated in 6 evaluable subjects, the third group then received rosvastatin 80 mg (F12675, lot number 2000022306) in like fashion. If the first dose of rosvastatin 80 mg was well tolerated, the third group of subjects received rosvastatin 80 mg once daily for 7 days beginning after a 4 to 10 day wash-out period.

**Key assessments:**

**Pharmacokinetic:** The primary end points were the maximum plasma concentration ($C_{\text{max}}$) and the areas under the plasma concentration-versus-time curves from time 0 to 24 hours ($AUC_{(0-24)}$) and from time 0 to the last observable plasma concentration for rosvastatin ($AUC_{(0-t)}$), all other end points were secondary. Blood specimens were collected for the determination of plasma concentrations of rosvastatin and N-desmethyl rosvastatin at predose and after the first dose of trial treatment at 0.5, 1, 2, 3, 4, 5, 6, 9, 12, 18, 24, 48, 72, and 96 hours; and from subjects receiving rosvastatin 80 mg at Day 7 predose and at 0.5, 1, 2, 3, 4, 5, 6, 9, 12, 18, and 24 hours after the administration on Day 7 in order to determine the following pharmacokinetic parameters for rosvastatin and its N-desmethyl metabolite: $C_{\text{max}}$, the time of the maximum plasma concentration ($t_{\text{max}}$), the terminal elimination rate constant ($\lambda_z$) and half-life ($t_{1/2}$), $AUC_{(0-t)}$, the area under the plasma concentration-versus-time curve from time 0 to infinity ($AUC$), and, for single administrations of trial treatment, the apparent oral clearance ($CL/f$) and apparent volume of distribution ($Vz/f$). Additionally, the accumulation ratios were calculated and time-dependent changes in pharmacokinetics were evaluated for rosvastatin and the N-desmethyl metabolite.

Urine specimens were collected from 0 to 6 hours, 6 to 12 hours, and from 12 to 24 hours after administration of trial treatment on Day 1 and, for subjects receiving a 7-day course, on Day 7 in order to determine the renal clearance ($CL_R$) of rosvastatin and its N-desmethyl metabolite and the fraction of unchanged rosvastatin in urine ($Fe$).

**Safety:** Safety of rosvastatin was assessed by monitoring adverse events, clinical laboratory data (blood chemistry, hepatic biochemistry, creatine kinase [CK], renal biochemistry, hematology, and urinalysis), vital signs (blood pressure, pulse rate, and oral temperature), electrocardiograms (ECGs), and physical examinations.
RESULTS

Demography: The first subject entered the trial on 30 July 2001 and the last subject completed the trial on 9 November 2001. The 18 subjects included 9 boys (8 Caucasian, 1 Black) and 9 girls (6 Caucasian, 3 Black), with mean age, height, weight, and body mass index of 14 years (range 10 to 17 years), 167 cm (range 142 to 180 cm), 67 kg (range 32 to 116 kg), and 24 (range 16 to 44), respectively. All subjects completed the trial. All subjects were evaluable for pharmacokinetic analysis and safety.
### Pharmacokinetics:

**Table A  Plasma pharmacokinetics of rosuvastatin**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Summary statistic</th>
<th>Single-dose</th>
<th>Multiple-dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>10 mg</td>
<td>40 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>N = 6</td>
<td>N = 6</td>
</tr>
<tr>
<td><strong>Primary endpoints</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( C_{\text{max}}, \text{ng/mL} )</td>
<td>gmean (CV)</td>
<td>6.3 (58.1)</td>
<td>23.5 (79.6)</td>
</tr>
<tr>
<td></td>
<td>range(^a)</td>
<td>2.6, 12.7</td>
<td>7.3, 56.6</td>
</tr>
<tr>
<td>n</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>( \text{AUC}_{(0-24)}, \text{ng-h/mL} )</td>
<td>gmean (CV)</td>
<td>48.7 (48.3)</td>
<td>234 (62.9)</td>
</tr>
<tr>
<td></td>
<td>range(^a)</td>
<td>21.3, 79.9</td>
<td>86.0, 432</td>
</tr>
<tr>
<td>n</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>( \text{AUC}_{(0-t)},^{b}\text{ng-h/mL} )</td>
<td>gmean (CV)</td>
<td>52.2 (52.3)</td>
<td>288 (65.2)</td>
</tr>
<tr>
<td></td>
<td>range(^a)</td>
<td>21.3, 79.9</td>
<td>101, 478</td>
</tr>
<tr>
<td>n</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>( \text{AUC}, \text{ng-h/mL} )</td>
<td>gmean (CV)</td>
<td>47.6 (71.6)</td>
<td>299 (63.5)</td>
</tr>
<tr>
<td></td>
<td>range(^a)</td>
<td>23.9, 85.5</td>
<td>105, 485</td>
</tr>
<tr>
<td>n</td>
<td>3</td>
<td>6</td>
<td>6</td>
</tr>
</tbody>
</table>

**Secondary endpoints**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Summary statistic</th>
<th>Single-dose</th>
<th>Multiple-dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( t_{\text{max}}, \text{h} )</td>
<td>median</td>
<td>2.5</td>
<td>3.0</td>
</tr>
<tr>
<td></td>
<td>range(^a)</td>
<td>0.5, 5.0</td>
<td>2.0, 6.0</td>
</tr>
<tr>
<td>n</td>
<td>6</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>( t_{1/2}, \text{h} )</td>
<td>mean(^a) (SD(^a))</td>
<td>8.6 (1.4)</td>
<td>14.8 (4.9)</td>
</tr>
<tr>
<td></td>
<td>range(^a)</td>
<td>7.0, 9.7</td>
<td>8.3, 21.0</td>
</tr>
<tr>
<td>n</td>
<td>3</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>( \text{CL/f}, \text{L/h} )</td>
<td>gmean (CV)</td>
<td>210 (71.5)</td>
<td>134 (63.5)</td>
</tr>
<tr>
<td></td>
<td>range(^a)</td>
<td>117, 418</td>
<td>82.4, 381</td>
</tr>
<tr>
<td>n</td>
<td>3</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>( \text{CL}_R, \text{L/h} )</td>
<td>gmean (CV)</td>
<td>6.0 (40)</td>
<td>9.3 (17)</td>
</tr>
<tr>
<td></td>
<td>range(^a)</td>
<td>4.1, 10.0</td>
<td>8.0, 11.7</td>
</tr>
<tr>
<td>n</td>
<td>6</td>
<td>6</td>
<td>5</td>
</tr>
</tbody>
</table>

*Data derived from Tables T5.2.1, T5.2.2, and T5.4.1.*

\(^a\) These statistics are calculated on untransformed data.

\(^b\) The last sampling time was 24 h for subjects in the multiple-dose group.

AUC = area under the plasma concentration-versus-time curve from time zero to infinity; \( \text{AUC}_{(0-24)} \) = area under the plasma concentration-versus-time curve from time zero to 24 hours; \( \text{AUC}_{(0-t)} \) = area under the plasma concentration-versus-time curve from time zero to the last quantifiable concentration; \( \text{CL/f} \) = apparent oral clearance; \( \text{CL}_R \) = renal clearance; \( C_{\text{max}} \) = maximum concentration; CV = coefficient of variation; Fe = fraction excreted in urine; gmean = geometric mean; NA = not applicable; NC = not calculated; SD = standard deviation; \( t_{1/2} \) = terminal elimination half-life; \( t_{\text{max}} \) = time of maximum concentration; \( X_u \) = amount excreted in urine.
### Table A  Plasma pharmacokinetics of rosuvastatin (continued)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Summary statistic</th>
<th>Single-dose</th>
<th>Multiple-dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>10 mg N = 6</td>
<td>40 mg N = 6</td>
<td>80 mg N = 6</td>
</tr>
<tr>
<td>Fe, %</td>
<td>gmean (CV)</td>
<td>2.9 (45)</td>
<td>5.5 (53)</td>
</tr>
<tr>
<td></td>
<td>range a</td>
<td>1.9, 6.1</td>
<td>2.5, 8.8</td>
</tr>
<tr>
<td>n</td>
<td>6</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Xu, µg</td>
<td>gmean (CV)</td>
<td>294 (45)</td>
<td>2180 (53)</td>
</tr>
<tr>
<td></td>
<td>range a</td>
<td>187, 609</td>
<td>1010, 3520</td>
</tr>
<tr>
<td>n</td>
<td>6</td>
<td>6</td>
<td>5</td>
</tr>
</tbody>
</table>

Data derived from Tables T5.2.1, T5.2.2, and T5.4.1.

* a These statistics are calculated on untransformed data.
* b The last sampling time was 24 h for subjects in the multiple-dose group.

AUC = area under the plasma concentration-versus-time curve from time zero to infinity; AUC_{(0-24)} = area under the plasma concentration-versus-time curve from time zero to 24 hours; AUC_{(0-t)} = area under the plasma concentration-versus-time curve from time zero to the last quantifiable concentration; CL/f = apparent oral clearance; CLR = renal clearance; C_{max} = maximum concentration; CV = coefficient of variation; Fe = fraction excreted in urine; gmean = geometric mean; NA = not applicable; NC = not calculated; SD = standard deviation; t_{1/2} = terminal elimination half-life; t_{max} = time of maximum concentration; Xu = amount excreted in urine.

Systemic exposure of rosuvastatin increased with single administrations of rosuvastatin 10 to 40 to 80 mg in children and adolescents with heterozygous familial hypercholesterolemia (Table A). For subjects receiving multiple doses of rosuvastatin 80 mg, C_{max} and AUC_{(0-24)} were approximately 19% and 49% greater, respectively, than the corresponding values after single-dose administrations. Pre-dose and 24-hour trough concentrations of rosuvastatin in plasma were comparable by inspection, suggesting that steady state was achieved by Day 7. The accumulation ratio of rosuvastatin was 1.5. No important time-dependent changes were observed when comparing the pharmacokinetics on Day 7 with Day 1. The apparent oral clearance of rosuvastatin appeared independent of dose. The maximum gmean renal excretion of rosuvastatin at any dose level was 5.5%. The exposure to N-desmethyl rosuvastatin, a metabolite of rosuvastatin, did not appear to increase with multiple administrations of rosuvastatin; mean first-dose and steady-state values of C_{max} were 8.0 and 6.5 ng/mL, AUC_{(0-t)} values were 45.4 and 45.7 ng·h/mL. The metabolite was rapidly formed and plasma concentrations quickly fell below the limit of quantification; it was not possible to determine t_{1/2} or renal clearance of the metabolite.

**Safety:** There were no withdrawals from the trial, no serious adverse events, and no deaths during the trial. The most frequent adverse events were headache (1 subject on 10 mg, 2 subjects on 40 mg, and 1 subject on 80 mg in the multiple-dose phase), and abdominal pain and nausea (2 subjects each on 40 mg and 1 subject on 80 mg in the multiple-dose phase). One subject had an adverse event attributed by the investigator to rosuvastatin, a mild elevation of ALT on Day 13 (rosuvastatin 80 mg multiple dose), 6 days following the last dose, that resolved without treatment. There were no clinically significant changes from screening in clinical
chemistry parameters, urinalyses, vital signs, ECGs, or physical findings. Rosuvastatin was well tolerated in doses up to 80 mg for up to 7 days in this subject population.

OVERALL CONCLUSIONS
Systemic exposure of rosuvastatin increased with dose following single administrations of rosuvastatin from 10 to 40 to 80 mg in children and adolescents with heterozygous familial hypercholesterolemia. For subjects receiving multiple doses of rosuvastatin 80 mg, $C_{\text{max}}$ and $\text{AUC}_{(0-24)}$ were approximately 19% and 49% greater than the corresponding values after single-dose administrations. No important time-dependent changes were observed when comparing the pharmacokinetics on Day 7 with Day 1. Rosuvastatin was well tolerated in doses up to 80 mg for up to 7 days in this subject population.