The clinical trial information provided in this public disclosure synopsis is supplied for informational purposes only.

Please note that the results reported in any single trial may not reflect the overall potential risks or benefits of a product which are based on an evaluation of an entire research program.

Before prescribing any Takeda products, healthcare professionals should consult prescribing information for the product approved in their country.
2.0 SYNOPSIS

Title of Study:
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

Name of Sponsor:
Takeda Global Research & Development Center, Inc.

Name of Finished Product:
TAK-491

Study Center:
PPD Phase I Clinic
7551 Metro Center Drive, Suite 200
Austin, TX 78744

Publications Based on the Study:
None

Study Period:
20 June 2006 to 30 June 2006

Phase of Development:
Phase 1

OBJECTIVES
Primary:
The primary objective of this study was to evaluate the effects of TAK-491 (80 mg) on the pharmacokinetics of multiple cytochrome P-450 (CYP) probes using a drug cocktail (caffeine 200 mg, tolbutamide 500 mg, dextromethorphan 30 mg, midazolam 4 mg, and fexofenadine 60 mg).

Secondary:
The secondary objective of this study was to evaluate the safety and tolerability of multiple doses of TAK-491 (80 mg) when coadministered with these CYP probes.

METHODS
This was a phase 1, open-label, single-sequence, pharmacokinetic drug interaction study involving 24 healthy adult subjects. On Day 1, subjects received a single oral dose of drug cocktail (caffeine 200 mg, tolbutamide 500 mg, dextromethorphan 30 mg, midazolam 4 mg, and fexofenadine 60 mg). On Days 4 through 8, subjects received TAK-491 80 mg once daily (QD), with coadministration of drug cocktail on the morning of Day 8.

Blood and urine samples for measurement of drug cocktail components and their respective metabolites were collected on Days 1 and 8 over the 72-hour postdosing period. Blood samples for measurement of TAK-491F, TAK-536, TAK 536 M-I, and TAK-536 M-II concentrations in plasma were collected predose on Days 4, 5, 6, and 7, and on Day 8 during the 72-hour postdosing period.

Number of Subjects (Planned and Analyzed):
Planned: 24 subjects.
Analyzed: Pharmacokinetics—24 subjects; Safety—24 subjects.
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Diagnosis and Main Criteria for Inclusion:
To qualify for study participation, subjects must have been healthy men or nonpregnant, nonlactating women; aged 18 to 45 years, inclusive; had a body mass index of 32 kg/m² or less; been able to comprehend and willing to sign an informed consent form; had a blood pressure reading of at least 110/70 mm Hg; had clinical laboratory results within the reference ranges or that were acceptable to the investigator; had negative urine tests for selected substances of abuse at Screening and Baseline; had hepatitis B vaccination(s) or a negative hepatitis panel at Screening; and had negative human immunodeficiency virus antibody at Screening.

Test Product, Dose and Mode of Administration, Lot Number:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Form</th>
<th>Route</th>
<th>Lot No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAK-491</td>
<td>80 mg</td>
<td>4 × 20 mg capsules</td>
<td>oral</td>
<td>Z6244021</td>
</tr>
</tbody>
</table>

Duration of Treatment:
The duration of the study for an individual subject ranged from 13 to 32 days, including Screening. Each subject received 2 oral single doses of the drug cocktail (separated by 7 days) and 5 consecutive oral doses of TAK-491 80 mg. The study duration was 11 days, with a single dose of drug cocktail administered on Day 1, multiple doses of TAK-491 administered on Days 4 through 7, and single doses of drug cocktail and TAK-491 administered on Day 8.

Reference Therapy, Dose and Mode of Administration, Lot Number:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Form</th>
<th>Route</th>
<th>Lot No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caffeine</td>
<td>200 mg</td>
<td>1 × 200 mg tablet</td>
<td>oral</td>
<td>5L19</td>
</tr>
<tr>
<td>Tolbutamide</td>
<td>500 mg</td>
<td>1 × 500 mg tablet</td>
<td>oral</td>
<td>1N0861</td>
</tr>
<tr>
<td>Dextromethorphan hydrobromide</td>
<td>30 mg</td>
<td>1 × 30 mg softgel capsule</td>
<td>oral</td>
<td>055013</td>
</tr>
<tr>
<td>Midazolam hydrochloride</td>
<td>4 mg</td>
<td>2 mL of 2 mg/mL syrup</td>
<td>oral</td>
<td>558509A</td>
</tr>
<tr>
<td>Fexofenadine hydrochloride</td>
<td>60 mg</td>
<td>1 × 60 mg tablet</td>
<td>oral</td>
<td>1087052</td>
</tr>
</tbody>
</table>

Criteria for Evaluation:
Pharmacokinetic:
The following plasma and urinary pharmacokinetic parameters for drug cocktail components and their respective metabolites (midazolam and 1-hydroxymidazolam; caffeine, and 1,7-paraxanthine; tolbutamide, 4-hydroxytolbutamide, and carboxytolbutamide; dextromethorphan and dextrorphan; and fexofenadine) were determined on Days 1 and 8: area under the plasma concentration-time curve (AUC) from time 0 to the time of last quantifiable concentration (AUC[0-tlqc]), AUC from time 0 to infinity (AUC[0-inf]), maximum observed plasma concentration (Cmax), time at which Cmax occurred (Tmax), terminal elimination rate constant (λz), terminal elimination half-life, mean residence time (MRT), apparent oral clearance, apparent volume of distribution at steady state for parent compounds, metabolic ratios for AUC(0-tlqc) and AUC(0-inf), renal clearance (CLR), fraction of drug excreted unchanged in urine, total amount of drug excreted in urine (Ae) from time 0 to time t, and urinary ratios of parent to metabolite.
The following pharmacokinetic parameters for TAK-491F, TAK-536, TAK-536 M-I, and TAK-536 M-II were determined on Day 8: minimum observed plasma concentration (Cmin) predose at the last dose of the multiple dosing; Cmin postdose at time tau, where tau is the length of the dosing interval (24 hours); Cmin from time 0 to time tau postdose, where tau is the length of the dosing intervals (24 hours); AUC from time 0 to time tau (24 hours); Cmax; Tmax; and MRT.
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Safety:
Safety variables included adverse events, clinical laboratory test results, vital signs, 12-lead electrocardiograms (ECGs), and physical examination findings.

Statistical Methods:
Pharmacokinetic Measures:
Between values on Day 1 and Day 8, a paired t-test was performed on λz and on the natural logarithms of AUC(0-tlqc), AUC(0-inf), Cmax, CLR, Ae from time 0 to 24 hours (Ae[0-24]), Ae from time 0 to 72 hours (Ae[0-72]), AUC(0-tlqc) metabolic ratio, AUC(0-inf) metabolic ratio, Ae(0-24) metabolic ratio, and Ae(0-72) metabolic ratio for each drug cocktail analyte. The Wilcoxon signed rank test was performed on Tmax. Within the framework of the paired t-test, the 90% confidence interval (CI) and the ratio of the test treatment mean (TAK-491 + drug cocktail, Day 8) relative to the reference treatment mean (drug cocktail, Day 1) were provided. The 90% CI on the original scale was obtained by taking the antilog of the 90% CI for the difference between the treatment means on the logarithmic scale.

Steady-state assessments of TAK-491F, TAK-536, TAK-536 M-I, and TAK-536 M-II plasma concentrations were based on the analysis of natural logarithms of predose concentrations on Days 5, 6, 7, and 8. In the analysis of variance model, day was the fixed effect while subject was random effect. Within the model, pairwise t-tests were used to assess the achievement of steady state by comparing the predose concentration level between study days.

SUMMARY OF RESULTS
Subject Disposition:
A total of 24 subjects (10 men and 14 women, mean age of 31.1 years) were enrolled in the study; all enrolled subjects completed treatment.

Pharmacokinetic Results:
A summary of the changes in ratios of geometric mean AUC(0-inf), Cmax, and Ae(0-72) when TAK-491 was coadministered with drug cocktail relative to drug cocktail alone is presented below:
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#### Ratio of Day 8 to Day 1 Geometric Mean (CI) For AUC(0-inf), Cmax, and Ae(0-72) for Drug Cocktail Components and Their Metabolites

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Geometric Mean Ratio (90% CI) (a)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AUC(0-inf)</td>
</tr>
<tr>
<td>Midazolam</td>
<td>96.63 (89.49, 104.36)</td>
</tr>
<tr>
<td>1-Hydroxymidazolam</td>
<td>106.08 (98.71, 114.01)</td>
</tr>
<tr>
<td>Tolbutamide</td>
<td>99.61 (96.96, 102.33)</td>
</tr>
<tr>
<td>4-Hydroxytolbutamide</td>
<td>98.55 (95.37, 101.83)</td>
</tr>
<tr>
<td>Carboxytolbutamide</td>
<td>94.70 (92.33, 97.14)</td>
</tr>
<tr>
<td>Caffeine</td>
<td>95.24 (89.11, 101.80)</td>
</tr>
<tr>
<td>1,7-Paraxanthine</td>
<td>95.35 (92.08, 98.73)</td>
</tr>
<tr>
<td>Dextromethorphan</td>
<td>98.28 (82.60, 116.93)</td>
</tr>
<tr>
<td>Dextrorphan</td>
<td>97.76 (92.58, 103.23)</td>
</tr>
<tr>
<td>Fexofenadine</td>
<td>84.11 (74.51, 94.95)</td>
</tr>
</tbody>
</table>

(a) Ratio of Day 8 geometric mean divided by Day 1 geometric mean. CI obtained by taking the antilog of the 90% CI for the difference between the geometric mean of Day 8 and Day 1 on the natural logarithmic scale, expressed as a percentage.

### Midazolam: CYP3A4 Probe
Coadministration of TAK-491 with drug cocktail did not have a clinically or statistically significant effect on midazolam or 1-hydroxymidazolam AUC(0-inf) or Cmax values (<7% change relative to drug cocktail alone) or Ae(0-72) (<7% change relative to drug cocktail alone). All of the 90% CIs for these values were within the 80% to 125% equivalence range.

### Tolbutamide: CYP2C9 Probe
Coadministration of TAK-491 with drug cocktail did not have a clinically or statistically significant effect on tolbutamide, 4-hydroxytolbutamide, or carboxytolbutamide AUC(0-inf) or Cmax values (<8% change relative to drug cocktail alone), or Ae(0-72) (<8% change relative to drug cocktail alone). All of the 90% CIs for these values were within the 80% to 125% equivalence range.

### Caffeine: CYP1A2 Probe
A number of subjects had measurable concentrations of caffeine prior to drug cocktail dosing. In order to determine if this had an effect on the study results, statistical analyses were performed on 2 subject populations: (1) all dosed subjects (primary analysis) and (2) subjects whose Day 1 predose plasma concentrations were 5% or less of the Cmax value (secondary analysis). For the secondary analyses, 1 subject was excluded from caffeine analysis, and 10 subjects were excluded from the 1,7-paraxanthine analyses.

In the primary analysis, coadministration of TAK-491 with drug cocktail did not have a clinically significant effect on caffeine or 1,7-paraxanthine AUC(0-inf) or Cmax values (<5% change relative to drug cocktail alone), or Ae(0-72) (4% decrease for caffeine and 20% decrease for the metabolite relative to drug cocktail alone). The 90% CIs for caffeine and 1,7-paraxanthine AUC and Cmax values were within the 80% to 125% equivalence range, but those for Ae(0-72) were not.
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The results of the secondary analyses support those of the primary analyses. The 90% CIs bounding the geometric mean ratios for caffeine and 1,7-paraxanthine AUC and Cmax values were within the 80% to 125% equivalence range, indicating that coadministration of TAK-491 with drug cocktail did not have an effect on the pharmacokinetic profile of caffeine relative to administration of drug cocktail alone.

**Dextromethorphan: CYP2D6 Probe**
Coadministration of TAK-491 with drug cocktail did not have a clinically significant effect on dextromethorphan or dextrorphan AUC(0-inf) or Cmax values (<10% change relative to drug cocktail alone) or Ae(0-72) (<4% change relative to drug cocktail alone). The 90% CIs for dextromethorphan AUC(0-inf) and dextrorphan AUC(0-inf), Cmax, and Ae(0-72) were within the 80% to 125% equivalence range; dextromethorphan Cmax and Ae(0-72) 90% CIs were slightly outside this range.

**Fexofenadine: P-Glycoprotein Probe**
Coadministration of TAK-491 and drug cocktail did not have a clinically important effect on fexofenadine AUC(0-inf) or Cmax values (<27% decrease relative to drug cocktail alone) or Ae(0-72) (27% decrease relative to drug cocktail alone); none of the 90% CIs for these values were within the 80% to 125% equivalence range.

**Pharmacokinetic Profile of TAK-491**
TAK-491F plasma concentrations were below the lower limit of detection for all subjects. TAK-536 was the primary metabolite present in plasma, followed by TAK-536 M-II. Steady-state plasma concentrations appear to have been reached by Day 6 for TAK-536 and TAK-546 M-I, and by Day 7 for TAK-536 M-II.

**Safety Results:**
Incidences of adverse events were greater when drug cocktail was administered (alone or concurrently with TAK-491) than when TAK-491 was administered alone (50% and 58%, respectively, vs 33%). The adverse event with the greatest incidence during drug cocktail administration (either alone or coadministered) was dizziness (33% during administration alone and 38% during coadministration). When TAK-491 was administered alone, the only adverse events reported by more than 5% of the subjects were constipation and headache (both 8.3%).

The percentages of subjects who experienced 1 or more adverse events that were considered possibly or probably related to study drug were 33% during administration of drug cocktail alone and TAK-491 alone and 50% during coadministration of TAK-491 with drug cocktail. The majority of the subjects experienced only mild adverse events. No adverse events causing withdrawal, serious adverse events, or deaths occurred.

Coadministration of drug cocktail alone on Day 1 was associated with higher mean systolic and diastolic blood pressure relative to coadministration of TAK-491 and drug cocktail on Day 8. No other significant findings were noted in the vital sign, physical examination, ECG, clinical laboratory, or pulse oximetry data.

**CONCLUSIONS:**
Administration of TAK-491 80 mg QD for 5 days did not have a clinically important effect (inhibition or induction) on the CYP1A2-mediated metabolism of caffeine, the CYP2C9-mediated metabolism of tolbutamide, the CYP3A4-mediated metabolism of midazolam, or the CYP2D6-mediated metabolism of dextromethorphan.
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Administration of TAK-491 80 mg QD for 5 days reduced the plasma and urine exposure to the P-glycoprotein substrate, fexofenadine (25% reduction in AUC[0-tlqc], 16% reduction in AUC[0-inf], and 27% reduction in Cmax and Ae[0-72]). A reduction of this magnitude does not indicate a clinically important interaction between TAK-491 and fexofenadine, but it does suggest further investigation may be needed to clarify the potential interaction between TAK-491 and P-glycoprotein substrates.

Administration of TAK-491 80 mg QD, with and without coadministration of drug cocktail, was safe and well tolerated. The majority of the adverse events were mild in severity, and none caused study withdrawal.

Date of Report:
12 February 2007