Name of Sponsor/Company: Astellas Pharma Global Development Inc		
Name of Finished Product: Not Applicable		
Name of Active Ingredient: ASP1707		

SYNOPSIS

Title of Study: A Phase 1, Open-label, Single-sequence, Drug Interaction Study to Evaluate the Pharmacokinetics of ASP1707 and Methotrexate in Patients with Rheumatoid Arthritis

Investigators/Coordinating Investigator: [redacted] MD, PhD

Study Center(s): 1 center in Europe

Publication Based on the Study: No publications based on the results of this study were available at the time this original report was approved.

Study Period: 3Q2016 (Jul-Aug 2016)

Study Initiation Date (Date of First Evaluation): 25 Jul 2016

Study Completion Date (Date of Last Evaluation): 30 Aug 2016

Phase of Development: Phase 1

Objectives: The primary objective of the study was to evaluate the effect of ASP1707 30 mg twice daily on the pharmacokinetics of once weekly oral methotrexate (MTX) 10 to 25 mg.

The secondary objectives were:

- To evaluate the effect of MTX on multiple-dose pharmacokinetics of ASP1707.
- To evaluate safety and tolerability of coadministration of ASP1707 and MTX in patients with rheumatoid arthritis (RA).

Methodology: This was an open-label, single-sequence, drug interaction study with twice-daily oral ASP1707 (30 mg) and stable oral MTX (10 to 25 mg) dosing. Approximately 10 patients with inactive RA or active RA currently being treated with MTX (10 to 25 mg) were to be enrolled into the study located in 1 center in Europe.

Patients checked into the clinic on day 1 and remained confined until all of the exit procedures were performed on the morning of day 10. Forty-three blood samples were taken from the patients for pharmacokinetic assessments. Urine samples were collected up to 48 hours on days 1 and 8.

On day 1, patients received their respective prescribed 10 to 25 mg morning dose of MTX. Beginning on day 3, patients received ASP1707 30 mg twice daily approximately 12 hours apart through the morning of day 9. A single 10 to 25 mg dose of MTX was coadministered on day 8.

Patients were dosed orally in the fed state except on days 1, 7 and 8 (intensive pharmacokinetic sampling days). On days 1, 7 and 8, the morning dose of study drug was given after the patient had fasted for at least 10 hours prior and remained fasted for 4 hours post dosing. Patients received their regular lunch and dinner

approximately 4 hours and 10 hours after dosing. On days 2 through 6 and day 9, study drug was administered to patients in a fed state. All study drugs administered in a fed state were administered within 30 (±5) minutes of starting a standard meal. Patients returned for 1 posttreatment follow-up visit on day 13 (±1 day).

Number of Patients (Planned, Enrolled and Analyzed): The number of patients planned for the study was approximately 10, and a total of 10 patients were enrolled and analyzed.

Diagnosis and Main Criteria for Inclusion: All patients must have provided written informed consent prior to any study-specific procedures and must have met all of the inclusion and none of the exclusion criteria to be eligible for participation. Waivers to the inclusion or exclusion criteria were not allowed.

Inclusion:

1. An Independent Ethics Committee-approved written informed consent and privacy language as per national regulations was obtained from the patient or legally authorized representative prior to any study-related procedures (including withdrawal of prohibited medication, if applicable).
2. Female patient was either:
    - Of nonchildbearing potential:
        - postmenopausal (defined as at least 2 years after last regular menstrual cycle) prior to screening and follicle-stimulating hormone (FSH) ≥ 30 IU/mL, or
        - documented surgically sterile
    - Or, if of childbearing potential,
        - Agreed not to try to become pregnant during the study and for 28 days or 5 half-lives, whichever was longer, after the final study drug administration
        - And had a negative urine pregnancy test at screening
        - And, if heterosexually active, agreed to consistently use 2 forms of highly effective birth control* (at least 1 of which must be a barrier method) starting at screening and throughout the study period and for 28 days or 5 half-lives, whichever was longer, after the final study drug administration.

*Highly effective forms of birth control included:

- Established intrauterine devices or intrauterine systems.
- Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository.
- Any male partner that has undergone effective surgical sterilization.

3. Male patient and his female spouse/partner who is of childbearing potential must have been using highly effective forms of contraception consisting of 2 forms of birth control (1 of which must be a barrier method) starting at screening and continuing throughout the study period and for 60 days after the final study drug administration.
4. Female patient must have agreed not to breastfeed starting at screening and throughout the study period, and for 28 days or 5 half-lives, whichever was longer, after the final study drug administration.
5. Female patient must not have donated ova starting at screening and throughout the study period, and for 28 days or 5 half-lives, whichever was longer, after the final study drug administration.
6. Male patient must not have donated sperm starting at screening and throughout the study period, and for 60 days after the final study drug administration.

7. Patient agreed not to participate in another interventional study while on treatment.
8. Patient was between 18 and 65 years of age, inclusive, at screening.
9. Patient had a body mass index (BMI) of ≤ 35 kg/m2, inclusive, and must have weighed at least 50 kg at screening.
10. Patient must have had a clinical diagnosis of RA according to the 2010 criteria of the American College of Rheumatology (ACR)/ European League Against Rheumatism at least 6 months prior to screening.
11. Patient met the ACR 1991 revised criteria for RA Global Functional Status I or II.
12. Patient must have been on concomitant MTX at a stable 10 to 25 mg/week dose for ≥ 28 days prior to day 1 and throughout the study.
13. Patient on other medications (excluding MTX) for the treatment or RA at the time of screening must have been able to discontinue these medications 28 days or 5 half-lives (whichever is longer) before first study drug dose:
    - Hydroxychloroquine, cyclosporine, leflunomide and sulfasalazine
14. Patient use of nonsteroidal anti-inflammatory drugs, cyclooxygenase 2 inhibitors, folic acid, low dose opioids, hormone replacement therapy, corticosteroids (prednisone equivalent of ≤ 5 mg/day) for treatment of RA was allowed in the study. These medications must have been stable for ≥ 28 days prior to screening and patients were to remain on their regimen throughout the study. Occasional acetaminophen use (less than 2 g/day) was allowed.
15. Patient use of conventional and biologic disease-modifying antirheumatic drugs used to treat RA was allowed in this study. These medications must have been stable for 4 weeks prior to the study and remained stable during the study. Prior approval for its use must have been obtained from the sponsor.

Exclusion:

1. Patient had a previous history of clinically significant systemic disease which, in the opinion of the Investigator or the patient's general practitioner, might have confounded the results of the study or posed an additional risk in administering study drug(s) to the patient. This may have included, but was not limited to, a history of drug or food allergies, uncompensated heart failure, uncontrolled diabetes mellitus, severe hepatic failure, severe pulmonary disease or history of mental disease.
2. Patient had a history of any malignancy in the past 5 years, except for adequately-treated nonmelanoma skin cancer and adequately-treated-in-situ cervical cancer.
3. Patient had a positive serology test for hepatitis B surface antigen or hepatitis C virus antibody or human immunodeficiency virus 1+2 antibodies.
4. Patient had received any breast cancer resistance protein transporter inhibitors or substrates, with the exception of MTX, within 28 days or 5 half-lives, whichever was longer, prior to day 1.
5. Patient with liver enzyme test abnormalities, aspartate aminotransferase, alanine aminotransferase or total bilirubin > 2 times the upper limit of normal.
6. Patient had a recent history (within the last 6 months) of drug or alcohol abuse (as defined by the investigator) or a positive urine screen for alcohol or drugs of abuse/illegal drugs at screening or check-in.
7. Patient had participated in a previous clinical study with treatment with ASP1707.
8. Patient had received any investigational agent within 28 days or 5 half-lives, whichever was longer, prior to day 1.
9. Patient had had any significant blood loss, donated 1 unit (450 mL) of blood, or more, or had received a transfusion of any blood or blood products within 60 days or donated plasma within 7 days prior to day 1.

10. Patient was an employee of the Astellas group or vendors involved with the study.

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

- ASP1707 5 mg tablets, oral, 30 mg twice daily, batch number [redacted]

Duration of Treatment (or Duration of Study, if applicable):

Patients checked into the clinic on day 1 and remained confined until all of the exit procedures had been performed on the morning of day 10. Patients returned for 1 posttreatment follow-up visit on day 13 (±1 day).

- MTX: Stable dose from 10 to 25 mg once weekly
- ASP1707: 7 days (days 3 through 9)

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

- MTX 10 to 25 mg tablets, oral, once weekly, supplied by each individual patient

Criteria for Evaluation: The primary objective of the study was to evaluate the effect of ASP1707 30 mg twice daily on the pharmacokinetics of once-weekly oral MTX 10 to 25 mg. The secondary objectives were to evaluate the effect of MTX on multiple-dose pharmacokinetics of ASP1707 and to evaluate safety and tolerability of coadministration of ASP1707 and MTX in patients with RA.

The primary pharmacokinetic variables assessed included:

- MTX on days 1 and 8: AUC_{inf} and C_{max}

The secondary pharmacokinetic variables assessed included:

- MTX and 7-hydroxymethrotrexate (7-OH-MTX) on days 1 and 8:
    - Plasma:
        - MTX: AUC_{last}, t_{max}, $t_{1/2}$, CL/F and V_z/F
        - 7-OH-MTX: AUC_{last}, t_{max}, $t_{1/2}$ and MPR
    - Urine: Ae_{last}, Ae_{last}% and CL_R
- ASP1707 (ASP1707 and its S-enantiomer AS1948006) on days 7 and 8 in plasma:
    - ASP1707: AUC_{tau}, C_{max}, t_{max}, CL/F and C_{trough} (on days 5 through 9)
    - AS1948006: AUC_{tau}, C_{max}, t_{max}, C_{trough} and MPR

The exploratory variables assessed included:

- Luteinizing hormone (LH), FSH, estradiol and testosterone concentrations were measured in serum samples.
- Evaluation of disease activity scores [DAS28-CRP(3)] and measurement of tender and swollen joints (TJC28 and SJC28).

The safety variables assessed included:

- Vital signs (blood pressure, pulse rate and body temperature)
- Safety laboratory tests (hematology, biochemistry, serology and urinalysis)
- Adverse events (AEs), physical examination and 12-lead ECGs

Statistical Methods:

A total of 10 patients were assigned to 1 single treatment sequence. Assuming a within-patient coefficient of variation (CV) of 17% for AUC_{inf} and 20% for C_{max}, with a sample size of 10, the half-width of 90% CI of the geometric mean ratio (GMR) of ASP1707 and MTX combination versus MTX alone would be no more than 15% and 18% of the midpoint of the 90% CI for AUC_{inf} and C_{max}, respectively. If an estimate of GMR of 1 would be observed and the observed within-patient CV would be 17% for AUC_{inf} and 20% for C_{max} then the 90% CI of GMR would be (0.87, 1.15) for AUC_{inf} and (0.85, 1.18) for C_{max}.

Three populations were used for the analyses: the registered analysis set (REG), the safety analysis set (SAF) and the pharmacokinetic analysis set (PKAS). Detailed criteria for analysis sets were described in the abbreviated statistical analysis plan and the clinical study protocol. The allocation of patients to analysis sets was determined prior to database hard lock.

Demographic and other baseline characteristics as well as AEs, laboratory assessments, vital signs and exploratory analyses are summarized by descriptive statistics. For continuous variables, descriptive statistics include the number of patients (n), mean, SD, median, minimum and maximum. Frequencies and percentages are displayed for categorical data. Percentages by categories are based on the number of patients with no missing data, i.e., add up to 100%.

In addition to descriptive statistics, summaries of PK concentrations and parameters also include CV, geometric CV and geometric mean. For t_{max} only, the number of patients (n), median, minimum and maximum are presented.

To assess the effect of ASP1707 on the pharmacokinetics of MTX, a mixed-effects analysis of variance (ANOVA) model with fixed effect for treatment (ASP1707 + MTX and MTX alone) and patient as a random effect was fitted on natural logarithm-transformed C_{max} and AUC_{inf}. Within the ANOVA, the least squares (LS) mean differences between ASP1707 + MTX and MTX alone along with 90% CIs for the differences were estimated.

The LS means for C_{max} and AUC_{inf} were back-transformed to produce the geometric LS means and presented with the number of patients for each treatment. The geometric LS mean ratios and their corresponding 90% CI for each pharmacokinetic parameter are presented by back transforming and expressed as percentages. The analysis was carried out for both dose-normalized and un-normalized C_{max} and AUC_{inf}.

To assess the effect of MTX on ASP1707, the pharmacokinetic parameters of ASP1707 were analyzed analogously to the MTX pharmacokinetic parameters without dose normalization.

The pharmacokinetic parameters were calculated following the Astellas Manual for Noncompartmental Analysis of Pharmacokinetic Data from Clinical Studies, version 1.0 or higher. All data processing, summarization and analyses including plasma concentration data of ASP1707, MTX and their metabolites were performed using Statistical Analysis System® Version 9.3 (or higher) on UNIX®. Non-compartmental Analysis for deriving PK parameters was done using Phoenix WinNonlin version 6.4 (or higher) (Pharsight Corp., Mountain View, CA, USA).

Treatments were coded and defined as follows:

- MTX administered alone (‘MTX Alone’)
- ASP1707 administered alone (‘ASP1707 Alone’)

- MTX and ASP1707 concomitant administration ('MTX + ASP1707')

Each patient received each treatment in the same sequence.

As a general principle, no imputation of missing data was done. Exceptions were missing start and stop dates of AEs and concomitant medications. Listings of the AEs and concomitant medications present the actual partial dates; imputed dates are not shown.

Summary of Results/Conclusions:

Population

In total, 11 patients provided written informed consent and 1 patient failed screening. Potential patients who did not meet 1 or more criteria required for participation in this clinical study were screen failures. Subsequently, 10 patients were registered for the clinical study and 10 patients received at least 1 dose of study drug. All 10 patients allocated to treatment were included in the SAF and PKAS [Table 1].

Table 1 Patient Disposition and Analysis Sets

Enrolled	**n=10**
Analysis Sets, n (%)	
Registered Analysis Set	10 (100)
Safety Analysis Set	10 (100)
Pharmacokinetic Analysis Set	10 (100)
Discontinuation, n	
Treatment Discontinuation	0
Study Discontinuation	0

All registered patients (Registered Analysis Set, REG); all patients who received at least 1 dose of study drug (Safety Analysis Set, SAF), for whom sufficient serum concentration data was available to facilitate derivation of at least 1 primary pharmacokinetic parameter (Pharmacokinetic Analysis Set, PKAS)

Source: End-of-Text Tables 12.1.1.1, 12.1.1.3.1 and 12.1.1.4

Of the 10 patients included in this clinical study, the majority were female (80%) and all were white. Patients had a mean age of 54.0 years, a mean weight of 67.41 kg, a mean height of 161.45 cm and a mean BMI of 25.80 kg/m^2 [Table 2].

Table 2 Summary of Demographics and Baseline Characteristics for Patients in the Safety Analysis Set

Parameter Category/ Statistics	Total (n = 10)
Sex, n (%)	
Male	2 (20%)
Female	8 (80%)
Race, n (%)	
White	10 (100%)
Black or African American	0
Asian	0
American Indian or Alaska Native	0
Native Hawaiian or other Pacific Islander	0
Other	0
Age, years	
Mean (SD)	54.0 (7.6)
Median	57.0
Min - Max	40 - 64
EudraCT Age Category	
≥ 18 years to ≤64 years	10 (100%)
≥ 65 years to ≤84 years	0
≥ 85 years	0
Weight (kg)	
Mean (SD)	67.41 (14.20)
Median	65.50
Min - Max	50.3 – 85.5
Height (cm)	
Mean (SD)	161.45 (8.54)
Median	161.00
Min - Max	145.5 – 177.0
BMI (kg/m^2)	
Mean (SD)	25.80 (4.89)
Median	25.22
Min - Max	20.1 – 34.7

All patients who took at least 1 dose of the study drug (Safety Analysis Set)
BMI: body mass index (weight [kg]/height [m^2]); Min: minimum; Max: maximum
Source: End-of-Text Table 12.1.2.1.2

Pharmacokinetic Results:

The coadministration of multiple oral doses of ASP1707 (30 mg twice daily for 6 days with a single 30-mg dose on the seventh day of dosing) and MTX (stable dose of 10 to 15 mg once weekly) resulted in a GMR of 114.86% for dose-normalized AUC_{inf} of MTX and a GMR of 108.95% for dose-normalized C_{max} of MTX compared to MTX alone. The 90% CI for the GMR for dose-normalized AUC_{inf} was (90.48%, 145.81%) and was (87.55%, 135.57%) for dose-normalized C_{max} Table 3. The study results show the coadministration of multiple oral doses of ASP1707 (30 mg twice daily for 6 days with a single 30-mg dose on the seventh day of dosing) resulted in a small increase of 14.86% in the mean AUC_{inf} and 8.95% in the mean C_{max} in patients with RA.

None of the estimated parameters for 7-OH-MTX, such as t_{max}, C_{max}, AUC_{inf} or $t_{1/2}$ changed substantially in the presence of ASP1707 (30 mg twice daily for 6 days with a single 30-mg dose on the seventh day of dosing).

The excretion of MTX or 7-OH-MTX into urine ($Ae_{last\%}$) as well as renal clearance (CL_R) were not affected by the presence of ASP1707.

The GMR for AUC_{tau} of the sum of ASP1707 and AS1948006 was 97.69% and for C_{max} was 91.21% in the presence of MTX compared with ASP1707 alone. The 90% CI for the GMR for AUC_{tau} was (91.41%, 104.40%) while the 90% CI for C_{max} was (85.42%, 97.40%) Table 4. These results show a lack of effect of coadministration of MTX on the AUC_{tau} of the sum of ASP1707 and AS1948006.

Table 3 Statistical Assessment of the Effect of ASP1707 on the Pharmacokinetics of MTX (Pharmacokinetic Analysis Set)

Parameter (units)	MTX Alone		MTX + ASP1707		Geometric LS Mean Ratio (%)	90% CI for Ratio (%)
	n	Geometric LS Mean	n	Geometric LS Mean		
$dAUC_{inf}$ (h*ng/mg)	9	73.1	9	84.0	114.86	(90.48, 145.81)
dC_{max} (ng/mL/mg)	10	18.5	10	20.1	108.95	(87.55, 135.57)

All patients who took at least 1 dose of study drug (Safety Analysis Set), for whom sufficient plasma concentration data were available to facilitate derivation of at least 1 pharmacokinetic parameter and for whom the time of dosing on the day of sampling was known (Pharmacokinetic Analysis Set).

$dAUC_{inf}$: dose-normalized AUC_{inf}, dC_{max}: dose-normalized C_{max}, CI: confidence interval; LS: least squares.

Assessment based on an analysis of variance performed on natural log-transformed parameters with treatment as a fixed effect and subject as a random effect.

Ratios and confidence limits are transformed back to raw scale and values are expressed as percentages.

Source: End-of-Text Table 12.4.3.1.1

Table 4 Statistical Assessment of the Effect of MTX on the Pharmacokinetics of ASP1707, AS1948006 and the Sum of ASP1707 and AS1948006 (Pharmacokinetic Analysis Set)

Plasma parameter (units)	Effect of MTX on ASP1707 n = 10		Effect of MTX on AS1948006 n = 10		Effect of MTX on the Sum of ASP1707 and AS1948006 n = 10	
Treatment	**ASP1707 Alone**	**MTX + ASP1707**	**ASP1707 Alone**	**MTX + ASP1707**	**ASP1707 Alone**	**MTX + ASP1707**
AUC_{tau} (h*ng/mL)						
Geometric LS Mean	203	206	935	906	1150	1120
Geometric LS Mean Ratio (%)	101.62		96.91		97.69	
90% CI of Ratio (%)	(94.02, 109.83)		(90.25, 104.07)		(91.41, 104.40)	
C_{max} (ng/mL)						
Geometric LS Mean	44.7	44.3	139	127	183	167
Geometric LS Mean Ratio (%)	99.09		91.19		91.21	
90% CI of Ratio (%)	(88.52, 110.92)		(84.01, 98.98)		(85.42, 97.40)	

All patients who took at least 1 dose of study drug (Safety Analysis Set), for whom sufficient plasma concentration data were available to facilitate derivation of at least 1 pharmacokinetic parameter and for whom the time of dosing on the day of sampling was known (Pharmacokinetic Analysis Set).

CI: confidence interval; LS: least squares

Assessment based on an analysis of variance performed on natural log-transformed parameters with treatment as a fixed effect and subject as a random effect.

Ratios and confidence limits are transformed back to raw scale and values are expressed as percentages.

Source: End-of-Text Tables 12.4.3.2, 12.4.3.3 and 12.4.3.4

Hormonal and Disease Activity Score Results:

The observed hormonal changes were consistent with the mechanism of action of ASP1707, a GnRH antagonist, reducing LH, FSH and gonadal steroid levels and avoiding the initial stimulation of LH and FSH induced by GnRH agonists.

No important notable changes from baseline to ESV were reported in the DAS28-CRP(3).

Safety Results:

There were no deaths, serious adverse events (SAEs), or treatment-emergent adverse events (TEAEs) leading to permanent discontinuation of study drug during the conduct of this clinical study. The only reported TEAE was nasopharyngitis. Nasopharyngitis that was not related to study treatment was reported for 1 patient (10%) when treated with ASP1707 alone. The coadministration of multiple oral doses of ASP1707 (30 mg twice daily for 6 days with a single 30-mg dose on the seventh day of dosing) and MTX (stable dose of 10 to 15 mg once weekly) in patients with RA was safe and well tolerated.

CONCLUSIONS:

The coadministration of multiple oral doses of ASP1707 (30 mg twice daily for 6 days with a single 30-mg dose on the seventh day of dosing) and MTX (stable dose of 10 to 15 mg once weekly) resulted in a GMR of

114.86% for dose-normalized AUC_{inf} of MTX and a GMR of 108.95% for dose-normalized C_{max} of MTX compared with MTX alone. The 90% CI for the GMR for dose-normalized AUC_{inf} was (90.48%, 145.81%) and was (87.55%, 135.57%) for dose-normalized C_{max}.

The GMR for AUC_{tau} of the sum of ASP1707 and AS1948006 was 97.69% and for C_{max} was 91.21% in the presence of MTX compared with ASP1707 alone. The 90% CI for the GMR for AUC_{tau} was (91.41%, 104.40%) while the 90% CI for C_{max} was (85.42%, 97.40%). These results show a lack of effect of coadministration of MTX on the AUC_{tau} of the sum of ASP1707 and AS1948006.

There were no deaths, SAEs or TEAEs leading to permanent discontinuation of study drug during the conduct of this clinical study.

No important changes were observed in vital signs, clinical laboratory values (hematology, chemistry, serology and urinalysis) or 12-lead ECGs.

Overall, 1 TEAE (nasopharyngitis) was reported for 1 patient (10%) during the clinical study. The TEAE occurred during the ASP1707 alone treatment period and was not considered by the investigator to be probably or possibly related to study drug.

In conclusion, the coadministration of multiple doses of ASP1707 (30 mg twice daily for 6 days with a single 30-mg dose on the seventh day of dosing) resulted in a 14.8% (90% CI: 90.48%, 145.81%) increase of mean AUC_{inf} and an 8.95% (90% CI: 87.55%, 135.57%) increase in mean C_{max}. in patients with RA. In addition, the coadministration of multiple oral doses of ASP1707 (30 mg twice daily for 6 days with a single 30-mg dose on the seventh day of dosing) and MTX (stable dose of 10 to 15 mg once weekly) in patients with RA was safe and well tolerated.

Date of Report: 31 Mar 2017