Evaluation of the effect of lanthanum carbonate hydrate on the pharmacokinetics of roxadustat in non-elderly healthy adult male subjects

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Funding information
This study was funded by Astellas Pharma Inc. (Tokyo, Japan). Roxadustat is being developed by FibroGen, AstraZeneca and Astellas.

Summary
What is known and objective: Roxadustat is a hypoxia-inducible factor prolyl hydroxylase inhibitor currently being investigated for the treatment of anemia in chronic kidney disease. Lanthanum carbonate is a phosphate binder that is commonly used to treat hyperphosphatemia in patients with chronic kidney disease. This study investigated the effect of lanthanum carbonate on the pharmacokinetics, safety and tolerability of a single oral dose of roxadustat in healthy non-elderly adult male subjects.

Methods: This was an open-label, randomized, two-period, two-sequence crossover study in non-elderly healthy adult males. Subjects randomized to Group 1 received roxadustat alone during Period 1 and roxadustat concomitantly with lanthanum carbonate during Period 2; subjects randomized to Group 2 received roxadustat concomitantly with lanthanum carbonate during Period 1 and roxadustat alone during Period 2. All subjects received a single oral dose of 100 mg roxadustat on Day 1 in both periods. Subjects receiving concomitant lanthanum carbonate received 750 mg lanthanum carbonate three times daily on Days 1 and 2. Pharmacokinetic assessments were conducted on Days 1-4 in both periods. The primary study outcomes were the area under the concentration-time curve from the time of dosing extrapolated to infinity (AUC_{inf}), and maximum concentration (C_{max}); the geometric least squares mean ratio (GMR; roxadustat + lanthanum carbonate/roxadustat alone) and corresponding 90% confidence interval (CI) was calculated for AUC_{inf} and C_{max}.

Safety was assessed by the occurrence of treatment-emergent adverse events (TEAEs), laboratory test results, vital signs and standard 12-lead electrocardiogram.

Results and discussion: A total of 18 subjects were enrolled (Group 1, n = 9; Group 2, n = 9); no subjects discontinued from the study. Roxadustat was rapidly absorbed, reaching maximum plasma concentration between 1 and 4 hours. The GMRs for AUC_{inf} and C_{max} were 88.00% (90% CI: 84.01, 92.17) and 98.58% (90% CI: 92.92, 104.58), respectively. The 90% CIs for both parameters were within the no-effect boundaries of 80% and 125%, indicating a lack of effect of lanthanum carbonate on roxadustat absorption. No deaths or serious TEAEs occurred.
1 | WHAT IS KNOWN AND OBJECTIVE

One of the functions of the kidneys is the synthesis of erythropoietin (EPO), a hormone that stimulates the production of red blood cells and maintains adequate levels of hemoglobin. In patients with chronic kidney disease (CKD), malfunction of the kidneys results in an insufficient rate of erythropoiesis due to decreased levels of EPO production. Renal anemia in patients with CKD becomes more prevalent as CKD progresses and is often associated with a reduced quality of life and work productivity, as well as an elevated risk for cardiovascular disease.

Roxadustat (ASP1517, FG-4592, AZD9941) is an orally bioavailable hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI) in development for the treatment of anemia in CKD. Roxadustat stimulates erythropoiesis by targeting hypoxia-inducible factors, a family of transcription factors that up-regulate EPO production in response to hypoxia. The ability of HIF-PHIs to increase blood EPO to levels close to the normal physiologic range, but lower than those induced by treatment with intravenous erythropoiesis-stimulating agents, may have the advantage of reduced adverse cardiovascular effects. In addition, roxadustat has been shown to improve iron availability by reducing hepcidin, and may reduce the need for intravenous iron.

Roxadustat reaches maximum plasma concentration within 2 hours of oral administration and is eliminated by phase I oxidation (cytochrome P450 2C8) and phase II conjugation (glucuronidation via uridine diphosphate-glucuronosyltransferase and glucosidation); the terminal elimination half-life ($t_{1/2}$) is approximately 12 hours in healthy subjects. The solubility of roxadustat is pH dependent and absorption has been shown to be unaffected by food (data on file). Roxadustat is currently in Phase 3 trials for the treatment of anemia in patients with CKD, and has demonstrated safety and efficacy in Phase 2 studies in patients with CKD on dialysis and not on dialysis.

Hyperphosphatemia is a common complication of CKD that is associated with cardiovascular adverse effects and elevated all-cause and cardiovascular mortality. Under normal conditions, the kidneys contribute to the maintenance of phosphate homeostasis via sodium-phosphate transporters that facilitate phosphate reabsorption, a process mediated by parathyroid hormone and fibroblast growth factor-23. As CKD progresses, this normal response is not sufficient for maintaining phosphate levels within a normal range, and hyperphosphatemia results. The mainstay of treatment of hyperphosphatemia includes oral phosphate binders, including aluminium-based, calcium-containing and non-calcium-containing compounds which reduce phosphate absorption by binding dietary phosphate in the intestinal tract and forming insoluble complexes that are excreted in the faeces.

Lanthanum carbonate hydrate (Fosrenol) is a non-calcium and non-aluminium phosphate binder commonly used for the treatment of hyperphosphatemia in patients with end-stage CKD. Lanthanum carbonate shows low gastrointestinal absorption and is eliminated almost completely via hepatobiliary excretion with negligible renal clearance. The physicochemical properties of lanthanum carbonate may cause an interaction with other drugs when administered concomitantly, thereby reducing their bioavailability. Previous studies have demonstrated that lanthanum carbonate decreases the area under the concentration-time curve (AUC) of oral ciprofloxacin and levothyroxine by 54% and 41%, respectively, when administered concomitantly. This effect may be due to formation of chelate complexes between lanthanum cations and ciprofloxacin or levothyroxine, which may result in a reduction in the systemic availability of these two drugs. Conversely, the administration of lanthanum carbonate has been shown to not affect the pharmacokinetics of metoprolol, digoxin or warfarin. Moreover, an in vitro study showed that in a simulated gastric fluid, lanthanum carbonate did not form insoluble complexes with warfarin, digoxin, furosemide, phenytoin, metoprolol or enalapril. Considering the potential for administration of lanthanum carbonate in CKD patients with anemia who are also treated with roxadustat, it is important to thoroughly evaluate any clinical situations that may impact the pharmacokinetics of roxadustat. Since any interaction between lanthanum carbonate and concomitant drugs would involve a physicochemical binding that occurs during the absorption phase, we would not expect any significant difference in this potential interaction among ethnicities. However, considering that lanthanum carbonate is widely used in Japanese HD patients, we evaluated the effect of concomitant administration of lanthanum carbonate on the pharmacokinetics (PK) and safety of a single oral dose of roxadustat in non-elderly healthy adult male Japanese subjects.

2 | METHODS

This study was conducted in accordance with the clinical study protocol, Good Clinical Practice, International Conference on...
Harmonisation guidelines, applicable regulations and guidelines governing clinical study conduct, and the ethical principles of the Declaration of Helsinki. The protocol was approved by an institutional review board and all subjects provided written informed consent.

2.1 | Study population

This study enrolled healthy male Japanese subjects aged 20-44 years, with a body weight of 50 to <80 kg and a body mass index of 17.6 to <26.4 kg/m². Subjects had to agree to use two forms of highly effective birth control and to not donate sperm from the time of informed consent to ≥84 days after the last administration of roxadustat.

Subjects were excluded from the study if they received or were scheduled to receive any investigational drug within 120 days before screening, had donated blood (≥400 mL) within 90 days before screening, or received or were scheduled to receive medications or supplements within 7 days before admission to the hospital. Other key exclusion criteria included deviation from normal range of blood pressure, heart rate, body temperature, standard 12-lead electrocardiogram (ECG), and laboratory tests; concurrent or previous drug allergies; hepatic, heart, respiratory, renal, endocrine, or gastrointestinal disease; concurrent or previous malignant tumour; a history of abdominal surgery or digestive tract excision; concurrent or previous retinal neovascular lesions and macular edema; and previous use of HIF-PHIs.

2.2 | Study design

This was an open-label, randomized, two-period, two-sequence crossover study (ClinicalTrials.gov; registration number: NCT02952040) in non-elderly healthy adult male subjects conducted at one contracted hospital in Japan. The study consisted of two sequential 4-day periods separated by a ≥3-day washout phase. Informed consent and screening were performed between Days −30 and Day −3. Hospital admission occurred on Day −1, during which subjects were randomized to one of the following two groups based on the sequence of study drug regimen: subjects in Group 1 received roxadustat alone during Period 1 and roxadustat concomitantly with lanthanum carbonate during Period 2; subjects in Group 2 received roxadustat concomitantly with lanthanum carbonate during Period 1 and roxadustat alone during Period 2. On the morning of Day 1 of Periods 1 and 2, all subjects received a single oral dose of 100 mg roxadustat. Subjects receiving roxadustat concomitantly with lanthanum carbonate received 750 mg three times daily (TID, 2250 mg/day) from Day 1 to Day 2 (Period 1 for Group 2 and Period 2 for Group 1). During Period 1, subjects remained in the hospital for PK and safety assessments until discharge on Day 4. After a washout period of ≥3 days, subjects returned to the hospital for Period 2, which followed the same procedure as Period 1. A follow-up visit for physical examination, laboratory tests, vital signs and standard 12-lead ECG occurred on Day 8, 4 days after discharge from Period 2.

A crossover design was selected for this study to compare the PK of roxadustat in the presence and absence of lanthanum carbonate in an intra-subject manner. The duration of the washout period was selected to ensure full clearance of roxadustat. Including PK and safety assessments and the ≥3-day washout, the total time between roxadustat doses was a minimum of 7 days, which is more than 10 times the t½ (~12 hours) of roxadustat, as reported in a previous Phase 1 study.9

The primary objective of this study was to evaluate the effect of 750 mg lanthanum carbonate TID (2250 mg/day) on the PK of a single oral dose of 100 mg roxadustat in non-elderly healthy adult male subjects. The secondary objective was to evaluate the safety of a single oral dose of 100 mg roxadustat administered concomitantly with lanthanum carbonate (750 mg, TID) in non-elderly healthy adult male Japanese subjects.

2.3 | Study drug administration

Roxadustat was provided as a single 100-mg tablet and was administered with 200 mL of water immediately after breakfast on Day 1. Lanthanum carbonate was provided in 3 packs of 250 mg granules per pack (750 mg/dose) TID (2250 mg/day) with 200 mL of water immediately after breakfast, lunch and dinner on Days 1 and 2. Subjects receiving roxadustat concomitantly with lanthanum carbonate received the doses simultaneously with 200 mL of water immediately after breakfast on Day 1. Food intake was not allowed from 22:00 on Day −1 until breakfast on Day 1, and for ≥4 hours after dosing. In both periods, lunch started 5 hours after breakfast, and dinner started 5 hours after lunch. Subjects had to consume the meal within 20 minutes and the study drug was administered within 5 minutes of meal consumption. Each breakfast, lunch and dinner contained a standard phosphorus content of 200, 500 and 500 mg, respectively. A dose of 100 mg roxadustat was selected for this study because it is within the therapeutic dose range and is considered safe and well tolerated based on two previous Japanese Phase 2 studies (ClinicalTrials.gov NCT01964196; and NCT01888445). The choice of a single dose of roxadustat in this study was based on the observation that the absorption of lanthanum carbonate in the intestinal tract is minimal;13,16 therefore, the drug-drug interaction between lanthanum carbonate and roxadustat occurs during roxadustat absorption and can be evaluated after a single dose of roxadustat. The dose of 2250 mg/day of lanthanum carbonate used in this study corresponds to the maximum dose recommended according to the package insert of Fosrenol Granules and was chosen to maximize the potential drug-drug interaction. The administration of lanthanum carbonate immediately after meals was also in accordance with the package insert of Fosrenol Granules.
2.4 Sample collection and assessments

Blood sampling for PK assessments was performed at pre-dose, and 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 60 and 72 hours after roxadustat dosing. The primary study outcomes were the AUC from the time of dosing extrapolated to infinity (AUC_{inf}) and maximum concentration (C_{max}). Key secondary outcomes were apparent total systemic clearance after single or multiple extra-vascular dosing (CL/F), \( t_{\text{max}} \), time of the maximum concentration, (\( f_{\text{max}} \)), apparent volume of distribution during the terminal elimination phase after single extra-vascular dosing (\( V_{\text{ss}}/F \)), and per cent extrapolated AUC of the AUC_{inf} (AUC_{extrap}).

Plasma concentrations of roxadustat were measured at SRL Inc. (Kanagawa, Japan) using a validated liquid chromatography (HPLC) with tandem mass spectrometry (MS/MS) method. In brief, an aliquot of internal standard (50 \( \mu \)L) and 50% acetonitrile (50 \( \mu \)L) were added to spiked plasma samples (100 \( \mu \)L). Samples were then diluted with an aqueous solution containing 0.1% formic acid, sodium citrate buffer (pH 3.25) and tert-butylmethylether, and vortexed. After centrifugation, the upper layer was separated and evaporated under a stream of nitrogen. The residue was then reconstituted in 200 \( \mu \)L of the HPLC mobile phase (purified water/acetonitrile [45/55] containing 0.1% formic acid), and centrifuged. The upper layer, containing roxadustat and the internal standard, was separated and then analysed using a HPLC-MS/MS system (Agilent 1100 series, MDS SCIEX API4000). The HPLC separation was performed using a C18 column, and detection was carried out by a MS/MS detector equipped with a Turbo Spray ion source. For each sample, the ratio between the peak area of roxadustat and internal standard, and the calibration curve equation were used to calculate the concentration of roxadustat using the Analyst 1.4.2 HF May 2008 software program (Applied Biosystems). The lower limit of quantification was 1.00 ng/mL, when using 0.05 mL of plasma. The intra-day precision (coefficient of variation) was 0.9%-4.4%, and the intra-day accuracy was 0.1%-10.7%. Plasma PK parameters were calculated using Phoenix™ WinNonlin® v6.3.

Safety was assessed by the occurrence of TEAEs, physical examination results, laboratory tests (haematology, biochemistry and urinalysis), vital signs (supine blood pressure, supine heart rate and axillary body temperature) and 12-lead ECGs. Physical examinations were conducted on Day −1, before dosing on Day 1, and 24, 48, and 72 hours after dosing with roxadustat; lab tests, vital signs and ECGs were conducted at Day −1 and 72 hours after dosing with roxadustat. TEAEs were graded in accordance with the "Classification of Seriousness of Adverse Drug Reaction of Medicinal Products" reported in the Pharmaceutical Affairs Bureau Safety Division's Notification No. 80 (June 29, 1992), and were coded using the Medical Dictionary for Regulatory Activities (MedDRA version 19.0).

2.5 Statistical methods

Statistical analysis was conducted using SAS® Drug Development v4.5 and SAS v9.4. The PK analysis set included all subjects who received roxadustat and provided at least one measurable PK parameter. The safety analysis set included all subjects who received at least one dose of the study drug. A sample size of 18 subjects was selected based on data from a previous study (ClinicalTrials.gov registration NCT00978198) that showed an intra-subject coefficient of variation (CV) of 16%. A sample size of 14 subjects with an assumed CV of 16% provided a half-width of the 90% confidence interval (CI) of 0.118 for the estimated differences in PK parameters on a natural log scale between roxadustat alone and roxadustat with lanthanum carbonate. Plasma concentration of roxadustat and PK parameters

| Parameter | Group 1 (n = 9) | Group 2 (n = 9) | Total (n = 18) |
|-----------|----------------|----------------|---------------|
| Age, y    |                |                |               |
| Mean (SD) | 33.4 (6.2)     | 32.3 (6.5)     | 32.9 (6.2)    |
| Median    | 35.0           | 35.0           | 35.0          |
| Range (min-max) | 25-43        | 24-39         | 24-43         |
| Weight, kg|                |                |               |
| Mean (SD) | 60.91 (8.12)   | 65.23 (10.59)  | 63.07 (9.42)  |
| Median    | 62.40          | 67.80          | 62.95         |
| Range (min-max) | 50.3-76.1    | 50.0-79.7     | 50.0-79.7     |
| Height, cm|                |                |               |
| Mean (SD) | 168.34 (5.42)  | 174.30 (4.07)  | 171.32 (5.57) |
| Median    | 168.20         | 174.80         | 171.65        |
| Range (min-max) | 161.8-178.8  | 167.5-181.0   | 161.8-181.0   |
| BMI, kg/m²|                |                |               |
| Mean (SD) | 21.41 (2.46)   | 21.37 (2.99)   | 21.39 (2.65)  |
| Median    | 20.10          | 21.90          | 21.25         |
| Range (min-max) | 19.1-25.7   | 17.7-26.3     | 17.7-26.3     |

BMI, body mass index; SD, standard deviation.

**TABLE 1** Subject demographics (safety analysis set)
were reported using summary statistics (number of observation [n], arithmetic mean, standard deviation, minimum, median, maximum, CV, geometric mean). To assess the impact of lanthanum carbonate on the PK of roxadustat, the natural log-transformed AUC_{inf} and C_{max} for roxadustat were analysed using a mixed effects analysis of variance model for treatment (roxadustat alone and roxadustat with lanthanum carbonate) with sequence and period as fixed effects and subject as a random effect. The GMR and corresponding 90% CI were calculated for AUC_{inf} and C_{max}.

3 | RESULTS

3.1 | Subject disposition and demographics

Out of 45 subjects who provided informed consent, 18 were enrolled and randomized to Group 1 (n = 9) or Group 2 (n = 9); all subjects completed the study in accordance with the protocol and were included in the PK analysis set and safety analysis set. Data from one subject were excluded from the PK analysis due to two episodes of vomiting, 6.5 and 9.75 hours after administration of roxadustat alone on Day 1. No subjects in the study received prior or concomitant medications or therapies. The mean age was 32.9 years (range: 24-43 years) and the mean body mass index was 21.39 kg/m^2 (range: 17.7-26.3 kg/m^2). Subject demographics and baseline characteristics are summarized in Table 1.

3.2 | Pharmacokinetic analyses

Roxadustat was rapidly absorbed and the C_{max} was reached within 1-4 hours when roxadustat was administered alone or concomitantly with lanthanum carbonate. The mean plasma concentration-time profiles of roxadustat were similar to one another whether administered alone or concomitantly with lanthanum carbonate (Figure 1).
The median $t_{\text{max}}$ of roxadustat was 2 hours when roxadustat was administered alone or concomitantly with lanthanum carbonate. The median $t_{\text{max}}$ of roxadustat was consistent whether administered alone (11.4 hours) or concomitantly with lanthanum carbonate (11.1 hours). Of note, $t_{\text{max}}$ was not attained from one subject who received roxadustat alone and three subjects who received roxadustat concomitantly with lanthanum carbonate due to insufficient sampling points to adequately evaluate $t_{\text{max}}$. Mean AUC$_{\text{int}}$ and $C_{\text{max}}$ were 12% and 1.42% lower, respectively, when roxadustat was administered concomitantly with lanthanum carbonate compared with administration of roxadustat alone (Table 2). However, the GMRs and 90% CIs for AUC$_{\text{int}}$ and $C_{\text{max}}$ were both within the no-effect boundaries of 80% and 125%, indicating a lack of effect of lanthanum carbonate on roxadustat absorption (Table 2). The median (range) AUC$_{\% \text{extrap}}$ for the whole population (roxadustat alone, n = 16; roxadustat + lanthanum carbonate, n = 15) was 0.6% (0.1%-7.6%).

### 3.3 | Safety

Throughout the study, one subject (5.6%) in the roxadustat alone group reported TEAEs of abdominal discomfort, nausea and vomiting that occurred on Day 1 after administration of roxadustat. These events were mild or moderate in severity and were considered possibly related to roxadustat. No deaths, serious TEAEs or TEAEs leading to study discontinuation occurred, and no abnormal results from laboratory tests, vital signs, and 12-lead ECGs were reported.

### 4 | DISCUSSION

The use of phosphate binders represents an important strategy to reduce phosphate absorption in the intestine. Given the potential for lanthanum carbonate and roxadustat to be administered concomitantly in patients with CKD and anemia in Japan, the primary objective of this study was to determine whether lanthanum carbonate affects roxadustat exposure in non-elderly healthy adult Japanese male subjects. Lanthanum carbonate has been shown in previous studies to decrease the AUC of oral ciprofloxacin$^{14}$ and levothyroxine$^{15}$ when administered concomitantly. These drug-drug interactions may be due to formation of chelate complexes between lanthanum cations and concomitant drugs, resulting in reduced bioavailability. A similar drug-drug interaction study evaluated the pharmacokinetics of roxadustat when administered concomitantly with spherical carbon adsorbent and with or without food and reported that both conditions did not have a clinically relevant impact on the absorption of roxadustat.$^{17}$ Given that the potential interaction between roxadustat and lanthanum carbonate in this study would occur in the gastrointestinal tract and in turn impact the absorption of roxadustat, it
is not anticipated that any major differences in drug-drug interaction would be observed between healthy subjects and those with CKD. Overall, we found the AUC_{inf} and C_{max} of roxadustat to be 12% and 1.42% lower, respectively, when administered concomitantly with lanthanum carbonate; however, the GMRs for AUC_{inf} and C_{max} were 88.00% (90% CI: 84.01-92.17) and 98.58% (90% CI: 92.92-104.58), respectively, and the 90% CIs were within the no-effect boundaries of 80% and 125%. The median t_{max} of roxadustat was 2 hours whether administered alone or concomitantly with lanthanum carbonate, and the median t_{\frac{1}{2}} was also similar between the two groups (~11 hours). A median AUC_{\text{extrap}} of 0.6 indicated that the sampling was sufficient to provide an accurate estimate of the total AUC. However, due to the lack of sufficient sampling points, the t_{\frac{1}{2}} could not be estimated for one subject in the roxadustat alone group and three subjects in the roxadustat plus lanthanum carbonate group. The ≥3-day washout period was selected to ensure full clearance of roxadustat between doses. Even with the highest observed t_{\frac{1}{2}} (24.6 hours), the minimum of 7 days between roxadustat doses allowed for ~7 half-lives between doses in this subject and ensured full clearance. There were no deaths, serious TEAEs or TEAEs resulting in discontinuation throughout this study. One subject (5.6%) treated with roxadustat alone reported TEAEs of abdominal discomfort, nausea and vomiting that were considered mild or moderate in severity, and possibly related to the administration of roxadustat.

5 | WHAT IS NEW AND CONCLUSION

Concomitant administration of a single oral dose of 100 mg roxadustat and 750 mg lanthanum carbonate TID for 2 days did not impact the AUC_{inf} and C_{max} of roxadustat in a clinically relevant manner, and was considered safe and well tolerated in non-elderly healthy adult male Japanese subjects. These results suggest that lanthanum carbonate may be safely administered concomitantly with roxadustat in CKD patients.

ACKNOWLEDGEMENTS

Medical writing and editorial assistance were provided by SuccinctChoice Medical Communications (Chicago, IL) and funded by Astellas Pharma Inc.

CONFLICTS OF INTEREST

Tomohisa Shibata, Yuki Nomura, Akitsu Takada, Shin Aoki and Masataka Katashima are employees of Astellas Pharma Inc. Harumi Murakami has no conflict of interest to declare.

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