CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

200796Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

APPENDIX TO CLINICAL PHARMACOLOGY REVIEW

NDA Number:	200796
Submission Type; Code:	N_000, original
Applicant Name:	Takeda Global Research Development
Submission Dates:	04/28/2010
Brand Name:	Edarbi®
Generic Name	Azilsartan medoxomil
Dosage Form:	Tablet
Dosage Strengths:	40, 80 mg
Proposed Indication:	Hypertension
OCP Division:	DCP 1
Primary Reviewer:	Divya Menon-Andersen, PhD
Team Leader:	Rajanikanth Madabushi, PhD

Table of contents

1 Dose – Response Analysis for Azilsartan 3
2 *In vitro* studies 13
2.1 Study TAK 491-00049_CYP450 (CYP Identification) 13
2.2 Study TAK 491-00050 (CYP Inhibition) 14
2.3 Study TAK 491-00086 (CYP Induction) 15
2.4 Study TAK 491-10051 and TAK 491-10052 (CYP Inhibition) 16
2.5 Study TAK 491-10053 and TAK 491-10054 (CYP Induction) 18
2.6 Study TAK 491-00214 and TAK 536-c-46-0045 (Permeability) 19
2.7 Study TAK 491-00215 and TAK 536-c-46-00446 (P-gp Inhibition) 21
3 Bioavailability 23
3.1 Study 01-06-TL-536-016 (Absolute and relative bioavailability) 23
3.2 Study 01-06-TL-491-015 (Relative BA, Food effect) 27
3.3 Study 01-05-TL-491-017 (MAD PK) 30
4 Pharmacokinetics 36
4.1 Study 01-05-TL-491-002 (MAD PK) 36
4.2 Study 01-05-TL-491-101 (MAD PK) 41
5 Mass balance 45
6 Intrinsic factors 48
6.1 Study TAK 491_103 (Renal Impairment) 48
6.2 Study TAK 491_102 (Hepatic Impairment) 50
6.3 Study 01-05-TL-491-003 (Age, sex, race) 53
7 Extrinsic factors 57
7.1 Study 01-06-TL- 491_013 (DDI- probe ‘cocktail’) 57
7.2 Study TAK-491_017 (DDI- Antacid (Mylanta)) 59
7.3 Study TAK 491_104 (DDI- Digoxin) 61
7.4 Study 01-04-TL-536 (DDI- Ketoconazole/Fluconazole) 63
7.5 Study 01-05-TL-536 (DDI- Warfarin) 65
7.6 Study 01-05-TL-536-010 (DDI- Glyburide) 68
7.7 Study 01-05-TL-491-004 (DDI- Chlorthalidone) 70
7.8 Study TAK 491-110 (DDI- Amlodipine) 72
7.9 Study 01-05-TL-536-011 (DDI- Metformin) 74
7.10 Study 01-05-TL-536-006 (DDI- Pioglitazone) 76

1 DOSE – RESPONSE ANALYSIS FOR AZILSARTAN

Introduction

Azilsartan medoxomil (AZM) is the pro-drug of azilsartan (AZ), an angiotensin II receptor (type 1) blocker that is formed via hydrolysis of AZM during absorption. Three doses of AZM, 20, 40 and 80 mg, were selected for testing in Phase III efficacy studies based on the results of two Phase II dose ranging studies.

Study **TAK 491_005** was an eight week study conducted with **AZM capsules** (5 – 80 mg). Similarly, study **TAK 536_002** (2.5 to 40 mg) was an eight week conducted using **AZ tablets**. Both studies were placebo and active (olmesartan) controlled 8 week studies in subjects with mild to moderate hypertension. Change from baseline in diastolic blood pressure (DBP) at week 8, as determined by clinic measurement was the primary endpoint. Twenty four hour ambulatory blood pressure measurement (ABPM) was recorded at baseline (pre-dose, study day 1) and at end of study.

When compared to the commercial formulation (**AZM tablet**), AZM capsule provides ~ 60%, and AZ tablet ~ 162% (with out correcting for MW) systemic exposure to AZ, respectively. On a mg/mg basis, systemic exposure to AZ following administration of the three dosage forms can be ranked as: AZ tablet > AZM tablet > AZM capsule.

The dose-response relationship for AZ following administration of AZM and AZ were evaluated and the results are provided in this document.

Objectives

The objectives of this analysis were the following.

- To characterize the dose-response relationship of azilsartan using data collected in the two Phase II dose ranging studies.
- To compare the cumulative distribution for blood pressure reduction attained with the three doses studied in Phase III monotherapy studies.

Methods

Data Sets

Analysis datasets submitted to the NDA were used and are listed in **Table 1**.

Table 1: Analysis Data Sets

Study Number	Name	Link to EDR
TAK 491_005 Phase II	adam.xpt adbp.xpt	\\Cdsesub1\evsprod\NDA200796\\0000\m5\datasets\01-05-tl-491-005\analysis\adam.xpt \\Cdsesub1\evsprod\NDA200796\\0000\m5\datasets\01-05-tl-491-005\analysis\adbp.xpt
TAK 536_002 Phase II	adam.xpt adbp.xpt	\\Cdsesub1\evsprod\NDA200796\\0000\m5\datasets\01-03-tl-536-002\analysis\adam.xpt \\Cdsesub1\evsprod\NDA200796\\0000\m5\datasets\01-03-tl-536-002\analysis\adbp.xpt
TAK 491_008 Phase III	adam.xpt adbp.xpt	\\Cdsesub1\evsprod\NDA200796\\0000\m5\datasets\01-05-tl-491-008\analysis\adam.xpt \\Cdsesub1\evsprod\NDA200796\\0000\m5\datasets\01-05-tl-491-008\analysis\adbp.xpt
TAK 491_019 Phase III	adam.xpt adbp.xpt	\\Cdsesub1\evsprod\NDA200796\\0000\m5\datasets\01-06-tl-491-019\analysis\adam.xpt \\Cdsesub1\evsprod\NDA200796\\0000\m5\datasets\01-06-tl-491-019\analysis\adbp.xpt

Software

S-plus 8.1, and SAS 9.2 were used for this analysis.

Methods

Dose-Response Analysis

The relationship between dose and change from baseline in SBP or DBP at trough (clinic and ABPM 22-24 h) was evaluated using naïve pooled analysis[1]. The data were best described by an inhibitory E_{max} model [2]. A sample code is provided in the Appendix.

Cumulative distribution

Cumulative distributions for all doses tested in Phase III monotherapy studies were constructed using PROC FREQ.

[1] Model fit to all individual data observations simultaneously.

[2] E = (E0-((Emax*Dose)/(ED50+Dose)))

Results

Dose-Response Analysis

TAK 491_005

As seen in **Figure 1**, there does not appear to be a dose dependent effect on change from baseline DBP or SBP, in the dose range tested (5 mg – 80 mg).

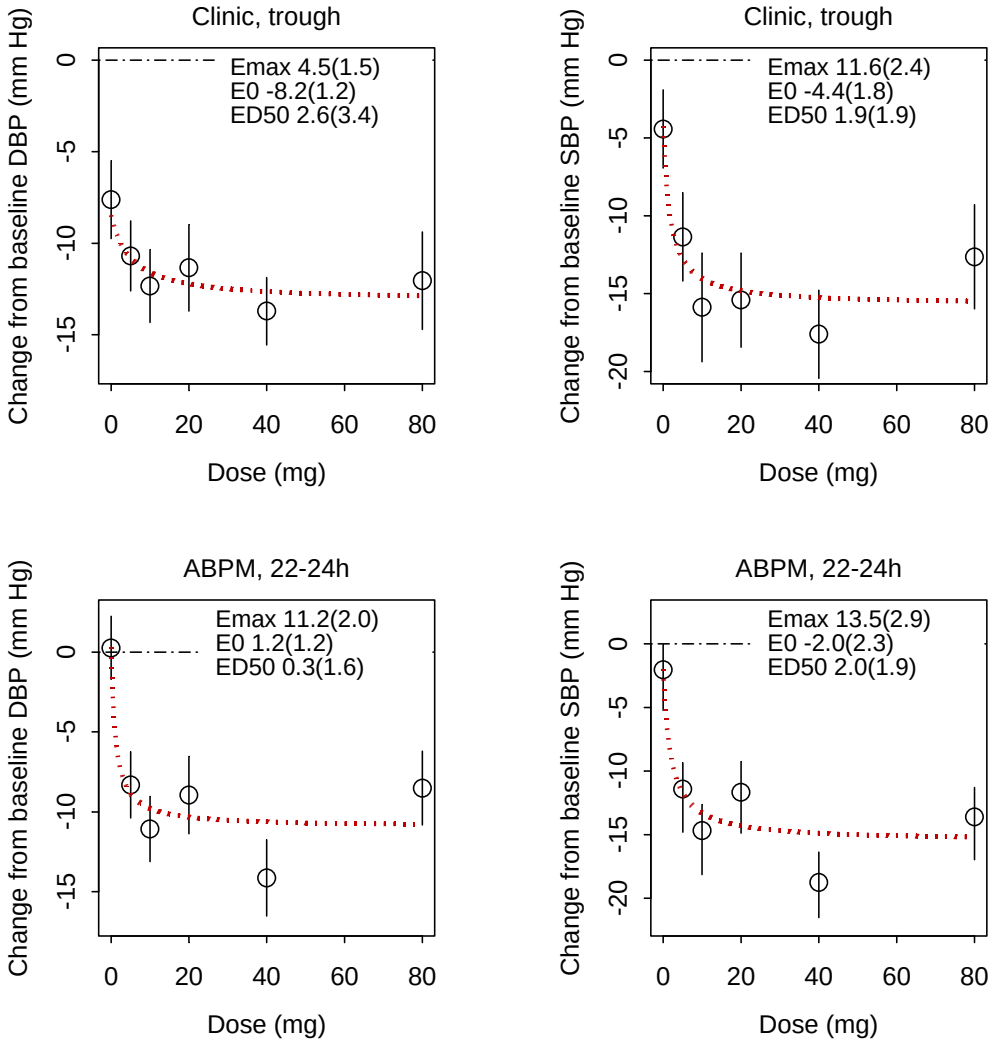


Figure 1 Change from baseline blood pressure at the end of week 8, as measured by clinic measurements at trough (*top panel*) and by ABPM at trough (*bottom panel*) for TAK 491_005. Symbols represent mean BP (2*SE), and the broken line represents the model fit. Model parameters are presented as mean (SE).

As seen from **Figures 1**, there is -1 to -2 mm Hg increase in effect on change in DBP when the dose is increased from 5 to 80 mg (16-fold). Similarly, there is a -3 to -3.5 mm Hg in effect on SBP with a 16-fold change in dose. It should be noted that for the capsule formulation, the BA is

60% relative to AZM tablet. Hence the dose range in terms of AZM tablet can be assumed as being ~3 – 50 mg.

TAK 536_002

In study TAK 536_002, a shallow dose-response relationship was observed when trough "cuff" measure data were evaluated. For a 16-fold change in dose, there appears to be a ~ -5 mm Hg increase in effect in DBP and ~ -7.5 mm Hg increase in effect in SBP (**Figure 2, *top panel***). However, this relationship was not apparent when ABPM trough data were evaluated (**Figure 2, *bottom panel***. An increase in dose from 2.5 mg to 40 mg resulted in only a -2.5 and -2 mm Hg increase in effect on DBP and SBP, respectively, consistent with the results of study TAK 491_005.

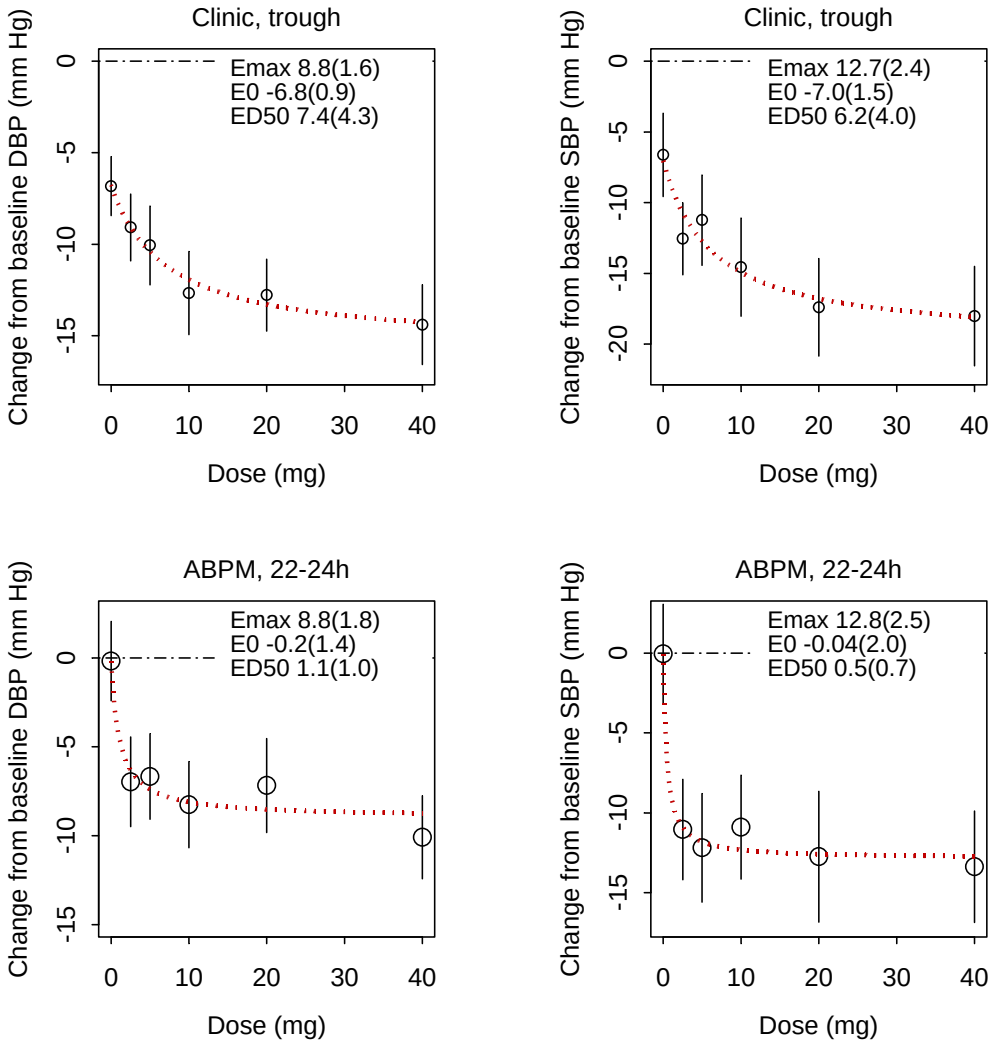


Figure 2 Change from baseline blood pressure at the end of week 8, as measured by clinic measurements at trough (*top panel*) and by ABPM at trough (*bottom panel*) for

TAK 536_002. Symbols represent mean BP (2*SE), and the broken line represents the model fit. Model parameters are presented as mean (SE).

It should be noted that for the AZ tablet formulation, the bioavailability is 162% relative to AZM tablet. Hence the dose range in terms of AZM tablet can be assumed as being 4 – 65 mg.

Azilsartan plasma concentrations data were not collected in either of the Phase II dose ranging studies; therefore, a concentration-response analysis is not feasible. However, a cross-study comparison of the plasma time course of azilsartan at steady state following administration of AZM tablets and ABPM (**Figure 3**) shows that a 5-fold difference in peak and trough plasma AZ concentrations does not translate into blood pressure effects at either peak or trough. This indicates that AZ has a shallow concentration-response relationship over the range of doses studied.

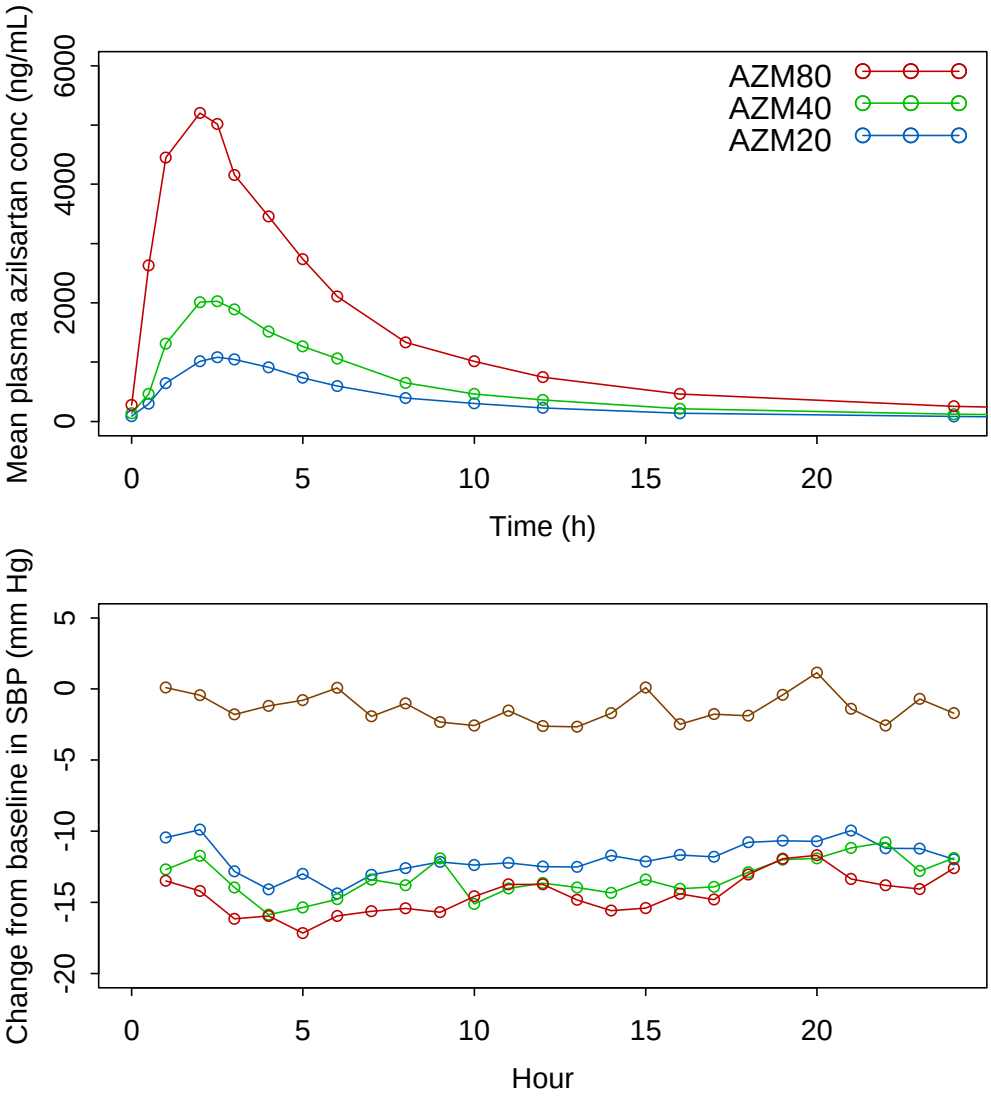


Figure 3 A comparison of pharmacokinetic time course of azilsartan at steady state (TAK 491_101) and blood pressure reduction effect (TAK 491_008)

Comparison of cumulative distributions of blood pressure response

Only AZM 40 and 80 mg were evaluated in most of the Phase III studies, making a formal Dose-Response analysis of data collected in Phase III not feasible.

A representative plot of the cumulative distribution of blood pressure reduction is presented in **Figure 4**. Cumulative distributions for all other AZM Phase III monotherapy studies are provided in Appendix 2.

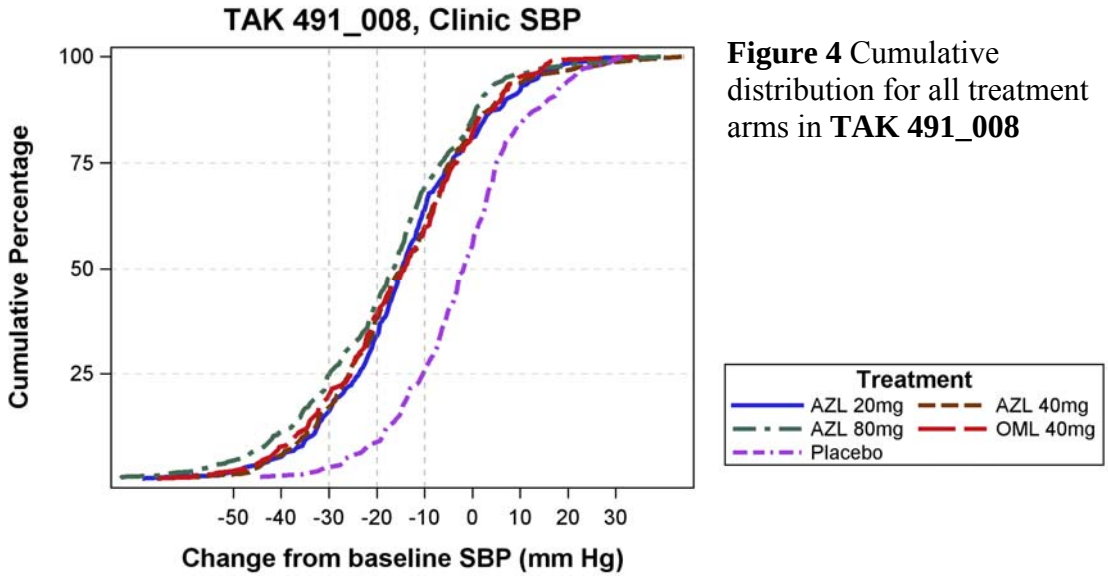


Figure 4 Cumulative distribution for all treatment arms in **TAK 491_008**

As seen in **Figure 4**, (1) the shape of the distributions is similar across AZM 20, 40, and 80 mg and (2) the range of responses are similar across AZM 20, 40 and 80 mg. Hence, there appears to be no clear benefit in terms of blood pressure reduction for the higher doses.

Conclusions

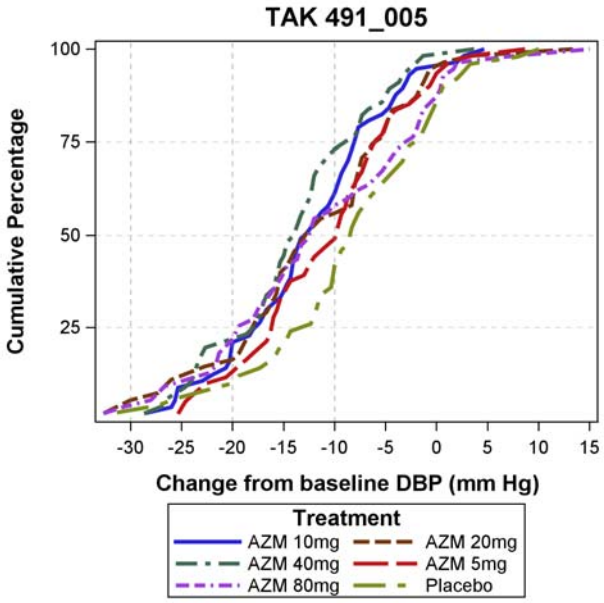
- A shallow Dose-Response relationship for AZ, with the maximal effect being attained ~10 mg for AZM Capsule and ~ 5 mg for AZ tablet, was seen across the two Phase II dose ranging studies.
- The shallow Dose-Response relationship is consistently demonstrated for trough ABPM measurements across the two studies.
- Blood pressure reduction effect corresponding to peak plasma AZ concentrations (1 to 3h) is similar to that seen at trough plasma concentrations (24h), indicating an E-R relationship similar to the D-R relationship at steady-state.
- The shape and the range of the cumulative distributions for blood pressure reduction are similar across all three strengths of AZM tablet, indicating a lack of benefit with the higher doses.

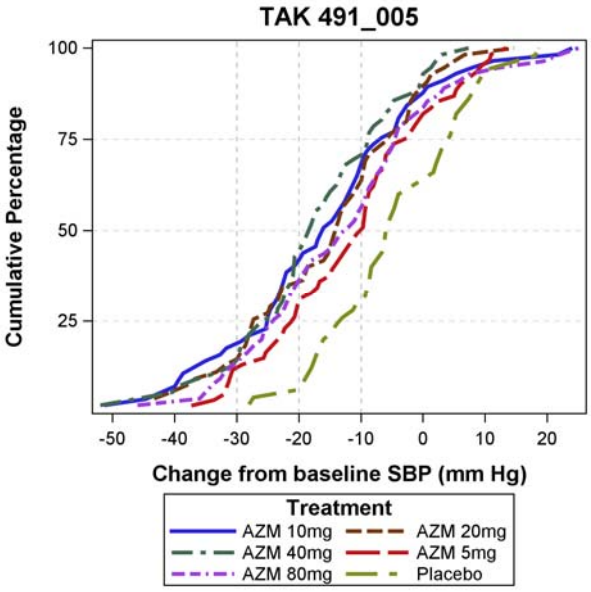
Appendix 1

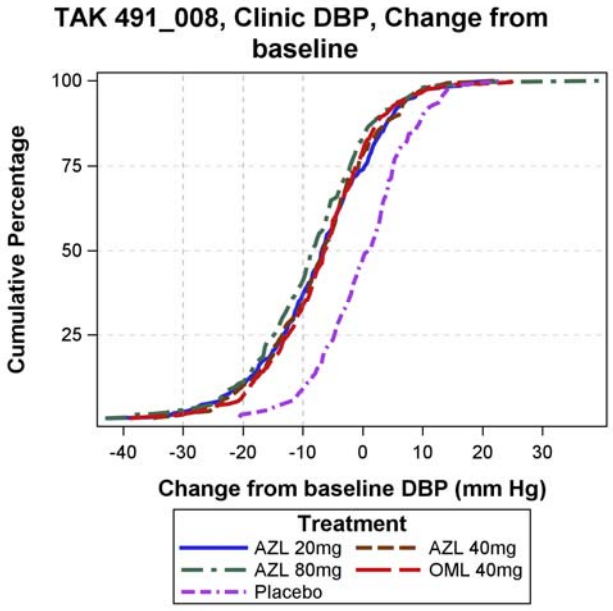
Sample code for Dose-Response analysis

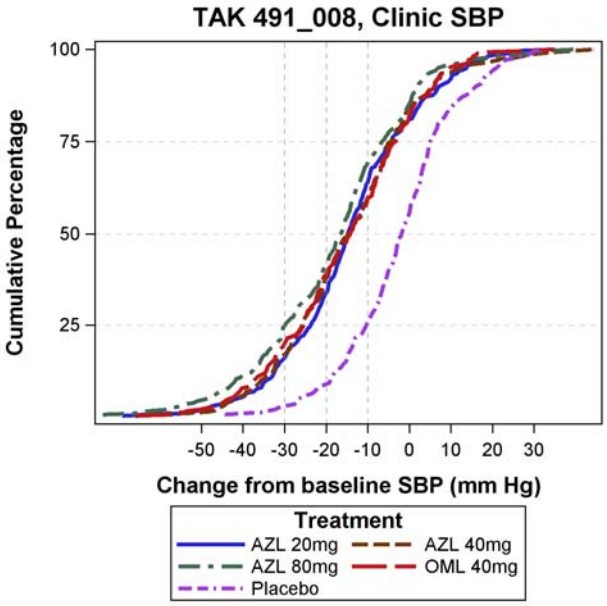
```
nfit.DATA1 <- nls(CHG~(E0-Emax*DOSE/(ED50+DOSE)), data= DATA1,
    start=list(ED50=3,E0=5,Emax=15))
summary(nfit.DATA1)
```

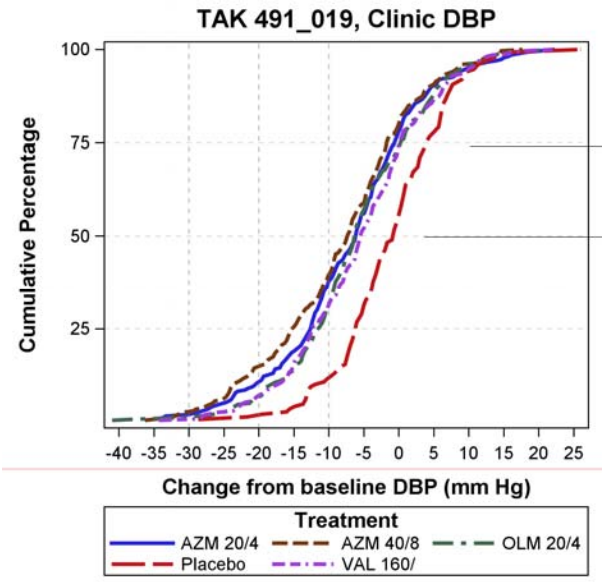
Appendix 2

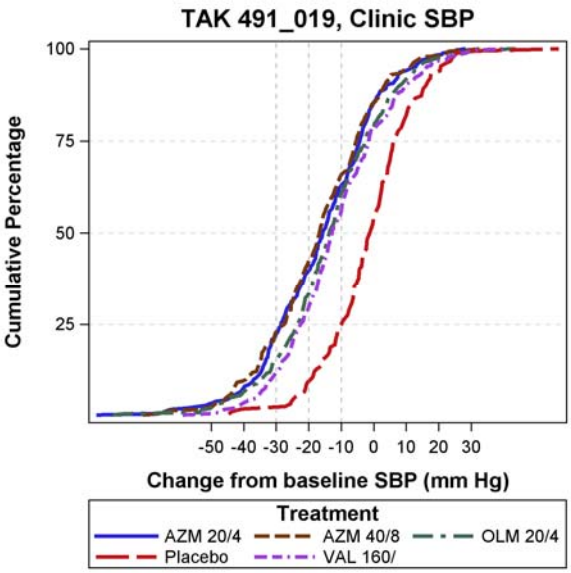

TAK 491_005
Cumulative Percentage
100
75
50
25
-30 -25 -20 -15 -10 -5 0 5 10 15
Change from baseline DBP (mm Hg)
Treatment
AZM 10mg
AZM 20mg
AZM 40mg
AZM 5mg
AZM 80mg
Placebo

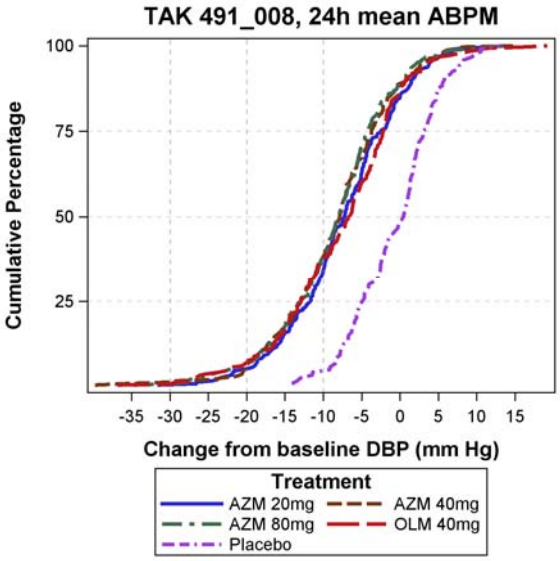

TAK 491_005
Cumulative Percentage
100
75
50
25
-50 -40 -30 -20 -10 0 10 20
Change from baseline SBP (mm Hg)
Treatment
AZM 10mg
AZM 20mg
AZM 40mg
AZM 5mg
AZM 80mg
Placebo

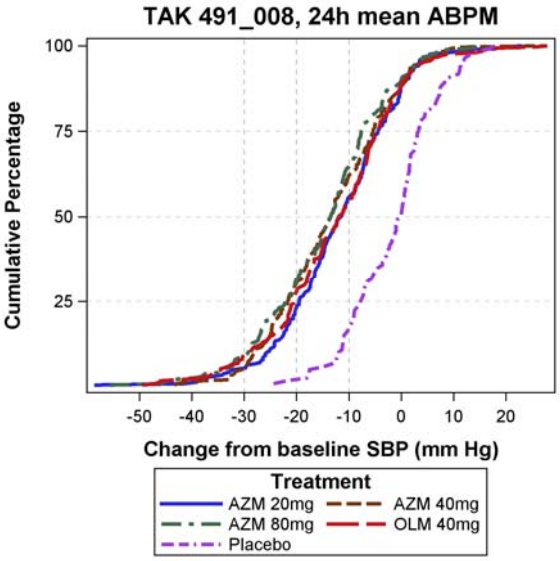

TAK 491_008, Clinic DBP, Change from baseline
Cumulative Percentage
100
75
50
25
-40 -30 -20 -10 0 10 20 30
Change from baseline DBP (mm Hg)
Treatment
AZL 20mg
AZL 40mg
AZL 80mg
OML 40mg
Placebo

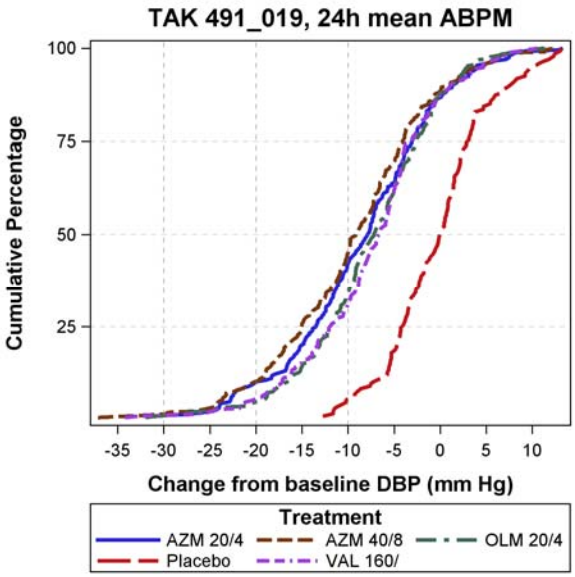

TAK 491_008, Clinic SBP
Cumulative Percentage
100
75
50
25
-50 -40 -30 -20 -10 0 10 20 30
Change from baseline SBP (mm Hg)
Treatment
AZL 20mg
AZL 40mg
AZL 80mg
OML 40mg
Placebo

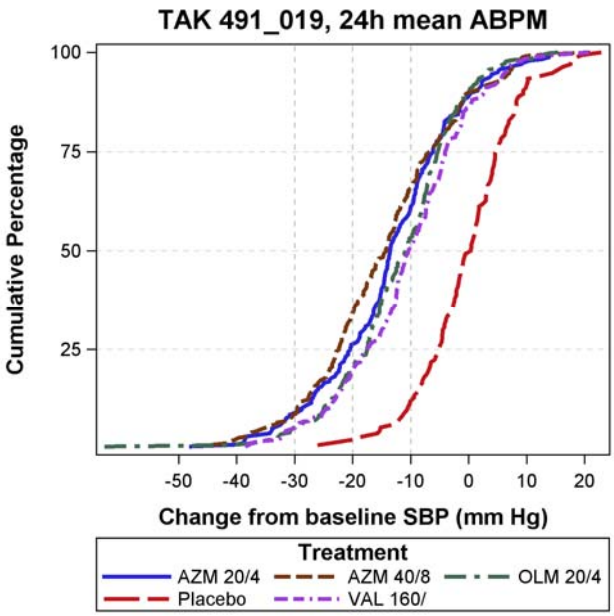

TAK 491_019, Clinic DBP
Cumulative Percentage
100
75
50
25
-40 -35 -30 -25 -20 -15 -10 -5 0 5 10 15 20 25
Change from baseline DBP (mm Hg)
Treatment
AZM 20/4
AZM 40/8
OLM 20/4
Placebo
VAL 160/


TAK 491_019, Clinic SBP
Cumulative Percentage
100
75
50
25
-50 -40 -30 -20 -10 0 10 20 30
Change from baseline SBP (mm Hg)
Treatment
AZM 20/4
AZM 40/8
OLM 20/4
Placebo
VAL 160/


TAK 491_008, 24h mean ABPM
Cumulative Percentage
100
75
50
25
-35 -30 -25 -20 -15 -10 -5 0 5 10 15
Change from baseline DBP (mm Hg)
Treatment
AZM 20mg
AZM 40mg
AZM 80mg
OLM 40mg
Placebo

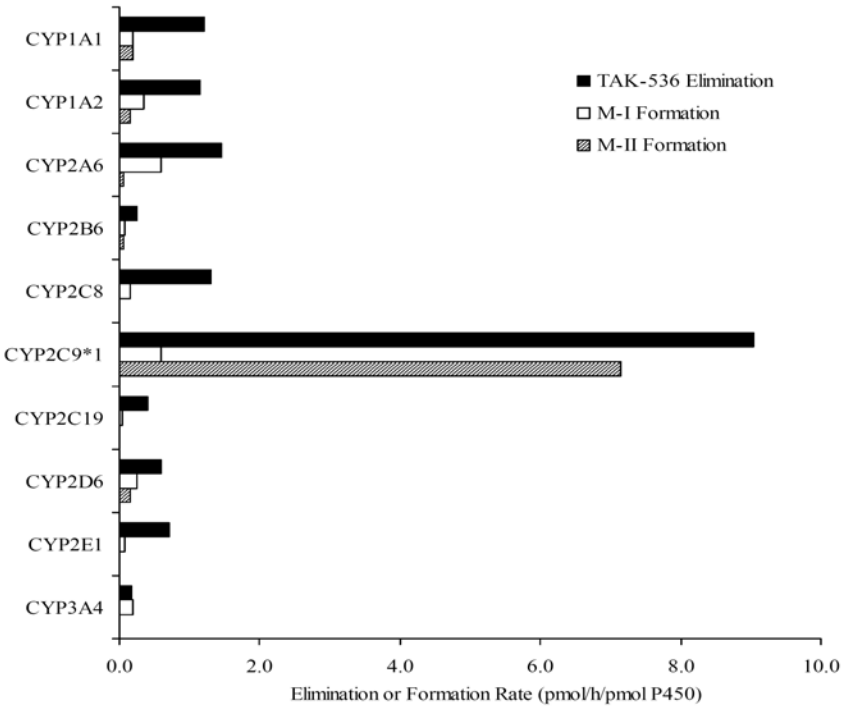

TAK 491_008, 24h mean ABPM
Cumulative Percentage
100
75
50
25
-50 -40 -30 -20 -10 0 10 20
Change from baseline SBP (mm Hg)
Treatment
AZM 20mg
AZM 40mg
AZM 80mg
OLM 40mg
Placebo





2 *IN VITRO* STUDIES

2.1 Study TAK 491-00049_CYP450 (CYP Identification)

Study Report # TAK 491-00049	**Study #** TAK491_00049[3]
Title: Identification of Cytochrome P450 Isoforms Involved in the Metabolism of TAK 536	
Objectives To identify CYP isoforms responsible for the metabolism of TAK 536.	
Study Design Reaction phenotyping experiments were conducted in human CYP expressing microsomes (CYP1A1, 1A2, 2A6, 2B6, 2C8, 2C9*1, 2C19, 2D6, 2E1, 3A4) and in a panel of human hepatic microsomes (probes for CYP 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4/5, 4A11) obtained from 16 individual donors, using a TAK 536 concentration of 4560 ng/mL (10 μM).	
Results  **Figure 1** Results of reaction phenotyping using human CYP expressing microsomes. TAK 536 is mostly metabolized by CYP2C9 to form its MII metabolite. • Correlation studies performed in a panel of hepatic microsomes from 16 individual donors also indicated that CYP2C9 was the major isoform involved in the metabolism of TAK 536.	
Conclusions 1. TAK 536 is primarily metabolized to its MII metabolite by CYP 2C9.	

[3] \\Cdsesub1\evsprod\NDA200796\\0000\m5\53-clin-stud-rep\532-rep-stud-pk-human-biomat\5322-rep-hep-metab-interact-stud\tak-491-00049\tak-491-00049.pdf

2.2 Study TAK 491-00050 (CYP Inhibition)

Study Report # TAK 491-00050	**Study #** TAK491_00050[4]

Title: Inhibitory effect of TAK 536 on CYP 450 isoform specific activity.

Objectives To evaluate the potential for TAK 536 to inhibit CYP 450.

Study Design

TAK 536 (3, 10, 30 or 100 μM) was incubated along with a marker substrate in human CYP expressing microsomes derived from B-lymphoblastoid cells (CYP1A1, 1A2, 2A6, 2B6, 2C8, 2C9*1, 2C19, 2D6, 2E1, 3A4). Formation of specific metabolites were monitored as given below.

CYP1A1, 1A2:	7-ethoxyresorufin *O*-deethylation
CYP2A6:	coumarin 7-hydroxylation
CYP2B6:	ethoxycoumarin *O*-deethylation
CYP2C8, 2C9*1, 2C9*2:	tolbutamide hydroxylation
CYP2C19:	(*S*)-mephenytoin 4'-hydroxylation
CYP2D6:	(±)-bufuralol 1'-hydroxylation
CYP2E1:	4-nitrophenol hydroxylation
CYP3A4:	testosterone 6*beta*-hydroxylation

Results

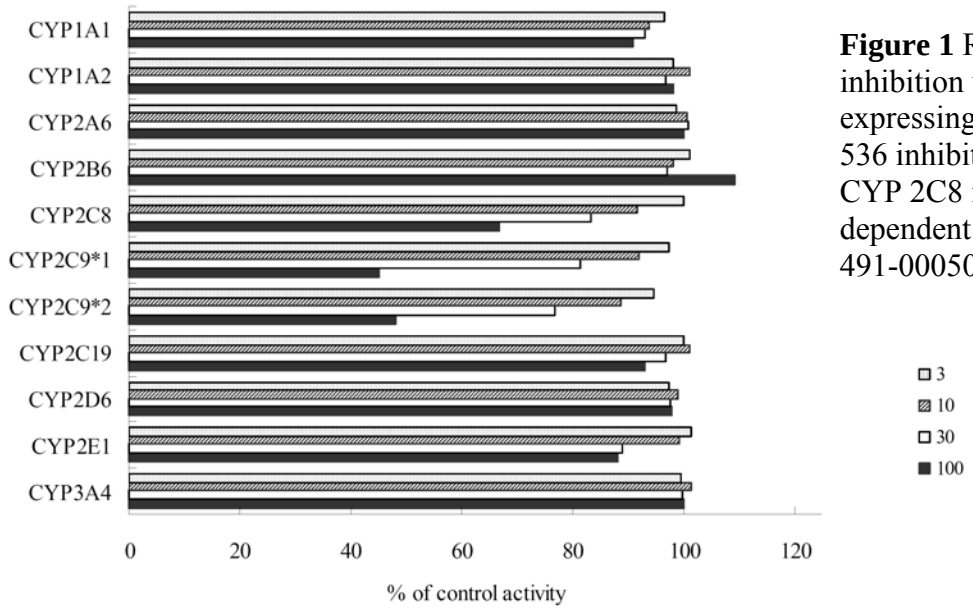


Figure 1 Results of CYP inhibition using human CYP expressing microsomes. TAK 536 inhibits CYP 2C9 and CYP 2C8 in a concentration dependent manner. (Ref: TAK 491-00050 study report, Fig 2)

Conclusions

TAK 536 may affect the metabolism of other concomitantly administered CYP 2C8 or CYP 2C9 substrates at plasma concentrations of~ 45 μg/mL (> 4X Cmax at AM 80 mg).

[4] \\Cdsesub1\evsprod\NDA200796\\0000\m5\53-clin-stud-rep\532-rep-stud-pk-human-biomat\5322-rep-hep-metab-interact-stud\tak-491-00050\tak-491-00050.pdf

2.3 Study TAK 491-00086 (CYP Induction)

Study Report # TAK 491-00086	**Study #** TAK491_00086[5]
Title: Evaluation of CYP 3A induction by TAK 536 in human hepatocytes.	
Objectives To evaluate the potential for TAK 536 to induce CYP 450 3A.	
Study Design Cultured human hepatocytes were incubated with testosterone (250 μM) for 2 h to establish baseline testosterone -6β- hydroxylation activity. The hepatocytes were then washed and incubated with TAK 536 (3, 10 or 30 μM) or rifampin (10 μM) for one day. At the end of the incubation period, hepatocytes were incubated with testosterone (250 μM) for 2 h.	
Results TAK 536 did not affect testosterone -6β- hydroxylation activity (same as the negative control), while rifampin increased it by over 300X.	
Conclusions TAK 536 does not induce CYP 3A.	

[5] \\Cdsesub1\evsprod\NDA200796\\0000\m5\53-clin-stud-rep\532-rep-stud-pk-human-biomat\5322-rep-hep-metab-interact-stud\tak-491-00086\tak-491-00086.pdf

2.4 Study TAK 491-10051 and TAK 491-10052 (CYP Inhibition)

Study Report #s TAK 491-10051, TAK 491-10052	**Study #** B090286, B090287[6]
Title: Inhibitory effect of TAK 491 and TAK 536 on CYP 450 isoform specific activity.	
Objectives To evaluate the potential for TAK 491 and TAK 536 to inhibit CYP 450.	
Study Design TAK 491 (or TAK 536 in study TAK 491-10052) (3, 10, 30 or 100 μM) was incubated along with a marker substrate in human liver microsomes. All substrate concentrations were below the recommended range of Km values[7]. Formation of specific metabolites were monitored as given below. CYP1A2: Phenacetin *O*-deethylation CYP2B6: Bupropion hydroxylation CYP2C8: Paclitaxel 6α-hydroxylation CYP2C9: Diclofenac 4'-hydroxylation CYP2C19: (*S*)-Mephenytoin 4'-hydroxylation CYP2D6: Bufuralol 1'-hydroxylation CYP2E1: Chlorzoxazone 6-hydroxylation CYP3A4: Midazolam 1'-hydroxylation CYP3A4: Testosterone 6β-hydroxylation	

[6] \\Cdsesub1\evsprod\NDA200796\\0000\m5\53-clin-stud-rep\532-rep-stud-pk-human-biomat\5322-rep-hep-metab-interact-stud\tak-491-10051\tak-491-10051.pdf

\\Cdsesub1\evsprod\NDA200796\\0000\m5\53-clin-stud-rep\532-rep-stud-pk-human-biomat\5322-rep-hep-metab-interact-stud\tak-491-10052\tak-491-10052.pdf

[7] *Guidance for Industry Drug interaction studies- study design, data analysis, and implications for labeling*

Results

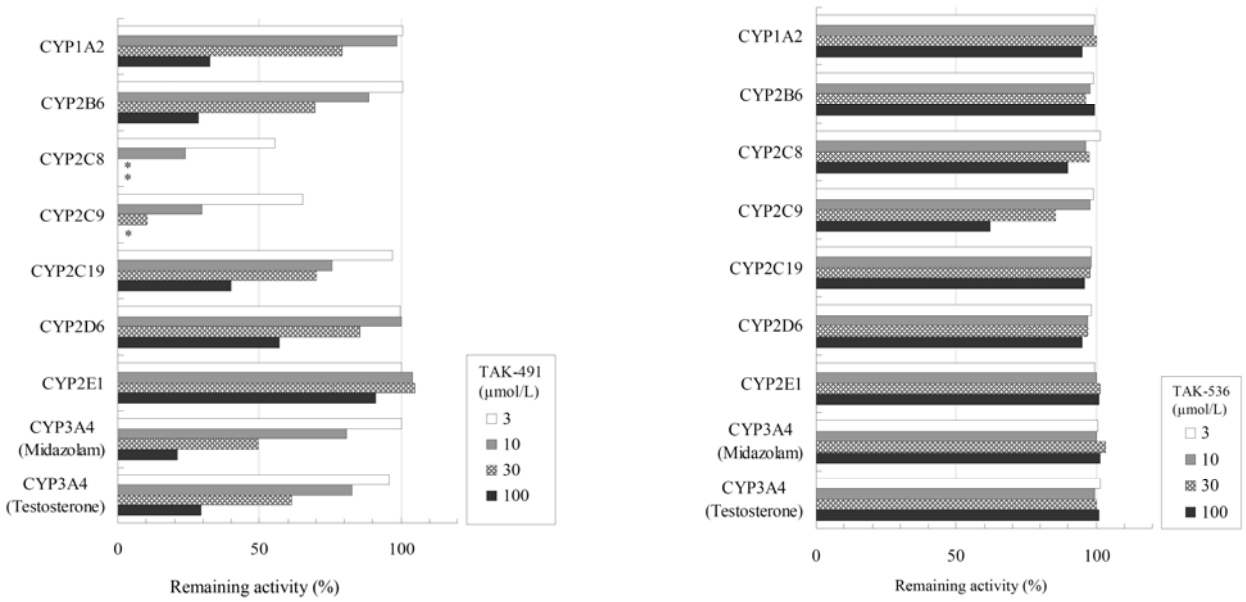


Figure 1 CYP inhibition by TAK 491 and TAK 536 (Ref: TAK 491-10051 and TAK 491-10052 study reports, Fig 1)

Conclusions

- TAK 491 may affect the metabolism of other concomitantly administered CYP 2C8 or CYP 2C9 substrates at plasma concentrations > 10 μg/mL.
- TAK 536 may not affect the metabolism of other concomitantly administered CYP substrates up to plasma concentrations ~ 100 μg/mL

2.5 Study TAK 491-10053 and TAK 491-10054 (CYP Induction)

Study Report #s TAK 491-10053, TAK 491-10054	**Study #** B113-491-039, B114-536-069[8]
Title: Evaluation of CYP 3A induction by TAK 491 and TAK 536 in human hepatocytes.	
Objectives To evaluate the potential for TAK 536 to induce CYP 450 3A.	
Study Design Cultured human hepatocytes were incubated with testosterone (250 μM) for 2 h to establish baseline testosterone -6β- hydroxylation activity. The hepatocytes were then washed and incubated with TAK 491 (or TAK 536 in study TAK 491-10054) (3, 10, 30 or 100 μM) or rifampin (10 μM) for one day. At the end of the incubation period, hepatocytes were incubated with testosterone (250 μM) for 2 h.	
Results TAK 491 and TAK 536 did not affect testosterone -6β- hydroxylation activity.	
Conclusions TAK 491 and TAK 536 do not induce CYP 3A.	

[8] \\Cdsesub1\evsprod\NDA200796\\0000\m5\53-clin-stud-rep\532-rep-stud-pk-human-biomat\5322-rep-hep-metab-interact-stud\tak-491-10053\tak-491-10053.pdf

\\Cdsesub1\evsprod\NDA200796\\0000\m5\53-clin-stud-rep\532-rep-stud-pk-human-biomat\5322-rep-hep-metab-interact-stud\tak-491-10054\tak-491-10054.pdf

2.6 Study TAK 491-00214 and TAK 536-c-46-0045 (Permeability)

Study Report # TAK 491-00214 and TAK 536-c-46-0045	**Study #** GE-0355 and GE-0356[9]
Title: Permeability Study of TAK 491 / TAK 536 Across Caco-2 cells	
Objectives To assess the transport of TAK 491 and TAK 536 across Caco-2 cell monolayer.	

Study Design

In both studies bi-directional transport of [^{14}C] TAK 491 (10 µmol/L; 0.6 µCi/mL) / [^{14}C] TAK 536 (10 µmol/L; 0.4 µCi/mL) was assessed across Caco-2 cell monolayers cultured and seeded according to standard procedure. Samples (50/200 µL) were collected at 1 and 2h post addition of the test solution, was added to 10 mL of scintillation fluid and radioactivity was measured using a liquid scintillation counter. [^{14}C] mannitol (10 µmol/L) and [^{14}C] antipyrine (10 µmol/L) were used as controls for paracellular and transcellular transport, respectively. Bi-directional transport of [^{3}H] digoxin (3 µmol/L) was also assessed in this experiment. Permeability coefficient (Papp) and Papp ratio for all compounds were calculated and presented.

Test substance

	TAK 491	TAK 536	Mannitol	Antipyrine	Digoxin
Specific radioactivity	3.89 MBq/mg	15.8 MBq/mL			
Batch #.	PU002811	PU002651	3441114	3406-248	3559975

[9] \\Cdsesub1\evsprod\NDA200796\\0000\m5\53-clin-stud-rep\532-rep-stud-pk-human-biomat\5323-stud-other-human-biomat\tak-491-00214\tak-491-00214.pdf

\\Cdsesub1\evsprod\NDA200796\\0000\m5\53-clin-stud-rep\532-rep-stud-pk-human-biomat\5323-stud-other-human-biomat\tak-536-c-46-00445\tak-536-c-46-00445.pdf

Results

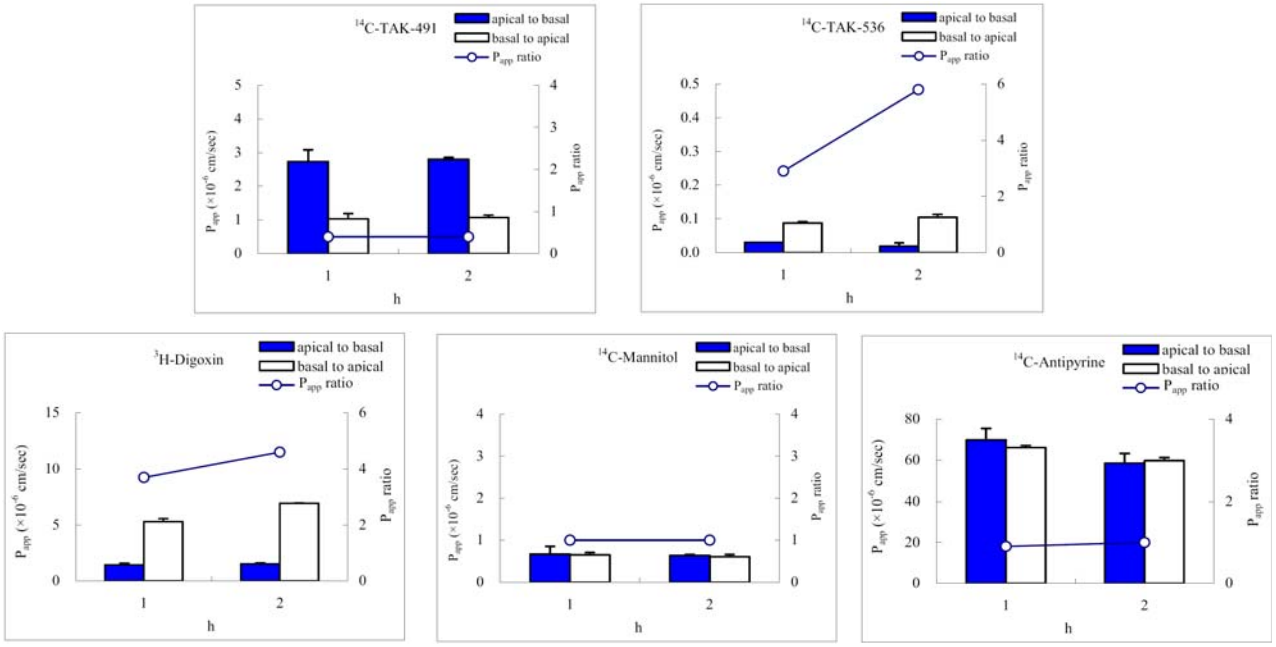


Figure 1 Mean (SD) permeability coefficient (bars) and ratios (open circles) for [^{14}C] TAK 491, [^{14}C] TAK 536, [^{3}H] digoxin, [^{14}C] mannitol, and [^{14}C] antipyrine,across Caco-2 monolayers (Ref: Figure 1, report # TAK 491-00214 and TAK 536-c-46-0045).

- Approximately 100% of radioactivity was recovered from the donor side at the end of 2h, in study TAK 536-c-46-0045 and [^{14}C] TAK 536 accounted for ~97%.
- Only ~ 80 to 85% of radioactivity was recovered from the donor side at the end of 2 h, in study TAK 491-00214; of which ~ 7% was [^{14}C]TAK 491 and 86% was [^{14}C]TAK 536, indicating of TAK 491 was transformed to TAK 536.

Conclusions

- TAK 491, the prodrug form of TAK 536, shows low permeability across Caco-2 cell monolayers. However, the observed permeability for the prodrug is higher than that for TAK 536.
- TAK 491 does not appear to be a P-gp substrate.

2.7 Study TAK 491-00215 and TAK 536-c-46-00446 (P-gp Inhibition)

Study Report # TAK 491-00215 and TAK 536-c-46-00446	**Study #** GE-0355 and GE-0384[10]
Title: Inhibitory Effect of TAK 491 / TAK 536 on ^{3}H - Digoxin Transport Across Caco-2 cells	
Objectives To assess the inhibitory effect of TAK 491 and TAK 536 on the transport of [^{3}H] digoxin across Caco-2 cell monolayer.	

Study Design

In both studies bi-directional transport of [^{3}H] digoxin (3 µmol/L) was assessed across Caco-2 cell monolayers cultured and seeded according to standard procedure in the presence of TAK 491 (0, 20, 100 or 250 µmol/L) or TAK 536 (0, 20, 100 or 500 µmol/L). Samples (50/200 µL) were collected at 1 and 2h post addition of the test solution, was added to 10 mL of scintillation fluid and radioactivity was measured using a liquid scintillation counter. [^{14}C] mannitol (10 µmol/L) and quinidine, a known P-gp inhibitor, were used as controls. Permeability coefficient (Papp) and Papp ratio for all compounds were calculated and presented.

Test substance

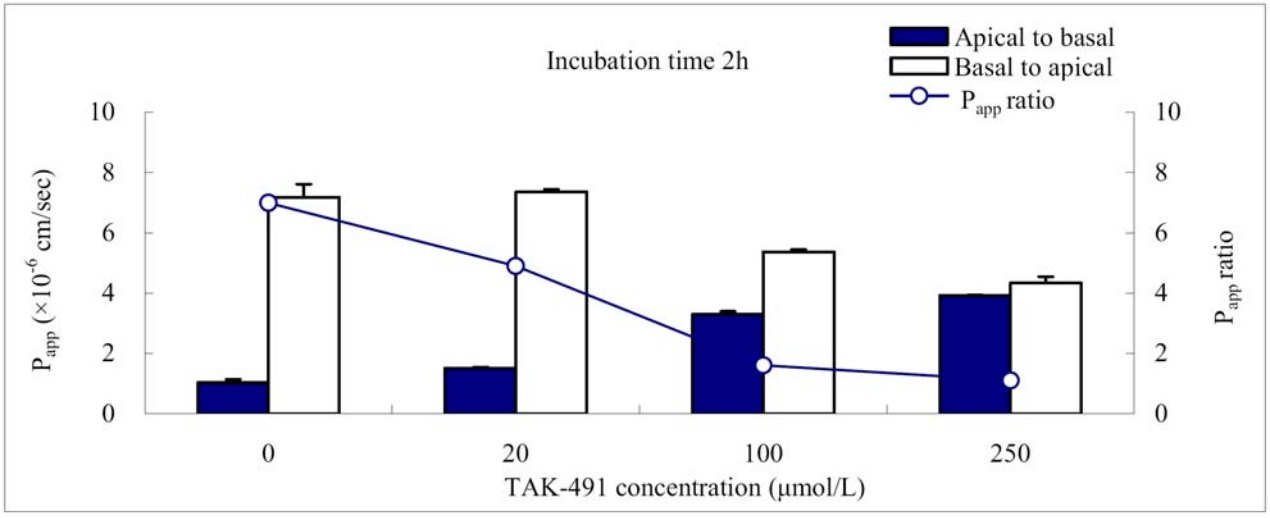
	Batch number
TAK 491	B18340-027-26
TAK 536	PU002651
Mannitol	3441114
Antipyrine	3406-248
Digoxin	3559975
Quinidine	074K2511

[10] \\Cdsesub1\evsprod\NDA200796\\0000\m5\53-clin-stud-rep\532-rep-stud-pk-human-biomat\5323-stud-other-human-biomat\tak-491-00215\tak-491-00215.pdf

\\Cdsesub1\evsprod\NDA200796\\0000\m5\53-clin-stud-rep\532-rep-stud-pk-human-biomat\5323-stud-other-human-biomat\tak-536-c-46-00446\tak-536-c-46-00446.pdf

Results

TAK 491



TAK 536

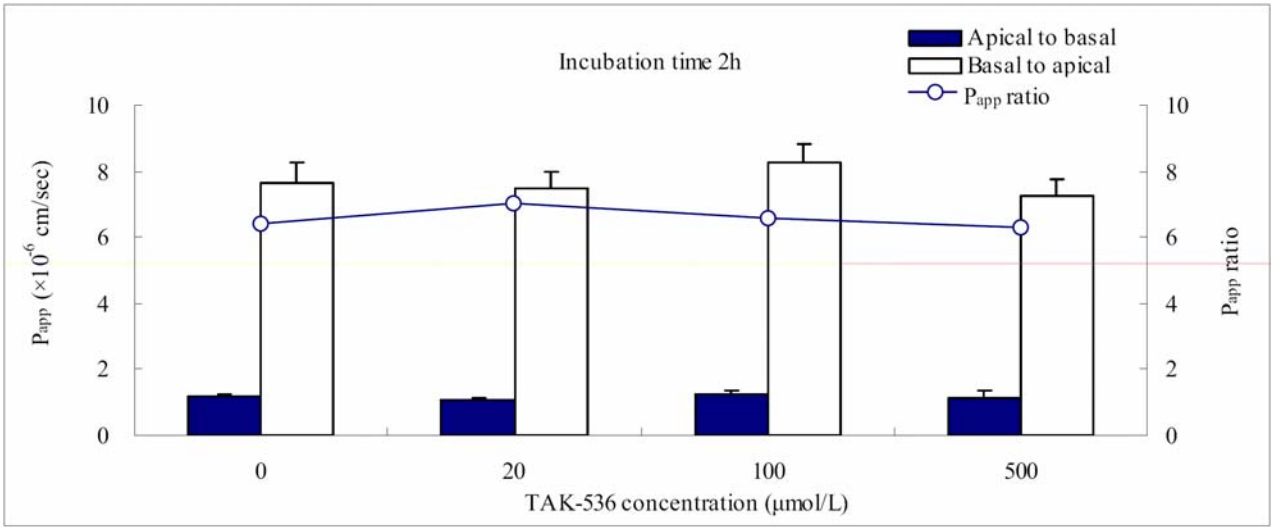


Figure 1 Mean (SD) permeability coefficient (bars) and ratios (open circles) for [^{3}H] digoxin in the presence of TAK 91 or TAK 536 (Ref: Figure 1, report # TAK 491-00215 and TAK 536-c-46-00446).

Conclusions

- TAK 491, the prodrug form of TAK 536, appears to be an inhibitor of the efflux transporter P-gp.
- TAK 536 does not appear to inhibit P-gp.

3 BIOAVAILABILITY

3.1 Study 01-06-TL-536-016 (Absolute and relative bioavailability)

Study Report # CSR 01-06-TL-536-016	**Protocol #** 01-06-TL-536-016 [11]

Title: An Open-Label, Randomized, Single-Dose, 3-Period Crossover Study to Evaluate the Absolute Bioavailability of TAK-536 and Relative Bioavailability of TAK-491 in Healthy Adult Subjects

Objectives Bioequivalence ☐ Bioavailability ☒ Food effect ☐

Study Design Parallel ☐ Crossover ☒

Each study period was separated by washout period of 7 days.

Study medication

	Test A – TAK 491	Test B – TAK 536	Reference – TAK 536
Dosage Form	Capsule	Tablet	IV infusion
Dosage Strength	4 x 20 mg (80 mg)	4 x 10 mg (40 mg)	10 mg/ 10 min
Batch #.	Z624D11		
Administration	Oral	Oral	IV

PK Sampling

Capsule/tablet: Blood samples were collected at pre-dose, 0.017, 0.033, 0.083, 0.117, 0.167, 0.333, 0.5, 0.53, 0.58, 0.66, 0.83, 1.0, 1.5, 2.5, 4, 5, 6, 8, 10, 12, 16, 24, 36, and 48 hours post dose.

IV infusion: Blood samples were collected form the arm contra-lateral to the infusion site at pre-dose and at 0.017, 0.033, 0.083, 0.117, 0.167 (immediately prior to end of infusion), 0.333, 0.5, 0.53, 0.58, 0.66, 0.83, 1.0, 1.5, 2.5, 4, 5, 6, 8, 10, 12, 16, 24, 36, and 48 hours after start of infusion.

Urine samples were collected at pre-dose and from 1 to 24 hours post dose.

Reviewer's comment: The sampling scheme is adequate for characterizing peak plasma levels and terminal elimination half-life of azilsartan and its inactive metabolite.

Statistical Method

ANOVA on log transformed parameters with fixed effects for sequence, period, and treatment, and random effect for subject within sequence. LS mean and 90% CI for the difference were constructed.

[11] \\Cdsesub1\evsprod\NDA200796\\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5311-ba-stud-rep\01-06-tl-536-016\csr-01-06-tl-536-016.pdf

Study population

Randomized/Completed/ Discontinued Due to AE	24/22/0*
Age [Median (range)] in years	31.4 [30.0 (20,53)]
Male/Female	11/13
Race (Caucasian/Black/Asian/other)	21/3/0/0
* Of the two subjects that discontinued, one discontinued because of a major protocol deviation, and the other because of Social Security fraud.	

Results

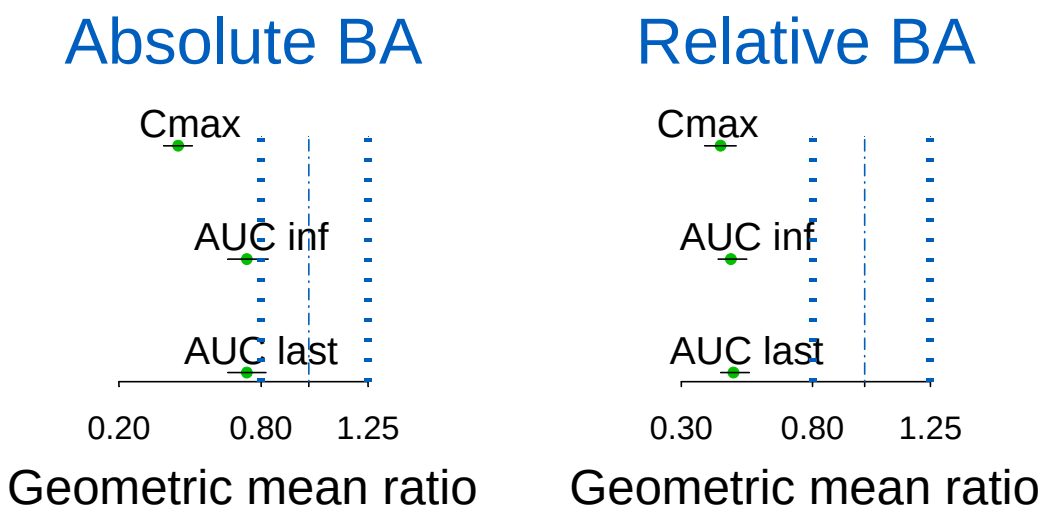


Figure 1 Results of the statistical analysis for dose-normalized azilsartan (TAK-536). The geometric mean ratios are depicted on the x-axis. The broken vertical lines represent the pre-determined BE limits. The closed circles represent the geometric mean of the BA/BE metrics and the horizontal line represents the 90%CI associated with the mean.

Site Inspection Performed: Yes ☐ No ☒

Assay Method

The performance of the assay method during study sample analysis is acceptable and is summarized in the table below (ref: 01-06-TL-536-016 Bioanalytical Report, 2006-12-21).

Plasma

Analyte	TAK 536	TAK 536 MI	TAK 536 MII
Method	HPLC/MS/MS		
LOQ (ng/mL)	1		
Range (ng/mL)	1 to 2500		
QCs (ng/mL)	3, 20, 150, 750, 2000		
Accuracy	95.0 to 108.0 %	95.7 to 101.5 %	89.7 to 106.0 %
Precision	4.8 to 10.9 %	3.4 to 11.9 %	5.0 to 10.2 %

Urine

Analyte	TAK 536	TAK 536 MI	TAK 536 MII
Method	HPLC/MS/MS		
LOQ (ng/mL)	20		
Range (ng/mL)	20 to 10000		
QCs (ng/mL)	60, 600, 8000		
Accuracy	98.1 to 100.8 %	99.1 to 101.0 %	94.8 to 104.8 %
Precision	4.1 to 6.7 %	4.5 to 9.2 %	5.6 to 7.2 %

Safety Death/SAE: **None**

Results and Conclusions

- Absolute mean bioavailability of TAK 536 following oral administration as a tablet is 75%.
- Mean bioavailability of TAK 536 following oral administration as TAK 491 capsules, relative to TAK 536 tablets, is 50%.
- Free TAK 491 was not detected following administration of TAK 491 capsules.
- The fraction of TAK 536 eliminated in urine following administration of TAK 491 capsules is approximately half that of TAK 536 tablet and one third that of TAK 536 IV infusion.

Detailed Results – Plasma pharmacokinetics

TAK 536 - Dose normalized PK measures are presented below.

	Geometric mean (%CV)					
	N	**TAK 491 Capsule**	**N**	**TAK 536 Tablet**	**N**	**TAL 536 IV infusion**
C_{max} (ng/mL)	22	52.9 (38.2)	22	116.7 (23.0)	22	260.0 (22.7)
t_{max} (h)[#]	22	2.5 (1.5,12.0)	22	2.5 (1.0,4.0)	22	0.3 (0.2,0.6)
$AUC_{0\text{-last}}$ (ng/mL*h)	22	382.5 (38.9)	22	750.5 (20.8)	22	1011.2 (17.7)
$AUC_{0\text{-}\infty}$ (ng/mL*h)	22	392.9 (39.3)	21	763.7 (21.5)	22	1036.2 (18.2)
$t_{1/2}$ (h)[##]	22	10.8 (0.94)	21	11.1 (1.5)	22	11.5 (1.5)
		Arithmetic mean (%CV)				
CL (L/h)[###]	22	2.8 (45.2)	21	1.3 (23.1)	22	0.984 (21.6)
MRT (h)	22	10.9 (20.7)	21	10.0 (16.8)	22	8.6 (18.9)
Vz (L) [###]	22	43.0 (44.7)	21	21.2 (22.0)	22	16.2 (20.5)
F	22	0.4 (32.4)	21	0.75 (12.2)		-

TAK 536 MI

	Geometric mean (%CV)					
	N	**TAK 491 Capsule**	**N**	**TAK 536 Tablet**	**N**	**TAL 536 IV infusion**
C_{max} (ng/mL)	22	64.5 (133.2)	22	85.8 (149.8)	22	115.8 (105.4)
t_{max} (h) #	23	1.5 (0.7,12)	23	1.5 (0.5,4.0)	23	0.4 (0.08,0.8)
$AUC_{0\text{-last}}$ (ng/mL*h)	23	302.5 (62)	23	394.0 (89.0)	23	158.2 (53.3)
$AUC_{0\text{-}\infty}$ (ng/mL*h)	15	345.6 (58.9)	12	383.7 (53.6)	13	155.4 (46.7)
$t_{1/2}$ (h) ##	16	9.7 (2.8)	12	8.5 (3.1)	13	6.1 (2.7)

TAK 536 MII

	Geometric mean (%CV)					
	N	**TAK 491 Capsule**	**N**	**TAK 536 Tablet**	**N**	**TAL 536 IV infusion**
C_{max} (ng/mL)	22	544.7 (42.8)	22	800.0 (27.1)	22	222.2 (25.4)
t_{max} (h) #	23	5.0 (4.0,12.0)	23	5.0 (2.5,10.0)	23	2.5 (2.5,6.0)
$AUC_{0\text{-last}}$ (ng/mL*h)	22	10758.6 (42.9)	22	14727.4 (27.4)	22	4090.1 (21.6)
$AUC_{0\text{-}\infty}$ (ng/mL*h)	22	12026.9 (43.7)	21	16376.8 (28.3)	22	4571.6 (22.0)
$t_{1/2}$ (h) ##	22	13.7 (2.0)	21	13.8 (2.3)	22	14.5 (2.4)

Median (range) ## Mean (SD) ### Parameter/F for capsule and tablet

Urine pharmacokinetics

TAK 536

	Arithmetic mean (%CV)					
	N	**TAK 491 Capsule**	**N**	**TAK 536 Tablet**	**N**	**TAL 536 IV infusion**
Ae (0-24), mg	22	4.5 (35.1)	22	6.2 (21.2)	22	2.3 (18.5)
Fe (%)	22	7.6	22	15.5	22	23.3

TAK 536 MI

	Arithmetic mean (%CV)					
	N	**TAK 491 Capsule**	**N**	**TAK 536 Tablet**	**N**	**TAL 536 IV infusion**
Ae (0-24), mg	22	0.05 (62.8)	22	0.013 (227.5)	22	0.003 (469.0)

TAK 536 MII

	Arithmetic mean (%CV)					
	N	**TAK 491 Capsule**	**N**	**TAK 536 Tablet**	**N**	**TAL 536 IV infusion**
Ae (0-24), mg	22	4.5 (40.4)	22	6.1 (22.0)	22	1.7 (23.0)

3.2 Study 01-06-TL-491-015 (Relative BA, Food effect)

Study Report # CSR 01-06-TL-491-015	**Protocol #** 01-06-TL-491-015 [12]

Title: An Open-Label, Randomized, 3-Period, Crossover Study to Evaluate the Relative Bioavailability of TAK-491 Capsule and Tablet Formulations and Food Effect of the Tablet Formulation in Healthy Adult Subjects

Objectives Bioequivalence ☐ Bioavailability ☒ Food effect ☒

Study Design Parallel ☐ Crossover ☒

Each study period was separated by washout period of 3 days. The effect of food on the bioavailability of azilsartan from the tablet formulation was also determined in this study. The composition and calorie content of the high fat meal used in the study is as per "*Guidance for Industry: Food-Effect Bioavailability and Fed Bioequivalence Studies*" and is therefore acceptable.

Study medication

	Test	**Reference**
Dosage Form	Tablet	Capsule
Dosage Strength	80 mg	4 x 20 mg
Batch #.	Z624D11	Z6247024
Administration	Oral	

PK Sampling Blood samples were collected at pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10 12, 24, 36, and 48 hours post-dose.

Reviewer's comment: The sampling scheme is adequate for characterizing peak plasma levels and terminal elimination half-life of azilsartan and its inactive metabolite

Statistical Method

ANOVA on log transformed parameters with fixed effects for sequence, period, and treatment, and random effect for subject within sequence. LS mean and 90% CI for the difference were constructed.

Study population

Randomized/Completed/ Discontinued Due to AE	24/23/1
Age [Median (range)] in years	31.4 [30.0 (20,53)]
Male/Female	17/7
Race (Caucasian/Black/Asian/other)	21/3/0/0

[12] \\Cdsesub1\evsprod\NDA200796\\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\01-06-tl-491-015\csr-01-06-tl-491-015.pdf

\\Cdsesub1\evsprod\NDA200796\\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\01-06-tl-491-015\01-06-tl-491-015-bioanalytical-report-2007-05-03.pdf

Results

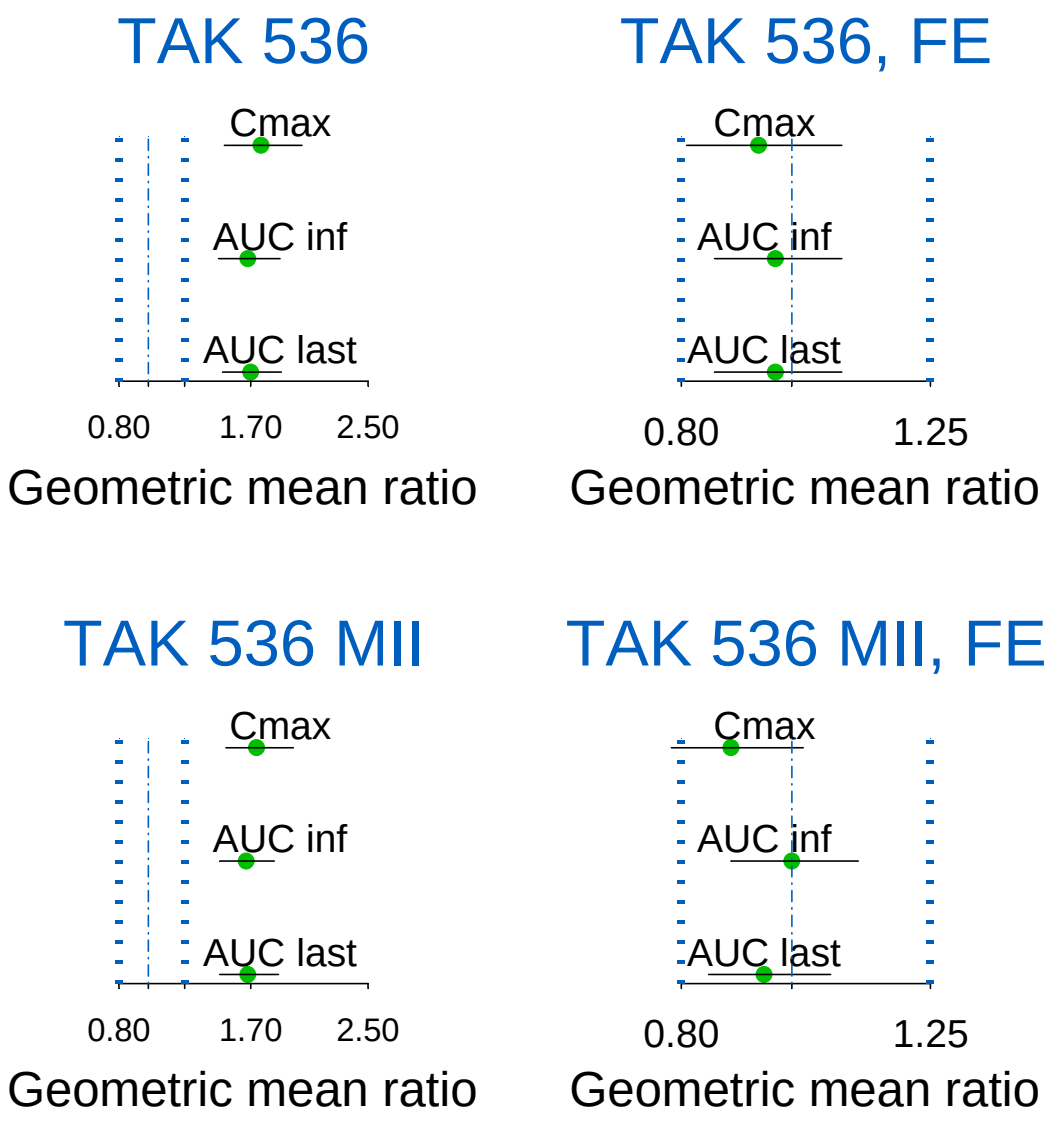


Figure 1 Results of the statistical analysis for azilsartan (TAK-536) and its active metabolite TAK-536 MII. The geometric mean ratios are depicted on the x-axis. The broken vertical lines represent the pre-determined BE limits. The closed circles represent the geometric mean of the BE metrics and the horizontal line represents the 90%CI associated with the mean.

Free TAK 491 and the MI metabolite were not detected in plasma.

Site Inspection Performed: Yes ☐ No ☒

Assay Method

The performance of the assay method during study sample analysis is acceptable and is

summarized in the table below (ref: 01-06-TL-491-015 Bioanalytical Report, 2007-05-03).

Analyte	TAK 536	TAK 536 MII
Method	HPLC/MS/MS – simultaneous detection of both analytes.	
LOQ (ng/mL)	0.5	0.025
Range (ng/mL)	0.5 to 200	0.025 to 10
QCs (ng/mL)	3, 20, 150, 750, 2000	3, 20, 150, 750, 2000
Accuracy/Bias	88.5 to 106%	90.5 to 108.5 %
Precision	5.9 to 19.1 % *	7.3 to 10.5 %

*QCs that failed to qualify were included in the calculation.

Safety Death/SAE: **None**

Conclusions

- Bioavailability of TAK 536 following administration of TAK 491 tablet is about 70% higher than that following administration of TAK 491 capsule.
- Food dose not affect the bioavailability of TAK 536 following administration of TAK 491 tablet.

Detailed Results

TAK 536

	Geometric mean (%CV)					
	N	**Capsule, fasted**	**N**	**Tablet, fasted**	**N**	**Tablet, fed**
C_{max} (ng/mL)	23	3362.314 (45.25)	23	5944.421 (22.74)	23	5632.456 (29.44)
t_{max} (h)*	23	2 (1.03,11.98)	23	1.98 (0.98,4.03)	23	3.0 (1.07,6.0)
$AUC_{0\text{-last}}$ (ng/mL*h)	23	23310.1 (37.07)	23	39438.1 (27.65)	23	38454.6 (24.92)
$AUC_{0\text{-}\infty}$ (ng/mL*h)	22	24022.1 (37.40)	23	40176.8 (28.09)	23	39216.0 (24.87)
$t_{1/2}$ (h)**	22	10.1 (1.8)	23	10.3 (1.6)	23	9.5 (1.4)

TAK 536 MII

	Geometric mean (%CV)					
	N	**Capsule, fasted**	**N**	**Tablet, fasted**	**N**	**Tablet, fed**
C_{max} (ng/mL)	23	655.517 (36.14)	23	1140.610 (28.66)	23	1026.528 (33.72)
t_{max} (h)*	23	6 (3.0,12)	23	6 (3.0,8.0)	23	6 (4.0,24.0)
$AUC_{0\text{-last}}$ (ng/mL*h)	23	13326.9 (33.33)	23	22312.5 (24.16)	23	21401.4 (27.03)
$AUC_{0\text{-}\infty}$ (ng/mL*h)	22	14574.1 (34.87)	23	24241.2 (24.31)	23	23949.2 (26.06)
$t_{1/2}$ (h)**	23	12.6 (1.9)	23	12.5 (1.6)	22	12.0 (2.1)

* Median (range) ** Mean (SD)

3.3 Study 01-05-TL-491-017 (MAD PK)

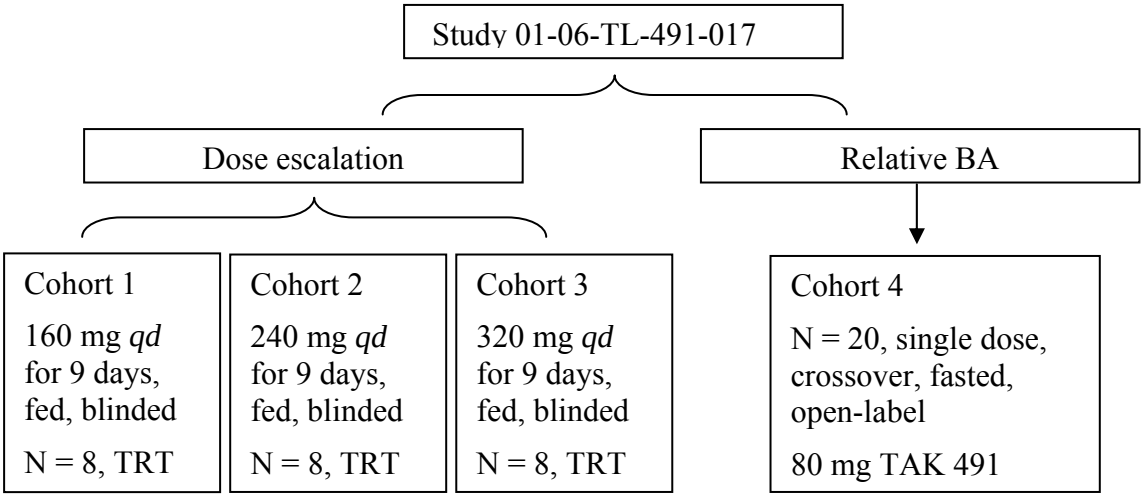
Study Report # CSR 01-05-TL-491-017	**Protocol #** 01-06-TL-491-017[13]

Title A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Sequential-Panel, Ascending Multiple-Dose Study of the Safety, Tolerability, and Pharmacokinetics of TAK-491 in Healthy Volunteers.

Objectives Bioequivalence ☐ Bioavailability☒ Food effect☐ Pharmacokinetics☒ Pharmacodynamics☒

Study Design

This study consisted of two parts. A dose escalation part (parallel design, each cohort received a different dose with n=8 TRT and n=2 PLC) and a relative BA part (crossover design). A schematic of the study design is presented in **Figure 1**. The study was initially designed to gather PK and tolerability information at doses > 80 mg, so as to aid in the design of the TQT study. Results from a previously conducted relative BA study showed that systemic exposure to TAK 536 following administration of TAK 491 tablets was 70% higher than that following administration of TAK 491 capsules. Hence, another cohort of 20 subjects was added to this study so as to compare systemic exposure to TAK 536 following administration of TAK 491 and TAK 536 tablets.



TRT – Treatment, PLC - Placebo

Figure 1 A schematic of the study design

The two study periods in the relative BA part of the study was separated by washout period of 7 days.

Study medication

	Placebo	TAK 491 tablets	TAK 536 tablets
Dosage Form	Tablet	Tablet	Tablet

[13] \\Cdsesub1\evsprod\NDA200796\\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5331-healthy-subj-pk-init-tol-stud-rep\01-06-tl-491-017\csr-01-06-tl-491-017.pdf

Dosage Strength	-	80 mg	40 mg
Batch #.	Z624C012	Z624D032	Z556H023
Administration	Oral	Oral	Oral

PK Sampling

Cohorts 1 – 3: Blood samples were collected at pre-dose, and at 0.25, 0.5, 1.0, 1.5, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48, and 72 hours post dose on days 1 and 10, and at pre-dose on days 5 to 9 of the study.

Cohort 4: : Blood samples were collected at pre-dose, and at 0.25, 0.5, 1.0, 1.5, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48, and 72 hours post dose.

Urine samples were collected at pre-dose and from 1 to 24 hours post dose.

Reviewer's comment: The sampling scheme is adequate for characterizing peak plasma levels and terminal elimination half-life of azilsartan and its inactive metabolite.

Statistical Method

Relative bioavailability

ANOVA on log transformed parameters with fixed effects for sequence, period, and treatment, and random effect for subject within sequence. LS mean and 90% CI for the difference were constructed.

MAD PK

Dose proportionality: Power model (ln(PKmetric) = ln(a)+b*ln(Dose))

Linear kinetics: ANCOVA on dose – normalized log transformed PK measures with fixed effects for dose, day, dose by day interaction, subject nested as a random effect within dose.

Pharmacokinetic steady state: ANOVA on dose – normalized log transformed pre-dose plasma concentrations on days 5 to 9 with fixed effects for dose, day, dose by day interaction, subject nested as a random effect within dose.

Study population

Randomized/Completed/ Discontinued Due to AE	50/48/0*
Age [Median (range)] in years	26.5 [23.0 (19,44)]
Male/Female	49/1
Race (Caucasian/Black/Asian/other)	44/4/2/0
* As per the study record, of the two subjects that discontinued, none discontinued due to AEs.	

Results

Relative BA

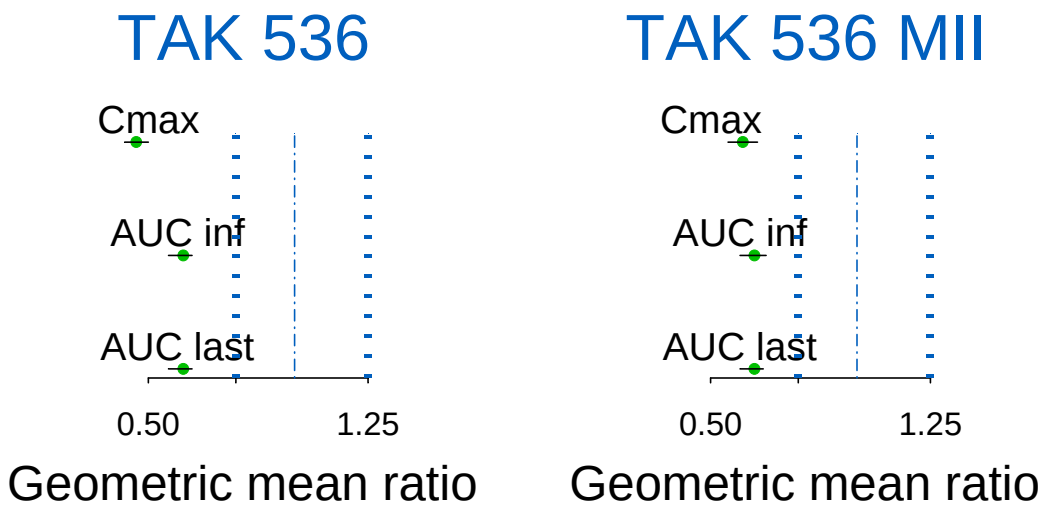


Figure 1 Results of the statistical analysis for azilsartan and its metabolite. The geometric mean ratios are depicted on the x-axis. The broken vertical lines represent the pre-determined BE limits. The closed circles represent the geometric mean of the BA/BE metrics and the horizontal line represents the 90%CI associated with the mean.

MAD PK – Dose proportionality

Table 1a Results of the statistical analysis for dose proportionality for day 1

Analyte Parameter (units)	N	Slope		
		Estimate	95% CI of Slope Estimate	P-Value for Testing Slope=1 (a)
TAK-536				
AUC(0-tlqc) (ng·hr/mL)	24	0.941	(0.637, 1.246)	0.694
AUC(0-inf) (ng·hr/mL)	24	0.938	(0.631, 1.245)	0.680
Cmax (ng/mL)	24	0.907	(0.580, 1.233)	0.559
TAK-536 M-II				
AUC(0-tlqc) (ng·hr/mL)	24	0.730	(0.372, 1.088)	0.132
AUC(0-inf) (ng·hr/mL)	24	0.706	(0.338, 1.075)	0.112
Cmax (ng/mL)	24	0.813	(0.465, 1.162)	0.279

Table 1b Results of the statistical analysis for dose proportionality for day 10.

Analyte Parameter (units)	N	Slope		
		Estimate	95% CI of Slope Estimate	P-Value for Testing Slope=1 (a)
TAK-536				
AUC(0- tau) (ng·hr/mL)	23	0.924	(0.593, 1.255)	0.638
Cmax (ng/mL)	23	1.025	(0.738, 1.312)	0.858
Cmin (ng/mL)	23	0.805	(0.267, 1.343)	0.459
TAK-536 M-II				
AUC(0-tau) (ng·hr/mL)	23	0.725	(0.419, 1.032)	0.076
Cmax (ng/mL)	23	0.742	(0.403, 1.081)	0.128
Cmin (ng/mL)	23	0.602	(0.199, 1.004)	0.052

Table 2 Results of the statistical analysis for linearity.

Analyte	N	Least Squares Mean (a)		Least Squares Mean Ratio (%) (Test/Reference) (b)	90% CI of Ratio (%) (c)	P-Value for Day Difference (d)
		Day 1 AUC(0-inf) (ng·hr/mL) (Reference)	Day 10 AUC(0-tau) (ng·hr/mL) (Test)			
TAK-536	23	496.1	517.1	104.23	(99.33, 109.37)	0.154
TAK-536 M-II	23	299.3	281.8	94.17	(89.44, 99.15)	0.058

Steady state plasma TAK 536 concentrations were attained by day 5 of the study.

Site Inspection Performed: Yes ☐ No ☒

Assay Method

The performance of the assay method during study sample analysis is acceptable and is summarized in the table below (ref: 01-06-TL-491-017-Bioanalytical-report-2007-07-20.pdf).

Analyte	TAK 536	TAK 536 MII
Method	HPLC/MS/MS	
LOQ (ng/mL)	10	2.0
Range (ng/mL)	10 to 5000	2.0 to 1000
QCs (ng/mL)	30,500,4000	6, 70, 800
Accuracy	101.4 to 105.5 %	101.1 to 106.3 %
Precision	3.6 to 7.8 %	5.6 to 12.6 %

Safety Death/SAE: **None**

Results and Conclusions

- Relative mean bioavailability of TAK 536 following oral administration as TAK 491 tablet is 80% compared to that following administration of TAK 536 tablet.
- Increase in systemic exposure to TAK 536 following administration of TAK 491 tablets is dose proportional.

Detailed Results – Relative bioavailability

TAK 536

	Geometric mean (%CV)			
	N	**TAK 491 Tablet**	**N**	**TAK 536 Tablet**
C_{max} (ng/mL)	19	4376.57 (19.4)	19	9422.9 (21.9)
t_{max} (h)[#]	19	2.5 (1.5,5.0)	19	1.5 (1.5,2.0)
$AUC_{0\text{-last}}$ (ng/mL*h)	19	39839.2 (27.8)	19	64866.9 (26.7)
$AUC_{0\text{-}\infty}$ (ng/mL*h)	19	40365.9 (28.1)	19	65578.2 (27.0)
$t_{1/2}$ (h)[##]	19	12.2 (2.6)	19	13.0 (2.0)
	Arithmetic mean (%CV)			
CL (L/h)	19	1.6 (31.9)	19	1.3 (35.3)
MRT (h)	19	11.5 (21.1)	19	10.9 (19.4)
Vz (L)	19	26.2 (21.5)	19	23.2 (24.2)

TAK 536 MII

	N	**TAK 491 Tablet**	**N**	**TAK 536 Tablet**
C_{max} (ng/mL)	19	929.439 (26.5)	19	1511.849 (26.9)
t_{max} (h)[#]	19	5.0 (4.0,8.0)	19	4.0 (3.0,5.0)
$AUC_{0\text{-last}}$ (ng/mL*h)	19	24291.4 (21.2)	19	37573.5 (25.7)
$AUC_{0\text{-}\infty}$ (ng/mL*h)	19	25618.7 (22.4)	19	39374.3 (26.9)
$t_{1/2}$ (h)[##]	19	16.0 (3.2)	19	15.4 (2.3)

Median (range) ## Mean (SD)

MAD PK

Day 1: TAK 536

	Geometric mean (%CV)					
	N	**TAK 491 160 mg**	**N**	**TAK 491 240 mg**	**N**	**TAK 491 320 mg**
C_{max} (ng/mL)	8	10612.5 (12.1)	8	16333.0 (34.2)	8	19744.3 (18.1)
C_{min} (ng/mL)						
t_{max} (h)[#]	8	2.5 (2.0,4.0)	8	2.5 (1.5,3.0)	8	2.5 (1.5,4.0)
$AUC_{0\text{-last}}$ (ng/mL*h)	8	78840.5 (26.9)	8	127650.6 (19.1)	8	149605.0 (14.2)
$AUC_{0\text{-}\infty}$ (ng/mL*h)	8	79547.2 (27.3)	8	129094.3 (19.0)	8	150513.0 (14.2)
$t_{1/2}$ (h)[##]	8	13.4 (1.8)	8	13.2 (2.0)	8	12.6 (0.8)
		Arithmetic mean (%CV)				
CL (L/h)	8	1.56 (24.9)	8	1.42 (18.8)	8	1.61 (14.3)
MRT (h)	8	10.7 (18.2)	8	11.6 (18.6)	8	10.1 (6.2)

Vz (L) ###	8	30.1 (29.7)	8	26.9 (21.3)	8	29.3 (15.2)

Day 1: TAK 536 MII

	Geometric mean (%CV)					
	N	**TAK 491 160 mg**	**N**	**TAK 491 240 mg**	**N**	**TAK 491 320 mg**
C_{max} (ng/mL)	8	2225.0 (10.1)	8	2789.1 (32.6)	8	3959.4 (10.6)
t_{max} (h)#	8	4 (4.0,6.0)	8	5 (5.0,6.0)	8	5 (4.0,8.0)
$AUC_{0\text{-last}}$ (ng/mL*h)	8	50793.7 (11.9)	8	68358.5 (30.3)	8	84234.8 (10.9)
$AUC_{0\text{-}\infty}$ (ng/mL*h)	8	52999.6 (13.2)	8	71757.2 (30.7)	8	86301.9 (11.2)
$t_{1/2}$ (h)##	8	15.3 (2.3)	8	15.33 (3.4)	8	13.17 (0.9)

Day 10: TAK 536

	Geometric mean (%CV)					
	N	**TAK 491 160 mg**	**N**	**TAK 491 240 mg**	**N**	**TAK 491 320 mg**
C_{max} (ng/mL)	8	10612.5 (12.1)	8	16333.0 (34.2)	8	19744.3 (18.1)
t_{max} (h)#	8	2.5 (2.0,4.0)	8	2.5 (1.5,3.0)	8	2.5 (1.5,4.0)
$AUC_{0\text{-last}}$ (ng/mL*h)	8	78840.5 (26.9)	8	127650.6 (19.1)	8	149605.0 (14.2)
$AUC_{0\text{-}\infty}$ (ng/mL*h)	8	79547.2 (27.3)	8	129094.3 (19.0)	8	150513.0 (14.2)
$t_{1/2}$ (h)##	8	13.4 (1.8)	8	13.2 (2.0)	8	12.6 (0.8)
		Arithmetic mean (%CV)				
CL (L/h)	8	1.56 (24.9)	8	1.42 (18.8)	8	1.61 (14.3)
MRT (h)	8	10.7 (18.2)	8	11.6 (18.6)	8	10.1 (6.2)
Vz (L) ###	8	30.1 (29.7)	8	26.9 (21.3)	8	29.3 (15.2)

Day 10: TAK 536 MII

	Geometric mean (%CV)					
	N	**TAK 491 160 mg**	**N**	**TAK 491 240 mg**	**N**	**TAK 491 320 mg**
C_{max} (ng/mL)	8	2225.0 (10.1)	8	2789.1 (32.6)	8	3959.4 (10.6)
t_{max} (h)#	8	4 (4.0,6.0)	8	5 (5.0,6.0)	8	5 (4.0,8.0)
$AUC_{0\text{-last}}$ (ng/mL*h)	8	50793.7 (11.9)	8	68358.5 (30.3)	8	84234.8 (10.9)
$AUC_{0\text{-}\infty}$ (ng/mL*h)	8	52999.6 (13.2)	8	71757.2 (30.7)	8	86301.9 (11.2)
$t_{1/2}$ (h)##	8	15.3 (2.3)	8	15.33 (3.4)	8	13.17 (0.9)

4 PHARMACOKINETICS

4.1 Study 01-05-TL-491-002 (MAD PK)

Study Report # CSR 01-05-TL-491-002	**Protocol #** 01-06-TL-491-002[14]

Title A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Sequential-Panel, Ascending Multiple-Dose Study of the Safety, Tolerability, and Pharmacokinetics of TAK-491 in Healthy Volunteers.

Objectives Bioequivalence ☐ Bioavailability☐ Food effect☐ Pharmacokinetics☒ Pharmacodynamics☒

Study Design

Subjects were randomized (n = 8 TAK 491, n = 2 PLC / dose level) to receive **0, 20, 60, 80, 160 mg** TAK 491 (as capsules). TAK 491 capsules were administered 30 minutes after consumption of a high fat breakfast (fed state) on days 1 and 10. Pharmacokinetic assessments were made for 72 h following administration of the first dose. Study subjects continued to receive study medication from days 4 through 10 of the study.

Study medication

	Placebo	**TAK 491**
Dosage Form	Capsule	Capsule
Dosage Strength	-	20 mg
Batch #.	Z624101G	Z6244019
Administration	Oral	Oral

PK Sampling

Blood samples were collected at pre-dose, and at 0.25, 0.5, 1.0, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48, and 72 hours post dose on days 1 and 10, and at pre-dose on days 5 to 9 of the study.

Urine samples collected -12 to 0 (pre-dose), 0-12h, 12-24h, 24-28h, and 48-72h on day 1 and at 0-12h, 12-24h, 24-28h, and 48-72h on day 10 of the study.

Reviewer's comment: The PK and PD sampling schemes are adequate for characterizing the PK and PD of azilsartan and its inactive metabolite.

Statistical Method

Dose proportionality: Power model (ln(PKmetric) = ln(a)+b*ln(Dose))

Linear kinetics: ANCOVA on dose – normalized log transformed PK measures with fixed effects for dose, day, dose by day interaction, subject nested as a random effect within dose.

Pharmacokinetic steady state: ANOVA on dose – normalized log transformed pre-dose

[14] \\Cdsesub1\evsprod\NDA200796\\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5331-healthy-subj-pk-init-tol-stud-rep\01-05-tl-491-002\csr-01-05-tl-491-002-amend-1.pdf

plasma concentrations on days 5 to 9 with fixed effects for dose, day, dose by day interaction, subject nested as a random effect within dose.

Study population

Randomized/Completed/ Discontinued Due to AE	40/38/0*
Age [Median (range)] in years	26.5 [23.0 (19,44)]
Male/Female	30/10
Race (Caucasian/Black/Asian/American Indian or Alaskan)	31/5/1/3
* As per the study record, of the two subjects that discontinued, none discontinued due to AEs.	

Results

Dose proportionality

Table 1a Results of the statistical analysis for dose proportionality for day 1

Day 1 Analyte & parameter	N	Slope		
		Estimate	95% CI of Slope Estimate	P-value for Testing Slope=1 (*)
TAK-536				
AUC(0-tlqc) (ng·hr/mL)	32	0.990	(0.860,1.120)	0.875
AUC(0-inf) (ng·hr /mL)	32	0.989	(0.857,1.120)	0.863
AUC (0-72) (ng·hr /mL)	32	0.990	(0.860,1.120)	0.875
Cmax (ng/mL)	32	1.059	(0.891,1.226)	0.481
TAK-536 M-I				
AUC(0-tlqc) (ng·hr/mL)	32	0.921	(0.650,1.192)	0.556
AUC(0-inf) (ng·hr /mL)	20	0.796	(0.404,1.188)	0.288
AUC (0-72) (ng·hr /mL)	32	0.893	(0.629,1.157)	0.415
Cmax (ng/mL)	32	0.843	(0.496,1.200)	0.384
TAK-536 M-II				
AUC(0-tlqc) (ng·hr/mL)	32	0.983	(0.886,1.081)	0.728
AUC(0-inf) (ng·hr /mL)	32	0.983	(0.887,1.079)	0.714
AUC (0-72) (ng·hr /mL)	32	0.983	(0.886,1.081)	0.728
Cmax (ng/mL)	32	0.957	(0.830,1.084)	0.497

Table 1b Results of the statistical analysis for dose proportionality for day 10.

Day 10 Analyte & parameter	N	Slope		
		Estimate	95% CI of Slope Estimate	P-value for Testing Slope=1 (*)
TAK-536				
AUC(0-24) (ng·hr/mL)	30	0.998	(0.860,1.137)	0.979
Cmax (ng/mL)	30	0.943	(0.786,1.101)	0.468
Cmin (ng/mL)	30	0.961	(0.674,1.248)	0.785
TAK-536 M-I				
AUC(0-24) (ng·hr/mL)	30	0.816	(0.574,1.058)	0.132
Cmax (ng/mL)	30	0.729	(0.449,1.009)	0.057
Cmin (ng/mL)	30	0.994	(0.691,1.298)	0.969
TAK-536 M-II				
AUC(0-24) (ng·hr/mL)	30	0.935	(0.806,1.065)	0.314
Cmax (ng/mL)	30	0.923	(0.802,1.044)	0.202
Cmin (ng/mL)	30	0.957	(0.762,1.153)	0.659

Table 2 Results of the statistical analysis for linearity.

	N	Geometric Mean		% Ratio (T/R)	90% CI of Ratio (%)	P-value for Difference (*)
		AUC(0-inf) (ng·hr/mL) Day 1 (Reference)	AUC(0-24) (ng·hr/mL) Day 10 (Test)			
TAK-536	30	499.1	469.2	94.01	(89.42, 98.83)	0.045
TAK-536 M-I	18	4.7	4.3	90.83	(71.90, 114.74)	0.484
TAK-536 M-II	30	324.2	265.8	81.98	(77.66, 86.54)	<0.001

Steady state plasma TAK 536 concentrations were attained by day 5 of the study.

Site Inspection Performed: Yes ☐ No ☒

Assay Method

The performance of the assay method during study sample analysis is acceptable and is summarized in the table below (ref: 01-06-TL-491-0002-Bioanalytical-report-2006-03-16.pdf).

Analyte	TAK 536		TAK 536 MII
Method			
LOQ (ng/mL)	10		2.0
Range (ng/mL)	1 to 2500		
QCs (ng/mL)	30, 150, 2000		
Accuracy	96 to 108 %		
Precision	3.6 to 11.9 %		

Safety Death/SAE: **None**

Results and Conclusions

Increase in systemic exposure to TAK 536 following administration of TAK 491 is dose proportional.

Detailed Results

Day 1: TAK 536

	N	**TAK 491 20 mg**	**N**	**TAK 491 60 mg**	**N**	**TAK 491 80 mg**	**N**	**TAK 491 160 mg**
C_{max} (ng/mL)	8	909.5 (32.4)	8	2434.0 (347.5)	8	4311.5 (45.0)	8	7964.1 (16.6)
C_{min} (ng/mL)								
t_{max} (h)[#]	8	6.5 (3.0, 12.0)	8	5.6 (3.0, 10.0)	8	5.0 (3.1, 8.0)		5.0 (2.5, 6.03)
$AUC_{0\text{-last}}$ (ng/mL*h)	8	10509.7 (36.2)	8	25425.4 (29.1)	8	42434.5 (19.4)	8	81077.3 (13.7)
$AUC_{0\text{-}\infty}$ (ng/mL*h)	8	10629.4 (36.8)	8	25610.5 (29.3)	8	42916.3 (19.3)	8	81765.2 (13.7)
$t_{1/2}$ (h)[##]	8	12.2 (1.3)	8	11.6 (1.0)	8	12.1 (1.8)		12.2 (0.8)

Day 10: TAK 536

	N	**TAK 491 20 mg**	**N**	**TAK 491 60 mg**	**N**	**TAK 491 80 mg**	**N**	**TAK 491 160 mg**
C_{max} (ng/mL)	8	1166.8 (31.2)	8	2816.3 (45.1)	8	4473.3 (27.6)	8	8208.0 (19.0)
C_{min} (ng/mL)		64.3 (63.5)		160.9 (65.1)		330.1 (45.8)		434.2 (31.9)
t_{max} (h)[#]	8	5.0 (4.0, 24)	8	5.5 (4.0, 10.0)	8	6.0 (4.0, 12.0)		8.0 (5.0,10.0)
$AUC_{0\text{-}\infty}$ (ng/mL*h)	8	9563.5 (33.9)	8	25612.2 (31.2)	8	41812.5 (23.2)	8	74188.1 (17.9)
$t_{1/2}$ (h)[##]	8	12.4 (1.4)	8	11.8 (1.4)	8	13.0 (1.9)		13.0 (1.1)

Day 1: TAK 536 MI

	N	**TAK 491 20 mg**	**N**	**TAK 491 60 mg**	**N**	**TAK 491 80 mg**	**N**	**TAK 491 160 mg**
C_{max} (ng/mL)	8	9.2 (56.2)	8	36.5 (135.4)	8	34.8 (89.7)	8	52.8 (66.8)
C_{min} (ng/mL)								
t_{max} (h)[#]	8	10.0 (2.5, 12.0)	8	5.0 (4.0, 8.0)	8	5.5 (4.0, 6.0)		5.5 (3.0, 8.0)
$AUC_{0\text{-last}}$ (ng/mL*h)	8	79.0 (60.1)	8	283.7 (117.4)	8	364.7 (52.1)	8	507.8 (54.2)
$AUC_{0\text{-}\infty}$	8	102.7	8	420.7	5	396.1	7	568.0

(ng/mL*h)		(61.2)		(106.6)		(60.7)		(51.7)
$t_{1/2}$ (h)[##]	8	17.3 (30.2)	8	10.5 (4.4)	5	11.7 (4.7)	7	12.4 (3.7)

Day 10: TAK 536 MI

	N	**TAK 491 20 mg**	**N**	**TAK 491 60 mg**	**N**	**TAK 491 80 mg**	**N**	**TAK 491 160 mg**
C_{max} (ng/mL)	8	10.8 (53.0)	8	31.2 (47.0)	7	38.5 (50.9)	7	45.4 (36.8)
C_{min} (ng/mL)		1.2 (282.8)		2.6 (106.2)	7	3.7 (36.1)	7	3.3 (35.2)
t_{max} (h)[#]	8	5.0 (4.0, 24)	8	5.5 (4.0, 10.0)	8	6.0 (4.0, 12.0)		8.0 (5.0,10.0)
$AUC_{0-\infty}$ (ng/mL*h)	8	78.4 (31.1)	8	256.2 (61.0)	7	366.2 (46.2)	7	380.6 (25.1)
$t_{1/2}$ (h)[##]	7	8.5 (2.2)	4	10.3 (1.2)	7	12.3 (2.4)	7	13.0 (3.0)

Day 1: TAK 536 MII

	N	**TAK 491 20 mg**	**N**	**TAK 491 60 mg**	**N**	**TAK 491 80 mg**	**N**	**TAK 491 160 mg**
C_{max} (ng/mL)	8	246.4 (24.1)	8	790.8 (22.1)	8	899.7 (35.2)	8	1827.3 (13.0)
C_{min} (ng/mL)								
t_{max} (h)[#]	8	9.0 (5.0, 24.0)	8	10.0 (6.0, 12.0)	8	10.0 (5.0, 12.0)		10.0 (6.0, 12.0)
AUC_{0-last} (ng/mL*h)	8	6171.7 (11.4)	8	19256.8 (22.8)	8	22931.5 (25.0)	8	48447.7 (13.7)
$AUC_{0-\infty}$ (ng/mL*h)	8	6441.3 (12.2)	8	19934.9 (23.8)	8	24000.1 (23.3)	8	50432.7 (14.3)
$t_{1/2}$ (h)[##]	8	13.9 (2.0)	8	13.4 (1.8)	8	14.2 (2.9)		14.2 (1.2)

Day 10: TAK 536 MII

	N	**TAK 491 20 mg**	**N**	**TAK 491 60 mg**	**N**	**TAK 491 80 mg**	**N**	**TAK 491 160 mg**
C_{max} (ng/mL)	8	342.9 (15.4)	8	1069.4 (33.5)	7	1319.8 (20.7)	7	2291.4 (26.0)
C_{min} (ng/mL)	8	86.7 (31.5)	8	290.5 (52.2)	7	411.4 (28.6)	7	594.2 (24.2)
t_{max} (h)[#]	8	10.0 (5.0, 24.0)	8	10.0 (8.0, 12.0)	7	8.2 (5.0, 24.0)	7	10.0 (8.1,12.0)
$AUC_{0-\infty}$ (ng/mL*h)	8	5416.0 (21.8)	8	17150.8 (35.9)	7	22475.9 (19.8)	7	36520.6 (21.3)
$t_{1/2}$ (h)[##]	8	14.0 (1.8)	8	13.3 (2.2)	8	14.7 (2.5)		14.8 (1.6)

[#] Median (range); [##] Mean (SD)

4.2 Study 01-05-TL-491-101 (MAD PK)

Study Report # CSR 01-05-TL-491-101	**Protocol #** 01-06-TL-491-101[15]

Title A Phase 1, Randomized, Open-Label, Ascending Single- and Multiple-Dose Study of the Safety, Tolerability, and Pharmacokinetics of 20, 40, and 80 mg of TAK-491 Tablets in Healthy Adult Subjects.

Objectives Bioequivalence ☐ Bioavailability☐ Food effect☐ Pharmacokinetics☒ Pharmacodynamics☐

Study Design

Subjects were randomized (n = 8 / dose level) to receive 20, 40, or 80 mg TAK 491 (as tablets). Pharmacokinetic assessments were made for 72 h following administration of the first dose. Study subjects continued to receive study medication from days 4 through 10 of the study.

Study medication

	TAK 491	**TAK 491**	**TAK 491**
Dosage Form	Tablet	Tablet	Tablet
Dosage Strength	20 mg	40 mg	80 mg
Batch #.	Z6249022	Z624B032	Z624D062
Administration		Oral	

PK Sampling

Blood samples were collected at pre-dose, and at 0.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48, and 72 hours post dose on days 1 and 10, and at pre-dose on days 5 to 9 of the study.

Urine samples collected -12 to 0 (pre-dose), 0-12h, 12-24h, 24-28h, and 48-72h on day 1 and at 0-12h, 12-24h, 24-28h, and 48-72h on day 10 of the study.

Reviewer's comment: The PK sampling scheme is adequate for characterizing the PK of azilsartan and its inactive metabolite.

Statistical Method

Dose proportionality: Power model (ln(PKmetric) = ln(a)+b*ln(Dose))

Linear kinetics: ANCOVA on dose – normalized log transformed PK measures with fixed effects for dose, day, dose by day interaction, subject nested as a random effect within dose.

Pharmacokinetic steady state: ANOVA on dose – normalized log transformed pre-dose plasma concentrations on days 5 to 9 with fixed effects for dose, day, dose by day interaction, subject nested as a random effect within dose.

[15] \\Cdsesub1\evsprod\NDA200796\\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5331-healthy-subj-pk-init-tol-stud-rep\tak-491-101\csr-tak-491-101.pdf

Study population

Randomized/Completed/ Discontinued Due to AE	24/22/0*
Age [Median (range)] in years	33.3 [23.0 (19,44)]
Male/Female	22/2
Race (Caucasian/Black/Asian/American Indian or Alaskan)	24/0/0/0
* As per the study record, two subjects withdrew consent (voluntary withdrawal).	

Results

Dose proportionality

Table 1a Results of the statistical analysis for dose proportionality for day 1

Analyte Parameter (units)	N	Slope Estimate	95% CI of Slope Estimate	P-Value for Testing Slope=1
TAK-536				
AUC(0-tlqc) (ng·hr/mL)	23	1.057	(0.868, 1.245)	0.539
AUC(0-inf) (ng·hr/mL)	23	1.037	(0.849, 1.226)	0.685
Cmax (ng/mL)	23	1.128	(0.923, 1.333)	0.209
TAK-536 M-II				
AUC(0-tlqc) (ng·hr/mL)	23	1.147	(1.008, 1.286)	0.040
AUC(0-inf) (ng·hr/mL)	22	1.161	(1.015, 1.307)	0.032
Cmax (ng/mL)	23	1.257	(1.060, 1.455)	0.013

Table 1b Results of the statistical analysis for dose proportionality for day 10.

Analyte Parameter (units)	N	Slope Estimate	95% CI of Slope Estimate	P-Value for Testing Slope=1
TAK-536				
AUC(0-tau) (ng·hr/mL)	22	1.023	(0.829, 1.217)	0.806
Cmax (ng/mL)	22	1.152	(0.963, 1.341)	0.109
Cmin(0) (ng/mL)	22	0.840	(0.512, 1.168)	0.322
TAK-536 M-II				
AUC(0-tau) (ng·hr/mL)	22	1.155	(0.990, 1.319)	0.064
Cmax (ng/mL)	22	1.227	(1.088, 1.366)	0.003
Cmin(0) (ng/mL)	22	0.988	(0.741, 1.236)	0.923

Table 2 Results of the statistical analysis for linearity.

		Least Squares Mean (a)					
Analyte	N	Day 1 AUC(0-inf) (ng·hr/mL) (Reference)	N	Day 10 AUC(0-tau) (ng·hr/mL) (Test)	(%) Ratio (Test/Reference) (b)	90% CI of Ratio (%) (c)	P-Value for Day Difference
TAK-536	23	415.4	22	398.3	95.89	(90.95, 101.10)	0.187
TAK-536 M-II	22	244.2	22	256.1	104.86	(99.46, 110.55)	0.137

Steady state plasma TAK 536 concentrations were attained by day 5 of the study.

Site Inspection Performed: Yes ☐ No ☒

Assay Method

The performance of the assay method during study sample analysis is acceptable and is summarized in the table below (ref: 01-06-TL-491-101-Bioanalytical-report-2008-04-09.pdf)

Analyte	TAK 536	TAK 536 MII
Method	HPLC/MS/MS	
LOQ (ng/mL)	10.0	2.0
Range (ng/mL)	10 to 5000	2 to 1000
QCs (ng/mL)	30, 500, 4000	6, 70, 800
Accuracy	96.5 to 103.0 %	99.8 to 107.4 %
Precision	1.2 to 4.2 %	1.4 to 9.9 %

Safety Death/SAE: **None**

Results and Conclusions

Increase in systemic exposure to TAK 536 following administration of TAK 491 is dose proportional.

Detailed Results

Day 1: TAK 536

	Geometric mean (%CV)					
	N	**TAK 491 20 mg**	**N**	**TAK 491 40 mg**	**N**	**TAK 491 80 mg**
C_{max} (ng/mL)	8	962.1 (20.3)	8	2014.9 (34.2)	8	4593.1 (30.2)
C_{min} (ng/mL)						
t_{max} (h)[#]	8	2.7 (2.0,3.0)	8	2.5 (2.5,4.0)	8	2.3 (1.0,5.0)
$AUC_{0\text{-last}}$ (ng/mL*h)	8	7960.3 (29.8)	8	15849.3 (23.3)	8	34442.2 (24.5)
$AUC_{0\text{-}\infty}$ (ng/mL*h)	8	8240.9 (29.6)	8	16119.0 (23.5)	8	34709.1 (24.3)
$t_{1/2}$ (h)[##]	8	10.7 (2.9)	8	10.2 (1.8)	8	12.3 (1.5)
		Arithmetic mean (%CV)				
CL (L/h)	*8*	*1.56 (24.9)*	*8*	*1.42 (18.8)*	*8*	*1.61 (14.3)*
MRT (h)	*8*	*10.7 (18.2)*	*8*	*11.6 (18.6)*	*8*	*10.1 (6.2)*
Vz (L) [###]	*8*	*30.1 (29.7)*	*8*	*26.9 (21.3)*	*8*	*29.3 (15.2)*

Day 1: TAK 536 MII

	Geometric mean (%CV)					
	N	**TAK 491 20 mg**	**N**	**TAK 491 40 mg**	**N**	**TAK 491 80 mg**
C_{max} (ng/mL)	8	212.9 (24.3)	7	417.3 (24.9)	8	1217.1 (27.1)
t_{max} (h)[#]	8	5 (4.0,8.0)	7	5 (5.0,6.0)	8	5 (3.0,6.0)
$AUC_{0\text{-last}}$ (ng/mL*h)	8	4597.9 (15.8)	7	8416.0 (16.1)	8	22540.7 (17.8)
$AUC_{0\text{-}\infty}$	8	4671.8 (16.4)	7	8619.4 (16.2)	8	23180.1 (17.8)

(ng/mL*h)						
$t_{1/2}$ (h)[##]	8	14.1 (1.3)	8	13.3 (1.1)	8	14.0 (1.1)

Day 10: TAK 536

	Geometric mean (%CV)					
	N	**TAK 491 20 mg**	**N**	**TAK 491 40 mg**	**N**	**TAK 491 80 mg**
C_{max} (ng/mL)	7	1126.4 (19.9)	7	2084.5 (24.6)	8	5520.9 (25.4)
C_{min} (ng/mL)	7	83.3 (46.6)	7	121.3 (52.6)	8	264.5 (33.0)
t_{max} (h)[#]	7	2.5 (2.0,4.0)	7	2.5 (2.0,3.0)	8	1.5 (1.0,4.0)
$AUC_{0-\infty}$ (ng/mL*h)	7	8191.1 (31.8)	7	14396.1 (20.5)	8	33628.1 (21.6)
$t_{1/2}$ (h)[##]	7	11.9 (1.6)	7	12.2 (4.7)	8	13.9 (1.4)
		Arithmetic mean (%CV)				
CL (L/h)	*8*	*1.56 (24.9)*	*8*	*1.42 (18.8)*	*8*	*1.61 (14.3)*
MRT (h)	*8*	*10.7 (18.2)*	*8*	*11.6 (18.6)*	*8*	*10.1 (6.2)*
Vz (L) [###]	*8*	*30.1 (29.7)*	*8*	*26.9 (21.3)*	*8*	*29.3 (15.2)*

Day 10: TAK 536 MII

	Geometric mean (%CV)					
	N	**TAK 491 160 mg**	**N**	**TAK 491 240 mg**	**N**	**TAK 491 320 mg**
C_{max} (ng/mL)	7	324.8 (12.8)	7	604.2 (12.4)	8	1763.6 (17.4)
C_{min} (ng/mL)	7	129.5 (20.7)	7	190.2 (39.7)	8	503.3 (26.7)
t_{max} (h)[#]	7	5.0 (3.0,6.0)	7	5 (3.0,6.0)	8	4.0 (4.0,6.0)
$AUC_{0-\infty}$ (ng/mL*h)	7	5054.8 (14.7)	7	8570.9 (19.3)	8	24774.3 (17.3)
$t_{1/2}$ (h)[##]	7	14.5 (1.0)	7	13.6 (2.5)	8	14.4 (1.0)

[#] Median (range); [##] Mean (SD)

5 MASS BALANCE

Study 01-05-TL-491-012 (ADME)

Study Report # CSR 01-05-TL-491-012	**Protocol #** 01-06-TL-491-012[16]

Title A Phase 1, Open-Label Mass Balance and Excretion Study of [^{14}C]TAK-491 Following Oral Administration in Healthy Male Subjects.

Objectives Bioequivalence ☐ Bioavailability☐ Food effect☐ Pharmacokinetics☒ Pharmacodynamics☐

Study Design

Subjects (n = 8) to received 80 mg TAK 491 with 100 μCi of radioactivity (suspension). Pharmacokinetic assessments were made for up to 10 days post-dosing.

Study medication

	TAK 491
Dosage Form	Suspension
Dosage Strength	80 mg / 100 μCi
Batch #.	1600-1600-06-001

PK Sampling

Blood samples were collected at pre-dose, and at 0.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48, 72, and 96 hours post dose.

Urine samples collected -12 to 0 (pre-dose), 0-2h, 2-4h, 4-8h, 8-12h, and 12-24h, and for eigth additional consecutive 24 h collections periods.

Fecal samples were collected prior to dosing on day 1 and trough day 10 of the study.

Reviewer's comment: The PK sampling scheme is adequate for characterizing the PK of azilsartan and its inactive metabolite.

Study population

Randomized/Completed/ Discontinued Due to AE	8/8/0
Age [Median (range)] in years	35.4
Male/Female	8/0
Race (Caucasian/Black/Asian/American Indian or Alaskan)	8/0/0/0

Results

About 97% of the administered radioactive dose was recovered in 14 days, of which 55% was recovered in feces and the other 42% in urine. The major component in urine was

[16] \\Cdsesub1\evsprod\NDA200796\\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5331-healthy-subj-pk-init-tol-stud-rep\01-06-tl-491-012\csr-01-06-tl-491-012.pdf

TAK 536 MII (46.4%), followed by TAK 536 (38.2%). TAK 536 MI accounted for only 0.2% of the radioactivity. The remaining 15% were unidentified metabolites. The major component in feces was TAK 536 MI (48.3%).

Site Inspection Performed: Yes ☐ No ☒

Assay Method

The performance of the assay method during study sample analysis is acceptable and is summarized in the table below (ref: 01-06-TL-491-012-Bioanalytical-report-2006-10-30.pdf)

Analyte	TAK 536	TAK 536 MII
Method	HPLC/MS/MS	
LOQ (ng/mL)	1.0	2.0
Range (ng/mL)	1 to 2500	1 to 2500
QCs (ng/mL)	3, 150, 2000	3, 150, 2000
Accuracy	91 to 112.0 %	90.5 to 101.3 %
Precision	3.9 to 9 %	3.6 to 7.6 %

Safety Death/SAE: **None**

Results and Conclusions

TAK 491 is eliminated both via feces and urine.

Detailed Results

Table Summary of pharmacokinetic measures for TAK 536 following administration of a single dose of [^{14}C]TAK-491

			TAK-536		
Parameter	**Units**	**N**	**Arithmetic Mean**	**%CV**	**Geometric Mean**
AUC(0-tlqc)	ng·hr/mL	8	59427.5	25.7	57857.4
AUC(0-inf)	ng·hr/mL	8	59724.9	25.8	58130.1
Cmax	ng/mL	8	6877.5	19.3	6777.7
Tmax (a)	hr	8	1.5 (1.0-3.0)		
T1/2	hr	8	14.5	6.3	-
MRT	hr	8	12.0	19.3	-
Ae(0-96)	mg	8	11.6	35.0	

Table Summary of pharmacokinetic measures for M-II following administration of a single dose of [^{14}C]TAK-491

			TAK-536 M-II		
Parameter	**Units**	**N**	**Arithmetic Mean**	**%CV**	**Geometric Mean**
AUC(0-tlqc)	ng·hr/mL	8	32140.8	21.9	31566.1
AUC(0-inf)	ng·hr/mL	8	32768.5	22.5	32149.8
Cmax	ng/mL	8	1208.9	16.2	1195.1
Tmax (a)	hr	8	4.0 (4.0-6.0)		
T1/2	hr	8	15.6	14.2	-
MRT	hr	8	25.2	17.4	-
Ae(0-96)	mg	8	14.3	15.1	-

Concentration time-course

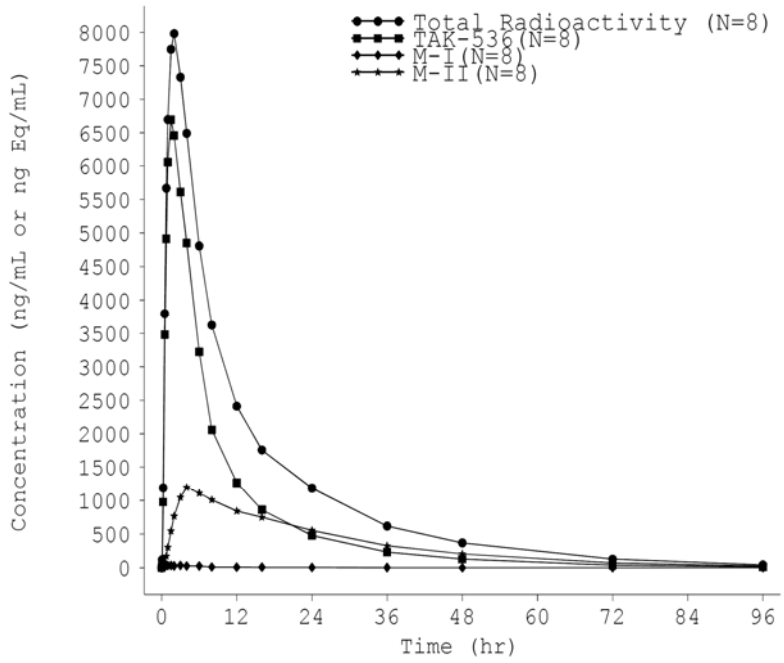


Figure 1 Mean plasma concentration versus time profile.

6 INTRINSIC FACTORS

6.1 Study TAK 491_103 (Renal Impairment)

Report # TAK – 491_103[17]	**Study Period** 04/03/08-04/09/08
Title	An open-label parallel group comparison study of single dose pharmacokinetics of TAK-491 in subjects with varying degrees of renal impairment and their healthy matched subjects.

Study Design

Single-Dose	Non-Randomized	Open-Label	Parallel		Single-Center
No. of Groups	☑Normal	☑Mild	☑Moderate	☑Severe	☑ESRD
No. of Subject /Completed	24	6	6	6	6
Males/Females	16/8	5/1	4/2	4/2	3/3
Age, Mean(range)	60.1 (11.05)	67.0 (8.8)0	69.5 (3.27)	61.8 (12.7)	49.0 (10.04)
Dose	40	40	40	40	40
Sampling Times: PK, plasma: pre-dose and at 0.08, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48, 72, 96, 120, and at approximately 168 hours (day 8) post dose. For hemodialysis subjects, arterial and venous samples were collected while on hemodialysis. Urine: Day -1 (-12 to 0 hrs) and on Days 1-6 at the following intervals: 0 to 12, 12to 24, 24 to 48, 48 to 72, 72 to 96, and 96 to 120 hours.					

- Classification of renal function is consistent with the FDA Guidance Recommendations: ☑ Yes ☐ No

- Renal function was determined via ☑ G-C formula ☐ MDRD formula
- Renal function was determined at: ☑ Screening ☑Baseline
- The control group is adequate ☑ Yes ☐ No
- The groups are matched by☑ Age ☑ Sex ☑ Body Weight ☑ Smoking Status ☑ Race
- The selected dose is acceptable ☑ Yes ☐ No
- Protein Binding: ☑All ☐Limited (in all subjects)
  Sampling Times: 3, 5, 7 h
  Method: Ultrafiltration
- Dosing is long enough to obtain steady state ☐ Yes ☐ No☑ Not Applicable
- Sample size was determined based on statistical analysis ☐ Yes ☑ No
- The overall study design acceptable: ☑ Yes ☐ No

Analytical Method (Study Samples Analysis)

- Study samples were analyzed within the established stability period ☑ Yes ☐ No
- Quality control samples range is acceptable ☑ Yes ☐ No
- Internal standard was used ☑ Yes ☐ No

[17] \\Cdsesub1\evsprod\NDA200796\\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5333-intrin-factor-pk-stud-rep\tak-491-103\tak-491-103-clinical-study-report-body.pdf

- Method was validated prior to use ☑ Yes ☐ No
- Chromatograms were provided ☑ Yes ☐ No
- Overall performance is acceptable ☑ Yes ☐ No

Pharmacokinetics

1. Is there a relationship between creatinine clearance and AUC? ☐ Yes ☑ No, if yes explain

2. Is there a relationship between creatinine clearance and C_{max}? ☐ Yes ☑ No, if yes explain

Table 1 Mean (%CV) pharmacokinetic parameters for AZ.

	Healthy (a) n=24		Mild Renal Impairment n=6		Moderate Renal Impairment n=6		Severe Renal Impairment n=6		ESRD n=6	
	N	Mean (%CV)	N	Mean (%CV)	N	Mean (%CV)	N	Mean (%CV)	N	Mean (%CV)
TAK-536										
AUC(0-tlqc) (b)	24	21927.4 (36)	6	27763.2 (45)	6	35656.8 (12)	6	34375.0 (31)	6	21389.8 (50)
AUC(0-inf) (b)	24	22244.5 (36)	6	28165.4 (44)	6	36009.1 (12)	6	34826.7 (31)	6	21607.0 (49)
AUC(0-24) (b)	24	18692.8 (31)	6	20938.7 (24)	6	27138.5 (13)	6	25166.8 (23)	6	17915.5 (45)
Cmax (ng/mL)	24	2508.8 (34)	6	2428.3 (13)	6	2871.7 (31)	6	2630.0 (18)	6	2291.7 (45)
Tmax (hr) (c)	24	2.25 (1.0, 4.0)	6	2.5 (2.0, 4.0)	6	2.0 (2.0, 6.0)	6	2.5 (2.5, 3.0)	6	3.52 (1.47, 5.15)
λz (1/hr)	24	0.059 (23)	6	0.052 (31)	6	0.043 (18)	6	0.042 (20)	6	0.066 (22)
T1/2 (hr)	24	12.5 (25)	6	14.7 (37)	6	16.7 (19)	6	17.2 (23)	6	11.0 (22)
Fe (%)	24	8.1 (36)	6	3.3 (58)	6	3.8 (87)	6	1.1 (110)		n/a
Ae(0-t) (μg)	24	2227.2 (36)	6	879.1 (56)	6	931.9 (97)	6	275.6 (90)		n/a
CLr (L/hr)	24	0.123 (38)	6	0.044 (54)	6	0.033 (96)	6	0.011 (75)		n/a

Renal Impairment	Geometric Mean Ratio (AUC) Renal Impairment/ Healthy Volunteers	
	Point Estimate	95% CI
Mild	129.8	93.7,179.9
Moderate	125.1	90.3,173.4
Severe	195.4	140.8,271.2
ESRD	104.1	75,144.6

Safety

Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA

Conclusions

Is there is a need to adjust the dose in patients with renal impairment? ☐ Yes ☑ No

Comments

Given the flat D-R relationship of AZM, and the absence of adverse events, dose adjustments are not necessary in this population.

6.2 Study TAK 491_102 (Hepatic Impairment)

Report # TAK 491_102[18]	**Study Period** 09/2007 - 11/2007
Title	Open label evaluation of the single dose and multiple dose pharmacokinetics of TAK 491 in subjects with and without hepatic impairment.

Study Design

Multiple-Dose	Non-Randomized	Open-Label	Parallel	Single-Center	
No. of Groups	☑Normal	☑Mild	☑Moderate	☒Severe	Total
No. of Subject /Completed	16	8	8	-	32
Males/Females	8/8	4/4	4/4		16/16
Age, Mean(SD)	54.1 (7)	58.0 (6)	59.4 (6.2)		
Dose	40 mg	40 mg	40 mg		

- Screening:
- Sampling Times:
  - PK, plasma: pre-dose and at 0.08, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48, 72 post dose after the first dose (day 1); at pre-dose on days 5,6,7; at pre-dose and at 0.08, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 16, 24 on day 8 (last dose)
- Classification of hepatic function is consistent with the FDA Guidance Recommendations: ☑ Yes ☐ No

- Hepatic function was determined via Child-Pugh classification ☑ Yes ☐ No
- Hepatic function was determined at: ☑ Screening ☑Baseline
- The control group is adequate ☑ Yes ☐ No
- The groups are matched by☑ Age ☑ Sex ☑ Body Weight ☑ Smoking Status ☑ Race
- The selected dose is acceptable ☑ Yes ☐ No
  TAK 491 tablets 40 mg administered on day 1 and then QD from study day 4 to 8
- Dosing is long enough to obtain steady state ☐ Yes ☐ No☑ Not Applicable
- Sample size was determined based on statistical analysis ☐ Yes ☑ No
- The overall study design acceptable: ☑ Yes ☐ No

Analytical Method (Study Samples Analysis)

[18] \\Cdsesub1\evsprod\NDA200796\\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5333-intrin-factor-pk-stud-rep\tak-491-102\csr-tak-491-102-revised.pdf

- Study samples were analyzed within the established stability period: ☑ Yes ☐ No
- Quality control samples range is acceptable ☑ Yes ☐ No
- Internal standard was used ☑ Yes ☐ No
- Method was validated prior to use ☑ Yes ☐ No
- Chromatograms were provided ☑ Yes ☐ No
- Overall performance is acceptable ☑ Yes ☐ No

☑ Yes ☐ No

Analyte	TAK 491	TAK 536	TAK 536 MII
Method	LC/MS/MS		
LOQ (ng/mL)	1.0	10.0	2.0
Range (ng/mL)	1 to 2500	10 to 5000	2 to 1000
QCs (ng/mL)	30, 500, 4000	30, 500, 4000	6, 70, 800
Accuracy	96.5 to 103.0 %	96.5 to 103.0 %	99.8 to 107.4 %
Precision	1.2 to 4.2 %	1.2 to 4.2 %	1.4 to 9.9 %

Pharmacokinetics

Table 1 Effect of mild to moderate hepatic impairment on TAK 536 (Ref: TAK 491_102 study report, synopsis).

	Mild Hepatic Impairment LS Mean (n=8)	Healthy Matched Control LS Mean (n=8)	LS Mean Ratio Mild/Control	90% CI for Ratio (a)
TAK-536, Day 1				
AUC(0-tlqc) (ng·hr/mL)	27913.38	20150.37	138.53	(107.12, 179.14)
AUC(0-inf) (ng·hr/mL)	28646.89	20513.61	139.65	(107.59, 181.26)
Cmax (ng/mL)	3018.72	2698.40	111.87	(90.94, 137.62)
Tmax (hr) (b)	2.00 (1.50, 4.00)	2.00 (1.50, 3.00)	n/a	n/a
TAK-536, Day 8				
AUC(0-tau) (ng·hr/mL)	24610.20	19238.97	127.92	(99.84, 163.89)
Cmax (ng/mL)	2609.97	2826.70	92.33	(75.87, 112.37)
Cmin(0) (ng/mL)	319.94	200.00	159.97	(106.21, 240.94)
Tmax (hr) (b)	3.00 (2.00, 4.00)	2.00 (1.00, 3.00)	n/a	n/a
M-II, Day 1				
AUC(0-tlqc) (ng·hr/mL)	12926.24	9599.69	134.65	(103.77, 174.73)
AUC(0-inf) (ng·hr/mL)	13927.16	9948.21	140.00	(106.59, 183.88)
Cmax (ng/mL)	426.75	451.71	94.48	(70.33, 126.90)
Tmax (hr) (b)	6.00 (4.00, 12.00)	5.00 (2.00, 8.00)	n/a	n/a
M-II, Day 8				
AUC(0-tau) (ng·hr/mL)	11895.35	9348.35	127.25	(95.53, 169.49)
Cmax (ng/mL)	648.49	590.77	109.77	(84.70, 142.26)
Cmin(0) (ng/mL)	347.12	260.58	133.21	(95.87, 185.09)
Tmax (hr) (b)	6.00 (3.00, 12.00)	4.00 (3.00, 6.00)	n/a	n/a

Safety

Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA

Conclusions

Should the TAK 491 dose be adjusted in subjects with hepatic impairment? ☐ Yes ☑ No

Comments

Given the flat D-R relationship of AZM, and the absence of adverse events, dose adjustments are not necessary in this population.

6.3 Study 01-05-TL-491-003 (Age, sex, race)

Study Report # CSR 01-05-TL-491-003	**Protocol #** 01-05-TL-491-003[19]

Title: A phase I, single blind, placebo controlled, randomized, parallel design study to evaluate the possible effects of age, gender, and race on the safety and pharmacokinetics of single and multiple doses of TAk 491 in healthy adult subjects.

Objectives Bioequivalence ☐ Bioavailability☒ Food effect☐ Pharmacokinetics☒

Study Design Parallel ☒ Crossover ☐

All study subjects (stratified according to age, sex and race) received a single dose of TAK 491/placebo on day 1. Samples fro pharmacokinetic analysis were collected on days 2 and 3. TAK 491/placebo was then administered QD from study days 4 to 8. Samples were collected for pharmacokinetic analysis following the last dose on day 9 of the study.

Study medication

	Placebo	**TAK 491**
Dosage Form	Capsule	Capsule
Dosage Strength	3 capsules	3 x 20 mg (60 mg)
Batch #.	Z6241021	Z6244021
Administration	Oral	Oral

PK Sampling

Blood samples were collected at pre-dose, 0.25, 0.5, 0.75, 1.0, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, and 72 hours post dose following the first dose; at pre-dose on days 5, 6, 7; at pre-dose and 0.25, 0.5, 0.75, 1.0, 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 h post dose on day 9.

Statistical Method

ANOVA on log transformed parameters with fixed effects for sequence, period, and treatment, and random effect for subject within sequence. LS mean and 90% CI for the difference were constructed.

Study population

Randomized/Completed/ Discontinued Due to AE	61/61/0
Age [mean(SD)] in years Young (n=32) Elderly (n=29)	49.4 (20.6) 31 (8.1) 69.6 (5.2)
Female/Male	32/29
Race (Black/white)	29/32

[19] \\Cdsesub1\evsprod\NDA200796\\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5333-intrin-factor-pk-stud-rep\01-05-tl-491-003\csr-01-05-tl-491-003.pdf

Results

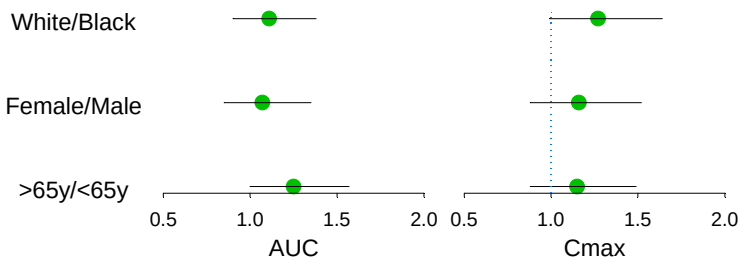


Figure 1 Results of the statistical analysis for azilsartan (TAK-536). The geometric mean ratios for AUC and C_{max} are depicted on the x-axis. The closed circles represent the geometric mean of the Test/Ref and the horizontal line represents the 90%CI associated with the mean.

Site Inspection Performed: Yes ☐ No ☒

Assay Method

The performance of the assay method during study sample analysis is acceptable and is summarized in the table below (ref: 01-05-TL-491-003 Bioanalytical Report, 7128-470).

Analyte	TAK 536	TAK 536 MI	TAK 536 MII
Method	HPLC/MS/MS		
LOQ (ng/mL)	1		
Range (ng/mL)	1 to 2500		
QCs (ng/mL)	3, 150, 2000		
Accuracy	95.0 to 108.0 %	100.0 to 103.0 %	90.0 to 106.0 %
Precision	3.6 to 8.0 %	0.7 to 7.0 %	5.2 to 10.8 %

Safety Death/SAE: **None**

Results and Conclusions

- Following repeat administration, C_{max} and AUC were 15% and 25% higher, respectively, in the elderly as compared to < 65y/o; C_{max} and AUC were 16% and 7% higher, respectively, in the females compared to males; C_{max} and AUC were 28% and 22% higher, respectively, in whites as compared to blacks.
- Dose adjustments based on age, sex or race are not necessary.

Detailed results

Table 1 Comparison of pharmacokinetic parameters of TAK 536 between the young and elderly (Ref: CSR 01-05-TL-491-003 synopsis)

Pharmacokinetic Parameters of TAK-536 and its Metabolites, TAK-536 M-I and TAK-536 M-II by Age

Analyte	Parameter (b)	N (a) R	N (a) T	LS MEAN Young (R)	LS MEAN Elderly (T)	% Ratio (T/R) (c)	90% CI of Ratio (d)
	Day 1						
TAK-536	AUC (0-tlqc) (ng·hr/mL)	24	23	19075.0	25733.2	134.9	(105.2, 172.9)
	AUC (0-inf) (ng·hr/mL)	23	22	19061.6	26003.3	136.4	(104.9, 177.4)
	Cmax (ng/mL)	24	23	2093.3	2876.3	137.4	(101.8, 185.6)
	Tmax (hr)	24	23	5.8	5.7		
TAK-536 M-I	AUC (0-tlqc) (ng·hr/mL)	24	23	212.9	378.0	177.6	(114.0, 276.5)
	AUC (0-inf) (ng·hr/mL)	9	20	399.5	428.6	107.3	(76.7, 150.0)
	Cmax (ng/mL)	24	23	34.0	48.0	141.4	(91.9, 217.6)
	Tmax (hr)	24	23	6.0	6.2		
TAK-536 M-II	AUC (0-tlqc) (ng·hr/mL)	24	23	10512.2	14570.0	138.6	(104.5, 183.9)
	AUC (0-inf) (ng·hr/mL)	23	22	10702.1	15561.5	145.4	(108.4, 195.1)
	Cmax (ng/mL)	24	23	432.5	524.8	121.4	(91.5, 161.0)
	Tmax (hr)	24	23	9.6	9.9		
	Day 8						
TAK-536	AUC(0-24) (ng·hr/mL)	24	23	19383.6	24374.8	125.8	(100.7, 157.1)
	Cmax (ng/mL)	24	23	2637.8	3036.0	115.1	(88.8, 149.3)
	Cmin(abs) (ng/mL)	24	23	171.8	201.5	117.3	(80.6, 170.7)
	Tmax (hr)	24	23	4.5	4.9		
TAK-536 M-I	AUC(0-24) (ng·hr/mL)	24	23	266.1	353.7	132.9	(95.4, 185.1)
	Cmax (ng/mL)	24	23	49.2	50.2	102.1	(71.6, 145.6)
	Cmin (abs) (ng/mL)	23	23	2.3	3.4	148.6	(118.3, 186.8)
	Tmax (hr)	24	23	4.6	5.3		
TAK-536 M-II	AUC(0-24) (ng·hr/mL)	24	23	10553.9	14429.3	136.7	(106.9, 174.8)
	Cmax (ng/mL)	24	23	647.0	848.8	131.2	(103.9, 165.6)
	Cmin (abs) (ng/mL)	24	23	232.3	289.2	124.5	(84.4, 183.7)
	Tmax (hr)	24	23	6.6	7.7		

Table 2 Comparison of pharmacokinetic parameters of TAK 536 between males and females (Ref: CSR 01-05-TL-491-003 synopsis)

Analyte	Parameter (b)	N (a) R	N (a) T	LS MEAN Male (R)	LS MEAN Female (T)	% Ratio (T/R) (c)	90% CI of Ratio (d)
	Day 1						
TAK-536	AUC (0-tlqc) (ng·hr /mL)	24	23	21918.9	22394.4	102.2	(79.0, 132.2)
	AUC (0-inf) (ng·hr/mL)	23	22	21954.9	22576.5	102.8	(77.9, 135.7)
	Cmax (ng/mL)	24	23	2430.1	2477.7	102.0	(74.7, 139.3)
	Tmax (hr)	24	23	5.8	5.6		
TAK-536 M-I	AUC (0-tlqc) (ng·hr/mL)	24	23	300.8	267.5	88.9	(56.2, 140.9)
	AUC (0-inf) (ng·hr/mL)	14	15	401.6	426.3	106.2	(75.8, 148.6)
	Cmax (ng/mL)	24	23	41.7	39.1	93.8	(60.0, 146.7)
	Tmax (hr)	24	23	5.7	6.4		
TAK-536 M-II	AUC (0-tlqc) (ng·hr/mL)	24	23	12865.2	11905.2	92.5	(69.0, 124.1)
	AUC (0-inf) (ng·hr/mL)	23	22	13282.3	12538.6	94.4	(69.2, 128.8)
	Cmax (ng/mL)	24	23	485.2	467.8	96.4	(71.9, 129.2)
	Tmax (hr)	24	23	9.7	9.8		
Analyte	**Parameter (b)**	**N (a) R**	**N (a) T**	**LS MEAN Male (R)**	**LS MEAN Female (T)**	**% Ratio (T/R) (c)**	**90% CI of Ratio (d)**
	Day 8						
TAK-536	AUC(0-24) (ng·hr/mL)	24	23	20937.9	22565.3	107.8	(85.6, 135.8)
	Cmax (ng/mL)	24	23	2626.6	3048.9	116.1	(88.6, 152.0)
	Cmin(abs) (ng/mL)	24	23	198.6	174.3	87.8	(59.5, 129.5)
	Tmax (hr)	24	23	4.4	4.9		
TAK-536 M-I	AUC(0-24) (ng·hr/mL)	24	23	303.0	310.6	102.5	(72.7, 144.5)
	Cmax (ng/mL)	24	23	43.0	57.5	133.6	(92.5, 193.1)
	Cmin (abs) (ng/mL)	24	22	2.8	2.7	95.8	(75.6, 121.4)
	Tmax (hr)	24	23	4.8	5.1		
TAK-536 M-II	AUC(0-24) (ng·hr/mL)	24	23	12699.1	11991.8	94.4	(73.2, 121.9)
	Cmax (ng/mL)	24	23	737.0	745.2	101.1	(79.4, 128.8)
	Cmin (abs) (ng/mL)	24	23	295.4	227.4	77.0	(51.4, 115.3)
	Tmax (hr)	24	23	7.6	6.7		

Table 3 Comparison of pharmacokinetic parameters of TAK 536 between the blacks and whites (Ref: CSR 01-05-TL-491-003 synopsis)

Analyte	Parameter (b)	N (a) R	N (a) T	LS MEAN Black (e) (R)	LS MEAN White (T)	% Ratio (T/R) (c)	90% CI of Ratio (d)
	Day 1						
TAK-536	AUC (0-tlqc) (ng·hr /mL)	23	24	19996.5	24547.3	122.8	(96.5, 156.2)
	AUC (0-inf) (ng·hr/mL)	22	23	20150.1	24598.7	122.1	(94.5, 157.7)
	Cmax (ng/mL)	23	24	2363.7	2547.2	107.8	(80.5, 144.3)
	Tmax (hr)	23	24	5.5	6.0		
TAK-536 M-I	AUC (0-tlqc) (ng·hr/mL)	23	24	269.5	298.5	110.8	(72.1, 170.3)
	AUC (0-inf) (ng·hr/mL)	14	15	471.0	363.6	77.2	(55.6, 107.2)
	Cmax (ng/mL)	23	24	38.6	42.3	109.5	(72.1, 166.4)
	Tmax (hr)	23	24	6.5	5.7		
TAK-536 M-II	AUC (0-tlqc) (ng·hr/mL)	23	24	10073.9	15203.9	150.9	(114.7, 198.6)
	AUC (0-inf) (ng·hr/mL)	22	23	10582.8	15737.0	148.7	(111.7, 198.0)
	Cmax (ng/mL)	23	24	415.5	546.3	131.5	(100.0, 173.0)
	Tmax (hr)	23	24	9.2	10.3		
	Day 8						
TAK-536	AUC(0-24) (ng·hr/mL)	23	24	20565.1	22974.4	111.7	(90.0, 138.7)
	Cmax (ng/mL)	23	24	2502.1	3200.6	127.9	(99.4, 164.6)
	Cmin(abs) (ng/mL)	23	24	164.4	210.5	128.0	(88.9, 184.3)
	Tmax (hr)	23	24	4.5	4.9		
TAK-536 M-I	AUC(0-24) (ng·hr/mL)	23	24	304.1	309.6	101.8	(73.8, 140.4)
	Cmax (ng/mL)	23	24	51.5	48.1	93.4	(66.2, 131.8)
	Cmin (abs) (ng/mL)	22	24	2.9	2.6	87.1	(69.7, 108.7)
	Tmax (hr)	23	24	5.1	4.8		
TAK-536 M-II	AUC(0-24) (ng·hr/mL)	23	24	10929.9	13932.9	127.5	(100.4, 161.8)
	Cmax (ng/mL)	23	24	647.8	847.8	130.9	(104.4, 164.1)
	Cmin (abs) (ng/mL)	23	24	211.3	318.0	150.5	(103.2, 219.7)
	Tmax (hr)	23	24	7.8	6.5		

7 EXTRINSIC FACTORS

7.1 Study 01-06-TL- 491_013 (DDI- probe 'cocktail')

Report # 01-06-TL-491-013[20]	**Study Period** 06/20/06-06/30/06	
Title	An Open-Label, Multiple-Dose Study to Assess the Drug-Drug Interaction Between TAK-491 and Caffeine, Tolbutamide, Dextromethorphan, Midazolam, and Fexofenadine Administered Concomitantly to Healthy Adult Subjects	
Study Design		
Rationale: Based on the results of in vitro studies, AZ is metabolized mainly by CYP 2C9, and to smaller extent by other CYP isozymes. This study using a CYP and P-gp probe cocktail is expected to confirm/evaluate this in vivo.		
Multiple-Dose Randomized Single-Blind single-sequence Single-Center 2-Period Healthy subjects		
Screening: 21 days	**Washout:**2-3 days between period 1 and 2	
Period 1/2	1 day of cocktail, 5 days of AZM 80 mg QD, 1 day of AZM 80 mg + single dose of probe cocktail, inpatient stay ☑Y ☐ N	
Sequence	**A** Probe cocktail, single dose	**B** AZM 80 mg, QD, AZM 80 mg + single dose probe cocktail
Treatments: • Caffeine 200 mg, tolbutamide 500 mg, dextromethorphan 30 mg, midazolam 4 mg, and fexofenadine 60 mg) • AZM capsule (lot # Z556A029)		
▪ **Sampling Times** Days 1 and 8 – pre-dose, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, and 72 h post dose		

Analytical Method

Analyte	Caffeine	Tolbutamide	Dextromethorphan	Midazolam	Fexofenadine
Method	LC/MS/MS	LC/MS/MS	LC/MS/MS	LC/MS/MS	LC/MS/MS
Matrix	Plasma	Plasma	Plasma	Plasma	Plasma
Range (ng/mL)	0.25-25000	100-100000	0.05-50	0.1-100	0.5-500
Performance	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable

Statistical Method: ANOVA on log transformed parameters fitting for sequence, period, and treatment. LS mean and 90% CI for the difference were constructed.

Study Population :

[20] \\Cdsesub1\evsprod\NDA200796\\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5334-extrin-factor-pk-stud-rep\01-06-tl-491-013\csr-01-06-tl-491-013.pdf

Randomized/Completed/ Discontinued Due to AE	24/24/0
Age (SD)	31.1 (7.0)
Male/Female	10/14
Race (Caucasian/Black/Asian/Hispanic/American Indian)	20/2/1/0/3*[*]

Results

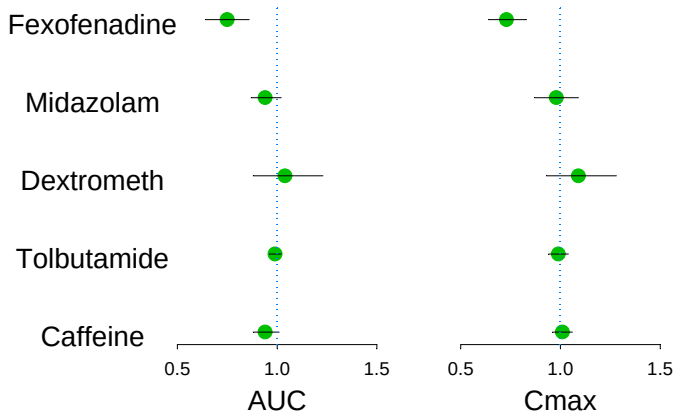


Figure 1 Effect of AZ on systemic exposure to components of the probe cocktail.

Safety

- Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA

Conclusion

AZ is not expected to significantly affect systemic exposure to other co-administered medication.

Comments

[*] Two subjects were multiracial as indicated in CRF

7.2 Study TAK-491_017 (DDI- Antacid (Mylanta))

Report # TAK-491_107[21]	**Study Period** 04/02/08-04/09/08	
Title	The effect of antacid on the pharmacokinetic profile of TAK-491	

Study Design

Rationale: AZM is practically insoluble in aqueous solutions at acidic to neutral pH (pH 1 to 7), slightly soluble at basic pH (9 to 11). Antacids may increase the solubility of AZM and thereby affect systemic exposure to AZ. Alternately, antacids can also chelate drugs and reduce systemic availability.

Single-Dose Randomized Open-Label Cross-Over Single-Center 2-Period Healthy subjects

Screening: 28 days	**Washout:**2 days between period 1 and 2

Period 1/2	AZM 80 mg, AZM 80 mg + Mylanta® maximum strength, inpatient stay ☑Y ☐ N	
Sequence	**A**	**B**
	AZM 80 mg AZM 80 mg + Mylanta® 30 mL followed by an additional 30 mL 1 h later	AZM 80 mg + Mylanta® 30 mL followed by an additional 30 mL 1 h later AZM 80 mg

Treatments:

- Mylanta® maximum strength (lot # PPF078))
- AZM tablets (lot # Z624D062)

▪ **Sampling Times**

Pre-dose, 0.08, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, and 72 h post dose

Analytical Method

Analyte	AZM	AZ	M-II
Method	LC/MS/MS	LC/MS/MS	LC/MS/MS
Matrix	Plasma	Plasma	Plasma
Range (ng/mL)	1-2500	10-5000	2-1000
Performance	Acceptable	Acceptable	Acceptable

Statistical Method: ANOVA on log transformed parameters fitting for sequence, period, and treatment. LS mean and 90% CI for the difference were constructed.

Study Population :

Randomized/Completed/ Discontinued Due to AE	24/24/0
Age (SD)	30.7 (9.6)
Male/Female	20/4
Race (Caucasian/Black/Asian/Hispanic/American Indian)	20/3/0/0/1

[21] \\Cdsesub1\evsprod\NDA200796\\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5334-extrin-factor-pk-stud-rep\tak-491-107\csr-tak-491-107.pdf

Results

- The geometric mean ratio (90%CIs) for AUC and C_{max} for AZ when AZM was given with Mylanta® was 82.5% (73.5-92.6) and 96.2% (83-111.3), respectively.
- The geometric mean ratio (90%CIs) for AUC and C_{max} for M-II when AZM was given with Mylanta® was 85.2% (76.7-94.8) and 85% (76.7-94.3), respectively.
- Peak AZ levels were attained earlier when AZM was administered along with an antacid (1.5 vs. 3).

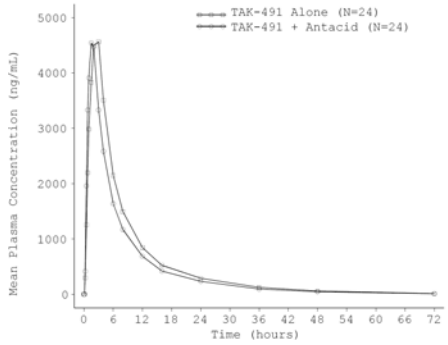


Figure 1 Plot of AZ versus time following administration of AZM alone or with Mylanta.

Safety

- Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA

Conclusion

Systemic exposure to AZ is not significantly affected by co-administration with antacids.

Comments

7.3 Study TAK 491_104 (DDI- Digoxin)

Report # TAK-491_104[22]	**Study Period** 01/05/08-03/08/08	
Title	A phase 1, multiple dose, open label, randomized, 3 period crossover study to evaluate the effect of TAK 536 formed from TAK 491 on the pharmacokinetics of digoxin in healthy subjects.	

Study Design

Rationale: Based on the results of in vitro studies, AZM is a P-gp inhibitor. Digoxin is a sensitive substrate with a narrow therapeutic index.

Multiple-Dose Randomized Open-Label Cross-Over Single-Center 3-Period Healthy subjects

Screening: 21 days	**Washout:**10 days between study periods
Period 1/2/3	AZM 80 mg QD, Digoxin 200 μg QD, AZM 80 mg QD + Digoxin 200 μg QD, inpatient stay ☑Y ☐ N

Treatments:

- Digoxin (Lanoxicaps, lot # 493512)
- AZM tablet (lot # Z624D062)

▪ **Sampling Times**

Day 10 – pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 16 h post dose. Trough samples were collected on day 1 and on days 7 through 9.

Analytical Method

Analyte	AZ	M-II	Digoxin
Method	LC/MS/MS	LC/MS/MS	LC/MS/MS
Matrix	Plasma	Plasma	Plasma
Range (ng/mL)	10-5000	2-1000	0.1-50
Performance	Acceptable	Acceptable	Acceptable

Statistical Method: ANOVA on log transformed parameters fitting for sequence, period, and treatment. LS mean and 90% CI for the difference were constructed.

Study Population :

Randomized/Completed/ Discontinued Due to AE	24/22/1
Age (SD)	31.8 (7.0)
Male/Female	17/7
Race (Caucasian/Black/Asian/Hispanic/American Indian)	16/6/2/0/1*

Results

[22] \\Cdsesub1\evsprod\NDA200796\\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5334-extrin-factor-pk-stud-rep\tak-491-104\csr-tak-491-104-amend-1.pdf

* One subject was multiracial as indicated in CRF

Table 1 Systemic exposure to digoxin is not affected by AZ (Ref. CSR 491_104, Table 11b)

Analyte/ Parameter (unit)	N	LS Means Treatment C (Test)	LS Means Treatment B (Reference)	% Ratio (C/B) (100*Test/ Reference)	90% CI for Ratio (%)
Digoxin					
AUC(0-tau) (ng·hr/mL)	23	16.989	16.514	102.87	(97.80, 108.21)
Cmax (ng/mL)	23	1.998	2.119	94.29	(85.35, 104.17)
Cmin(0) (ng/mL)	23	0.511	0.489	104.37	(98.78, 110.28)
Tmax (hr) (a)	22	1.00	1.00		

Table 2 Systemic exposure to AZ is not affected by digoxin (Ref. CSR 491_104, Table 11e)

Analyte/ Parameter (unit)	N	LS Means Treatment C (Test)	LS Means Treatment A (Reference)	% Ratio (C/A) (100*Test/ Reference)	90% CI for Ratio (%)
TAK-536					
AUC(0-tau) (ng·hr/mL)	23	44,683.0	45,395.0	98.43	(94.35, 102.69)
Cmax (ng/mL)	23	5613.2	5595.0	100.33	(92.03, 109.37)
Cmin(0) (ng/mL)	23	404.8	448.8	90.21	(82.88, 98.20)
Tmax (hr) (a)	22	2.00	2.00		
TAK-536 M-II					
AUC(0-tau) (ng·hr/mL)	23	25,396.0	26,507.8	95.81	(90.81, 101.07)
Cmax (ng/mL)	23	1630.4	1652.4	98.67	(94.02, 103.54)
Cmin(0) (ng/mL)	23	579.7	632.3	91.68	(85.23, 98.61)
Tmax (hr) (a)	22	4.00	4.00		

Safety

- Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA

Conclusion

AZ does not affect systemic exposure to digoxin.

Comments

7.4 Study 01-04-TL-536 (DDI- Ketoconazole/Fluconazole)

Report # 01-04-TL-536-005[23]	**Study Period** 09/14/04-09/26/04	
Title	The effect of multiple doses of fluconazole or ketoconazole on the single-dose pharmacokinetic profile of TAK 536 in healthy subjects.	

Study Design

Rationale: Based on the results of in vitro studies, AZ is metabolized mainly by CYP 2C9, and to smaller extent by other CYP isozymes. Fluconazole is a CYP 2C9 inhibitor. Ketoconazole is a CYP 3A4/5 inhibitor.

Multiple-Dose Randomized Open-Label Parallel Single-Center 2-Period Healthy subjects

Screening: 21 days	**Washout:**3 days between period 1 and 2

Period 1/2	AZ 40 mg, 5 days of fluconazole 200 mg QD/ ketoconazole 400 mg QD, 1 day of AZ 40 mg + fluconazole 200 mg / ketoconazole 400 mg, inpatient stay ☑Y ☐ N

Sequence	**A**	**B**
	AZ tablet, fluconazole 200 mg QD, AZ tablet + fluconazole 200 mg	AZ tablet, ketoconazole 400 mg QD, AZ tablet + ketoconazole 400 mg

Treatments:

- Fluconazole (lot # 44P011E)
- Ketoconazole (lot # 21069)
- AZ tablet (lot # Z556A023)

- **Sampling Times**

For AZ on days 1 and 10: Pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, and 72 h post dose

For fluconazole/ketoconazole: Pre-dose on days 7, 8, 9, and at pre-dose, 1, 2, 3, 4, 8, 12, 16, and 24 h post dose on day 10.

Analytical Method

Analyte	AZ	Ketoconazole	Fluconazole
Method	LC/MS/MS	LC/MS/MS	LC/MS/MS
Matrix	Plasma	Plasma	Plasma
Range (ng/mL)	2-1000	5-1000	10-5000
Performance	Acceptable	Acceptable	Acceptable

Statistical Method: ANOVA on log transformed parameters fitting for sequence, period, and treatment. LS mean and 90% CI for the difference were constructed.

[23] \\Cdsesub1\evsprod\NDA200796\\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5334-extrin-factor-pk-stud-rep\01-04-tl-536-005\csr-01-04-tl-536-005.pdf

Study Population :

Randomized/Completed/ Discontinued Due to AE	36/36/0
Age (SD)	30.1 (7.3)
Male/Female	26/10
Race (Caucasian/Black/Asian/Hispanic/American Indian)	29/6/0/0/1

Results

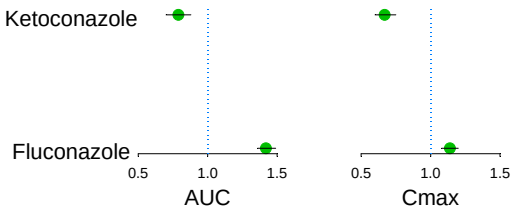


Figure 1 Effect of repeat administration of fluconazole or ketoconazole on AZ.

Safety

- Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA

Conclusion

- Clearance of AZ is reduced when co-administered with fluconazole, a CYP 2C9 inhibitor. This is evident from the ~ 40% increase in AUC, but only ~ 14% increase in C_{max}. However, this is not of clinical significance given the flat D-R relationship for AZ and the absence of serious adverse events.
- When co-administered with ketoconazole, Cmax of AZ decreased by ~ 30% and AUC by ~ 20%. However, the reason for this is not apparent.

Comments

Plasma M-II was not measured in this study. M-II is an inactive metabolite, and therefore is not critical to quantify.

7.5 Study 01-05-TL-536 (DDI- Warfarin)

Report # 01-05-TL-536-009[24]	**Study Period** 05/29/05-05/31/05	
Title	A randomized, single blind, placebo controlled assessment of the pharmacokinetics and pharmacodynamics of warfarin in the presence of multiple doses of TAK 536 in healthy male and female subjects	

Study Design

Rationale: Based on the results of in vitro studies, AZ is metabolized mainly by CYP 2C9, and to smaller extent by other CYP isozymes. Warfarin is CYP 2C9 substrate with a narrow therapeutic window.

Multiple-Dose Randomized Single-Blind single-sequence Single-Center 2-Period Healthy subjects

Screening: 28 days	**Washout:**-

Period 1/2	Warfarin QD for 7 days, Warfarin + AZ 40 mg QD, inpatient stay ☑Y ☐ N	
Sequence	**A**	**B**
	Warfarin[25] QD targeting an INR of 1.2 to 1.8	Stable warfarin dose QD + AZ tablet 40 mg QD

Treatments:

- Warfarin (Coumadin®, lot # ETA001B, ETA004A))
- AZ tablet (lot # Z556A029)
- Placebo (lot # Z5567044)

- **Sampling Times**

Day 7 and 14 – pre-dose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, and 24 h post dose
Trough samples were collected on all other days.

Analytical Method

Analyte	AZ	M-II	M-I	R-Warfarin	S-Warfarin
Method	LC/MS/MS	LC/MS/MS	LC/MS/MS	LC/MS/MS	LC/MS/MS
Matrix	Plasma	Plasma	Plasma	Plasma	Plasma
Range (ng/mL)	10-5000	2-1000	2-1000	5-1500	5-1500
Performance	Acceptable	Acceptable	Acceptable	Acceptable	Acceptable

Statistical Method: ANOVA on log transformed parameters fitting for sequence, period, and treatment. LS mean and 90% CI for the difference were constructed.

Study Population :

Randomized/Completed/ Discontinued Due to AE	36/33/0
Age (SD)	39 ()
Male/Female	21/15
Race (Caucasian/Black/Asian/Hispanic/American Indian)	27/9/0/0/0

[24] \\Cdsesub1\evsprod\NDA200796\\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5334-extrin-factor-pk-stud-rep\01-05-tl-536-009\csr-01-05-tl-536-009.pdf

[25] Warfarin loading dose was 6 mg for males and 5 mg for females.

Results

Table 1 Systemic exposure to warfarin is not affected by AZ (Ref: CSR 536_009, Table 11.a)

Analyte and Parameter	Warfarin + TAK-536 40 mg (T) N=17	Warfarin + TAK-536 Placebo (C) N=16	% Ratio (T/C)	90% CI of Ratio	P-value
R-warfarin					
AUC(0-24) (hr·ng/mL)	3485.72	3431.03	101.59	(97.85, 105.48)	0.480
Cmax (ng/mL/mg)	203.05	198.24	102.42	(96.99, 108.16)	0.461
Cmin (ng/mL/mg)	115.51	117.04	98.70	(93.69, 103.98)	0.673
Tmax (hr)	1.00	1.50	-	-	0.070
S-warfarin					
AUC(0-24) (hr·ng/mL)	2046.51	1972.47	103.75	(100.00, 107.64)	0.100
Cmax (ng/mL/mg)	144.51	135.31	106.80	(100.92, 113.01)	0.058
Cmin (ng/mL/mg)	60.27	60.95	98.87	(93.76, 104.27)	0.720
Tmax (hr)	0.50	0.75	-	-	0.030

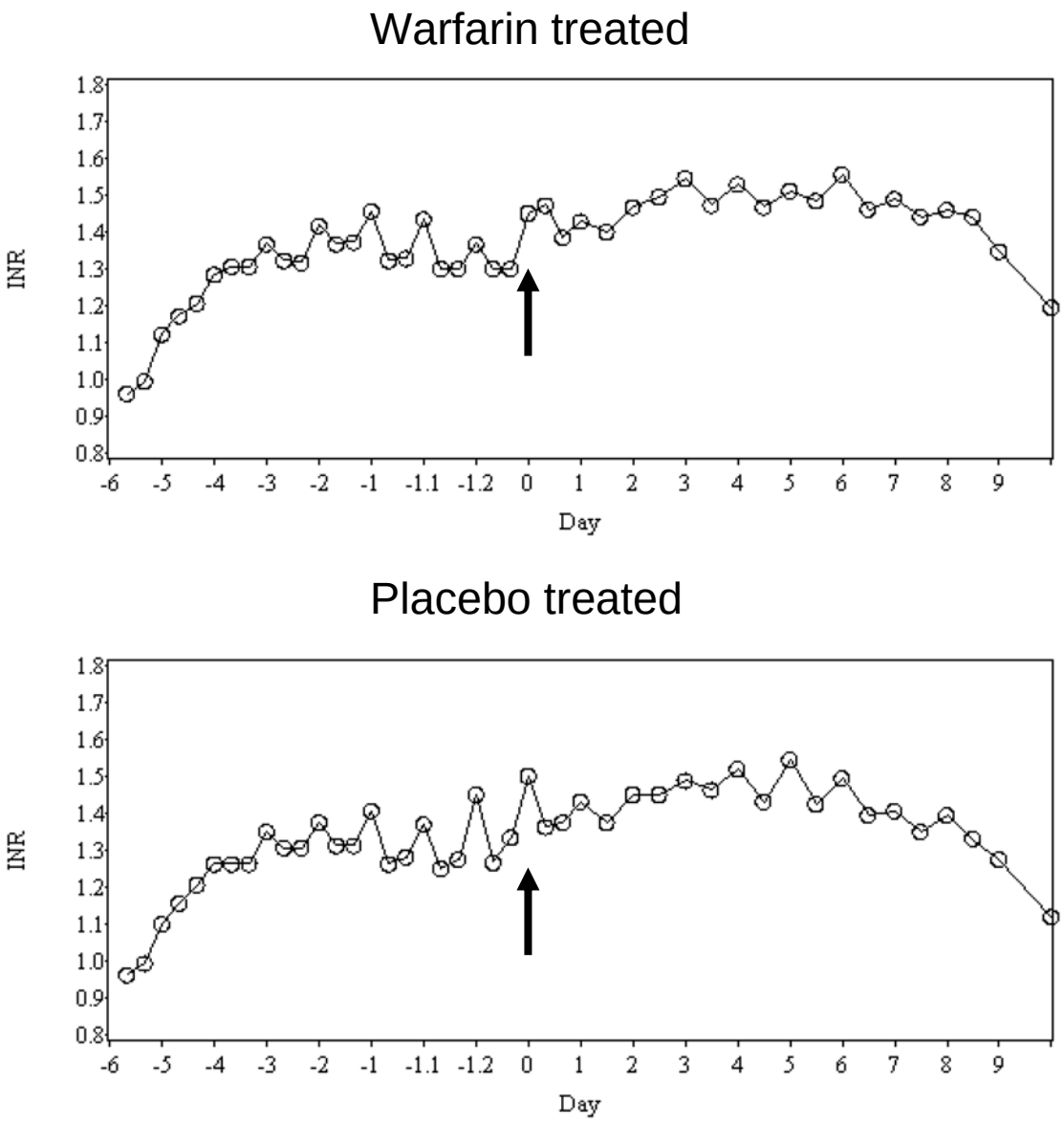


Figure 1 Mean daily INR values are not affected by AZ. The arrow indicates start of co-adminsitration of warfarin and AZ (Ref: CSR 01-05-TL-536-009).

Safety
▪ Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA
Conclusion
AZ dose not affect the pharmacokinetics and pharmacodynamics of warfarin and is not expected to significantly affect systemic exposure to other CYP 2C9 substartes.
Comments

7.6 Study 01-05-TL-536-010 (DDI- Glyburide)

Report # 01-05-TL-536-010	**Study Period** 01/20/06 to 01/31/06	**EDR Link**[26]

Title	A placebo controlled study of the effect of multiple doses of TAK 536 on the single dose pharmacokinetic profile of glyburide in healthy adult subjects.

Study Design

Rationale: Co-administered with AZM.

Multiple-Dose Randomized Open-Label Parallel Single-Center 1-Peiod Healthy subjects

Screening: 21 days	**Washout:**7 days between study periods

Period 1/2/3	AZ 40 mg QD + placebo, AZ 40 mg QD + glyburide 5 mg, inpatient stay ☑Y ☐ N

Treatments:

- Glyburide (lot # 3042625)
- AZ tablet (lot # Z556A031)

▪ **Sampling Times**

Day 10 – pre-dose, 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 36, and 48 h post dose. Pre-dose samples were collected on days 8 and 9.

Analytical Method

Analyte	AZ	Glyburide
Method	LC/MS/MS	LC/MS/MS
Matrix	Plasma	Plasma
Range (ng/mL)	10-5000	1-500
QC (ng/mL)	30, 500, 4000	3, 15, 150, 375
Performance	Acceptable	Acceptable

Statistical Method: ANOVA on log transformed parameters fitting for sequence, period, and treatment. LS mean and 90% CI for the difference were constructed.

Study Population :

Randomized/Completed/ Discontinued Due to AE	32/32/0
Age in years	41
Male/Female	21/11
Race (Caucasian/Black/Native Hawaiian or pacific islaner)	28/3/1

[26] \\Cdsesub1\evsprod\NDA200796\\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5334-extrin-factor-pk-stud-rep\01-05-tl-536-010\csr-01-05-tl-536-010.pdf

Results

Table 1 Systemic exposure to glyburide is not affected by AZ (Ref. CSR 01-05-TL-536-010)

Analyte & Parameter	N	LSMs (a) TAK-536 +Glyburide (T)	LSMs (a) Glyburide (R)	% Ratio (T/R)	90% CI of Ratio	P-value
AUC(0-tlqc) (ng·hr/mL)	23	663.4	662.2	100.2	(93.8, 107.0)	0.963
AUC(0-inf) (ng·hr/mL)	22	697.8	699.3	99.8	(93.9, 106.0)	0.952
Cmax (ng/mL)	23	109.6	114.9	95.3	(87.9, 103.4)	0.321
Tmax (hr)	23	2.0	2.5	-	-	0.215

(a) Means for AUC(0-tlqc), AUC(0-inf), and Cmax were obtained by taking the antilog of the least squares mean (LSM) from log-transformed values. For Tmax, medians are presented.

Safety

- Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA

Conclusion

Systemic exposure to glyburide is not affected by AZ.

Comments

The effect of a single dose of glyburide on the steady state PK of TAK 536 was not evaluated in this study.

7.7 Study 01-05-TL-491-004 (DDI- Chlorthalidone)

Report # 01-05-TL-491-004	**Study Period** 01/31/06 to 04/01/06	**EDR Link**[27]

Title	A phase 1 multiple dose open label randomized six sequence three period crossover study to assess the drug-drug interaction between TAK 491 and chlorthalidone.

Study Design

Rationale: Co-administered with AZM.

Multiple-Dose Randomized Open-Label Cross-Over Single-Center 1-Peiod Patients[28]

Screening: 21 days	**Washout:** Atleast 10 days between study periods.

Period 1/2/3	AZM 80 mg QD, Chlorthalidone 15 mg QD, Chlorthalidone 15 mg QD + AZM 80 mg QD, inpatient stay ☑Y ☐ N

Sequence	**A** AZM 80 mg QD	**B** Chlorthalidone 15 mg QD	**C** Chlorthalidone 15 mg QD + AZM 80 mg QD

Treatments:

- Chlorthalidone (lot # 21206)
- AZM capsule (lot # Z6244021)

- **Sampling Times**

Day 7 – pre-dose, 0.25, 0.5, 0.75,1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 h post dose. Pre-dose samples were collected on days 5 and 6.

Analytical Method

Analyte	AZ, M-I, M-II	Chlorthalidone
Method	LC/MS/MS	LC/MS/MS
Matrix	Plasma	Plasma
Range (ng/mL)	1-2500	2-1000
QC (ng/mL)	30, 150, 2000	5, 30, 125, 750
Performance	Acceptable	Acceptable

Statistical Method: ANOVA on log transformed parameters fitting for sequence, period, and treatment. LS mean and 90% CI for the difference were constructed.

Study Population :

Randomized/Completed/ Discontinued Due to AE	24/22/0
Age (Mean (SD)) in years	30.5 (9.5)
Male/Female	23/1
Race (Caucasian/Black/American indian or alsakan native)	20/3/1

[27] \\Cdsesub1\evsprod\NDA200796\\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5334-extrin-factor-pk-stud-rep\01-05-tl-491-004\csr-01-05-tl-491-004.pdf

[28] Subjects with mild hypertension

Results

Table 1 Systemic exposure to AZ is not affected by chlorthalidone (Ref. CSR 01-05-TL-491-004)

Analyte Parameter (unit)	N	TAK-491 + Chlorthalidone (T)	TAK-491 (R)	LSM % Ratio (T/R)	90% CI of Ratio	P-value (c)
TAK-536						
AUC(0-24) (ng·hr/mL)	21	25546.3	23814.9	107.3	(97.3, 118.2)	0.227
Cmax (ng/mL)	22	3426.7	3219.8	106.4	(94.0, 120.5)	0.396
Cmin (ng/mL)	22	224.2	183.1	122.4	(111.9, 133.9)	<0.001
Tmax (hr) (a)	22	4.0	4.0			0.766
TAK-536 M-I						
AUC(0-24) (ng·hr/mL)	21	203.7	183.3	111.1	(88.1, 140.2)	0.442
Cmax (ng/mL)	22	25.6	22.5	114.0	(84.6, 153.6)	0.458
Cmin (ng/mL) (b)	22	1.4	0.3	437.2	(134.8, 418.1)	0.043
Tmax (hr) (a)	22	6.0	4.0			0.448
TAK-536 M-II						
AUC(0-24) (ng·hr/mL)	21	13133.6	11353.0	115.7	(106.3, 125.9)	0.008
Cmax (ng/mL)	22	791.7	703.2	112.6	(103.1, 123.0)	0.032
Cmin (ng/mL)	22	287.2	220.6	130.2	(118.1, 143.5)	<0.001
Tmax (hr) (a)	22	8.0	8.0			0.236

Table 2 Systemic exposure to chlorthalidone is not affected by AZ (Ref. CSR 01-05-TL-491-004)

Chlorthalidone Parameter (unit)	N	TAK-491+ Chlorthalidone (T)	Chlor-thalidone (R)	LSM % Ratio (T/R)	90% CI of Ratio	P-value (b)
AUC(0-24) (ng·hr/mL)	23	2358.5	2127.7	110.6	(107.8, 114.0)	<0.001
Cmax (ng/mL)	23	192.2	183.2	104.9	(100.2, 109.8)	0.088
Cmin (ng/mL)	23	67.3	58.6	114.8	(110.7, 119.1)	<0.001
Tmax (hr) (a)	23	2.0	1.5			0.093

T=Test, R=Reference.
(a) Median values are presented for Tmax.
(b) P-value for AUC(0-24), Cmax, and Cmin was based on an ANOVA model with fixed effects for sequence, period, treatment, and random effect for subject nested with sequence. Analysis of Tmax was performed using Wilcoxon's signed rank test.

Comments: Blood pressure reduction was not measured in this study. A dose dependant increase in serum creatinine was observed in the efficacy study (01-05-TL-491-009). Please refer to the clinical review for details.

Safety

- Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA

Conclusion

Chlorthalidone does not affect systemic exposure to AZ, and systemic exposure to chlorthalidone is not affected by AZ.

Comments

7.8 Study TAK 491-110 (DDI- Amlodipine)

Report # TAK491_110	**Study Period** 10/21/08 to 01/22/09	**EDR Link**[29]

Title	A phase 1 multiple dose open label randomized three period crossover study to assess the drug-drug interaction between TAK 491 and amlodipine in healthy subjects.

Study Design

Rationale: Co-administered with AZM.

Multiple-Dose Randomized Open-Label Cross-Over Single-Center 3-Period Healthy subjects

Screening: 21 days	**Washout:** Atleast 10 days between study periods.

Period 1/2/3	AZM 80 mg QD, Amlodipine 10 mg QD, AZM 80 mg QD + Amlodipine 10 mg QD, inpatient stay ☑Y ☐ N		
Sequence	**A** AZM 80 mg QD	**B** Amlodipine 10 mg QD	**C** AZM 80 mg QD + Amlodipine 10 mg QD

Treatments:

- Amlodipine (Istin ®, lot # 0505024A1)
- AZM tablet (lot # Z624D121)

- **Sampling Times**

Day 12 – pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 12, 16, and 24 h post dose. Pre-dose samples were collected on days 5 and 6.

Analytical Method

Analyte	AZ	M-II	Amlodipine
Method	LC/MS/MS	LC/MS/MS	LC/MS/MS
Matrix	Plasma	Plasma	Plasma
Range (ng/mL)	10-5000	2-1000	0.1-50
QC (ng/mL)	30, 500, 4000	6, 70, 800	0.25, 0.65, 2.25, 7.75, 38.0
Performance	Acceptable	Acceptable	Acceptable

Statistical Method: ANOVA on log transformed parameters fitting for sequence, period, and treatment. LS mean and 90% CI for the difference were constructed.

Study Population :

Randomized/Completed/ Discontinued Due to AE	24/24/0
Age (Mean (SD)) in years	29.1 (7.6)
Male/Female	22/2
Race (Caucasian/Black/American indian or alsakan native)	24/0/0

[29] \\Cdsesub1\evsprod\NDA200796\\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5334-extrin-factor-pk-stud-rep\tak-491-110\csr-tak-491-110.pdf

Results

Table 1 Pharmacokinetic measures and statistical analysis for AZ and amlodipine on day 12 (Ref. CSR TAK 491_110)

Analyte and Parameter	N	Geometric mean: TAK-491 + amlodipine (C)	Geometric mean: TAK-491 (A)	% Ratio (C/A)	90% CI of Ratio
TAK-536					
AUC(0-tau) (ng·hr/mL)	23	40676.6	39801.6	102.2	(98.4, 106.2)
Cmax (ng/mL)	23	5005.4	5305.4	94.4	(88.4, 100.8)
Cmin(0) (ng/mL)	23	322.9	334.4	96.6	(91.5, 101.9)
Tmax (hr) (a)	23	2.0	2.0	-	-
TAK-536 M-II					
AUC(0-tau) (ng·hr/mL)	23	24928.6	25512.4	97.7	(94.5, 101.1)
Cmax (ng/mL)	23	1498.9	1531.0	97.9	(93.4, 102.6)
Cmin(0) (ng/mL)	23	528.9	551.3	95.9	(91.8, 100.3)
Tmax (hr) (a)	23	4.0	4.0	-	-

Statistical Analysis of Plasma Pharmacokinetic Parameters of Amlodipine on Day 12

Amlodipine Parameter	N	Geometric mean: TAK-491+ Amlodipine (C)	Geometric mean: Amlodipine (B)	% Ratio (C/B)	90% CI of Ratio
AUC(0-tau) (ng·hr/mL)	23	374.6	379.1	98.8	(96.6, 101.0)
Cmax (ng/mL)	23	18.9	18.9	100.0	(97.0, 103.0)
Cmin(0) (ng/mL)	23	12.6	12.4	102.3	(98.4, 106.5)
Tmax (hr) (a)	23	8.0	8.0	-	-

A=TAK-491 80 mg QD on Days 1 through 12; B=amlodipine 10 mg QD on Days 1 through 12;
C=TAK-491 80 mg QD + amlodipine 10 mg QD on Days 1 through 12.
(a) Median values are presented for Tmax.

Comment: Blood pressure was not measured in this study.

Safety

- Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA

Conclusion

Amlodipine does not affect systemic exposure to AZ, and systemic exposure to amlodipine is not affected by AZ.

Comments

7.9 Study 01-05-TL-536-011 (DDI- Metformin)

Report # 01-05-TL-536-011	**Study Period** 02/17/06 to 03/24/06	**EDR Link**[30]

Title	An open label randomized multiple dose three period crossover study to evaluate the pharmacokinetic drug-drug interaction between TAK 536 and metformin in healthy adult subjects.

Study Design

Rationale: Co-administered with AZM.

Multiple-Dose Randomized Open-Label Cross-Over Single-Center 3-Period Healthy subjects

Screening: 21 days	**Washout:**7 days between study periods

Period 1/2/3	AZ 40 mg QD, metformin 500 mg bid, AZ 40 mg QD + metformin 500 mg bid, inpatient stay ☑Y ☐ N		
Sequence	**A** AZ 40 mg QD	**B** metformin 500 mg bid	**C** AZ 40 mg QD + metformin 500 mg bid

Treatments:

- Metformin (Glucophage®, lot # 5L02154)
- AZ tablet (lot # Z556A031)

- **Sampling Times**

Day 7 – pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 h post dose. Pre-dose samples were collected on days 1, 5 and 6.

Analytical Method

Analyte	AZ	M-II	Metformin
Method	LC/MS/MS	LC/MS/MS	LC/MS/MS
Matrix	Plasma	Plasma	Plasma
Range (ng/mL)	10-5000	2-1000	2-2000
QC (ng/mL)	30, 500, 4000	6, 70, 800	5, 25, 160, 1600
Performance	Acceptable	Acceptable	Acceptable

Statistical Method: ANOVA on log transformed parameters fitting for sequence, period, and treatment. LS mean and 90% CI for the difference were constructed.

Study Population :

Randomized/Completed/ Discontinued Due to AE	24/24/0
Age (SD)	39.3 (10.1))
Male/Female	11/13
Race (Caucasian/Black/Asian/Hispanic/American Indian)	21/3/0/0/0

[30] \\Cdsesub1\evsprod\NDA200796\\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5334-extrin-factor-pk-stud-rep\01-05-tl-536-011\csr-01-05-tl-536-011.pdf

Results

Table 1 Systemic exposure to metformin is not affected by AZ (Ref. CSR 01-05-TL-536-0011)

	TAK-536 40 mg QD + Metformin 500 mg BID (Test) N=24		Metformin 500 mg BID Alone (Reference) N=24		LS Mean Ratio (%) (Test/ Reference)	90% CI (a) for Ratio
	Mean (%CV)	LS Mean	Mean (%CV)	LS Mean		
Metformin						
AUC(0-12) (ng·hr/mL)	5873.6 (33)	5590.8	7226.0 (27)	6969.3	80.22	(73.76, 87.25)
Cmax (ng/mL)	1071.92 (29)	1028.55	1308.33 (28)	1258.94	81.70	(74.07, 90.11)
Ctrough (ng/mL)	208.91 (40)	191.98	226.79 (33)	214.26	89.60	(79.09, 101.51)
Tmax (hr) (b)	1.50 (0.50, 4.00)		1.50 (0.50, 4.00)		n/a	n/a

Table 2 Systemic exposure to AZ is not affected by metformin (Ref. CSR 01-05-TL-536-0011)

		TAK-536 40 mg QD + Metformin 500 mg BID (Test)		TAK-536 40 mg QD Alone (Reference)		LS Mean Ratio (%) (Test/ Reference)	90% CI (a) for Ratio
	N	Mean (%CV)	LS Mean	Mean (%CV)	LS Mean		
TAK-536							
AUC(0-24) (ng·hr/mL)	24	37081.1 (24)	36046.2	34963.0 (22)	34149.1	105.56	(100.94, 110.39)
Cmax (ng/mL)	24	5724.58 (23)	5579.45	5886.25 (22)	5755.18	96.95	(90.92, 103.37)
Ctrough (ng/mL)	24	310.42 (45)	284.18	281.63 (41)	260.34	109.15	(101.71, 117.15)
Tmax (hr) (b)	24	2.00 (1.00, 6.00)		1.50 (1.00, 4.00)		n/a	n/a
M-I							
AUC(0-24) (ng·hr/mL)	(c)	10.9879 (61)	4.9136	6.1642 (55)	7.2027	68.22	(33.42, 139.26)
Cmax (ng/mL)	11	3.121 (32)	3.271	2.897 (38)	2.910	112.42	(87.87, 143.83)
Ctrough (ng/mL)	12	0	n/a	0	n/a	n/a	n/a
Tmax (hr) (b)	(d)	3.00 (1.00, 6.00)		3.00 (1.50, 8.00)		n/a	n/a
M-II							
AUC(0-24) (ng·hr/mL)	24	22783.1 (24)	22126.3	19886.2 (25)	19283.0	114.74	(107.24, 122.77)
Cmax (ng/mL)	24	1587.5 (20)	1557.0	1465.1 (24)	1424.2	109.32	(102.68, 116.40)
Ctrough (ng/mL)	24	480.8 (33)	454.9	403.8 (28)	386.2	117.80	(110.13, 126.01)
Tmax (hr) (b)	24	4.0 (2.50, 8.00)		4.0 (2.50, 8.00)		n/a	n/a

Safety

- Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA

Conclusion

Metformin does not affect systemic exposure to AZ

Systemic exposure to metformin was reduced by about 20%. However, no dose adjustments are required for metformin when dosed along with AZ. Given that a 60% increase (Metformin label) in exposure to metformin does not necessitate a dose adjustment, a 20% decrease may not be clinically meaningful either.

Comments

7.10 Study 01-05-TL-536-006 (DDI- Pioglitazone)

Report # 01-05-TL-536-006	**Study Period** 01/18/05 to 02/23/05	**EDR Link**[31]

Title	Open label randomized multiple dose crossover study to assess drug-drug interaction between TAK 536 and pioglitazone.

Study Design

Rationale: Co-administered with AZM.

Multiple-Dose Randomized Open-Label Cross-Over Single-Center 3-Period Healthy subjects

Screening: 21 days	**Washout:**7 days between study periods

Period 1/2/3	AZ 40 mg QD, pioglitazone 45 mg QD, AZ 40 mg QD + pioglitazone 45 mg QD, inpatient stay ☑Y ☐ N

Sequence	**A** AZ 40 mg QD	**B** pioglitazone 45 mg QD	**C** AZ 40 mg QD + pioglitazone 45 mg QD

Treatments:

- Pioglitazone (lot # C10322)
- AZ tablet (lot # Z556A025)

- **Sampling Times**

Day 7 – pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 h post dose. Pre-dose samples were collected on days 1, 5 and 6.

Analytical Method

Analyte	AZ	Pioglitazone
Method	LC/MS/MS	LC/MS/MS
Matrix	Plasma	Plasma
Range (ng/mL)	10-5000	25-2500
QC (ng/mL)	30, 500, 4000	74.9, 1000, 2000
Performance	Acceptable	Acceptable

Statistical Method: ANOVA on log transformed parameters fitting for sequence, period, and treatment. LS mean and 90% CI for the difference were constructed.

Study Population :

Randomized/Completed/ Discontinued Due to AE	24/24/0
Age (SD)	39.3 (10.1))
Male/Female	11/13
Race (Caucasian/Black/Asian/Hispanic/American Indian)	21/3/0/0/0

[31] \\Cdsesub1\evsprod\NDA200796\\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5334-extrin-factor-pk-stud-rep\01-04-tl-536-006\csr-01-04-tl-536-006.pdf

Results

Table 1 Systemic exposure to AZ is not affected by pioglitazone (Ref. CSR 01-05-TL-536-006)

Parameter	N	Means (a)		Ratio (T/R)	90% CI of Ratio (T/R)	Treatment Difference P-value
		TAK-536 (R)	TAK-536 + Pioglitazone (T)			
AUC(0-24)(ng·hr/mL)	30	32618.4	33052.9	101.33	(97.80, 104.99)	0.530
Cmax (ng/mL)	30	5013.71	5045.27	100.63	(94.75, 106.87)	0.860
Cmin (ng/mL)	30	277.14	280.46	101.20	(94.79, 108.05)	0.759
λz (1/hr)	30	0.0605	0.0588	--	--	0.192
Tmax (hr)	30	1.500	1.750	--	--	0.542

T=Test; R=Reference.
(a) For AUC, Cmax, and Cmin, geometric means are presented, for λz, arithmetic means, and for Tmax, medians.

Table 2 Systemic exposure to pioglitazone is not affected by AZ (Ref. CSR 01-05-TL-536-006)

Parameter	N	Means (a)		Ratio (T/R)	90% CI of Ratio (T/R)	Treatment Difference P-value
		Pioglitazone (R)	TAK-536 Pioglitazone (T)			
AUC(0-24)(ng·hr/mL)	30	9900.6	10630.0	107.37	(99.42, 115.94)	0.127
Cmax (ng/mL)	30	1203.26	1375.87	114.35	(100.31, 130.34)	0.093
Cmin (ng/mL)	30	108.26	108.99	100.67	(89.46, 113.28)	0.924
Tmax (hr)	30	1.500	1.500	--	--	0.749
λz (1/hr)	28	0.0575	0.0611	--	--	0.354

T = Test; R = Reference
(a) For AUC, Cmax, and Cmin, geometric means are presented for λz, arithmetic means, and for Tmax, medians.

Safety

- Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA

Conclusion

Pioglitazone does not affect systemic exposure to AZ, and systemic exposure to pioglitazone is not affected by AZ.

Comments

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DIVYA MENON ANDERSEN
01/26/2011

RAJANIKANTH MADABUSHI
01/26/2011
concur

ADDENDUM to ONDQA BIOPHARMACEUTICS REVIEW

NDA#:	200-796/N-000
Submission Date:	04/22/10, 10/15/10, 12/13/10, and 01/06/11
Brand Name:	Pending
Generic Name:	Azilsartan Medoxomil
Formulation:	Immediate release (IR) tablet
Strength:	20, 40, and 80 mg
Sponsor:	Takeda Global Research & Development Center, Inc. (TGRD)
Type of submission:	Original
Reviewer:	Tien-Mien Chen, Ph.D.

SUMMARY

On 04/22/10, TGRD submitted NDA 200-796 (N-000) for TAK-491 (azilsartan medoxomil). All three IR tablet strengths submitted, 20, 40, and 80 mg, are (b) (4) and they all had been tested clinically. However, for this NDA, the sponsor was only seeking approval for the 40 and 80 mg IR tablet strengths. Therefore, the Biopharmaceutics team only completed the review of the dissolution information on the 40 and 80 mg tablet strengths on 12/20/10.

The proposed dissolution methodology and the newly tightened dissolution specifications submitted (in an amendment dated 01/06/11, i.e., (b) (4) as agreed upon with the Agency) are acceptable as shown below.

Apparatus:	**2 (Paddle) x 50 rpm**
Medium:	(b) (4) **USP Phosphate Buffer (pH 7.8) 900 mL at 37ºC**
Sampling time:	**10, 15, 20, 30, and 45 min**
Specifications:	**Q=** (b) (4)

During the review process, although the sponsor did not propose a 20 mg strength for approval, the medical division felt that the sponsor should make the 20 mg tablet strength available for patients who may need a lower starting dose. The dissolution data for the 20 mg strength are therefore reviewed in this addendum.

The results show that the 20 mg IR tablet strength has similar dissolution characteristics as those for the 40 and 80 mg, therefore, the above dissolution methodology and specifications are applicable to the 20 mg IR tablet strength as well.

RECOMMENDATION

From the Biopharmaceutics perspective, the proposed dissolution methodology is acceptable and the newly tightened specifications (Q= (b) (4)) are applicable to all the three IR tablet strengths 20, 40, and 80 mg. Therefore, no further action is required at this time.

BACKGROUND

On 04/22/10, TGRD submitted NDA 200-796 (N-000) for TAK-491 (azilsartan medoxomil). All three tablet strengths, 20, 40 and 80 mg, (b) (4) (b) (4), and they all had been tested clinically. However, for this NDA, the sponsor only proposed 40 and 80 mg IR tablet strengths seeking approval for the once-daily treatment of hypertension, either alone or in combination with other antihypertensive agents.

The composition/formulation, the dissolution development report, the proposed dissolution methodology and specifications, and the dissolution data for all three IR tablet strengths, 20, 40, and 80 mg, were submitted in the original NDA. Upon Agency's request, comparative dissolution data/profiles between the clinically tested (not-Debossed) and the to-be-marketed (Debossed) formulations were further submitted on 12/13/10 for all three strengths. However, the Biopharmaceutics team only reviewed the dissolution data pertaining to the 40 and 80 mg strengths. Please see original NDA submission and 12/20/10 Biopharmaceutics review for details.

During the review process, although the sponsor did not propose a 20 mg strength for approval, the medical division felt that the sponsor should make the 20 mg strength available for patients who may need a lower starting dose. The dissolution data for the 20 mg strength are therefore reviewed in this addendum.

FORMULATION COMPASIONS

All three IR tablet strengths, 20, 40, and 80 mg, (b) (4) - (b) (4)

Table 1. Composition and Formulation of Azilsartan Medoxomil (TAK-491) IR Tablets

Component	Reference to Quality Standards	Function	Quantity per Tablet (mg)		
			20 mg tablets	40 mg tablets	80 mg tablets
TAK-491 [1] (As the free acid)	In-house standard	Active ingredient	(b) (4)	42.68[1] (40)	85.36 [1] (80)
Mannitol	Ph.Eur., USP	(b) (4)			
Fumaric Acid	NF				
Sodium Hydroxide	Ph.Eur., NF				
Hydroxypropyl cellulose	Ph.Eur., NF				
Croscarmellose sodium	Ph.Eur., NF				
Microcrystalline cellulose (b) (4)	Ph.Eur., NF				
Magnesium stearate	Ph.Eur., NF				
(b) (4)	Ph.Eur., USP				
Tablet weight			(b) (4)	180	360
(b) (4)					

DISSOLUTION METHODOLOGY AND SPECIFICATIONS

The proposed dissolution methodology as shown below was reviewed previously and found acceptable.

Apparatus: **2 (Paddle) x 50 rpm**
Medium: (b) (4) **USP Phosphate Buffer (pH 7.8) 900 mL at 37ºC**
Sampling time: **10, 15, 20, 30, and 45 min**

For the proposed dissolution specifications, the sponsor agreed with the Agency's recommendation to tighten the specifications and submitted a revision to an amendment on 01/06/11 as follows. Please see Appendix 1 for details.

Change Specifications: From Q= (b) (4)
To Q= (b) (4)

In this addendum, only the dissolution data/profile for the 20 mg are reviewed here. The mean dissolution data and profile for the 20 mg tablet strength are shown below.

Table 2. Mean (SD) Dissolution Data (in %) and Profile for TAK-491 (Azilsartan Medoxomil) IR 20 mg Tablet (N=12 Tablets/Batch)

Strengths\Time Point (Not debossed)	10 min	15 min	20 min	30 min	45 min
20 mg (Registration stability batch, No. Z624906; 504,000 tablets)	(b) (4)				

Figure 1. Mean Dissolution Profile of TAK-491 (Azilsartan Medoxomil) IR 20 mg Tablet (N=12 Tablets/Batch)

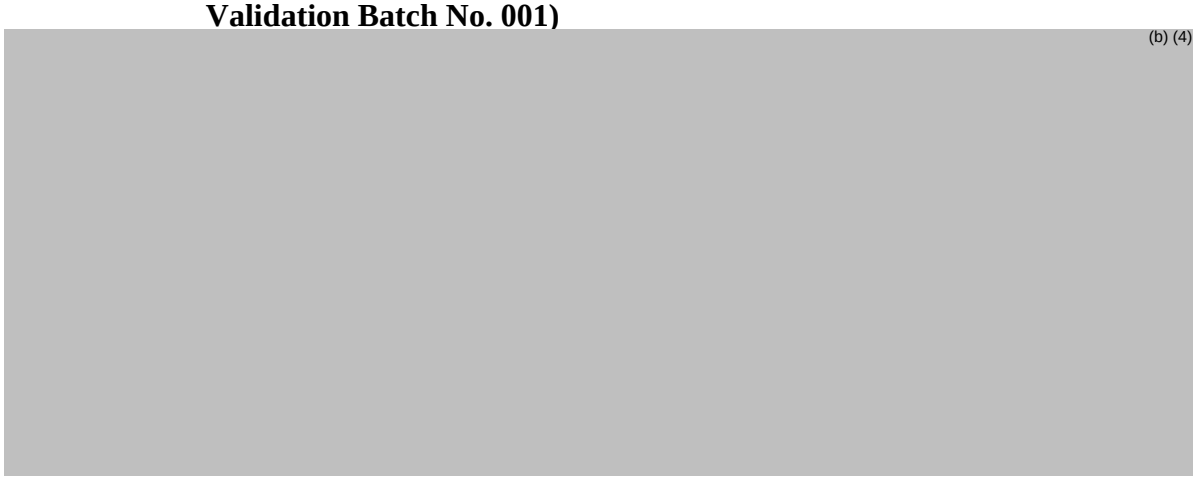
(b) (4)

For the 20 mg tablet strength, the batch used and the comparative dissolution data/profiles between the clinically tested (not-Debossed) and the to-be-marketed (Debossed) formulations were shown below which demonstrated similar dissolution profiles.

Table 3. The Batch for 20 mg Tablet Strength Used in the Comparative Dissolution Study (Not-Debossed vs. Debossed)

Strength	Phase 3 / Registration Stability Batches (Not Debossed)	Commercial / Process Validation Batches (Debossed)
20 mg	Z624906	001

Figure 2. Comparative Dissolution Profiles for TAK-491 IR Tablet 40 mg: Not Debossed (Batch Z624906) vs. Debossed (Commercial/Process Validation Batch No. 001)



Note: For the individual dissolution data of the 20 mg table batch (No. Z624906), please see 12/20/10 original Biopharmaceutics review for details.

Reviewer's Comment:
The 20 mg tablet strength shows similar dissolution characteristics as those for the 40 and 80 mg. Therefore, the proposed dissolution methodology and the newly tightened dissolution specifications, i.e., Q=(b) (4), are acceptable and applicable to the 20 mg strength as well.

_____ 01/14/11

Tien-Mien Chen, Ph.D. Date
Reviewer
ONDQA Biopharmaceutics

_____ 01/14/11

Patrick Marroum, Ph.D. Date
ONDQA Biopharmaceutics

CC: NDA
Patrick Marroum, Angelica Dorantes, Tien-Mien Chen

NDA 200-796 for Azilsartan Medoxomil (TAK-491) IR Tablets, 20, 40 and 80 mg

Appendix 1

01/06/11 Amendment to Module 3.2.P.5.1 In Agreement With The Agency to Tighten The Dissolution Specifications for 20, 40, and 80 mg Tablet Strengths

The newly tightened dissolution specifications for Azilsartan Medoxomil IR tablets 20 mg, 40 mg, and 80 mg are listed in Table 1, Table 2 and Table 3, respectively.

Table 1 Specifications of TAK-491 Tablets (20 mg)

Test	Analytical procedure	Acceptance criteria
Appearance	TAK-491-10606	(b) (4)
Identification		(b) (4)
A. Ultraviolet Spectrum	TAK-491-10607	
B. Liquid Chromatography	TAK-491-10608	
Related Substances	TAK-491-10609 (primary) or TAK-491-10610 (alternative)	
(b) (4)		
Others (individual)		
Total (unspecified)		
Total		
Content Uniformity	TAK-491-10611 (primary) or TAK-491-10612 (alternative)	
Dissolution	TAK-491-10613	
Assay	TAK-491-10615 (primary) or TAK-491-10616 (alternative)	
Microbiological Examination[1]	TAK-491-13324	
Total aerobic microbial count		
Total combined yeasts and molds count		
Escherichia coli		
(b) (4)		

Table 2 Specifications of TAK-491 Tablets (40 mg)

Test	Analytical procedure	Acceptance criteria
Appearance	TAK-491-10606	White to nearly white round tablets with "ASL" debossed on one side and "40" debossed on the other side
Identification		(b) (4)
A. Ultraviolet Spectrum	TAK-491-10607	
B. Liquid Chromatography	TAK-491-10608	
Related Substances	TAK-491-10609 (primary) or TAK-491-10610 (alternative)	
(b) (4)		
Others (individual)		
Total (unspecified)		
Total		
Content Uniformity	TAK-491-10611 (primary) or TAK-491-10612 (alternative)	
Dissolution	TAK-491-10613	
Assay	TAK-491-10615 (primary) or TAK-491-10616 (alternative)	
Microbiological Examination[1]	TAK-491-13324	
Total aerobic microbial count		
Total combined yeasts and molds count		
Escherichia coli		
(b) (4)		

Table 3 Specifications of TAK-491 Tablets (80 mg)

Test	Analytical procedure	Acceptance criteria
Appearance	TAK-491-10606	White to nearly white round tablets with "ASL" debossed on one side and "80" debossed on the other side
Identification		(b) (4)
A. Ultraviolet Spectrum	TAK-491-10607	
B. Liquid Chromatography	TAK-491-10608	
Related Substances	TAK-491-10609 (primary) or TAK-491-10610 (alternative)	
(b) (4)		
Others (individual)		
Total (unspecified)		
Total		
Content Uniformity	TAK-491-10611 (primary) or TAK-491-10612 (alternative)	
Dissolution	TAK-491-10613	
Assay	TAK-491-10615 (primary) or TAK-491-10616 (alternative)	
Microbiological Examination[1]	TAK-491-13324	
Total aerobic microbial count		
Total combined yeasts and molds count		
Escherichia coli		
(b) (4)		

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

TIEN MIEN CHEN
01/14/2011

PATRICK J MARROUM
01/18/2011

CLINICAL PHARMACOLOGY REVIEW

NDA Number:	200796
Submission Type; Code:	N_000, original
Applicant Name:	Takeda Global Research Development
Submission Dates:	04/28/2010
Brand Name:	Edarbi
Generic Name	Azilsartan medoxomil
Dosage Form:	Tablet
Dosage Strengths:	40, 80 mg
Proposed Indication:	Hypertension
OCP Division:	DCP 1
Primary Reviewer:	Divya Menon-Andersen, PhD
Team Leader:	Rajanikanth Madabushi, PhD

TABLE OF CONTENTS

1 Executive Summary 3
1.1 Recommendations 3
1.2 Phase 4 Commitments 3
1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings 4
2 Question Based Review 6
2.1 General Attributes of the Drug 6
2.2 General Clinical Pharmacology 7
2.3 Intrinsic Factors 15
2.4 Extrinsic Factors 17
2.5 General Biopharmaceutics 20
2.6 Analytical Section 22
3 Detailed Labeling Recommendations 24

1 EXECUTIVE SUMMARY

In this NDA, Takeda Global Research and Development is seeking approval of azilsartan medoxomil **(AZM)** tablets 40 and 80 mg, for use in treatment of hypertension. Azilsartan medoxomil is the pro-drug of azilsartan **(AZ)**, an angiotensin II receptor (type 1) blocker that is formed via hydrolysis of AZM during absorption.

The primary purpose of this review is to evaluate available pharmacokinetic, pharmacodynamic, and dose ranging studies conducted with AZ and AZM to provide a context in which to evaluate the findings of the efficacy and safety studies.

In support of the hypertension indication, the sponsor conducted 47 clinical pharmacology studies, two Phase 2 dose-ranging studies, five placebo/active controlled efficacy and safety studies, and three long-term safety studies. The final to-be marketed formulation of AZM tablet was used in all Phase 3 studies, while AZM capsules or AZ tablet was used in the Phase 1 / 2 studies.

At all the doses studied, AZM showed a statistically significant lowering of systolic blood pressure compared to placebo.

1.1 Recommendations

The Office of Clinical Pharmacology has reviewed clinical pharmacology and biopharmaceutics information submitted under NDA 200-796, and recommends approval.

The dose response relationship of AZM is flat over the range of 10 – 80 mg, with no consistent benefit of AZM 80 mg over AZM 40 mg in the Phase 3 trials. Hence, we recommend approval of AZM 40 mg as the highest strength.

1.2 Phase 4 Commitments

None.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

The key findings are listed below.

- Pharmacokinetics

  The pharmacokinetics of AZ following administration of single and repeat doses of AZM tablet are dose proportional in the range of 20 to 320 mg. The absolute bioavailability of AZ following administration of AZM tablet is 58%. Peak AZ concentrations are attained within 3 h post dose. AZ is metabolized, mainly by CYP 2C9, to form inactive metabolites. It does not inhibit or induce CYPs. AZ is > 99% bound to plasma albumin. Protein binding is concentration independent. AZM is an inhibitor of the efflux transporter, p-glycoprotein. It is eliminated mainly in urine (~ 72% of absorbed dose) as inactive metabolites. The mean half-life of AZ is about 12 h.

- Specific populations

  Age, sex, race

  Following repeat administration, C_{max} and AUC were 15% and 25% higher, respectively, in the elderly as compared to < 65y/o; C_{max} and AUC were 16% and 7% higher, respectively, in the females compared to males; C_{max} and AUC were 28% and 22% higher, respectively, in whites as compared to blacks. Dose adjustments based on age, sex or race are not necessary.

  Renal impairment

  In a single dose study, a 200% increase in C_{max} and AUC was observed in subjects with severe renal impairment as compared to subjects with normal renal function. However, given the shallow nature of the D-R relationship for AZ and the absence of any significant tolerability issues and adverse reactions, this is not of clinical significance. A smaller increase of ~ 25% in total exposure to AZ was observed in subjects with mild or moderate renal impairment as compared to subjects with normal renal function. Dose adjustments are not required in this population.

  Hemodialysis does not remove AZ from systemic circulation.

  Hepatic impairment

  Following repeat administration C_{max} and AUC were ~ 20% and 75% higher in subjects with moderate hepatic impairment as compared to subjects with normal hepatic function. Systemic exposure to AZ was not studied in subjects with severe hepatic impairment.

  No dose adjustments are required in subjects with moderate hepatic impairment.

- Drug interactions

  Effect of co-administered drugs on AZ

  There was no clinically significant change in systemic exposure to AZ when administered with CYP 2C9 inhibitor (fluconazole), p-gp inhibitor (ketoconazole), p-gp substrate (digoxin), antihypertensives (amlodipine, chlorthalidone), antidiabetics (metformin, pioglitazone) and antacids (Mylanta).

Effect of AZ on co-administered drugs

There was no clinically significant change in systemic exposure to midazolam (CYP 3A4/5 substrate), dextromethorphan (CYP 2D6 substrate), tolbutamide (CYP 2C9 substrate), caffeine (CYP 1A2 substrate), fexofenadine (P-gp substrate), warfarin, glyburide, metformin, chlorthalidone, digoxin (P-gp substrate), amlodipine, pioglitazone following repeat administration of AZM.

- Dose-response

In the Phase 2 dose-ranging study (dose range of 5 to 80 mg of AZM capsule) maximal reduction in blood pressure was attained after 4 weeks of treatment at all doses tested. AZM was found to be significantly ($p<0.05$) different from placebo at all doses tested. However, there does not appear to be a dose dependent effect on change from baseline diastolic blood pressure and systolic blood pressure, in the dose range tested.

- Biopharmaceutics

The final to-be marketed formulation of AZM tablet was used in all Phase 3 studies. All Phase 1 / 2 studies were conducted with AZM capsule or AZ tablet.

The relative AZ bioavailability of AZM tablet and AZM capsule compared to equal dose of AZ tablet (reference) is about 80% and 50%, respectively.

Food dose not affect systemic exposure to AZ following administration of AZM tablet.

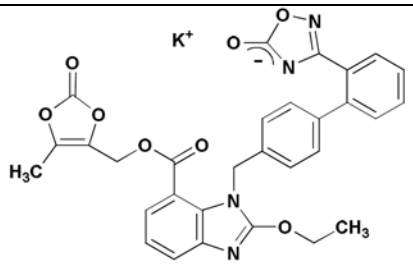
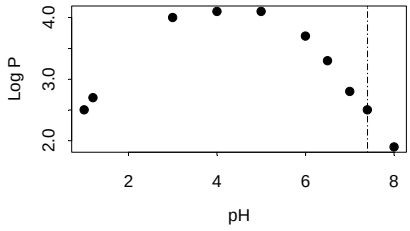
2 QUESTION BASED REVIEW

2.1 General Attributes of the Drug

Azilsartan medoxomil[1] is the prodrug form of AZ, an angiotensin receptor blocker (ARB). The sponsor is seeking approval of AZM for use in the treatment of hypertension. The development program for AZM was conducted under IND 71,867. On approval, AZM will be the eight ARB approved for this indication.

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Drug substance (AZM)

Appearance	White (b) (4) powder
Chemical name	1H-Benzimidazole-7-carboxylic acid,1-[[2'-(2,5-dihydro-5-oxo-1,2,4-oxadiazol-3-yl)[1,1'-biphenyl]-4-yl]methyl]-2-ethoxy-,(5-methyl-2-oxo-1,3-dioxol-4-yl)methyl ester, potassium salt(1:1)
Molecular formula	$C_{30}H_{23}KN_4O_8$
Molecular weight	606.62
Structural formula	
Solubility	Soluble in most organic solvents, practically insoluble in aqueous solutions at acidic to neutral pH (pH 1 to 7), slightly soluble at basic pH (9 to 11).
pKa	2.5 and 5.7
Partition coefficients	Log P at physiologic pH is 2.5 (vertical line in below figure) 

[1] Azilsartan medoxomil (AZM) is referred to as TAK 491, and azilsartan (AZ) as TAK 536 in the submission and in the individual study reviews.

Drug product (AZM tablet)

Azilsartan medoxomil was formulated as round, biconvex, (b) (4) tablets in 20, 40 or 80 mg strength, differentiated by size and debossing. The excipients were mannitol, fumaric acid / sodium hydroxide, hydroxypropyl cellulose, croscarmellose sodium, microcrystalline cellulose, magnesium stearate.

2.1.2 What are the proposed mechanism of action and therapeutic indications?

Azilsartan medoxomil is a prodrug. Azilsartan, the active form of AZM is formed by hydrolysis during absorption, and is an angiotensin II receptor type 1 antagonist.

Azilsartan is indicated in the treatment of hypertension.

2.1.3 What are the proposed dosages and routes of administration?

Azilsartan medoxomil will be formulated as tablets (20, 40 or 80 mg) for oral administration. The sponsor is seeking approval of the 40 and 80 mg strengths.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and the clinical studies used to support dosing or claims?

The clinical pharmacology program for AZM consisted of 47 studies. These included characterization of AZ pharmacokinetics and pharmacodynamics following single and multiple doses, mass balance studies, drug interactions studies, relative bioavailability studies, food effect studies, and studies in specific populations, conducted with AZM and AZ. In the PK/PD studies doses of AZM ranging from 20 to 320 mg were studied, and all studies were conducted in healthy subjects. *In vitro* studies were conducted identify the relevant enzymes and transporters involved in the disposition of AZ, and to determine the protein binding and RBC distribution characteristics of AZ. Thirty seven of the submitted studies were reviewed (Individual study reviews are in DARRTS as an Appendix to this review).

The efficacy and safety of AZM was established in five placebo/active controlled Phase 3 studies conducted in subjects with mild to moderate hypertension. Doses of 20, 40 and 80 mg of AZM were evaluated in these studies.

2.2.2 What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology studies?

Change from baseline in diastolic blood pressure (DBP) and systolic blood pressure (SBP), were the response endpoints measured in Phase 2 and Phase 3 studies respectively.

In the two placebo/active controlled Phase 2 dose – ranging studies, trough seated ‘cuff’ DBP at week 8, was the primary endpoint; while mean 24 h ambulatory SBP was the primary endpoint in the pivotal efficacy studies in Phase 3.

Azilsartan is an anti-hypertensive agent. Hence, change from baseline in blood pressure at end of study is an appropriate measure of its effect. Clinic 'cuff' blood pressure was measured in triplicate using either a mercury sphygmomanometer or a certified automated and calibrated blood pressure device. Ambulatory blood pressure was measured using a Spacelabs Medical Model 90207 device, which was set to measure at intervals of 15 minutes during the day and at 20 minutes at night.

2.2.3 Are the active moieties in plasma appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Azilsartan is the only active moiety in plasma. Azilsartan and its inactive metabolites (M-II, M-I) were appropriately identified and measured in plasma to enable adequate assessment of pharmacokinetics.

2.2.4 Exposure-Response

2.2.4.1 What are the characteristics of the exposure-response relationships for efficacy?

Dose-response relationship for efficacy following administration of AZM was evaluated in a Phase 2 dose ranging study (**491_005**). Study **491_005** was a placebo and active (olmesartan) controlled 8 week study in which subjects with mild to moderate hypertension received 5 to 80 mg of AZM, once daily as a capsule. Change from baseline in DBP at week 8, as determined by 'cuff' measurement was the primary endpoint. Maximal reduction in blood pressure was attained after 4 weeks (**Figure 1, left panel**) of treatment at all doses tested. AZM (5 to 80 mg) was found to be significantly ($p<0.05$) different from placebo. However, there does not appear to be a dose dependent effect on change from baseline DBP, in the dose range tested (**Figure 1, right panel**). This is also highlighted by the fact that a precise estimate for ED50 could not be derived over the dose range of 5 – 80 mg. A similar relationship was observed for change from baseline SBP.

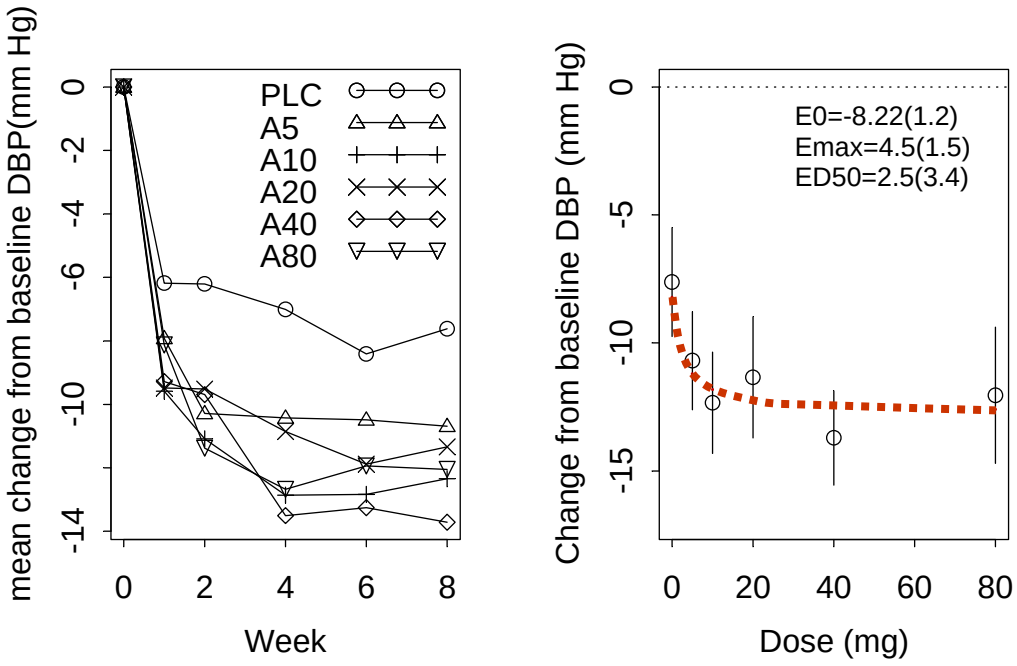


Figure 1 All the tested doses of AZM produce a significant lowering of DBP. Steady-state effect is reached by about week 4 (left panel). Symbols represent mean DBP. There is no dose dependent decrease in DBP in the range tested (right panel). The red line represents mean fit for all subjects using an inhibitory Emax model. Model parameters are presented as mean (SE).

Plasma AZ concentrations were not collected in any of the Phase 2 or Phase 3 studies for AZM. Hence, E-R analysis was not feasible. Further, as seen in **Figure 3** blood pressure reduction effect corresponding to peak plasma AZ concentrations (1 to 3h) is similar to that seen at trough plasma concentrations (24h), indicating a shallow E-R relationship similar to the D-R relationship at steady-state.

2.2.4.2 What are the characteristics of the exposure-response relationships for safety?

No serious adverse events or tolerability issues were observed with AZ. Exposure – response relationships for safety were not evaluated. Serum creatinine elevation that resolved with stopping of treatment with AZM was the most serious adverse reaction. A dose-dependent increase in serum creatinine was reported for AZM with chlorthialidone over the range of 40 – 80 mg.

2.2.4.3 Does this drug prolong QT/QTc Interval?

AZ does not prolong QTc interval. The effect of AZ following administration of a single dose of AZM 320 mg was assessed in a 'TQT' study. The study was reviewed by the Interdisciplinary Review Team for QT Studies Consultation (DARRTS date 11/13/2009).

2.2.4.4 Is the dose and dosing regimen selected by the sponsor consistent with the known E-R relationship?

The sponsor is seeking approval of AZM 40 and 80 mg, to be administered once daily. The proposed dosing frequency is consistent with the duration of the effect over the inter-dosing interval, however, the need for approving doses as high as 80 mg is not justified based on the D-R relationship.

As seen in **Figure 1**, there is no significant difference in blood pressure reduction with the higher dose of 80 mg when compared to lower doses of 5, 10, 20 or 40 mg. The shape of the cumulative distribution for blood pressure reduction is similar for the range of doses tested in the Phase 2 trial and no distinct advantage is evident for highest dose of 80 mg (**Figure 2**).This is further evident from the ABPM data presented in **Figure 3**.

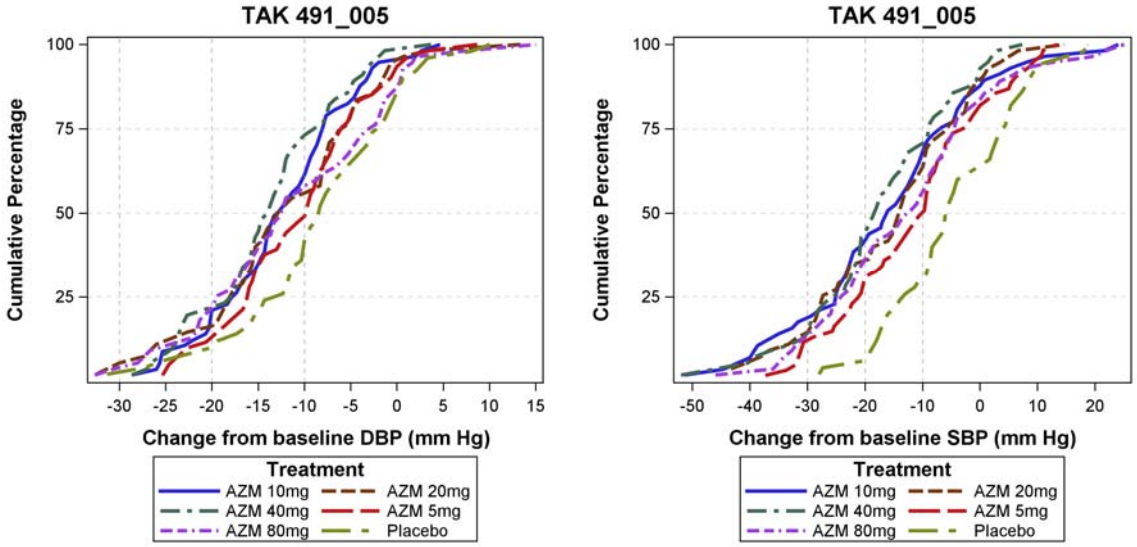


Figure 2 The range of blood pressure reduction is similar for all the tested doses of AZM.

Overall, doses ≥ 5 mg appear to be effective in lowering blood pressure, with no significant benefit of AZM 80 mg over AZM 40 or 20 mg. Similarly, AZM 80 mg did not show consistent benefit over AZM 40 mg in Phase 3 studies (Please refer to Appendix 2 for the CDFs for the Phase 3 AZM monotherapy trials). Given this, there may not be much value in approving the higher strength of AZM 80 mg.

As seen from ABPM data (**Figure 3**), following once daily administration, AZM maintains its blood pressure reduction effect throughout the dosing interval. Blood pressure reduction effect corresponding to peak plasma AZ concentrations (1 to 3h) is similar to that seen at trough plasma concentrations (24h), indicating a shallow E-R relationship at steady-state. Further, placebo corrected peak (maximal effect post dosing) to trough ratio ranged from 0.8 to 1.34 for the doses tested. Hence, the selected dosing regimen is acceptable.

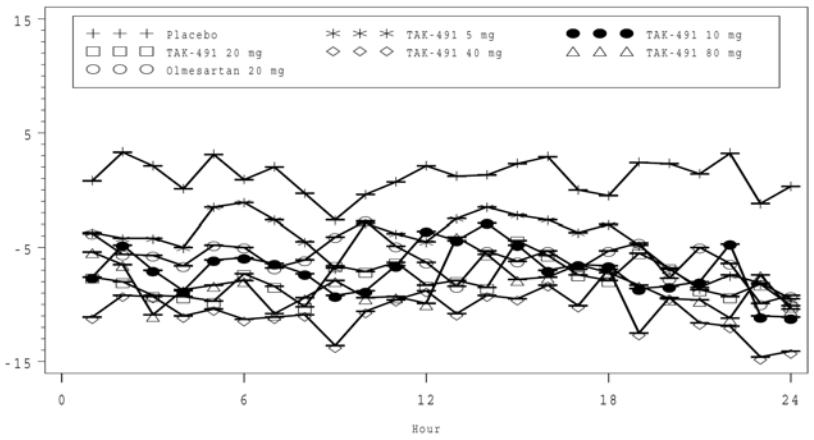


Figure 3 Blood pressure reduction effect is maintained throughout the inter-dosing interval. (Ref. CSR 491_005, Figure 15.2.5.3)

2.2.5 What are the PK characteristics of the drug?

2.2.5.1 What are the single and multiple dose PK parameters?

Single and multiple dose PK characteristics of AZ following administration of 20 to 320 mg of AZM were determined in several multiple ascending dose studies (**491_017**, **491_002**, **491_101**). Azilsartan exhibited dose proportional PK in this range. Accumulation ratio for AZ following once daily administration for 10 days was ~ 1.2. Mean CL/F was about 1.5 L/h and the mean elimination half-life was ~ 12 h. Peak plasma AZ concentrations are attained in 1 to 3 h post dose. Peak to trough ratio (C_{max}/C_{trough}) at steady state was ~ 5.

Plasma time course of AZ following administration of a single dose of AZM tablet, and at steady state following once daily administration of AZM tablet is presented in **Figure 4**.

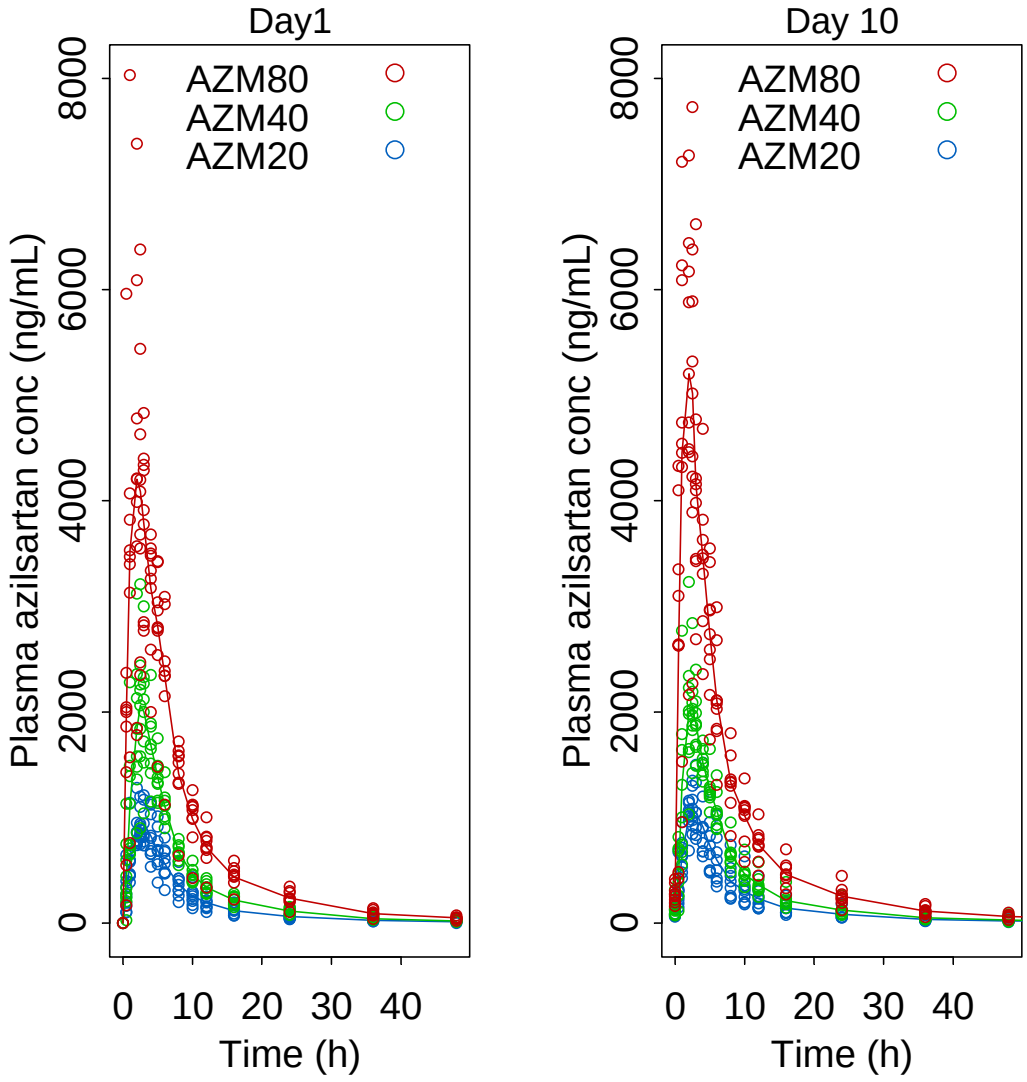


Figure 4 Plot of AZ plasma concentration versus time (a) following administration of a single dose and (b) at steady state. The solid line represents the mean and the circles represent individual observations.

2.2.5.2 How does the PK of the drug and its major metabolites in healthy adults compare to that in patients?

The PK of AZ was not assessed in hypertensive subjects. However, given the mechanism of its clearance, its PK is expected to be similar between healthy and hypertensive subjects.

2.2.5.3 What are the characteristics of drug absorption?

Following oral administration, during absorption, AZM is hydrolyzed to form azilsartan. AZM exhibits poor solubility and permeability characteristics, making it a BCS class IV compound. AZM was not detected in plasma at anytime at doses up to 320 mg.

AZ was detected in plasma 15 minutes (earliest sampling time) post administration. Peak plasma concentrations of AZ were observed within 1 to 3 h of administration. The absolute bioavailability of AZ following administration of AZM tablet is ~ 58% (**536_016**, **491_017**).

2.2.5.4 What are the characteristics of drug distribution?

AZ does not appear to distribute extensively into tissues. The apparent volume of distribution across PK studies was estimated to be about 30 L in healthy subjects. AZ is > 99% bound to albumin, and is concentration independent (0.3 to 30 μg/mL). Distribution of AZ into RBCs is ~ 2% and is concentration independent (0.3 to 30 μg/mL). It should be noted that peak AZ concentrations at steady state following administration of 80 mg of AZM do not exceed 10 μg/mL (**Figure 4**).

2.2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?

AZ is eliminated mainly in urine as inactive metabolites. Following oral administration of ^{14}C-AZM as an aqueous solution, about 97% of the administered dose was recovered in 14 days, of which 42% was recovered in urine and 55% in feces.

Factoring in the absolute bioavailability of AZ (F=0.58), about 72% of the systemically available dose is eliminated in urine and about 22% is eliminated in feces.

2.2.5.6 What are the characteristics of drug metabolism?

AZM is hydrolyzed to from AZ during absorption. Azilsartan is mainly metabolized to form its M-II (inactive) metabolite by CYP 2C9. It is also metabolized to a smaller extent by CYP 2B6, CYP 2C8 to form the M-I (inactive) metabolite (**Figure 5**).

Following oral administration, AZM was not detected in plasma at anytime up to 320 mg. AZ and its two inactive metabolites were detected and their respective time courses were characterized.

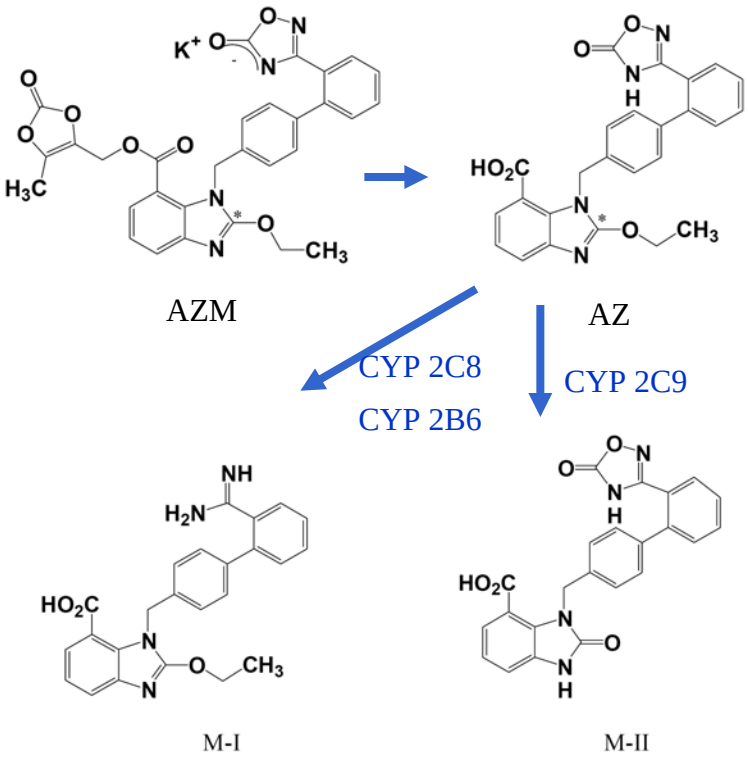


Figure 5 AZM is hydrolyzed to form AZ, which is metabolized to form M-II (major inactive metabolite) and M-I (minor inactive metabolite) (Ref: Summary of clinical pharmacology).

2.2.5.7 What are the characteristics of drug elimination?

Azilsartan is eliminated mainly in urine as metabolites. See section 2.2.5.5

2.2.5.8 Based on PK parameters, what is the degree of linearity in the dose-concentration relationship?

Azilsartan exhibited dose-proportional PK following oral administration of 20 to 320 mg of AZM (**491_101**, **491_017**). Relationship between dose and C_{max}/AUC_{inf} for AZ following single dose at steady state is presented in **Figure 6.** A similar relationship between dose and C_{max}/AUC_{inf} was observed at steady state.

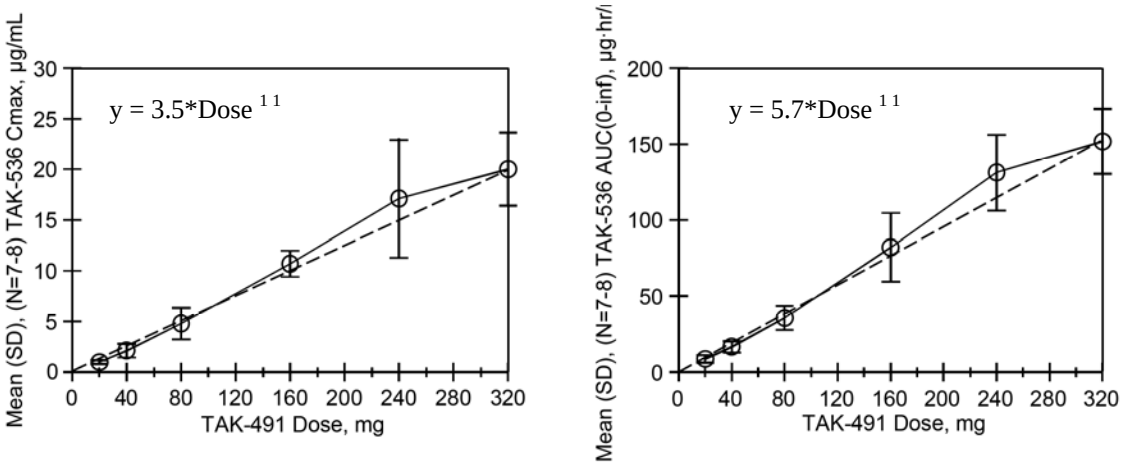


Figure 6 Dose proportional increase in AZ C_{max} and AUC_{inf} following administration of single doses of AZM 20 to 320 mg (Ref: Summary of Clinical Pharmacology, Table 2.2, Figure 3a).

2.2.5.9 How do the PK parameters change with time following chronic dosing?

Azilsartan does not exhibit time dependant PK.

2.2.5.10 What is the inter- and intra-subject variability of PK parameters in healthy subjects and patients?

The between subject variability in the PK parameters for AZ in healthy subjects is low. The mean estimate for between subject variability in CL/F and V/F was ~ 20 to 30%. This was assessed from study **491_101** conducted using the final to be marketed formulation.

2.3 Intrinsic Factors

2.3.1 What intrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

Systemic exposure to AZ was not significantly influenced by any of the intrinsic factors evaluated (**Figures 7 - 9**).

Age, sex, race

The effect of age, sex and race on AZ exposure was assessed in a dedicated PK study (**491_003**) following repeat once daily administration of 60 mg of AZM. There were no clinically significant increases in AZ exposures because of age, sex or race.

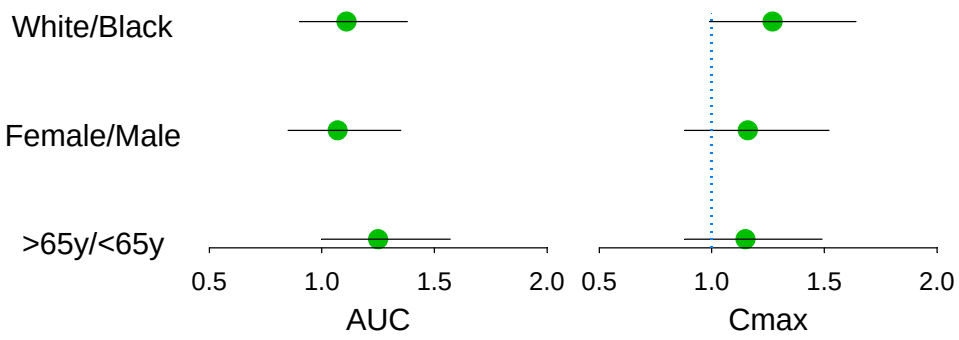


Figure 7 Increase in AZ exposure (Test/Ref) in elderly, females and whites. The closed circles represent the mean with the associated 95% CI.

Renal impairment

The effect of renal impairment was assessed following administration of a single dose of 40 mg of AZM (**491-103**) conducted in subjects with mild, moderate, severe renal impairment or end stage renal disease. A 200% increase in total AZ exposure was observed in subjects with sever renal impairment as compared to subjects with normal renal function. However, given the shallow nature of the D-R relationship for AZ and the absence of any significant tolerability issues, this is not of clinical significance. Dose adjustments are not required in this population.

Hemodialysis does not remove AZ from systemic circulation

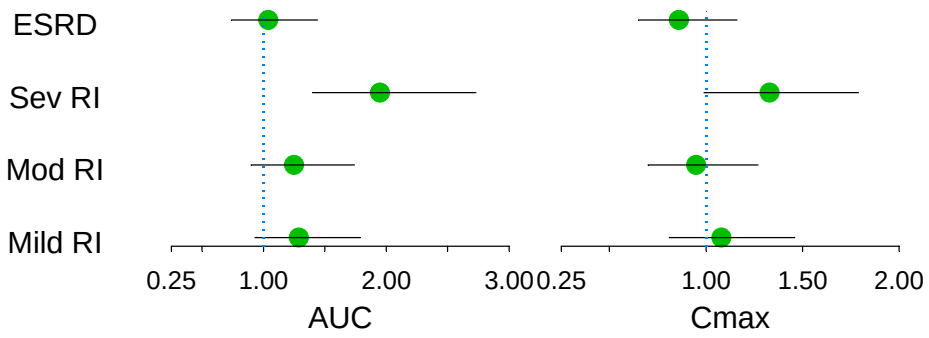


Figure 8 Increased AZ exposure in subjects with renal impairment (test) when compared to healthy subjects (Ref).

Hepatic impairment

The effect of hepatic impairment was assessed in a repeat dose PK study (**491-102**) in subjects with mild or moderate hepatic impairment following once daily administration

of 40 mg of AZM. There were no clinically significant increases in AZ exposures. There is no experience in subjects with severe hepatic impairment.

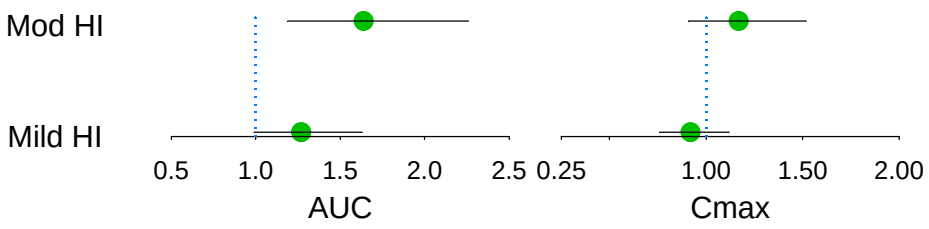


Figure 9 Increased AZ exposure in subjects with hepatic impairment (test) when compared to healthy subjects (Ref).

2.3.2 What pregnancy and lactation use information is there in the label?

Azilsartan, like all other RAAS agents, should not be used during pregnancy.

2.4 Extrinsic Factors

2.4.1 What extrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

Systemic exposure to AZ was not significantly influenced by any of the extrinsic factors evaluated.

2.4.2 Is there an in vitro basis to suspect in vivo drug-drug interactions?

Yes. Azilsartan is a substrate for CYP 2C9. Its prodrug AZM is an inhibitor of P-gp. In addition drugs that increase gastric pH may increase the solubility of AZM and consequently the bioavailability of AZ. Therefore, there is potential for drug interactions with co-administered drugs that are CYP2C9 substrates or inhibitors, P-gp substrates or antacids.

2.4.3 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

Azilsartan is a substrate for CYP 2C9.

2.4.4 Is the drug an inhibitor and/or an inducer of CYP enzymes?

No, AZM and AZ are not inhibitors or inducers of CYP enzymes.

2.4.5 Is the drug an inhibitor and/or an inducer of Pgp transport processes?

Azilsartan medoxomil is an inhibitor of the efflux transporter P-gp.

2.4.6 What are the drug-drug interactions?

The potential/extent for drug interaction with CYP substrates/inhibitors, and other concomitant medication was evaluated in several dedicated studies conducted in healthy subjects. Most studies were repeat dosing studies and measured systemic exposure to AZ and the interacting drug. Different formulations and of AZ (AZ tablet, AZM tablet, AZM capsule) were used in these studies. (Note: Systemic exposure to AZ following administration of equal doses of AZ tablet, and AZM tablet and capsule is about 20 % and 50%, respectively. When compared to AZM capsule, systemic exposure to AZ following administration of AZM tablet is ~ 70% higher). All studies conducted with AZM used a dose of 80 mg while studies conducted with AZ tablet, used 40 mg.

All studies were reviewed (Appendix/ISR). Results of the studies are presented in **Figures 10** and **11**.

Effect of co-administered drugs on AZ

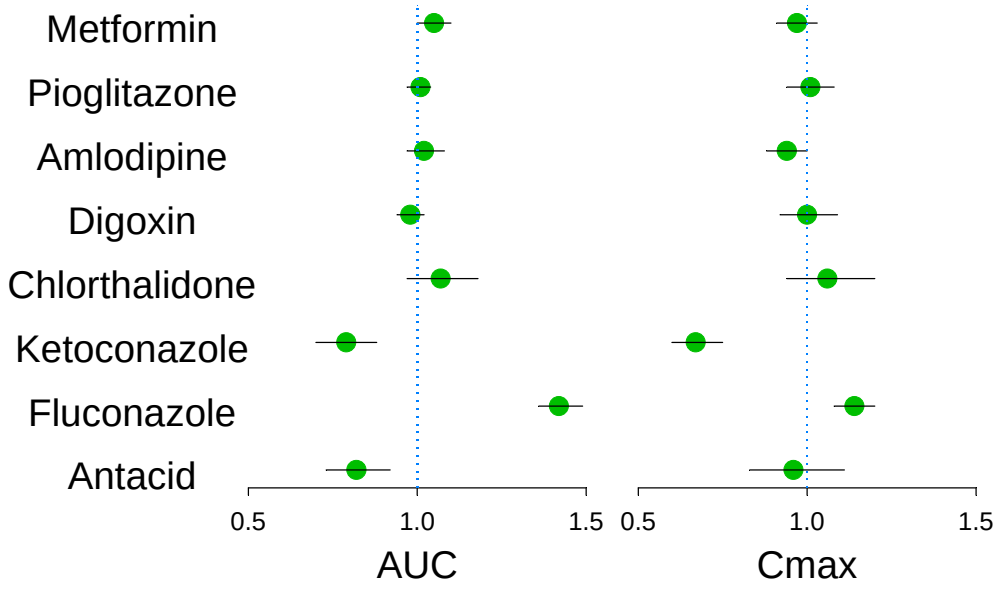


Figure 10 Effect of CYP substrates/inhibitors and other concomitantly administered drugs on systemic exposure to AZ. The x-axis represents the geometric mean ratio (Interacting drug + AZM/AZ alone).

Total systemic exposure to AZ was decreased by ~ 20% when AZM 80 mg was co-administered with Mylanta® maximum strength. In a single dose study (**491_107**), when 30 mL Mylanta was co-administered with AZM followed by an additional 30 mL an hour later, AUC of AZ was reduced by ~ 20%, while C_{max} and $t_{1/2}$ remained unaffected. Peak AZ levels were also attained earlier (1.5 h as compared to 3h) when AZM was administered along with Mylanta.

Fluconazole, a CYP 2C9 inhibitor decreases the clearance of AZ. This is apparent from ~ 40% increase in the AUC of AZ, with only a ~ 14% increase in Cmax. In study **536_005**, the effect of administration of repeat doses of fluconazole 200 mg QD or ketoconazole 400 mg was assessed on the systemic exposure to AZ tablet 40 mg. The observed increase in AUC is not concerning given the flat D-R relationship for AZ and the absence of severe adverse events or tolerability issues.

Effect of AZ on co-administered drugs

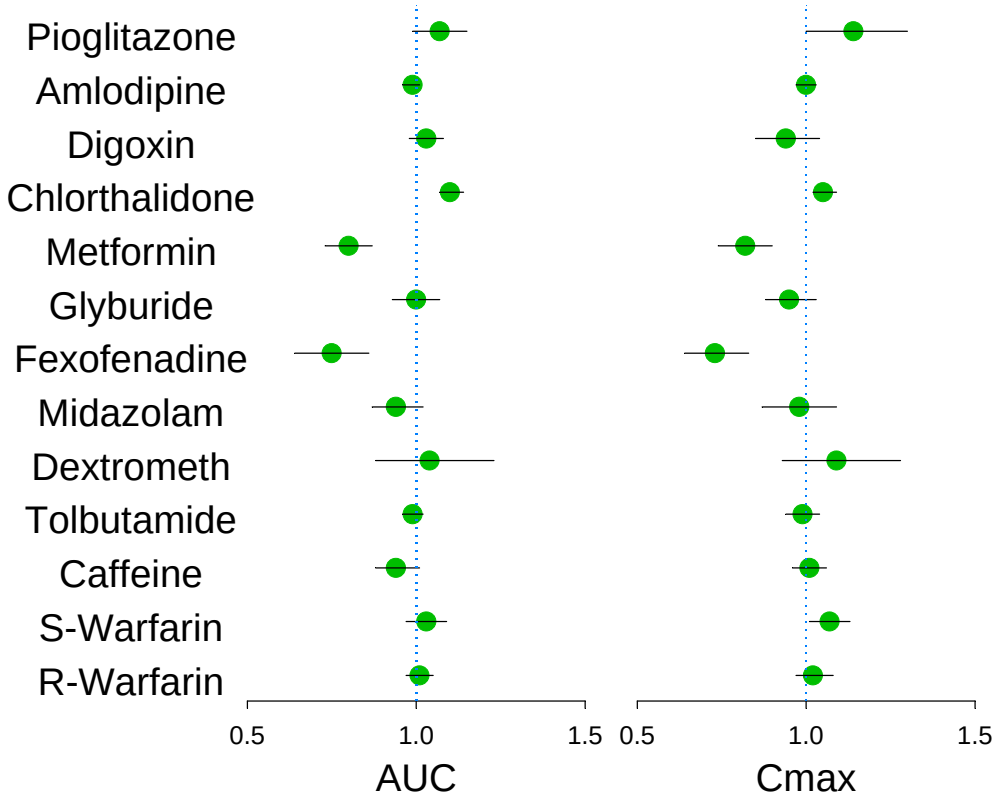


Figure 11 Effect of AZM on systemic exposure to CYP substrates/inhibitors and other concomitantly administered drugs. The x-axis represents the geometric mean ratio (Interacting drug + AZM/Interacting drug alone).

Systemic exposure to fexofenadine was decreased by ~ 20% following repeat administration of AZM. Fexofenadine is considered to be a sensitive P-gp substrate and was part of the phenotyping cocktail used in study **491_013**. In this study, a single dose of the probe cocktail was administered on day 1 followed by daily administration of 80 mg of AZM, once daily for 5 days (dosing to PK steady state). On the last day of dosing AZM was administered along with a single dose of the cocktail. Both AUC and Cmax of fexofenadine were reduced, and elimination was unaffected. In contrast to this, systemic

exposure to digoxin was not altered following repeat once daily administration of AZM 80 mg (**491_104**). Digoxin is a sensitive P-gp susbstrate and has been extensively used in PK studies. While AZM was shown to be a P-gp inhibitor in *in vitro* studies, AZ was not. Given that AZM is not systemically available and is rapidly hydrolyzed during absorption to form AZ, the observed results with fexofenadine are not of concern.

2.4.7 What other co-medications are likely to be administered to the target population?

AZM is indicated for use in the treatment of hypertension. Hence, it may be used in combination with other antihypertensive agents for adequate blood pressure control.

2.4.8 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions?

Potentiation of blood pressure lowering effect of AZ is expected when AZ is administered along with other antihypertensive agents. Antihypertensives are titrated to effect, therefore this possible pharmacodynamic interaction is not a cause for concern.

2.4.9 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions, or protein binding?

No.

2.4.10 What issues related to dose, dosing regimens, or administration are unresolved and represent significant omissions?

There are no major unresolved issues related to dose and administration.

2.5 General Biopharmaceutics

2.5.1 Based on the biopharmaceutics classification system principles, in what class is this drug? What solubility, permeability data support this classification?

AZM is a BCS class IV (low solubility, low permeability) drug.

It is practically insoluble in aqueous solutions at acidic to neutral pH (pH 1 to 7), slightly soluble at basic pH (9 to 11).

The permeability of AZM across Caco-2 cell monolayers was only about twice that that of mannitol, a marker compound with low permeability, and > 20 fold lower than that of antipyrine, a marker compound with high permeability (**TAK 491-00214, TAK 536-c-46-0045**).

2.5.2 What is the relative bioavailability of the proposed to-be marketed formulation to the pivotal clinical trial?

The final to-be marketed formulation was used in the pivotal clinical trial. Hence, bioequivalence studies were not conducted for AZM.

2.5.3 What is the effect of food on the bioavailability of the drug from the dosage form?

Food does not significantly affect systemic exposure to AZ following administration of AZM tablet (80 mg) with a standard high fat meal (**491_015**). The 90% CI for AUC and Cmax were contained within the pre-determined 80 to 125% BE limits (**Figure 12**).

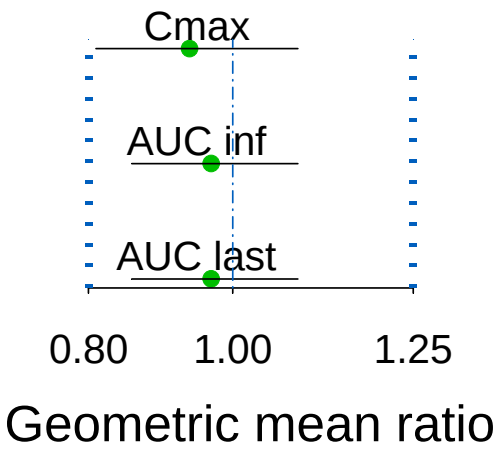


Figure 12 Food does not significantly affect systemic exposure to AZ. The x-axis represents the geometric mean ratio, and the pre-determined BE limits are represented by the broken vertical lines.

2.5.4 How dose systemic exposure to AZM tablet compare with that following administration AZM capsule and AZ tablet?

Following administration of a single dose of AZM tablet, systemic exposure to AZ is about 70% higher than that following administration of AZM capsule.

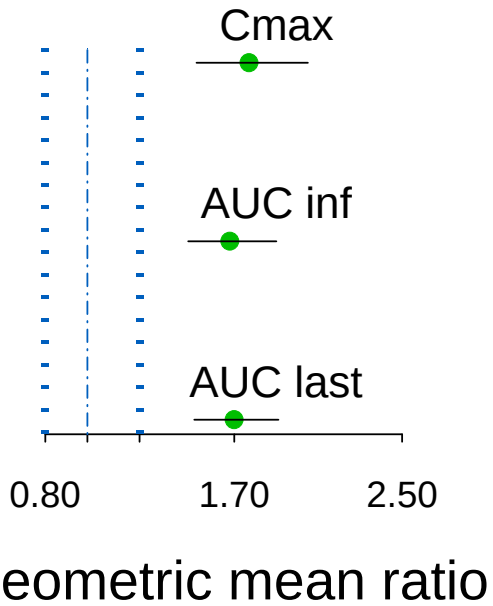


Figure 13 Systemic exposure to AZ following administration of AZM tablet is 70% higher when compared to AZM capsule. The x-axis represents the geometric mean ratio, and the pre-determined BE limits are represented by the broken vertical lines.

At equivalent doses, systemic exposure to AZ following administration of a single dose of AZM tablet is about 20% lower than that following administration of AZ tablet (**491_017**, **491_101**). AZM tablet was used in the pivotal clinical trial and all Phase 3 studies in the AZ development program. AZM capsules and AZ tablets were used in the Phase 1 / 2 studies including the dose ranging studies.

2.6 Analytical Section

2.6.1 How are the active moieties identified and measured in the plasma?

Azilsartan was identified and measured using a validated LC/MS/MS method. The range of the calibration curve and sample preparation varied across studies. The method satisfied all criteria for 'method validation' and 'application to routine analysis' set by the Bioanalytical Guidance, and were therefore acceptable.

Table Summary of the bio-analytical methods used.

Report #	Method	Range	Matrix	Validation	In-study validation
7128-362	LC/MS/MS	1 - 2500	plasma	Acceptable	Acceptable
7128-365	LC/MS/MS	50 - 10000	urine	Acceptable	Acceptable
7128-364	LC/MS/MS	2 - 1000	plasma	Acceptable	Acceptable
7128-363	LC/MS/MS	20 - 10000	urine	Acceptable	Acceptable
TAK-491-0070	LC/MS/MS	1-2500	plasma	Acceptable	Acceptable
TAK-491-001R	LC/MS/MS	20-10000	urine	Acceptable	Acceptable

2.6.2 Which metabolites have been selected for analysis and why?

Both inactive metabolites of AZ, M-II and M-I were measured in all studies.

2.6.3 For all moieties measured, is free, bound, or total measured?

Total concentrations were measured for AZ, M-II and M-I.

3 DETAILED LABELING RECOMMENDATIONS

The Office of Clinical Pharmacology (OCP/DCP-1) has reviewed the package insert labeling for NDA 200-796 (Edarbi) and finds it acceptable pending the following revisions shown in appendix **Error! Reference source not found.**. ~~Strikethrough text~~ is recommended to be deleted and underlined text is recommended to be added. Labeling discussions are currently ongoing

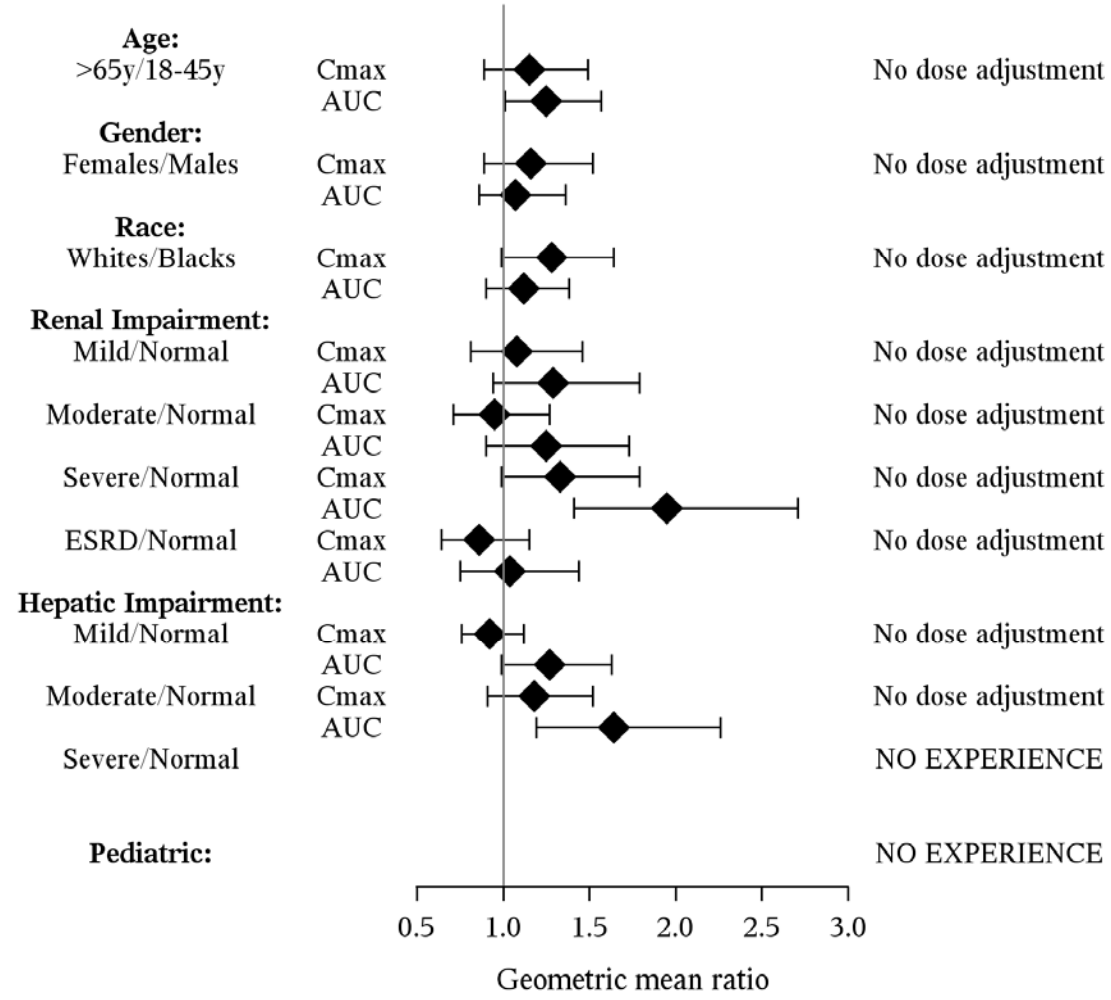
10 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

(b) (4)

1 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

Impact of intrinsic factors on Azilsartan Pharmacokinetics(PK)



This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DIVYA MENON ANDERSEN
01/11/2011

RAJANIKANTH MADABUSHI
01/11/2011
Concur with the reviewer's findings and recommendations

ONDQA BIOPHARMACEUTICS REVIEW

NDA#:	200-796/N-000
Submission Date:	04/22/10, 10/15/10, and 12/13/10
Brand Name:	Pending
Generic Name:	Azilsartan Medoxomil
Formulation:	Immediate release (IR) tablet
Strength:	40 and 80 mg
Sponsor:	Takeda Global Research & Development Center, Inc. (TGRD)
Type of submission:	Original
Reviewer:	Tien-Mien Chen, Ph.D.

SUMMARY

TGRD is developing the angiotensin II receptor blocker (ARB), TAK-491 (azilsartan medoxomil). TAK-491, a new molecular entity (NME), is reportedly a prodrug of the active moiety, TAK-536 (azilsartan). The sponsor indicated that 1). TAK-491 is a BCS (Biopharmaceutics Classification System) Class 4 compound, 2). TAK-491 when administered orally is hydrolyzed rapidly to TAK-536, 3). The salt-free form of TAK-491 was not detectable in human plasma in any *in vivo* studies, and 4). The *in vitro* results indicated that TAK-536 is a potent, selective antagonist of human angiotensin II type 1 (AT1) receptors.

On 04/22/10, TGRD submitted NDA 200-796 (N-000) for TAK-491 and proposed 40 and 80 mg IR tablet strengths seeking approval for the once-daily treatment of hypertension, either alone or in combination with other antihypertensive agents.

Both 40 and 80 mg are (b) (4) and both strengths had been tested clinically, therefore, there is no biowaiver issue. However, the sponsor stated that the phase-3 formulations are the same as the to-be-marketed (TBM) formulation except for the tablet debossing.

The dissolution development report, proposed dissolution methodology and specifications, and dissolution data for the 40 and 80 mg IR tablets (Not debossed) using the proposed dissolution method are submitted and therefore, reviewed here. The proposed dissolution method and the specifications are shown below:

Apparatus:	**2 (Paddle) x 50 rpm**
Medium:	(b) (4) **USP Phosphate Buffer (pH 7.8) 900 mL at 37ºC**
Sampling time:	**10, 15, 20, 30, and 45 min**
Specifications:	**Q=** (b) (4)

An additional information request was sent to the sponsor on 10/04/10 regarding the development of the dissolution methodology. The sponsor responded on 10/15/10 which is also reviewed and found acceptable. Further information request was sent to the sponsor on 12/10/10 regarding the issue on the difference in tablet debossing. The sponsor responded on 12/13/10 and submitted the comparative dissolution data/profiles.

The above comparative dissolution data showed similar dissolution profiles between the clinically tested formulations (Not debossed 40 and 80 mg tablet batches) and the commercial/process validation batches (Debossed).

Finally, the prodrug, TAK-491, dissolved rapidly using the sponsor's proposed dissolution method, i.e., (b) (4), therefore, the specification should be tightened. Please see the following comment section for details.

RECOMMENDATION
From the Biopharmaceutics perspective, the proposed dissolution methodology is acceptable, however, the specifications need to be revised. The following comment needs to be conveyed to the sponsor as soon as possible.

COMMENT: (Needs to be sent to the sponsor)
Your proposed dissolution methodology as shown below is acceptable.

Apparatus:	**2 (Paddle) x 50 rpm**
Medium:	(b) (4) **USP Phosphate Buffer (pH 7.8) 900 mL at 37ºC**
Sampling time:	**10, 15, 20, 30, and 45 min**

However, azilsartan medoxomil immediately release tablets dissolved rapidly using the above dissolution method, i.e., (b) (4), therefore, specifications should be revised as follows.

Specifications:	**From Q=** (b) (4)
	To Q= (b) (4)

BACKGROUND

TGRD is developing the angiotensin II receptor blocker, TAK-491 (azilsartan medoxomil), for the treatment of hypertension. TAK-491, an NME, is reportedly a prodrug of the active moiety, TAK-536 (azilsartan). The sponsor indicated that 1). TAK-491 is a BCS Class 4 compound, 2). TAK-491 when administered orally is hydrolyzed rapidly to TAK-536, 3). The salt-free form of TAK-491 was not detectable in human plasma in any *in vivo* studies, and 4). The *in vitro* results indicated that TAK-536 is a potent, selective antagonist of human angiotensin II type 1 (AT1) receptors.

CURRENT SUBMISSION

On 04/22/10, TGRD submitted NDA 200-796 (N-000) for TAK-491 (azilsartan medoxomil) and proposed 40 and 80 mg IR tablet strengths seeking approval for the once-daily treatment of hypertension, either alone or in combination with other antihypertensive agents.

Both 40 and 80 mg strengths had been tested clinically, therefore, there is no biowaiver issue. However, the sponsor stated that the phase-3 formulations are the same as the to-be-marketed (TBM) formulation except for the tablet debossing. The dissolution development report, the proposed dissolution methodology and specifications, and dissolution data for 40 and 80 mg IR tablets using the proposed dissolution method are reviewed here.

FORMULATION COMPARISONS

TAK-491 has been classified as a BCS Class 4 compound (low solubility and low permeability) based on *in vitro* permeability data from Caco-2 cells and *in vitro* solubility data. The compositions and the formulation developed for commercial use are shown below.

Table 1. Composition and Formulation of Azilsartan Medoxomil (TAK-491) IR Tablets

Component	Reference to Quality Standards	Function	Quantity per Tablet (mg)		
			20 mg tablets	40 mg tablets	80 mg tablets
TAK-491 [1] (As the free acid)	In-house standard	Active ingredient	(b) (4)	42.68[1] (40)	85.36 [1] (80)
Mannitol	Ph.Eur., USP				(b) (4)
Fumaric Acid	NF				
Sodium Hydroxide	Ph.Eur., NF				
Hydroxypropyl cellulose	Ph.Eur., NF				
Croscarmellose sodium	Ph.Eur., NF				
Microcrystalline cellulose (b) (4)	Ph.Eur., NF				
Magnesium stearate	Ph.Eur., NF				
(b) (4)	Ph.Eur., USP				
Tablet weight			(b) (4)	180	360
					(b) (4)

[redacted]. However, the sponsor only seeks approval for 40 and 80 mg IR tablets at this time.

DISSOLUTION METHODOLOGY AND SPECIFICATIONS

The dissolution development report included [redacted], apparatus, and rotational speeds. Please see the summary of the dissolution development report in Appendix 1 for details. The selected/proposed dissolution method and the specifications are shown below:

Apparatus: **2 (Paddle) x 50 rpm**
Medium: [redacted] **USP Phosphate Buffer (pH 7.8), 900 mL at 37°C**
Sampling time: **10, 15, 20, 30, and 45 min**
Specifications: **Q=** [redacted]

The mean dissolution data and profiles of TAK-491 (azilsartan medoxomil) 40 and 80 mg tablet batches (all not debossed) are shown below.

Table 2. Mean (SD) Dissolution Data (in %) and Profiles for TAK-491 (Azilsartan Medoxomil) IR 40 and 80 mg Tablets (N=12 Tablets/Batch)

Strengths\Time Point (All not debossed)	10 min	15 min	20 min	30 min	45 min
40 mg (Registration stability batch, No. Z624B08; 252,000 tablets)	[redacted]				
80 mg (Registration Stability and Phase-3 Batch, No. Z624D15; 155,000 tablets)					

Note: The 80 mg batch (No. Z624D15) was used in a Phase 3 trial No. 01-05-TL-491-006.

Figure 1. Mean Dissolution Profiles of TAK-491 (Azilsartan Medoxomil) IR 40 and 80 mg Tablets (N=12 Tablets/Batch)

[redacted]

Please see individual and mean dissolution data/profile in Appendix 2 for details.

On 10/04/10, the Biopharmaceutics team sent out an information request regarding the justification of using the proposed medium of pH 7.8 instead of pH 7.6 and the sponsor responded on 10/15/10. The sponsor's response is reviewed and found acceptable. Please see the sponsor's response in Appendix 3 for details.

The sponsor indicates in the section 3.2.P.2.2, page 8 of 35, that "Potential commercial formulations are the same as phase 3 formulations except for tablet debossing." However, the comparative dissolution testing to address the difference in tablet debossing between the clinically tested (Not debossed) formulation and the commercial TBM (Debossed) formulation was not located in the submission. On 12/10/10, an information request was sent to the sponsor and the sponsor responded on 12/13/10. Their response is reviewed here. Please see the comparative dissolution testing/individual and mean data/profiles (n=12 tablets/batch) for Not debossed vs. Debossed tablets in Appendix 4 for details.

The batches used in the comparative dissolution testing to address the difference in tablet debossing and the mean dissolution profiles are shown below.

Table 3. Batches Used in the Comparative Dissolution Study (Not Debossed vs. Debossed)

Strength	Phase 3 / Registration Stability Batches (Not Debossed)	Commercial / Process Validation Batches (Debossed)
40 mg	Z624B08	001
80 mg	Z624D15	001

Figure 2. Comparative Dissolution Profiles for TAK-491 IR Tablet 40 mg: Not Debossed (Batch Z624B08) vs. Debossed (Commercial/Process Validation Batch No. 001)

(b) (4)

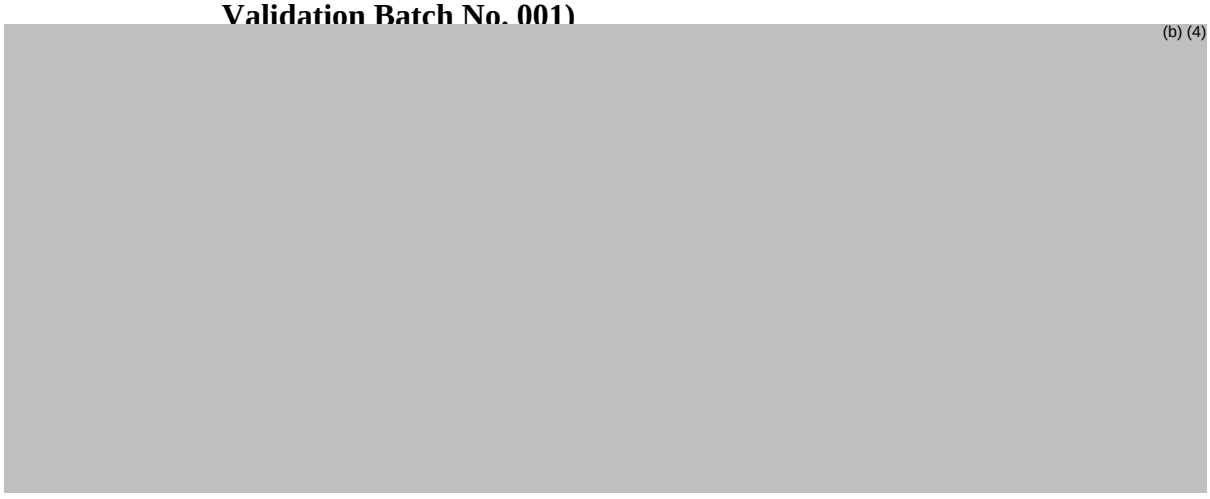
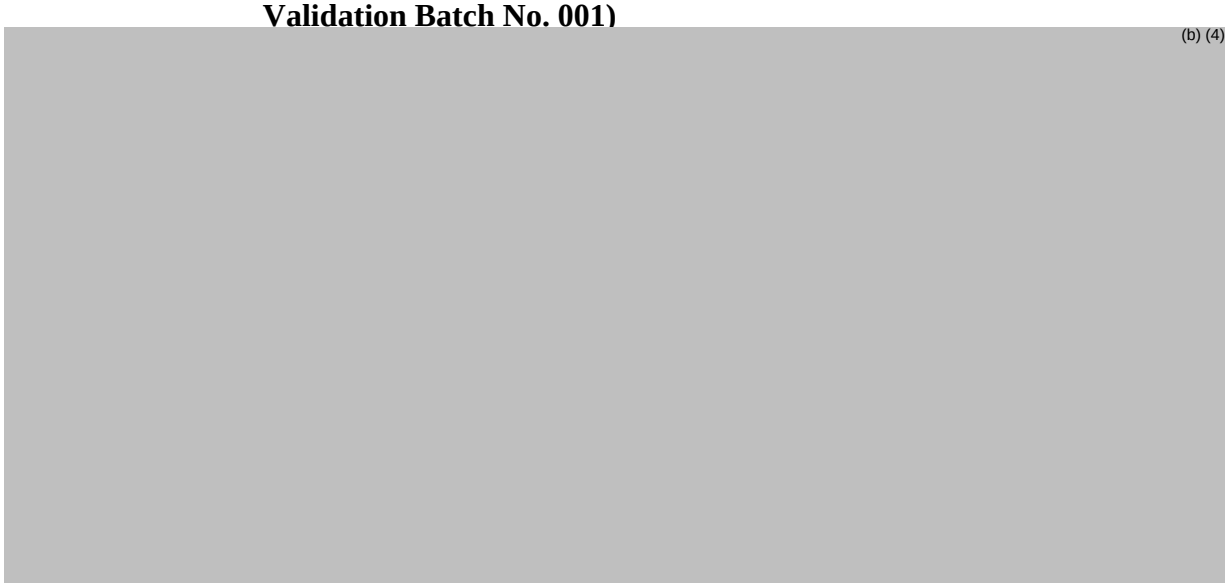


Figure 3. Comparative Dissolution Profiles for TAK-491 IR Tablet 80 mg: Not Debossed (Batch Z624D15) vs. Debossed (Commercial/Process Validation Batch No. 001)



Reviewer's Comments:

1. The proposed dissolution methodology is adequately justified by the sponsor and the submitted dissolution data are reviewed and found acceptable.
2. The sponsor adequately addressed the difference in tablet debossing between the clinically tested (Not debossed) and the commercial TBM (Debossed) formulations.
3. The prodrug TAK-491, a BCS Class 4 compound, dissolved rapidly using the sponsor's proposed dissolution method (Table 1 and Figure 1), i.e., (b) (4) , therefore, the specification should be revised as follows:

From Q= (b) (4)
To Q= (b) (4)

_____ 12/14/10
Tien-Mien Chen, Ph.D. Date
Reviewer
ONDQA Biopharmaceutics

_____ 12/14/10
Patrick Marroum, Ph.D. Date
ONDQA Biopharmaceutics

CC: NDA
Patrick Marroum, Angelica Dorantes, Tien-Mien Chen

15 Page(s) has been Withheld in Full as B4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

TIEN MIEN CHEN
12/16/2010

PATRICK J MARROUM
12/20/2010

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	200-796	**Brand Name**	(b) (4)
OCP Division (I, II, III, IV, V)	OCP I	**Generic Name**	Azilsartan medoxomil
Medical Division	DCRP	**Drug Class**	Antihypertensive
OCP Reviewer	Divya Menon-Andersen	**Indication(s)**	Hypertension
OCP Team Leader	Rajanikanth Madabushi	**Dosage Form**	Tablet
Pharmacometrics Reviewer	-	**Dosing Regimen**	Once daily
Date of Submission	04/26/10	**Route of Administration**	Oral
Estimated Due Date of OCP Review	12/26/10	**Sponsor**	Takeda
Medical Division Due Date		**Priority Classification**	Standard
PDUFA Due Date	02/27/11		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X	6	6	Six method validation reports
I. Clinical Pharmacology				
Mass balance:	X	2	1	
CYP Isozyme characterization:	X	1	1	
Blood/plasma ratio:	X	1	1	
Plasma protein binding:	X	2	2	
Pharmacokinetics (e.g., Phase I) -	X			
Healthy Volunteers-				
single dose:	X	4	2	
multiple dose:	X	6	6	
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	X	4		Same studies as Single and multiple dose studies
fasting / non-fasting multiple dose:	X	6		
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	11	11	
In-vivo effects of primary drug:	X	11	11	
In-vitro:	X	6	6	
Subpopulation studies -				
ethnicity:	X	2	1	Single study evaluating the effect of age, race and sex.
gender:	X			
pediatrics:				
geriatrics:	X			

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

renal impairment:	X	1	1	
hepatic impairment:	X	1	1	
PD -				
Phase 2:	X	1	1	
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:	X	8		Same studies as Single and multiple dose studies
Phase 3 clinical trial:				
Population Analyses -				
Data rich:	X	1	1	
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability	X	1	1	Absolute BA for TAK 536
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	X	3	2	Not counting the one above
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies	X	3	2	
Bio-waiver request based on BCS	No			
BCS class	X	2	1	Permeability studies
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		65	47	

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	Phase 3 studies were conducted with the final formulation
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
Yes

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.
Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Divya Menon-Andersen
Reviewing Clinical Pharmacologist Date: June 4, 2010

Rajanikanth Madabushi
Team Leader/Supervisor Date: June 4, 2010

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement 090808

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200796	ORIG-1	TAKEDA PHARMACEUTICALS NORTH AMERICA INC	azilsartan medoxomil

---

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DIVYA MENON ANDERSEN
06/09/2010

RAJANIKANTH MADABUSHI
06/09/2010
concur

PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)

NDA Number: 200,796 **Applicant: Takeda Pharmaceuticals North America.** **Stamp Date: 28-Apr-2010**

Established/Proper Name: Azilsartan Medoxomil **NDA Type: Commercial/Standard**

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	X		Looks to be in standard eCTD format.
2	Is the section indexed and paginated adequately?	X		appears to be
3	On its face, is the section legible?	X		appears to be
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	X		Six facilities identified, all have complete addresses, all have FEI Numbers.
5	Is a statement provided that all facilities are ready for GMP inspection?	X		It is mentioned that all six listed sites are ready for inspection.
6	Has an environmental assessment report or categorical exclusion been provided?	X		A report has been provided and categorical exclusion is requested.
7	Does the section contain controls for the drug substance?	X		3.2.S.4. Control of Drug Substance with 5 sub-sections.
8	Does the section contain controls for the drug product?			3.2.P.5. Control of Drug Product with 6 sub-sections
9	Has stability data and analysis been provided to support the requested expiration date?	X		DS retest period proposed (b) (4). (appears to be supported by adequate stability studies) DP expiration dating proposed 24 mos. for all strength/pkg configurations (appears to be supported by adequate stability studies)
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		
11	Have draft container labels been provided?	X		Blister Labels (7 and 10 cnt), Blister Carton Labels (7 and 30 cnt), Bottle Labels (30 and 90 cnt), Blister Trays (5x7 cnt), each for 40 mg and 80 mg products.
12	Has the draft package insert been provided?	X		Draft of a 17 page insert

PRODUCT QUALITY (Small Molecule)

FILING REVIEW FOR NDA or Supplement (ONDQA)

13	Has an investigational formulations section been provided?	X		Appears to be present in 3.2.P.2. Pharmaceutical development and in 3.2.P.5.4. Batch Analysis in the Control of Drug Product section. (formulation history provided)
14	Is there a Methods Validation package?	X		3.2.S.4.3. Validation of Analytical Procedures and 3.2.P.5.3. Validation of Analytical Procedures.
15	Is a separate microbiological section included?		X	Microbiological testing included in DS and DP sections.

Have all DMF references been identified? Yes

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)			(b) (4)	2-2-2010	
				1-28-2010	
				12-15-2009	
				1-27-2010	
				2-17-2010	
				2-12-2010	
				2-23-2010	
				2-11-2010	

IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA is not fileable from the product quality perspective, state the reasons and provide comments to be sent to the Applicant. - Appears to be fileable from the CMC standpoint.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter. None identified so far.

Charles F. Jewell – DS; Prafull Shiromani - DP 18-May-2010

Product Quality Reviewer Date

Team Leader/Supervisor Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200796	ORIG-1	TAKEDA PHARMACEUTICALS NORTH AMERICA INC	azilsartan medoxomil

---

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CHARLES F JEWELL
06/08/2010

RAMESH K SOOD
06/08/2010