# 2.0 Synopsis

<table>
<tr><td>AbbVie Inc.</td><td rowspan="3">Individual Study Table Referring to Part of Dossier:<br>Volume:<br><br>Page:</td><td rowspan="3">(For National Authority Use Only)</td></tr>
<tr><td>Name of Study Drug:<br>Risankizumab</td></tr>
<tr><td>Name of Active Ingredient:<br>Risankizumab</td></tr>
<tr><td colspan="3">Title of Study: The Effect of Multiple Subcutaneous Doses of Risankizumab on the Single Dose Pharmacokinetics of Cytochrome P450 Substrates (Caffeine, Warfarin, Omeprazole, Metoprolol and Midazolam) Administered Orally in an Open-Label, One-Sequence Trial in Patients with Plaque Psoriasis with or without Concomitant Psoriatic Arthritis</td></tr>
<tr><td colspan="3">Investigator: Dr. med. Stanislav Ignatenko, MD</td></tr>
<tr><td colspan="3">Study Site: Single Center</td></tr>
<tr><td colspan="2">Studied Period (Years):<br>First Subject First Visit: 15 September 2016<br>Last Subject Last Visit: 22 September 2017</td><td>Phase of Development: 1</td></tr>
<tr><td colspan="3">Objective:<br>To assess the influence of risankizumab on the pharmacokinetics (PK) of cytochrome P450 (CYP) probe substrates as a means of predicting drug-drug interactions. These probe substrates are caffeine (for CYP1A2), warfarin (for CYP2C9), omeprazole (for CYP2C19), metoprolol (for CYP2D6) and midazolam (for CYP3A).</td></tr>
<tr><td colspan="3">Methodology:<br>Open-label, one fixed-treatment sequence study design that included up to a 28-day screening period, a 15-week treatment period and a 14 week follow-up period.<br>Twenty-one subjects received the following study drugs:<br>• 100 mg caffeine, 10 mg warfarin, 20 mg omeprazole, 50 mg metoprolol and 2 mg midazolam as single dose on Days 1 and 98<br>• 150 mg risankizumab subcutaneous (SC) every 4 weeks (E4W) for a total duration of 12 weeks starting on Day 8<br>Blood samples for risankizumab assay were collected on Days 8, 36, 64, 92, 98, 105 and 204. Blood samples for determination of risankizumab ADA titer were collected on Days 8, 36, 64, 92, 105 and 204. Blood samples for assay of CYP probe substrates and their relevant metabolites were collected for up to 168 hours after dosing on Days 1 and 98.</td></tr>
<tr><td colspan="3">Number of Subjects (Planned and Analyzed):<br>Planned: 20, Entered: 21, Completed: 21, Evaluated for Safety: 21,<br>Evaluated for Pharmacokinetics: 21</td></tr>
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**Diagnosis and Main Criteria for Inclusion:**

Male or female patients with plaque psoriasis with or without concomitant psoriatic arthritis and whose ages were 18 years to 75 years at screening.

**Test Product, Dose/Strength/Concentration, and Mode of Administration:**

Risankizumab 90 mg/mL SC injection, caffeine 50 mg tablet, warfarin 5 mg tablet, omeprazole 20 mg tablet, metoprolol 50 mg tablet and midazolam 2 mg/mL oral solution for oral administration.

**Duration of Treatment:** Subjects received single doses of caffeine, warfarin, omeprazole, metoprolol and midazolam on Days 1 and 98. In addition, subjects received multiple doses of 150 mg risankizumab SC E4W for a total duration of 12 weeks (Weeks 1 – 13) starting on Day 8.

**Criteria for Evaluation**

**Pharmacokinetic:**

Primary endpoints: $C_{max}$ and $AUC_{0-t}$ for the probe substrates caffeine (CYP 1A2), warfarin (specifically S-warfarin (CYP 2C9)), omeprazole (CYP 2C19), metoprolol (CYD 2D6) and midazolam (CYP 3A4) when administered without risankizumab, and risankizumab at steady-state.

Further endpoints: $C_{max}$ and $AUC_{0-t}$ for probe substrate metabolites; $AUC_{0-\infty}$, $t_{max}$, $t_{1/2}$, CL/F, $V_z$/F and $RAUC_{0-\infty, M/P}$ for the probe substrates (and metabolites); $C_{trough}$ for risankizumab.

**Safety:**

Adverse events (AE) including clinically relevant findings from the physical examination, safety laboratory tests, vital signs.

**Statistical Methods**

**Pharmacokinetic:**

To assess the effect of co-administration of multiple-doses of risankizumab on the CYP probe substrates and corresponding metabolites, repeated measures analyses was performed on the natural logarithms of $C_{max}$, $AUC_t$ and $AUC_\infty$ for all evaluated substrates and metabolites. A similar analysis was conducted for the metabolite to parent drug AUC ratio for CYP substrates, such as paraxanthine to caffeine AUC ratio, 5 hydroxy-omeprazole to omeprazole AUC ratio, metoprolol to alpha-hydroxymetoprolol AUC ratio and midazolam to 1-hydroxymidazolam AUC ratio.

Based on the repeated measures analyses, point estimates of the ratios of the geometric means (test/reference) for the primary endpoints and the additional endpoints $RAUC_{0-\infty}$ ($AUC_\infty$ metabolite/$AUC_\infty$ parent) for caffeine (paraxanthine/caffeine), metoprolol (α-OH-metoprolol/metoprolol), midazolam (1-OH-midazolam/midazolam), omeprazole (5-OH-omeprazole/omeprazole), and their two-sided 90% confidence intervals (CIs) were provided.

The statistical model to explore the attainment of steady state of risankizumab plasma concentration using the pre-dose (trough) concentrations was a repeated measures linear mixed effects model on the logarithmic scale including 'time' as a repeated effect and 'subject' as random effect.

**Statistical Methods (Continued)**

**Safety:**

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. Standard AbbVie summary tables and listings were produced. Frequency, severity, and causal relationship of adverse events were tabulated by system organ class and preferred term after coding according to the current version of the Medical Dictionary for Drug Regulatory Activities (MedDRA).

Summary of baseline, post-dose and change from baseline values were provided for laboratory variables and vital signs. For laboratory variables and vital signs, the baseline value was the last value obtained prior to dosing.

Laboratory test values and vital signs measurements, that were potentially clinically significant, according to predefined criteria, were identified.

**Summary/Conclusions**

**Pharmacokinetic Results:**

| Regimens Test vs. Reference | Pharmacokinetic Parameter | Central Value | | Exposure Ratio | |
|---|---|---|---|---|---|
| | | Test | Reference | Point Estimate | 90% Confidence Interval |
| | **Caffeine (CYP1A2 Probe Substrate)** | | | | |
| Administration with risankizumab[a] vs. Administration without risankizumab[b] | $C_{max}$ | 2950 | 2700 | 1.090 | 0.964 – 1.234 |
| | $AUC_{0-t}$ | 21500 | 20900 | 1.029 | 0.891 – 1.190 |
| | $AUC_{\infty}$ | 22400 | 21700 | 1.032 | 0.895 – 1.191 |
| | **S-Warfarin (CYP2C9 Probe Substrate)** | | | | |
| Administration with risankizumab[a] vs. Administration without risankizumab[b] | $C_{max}$ | 490 | 534 | 0.916 | 0.859 – 0.977 |
| | $AUC_{0-t}$ | 14600 | 15800 | 0.925 | 0.894 – 0.957 |
| | $AUC_{\infty}$ | 15700 | 16900 | 0.931 | 0.896 – 0.968 |
| | **Omeprazole (CYP2C19 Probe Substrate)** | | | | |
| Administration with risankizumab[a] vs. Administration without risankizumab[b] | $C_{max}$ | 192 | 226 | 0.849 | 0.725 – 0.994 |
| | $AUC_{0-t}$ | 431 | 464 | 0.928 | 0.820 – 1.051 |
| | $AUC_{\infty}$ | 471 | 503 | 0.938 | 0.819 – 1.073 |

**Summary/Conclusions (Continued)**
**Pharmacokinetic Results (Continued):**

| Regimens Test vs. Reference | Pharmacokinetic Parameter | Central Value | | Exposure Ratio | |
|---|---|---|---|---|---|
| | | Test | Reference | Point Estimate | 90% Confidence Interval |
| | **Metoprolol (CYP2D6 Probe Substrate)** | | | | |
| Administration with risankizumab[a] vs. Administration without risankizumab[b] | $C_{max}$ | 31.0 | 32.1 | 0.968 | 0.880 – 1.065 |
| | $AUC_{0-t}$ | 179 | 177 | 1.013 | 0.927 – 1.106 |
| | $AUC_{\infty}$ | 184 | 183 | 1.008 | 0.922 – 1.103 |
| | **Midazolam (CYP3A Probe Substrate)** | | | | |
| Administration with risankizumab[a] vs. Administration without risankizumab[b] | $C_{max}$ | 8.91 | 8.70 | 1.025 | 0.960 – 1.093 |
| | $AUC_{0-t}$ | 27.0 | 26.7 | 1.010 | 0.939 – 1.086 |
| | $AUC_{\infty}$ | 28.2 | 27.9 | 1.012 | 0.942 – 1.087 |

a. Visit 7 Day 98: CYP cocktail (caffeine 100 mg + warfarin 10 mg + omeprazole 20 mg + metoprolol 50 mg + midazolam 2 mg) + risankizumab 150 mg SC (test).

b. Visit 2 Day 1: CYP cocktail (caffeine 100 mg + warfarin 10 mg + omeprazole 20 mg + metoprolol 50 mg + midazolam 2 mg) (reference).

**Summary/Conclusions (Continued)**
**Pharmacokinetic Results (Continued):**

| Regimens Test vs. Reference | Pharmacokinetic Parameter | Central Value | | Exposure Ratio | |
|---|---|---|---|---|---|
| | | Test | Reference | Point Estimate | 90% Confidence Interval |
| | **Paraxanthine to Caffeine AUC Ratio CYP1A2 Activity Marker** | | | | |
| Administration with risankizumab[a] vs. Administration without risankizumab[b] | $AUC_{0-t}$ | 0.727 | 0.750 | 0.969 | 0.891 – 1.053 |
| | $AUC_{\infty}$ | 0.815 | 0.810 | 1.007 | 0.934 – 1.085 |
| | **5-Hydroxy-Omeprazole to Omeprazole AUC Ratio CPY2C19 Activity Marker** | | | | |
| Administration with risankizumab[a] vs. Administration without risankizumab[b] | $AUC_{0-t}$ | 1.04 | 1.06 | 0.981 | 0.908 – 1.060 |
| | $AUC_{\infty}$ | 1.07 | 1.08 | 0.991 | 0.911 – 1.078 |
| | **Metoprolol to Alpha-Hydroxymetoprolol AUC Ratio CYP2D6 Activity Marker** | | | | |
| Administration with risankizumab[a] vs. Administration without risankizumab[b] | $AUC_{0-t}$ | 1.56 | 1.59 | 0.982 | 0.901 – 1.071 |
| | $AUC_{\infty}$ | 1.72 | 1.77 | 0.970 | 0.887 – 1.060 |
| | **Midazolam to 1-Hydroxy-Midazolam AUC Ratio CYP3A Activity Marker** | | | | |
| Administration with risankizumab[a] vs. Administration without risankizumab[b] | $AUC_{0-t}$ | 0.233 | 0.250 | 0.930 | 0.844 – 1.024 |
| | $AUC_{\infty}$ | 0.237 | 0.254 | 0.933 | 0.851 – 1.023 |

a. Visit 7 Day 98: CYP cocktail (caffeine 100 mg + warfarin 10 mg + omeprazole 20 mg + metoprolol 50 mg + midazolam 2 mg) + risankizumab 150 mg SC (test).

b. Visit 2 Day 1: CYP cocktail (caffeine 100 mg + warfarin 10 mg + omeprazole 20 mg + metoprolol 50 mg + midazolam 2 mg) (reference).

**Summary/Conclusions (Continued)**

**Safety Results:**

The regimens tested were generally well tolerated by the subjects. No clinically significant vital signs or laboratory measurements were observed during the course of the study. There was no pattern to the adverse events reported, and no new safety issues were identified from this study.

**Conclusions:**

Repeated administration of risankizumab 150 mg SC every 4 weeks had no effect on the exposures of probe substrates of CYP1A2 (caffeine 100 mg), CYP2C9 (warfarin 10 mg), CYP2C19 (omeprazole 20 mg), CYP2D6 (metoprolol 50 mg) and CYP3A (midazolam 2 mg) in subjects with plaque psoriasis. The 90% confidence intervals for the ratios of the probe substrates $C_{max}$, $AUC_{0-t,}$ and $AUC_{0-\infty}$ when administered 6 days following the fourth dose of risankizumab 150 mg SC every 4 weeks versus when these substrates were administered prior to initiating risankizumab treatment were within the default no-effect boundaries of 0.8 to 1.25 (with exception of the lower 90% confidence bound for omeprazole $C_{max}$ ratio which extended slightly below 0.8). Consistent with these results, risankizumab had no effect on evaluated metabolite-to-parent AUC ratios for these probe substrates.

Risankizumab plasma exposures evaluated with the every-4-week 150 mg SC administration in this study significantly exceeded the exposures for the proposed risankizumab clinical regimen (150 mg at Week 0, 4 and every 12 weeks thereafter) in subjects with psoriasis.