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An Open-Label Clinical Trial of the Effects of Age and Gender on the Pharmacodynamics, Pharmacokinetics and Safety of the Ghrelin Receptor Agonist Anamorelin

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Abstract

Purpose: To assess the effect of age and gender on the pharmacokinetics (PK) of the ghrelin receptor agonist anamorelin.

Methods: Three demographic cohorts of healthy subjects were enrolled in this single-center, open-label study. Subjects received a single oral dose (25 mg) of anamorelin HCl. Serial blood samples were collected over 24 hours to assess anamorelin PK and circulating growth hormone (GH) levels. Data were compared with a reference cohort.

Results: Anamorelin was rapidly absorbed in all cohorts; peak concentrations were observed 30–45 minutes and 2–4 hours post-dose, which declined biexponentially with mean terminal half-lives of 6–7 hours. An age effect on C_{max} and AUC_{∞} was not apparent; however, mean AUC_{∞} values were approximately 1.8–1.9-fold higher in the female cohorts than in the reference male cohort. GH increase was rapid and virtually identical in both sexes, though attenuated in elderly subjects. No clinically significant safety or tolerability findings were observed.

Conclusions: While PK parameters do suggest higher exposure in females, this effect is considered to be modest given the variability of the 6–8 subjects per cohort. Moreover, no such effect was observed in the pharmacodynamic responses, thus, dose adjustment for age and gender is considered unnecessary.

Keywords

cancer cachexia, anamorelin, pharmacokinetics, age, gender

Cachexia occurs in up to 80% of patients with advanced cancer and is characterized by involuntary weight loss, frequently accompanied by anorexia and altered metabolism.[1–5] It is associated with poorer survival, a decline in physical functioning and quality of life, increased risk of treatment failure and toxicity, and a greater symptom burden.[2,6,7] Despite the negative impact of cachexia on cancer patients, the syndrome is under-recognized and often left untreated.[8] Cancer cachexia is a complex syndrome that is not fully understood, but the underlying mechanisms are thought to include the metabolic, endocrine and central nervous systems.[3,7] Treatments for cancer cachexia are unfortunately lacking. With no standard effective therapies available worldwide, cachexia remains a critically unmet need in cancer supportive care.[9,10]

Ghrelin and ghrelin receptor agonists are being explored for their potential impact on clinical conditions such as anorexia and cancer cachexia. These compounds have been found to have clinical attributes which make them well-suited for the treatment of cachexia. Ghrelin plays an important role in stimulating appetite and encouraging food intake. Activation of the ghrelin receptor (otherwise called the growth hormone [GH] secretagogue receptor) increases lean body mass and fat mass through the secretion of GH.[11,12]

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Anamorelin (RC-1291) is an orally-active ghrelin receptor agonist which may assist in the treatment of cancer cachexia through its appetite-enhancing, anabolic effects.[13–16] It is rapidly absorbed whilst experiments with radio-labeled (^{14}C) anamorelin have shown that it is primarily eliminated in the feces (92%; urine 8%).[13,17]

In a phase I study in healthy volunteers, 5–6 days treatment with anamorelin HCl, hereafter referred to as anamorelin, led to dose-related increases in body weight with no dose-limiting adverse effects; 25 and 50 mg anamorelin also produced a significant increase in appetite (VAS–Hunger scores) at virtually every pre-prandial timepoint assessed. Food intake at the 4-hour timepoint was increased on average by 18.4% compared to placebo ($P < .05$, 25 and 50 mg anamorelin).[18] Anamorelin also produced dose-related increases in body weight[19] and increased levels of GH, insulin-like growth factor-1 and insulin-like growth factor binding protein 3, without affecting other anterior pituitary axes or fasting glucose levels.[20] Furthermore, in a randomized, double-blind, placebo-controlled, crossover study of 16 patients with different cancer types and cachexia, 3-day treatment with anamorelin had significantly beneficial effects on body weight, metabolic markers and patient-report assessments of symptoms including appetite.[15] Benefits were also observed in a larger phase II study of 81 patients with cancer cachexia, in which 12-week treatment with anamorelin led to improvements in lean body mass, total body mass and handgrip strength.[14] In all of the above studies, anamorelin was well-tolerated.[14,18]

Anamorelin is currently in phase III development, with two parallel trials in non-small-cell lung cancer cachexia recently completed (ROMANA-1 [NCT01387269][21,22] and ROMANA-2 [NCT01387282]).[22,23] In addition, patients from these studies had the option of continuing treatment in a 12-week safety extension study (ROMANA-3 [NCT01395914]).[24,25]

The purpose of this phase I study was to determine the effects of age and gender on the systemic pharmacokinetics (PK) of anamorelin in healthy subjects.

Methods

This single-center, open-label, single-dose study (RC-1291–107), conducted at Quintiles Phase I services, Inc., (Lenexa, KS) and approved by Heartland IRB (Lenexa, KS), consisted of three demographic cohorts of healthy subjects who received a single oral dose (25 mg) of anamorelin HCL. The data from these subjects were compared with that of a reference population of healthy young males (aged 18–40 years) who received 25 mg of anamorelin in a randomized, double-blind, placebo-controlled, single, dose-escalation study (RC-1291–101), conducted at Buffalo Clinical Research Center (Buffalo, NY) and approved by IntegReview IRB (Austin, TX).[18]

Subjects and Treatment

The three demographically-defined subject cohorts in the open-label study were composed of eight healthy, surgically sterile young adult females (aged 18–40 years), eight healthy elderly females (aged $\geq$65 years) and eight healthy elderly males (aged $\geq$65 years). The reference dose-escalation study enrolled nine healthy young adult males (aged 18–40 years), six of whom received 25 mg anamorelin.[19] To ensure consistency with the reference population, subjects in the open-label study were required to have a body mass index (BMI) within 18–29 kg/m^2. For all subject cohorts, exclusion criteria included a history of significant medical abnormalities, any conditions that might have interfered with the absorption, metabolism or elimination of the study drug, and participation in a clinical study with an investigational agent within the 30 days prior to study treatment.

Subjects in the open-label study received a single dose of study drug (25 mg anamorelin as a capsule formulation) in the fasting state followed by a 24-hour assessment period during which they were confined to the clinical study unit. Standardized meals were provided at 4 and 10 hours and subjects could eat and drink ad libitum after the 12 hours post-dose assessments. Subjects returned to the clinical study unit for safety monitoring 10–14 days after study drug treatment.

The dose-escalation study consisted of three 24-hour treatment periods, each separated by 7 days. In each of the study periods, subjects were administered single doses of study drug (10, 25, or 50 mg anamorelin, or matching placebo as a capsule formulation) in the fasting state. Post-dose procedures were the same as for the open-label study. The follow-up visit for safety monitoring took place 10–14 days after the third study period.

Both studies were conducted in accordance with the provisions of the Declaration of Helsinki and its amendments, guidelines of the International Conference on Harmonization (ICH), and Good Clinical Practice (GCP). All subjects provided written informed consent.

Assessments

Safety. Safety assessments consisted of: monitoring adverse events (AEs) continuously throughout the studies; clinical laboratory tests (screening, day −1, at discharge [day 2], and post-study); 12-lead electrocardiograms (ECGs) (screening, day −1, 1-hour post-dose on day 1, and at discharge [day 2]); and vital signs including supine blood pressure and heart rate (screening, day −1, at frequent intervals before and after the dose of study drug on day 1, at discharge [day 2], and post-study).

Pharmacokinetic Analysis. In order to assess the PK properties of anamorelin, serial blood samples were

collected at the following time points: pre-dose (−15 min); 15, 30 and 45 minutes post-dose; 1, 1.5, 2, 2.5, 3, 4, 6, 9, 12, 18, and 24 hours post-dose. Samples were assayed for anamorelin concentration by KCAS, LLC (formerly AAI Development Services, Shawnee, Kansas, USA) and the results analyzed by PK/PD International, Inc., (Tucson, Arizona, USA). Quantification of anamorelin in human plasma was performed using a validated liquid chromatographic mass spectrophotometric method, operating within a concentration range of 0.08–40 ng/mL (concentrations below the quantification limit were assigned values of zero), in which anamorelin and the internal standard (RC-1141) were extracted from lithium heparin human plasma samples using liquid–liquid extraction. This extract was then dried, reconstituted and subjected to reverse-phase high performance liquid chromatography using an Aquasil C-18, 5 μm, 50 × 2.1 mm analytical column. Anamorelin and the internal standard in the effluent were detected using a PE/Sciex 3000 LC/MS/MS system operating in MRM mode; quantification was achieved by monitoring the product and precursor ions (m/z 547→276.3 for anamorelin and 637.5→306.3 m/z for the internal standard).

The PK parameters of interest were: maximum plasma concentration (C_{max}); time to C_{max} (T_{max}); area under the concentration–time curve calculated from time zero to the last observable concentration (C_T) at time T (AUC_T); area under the concentration–time curve from time zero to infinity (AUC_∞); terminal-phase elimination half-life ($t_{1/2,Z}$); total body clearance of drug following extravascular administration (CL/F); C_{max}/dose; AUC_∞/dose. C_{max} and T_{max} were taken directly from the observed data and AUC_T was calculated using the linear trapezoidal rule. The area under the concentration–time curve from time zero to infinity (AUC_∞) was calculated as $AUC_T + C_T/\lambda_Z$. The first-order rate constant associated with the terminal (log-linear) portion of the concentration–time curve (λ_Z) was determined by linear regression of at least three log concentrations versus time in the terminal-phase of the concentration–time profile. The terminal half-life ($t_{1/2,Z}$) was obtained as $0.693/\lambda_Z$. CL/F was determined as the quotient of the dose divided by AUC_∞. C_{max}/dose and AUC_∞/dose were generated by dividing individual parameter estimates (C_{max} and AUC_∞) by the mg/kg anamorelin dose.

Pharmacodynamic Analysis. Timed blood samples were obtained at the following points to assess the pharmacodynamic (PD) effect of anamorelin on circulating GH: pre-dose (−15 min); 30 and 45 minutes post-dose; 1, 1.5, 2, 3, and 4 hours post-dose (also at 2.5 and 6 hours post-dose for the reference group). Quantification of GH was achieved using an IMMULITE 2000® (Siemens Healthcare) solid-phase, two-site chemiluminescent immunometric assay.

Determination of Sample Size

The purpose of this study was to determine if there was a difference in plasma AUC_∞ between each of the three cohorts in the open-label study (healthy young adult women, healthy elderly men, and healthy elderly women) compared with the reference group of healthy young adult men. It was inferred that there would be no difference in plasma concentrations if AUC_∞ for each demographic group was within ±50% of the reference group. The mean AUC_∞ for the reference group (healthy males) was 197 ng*hr/mL, with a standard deviation of 60. Assuming two 1-sided tests with alpha = 0.025 on each side, eight completed subjects would give 86% power to declare no difference (equivalence) between groups.

Statistical Analysis

Two subject populations were defined. The intent-to-treat population (ITT) comprised all subjects who received at least one dose of study drug and had at least one post-baseline PD hormonal GH serum concentration assessment. The safety population comprised all subjects who received at least one dose of study drug. Demographic and baseline characteristics, GH concentrations and safety variables (vital signs, ECG parameters and abnormal laboratory values) were summarized descriptively. In addition, changes from baseline in both ECG parameters and vital signs were calculated. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 7.0.

The calculated parameters for GH (AUC, C_{max} and T_{max}) were analyzed using an Analysis of Variance (ANOVA) model with a term for demographic group. All pair-wise comparisons and 95% confidence intervals (CI) came from this model (via contrast statements). Pair-wise comparisons of each demographic group versus the reference population of healthy young male subjects from Study RC-1291–101 are presented. Three ANOVA methods were employed to test for differences in PK parameters between the study and reference groups. For T_{max}, the nonparametric Cochran–Mantel–Haenszel test with modified ridit scores was used to calculate the effect of age adjusted for gender, and gender adjusted for age. For all statistical tests, a difference was considered to be statistically significant if a *P*-value of <0.05 was observed for the comparisons. Statistical analyses were conducted by Scirex Corporation, Bloomingdale, IL, USA.

Results

Study Population

All 24 subjects in the open-label study completed all evaluations and were included in the ITT and safety populations. No subjects were withdrawn from the study. In the reference dose-escalation study, all six subjects

Table 1. Baseline Subject Characteristics For ITT and Safety Populations

Characteristic	Young males* (N = 6)	Young females (N = 8)	Elderly males (N = 8)	Elderly females (N = 8)
Race (N)				
White	5	4	8	8
Black	1	4	0	0
Age (yrs)				
Mean ± SD	29.2 ± 7.4	31.6 ± 5.5	71.1 ± 4.4	75.1 ± 5.1
Range	20–36	24–39	65–77	68–83
Weight (kg)				
Mean ± SD	73.9 ± 14.2	65.5 ± 8.9	78.3 ± 12.0	66.9 ± 8.9
Range	57.9–91.9	52.6–77.6	60.1–95.7	56.1–81.3
BMI (kg/m^2)				
Mean ± SD	23.8 ± 2.8	24.7 ± 3.9	26.1 ± 2.7	25.6 ± 3.0
Range	20.2–28.1	18.6–29.5	22.7–29.9	20.0–29.3

BMI, body mass index; ITT, intention-to-treat; SD, standard deviation.
*Reference subject population who were enrolled in the RC-1291–101 dose-escalation study who received a 25 mg dose of study drug.

dosed with 25 mg completed all evaluations and there were no study discontinuations.

Table 1 summarizes the demographic characteristics for each cohort in the open-label study and for the cohort of young male subjects from the dose-escalation study who received the 25 mg dose of anamorelin (N = 6). The age range for the young female and male subjects combined was 20–39 years, and the age range for the elderly female and male subjects combined was 65–83 years. Mean body weight in the male cohorts was higher than in the female cohorts.

Pharmacodynamic Hormonal Response

The variability in baseline GH levels was wide, especially in the young and elderly female cohorts (Table 1). Anamorelin produced increases in serum GH in all four cohorts (Figure 1). Mean peak GH levels of 61.79, 62.80, 19.85, and 27.52 ng/mL were recorded post-dose in the young adult male, young adult female, elderly male, and elderly female cohorts, respectively. By comparison, a mean peak GH level of 5.38 ± 5.79 ng/mL was recorded in the reference cohort of young adult males when given placebo in the RC-1291–101 study (data not shown).

The magnitude of the GH response after anamorelin dosing was virtually identical in male and female subjects, and an attenuation of GH response was observed in elderly subjects. However, significant differences were found in C_{max} and AUC when individual demographic cohorts in the open-label study were compared with the reference cohort of young males (Table 2). Peak serum concentration (C_{max}) and AUC of GH were significantly lower in elderly males compared with the younger males ($P < .05$). GH AUC was also significantly lower in elderly females ($P < .05$) compared with younger males, and the difference in C_{max} between these two cohorts approached statistical significance ($P = .052$). There were no significant differences in GH response (C_{max}, AUC or T_{max}) between young females and young males.

Pharmacokinetics

Mean plasma anamorelin concentration–time profiles following single-dose oral administration of 25 mg anamorelin are shown in Figure 2a-b. Anamorelin was rapidly absorbed in all cohorts, reaching initial 'peak' plasma concentrations within 30–45 minutes post-dose, followed by a temporary decrease and a second 'peak' occurring about 2–4 hours post-dose. Median T_{max} values ranged from 0.5 to 1.75 hours. No differences in T_{max} values were observed among the study groups. Following T_{max}, and/or after the time of the second 'peak' concentration, mean plasma anamorelin concentrations declined in a biexponential manner, with similar mean half-lives among cohorts (ranging from 6.08 hours in young female subjects to 7.03 hours in young male subjects). There did not appear to be an age effect on C_{max} or AUC_{∞} of single doses of anamorelin (Table 3). A gender effect of anamorelin on C_{max} and AUC_{∞} was seen, with mean estimates of AUC_{∞} approximately 1.9-fold and 1.8-fold higher in healthy young and elderly female subjects, respectively, than in young male subjects (Table 3). The differences in C_{max} and AUC_{∞} between genders could be attributed in part to normal differences in body weight observed between the genders, with higher mean values in males compared with females (Table 1). However, differences in CL/F (determined as a weight-normalized parameter estimate), C_{max}/dose and AUC_{∞}/dose (both determined as mg/kg dose-normalized parameter estimates) (Table 3) indicated that factors other than, or in addition to, body weight contributed to differences in the PK characteristics of anamorelin observed between young and elderly female and young male subjects. The variability recorded in individual PK

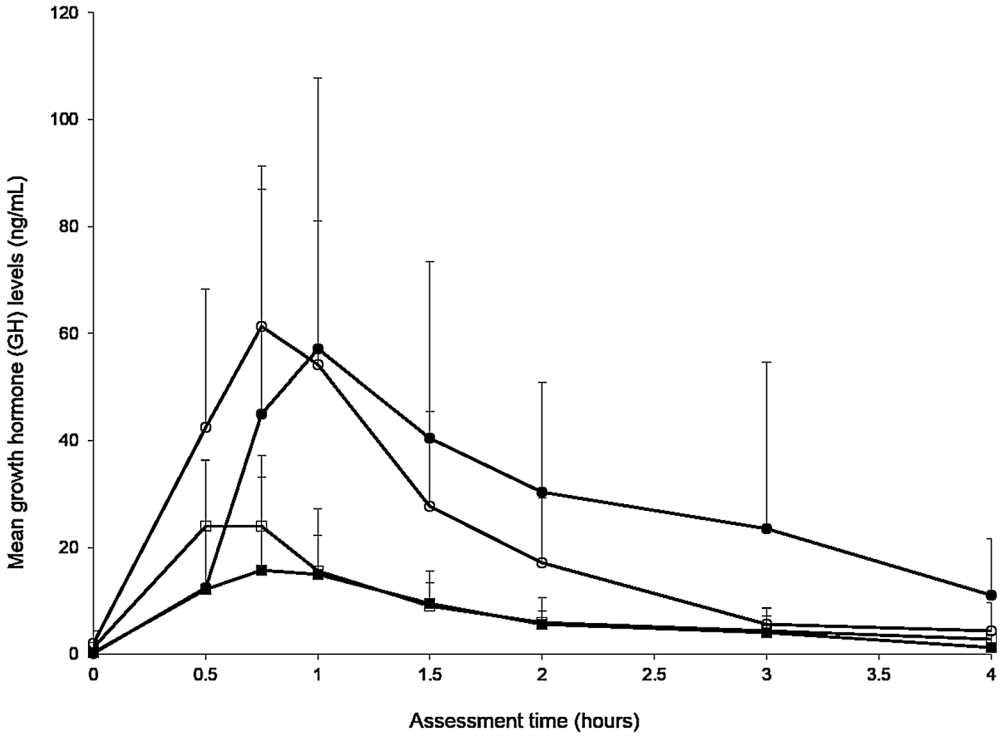

Figure 1. Mean circulating growth hormone (GH) concentration over time following single-dose oral administration of 25 mg anamorelin to healthy young male (●), young female (○), elderly male (■) and female (□) subjects.

responses is shown by Figures 3a-b. Both figures show that despite the gender differences in mean C_{max} and mean AUC_{∞}, the large ranges of PK responses recorded within each cohort result in considerable overlap between male and female subjects. Furthermore, this effect does not translate into an observable pharmacodynamic response. Taken together, the observed gender difference is considered to be a modest effect.

Safety

The only AE reported by more than one subject was headache, reported in three elderly females, two young males and one young female. The investigator considered three of these reports (in two elderly females and one young male) to be possibly related to the study drug, whilst one report (in a young male) was considered to be probably related to the study drug. Furthermore, one report of change of bowel habit (in an elderly male) and one of frequent bowel movements (in an elderly female) were also considered to be possibly related to the study drug by the investigator. All remaining reports of AEs were mild, transient and considered to be unrelated to the study drug.

There were no changes of any clinical relevance in any of the laboratory or ECG parameters. Decreases in systolic and diastolic blood pressure were evident in the elderly male and female subjects; minimal and inconsistent changes in systolic blood pressure were observed in the young adult female and young adult male subjects. The magnitude of effect on blood pressure was generally modest and without clinical consequence.

Table 2. Circulating Growth Hormone Response (mean ± SD) Following Single-Dose Oral Administration of 25 mg Anamorelin (ITT Population)

Parameter	Young males (N = 6)	Young females (N = 8)	Elderly males (N = 8)	Elderly females (N = 8)
Pre-dose growth hormone concentrations (ng/mL)				
Mean ± SD Range	0.17 ± 0.18 0.07–0.53	2.11 ± 2.27 0.17–5.74	0.38 ± 0.61 0.00–1.84	1.20 ± 0.96 0.12–2.90
C_{max} (ng/mL)	61.79 ± 56.82	62.80 ± 26.36	19.85 ± 8.73*	27.52 ± 23.01
AUC (ng•hr/mL)	109.48 ± 100.97	86.63 ± 41.50	27.90 ± 11.53*	35.92 ± 21.87*
T_{max} (hr)	1.21 ± 0.46	0.78 ± 0.16	0.94 ± 0.48	0.78 ± 0.34

AUC, area under the concentration curve; C_{max}, maximum plasma concentration; ITT, intention-to-treat; SD, standard deviation; T_{max}, time to C_{max}.
*$P < .05$ versus young males.

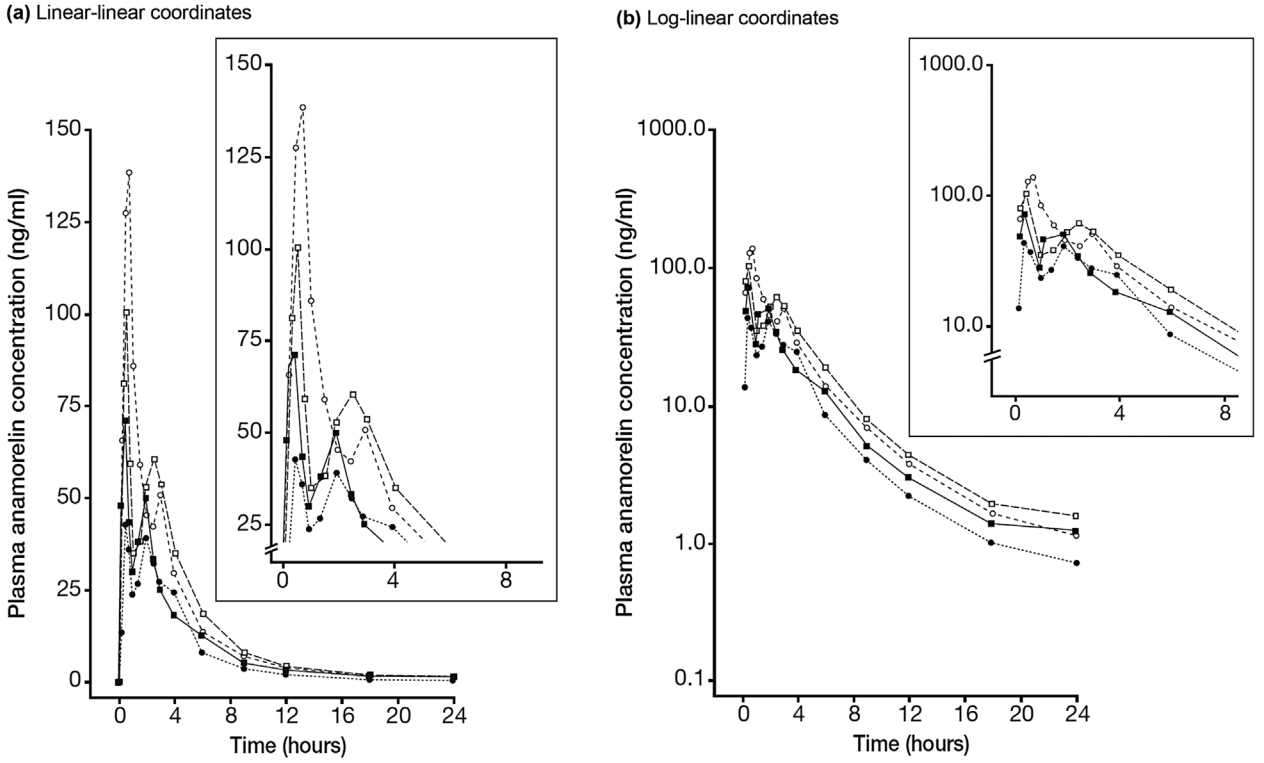

Figure 2. Mean plasma anamorelin concentrations ((**a**) Linear-linear coordinates, (**b**) Log-linear coordinates) following single-dose oral administration of 25 mg anamorelin to healthy young male (●), young female (○), elderly male (■) and female (□) subjects.

Discussion

While the ability of the ghrelin receptor agonist anamorelin to increase GH levels has been reported previously,[15,20] the goal of the present study was to explore the effect of demographic factors on this parameter following anamorelin administration in healthy subjects. This study also aimed to assess the effect of age and gender on the PK and safety of anamorelin.

A single oral dose of 25 mg anamorelin increased circulating GH levels in all cohorts, consistent with its activity as an orally available ghrelin receptor agonist. The rapid onset of the GH response reflects the rapid absorption of anamorelin following oral administration. The magnitude of this effect was virtually identical in males and females, indicating that there was no gender effect on GH response. The wide variability in baseline GH levels, especially in the young and elderly female

Table 3. Pharmacokinetic Parameters (mean ± SD) Following Single-Dose Oral Administration of 25 mg Anamorelin

Parameter	Young males (N = 6)	Young females (N = 8)	Elderly males (N = 8)	Elderly females (N = 8)
C_{max} (ng/mL)	80.6 ± 28.1	184* ± 92.6	110 ± 74.4	154 ± 92.4
C_{max}/Dose ([ng/mL]/[mg/kg])	237 ± 89.9	468 ± 214	321 ± 170	398 ± 215
AUC_{∞} (ng•hr/mL)	197 ± 60.2	366** ± 99.5	242 ± 177	364* ± 140
AUC_{∞}/Dose ([ng*hr/mL]/[mg/kg])	565 ± 131	945 ± 247	708 ± 391	938 ± 266
T_{max} (hr)	1.88 ± 1.28	0.66* ± 0.42	0.63* ± 0.58	1.71 ± 1.49
Median T_{max} (range)	1.75 (0.5–4)	0.5 (0.25–1.5)	0.5 (0.25–2)	1.5 (0.25–4)
$t_{1/2}$ (hr)	7.03 ± 1.26	6.08 ± 0.64	6.85 ± 0.99	6.63 ± 1.14
CL/F (L/hr/kg)	1.87 ± 0.55	1.12** ± 0.28	1.68 ± 0.60	1.14** ± 0.31

Mean ± standard deviation; AUC_{∞}, area under the concentration-time curve from time zero to infinity; CL/F, total body clearance of drug following extra-vascular administration; C_{max}, maximum plasma concentration; SD, standard deviation; $t_{1/2}$, half-life; T_{max}, time to maximum plasma concentration.

*$P < .05$ versus young males. **$P < .01$ versus young males.

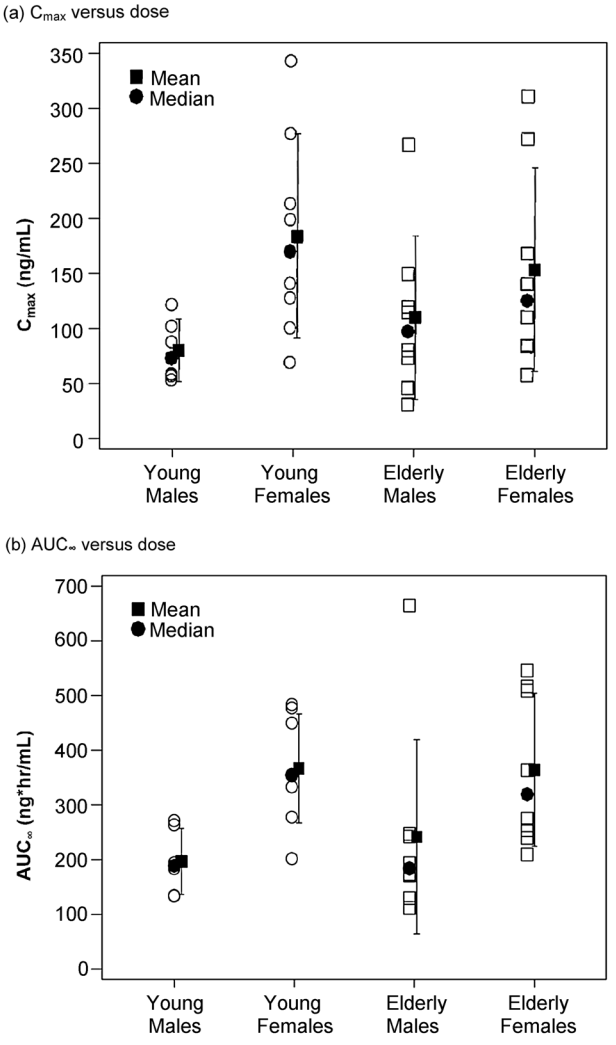

Figure 3. Individual, median, and mean (SD) ((**a**) C_{max} versus dose, (**b**) AUC_{∞} versus dose) following single-dose oral administration of 25 mg anamorelin to healthy young and elderly male and female subjects.

cohorts, is likely to reflect a normal physiological response, whereby GH is secreted into the bloodstream in small, pulsatile bursts.[26,27] The lower GH response seen in elderly men and women compared with their younger counterparts was expected, as attenuation of GH response with age is a well-characterized phenomenon[28] and has also been demonstrated with administration of intravenous GH-releasing peptide.[29]

Following administration of a single oral dose of 25 mg anamorelin, the concentration–time profile of anamorelin was similar in all cohorts and characterized by two 'peaks' at 30–45 minutes and 2–4 hours post-dose. Within gender, the PK characteristics of anamorelin were similar between young and elderly subjects, indicating that no alteration in anamorelin dose will be required in the elderly. C_{max} and AUC_{∞} differed between genders, with mean AUC_{∞} values approximately 1.8–1.9-fold higher in young and elderly female subjects compared with the young male reference cohort. These data suggest that administration of equivalent mg doses of anamorelin may result in higher plasma concentrations of anamorelin but similar elimination half-lives in females compared with males, irrespective of age. A higher weight-normalized parameter estimate of CL/F, along with mg/kg dose-normalized parameter estimates of C_{max}/dose and AUC_{∞}/dose, were also evident among females, suggesting that factors other than, or in addition to, body weight contribute to gender-specific differences in systemic exposure. However, despite the lower plasma concentrations of anamorelin observed in males compared with females within these studies, the pharmacodynamic response of GH secretion did not differ between genders.

The safety and tolerability profile of a single 25 mg dose of anamorelin in healthy young and elderly males and females was excellent. AEs were minor and clinically insignificant, without any pattern suggestive of a relationship to the study drug. The laboratory and ECG data similarly revealed no evidence of any clinically relevant toxicity/changes. There were no meaningful treatment-related effects on vital signs, although a modest and asymptomatic decrease in systolic and diastolic blood pressures was observed in elderly subjects, in line with those reported for reference subjects.

In conclusion, the PK parameters indicate that plasma concentrations of anamorelin after a 25 mg dose in these studies are higher in female subjects than they are in male subjects, although there was a small sample size and high variability. Despite this, the PK gender-effect does not appear to translate into an equivalent PD response; the magnitude of the increase in circulating GH, from baseline levels, is comparable between the two sexes. As expected, this GH effect is attenuated in the elderly cohorts. Of note, subsequent studies with anamorelin at the target therapeutic dose of 100 mg in both healthy volunteers and NSCLC patients have indicated a lack of gender effect on plasma concentrations and associated PK parameters (unpublished data). As a result, there is likely to be no need for dose adjustment of anamorelin due to gender or age. The outcome of ongoing phase III studies will provide further information on the safety and efficacy of anamorelin and its potential role in treating cancer cachexia.[26,27]

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Declaration of Conflicting Interests

JMT received financial support from Rejuvenon Corporation (now Helsinn Therapeutics [US], Inc.). EdG is an employee of Helsinn Therapeutics (US), Inc. PTL and RAB were investigators on studies funded by Rejuvenon Corporation (now Helsinn Therapeutics (US), Inc.).

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