Name of Sponsor/Company: Astellas Pharma Global Development, Inc. (APGD) (formerly Astellas Pharma US, Inc.)		
Name of Finished Product: Not yet named		
Name of Active Ingredient: ASP015K		

SYNOPSIS

Title of Study: A Phase 1b, Open-Label, Single Sequence, Drug Interaction Study to Evaluate the Pharmacokinetics of ASP015K and Methotrexate in Subjects with Rheumatoid Arthritis

Responsible Medical Officer/Investigators: [redacted] PhD; [redacted] Astellas Pharma Global Development, Inc.

Study Center(s): One study center: [redacted] United States

Publication (reference): None

Study Period: Up to 31 days, including screening

Date of first enrollment (Study initiation date): January 22, 2010

Date of last evaluation (Study completion date): March 25, 2010

Phase of Development: Phase 1b

Objectives: The primary objective of the study was to evaluate the effect of ASP015K 100 mg twice daily on the pharmacokinetics of once weekly oral methotrexate 15 to 25 mg.

The secondary objectives were:

- To evaluate the effect of methotrexate on steady-state pharmacokinetics of ASP015K.
- To evaluate safety and tolerability of coadministration of ASP015K and methotrexate in subjects with rheumatoid arthritis (RA).

Methodology: This was an open-label, single sequence, drug interaction study with twice daily oral ASP015K (100 mg) and once weekly oral methotrexate (15 to 25 mg). Sixteen (16) subjects with RA and currently being treated with methotrexate (15 to 25 mg) were to be enrolled into the study.

Subjects checked in on day -1 and remained confined until all the exit procedures had been performed on the morning of day 10. Subjects were dosed in the fed state. On day 1, subjects received their respective prescribed 15 to 25 mg morning dose of methotrexate. Beginning on day 3, subjects received ASP015K 100 mg twice daily approximately 12 hours apart through the morning of day 9. A single 15 to 25 mg dose of methotrexate was coadministered on day 8. Subjects returned for 1 posttreatment follow-up visit on day 13.

Serial blood samples were obtained for pharmacokinetic assessments of methotrexate and 7-hydroxymethotrexate (7-OH-MTX) on days 1 and 8 at predose and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36 and 48 hours postdose. Serial blood samples for pharmacokinetic assessments of ASP015K were obtained on days 7 and 8 at predose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 12 hours after the morning dose of ASP015K. For the

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determination of trough levels, blood samples were also to be collected prior to the morning dose of ASP015K on days 3, 4, 5, 6 and 9.

Serial urine samples were collected for methotrexate and 7-OH-MTX pharmacokinetic assessments on days 1 and 8 at predose and at intervals of 0 to 4, 4 to 8, 8 to 12, 12 to 24 and 24 to 48 hours postdose. Serial urine samples for pharmacokinetic assessments of ASP015K were obtained on days 7 and 8 at predose and at intervals of 0 to 4, 4 to 8 and 8 to 12 hours after the morning dose of ASP015K.

Vital sign measurements, physical examinations, 12-lead electrocardiograms (ECGs), and clinical laboratory testing (chemistry, hematology, and urinalysis) were performed at predetermined timepoints.

Number of Subjects (planned, enrolled and analyzed): A total of 16 subjects with RA were planned; 15 subjects with RA were enrolled.

The Safety Analysis Set (SAF) was defined as all enrolled subjects who received study drug (methotrexate or ASP015K). All 15 subjects were included in this analysis set.

The Pharmacokinetic Analysis Set (PKAS) was defined as all subjects in the SAF whose pharmacokinetic data were adequate, as defined by the pharmacokineticist, for the calculation of at least one primary plasma pharmacokinetic parameter, AUC_{inf} or C_{max} of methotrexate. All 15 subjects were included in this analysis set.

Diagnosis and Main Criteria for Inclusion: Subjects or their legally authorized representatives must have signed an informed consent form (ICF) and Health Insurance Portability and Accountability Act (HIPAA) authorization form. The subjects must have had a clinical diagnosis of RA at least 6 months prior to screening and have been on a stable 15 to 25 mg dose of methotrexate for at least 28 days prior to screening. Female subjects had to be at least 2 years post menopausal or surgically sterile. Male subjects agreed to sexual abstinence and/or used a highly effective method of birth control during the study period and for 60 days after the last dose of study drug. Subjects were excluded if they had any clinically significant illness, medical condition or laboratory abnormality that, in the opinion of the investigator, precluded the subject from participating in the study; were receiving a biologic disease modifying antirheumatic drug (DMARD) therapy or had received live virus vaccination within the last 30 days prior to study drug administration; had a body mass index greater than 35 kg/m^2 or an absolute neutrophil count less than 2500 $cells/mm^3$; or had a history of a positive test result for hepatitis B surface antigen, hepatitis C antibody or human immunodeficiency virus infection.

Test Product, Dose and Mode of Administration, Batch Numbers:

ASP015K 100 mg (lot number 28576.1) was administered orally twice daily. Methotrexate 15 to 25 mg (lot number 28576.2) was administered orally once weekly.

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Duration of Treatment:

Methotrexate (15-25 mg) was administered on day 1 and day 8. ASP015K (100 mg) was administered twice daily on days 3 to 8, inclusive, and on the morning of day 9.

Reference Product, Dose and Mode of Administration, Batch Numbers: None

Criteria for Evaluation: Efficacy was not evaluated in this study. The primary pharmacokinetic variables were the area under the concentration-time curve in plasma from time 0 extrapolated to infinity (AUC_{inf}) and the maximum observed concentration in plasma (C_{max}) for methotrexate on days 1 and 8. Additional plasma pharmacokinetic variables for methotrexate and 7-OH-MTX (days 1 and 8) included the following: area under the concentration-time curve in plasma from the time of dosing to the last quantifiable concentration (AUC_{last}), time to attain C_{max} (t_{max}), apparent terminal elimination half-life ($t_{1/2}$), apparent body clearance (CL/F) (only for methotrexate), apparent volume of distribution (Vz/F) (only for methotrexate) and metabolite ratio (MR) defined as AUC_{inf}(7-OH-MTX)/AUC_{inf}(methotrexate). Urine pharmacokinetic variables for methotrexate and 7-OH-MTX (days 1 and 8) included the following: cumulative amount of analyte excreted into the urine up to the collection time of the last measurable concentration (Ae_{last}), fraction of analyte excreted in urine up to the collection time of the last measurable concentration and expressed as a percentage (Ae_{last}%) and renal clearance (CL_R). Additional plasma pharmacokinetic variables for ASP015K (days 7 and 8) included the following: area under the concentration-time curve in plasma during the time interval between consecutive dosing (AUC_{tau}), maximum observed concentration in plasma at steady-state ($C_{max, ss}$), time to attain $C_{max, ss}$ ($t_{max, ss}$), average concentration (C_{avg}), apparent body clearance at steady-state (calculated as dose/AUC_{tau} [CL/F_{ss}]), apparent volume of distribution during terminal phase at steady-state (calculated as CL/F_{ss}/kel [Vz/F_{ss}]), morning trough concentration ($C_{trough, AM}$) and evening trough concentration ($C_{trough, PM}$). Urine pharmacokinetic variables for ASP015K included Ae_{last}, Ae_{last}% and CL_R.

Safety assessment included evaluation of adverse events (AEs), clinical laboratory tests (hematology, chemistry, urinalysis and lipid profile), vital sign measurements, physical examination findings, and 12-lead ECGs.

Statistical Methods: All data processing, summarization and analyses were performed using SAS® Version 9.1.

Individual subject plasma and urine concentrations for methotrexate and its metabolite 7-OH-MTX were listed and summarized using descriptive statistics on days 1 and 8 at each timepoint/interval. Individual subject plasma and urine concentrations for ASP015K were listed and summarized using descriptive statistics on days 7 and 8 at each timepoint/interval; trough concentrations for ASP015K were similarly listed and summarized on days 3, 4, 5, 6, 7, 8 and 9. Values below the lower limit of quantification (LLOQ) were set to 0 for calculation of descriptive statistics. Standard graphics for plasma concentrations for methotrexate and its metabolite 7-OH-MTX including mean concentration-time profiles (both linear and semi-log), individual subject concentration-time profiles (both linear and semi-log), and overlay plots of concentration-time profiles on

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days 1 and 8 were produced. Similar graphics for plasma concentration for ASP015K on days 7 and 8 were also produced.

Individual subject plasma pharmacokinetic parameters for methotrexate and its metabolite 7-OH-MTX were listed and summarized using descriptive statistics on days 1 and 8. Individual subject plasma pharmacokinetic parameters for ASP015K were listed and summarized using descriptive statistics on days 7 and 8. As an exploratory analysis, the summary tables and mean plots were created by sex.

The primary variables were the AUC_{inf} and C_{max} of methotrexate. To assess drug interaction, a 90% confidence interval (CI) was constructed for the ratio of geometric means of plasma AUC_{inf} and C_{max} of methotrexate plus ASP015K (day 8) versus methotrexate alone (day 1), based on a mixed-effects model on natural logarithm (log) transformed AUC_{inf} and C_{max} with treatment as the fixed effect and subject as a random effect. Absence of effect of ASP015K on methotrexate would be concluded if the 90% CI for both AUC_{inf} and C_{max} ratios fell within the interval of 0.80 and 1.25. Similar statistics were for the MR provided AUC_{inf} for 7-OH-MTX could be adequately calculated. Similar to the primary analysis, the 90% CI was constructed for the geometric mean ratio of AUC_{tau} and $C_{max, ss}$ of ASP015K, with ASP015K alone (day 7) versus ASP015K plus methotrexate (day 8), to investigate whether methotrexate had an effect on the steady-state pharmacokinetics of ASP015K.

Assessment of steady-state of ASP015K was performed using trough morning dose concentrations on days 4 to 8. The subject was treated as a random effect while day was treated as a fixed effect. Within the framework of the analysis of variance (ANOVA) model, the following contrast was assessed: day 4 versus the average of troughs on days 5 through 8. Steady-state was assumed if the P value for the contrast was above 0.05. If steady-state was not established, the contrast was repeated with the next day versus the average of other trough concentrations beyond next day. In addition, a plot of the mean trough concentration versus day was generated as a visual inspection for the attainment of steady-state. Additional exploratory analyses were performed as appropriate.

In this study, individual subjects were to receive their respective prescribed 15 to 25 mg dose of methotrexate. Although not specified in the SAP, descriptive statistics for plasma and urine concentrations of methotrexate and 7-OH-MTX were also presented as dose-normalized values. Figures were created for plasma concentrations of methotrexate and 7-OH-MTX using dose-normalized values. Scatter plots were generated depicting plasma methotrexate or 7-OH-MTX pharmacokinetic parameters versus methotrexate dose by visit. A summary of plasma methotrexate pharmacokinetic parameters by methotrexate dose was also presented. Among the enrolled subjects, 10 subjects received 15 mg methotrexate as their prescribed dose. Summary descriptive statistics for plasma concentrations of methotrexate and 7-OH-MTX and a statistical assessment of the effect of ASP015K on the pharmacokinetics of methotrexate were presented for this subset of subjects receiving methotrexate 15 mg. Figures depicting plasma methotrexate concentrations over time were also generated for this group of subjects. In addition, a statistical assessment of the effect of ASP015K on the

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pharmacokinetics of methotrexate was presented for subjects in the PKAS who completed the study; this analysis excluded 1 of the 15 subjects. For ASP015K, V_z/F at steady-state was not calculated because the apparent elimination rate was impossible to estimate within the time span of the dosing interval. In addition, for ASP05K, Ae_{12} and Ae_{12}% were used instead of Ae_{last} and Ae_{last}% as notations for the cumulative amount excreted and fraction of analyte excreted and expressed as a percentage.

Summary tables were provided for safety variables, including AEs, clinical laboratory test results, vital sign measurements and 12-lead ECG findings. Safety data for individual subjects were provided in the data listings.

Summary of Results/Conclusions:

Disposition and Demographics: A total of 15 subjects were enrolled in this study; 14 subjects completed the study. One subject discontinued the study due to a serious adverse event (SAE). The subject experienced an SAE of urinary tract infection prior to receiving the first dose of methotrexate as part of the study, and subsequently experienced another SAE of gastroenteritis after receiving the day 1 dose of methotrexate but before receiving ASP015K [Table 1].

The majority of subjects enrolled in the study were white (93.3%). A total of 73.3% (11/15) of subjects were female and 26.7% (4/15) were male [Table 2].

Study Drug Exposure: In this study, the treatment included treatment with methotrexate on days 1 and 8, and ASP015K twice daily on days 3 to 8 and the morning of day 9. All 15 subjects received the first dose of methotrexate. One subject was discontinued from the study after receiving the first methotrexate dose within the study and before receiving ASP015K; the remaining 14 subjects received methotrexate and ASP015K on the specified days of treatment.

Pharmacokinetic Results:

Effect of ASP015K on Methotrexate

The mean plasma concentrations of methotrexate over time were similar on day 1 (a single dose of 15 to 25 mg methotrexate, alone) and day 8 (15 to 25 mg methotrexate plus ASP015K 100 mg twice daily). The median t_{max} for methotrexate was 1.5 and 1.8 hours on days 1 and 8, respectively. The median t_{max} for 7-OH-MTX was 6.0 and 11.9 hours on days 1 and 8, respectively. Median $t_{1/2}$ values were also longer for 7-OH-MTX compared with methotrexate (3.6 and 4.5 hours for methotrexate vs 9.5 and 11.2 hours for 7-OH-MTX on days 1 and 8, respectively). Mean MR decreased from 0.74 on day 1 with methotrexate alone to 0.53 on day 8 for methotrexate in the presence of ASP015K [Table 3].

The geometric mean ratios for coadministration of ASP015K 100 mg twice daily with a single dose of methotrexate 15 to 25 mg relative to methotrexate 15 to 25 mg alone were 103% for AUC_{inf} and 92% for C_{max} for the 14 subjects who received both scheduled methotrexate doses; the 90% CIs for all these parameters were

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within the 80% to 125% equivalence range [Table 4]. Similar results were obtained with data from all 15 subjects and from the 10 subjects who received the same 15 mg dose of methotrexate. These results indicate that coadministration of methotrexate and ASP015K had no effect on the pharmacokinetic profile of methotrexate. For the MR, the geometric mean ratio for coadministration of ASP015K 100 mg twice daily with a single dose of methotrexate 15 to 25 mg relative to methotrexate 15 to 25 mg alone was 73 with a 90% CI from 66 to 80 [Table 4], suggesting an approximately 27% decrease in the exposure to 7-OH-MTX.

Median Ae_{last}% and CL_R for methotrexate were similar between day 1 and day 8. Median Ae_{last}% for 7-OH-MTX was lower on day 8 compared to day 1. Median CL_R for 7-OH-MTX was also lower on day 8 compared to day 1, but large variations were noted in these values [Table 5].

Effect of Methotrexate on ASP015K

The mean plasma concentrations of ASP015K over time were similar on day 7 (ASP015K 100 mg twice daily, alone) and day 8 (methotrexate 15 to 25 mg plus ASP015K 100 mg twice daily) [Table 6]. Visual examination of the mean trough concentration plot and statistical analysis of steady-state using trough concentrations ($P = 0.8309$ on day 5) suggest that steady-state for ASP015K was reached on day 5.

The geometric mean ratios for coadministration of ASP015K 100 mg twice daily with a single dose of methotrexate 15 to 25 mg relative to ASP015K alone were 98% for $AUC_{tau, ss}$ and 92% for $C_{max, ss}$. The 90% CI for ASP015K $AUC_{tau, ss}$ was within the 80% to 125% equivalence range; therefore, coadministration of a single dose of methotrexate 15 to 25 mg with ASP015K 100 mg twice daily did not appear to affect this parameter. Mean $C_{max, ss}$ was slightly reduced in the presence of methotrexate (255.51 ng/mL for ASP015K alone vs 234.94 ng/mL for ASP015K plus methotrexate) [Table 7]. The lower limit of the 90% CI for ASP015K $C_{max, ss,}$ 78%, was slightly below 80%.

Urine pharmacokinetic parameters for ASP015K were summarized. Mean Ae_{12}, Ae_{12}% (defined as Ae_{12} divided by ASP015K dose x 100) and CL_R were similar on day 7 (ASP015K 100 mg twice daily alone) and day 8 (15 to 25 mg methotrexate plus ASP015K 100 mg twice daily) [Table 8].

Pharmacokinetic Conclusions

Administration of ASP015K 100 mg twice daily did not result in changes in AUC_{inf} and C_{max} of methotrexate in plasma following administration of a single oral 15 to 25 mg dose of methotrexate.

A single oral 15 to 25 mg dose of methotrexate did not affect steady-state AUC_{tau} of ASP015K.

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Safety Results:

- Eleven subjects (73.3%) reported a total of 44 TEAEs during the study [Table 9].
- There were no deaths.
- One subject experienced 2 SAEs, urinary tract infection and gastroenteritis, and was discontinued from the study. The subject received the day 1 dose of methotrexate but did receive any dose of ASP015K.
- A total of 7 subjects had mild AEs, 3 subjects had moderate AEs and 1 subject had severe or medically significant AEs as per the NCI-CTC grading scale.
- Overall, 6 (40.0%) subjects experienced TEAEs that were considered to be related to study drug; 2 (13.3%) subjects in the methotrexate alone group, 4 (28.6%) subjects in the ASP015K alone group and 2 (14.3%) subjects in the methotrexate plus ASP015K group experienced drug-related TEAEs. The drug-related AEs were all within the SOC of gastrointestinal disorders.
- There were no clinically meaningful changes from baseline for any of the clinical laboratory parameters (hematology, biochemistry or urinalysis) assessed during this study. No abnormal clinical laboratory values were reported as AEs and no subject discontinued from the study due to an abnormal laboratory value.
- Few clinically relevant changes from baseline were observed for any of the vital sign measurements. One subject experienced an AE of sinus tachycardia in conjunction with SAEs of urinary tract infection and gastroenteritis. No other changes in vital sign measurements were reported as AEs.
- No clinically significant ECG findings were observed.

CONCLUSIONS: The administration of ASP015K 100 mg twice daily did not affect the pharmacokinetics of a single methotrexate dose. The administration of a single dose of methotrexate 15 to 25 mg did not affect the area under the concentration-time curve at steady state of ASP015K. The coadministration of a single dose of methotrexate 15 to 25 mg with ASP015K 100 mg twice daily was well tolerated in this study with no indication of safety concerns.

Date of Report: 04 Nov 2010

Table 1 Subject Disposition

Analysis Set	Treatment Period			Overall n = 15
	MTX Alone† n = 15	ASP015K Alone‡ n = 14	MTX + ASP015K§ n = 14	
Safety Analysis Set (SAF), n (%)	15 (100.0)	14 (100.0)	14 (100.0)	15 (100.0)
Pharmacokinetic Analysis Set (PKAS), n (%)	15 (100.0)	14 (100.0)	14 (100.0)	15 (100.0)
Treatment discontinuation ¶, n (%)				
Yes	1 (6.7)	0	0	1 (6.7)
No	14 (93.3)	14 (100.0)	14 (100.0)	14 (93.3)
Primary reason for discontinuation, n (%)				
Adverse event	1 (6.7)	0	0	1 (6.7)
Study discontinuation ††, n (%)				
Yes	1 (6.7)	0	0	1 (6.7)
No	14 (93.3)	14 (100.0)	14 (100.0)	14 (93.3)
Primary reason for discontinuation, n (%)				
Adverse event‡‡	1 (6.7)	0	0	1 (6.7)

All subjects who received at least 1 dose of study drug (SAF) and whose pharmacokinetic data were adequate, as defined by the pharmacokineticist, for the calculation of at least one primary plasma pharmacokinetic parameter (PKAS). MTX (15-25 mg) was administered on day 1 and day 8. ASP015K (100 mg) was administered twice daily on days 3 to 8, inclusive, and on the morning of day 9.

MTX: methotrexate; PKAS: Pharmacokinetic Analysis Set; SAF: Safety Analysis Set

† MTX alone was day 1 (after MTX dose) to day 3 (prior to ASP015K dose).

‡ ASP015K alone was day 3 (after ASP015K dose) to day 8 (prior to MTX dose).

§ MTX + ASP015K was day 8 (after MTX dose) to end of study.

¶ Subjects who did not complete the treatment on day 9

†† Subjects who did not complete the study (day 13 visit)

‡‡ The reason for discontinuation was listed as "Other" on Table 12.1.1.3.1; however, this refers to a discontinuation due to a serious adverse event [Appendix 13.2.1.2] and is listed as such here. This is the same subject who discontinued treatment. The subject experienced a nontreatment-emergent serious adverse event of urinary tract infection prior to receiving the first dose of methotrexate as part of the study and subsequently experienced another serious adverse event of gastroenteritis after receiving the day 1 dose of methotrexate but before receiving ASP015K. The subject was discontinued from the study; a narrative is provided in Attachment 1.

Source: Table 12.1.1.1, Table 12.1.1.2.1, Table 12.1.1.3.1

Table 2 Summary of Demographics and Baseline Characteristics (SAF)

Parameter Category/Statistic	**Overall** **n=15**
Sex, n (%)	
Male	4 (26.7)
Female	11 (73.3)
Race, n (%)	
White	14 (93.3)
Black or African American	1 (6.7)
Ethnicity, n (%)	
Not Hispanic or Latino	13 (86.7)
Hispanic or Latino	2 (13.3)
Age† (years)	
Mean (SD)	56.13 (7.999)
Median	58.00
Minimum–Maximum	35.0 – 64.0
Weight‡ (kg)	
Mean (SD)	69.71 (12.409)
Median	70.50
Minimum–Maximum	44.5 – 86.8
Height (cm)	
Mean (SD)	166.70 (9.430)
Median	165.00
Minimum–Maximum	156.8 – 185.4
Body Mass Index‡ (kg/m^2)	
Mean (SD)	24.97 (3.096)
Median	25.90
Minimum–Maximum	18.0 – 28.7

All subjects who received at least 1 dose of study drug (Safety Analysis Set [SAF]).

Body mass index = weight (kg)/height (m^2)

† Age was calculated using the first dose date of methotrexate and the date of birth.

‡ Weight corresponded to the screening visit. Weight at screening was used for the body mass index.

Source: Table 12.1.2.1

Table 3 Summary of Plasma Pharmacokinetic Parameters of Methotrexate and the Metabolite 7-OH-MTX

Parameter (units)	**Methotrexate**		**7-OH-MTX**	
	Day 1† n = 15	**Day 8† n = 14**	**Day 1† n = 15**	**Day 8† n = 14**
AUC_{inf} (h•ng/mL)				
Mean	2056.67	2069.83	1501.42	1106.16
SD	658.681	656.130	792.467	752.969
Median	2150.88	2189.66	1451.37	906.98
Min	864.8	801.3	371.6	385.0
Max	2866.4	3079.0	3639.5	3414.0
C_{max} (ng/mL)				
Mean	401.02	356.95	65.27	41.81
SD	135.422	105.662	28.370	19.943
Median	411.28	358.87	64.94	37.86
Min	115.7	121.9	20.5	18.1
Max	582.7	523.3	113.2	92.2
AUC_{last} (h•ng/mL)				
Mean	2041.64	2050.91	1395.81	977.92
SD	659.134	656.787	683.222	603.700
Median	2132.24	2164.65	1374.50	844.75
Min	842.6	779.7	359.6	365.2
Max	2852.8	3063.7	3118.8	2796.3
t_{max} (h)				
Mean	1.922	1.826	7.751	9.964
SD	0.9298	0.7474	2.4052	2.8937
Median	1.500	1.767	6.017	11.900
Min	1.00	0.50	6.00	4.00
Max	4.00	4.00	12.33	12.00
$t_{1/2}$ (h)				
Mean	4.406	5.605	9.994	12.372
SD	1.6926	2.7508	2.1372	3.4764
Median	3.637	4.497	9.493	11.203
Min	2.99	3.05	6.59	8.69
Max	8.57	11.35	14.63	21.70
CL/F (L/h)				
Mean	8.836	9.010	NA	NA
SD	2.9733	4.1754		
Median	7.687	7.282		
Min	6.11	5.68		
Max	17.35	18.72		
V_Z/F (L)				
Mean	55.864	70.238	NA	NA
SD	26.3903	38.9717		
Median	48.373	50.775		
Min	27.17	31.74		
Max	112.66	142.94		
AUC%Extrapolated				
Mean	0.845	1.061	5.854	9.472
SD	0.5429	0.6119	3.1906	5.5727
Median	0.698	0.839	4.593	7.393
Min	0.38	0.50	2.90	3.14
Max	2.57	2.69	14.31	22.37

Table continued on next page

Parameter (units)	Methotrexate		7-OH-MTX	
	Day 1† n = 15	Day 8† n = 14	Day 1† n = 15	Day 8† n = 14
Metabolite Ratio‡				
Mean	NA	NA	0.7402	0.5316
SD			0.30683	0.24284
Median			0.7702	0.4975
Min			0.271	0.242
Max			1.276	1.109

All subjects who received at least 1 dose of study drug (Safety Analysis Set) and whose pharmacokinetic data were adequate, as defined by the pharmacokineticist, for the calculation of at least one primary plasma pharmacokinetic parameter (Pharmacokinetic Analysis Set).

AUC_{inf}: area under the plasma concentration-time curve from time 0 extrapolated to infinity; AUC_{last}: area under the plasma concentration-time curve from the time of dose initiation to the time of the last measurable concentration; AUC%Extrapolated: percentage of AUC_{inf} attributed to C_{last}/k_{el}; CL/F: total body clearance; C_{max}: maximum observed concentration; Max: maximum; Min: minimum; MTX: methotrexate; NA: not applicable; $t_{1/2}$: apparent terminal elimination half-life; t_{max}: time to attain maximum observed concentration; V_Z/F: volume of distribution

† Methotrexate (15-25 mg) was administered on day 1 and day 8. ASP015K (100 mg) was administered twice daily on days 3 to 8, inclusive, and on the morning of day 9.

‡ The metabolite ratio was defined as AUC_{inf}(7-OH-MTX)/AUC_{inf}(methotrexate).

Source: Table 12.4.4.1 and Table 12.4.4.2

Table 4 Statistical Analysis of the Effect of ASP015K on Pharmacokinetics of Methotrexate

Parameter (units)	Geometric Means†		Geometric Mean Ratio‡ (MTX + ASP015K / MTX Alone)	90% CI for Geometric Mean Ratio‡
	MTX Alone n=14§	MTX + ASP015K n=14		
AUC_{inf} (h•ng/mL)	1899.87	1951.11	102.70	92.98, 113.43
C_{max} (ng/mL)	365.86	338.00	92.38	83.06, 102.76
Metabolite Ratio ¶	0.67	0.48	72.67	65.63, 80.46

All subjects who received at least 1 dose of study drug (Safety Analysis Set) and whose pharmacokinetic data were adequate, as defined by the pharmacokineticist, for the calculation of at least one primary plasma pharmacokinetic parameter and who completed the study.

MTX (15-25 mg) was administered on day 1 and day 8. ASP015K (100 mg) was administered twice daily on days 3 to 8, inclusive, and on the morning of day 9.

AUC_{inf}: area under the plasma concentration-time curve from time 0 extrapolated to infinity; C_{max}: maximum observed concentration; MTX: methotrexate

† Exponentiated values of the least square mean from the mixed-effects model of the log-transformed data.

‡ Geometric mean ratio and the corresponding confidence limits are expressed as percentages.

§ One subject did not complete the study and was excluded from this analysis.

¶ The metabolite ratio was defined as AUC_{inf}(7-OH-MTX)/AUC_{inf}(methotrexate).

Source: Table 12.4.6.5

Table 5 Summary of Urine Pharmacokinetic Parameters of Methotrexate and the Metabolite 7-OH-MTX

Parameter	Methotrexate		7-OH-MTX	
	Day 1† n = 15	**Day 8† n = 14**	**Day 1† n = 15**	**Day 8† n = 14**
Ae_{last}%				
Mean (SD)	92.048 (87.0283)	67.053 (21.0537)	5.520 (2.7312)	2.800 (2.1638)
%CV	94.55	31.40	49.48	77.29
Median	73.923	73.483	5.269	2.323
Min – Max	31.45 – 398.55	21.26 – 90.00	1.36 – 9.34	0.19 – 8.30
Geometric Mean	75.350	62.762	4.774	1.921
CL_R(L/h)				
Mean (SD)	7.531 (5.8240)	5.675 (1.8411)	0.748 (0.4914)	0.455 (0.2563)
%CV	77.34	32.45	65.70	56.29
Median	6.784	5.715	0.675	0.464
Min – Max	2.43 – 27.56	1.36 – 9.01	0.21 – 2.26	0.04 – 0.94
Geometric Mean	6.431	5.278	0.638	0.365

All subjects who received at least 1 dose of study drug (Safety Analysis Set) and whose pharmacokinetic data were adequate, as defined by the pharmacokineticist, for the calculation of at least one primary plasma pharmacokinetic parameter (Pharmacokinetic Analysis Set).

Ae_{last}%: fraction of analyte excreted in urine up to the collection time of the last measurable concentration and expressed as a percentage; CL_R: renal clearance; CV: coefficient of variation; Max: maximum; Min: minimum; MTX: methotrexate

$Ae_{last}\% = (Ae_{last}/\text{methotrexate dose}) \times 100$

† Methotrexate (15-25 mg) was administered on day 1 and day 8. ASP015K (100 mg) was administered twice daily on days 3 to 8, inclusive, and on the morning of day 9.

Source: Table 12.4.5.1 and Table 12.4.5.2

Table 6 Summary of Plasma Pharmacokinetic Parameters of ASP015K

Parameter	ASP015K	
	Day 7† n = 14	**Day 8† n = 14**
$AUC_{tau, ss}$ (h•ng/mL) Mean (SD) Median Min – Max	 1009.68 (330.471) 931.51 465.2 – 1645.6	 1009.42 (366.166) 984.27 386.6 – 1717.3
$C_{max, ss}$ (ng/mL) Mean (SD) Median Min – Max	 266.28 (78.775) 261.19 156.5 – 389.4	 253.20 (87.857) 270.81 78.4 – 404.7
$t_{max, ss}$ (h) Mean (SD) Median Min – Max	 1.902 (0.7816) 1.542 0.98 – 3.00	 2.189 (1.8315) 1.767 0.55 – 8.08
C_{avg} (ng/mL) Mean (SD) Median Min – Max	 84.140 (27.5392) 77.626 38.77 – 137.13	 84.118 (30.5138) 82.022 32.21 – 143.11
CL/F_{ss} (L/h) Mean (SD) Median Min – Max	 110.342 (40.1995) 107.818 60.77 – 214.94	 115.671 (54.6023) 101.680 58.23 – 258.70
$C_{trough, AM}$ (ng/mL) Mean (SD) Median Min – Max	 36.966 (45.3504) 18.475 2.23 – 178.51	 29.901 (29.7136) 17.940 3.32 – 97.51
$C_{trough, PM}$ (ng/mL) Mean (SD) Median Min – Max	 16.704 (10.4535) 12.530 3.08 – 41.61	 18.298 (10.7071) 13.725 2.51 – 38.53

All subjects who received at least 1 dose of study drug (Safety Analysis Set) and whose pharmacokinetic data were adequate, as defined by the pharmacokineticist, for the calculation of at least one primary plasma pharmacokinetic parameter (Pharmacokinetic Analysis Set).

$AUC_{tau, ss}$: area under the plasma concentration-time curve during the time interval between consecutive dosing at steady-state; C_{avg}: average concentration; CL/F_{ss}: apparent body clearance at steady-state, calculated as dose/AUC_{tau}; $C_{max, ss}$: maximum observed concentration in plasma at steady-state; $C_{trough, AM}$: morning trough concentration; $C_{trough, PM}$: evening trough concentration; $t_{max, ss}$: time to attain $C_{max, ss}$

†Methotrexate (15-25 mg) was administered on day 1 and day 8. ASP015K (100 mg) was administered twice daily on days 3 to 8, inclusive, and on the morning of day 9.

Source: Table 12.4.4.3

Table 7 Statistical Analysis of the Effect of Methotrexate on Pharmacokinetics of ASP015K

Parameter (units)	Geometric Means†		Geometric Mean Ratio‡ (MTX + ASP015K / ASP015K Alone)	90% CI for Geometric Mean Ratio‡
	ASP015K Alone n=14	MTX + ASP015K n=14		
$AUC_{tau, ss}$ (h•ng/mL)	958.36	940.67	98.15	91.04, 105.82
$C_{max, ss}$ (ng/mL)	255.51	234.94	91.95	78.21, 108.09

All subjects who received at least 1 dose of study drug (Safety Analysis Set) and whose pharmacokinetic data were adequate, as defined by the pharmacokineticist, for the calculation of at least one primary plasma pharmacokinetic parameter (Pharmacokinetic Analysis Set).

MTX (15-25 mg) was administered on day 1 and day 8. ASP015K (100 mg) was administered twice daily on days 3 to 8, inclusive, and on the morning of day 9.

$AUC_{tau, ss}$: area under the plasma concentration-time curve during the time interval between consecutive dosing at steady-state; $C_{max, ss}$: maximum observed concentration in plasma at steady-state; MTX: methotrexate

† Exponentiated values of the least square mean from the mixed-effects model of the log-transformed data.

‡ Geometric mean ratio and the corresponding confidence limits are expressed as percentages.

Source: Table 12.4.6.2

Table 8 Summary of Urine Pharmacokinetic Parameters of ASP015K

Parameter (unit)	ASP015K	
	Day 7† n=14	Day 8† n=14
Ae_{12}%		
Mean (SD)	6.905 (4.5118)	5.909 (2.9898)
%CV	65.34	50.60
Median	5.426	5.762
Min – Max	1.74 – 16.21	1.80 – 11.70
Geometric Mean	5.570	5.097
CL_R(L/h)		
Mean (SD)	6.839 (3.6971)	5.888 (2.4128)
%CV	54.06	40.98
Median	5.994	5.348
Min – Max	1.54 – 13.84	2.04 – 10.60
Geometric Mean	5.819	5.425

All subjects who received at least 1 dose of study drug (Safety Analysis Set) and whose pharmacokinetic data were adequate, as defined by the pharmacokineticist, for the calculation of at least one primary plasma pharmacokinetic parameter (Pharmacokinetic Analysis Set).

Ae_{12}%: fraction of analyte excreted in urine up to the 12-hour collection time and expressed as a percentage; CL_R: renal clearance; CV: coefficient of variation; Max: maximum; Min: minimum

Ae_{12}% = (Ae_{12}/ASP015K dose) x 100

† Methotrexate (15-25 mg) was administered on day 1 and day 8. ASP015K (100 mg) was administered twice daily on days 3 to 8, inclusive, and on the morning of day 9.

Source: Table 12.4.5.3

Table 9 Treatment-Emergent Adverse Events

System Organ Class¶ Preferred Term (MedDRA v11.1)	Treatment Period MTX Alone† n=15	ASP015K Alone‡ n=14	MTX + ASP015K§ n=14	Overall n=15
	n (%)			
Overall - Subjects with at least 1 TEAE	**5 (33.3)**	**7 (50.0)**	**7 (50.0)**	**11 (73.3)**
Cardiac Disorders	**1 (6.7)**	**0**	**0**	**1 (6.7)**
Sinus tachycardia	1 (6.7)	0	0	1 (6.7)
Eye Disorders	**0**	**0**	**1 (7.1)**	**1 (6.7)**
Borderline glaucoma	0	0	1 (7.1)	1 (6.7)
Cataract	0	0	1 (7.1)	1 (6.7)
Conjunctival haemorrhage	0	0	1 (7.1)	1 (6.7)
Ocular hypertension	0	0	1 (7.1)	1 (6.7)
Gastrointestinal Disorders	**3 (20.0)**	**6 (42.9)**	**3 (21.4)**	**8 (53.3)**
Abdominal distension	1 (6.7)	0	0	1 (6.7)
Diarrhoea	1 (6.7)	1 (7.1)	1 (7.1)	2 (13.3)
Dry mouth	0	1 (7.1)	0	1 (6.7)
Dyspepsia	1 (6.7)	0	0	1 (6.7)
Eructation	0	1 (7.1)	1 (7.1)	1 (6.7)
Flatulence	0	4 (28.6)	1 (7.1)	4 (26.7)
Gastrooesophageal reflux disease	1 (6.7)	0	0	1 (6.7)
Glossodynia	0	0	1 (7.1)	1 (6.7)
Nausea	2 (13.3)	0	0	2 (13.3)
Vomiting	1 (6.7)	0	0	1 (6.7)
General Disorders and Administration Site Conditions	**1 (6.7)**	**0**	**0**	**1 (6.7)**
Pyrexia	1 (6.7)	0	0	1 (6.7)
Infections and Infestations	**1 (6.7)**	**0**	**2 (14.3)**	**3 (20.0)**
Gastroenteritis	1 (6.7)††	0	0	1 (6.7)
Pharyngitis	0	0	1 (7.1)	1 (6.7)
Urinary tract infection	0	0	1(7.1)	1 (6.7)
Injury, Poisoning and Procedural Complications	**0**	**0**	**1 (7.1)**	**1 (6.7)**
Retinal scar	0	0	1 (7.1)	1 (6.7)
Musculoskeletal and Connective Tissue Disorders	**1 (6.7)**	**2 (14.3)**	**1 (7.1)**	**2 (13.3)**
Muscle spasms	1 (6.7)	2 (14.3)	1 (7.1)	2 (13.3)
Nervous system disorders	**1 (6.7)**	**0**	**1 (7.1)**	**2 (13.3)**
Headache	1 (6.7)	0	1 (7.1)	2 (13.3)
Respiratory, Thoracic and Mediastinal Disorders	**0**	**1 (7.1)**	**1 (7.1)**	**2 (13.3)**
Oropharyngeal pain	0	1 (7.1)	1 (7.1)	2 (13.3)

All subjects who received at least 1 dose of study drug (Safety Analysis Set). MTX (15-25 mg) was administered on day 1 and day 8. ASP015K (100 mg) was administered twice daily on days 3 to 8, inclusive, and on the morning of day 9.

MTX: methotrexate; TEAE: treatment-emergent adverse event

† MTX alone was day 1 (after MTX dose) to day 3 (prior to ASP015K dose).

‡ ASP015K alone was day 3 (after ASP015K dose) to day 8 (prior to MTX dose).

§ MTX + ASP015K was day 8 (after MTX dose) to end of study.

¶ Within an SOC, a subject may have reported more than 1 type of AE.

Table footnotes continued on next page

†† The event of gastroenteritis was a serious adverse event that led to discontinuation of study drug. This subject also experienced a nontreatment-emergent serious adverse event of urinary tract infection prior to the first dose of methotrexate. A narrative for this subject is provided in Attachment 1.

Source: Table 12.6.1.2