Ataluren Pharmacokinetics in Healthy Japanese and Caucasian Subjects

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Abstract

To evaluate the potential for ethnicity-related differences in ataluren pharmacokinetics (PK) and safety, a phase 1 single-dose study was conducted in 48 healthy (24 Japanese and 24 Caucasian subjects), nonsmoking male volunteers who were equally divided into 3 cohorts of oral doses at 5, 10, and 20 mg/kg. Blood samples were collected until 48 hours postdose. PK results demonstrated rapid absorption of ataluren, with peak plasma levels (C_{max}) being attained between 0.875 and 2.5 hours after dosing. The mean C_{max} and area under the concentration-time curve ($AUC_{(0-last)}$) increased with each increasing dose level in both Japanese and Caucasian subjects. Although the C_{max} was similar across all subjects at each dose regardless of ethnicity, Japanese subjects had a mean $AUC_{(0-last)}$ approximately 14% to 34% lower than that of Caucasian subjects across the 3 dose levels. This difference was likely due to the higher variability of AUC values in Caucasian subjects and the relatively small study population. In conclusion, similar ataluren PK profiles were observed in healthy Japanese and Caucasian subjects following single oral administration of ataluren at all dose levels.

Ataluren is a novel orally bioavailable small-molecule drug for the treatment of nonsense mutation genetic disorders. A nonsense mutation in DNA results in a premature stop codon within the protein-coding region of messenger RNA. This premature stop codon causes early termination of protein translation, resulting in a truncated, nonfunctional protein. Ataluren enables ribosomal read-through of messenger RNA containing such a premature stop codon, resulting in production of a full-length functional protein.[1–4]

Duchenne muscular dystrophy (DMD) is an X-linked genetic muscle disorder that results from a mutation in the dystrophin gene.[5–7] Dystrophin is a 427-kDa structural protein present at the muscle sarcolemma.[5,8] It provides stability to the muscle, is expressed in skeletal, respiratory, and cardiac muscle, and acts as a shock absorber, bearing the mechanical stresses that occur during muscle contraction, stabilizing muscle cell membranes, and protecting muscles from injury.[5–7,9] In the absence of dystrophin the shear placed on the membranes during contractions causes them to tear,[8,10] resulting in muscle damage and leading to the clinical features of motor developmental delay, calf hypertrophy, joint contractures, and progressive muscle weakness in affected boys.[5,11] Over time, the progressive loss of muscle function results in loss of ambulation and ongoing impairment of respiratory and cardiac function.[12] Death typically occurs due to respiratory complications and cardiac failure.[12]

Approximately 10% to 15% of boys with DMD (~1800 to 2700 boys in the United States) have the disease due to a nonsense mutation (nmDMD).[13–15] In 2 multicenter randomized clinical studies, ataluren showed clinical benefit by slowing disease progression in patients with nmDMD.[2,16] Ataluren is conditionally approved by the European Medicines Agency and in Israel and South Korea for the treatment of ambulatory patients aged ≥5 years with nmDMD.[17] The drug is currently under review at the Food and Drug Administration in the United States for the treatment of nmDMD.

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Ataluren is generally well tolerated when administered as a single oral dose in healthy male and female subjects and for chronic administration in patients of all ages with nmDMD. Ataluren is readily absorbed after oral administration as a suspension, with ≥55% bioavailability as demonstrated in a clinical study using ^{14}C-radiolabeled ataluren in which 55% of radioactivity was recovered in the urine. In this study ataluren was extensively metabolized with ataluren acyl glucuronide being the most prominent metabolite in plasma, and unchanged ataluren and the acyl glucuronide metabolite in the urine accounted for <1% and 49%, respectively, of the administered dose. Peak plasma levels of ataluren were attained after approximately 1.5 hours of dosing. Ataluren plasma concentrations at steady state increased proportionally with increasing dose in healthy volunteers between 10 and 50 mg/kg, with no accumulation after repeated dosing.[18] Additionally, gender did not appear to affect ataluren exposure.[18] Ataluren plasma half-life ranges from 2 to 6 hours and is unaffected by either dose or repeated administration, with a majority of the absorbed dose clearing from the body within 24 hours after dosing.[18]

In vitro drug metabolism studies using cytochrome P450 isozymes, uridine 5'-diphosphoglucuronosyltransferase (UGT) enzymes, and human liver microsomes have shown that ataluren is primarily metabolized by UGT1A9 and not metabolized by cytochrome P450 isoenzymes. However, a clinical drug-drug interaction study has demonstrated that coadministration of a UGT1A9 inducer (rifampin) with ataluren had minimal effect on ataluren plasma pharmacokinetics (PK).

Most studies investigating the PK, pharmacodynamics (PD; concentration-response relationship), and safety and efficacy of ataluren have been performed in Caucasians.[2,4] Given that nmDMD is present in all ethnic groups, it is important to evaluate the possible effect of ethnic background on ataluren PK; differences in PK and PD among various ethnic groups are critical factors for understanding intersubject variability of a therapeutic agent.[19–22] Ethnic differences in kinetics and dynamics are mainly attributed to differences in weight,[23] absorption (mainly active absorption),[23] distribution (plasma protein/tissue binding differences),[24,25] hepatic metabolism,[26–30] and renal elimination (mainly active tubular secretion)[27,31] of therapeutic agents among various ethnic groups. Additionally, ethnic extrinsic factors associated with environment, culture (such as diet), climate, medical practice, socioeconomic status, drug compliance, dosage regimen, and route of administration may also affect the PK and PD differences observed in various ethnic populations.[22,32]

The primary objective of this study was to investigate the PK of ataluren in healthy Japanese and Caucasian subjects. The entry criteria for Japanese subjects were designed to ensure that the genetic and physiologic (intrinsic), and cultural and environmental (extrinsic) characteristics of the study population were comparable to those of people living in Japan. This phase 1 PK study was conducted at the Paraxel-Early Phase Clinical Unit, Glendale, California.

Methods

Ethics
The study was conducted in accordance with the principles outlined in the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice. The Institutional Review Board reviewed and approved the clinical study protocol, any clinical study protocol amendments, subject information sheets, written informed consent forms, and other relevant documentation. Before participating in the study, each subject was apprised of the nature and purpose of the study, and written informed consent was obtained.

Study Population
A total of 48 healthy subjects (24 Japanese and 24 Caucasian) were planned for study enrollment. Healthy male subjects aged 18 to 55 years, with a body mass index ≥18.5 kg/m^2 and ≤33 kg/m^2 were eligible for study participation. The Caucasian subjects enrolled in the study were subjects of European or Caucasian Latin American descent. For Japanese subjects, the entry criteria were designed to ensure that the genetic and physiologic (intrinsic) and cultural and environmental (extrinsic) characteristics of the study population were comparable to those of people living in Japan. To address intrinsic factors, Japanese subjects defined as persons born in Japan and having biological Japanese parents and Japanese maternal and paternal grandparents were enrolled. To address extrinsic factors, Japanese subjects must have lived outside of Japan for <10 years and have completed a lifestyle questionnaire to ensure that their lifestyles, including diet, had not changed significantly since leaving Japan.

Study Design and Drug Administration
This phase 1, open-label, single-dose parallel-group study evaluated the potential ethnicity-related differences in ataluren PK and safety following administration of 1 of 3 dose levels of ataluren: 5, 10, or 20 mg/kg. Subjects in cohort A received a single oral dose of 5 mg/kg ataluren, subjects in cohort B received a single oral dose of 10 mg/kg ataluren, and subjects in cohort C received a single oral dose of 20 mg/kg ataluren. Ataluren dose for each subject was adjusted according to that subject's body weight and designated dose level. The rationale for selection of the 3 doses was to ensure

that the study covered the known plasma concentration range associated with therapeutic benefit.

The study included 24 healthy Japanese and 24 healthy Caucasian subjects (N = 48). Equal numbers of subjects (n = 16; 8 Japanese and 8 Caucasian) were assigned to each of the 3 dose levels (5, 10, or 20 mg/kg).

The study drug was manufactured in accordance with good manufacturing practices. Ataluren was provided to subjects in oral suspension form (by suspending a body weight–adjusted amount of ataluren powder for oral suspension in approximately 30 mL of water), followed by 2 rinses of approximately 30 mL of water. Ataluren was orally administered to subjects following an overnight fast of at least 10 hours predose and a fast of 4 hours postdose, and abstinence from fluids 1 hour before and 1 hour after dosing.

Plasma Sample Bioanalysis

Blood samples for PK analysis of ataluren concentration were collected at 1 hour predose and then at 10, 20, 30, and 45 minutes and 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, and 48 hours postdose in K_3EDTA-coated vacutainer tubes and centrifuged at 4°C for extraction of plasma. The plasma samples were stored at −70°C until analysis.

The plasma samples were analyzed using liquid chromatography with tandem mass spectrometric detection. The bioanalytical methods were validated, and their performances were within the limits specified in current regulatory guidance. Briefly, the assay involved extraction of ataluren and its internal standard (ataluren-d_4) from a 0.100-mL plasma sample by a liquid-liquid extraction procedure, followed by subjecting the extracts to a reverse-phase column (Synergi 4 μm Polar-RP, 50 × 2 mm; Phenomenex, Torrance, California) using a gradient system with 0.1% formic acid in acetonitrile/water (5/95; volume/volume) and 0.1% formic acid in acetonitrile. Ataluren was detected and quantified by tandem mass spectrometer (MDS Sciex API 4000 equipped with a Turbo Ionspray interface;

Sciex, Framingham, Massachusetts) in positive-ion mode. The transition ions m/z 285 → 123 and m/z 289 → 127 were monitored for ataluren and ataluren-d_4, respectively. For the assay of ataluren, 2 sets of calibration curves were prepared in human plasma, with ranges of 1 to 500 ng/mL and 0.5 to 200 μg/mL. Quality control plasma samples were prepared at 3 levels and analyzed in duplicate for each calibration range. Each analytical run contained 1 set of calibration plasma standards, control blank plasma samples, duplicate quality control samples at each of the 3 concentration levels and study samples. A weighted ($1/x^2$) least-squares linear regression was used for quantification based on peak area ratios. The correlation coefficient (r) for all analytical batches was always greater than 0.9965. The precision and accuracy of ataluren standards were within 8.57% and ±4.00%, respectively, for 2 calibration curve ranges. The precision and accuracy of all ataluren quality control samples were within 9.24% and ±6.40%, respectively.

PK Analysis

Noncompartmental analyses (Phoenix WinNonlin version 6.3; Certara, Princeton, New Jersey) of plasma concentrations and the actual sampling times were used to estimate the following PK parameters: maximum concentration (C_{max}), time to maximum concentration (T_{max}), area under the concentration-time curve from time 0 to the last quantifiable time point ($AUC_{[0-last]}$), area under the concentration-time curve from time 0 to infinity ($AUC_{[0-inf]}$), area under the concentration-time curve extrapolated to infinity (AUC_{extrap}), half-life ($t_{1/2}$), apparent clearance (CL/F), and apparent volume of distribution. The PK profiles were evaluated within the same ethnic population and between the Japanese and Caucasian populations.

Results

Ataluren Plasma Concentration-Time Profile

Comparable demographic characteristics were observed across the 3 dose cohorts (Table 1) and between

Table 1. Demographic Summary for All Enrolled Subjects per Cohort

|	5 mg/kg			10 mg/kg			20 mg/kg		
	Caucasian (N = 8)	Japanese (N = 8)	Overall (N = 16)	Caucasian (N = 8)	Japanese (N = 8)	Overall (N = 16)	Caucasian (N = 8)	Japanese (N = 8)	Overall (N = 16)
Age (y), mean (SD)	34.5 (7.2)	35.3 (8.6)	34.9 (7.7)	31.6 (10.2)	35.4 (4.9)	33.5 (8.0)	29.5 (6.9)	37.4 (8.3)	33.4 (8.4)
Height (cm), mean (SD)	178.5 (8.2)	168.8 (6.0)	173.6 (8.6)	179.5 (5.2)	173.5 (5.4)	176.5 (6.0)	177.9 (7.6)	171.8 (6.0)	174.8 (7.3)
Weight (kg), mean (SD)	77.5 (8.1)	61.2 (8.5)	69.4 (11.6)	79.7 (15.5)	66.5 (7.7)	73.1 (13.6)	76.9 (13.5)	72.4 (14.5)	74.7 (13.8)
BMI (kg/m^2), mean (SD)	24.3 (1.3)	21.4 (1.7)	22.8 (2.1)	24.6 (3.8)	22.1 (2.4)	23.3 (3.3)	24.2 (2.6)	24.4 (4.0)	24.3 (3.3)
Ethnicity, n (%)									
Hispanic or Latino	1 (12.5)		1 (6.3)	1 (12.5)		1 (6.3)			
Not Hispanic or Latino	7 (87.5)	8 (100.0)	15 (93.8)	6 (75.0)	8 (100.0)	14 (87.5)	7 (87.5)	8 (100.0)	15 (93.8)
Not reported				1 (12.5)		1 (6.3)	1 (12.5)		1 (6.3)
Sex, n (%)									
Male	8 (100.0)	8 (100.0)	16 (100.0)	8 (100.0)	8 (100.0)	16 (100.0)	8 (100.0)	8 (100.0)	16 (100.0)

BMI indicates body mass index.
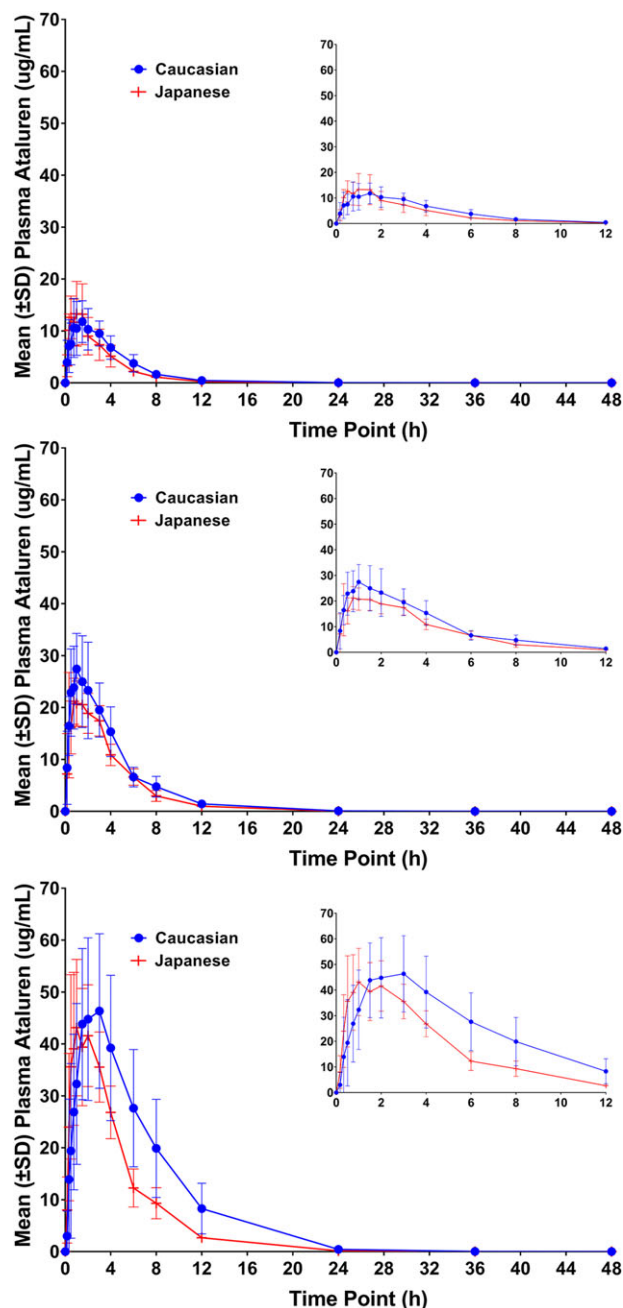
Figure 1. Mean (±SD) ataluren concentration-time profiles, linear scale (top, 5 mg/kg; center, 10 mg/kg; bottom, 20 mg/kg). Insets show expanded time scale.

Japanese and Caucasian subjects. Of the 48 subjects enrolled (24 Japanese and 24 Caucasian), all completed the PK sample draw and were included in PK analysis. Following administration of single escalating doses of ataluren, observation of the plasma concentration-time profiles revealed rapid absorption of ataluren, with T_{max} occurring between 0.875 and 2.5 hours (median values) (Figure 1). The mean C_{max} was similar for Caucasian and Japanese subjects when each dose cohort was considered (Table 2); for instance, in the

5 mg/kg cohort of Japanese subjects, mean C_{max} of 15.88 ± 5.703 µg/mL was observed, whereas for Caucasian subjects, a mean C_{max} of 13.47 ± 4.532 µg/mL was seen. The elimination phase showed similar patterns for all 3 dose cohorts in both groups. AUC_{extrap} values were not listed in Table 2 because these values were less than 6% of $AUC_{(0-inf)}$ values for all cohorts.

PK in Healthy Adult Japanese Subjects
Mean C_{max} and mean AUC values increased in direct proportion with increasing dose in Japanese subjects (Table 2). Median T_{max} and mean $t_{1/2}$ ranged from 0.9 to 1.5 hours and 3.2 to 3.4 hours, respectively. The mean CL/F of ataluren was independent of dose and remained consistent at approximately 6491 to 6609 mL/h across the 5, 10, and 20 mg/kg dose levels (Table 2).

PK in Healthy Adult Caucasian Subjects
Following single-dose administration of ataluren, the mean C_{max} and AUC values increased with each increasing dose in the Caucasian group. Median T_{max} and mean $t_{1/2}$ ranged from 1 to 2.5 hours and 3.2 to 3.4 hours, respectively. Mean CL/F values were 7719 mL/h at 5 mg/kg dose, 6459 mL/h at 10 mg/kg dose, and 4996 mL/h at 20 mg/kg dose, respectively (Table 2).

Of note, 2 subjects in the 20 mg/kg Caucasian cohort had higher AUC values compared with those of the other subjects in the same group. In 1 of these subjects, $AUC_{(0-last)}$ and $AUC_{(0-inf)}$ were 633.3 h·µg/mL and 633.4 h·µg/mL, respectively; in the other subject, the values were 467.5 h·µg/mL and 467.6 h·µg/mL. Analyses showed that, if these subjects were excluded from the PK analysis, the mean $AUC_{(0-last)}$ and $AUC_{(0-inf)}$ values of the remaining subjects dropped to 276.7 ± 39.9 h·µg/mL (mean ± SD, coefficient of variation = ±14%), while the mean CL/F values increased to 5877 ± 506 mL/h, which was similar to the values in the 5 mg/kg and 10 mg/kg groups.

Comparison of PK in Healthy Adult Japanese Subjects Versus Caucasian Subjects
The C_{max} values were very similar for both ethnic populations across the 5, 10, and 20 mg/kg dose levels. However, the mean $AUC_{(0-last)}$ values were 14% to 34% lower in Japanese subjects than in Caucasian subjects across the 3 dose levels. Furthermore, the variability of AUC between subjects (CV) was higher in the Caucasian than in the Japanese population: 35.8%, 31.8%, and 36.1% for the 5, 10, and 20 mg/kg doses, respectively, in the Caucasian population versus 31%, 15.2%, and 18.3% in the Japanese counterparts. The Japanese and Caucasian subjects showed similar mean half-life values of approximately 3.4 hours. The half-life was not dose dependent in either group. The Japanese subjects had consistent

Table 2. Summary of Ataluren Plasma Pharmacokinetic Parameters

Dose Level Ethnicity	Statistics	$AUC_{(0\text{-}last)}$ (h·μg/mL)	$AUC_{(0\text{-}inf)}$ (h·μg/mL)	C_{max} (μg/mL)	T_{max}[a] (h)	$t_{1/2}$ (h)	CL/F (mL/h)
5 mg/kg							
Japanese (n = 8)	Arith mean (SD)	49.3 (15.3)	49.3 (15.3)	15.9 (5.7)	0.9	3.2 (0.4)	6609 (1741)
	Geo mean (CV%)	47.3 (31.0)	47.3 (31.0)	15.2 (31.8)		3.2 (12.5)	6402 (28)
	Range (min-max)	29.2–80.3	29.2–80.3	11.2–28.3	0.3–1.5	2.7–3.9	3958–9496
Caucasian (n = 8)	Arith mean (SD)	57.2 (16.1)	57.2 (16.1)	13.5 (4.5)	1.5	3.2 (0.5)	7719 (4118)
	Geo mean (CV%)	54.7 (35.8)	54.7 (35.8)	12.7 (40.9)		3.2 (16.6)	7078 (43)
	Range (min-max)	25.2–80.2	25.2–80.2	5.5–21.6	0.3–3	2.1–3.6	4690–17 530
10 mg/kg							
Japanese (n = 8)	Arith mean (SD)	104.5 (15.2)	104.5 (15.2)	25.2 (6.4)	1.5	3.3 (0.1)	6557 (1422)
	Geo mean (CV%)	103.5 (15.2)	103.5 (15.2)	24.6 (23.4)		3.3 (2.5)	6435 (21)
	Range (min-max)	77.4–129.9	77.4–129.9	18.4–38.8	0.3–3	3.2–3.5	4949–9572
Caucasian (n = 8)	Arith mean (SD)	131 (38.2)	131.1 (38.2)	29.9 (7.1)	1	3.4 (0.2)	6459 (1496)
	Geo mean (CV%)	125.9 (31.8)	125.9 (31.8)	29.1 (27.5)		3.4 (5.8)	6325 (22)
	Range (min-max)	71.7–180.4	71.7–180.4	16.4–38.3	0.5–2	3.3–3.9	5249–9563
20 mg/kg							
Japanese (n = 8)	Arith mean (SD)	228.4 (42.8)	228.5 (42.8)	47.1 (12.8)	1.3	3.4 (0.2)	6491 (1760)
	Geo mean (CV%)	225.1 (18.3)	225.1 (18.3)	45.7 (25.5)		3.4 (6.6)	6294 (27)
	Range (min-max)	176.8–298.3	176.9–298.4	33.8–71.8	0.5–2	3.2–4.0	4296–9426
Caucasian (n = 8)	Arith mean (SD)	345.1 (138.4)	345.2 (138.4)	48.8 (14.0)	2.5	3.4 (0.1)	4996 (1700)
	Geo mean (CV%)	325.5 (36.1)	325.5 (36.1)	47.2 (27.7)		3.4 (3.7)	4647 (47)
	Range (min-max)	224.4–633.3	224.4–633.4	35.3–71.2	1.5–3	3.2–3.6	1948–6755

Arith mean indicates arithmetic mean; AUC, area under the curve; CL/F, clearance; C_{max}, maximum concentration; Geo mean, geometric mean; T_{max}, time of maximum concentration; $t_{1/2}$, half-life.

[a] T_{max} is summarized by median and range.

CL/F among the 3 dose groups; although CL/F values for Caucasian subjects appeared to be consistent across the 5 mg/kg and 10 mg/kg dose groups but slightly decreased at the 20 mg/kg dose, which likely resulted from the high variability. The variability in AUC and low sample size at each dose level should be taken into consideration in evaluating the data (Table 2).

Discussion

This study investigated if background, ie, Caucasian or Japanese, impacted the PK of ataluren. Plasma concentration-time profiles of ataluren were characterized by rapid absorption, reaching maximum concentration between 0.9 and 2.5 hours. These data are in line with those observed in the study conducted by Hirawat and colleagues.[18] Japanese and Caucasian subjects showed similar mean C_{max} values at each of the 3 doses, although the mean C_{max} and AUC values increased with increasing dose. However, the mean $AUC_{(0\text{-}last)}$ for Caucasians was higher than that observed for Japanese subjects when ataluren was given at the same dose. Japanese subjects had consistent CL/F values across all dose levels, whereas for Caucasian subjects, the CL/F values appeared to be consistent across 5 mg/kg and 10 mg/kg but slightly decreased at the 20 mg/kg dose. Both Japanese and Caucasian subjects showed similar mean half-life values at approximately

3.4 hours. The half-life was not dose dependent in either group and was similar to those previously observed.[18] Slight higher exposure (14% to 34%, AUC) in Caucasian subjects compared with Japanese subjects was likely due to the higher variability in Caucasian subjects and the small sample size. The overall similarity in PK profiles observed between the Caucasian and Japanese subjects suggests that the absorption, metabolism, and disposition of ataluren are not dependent on race.

The influence of body weight on the AUC did not have a clear trend between the 2 populations. At the 5 mg/kg dose, the difference of body weight (Caucasian/Japanese) was approximately 27%, but the AUC difference was less than 16% (geometric mean ratio). However, at the 20 mg/kg dose, the difference of body weight (Caucasian/Japanese) was 6%, but the AUC difference was approximately 34%.

The elimination of ataluren is dependent on glucuronidation of ataluren followed by renal and/or biliary excretion of the resulting glucuronide metabolite. Ataluren is metabolized via UGT enzymes, mainly by UGT1A9. Very few polymorphisms of UGT1A9, which might affect ataluren metabolism, have been identified. One UGT1A9 polymorphism (UGT1A9*22) has been reported to be present only in Japanese populations; however, the allele frequency of this polymorphism is less than 0.7% in the Japanese population[33,34]; therefore, polymorphisms of UGT1A9

are not expected to influence the PK of ataluren in Japanese subjects. Regarding the potential for any type of polymorphism of metabolic enzymes to impact the PK of ataluren, no subjects who were considered significant outliers were observed within any dose or demographic group, although the lack of genotyping in study subjects does not eliminate the possibility of a genetic polymorphism that would result in a greater extent of acyl glucuronidation. This was particularly the case with the Japanese subjects, in whom the intersubject variability was markedly lower than that for Caucasians at the 10 and 20 mg/kg dose levels, as evidenced by CV percentages for the AUC values in Japanese subjects being smaller than those in the corresponding Caucasian group; CV = 14.5% and 29.1% at 10 mg/kg and 19% and 40% at 20 mg/kg in Japanese and Caucasians, respectively.

Conclusions

Following single oral administration, ataluren was rapidly absorbed, with median T_{max} ranging between 0.9 and 2.5 hours. C_{max} and AUC increased with increasing dose in both the Caucasian and Japanese populations. Likewise, the half-life of ataluren did not vary with dose and ethnicity (~3.4 hours). However, the $AUC_{(0-last)}$ and intersubject variability were lower in Japanese subjects compared with Caucasian subjects. Moreover, whereas in the Japanese subjects the CL/F values remained constant across the 3 dose levels, the values dropped for the Caucasian counterparts at the 20 mg/kg dose. Of note, the drop in these values was due to 2 Caucasian subjects in the 20 mg/kg cohort who had comparatively higher AUC values, which impacted the CL/F values observed. Therefore, the variability and low sample size at each dose level should be taken into consideration in evaluating the comparability of the data. Overall, the ataluren PK profiles in these 2 populations were similar.

Conflicts of Interest

There are no conflicts of interest.

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