Pharmacokinetic and Pharmacodynamic Properties of Cinacalcet (KRN1493) in Chinese Healthy Volunteers: A Randomized, Open-label, Single Ascending–dose and Multiple-dose, Parallel-group Study

Hongzhong Liu, MD; Hongyun Wang, PhD; Tao Liu, BSc; Ji Jiang, PhD; Xia Chen, MD; Feng Gao, BSc; and Pei Hu, MD

1Clinical Pharmacology Research Centre, Peking Union Medical College Hospital, Beijing, China; and 2Kyowa Hakko Kirin China Pharmaceutical Co, Ltd, Shanghai, China

ABSTRACT

Purpose: The aim of this study was to assess the pharmacokinetic (PK) and pharmacodynamic (PD) properties and safety of single and multiple doses of cinacalcet in Chinese healthy volunteers (HVs) for the purposes of a New Drug Application package for the Chinese Food and Drug Administration.

Methods: In this randomized, open-label, single ascending–dose and multiple-dose, parallel-group study, 42 Chinese HVs were randomized to receive a single oral dose of 25, 50, or 100 mg of cinacalcet and multiple doses of 50 mg of cinacalcet once daily for 7 days. Plasma cinacalcet concentrations were analyzed by HPLC-MS/MS. The PK parameters were assessed with noncompartmental analysis. Plasma intact parathyroid hormone, serum calcium, and phosphorus concentrations were measured for PD evaluation. The safety profile was also assessed. Adverse events (AEs) were noted during the study.

Findings: Of the 42 randomized HVs, 41 completed the study per protocol; 1 prematurely discontinued the study because of AEs. Cinacalcet has nonlinear PK properties over a dose range of 25 to 100 mg after a single dose. Mean (SD) Cmax values were 7.68 (4.25), 17 (6.33), and 31.3 (16.42) ng/mL with single doses of 25, 50, and 100 mg of cinacalcet, respectively. Mean (SD) AUC0–last values were 58.4 (25.38), 187 (70.7), and 367 (180.03) hr·ng/mL with single doses of 25, 50, and 100 mg of cinacalcet, respectively. Steady state was attained within 7 doses of successive daily administration of 50 mg of cinacalcet. At steady state, the mean (SD) Cmax and AUC0–last values were 20.6 (9.63) ng/mL and 297 (146.15) ng·h/mL. The accumulation ratios of Cmax and AUC (AUC0–τ/AUC0–24) were 1.21 and 1.32. Plasma intact parathyroid hormone and serum calcium concentrations had similar patterns, both decreased after administration of cinacalcet, whether after single dose or multiple doses. A total of 52 AEs were reported in 20 HVs (47.6%). The most frequently reported AEs after single-dose and multiple-dose cinacalcet administration were hypocalcemia, numbness, dizziness, and muscle soreness. No serious AEs were reported.

Implications: Cinacalcet was well tolerated and effective after administration of a single oral dose up to 100 mg and multiple doses of 50 mg of cinacalcet once daily for 7 days. Cinacalcet has nonlinear PK properties over a dose range of 25 to 100 mg after a single dose. PK profiles after multiple doses were similar to those after a single dose with no accumulation. Cinacalcet had similar PK and safety profiles between Chinese and Western HVs at the same dose levels. (Clin Ther. 2016;38:348–357) © 2016 Elsevier HS Journals, Inc. All rights reserved.

Key words: Chinese healthy volunteers, cinacalcet, pharmacodynamic properties, pharmacokinetic properties, secondary hyperparathyroidism.

INTRODUCTION

Secondary hyperparathyroidism is a common complication in patients with chronic kidney disease.1,2 This condition is characterized by an increased level of circulating parathyroid hormone (PTH) and derangements in calcium and phosphorus metabolism.3

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If not adequately controlled, secondary hyperparathyroidism contributes to an increased risk of mortality, vascular calcification, and metabolic bone disease, causing disability and a risk of skeletal fracture.

Traditional therapies for secondary hyperparathyroidism frequently involve the use of phosphate binders and vitamin D sterols. However, these conventional therapies may contribute to hypercalcemia and/or hyperphosphatemia. Therefore, few patients achieve treatment targets for calcium, phosphate, calcium-phosphorus product, or PTH. Thus, there is a significant unmet medical need in the treatment of secondary hyperparathyroidism.

Cinacalcet (KRN1493) is a calcimimetic approved for the treatment of secondary hyperparathyroidism in patients with chronic kidney disease and for the treatment of hypercalcemia in patients with parathyroid carcinoma. Cinacalcet increases the sensitivity of the calcium-sensing receptor to extracellular calcium, which leads to a decrease of PTH secretion and subsequently to lower serum calcium concentrations. Cinacalcet has been successfully used in dialysis patients and in patients with primary hyperparathyroidism. The pharmacokinetic (PK) and pharmacodynamics (PD) properties of cinacalcet have been investigated in Westerners, including healthy volunteers (HVs), patients with chronic kidney disease, patients after renal transplantation, and patients with hepatic impairment. After oral administration, peak plasma concentrations of cinacalcet occur within 2 to 6 hours. The absolute bioavailability is 20% to 25%. The terminal t½ is 30 to 40 hours, and steady-state concentrations are achieved within 7 days. The PK properties of cinacalcet are dose proportional over the dose range of 30 to 180 mg. Differences in the PK and PD properties among ethnic groups have been reported with several drugs, with one of the major causes of differences being related to ethnic-specific genetic polymorphisms in drug-metabolizing isozymes, such as cytochrome P450 (CYP) 3A4, 1A2, and 2D6. The drug is extensively metabolized primarily by the CYP3A4, CYP2D6, and CYP1A2 to N-dealkylation and β-oxidation derivatives that have little or no pharmacologic activity. The PK and PD properties of cinacalcet have also been investigated in healthy male Korean populations and Japanese populations, but they have not ever been investigated in Chinese populations.

The objective of the present study was to evaluate the PK and PD properties and safety of a single ascending dose of 25, 50, and 100 mg of cinacalcet and multiple doses of 50 mg of cinacalcet once daily for 7 days in Chinese HVs for the purposes of a New Drug Application package for the Chinese Food and Drug Administration.

METHODS
Subjects
Forty-two Chinese HVs (30 for single dose and 12 for multiple doses) between the ages of 20 and 36 years with a body mass index (BMI) in the range of 18.8 to 24.4 kg/m² were enrolled in this study. The percentage of male to female is 50/50. Before enrollment, subjects were examined to confirm that they were of good physical and mental health. Subjects who consumed any medicine, food, or beverage known to be CYP2D6, CYP1A2, or CYP3A4 inducers or inhibitors within 2 weeks before the study initiation were excluded from the study.

Study Design
This was a randomized, open-label, single ascending–dose and multiple-dose, parallel-group study. Thirty HVs were randomly assigned to receive a single dose of 25, 50, or 100 mg of oral cinacalcet. After the single-dose study was finished, other 12 HVs were assigned to receive multiple doses of 50 mg of oral cinacalcet once daily for 7 days. All study medications were provided as 25-mg or 75-mg tablets. The HVs were admitted to the Peking Union Medical College Hospital (PUMCH) Clinical Pharmacology Research Centre 1 day before dosing. On the day of dosing, HVs received study medication together with 240 mL of water in the overnight-fasted state.

This study was sponsored by Kyowa Hakko Kirin China Pharmaceutical Co, Ltd. All study procedures were conducted in accordance with Chinese Good Clinical Practice and the Declaration of Helsinki. The Independent Ethics Committee of PUMCH (Beijing, China) approved the study protocol. All participants provided written informed consent before any study procedures, including screening tests, were conducted.

PK Assessments
Blood samples (4 mL each) were taken to determine plasma cinacalcet concentrations before dosing and at
0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 12, 24, 48, 72, 96, and 120 hours after administration of single-dose and the seventh dose during the multiple-dose period. Otherwise, blood samples were also taken before dosing on day 1 to day 6 of the multiple-dose period. These blood samples were collected into sodium heparin–containing tubes and centrifuged at 2500g for 10 minutes at 4°C. Plasma was separated and stored at −20°C for further analysis. Plasma cinacalcet concentrations were measured using a validated HPLC-MS/MS assay method with a lower limit of quantitation of 0.1 ng/mL. The analyte was extracted from plasma samples using a 96-well plate automatic solid-phase extraction device and chromatographed on an Inertsil SIL-150 (2.1 × 50 mm; inside diameter, 5 μm) column using acetonitrile–water–formic acid (90:10:1) as the mobile phase with an isocratic flow rate of 0.35 mL/min. The detection was performed on a triple quadrupole tandem mass spectrometer in multiple reaction monitoring mode using positive electrospray ionization. The method was validated over the concentration range of 0.1 to 25 ng/mL. The indicators of interday and intraday precision were all within 15.1%, and the accuracy was within ±15%. The mean extraction recovery was 51.7%, and the detection was not affected by the matrix. The method was successfully applied to a PK study of cinacalcet hydrochloride in Chinese HVs.

The PK parameters were estimated by Phoenix software, version 6.3 (Pharsight Corp., Mountain View, California), using noncompartmental analysis (NCA). The reported NCA PK parameters include AUC0–last, AUC0–∞, Cmax, CL/F, apparent volume of distribution, and t1/2 for single-dose cinacalcet. For multiple-dose, steady-state PK parameters, including AUC0–last,ss, Cmax,ss, t1/2, and CLss/F, were presented. The accumulation ratio (AR) of multiple-dose cinacalcet once daily was calculated as AUC0–24,ss on day 7 (last dose day) divided by AUC0–24 on day 1 after the single dose. The AR of Cmax was calculated as Cmax on day 7 divided by Cmax on day 1 after a single dose. The AR was performed only for single-dose and multiple-dose data of 50 mg of cinacalcet.

PD Assessments
Serial blood samples to assess plasma intact PTH (iPTH), serum calcium, and serum phosphorus concentrations were collected before dosing and at 4, 8, 12, 24, and 48 hours after dosing during the single-dose period. For the multiple-dose period, these measurements were taken before dosing on days 1 to 7 and at 24, 48, 72, 96, and 120 hours after the last dose.

The maximum changes in plasma iPTH, serum calcium, and phosphorus concentrations, time of maximum changes, and time at which the levels returned to baseline values were determined by direct inspections of the observed values.

Safety Assessments
Adverse events (AEs) were monitored throughout the study. During each period, vital signs, 12-lead ECG, and clinical laboratory evaluations (clinical chemical analysis, hematologic testing, and urinalysis) were recorded. All AEs were assessed by the investigators with respect to severity, course, outcome, seriousness, and relationship to the study drug. Clinical laboratory tests were performed by the central laboratory of PUMCH, which obtained College of American Pathologists Laboratory Accreditation Certificate.

Statistical Analysis
The PK set (by treatment) consisted of all HVs who received the dose of cinacalcet and provided evaluable PK profiles for the treatment. The safety set included all HVs who received at least one dose of cinacalcet (even those who took only part of the scheduled dose were considered). Descriptive statistics of PK parameters from NCA in Chinese HVs were summarized by single-dose and multiple-dose cinacalcet treatments. Dose-exposure proportionality analysis was evaluated by POWER model.

RESULTS
Participant Demographic Characteristics and Disposition
A total of 42 HVs were enrolled and randomly assigned to single-dose groups (25, 50, or 100 mg) and multiple-dose group (50 mg once daily for 7 days). Forty-one completed the study per protocol. One HV prematurely discontinued the study because of AEs on day 5 of multiple-dose treatments. The dropout case was still included in the safety assessments. For PK analysis, HVs with sufficient PK time point data to adequately calculate PK parameters were included.
All HVs in this study were Chinese, with a mean (SD) age of 24.4 (3.49) years, weight of 60.2 (9.12) kg, and BMI of 21.6 (1.54) kg/m². Demographic parameters were similar among the 4 dose groups (Table I).

PK Results

**Single-dose Cinacalcet PK Profile**

Cinacalcet arithmetic mean (SD) concentration-time profiles after a single dose of cinacalcet of 25, 50, or 100 mg are given in Figure 1A. In the 50- and 100-mg groups, the median $T_{\text{max}}$ was 5 hours after dosing, but in the 25-mg group, the median $T_{\text{max}}$ was 2.5 hours after dosing. Plasma cinacalcet concentrations subsequently decreased in a biphasic manner during the 96-hour observation period for all test dose levels. The summary of descriptive statistics of PK parameters for single-dose cinacalcet is presented in Table II. Mean (SD) $C_{\text{max}}$ values were 7.68 (4.25), 17 (6.33), and 31.3 (16.42) ng/mL with 25, 50, and 100 mg of cinacalcet, respectively. Mean (SD) $AUC_{0-\text{last}}$ values were 58.4 (25.38), 187 (70.7), and 367 (180.03) ng·h/mL, and $t_{1/2}$ values were 23.3 (15.72),

<table>
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<tr>
<th>Characteristic</th>
<th>25 mg (n = 10)</th>
<th>50 mg (n = 10)</th>
<th>100 mg (n = 10)</th>
<th>50 mg Once Daily (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>23.5 (1.9)</td>
<td>23.0 (2.75)</td>
<td>24.6 (4.35)</td>
<td>26.3 (4.94)</td>
</tr>
<tr>
<td>Height, m</td>
<td>1.66 (0.068)</td>
<td>1.64 (0.0902)</td>
<td>1.69 (0.0899)</td>
<td>1.66 (0.0981)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>61.2 (7.68)</td>
<td>58.0 (8.92)</td>
<td>60.8 (10.1)</td>
<td>60.6 (9.77)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>22.2 (1.43)</td>
<td>21.4 (1.42)</td>
<td>21.1 (1.58)</td>
<td>21.7 (1.73)</td>
</tr>
</tbody>
</table>

BMI = body mass index.
*Data are presented as mean (SD).

Figure 1. Mean (SD) plasma concentration–time profiles of cinacalcet. (A) Single doses (25, 50, and 100 mg). (B) Multiple once-daily dose of 50 mg of cinacalcet.
Dose-exposure proportionality analysis was evaluated by the POWER model. Proportionality can be concluded only if the 90% CI for geometric mean values was contained completely within 0.8 to 1.25. In the dose-exposure proportionality analysis, the estimated point for AUC<sub>0-last</sub> was 1.32, with a 90% CI of 0.8 to 1.5. The 90% CI for the geometric mean ratios of the PK exposure parameters (AUC and C<sub>max</sub>) were not within the predefined target interval (90% CI, 0.8-1.25). These findings suggest that cinacalcet has nonlinear PK properties over a dose range of 25 to 100 mg.

**Multiple-dose Cinacalcet PK Profile**

For the multiple once-daily dosing, cinacalcet plasma concentration–time profiles after the last dose were similar to the single-dose profiles (Figure 1B). The summary of descriptive statistics of PK parameters from cinacalcet 50-mg multiple dosing is given in Table II. Steady state was attained within 7 doses of successive daily administration of 50 mg of cinacalcet with a mean (SD) C<sub>min</sub> of 3.53 (1.98) ng/mL before dosing on day 7. At steady state, the mean (SD) C<sub>max</sub> value was 20.6 (9.63) ng/mL, the mean (SD) AUC<sub>0-last</sub> value was 297 (146.15) ng·h/mL, and the mean (SD) t<sub>1/2</sub> value was 55.3 (33.25) h. The AR<sub>Cmax</sub> and AR<sub>AUC</sub> (AUC<sub>τ</sub>/AUC<sub>0-24</sub>) were 1.21 and 1.32.

**PD Results**

After single oral dose of cinacalcet, concentrations of plasma iPTH and serum calcium were decreased and then increased with time, but the serum phosphorus concentration decreased and recovered quickly to the baseline level and then decreased again to a lower level (Figure 2A-C). After a single oral administration of 25, 50, or 100 mg of cinacalcet, the mean (SD) maximum decreases of plasma iPTH concentration from baseline were 32.5 (14.2) pg/mL (67.8% [18.7%]), 40.3 (28.9) pg/mL (84.1% [12.5%]), and 47.8 (16.9) pg/mL (90.0% [7.3%]), respectively, which were all observed at medians of 4 hours after dosing. Plasma iPTH concentrations did not return to baseline values within 144 hours after dosing for each respective dose group. Serum calcium concentrations had patterns similar to those of plasma iPTH; the
decreased level of iPTH and calcium are proportional to the dose administered. Mean (SD) maximum decreases from baseline were 0.13 (0.06) mg/dL (5.5% [2.2%]), 0.18 (0.06) mg/dL (7.3% [2.5%]), and 0.28 (0.08) mg/dL (9.6% [2.8%]), respectively, which were observed at medians of 8, 8, and 12 hours after dosing. The plasma phosphorus concentration profiles in 3 dose groups were similar. After single oral administration of cinacalcet (25, 50, and 100 mg), the levels of serum phosphorus decreased and recovered quickly to the baseline level at approximately 12 hours after dosing, then decreased again to a lower level.

Figure 2. Mean (SD) percentage change from baseline of plasma intact parathyroid hormone (iPTH) (A), serum calcium concentration (B), and serum phosphorus (C) after single-dose administration of 25, 50, or 100 mg of oral cinacalcet.
After administration of 50 mg of cinacalcet once daily for 7 days, the treatment did not produce a significant change in the concentration of plasma iPTH and serum calcium in this study. We hypothesize that the reason was the small sample size and the variability in response of HVs at 7 days. Serum phosphate level remains higher than the predose level during the treatment (Figure 3).

Safety Results

AEs are summarized as preferred terms by treatment in Table III. One participant discontinued study treatment during the multiple-dose period because of the development of premature ventricular contraction and premature atrial contraction accompanied by chest tightness and palpitation on day 5 after receiving 5 doses of 50 mg of cinacalcet. The serum calcium level of this participant after receiving 5 doses of cinacalcet was 2.38 mmol/L, which is in the normal range.

Overall, 20 (47.6%) of 42 HVs reported at least 1 AE during the study. Of the HVs, 1 (10%), 4 (40%), and 4 (40%) reported AE after a single dose of 25, 50, and 100 mg of cinacalcet, respectively, and 11 (91.7%) reported AEs after a multiple dose of 50 mg of cinacalcet. The most frequently reported AEs overall were hypocalcemia (14.3%), hypoesthesia (14.3%), dizziness, (11.9%), and muscle soreness (11.9%). Higher incidences for those events were observed in the multiple-dose group compared with the single-dose group. The incidence of AEs increased with dose level, especially in female subjects after a single dose of 100 mg of cinacalcet, and was significantly higher than other single-dose group. The serum calcium value of those with hypocalcemia was approximately 2.10 mmol/L, with the lowest level of 1.99 mmol/L. Some participants experienced symptoms of hypoesthesia and muscle spasms. These AEs may be considered symptoms of hypocalcemia. No clinically significant findings were observed on physical examination, including vital sign measurements. All the AEs that emerged during the study were mild and resolved without treatment. A total of 15 AEs (28.8%) were considered treatment related by the investigators. No serious AEs were reported during the study.

DISCUSSION

The plasma concentration–time profiles of single-dose cinacalcet (25, 50, and 100 mg) in Chinese HVs exhibited similar characteristics as observed previously in Western, Japanese, and Korean HVs. The Cmax of cinacalcet was observed at approximately 5 hours (Tmax) after dosing in Asian (Chinese, Japanese, Korean) and 6 hours after dosing in Western HVs. The absorption and disposition phases of cinacalcet were similar between Asian and Western HVs. After the single dose, the geometric mean AUC0–∞ and Cmax levels in Chinese HVs were slightly higher than Western HVs, the magnitudes of differences were mild (11.7% and 30%, respectively), but the mean weights and age of Chinese HVs were approximately 25 kg and 27 years lower than those of Western study HVs, respectively. Although these comparisons have limitations due to differences in study design, formulation of the study drug, and characteristics of participants (eg, age, sex, weight), these comparisons suggest that there are no ethnic differences with cinacalcet after a single dose with respect to PK characteristics, considering the pronounced interindividuval variability with cinacalcet. With an increasing dose, the apparent clearance (CL/F) decreases and the t1/2 is prolonged; therefore, we think that there may be metabolic
saturation of cinacalcet. The same results were observed within Japanese HVs.21

In contrast to findings from a previous study that reported PK linearity over a dose range of 25 to 200 mg in patients undergoing hemodialysis,14 in the present study, nonlinear PK properties were observed, which were evaluated by the POWER model within the dose range of 25 to 100 mg in these Chinese HVs. The authors hypothesize that the inconsistency between the 2 studies may have resulted from the differences in subjects’ characteristics and the relatively small sample size in the present study. Nonlinear PK properties were also observed in Korean HVs with the dose range of 50 to 100 mg and Japanese HVs with the dose range of 25 to 100 mg.21 The same reasons was also explained in Korean HVs.

After multiple dosing of 50 mg of cinacalcet once daily for 7 days, the PK profiles were similar to those after a single dose with no accumulation (RAUC of approximately 1.32 and R Cmax of approximately 1.21). The PK parameters in Chinese HVs were comparable to those of Western patients with primary and secondary hyperparathyroidism after multiple dosing of 50 mg of cinacalcet once daily.10 The mean Cmax values after multiple doses in Chinese HVs and Western patients with primary and secondary hyperparathyroidism were 20.6, 18.6 and 20.2 ng/mL, respectively.10 The terminal t½ ranges from 30 to 40 hours, and steady state is achieved within 7 days in Western patients.10 In the present study in Chinese HVs, the terminal t½ is 55 hours and also achieved within 7 days.

This study also investigated the effects of cinacalcet on plasma iPTH, serum calcium, and serum phosphorus. The plasma iPTH and serum calcium levels decreased after administration of a single dose of cinacalcet. The decrease of plasma iPTH and serum calcium concentrations had an apparent proportional relationship with the dose. The serum iPTH concentration increased gradually and stabilized at a certain level. Only some participants returned to their predose

<table>
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<tr>
<th>Table III. Number (percentage) of adverse events by preferred term and treatment in Chinese healthy volunteers (safety set).</th>
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<tbody>
<tr>
<td>Adverse Event</td>
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<tr>
<td></td>
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<tr>
<td>Conjunctivitis</td>
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<td>Nausea</td>
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<td>Vomiting</td>
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<td>Dry mouth</td>
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<td>Chest tightness</td>
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<td>QT interval prolongation</td>
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<td>Dizziness</td>
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<td>Hypoesthesia</td>
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<td>Muscle soreness</td>
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<td>White blood cell count decreased</td>
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level within the period of blood collection. The serum calcium level recovered to the predose level within the period of blood collection. Serum phosphorus levels had a different pattern compared with plasma iPTH and serum calcium levels, and the level at 12 hours after dosing was higher than the levels at other time points. The transient increase in phosphorus at a single time point was caused by the diurnal variation in plasma phosphorus levels. These study findings have provided supportive data regarding the iPTH-lowering effect and favorable mineral changes with cinacalcet use, which are the clinical targets for managing secondary hyperparathyroidism.

Overall, single and multiple doses of cinacalcet were well tolerated in Chinese HVs. The observed AE profile was as expected based on previous studies. The incidence of AEs increased with dose level, especially in female subjects after a single dose of 100 mg of cinacalcet, and was significantly higher than in the other single-dose group. The incidence of AEs after multiple doses was higher than that after a single dose, especially hypocalcemia and hypoesthesia. In addition, all the AEs were mild and transient and recovered without any treatment. Fifteen AEs (28.8%) was considered to be treatment related by the investigators.

This study was not designed as a blind placebo-controlled trial. Interpretations of treatment-related AEs should keep these limitations in mind. Moreover, the present study was also limited by the small sample size and only one dose level in the multiple-dose study.

CONCLUSIONS
The findings of the present study suggest nonlinear PK characteristics of cinacalcet after administration of a single dose. The PK profiles after multiple doses were similar to those after a single dose with no accumulation. Cinacalcet had similar PK and safety profiles between Chinese and Westerners at the same dose levels. The findings also suggest accompanying PD changes of cinacalcet (decreases in the concentrations of plasma iPTH and serum calcium) in this small, selected population of Chinese HVs. Cinacalcet was well tolerated after the administration of a single oral dose up to 100 mg and multiple doses of 50 mg of cinacalcet once daily for 7 days in the same population.

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All the authors provided substantial contributions to the development and conduct of the study. Drs H. Liu, T. Liu, and P. Hu contributed to the study design, data analyses, literature searches, and manuscript writing. All authors contributed to the design of the article and revised and accepted the final manuscript. We acknowledge all study participants and investigators for their contributions to the study. Prof. Hu received research grant 2012ZX09303006-002 from the National Program on Key Research Project of New Drug Innovation for the submitted work.

CONFLICTS OF INTEREST
This research and its publication were sponsored by Kyowa Hakko Kirin China Pharmaceutical Co, Ltd. The sponsor ensured that the study was conducted according to the protocol and reviewed the study design and the manuscript. The authors have indicated that they have no other conflicts of interest with regard to the content of this article.

REFERENCES


