

# Effects of Food Intake on the Pharmacokinetics of Azilsartan Medoxomil and Chlorthalidone Alone and in Fixed-Dose Combination in Healthy Adults

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## Abstract

Azilsartan medoxomil is a long-acting angiotensin II receptor blocker used to treat hypertension as monotherapy or in fixed-dose combination (FDC) with chlorthalidone. This study assessed the effects of food intake on the plasma pharmacokinetics of the active moiety, azilsartan, and of chlorthalidone when administered as separate tablets or in FDC. Cohort 1 ( $n = 24$ ) received azilsartan medoxomil (80 mg) and chlorthalidone (25 mg) once in a fasted condition and once 30 minutes after the initiation of a high-fat meal (fed). Cohort 2 ( $n = 24$ ) received the same drugs as an FDC tablet in the fasted and fed conditions. In cohort 1, the fed-fasted ratios for  $AUC_{0-\infty}$  and  $C_{max}$  were 108.3 (101.6–115.5) and 103.7 (94.3–114.1), respectively, for azilsartan and 112.3 (106.5–118.4) and 100.3 (90.6–111.1), respectively, for chlorthalidone. In cohort 2, the corresponding ratios were 78.6 (67.6–91.4) and 78.6 (64.4–96.0) for azilsartan and 101.0 (96.5–86.7) and 75.9 (66.5–86.7) for chlorthalidone. The combination therapies were well tolerated, and food intake had no consistent effect on adverse events. Food intake had a somewhat greater effect on plasma pharmacokinetics after administration of the FDC tablet than after administration of separate tablets, but the effects of food on the plasma pharmacokinetics of the FDC were not expected to be clinically meaningful.

## Keywords

hypertension, AUC,  $C_{max}$ , half-life, angiotensin II receptor blocker

Azilsartan medoxomil is a long-acting angiotensin II receptor blocker approved to treat hypertension.<sup>1</sup> It is available as monotherapy or as part of a fixed-dose combination with chlorthalidone. Chlorthalidone is a long-acting thiazide-like diuretic that is more potent than hydrochlorothiazide at lowering systolic blood pressure<sup>2</sup> and is associated with strong reductions in the risk of cardiovascular events.<sup>3,4</sup> A fixed-dose combination of azilsartan medoxomil and chlorthalidone was developed to increase antihypertensive efficacy, to reduce pill burden, and because both were suitable for once-daily dosing.<sup>5–7</sup>

Azilsartan medoxomil is a prodrug that is rapidly hydrolyzed to the active moiety, azilsartan. Peak plasma concentrations of azilsartan are reached within 1.5–3 hours after oral administration of the prodrug, and the elimination half-life of azilsartan is approximately 11 hours. Coadministration with food has minimal effects on bioavailability.<sup>8</sup> Chlorthalidone reaches peak plasma concentrations about 2–6 hours after oral administration, and the drug has a half-life of about

42 hours.<sup>9</sup> There is no evidence of significant pharmacokinetic interactions between azilsartan medoxomil and chlorthalidone.<sup>9</sup>

Food intake can affect the bioavailability of some antihypertensive drugs or drug combinations, and this effect may depend on the specific drug formulation.<sup>10</sup> Therefore, we characterized the effects of food intake on the bioavailability of the fixed-dose combination of azilsartan medoxomil and chlorthalidone. We

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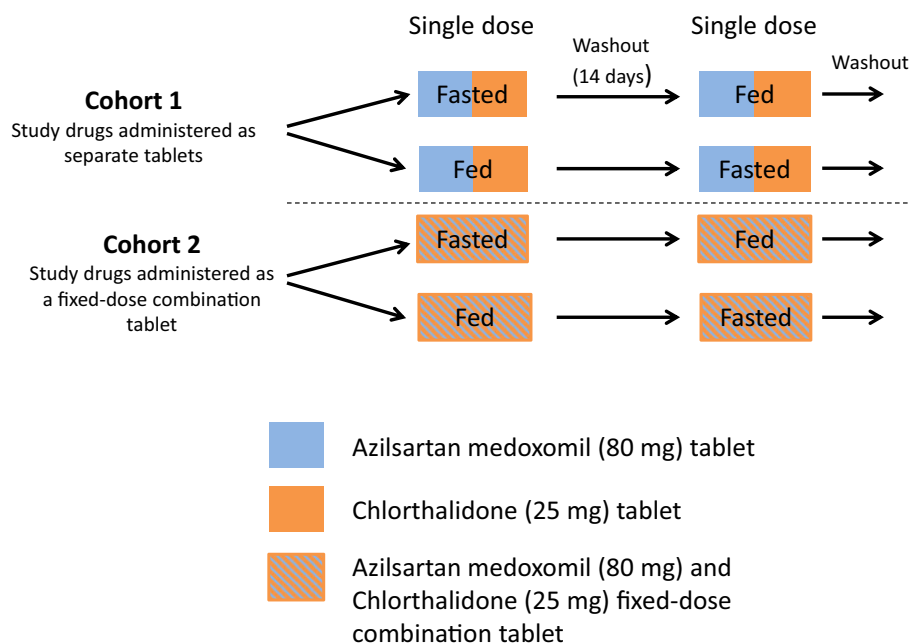
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**Figure 1.** Schematic of study design. Cohort 1 and cohort 2 participated in separate study components. Each cohort received azilsartan medoxomil (80 mg) and chlorthalidone (25 mg) once in a fasted condition and once in a fed condition in random sequence and separated by a 14-day washout period. Cohort 1 received study drugs as separate tablets, whereas cohort 2 received study drugs as a single fixed-dose combination tablet.

conducted a 2-cohort study to assess the effects of a high-fat meal on the pharmacokinetics of azilsartan (the active moiety of the prodrug azilsartan medoxomil) and chlorthalidone administered simultaneously in 2 different formulations. Cohort 1 received study drugs as individual tablets administered simultaneously, and cohort 2 received the same drugs and doses administered as a single fixed-dose combination tablet. Within each cohort, participants received study drugs while in a fasted state or after consumption of a high-fat meal to compare how food consumption affected the bioavailability of each formulation.

## Methods

### Participants

Eligible participants were healthy men and women aged 18 to 55 years. Women were required to be nonpregnant and nonlactating and to use acceptable contraception if they were of childbearing potential. Participants were excluded if they used tobacco products, prescription medications, supplements, or over-the-counter medications (except occasional acetaminophen), had a history of alcohol abuse, if their systolic blood pressure was >160 mm Hg or <100 mm Hg, or if their diastolic blood pressure was >100 mm Hg or <60 mm Hg.

The study was conducted at PPD Development, LLC, Clinics in Austin, Texas. The study protocol and consent form were approved by the institutional review

board, IntegReview, LTD (Austin, Texas). The study was conducted according to the World Medical Association Declaration of Helsinki, the ICH Harmonised Tripartite Guidelines for Good Clinical Practice, and all applicable local and federal regulatory requirements. Written consent was obtained from each participant before any study procedures were performed.

### Study Procedures

Enrolled participants were randomly assigned to 1 of 2 cohorts (Figure 1). Cohort 1 received azilsartan medoxomil (80 mg) and chlorthalidone (25 mg) as separate tablets administered simultaneously. Cohort 2 received a fixed-dose combination tablet containing azilsartan medoxomil (80 mg) and chlorthalidone (25 mg). Within each cohort, participants received study drugs on 2 occasions in random sequence and separated by a 14-day washout period. One dose was administered while the participant was in a fasted condition, defined as having fasted overnight for at least 10 hours before dose administration and for at least 4 hours after study drug administration. The other dose was administered while the participant was in a fed condition, defined as having fasted for 10 hours overnight, then having consumed a high-fat meal. The high-fat meal consisted of 2 eggs fried in butter, 2 strips of bacon, 2 slices of toast with butter, 4 ounces of hash brown potatoes, and 8 ounces of whole milk; it consisted of approximately 800 to 1000

calories, approximately 50% of which came from fat. Study drugs were administered 30 minutes after the start of the meal. All study drugs were administered in an open-label manner with 240 mL of water. Participants were confined to the clinic beginning 1 day before study drug administration and extending to 120 hours (5 days) after drug administration.

Venous blood samples were obtained from each participant before drug administration and at predefined times after drug administration. Blood samples for determination of azilsartan concentrations were obtained 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 16, 24, 32, 36, 48, and 72 hours after drug administration. For determination of chlorthalidone concentrations, blood samples were obtained 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 16, 24, 48, 72, 96, and 120 hours after drug administration. Drug concentrations were determined from plasma. Azilsartan medoxomil is a prodrug that is rapidly hydrolyzed in the gut to the active component, azilsartan. Therefore, plasma concentrations of the active azilsartan were measured and displayed.

Individual methods of liquid chromatography (LC) using tandem mass spectrometric detection (MS/MS) were used for the quantification of azilsartan and chlorthalidone concentrations in plasma samples. For the determination of azilsartan, 2% acetic acid in acetonitrile solution and the internal standard (T-61265) were added to the samples for protein precipitation. LC separation was obtained using a Chromolith SpeedROD RP-18e column (EMD Millipore; 50 × 4.6 mm); the mobile phase consisted of a gradient of 0.1% acetic acid in water to 0.1% acetic acid in methanol. For the determination of chlorthalidone, the internal standard (chlorthalidone-d4) was added to the sample before solid-phase extraction using Waters Oasis Max 10 mg 96-well plates. LC separation was obtained using a Synergi Hydro-RP column (Phenomenex, 50 × 2.0 mm); the mobile phase consisted of 50% 0.005% acetic acid in 25:75 acetonitrile/water, v/v, and 50% 0.005% acetic acid in 10:25:65 water/acetonitrile/methanol, v/v/v.

For detection of analytes, an API 3000 mass spectrometer (AB Sciex, Framingham, Massachusetts) was used in multiple reaction monitoring mode with positive ion electrospray for azilsartan or negative ion electrospray for chlorthalidone. The transition monitored for azilsartan was 457.3→233.1, and for chlorthalidone it was 336.8→146.0. For azilsartan, the LC-MS/MS assay parameters were as follows: range, 10.0–5000 ng/mL; accuracy, 95.5% to 109.6% of the theoretical concentration; precision, 5.7%–9.5% coefficient of variation. For chlorthalidone, the assay parameters were: range, 2.00–1000 ng/mL; accuracy, 98.4% to 100.8% of the theoretical concentration; precision, 3.95% to 6.76% coefficient of variation. These param-

eters may include quality control values that failed acceptance criteria, but the acceptance criteria for each run were met.

Pharmacokinetic parameters are given as arithmetic means (systemic exposure [ $AUC_{0-inf}$ ], maximum plasma concentration [ $C_{max}$ ], plasma half-life [ $T_{1/2}$ ]) or medians (time to maximum plasma concentration [ $T_{max}$ ]). Plasma concentrations below the limit of quantification were set to zero and included as such in calculations of means. An analysis of variance model with fixed effects for sequence, period, and treatment and a random effect for participant nested within sequence was performed on the natural logarithms of  $AUC_{0-inf}$  and  $C_{max}$ . The ratio and the 90% confidence interval (CI) for the ratio of the test treatment (drug administration after a high-fat meal) least-squares mean relative to the reference treatment (drug administration while fasted) were provided for these pharmacokinetic parameters. According to guidance for bioequivalence from the U.S. Food and Drug Administration, there is no significant food effect if the 90% confidence intervals for  $C_{max}$  and  $AUC_{0-inf}$  are within the no-effect boundaries of 80% to 125%. Comparison of treatments for median  $T_{max}$  was performed using the Wilcoxon signed rank test.

Participants were also monitored for adverse events and by clinical laboratory tests, measurement of vital signs, 12-lead electrocardiogram, and physical examination. Treatment-emergent adverse events were tabulated, and vital signs were analyzed with descriptive statistics. Adverse events were defined as mild if they were transient and easily tolerated and moderate if they caused discomfort and interrupted normal activities.

## Results

Twenty-four participants were enrolled in cohort 1, and 21 completed all study procedures. Reasons for withdrawal were 1 participant who experienced an adverse event of vomiting, 1 participant withdrew consent, and 1 participant had a major protocol deviation. Twenty-four participants were enrolled in cohort 2, and 23 completed all study procedures. The 2 participants (1 in each cohort) who experienced vomiting, including the one who withdrew, were included in the pharmacokinetic analysis, as the vomiting occurred at least 11 hours after dose administration. One participant was lost to follow-up. Average demographic and baseline characteristics of participants in the 2 cohorts are shown in Table 1.

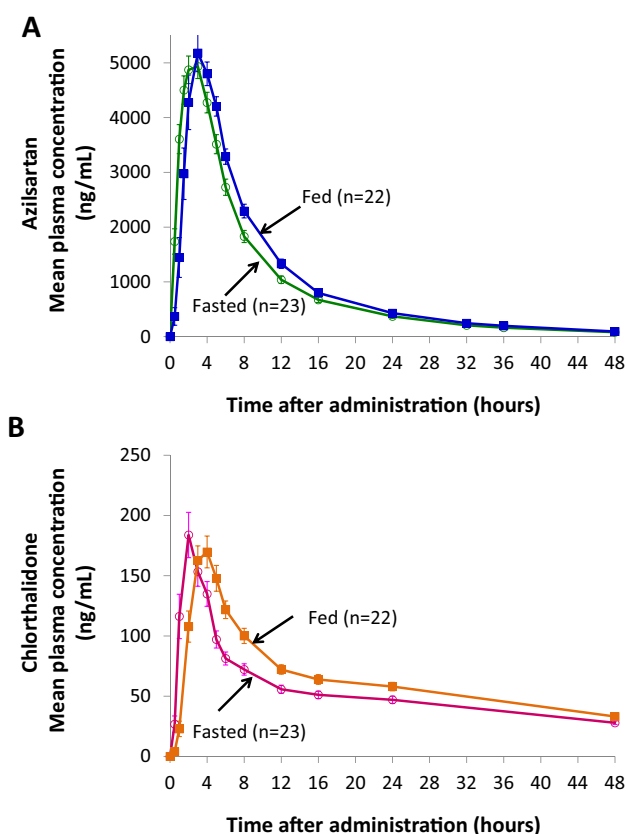
### *Cohort 1: Effects of Food Intake on the Pharmacokinetics of Azilsartan and Chlorthalidone Administered as Separate Tablets*

Figure 2 shows mean plasma concentrations of azilsartan and chlorthalidone after a single dose of

**Table 1.** Demographic and Baseline Characteristics of Participants in the 2 Separate Cohorts

Characteristic	Cohort 1 (n = 24)	Cohort 2 (n = 24)
Age (y), mean (SD)	32.7 (11.1)	33.0 (11.7)
Female, n (%)	13 (54)	10 (42)
Weight (kg), mean (SD)	72.2 (10.9)	74.1 (14.6)
Height (cm), mean (SD)	166.3 (10.3)	169.5 (11.7)
BMI (kg/m <sup>2</sup> ), mean (SD)	26.1 (2.8)	25.6 (2.9)
Race/ethnicity, n (%)		
White	18 (75)	17 (71)
Hispanic or Latino	11 (46)	10 (42)
Black	6 (25)	5 (21)
Asian	0	2 (8)

Participants in cohort 1 received azilsartan medoxomil (80 mg) and chlorthalidone (25 mg) as separate tablets, and participants in cohort 2 received the same drugs and doses in a single fixed-dose combination tablet. BMI, body mass index; SD, standard deviation.



**Figure 2.** Mean (SE) plasma concentrations of azilsartan (A) and chlorthalidone (B) after administration of study drugs as separate tablets to participants in cohort 1 in either the fasted condition or 30 minutes after the initiation of a high-fat meal.

azilsartan medoxomil (80 mg) and chlorthalidone (25 mg) administered as separate tablets under either fasted or fed conditions. A summary of plasma pharmacokinetic parameters is shown in Table 2, comparing the fasted and fed conditions. Compared with study drug administration in a fasted condition, drug admin-

istration 30 minutes after initiation of a high-fat meal had only minor effects on the plasma pharmacokinetics of both azilsartan and chlorthalidone.

#### Cohort 2: Effects of Food Intake on the Pharmacokinetics of Azilsartan and Chlorthalidone Administered as a Single Fixed-Dose Combination Tablet

Figure 3 shows mean plasma concentrations of azilsartan and chlorthalidone after a single dose of azilsartan medoxomil (80 mg) and chlorthalidone (25 mg) administered as a fixed-dose combination tablet under either fasted or fed conditions. A summary of plasma pharmacokinetic parameters is shown in Table 3, comparing the fasted and fed conditions. The fed-fasted ratios for  $AUC_{0-\infty}$  and  $C_{max}$  indicate that food intake had modest effects on the pharmacokinetics of the fixed-dose combination tablet, reducing the  $AUC_{0-\infty}$  and  $C_{max}$  of azilsartan and reducing the  $C_{max}$  of chlorthalidone. However, the upper bounds of the 90% confidence intervals remained within the no-effect boundary, and the effects of food intake were not expected to be clinically meaningful (see Discussion).

#### Adverse Effects

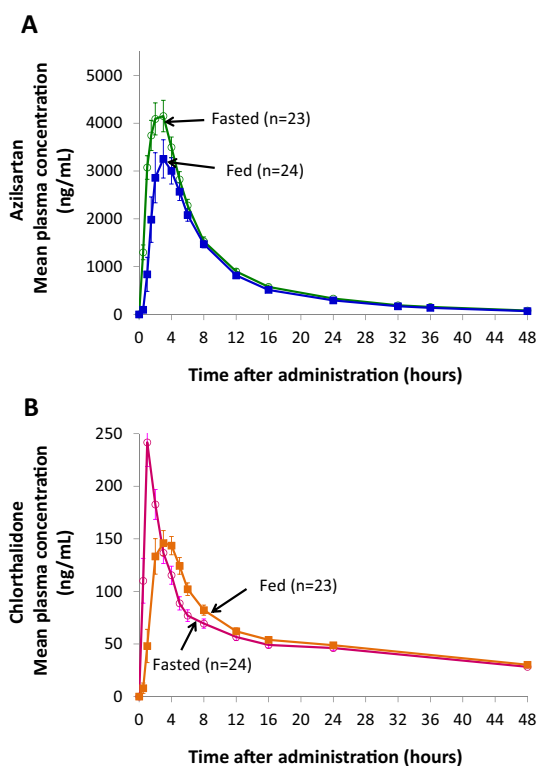
The only adverse events reported in more than 1 participant in either cohort were headache (reported in 2 participants in cohort 1 and 4 participants in cohort 2) and dizziness (reported in 3 participants in cohort 1 and 2 participants in cohort 2). Most adverse events were of mild intensity, except 1 participant in cohort 1 (separate tablets) who experienced moderate dizziness and vomiting after drug administration in the fasted condition and 1 participant in cohort 2 (fixed-dose tablet) who experienced moderate vomiting after drug administration in the fed condition. There were no notable differences in adverse events between the fasted condition and the fed condition in either cohort. Neither cohort

**Table 2.** Cohort 1: Azilsartan Medoxomil (80 mg) and Chlorthalidone (25 mg) Administered as Separate Tablets

	Fasted		Fed		Ratio, <sup>a</sup> Fed/Fasted (90%CI)
	No. of Participants	Arithmetic Mean or Median	No. of Participants	Arithmetic Mean or Median	
<b>Azilsartan</b>					
Mean AUC <sub>0–inf</sub> , ng·h/mL (SD)	23	46 688.2 (10 620.1)	22	49 887.8 (11 492.9)	108.3 (101.6–115.5)
Mean C <sub>max</sub> , ng/mL (SD)	23	5355.71 (1056.0)	22	5717.7 (1465.2)	103.7 (94.3–114.1)
Median T <sub>max</sub> , h (min, max)	23	3 (1.5, 4.0)	22	3 (2.0, 5.0)	
Mean T <sub>1/2</sub> , h (SD)	23	12.1 (1.5)	22	12.0 (1.5)	
<b>Chlorthalidone</b>					
Mean AUC <sub>0–inf</sub> , ng·h/mL	19	4437.3 (1041.6)	20	5019.5 (1005.8)	112.3 (106.5–118.4)
Mean C <sub>max</sub> , ng/mL	23	200.1 (89.2)	22	192.2 (50.4)	100.3 (90.6–111.1)
Median T <sub>max</sub> , h	23	2 (1.0, 4.0)	22	4 (2.0, 5.1)	
Mean T <sub>1/2</sub> , h (SD)	23	41.2 (9.4)	22	38.6 (8.5)	

Mean or median plasma pharmacokinetic parameters for azilsartan and chlorthalidone after administration of study drugs to participants in a fasted state or 30 minutes after initiation of a high-fat meal (fed). AUC<sub>0–inf</sub>, area under the plasma concentration–time curve from time 0 (time of dose administration) to infinity, calculated from the last quantifiable concentration and the terminal elimination rate constant; C<sub>max</sub>, maximum observed plasma concentration; CV, coefficient of variation; SD, standard deviation; T<sub>max</sub>, time from dose administration to C<sub>max</sub>; T<sub>1/2</sub>, plasma half-life.

<sup>a</sup>Ratio of least-squares means.



**Figure 3.** Mean (SE) plasma concentrations of azilsartan (A) and chlorthalidone (B) after administration of study drugs as a single fixed-dose combination tablet to participants in cohort 2 in either the fasted condition or 30 minutes after the initiation of a high-fat meal.

experienced clinically significant changes in vital signs, electrocardiogram, physical examination results, or clinical laboratory findings during the study.

## Discussion

In healthy adult participants, consumption of a high-fat meal just before dosing of study drugs had only minor effects on the plasma pharmacokinetics of azilsartan or chlorthalidone when the parent compounds were administered as separate tablets. In the cohort that received the fixed-dose combination tablet, the high-fat meal had a somewhat greater effect on the pharmacokinetics of azilsartan and chlorthalidone, with 3 of 4 pharmacokinetic ratios falling below the pre-specified no-effect boundary of 80%. The explanation for this difference is unclear. One possible factor is that the active ingredients of the fixed-dose tablets were micronized. Further studies will be required to determine if that difference or other factors involved in cocompounding influenced how food affected the pharmacokinetics of the fixed-dose combination tablet. In a previous study, the blood pressure–lowering effects of the fixed-dose combination had a nearly flat dose–response relationship at doses of azilsartan  $\geq 20$  mg and chlorthalidone doses  $\geq 12.5$  mg.<sup>5</sup> Thus, the relatively modest effects of food intake on plasma concentrations in the current study are unlikely to have clinically meaningful effects on blood pressure.

The effects of food intake on the pharmacokinetics of chlorthalidone have not been reported previously, and the current study provides evidence that there is no need to adjust dosage timing relative to food intake. Similarly, the study indicates that there is no reason to be concerned about the timing of administration for the fixed-dose combination tablet containing azilsartan medoxomil (80 mg) and chlorthalidone (25 mg).



**Table 3.** Cohort 2: Azilsartan Medoxomil (80 mg) and Chlorthalidone (25 mg) Administered as a Single Fixed-Dose Combination Tablet

	Fasted		Fed		Ratio, <sup>a</sup> Fed/Fasted (90%CI)
	No. of Participants	Arithmetic Mean or Median	No. of Participants	Arithmetic Mean or Median	
<b>Azilsartan</b>					
Mean AUC <sub>0–inf</sub> , ng·h/mL (SD)	23	39 867.4 (11 603.3)	24	32 695.2 (14 511.6)	78.6 (67.6–91.4)
Mean C <sub>max</sub> , ng/mL (SD)	23	4465.2 (1541.3)	24	3854.2 (2167.4)	78.6 (64.4–96.0)
Median T <sub>max</sub> , h (min, max)	23	2 (1.5, 5.0)	24	3 (1.5, 6.0)	
Mean T <sub>1/2</sub> , h (SD)	23	12.9 (1.8)	24	12.6 (2.1)	
<b>Chlorthalidone</b>					
Mean AUC <sub>0–inf</sub> , ng·h/mL (SD)	20	4540.6 (945.0)	22	4515.6 (725.0)	101.0 (96.5–105.7)
Mean C <sub>max</sub> , ng/mL (SD)	23	259.1 (93.4)	24	189.7 (59.2)	75.9 (66.5–86.7)
Median T <sub>max</sub> , hours (min, max)	23	1 (0.58, 4.0)	24	2 (1.0, 5.0)	
Mean T <sub>1/2</sub> , hr (SD)	23	42.5 (8.5)	24	41.1 (8.2)	

Mean or median plasma pharmacokinetic parameters for azilsartan and chlorthalidone after administration of study drugs to participants in a fasted state or 30 minutes after initiation of a high-fat meal (fed). AUC<sub>0–inf</sub>, area under the plasma concentration–time curve from time 0 (time of dose administration) to infinity, calculated from the last quantifiable concentration and the terminal elimination rate constant; C<sub>max</sub>, maximum observed plasma concentration; CV, coefficient of variation; SD, standard deviation; T<sub>max</sub>, time from dose administration to C<sub>max</sub>; T<sub>1/2</sub>, plasma half-life.

<sup>a</sup>Ratio of least-squares means.

Although 2 participants in the current study reported vomiting, vomiting was not a common adverse event in previous studies of azilsartan and chlorthalidone. Other reported adverse events were consistent with previous studies of azilsartan and chlorthalidone.<sup>5,6</sup> Furthermore, there was no consistent evidence of any effects of food intake on the incidence, type, or severity of adverse events.

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## Declaration of Conflicting Interests

Caroline Dudkowski and Melvin Munsaka are employees of Takeda. Aziz Karim was an employee of Takeda at the time the study was conducted.

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