CLINICAL STUDY REPORT

Study Title	:	A Phase IIa, Multi-Centre, Randomised, Double-Blind, Two-Part, Controlled, Repeat Dose Study of AK106-001616 in Patients with Rheumatoid Arthritis This study assessed the effect of multiple, oral, ascending doses of AK106-001616, administered twice daily for a total of 3 weeks (200 mg for the first week, 400 mg for the second week and 600 mg for the third week), on the plasma and urine concentrations of methotrexate and its metabolite to determine if there was a drug-drug interaction and compared the safety and clinical efficacy of AK106-001616 with a placebo comparator.
ICON Study No.	:	2138/001: Part 1
Sponsor Study No.	:	AK106 II-01
EudraCT No.	:	2008-006075-75
Clinical Phase Start	:	12 May 2009
Clinical Phase End	:	02 October 2009
Principal Investigator	:	Multiple Investigators, see Appendix 16.1.1, Protocol
Report Author	:	Sally Rich, ICON Clinical Research and Affiliates
Report Status	:	FINAL
Date of Report	:	06 Jul 2010
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This study was performed in accordance with Good Clinical Practice (GCP), including the archiving of essential documents.

1. REPO RT APPROVAL

Sponsor Study No. AK106 II-01

Study Title: A Phase IIa, Multi-Centre, Randomised, Double-Blind, Two-Part, Controlled, Repeat Dose Study of AK106-001616 in Patients with Rheumatoid Arthritis

We, the undersigned, hereby declare that this work was performed by ourselves or under our supervision according to the procedures herein described and that this report represents a true and accurate record of the results obtained.

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2. SYNOPSIS

Name of Company: Asahi Kasei Pharma Corporation	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use only)*
Name of Finished Product:		
Name of Active Ingredient: AK106-001616		

Title of Study: A Phase IIa, Multi-Centre, Randomised, Double-Blind, Two-Part, Controlled, Repeat Dose Study of AK106-001616 in Patients with Rheumatoid Arthritis

Investigator: A list of investigators for the active sites is provided in Appendix 16.1.4.

Study Centre: Multiple centres; provided in Appendix 16.1.4.

Publication (reference): N/A

Study Period:Clinical Phase Start: 12 May 2009 **Clinical Phase End:** 02 October 2009	**Phase of Development:** IIa

Objectives: The primary objective of Part 1 of the study was to assess the potential for a drug-drug interaction between AK106-001616 and methotrexate (MTX).

The secondary objectives of Part 1 were to assess: 1) the effects of multiple, oral, ascending, repeat doses of AK106-001616 on the plasma and urine concentrations of MTX and its metabolite 7-hydroxy MTX, when administered to patients with rheumatoid arthritis (RA); 2) the plasma pharmacokinetics (PK) of AK106-001616 and its active metabolite AK106-001640, when administered to patients with RA who were taking MTX; 3) the urine pharmacodynamic (PD) effects of AK106-001616 compared with those of placebo when administered to patients with RA who were taking MTX; and 4) the safety and clinical efficacy of AK106-001616 compared with placebo when administered to patients with RA who were taking MTX.

Study Design and Methodol ogy: This was planned as a Phase IIa, multi-centre, randomised, double-blind, two-part, controlled, repeat ascending dose study of AK106-001616 in patients with RA, who were on a stable dose of MTX.

Part 1 of this study had a randomised, double-blind, parallel-group, placebo controlled, repeat ascending dose design and investigated whether there was a drug-drug interaction between AK106-001616 and MTX. Patients with RA who were taking a stable dose of MTX were randomly assigned to one of the following treatment arms:

- multiple, ascending doses of AK106-001616 administered twice daily (bid) for a total of 3 weeks (200 mg for the first week, 400 mg for the second week, and 600 mg for the third week) or
- matched placebo bid for 3 weeks.

A blinded interim PK analysis was planned and performed to investigate whether there was a drug-drug interaction between AK106-001616 and MTX, to determine whether Part 2 of the study would be conducted, and if so, to select the dose level for Part 2. Transition criteria were to be met in order to proceed from Part 1 to Part 2.

Part 2 was not to be conducted if none of the AK106-001616 doses (200, 400, and 600 mg) met the predefined transition criteria (see Protocol Section 4.1.3) that would indicate a PK interaction between AK106-001616 and MTX in Part 1 of the study. After review of this data, Asahi Kasei Pharma (hereafter, the Sponsor) intended to make a decision whether or not to proceed with Part 2 of the study.

Part 2 was to have a randomised, double-blind, double-dummy, parallel group, comparator-controlled, repeat dose design and was to compare the efficacy, safety, PK, and PD of multiple doses of AK106-001616 with a comparator drug in patients with RA. Patients in Part 2 were to have been randomly assigned to one of 2 treatment arms:

- multiple doses of AK106-001616 bid and comparator placebo for 4 weeks or

- multiple doses of comparator bid and placebo to match AK106-001616 for 4 weeks.

In order to proceed from Part 1 to Part 2, certain transition criteria concerning the PK of MTX in Part 1 were to be met. If all AK106-001616 doses (200, 400, and 600 mg) did not meet the criteria, then Part 2 would not be conducted. The criteria to be met in order to proceed to Part 2 of the study were:

- the 90% confidence intervals (CIs) for the geometric mean ratio of maximum plasma concentration (C_{max}) and the area under the plasma concentration-time profile from time zero to the last quantifiable time point post-dose (AUC_{0-t}) for MTX administered after multiple doses of AK106-001616 to MTX administered alone were to be within 80 to 125%;
- the increase in C_{max} for MTX administered after multiple doses of AK106-001616 were not to exceed 50% of the C_{max} for MTX alone (baseline value) in a total of 3 or more individual patients; and
- the increase in C_{max} for MTX administered after multiple doses of AK106-001616 were not to exceed 75% of the C_{max} for MTX alone (baseline value) in 1 or more individual patients.

However, there was no AK106-001616 dose that met all 3 criteria. Following normalisation for MTX dose:

- the upper limit of the 90% CIs for the geometric mean ratio of C_{max} for MTX administered with AK106-001616 400 mg and the geometric mean ratio of AUC_{0-t} for MTX administered with AK106-001616 400 mg and 600 mg compared with MTX alone exceeded 1.25;
- following AK106-001616 200 mg, 400 mg, and 600 mg bid doses on Days 8, 15, and 22, respectively, MTX:C_{max} ratios were >1.5 in 2, 3, and 4 patients, respectively; and
- at all dose levels of AK106-001616, 2 patients had MTX:C_{max} ratios >1.75.

In Part 1, none of the AK106-001616 doses (200, 400, and 600 mg) met the transition criteria (as defined in Protocol Section 4.1.3), indicating a PK interaction between AK106-001616 and MTX. Therefore, the Sponsor made the decision to not proceed with Part 2. Accordingly, only Part 1 of the study was performed and is reported in this clinical study report (CSR).

Number of Patients: Thirty (30) patients were planned for Part 1 of this study: 25 patients to receive AK106-001616 and 5 patients to receive placebo. A total of 31 patients were enrolled in the study: 26 patients received AK106-001616 and 5 patients received placebo.

Test Product, Dose and Mode of Administration, Batch Number, Expiry Date: AK106-001616, 200 mg hard capsules (2 capsules for 400 mg dose, 3 capsules for 600 mg dose), oral route, batch: PLQ012, expiry date: December 2011.

Reference Product, Dose and Mode of Administration, Batch Number, Expiry Date: AK106-001616 matching placebo; 200 mg hard capsules, oral route, batch: PLP014, expiry date: January 2012.

Duration of Study Drug Treatment: Patients were to participate in the study for approximately 7 weeks. Screening: Days -21 and -2.

Active treatment: 3 weeks

Follow-up: 6 days (±3 days) after last dose of study drug.

Criteria for Evaluation:

Pharmacokinetics:

PK parameters assessed for AK106-001616 and AK106-001640 were C_{max}, time to reach maximum concentration read as the actual sampling time corresponding to C_{max} (t_{max}), AUC_{0-t}, and concentration following investigational product administration at the end of the dosing interval read directly from the observed

concentrations (C_{min}).

Dose-normalised PK were assessed for MTX and 7-hydroxy MTX using the parameters C_{max}, t_{max}, AUC_{0-t}, area under the plasma concentration-time profile from time zero to 24 hours (AUC_{0-24}), total urinary excretion of test product unchanged in urine from time zero to 24 hours calculated as urine volume times concentration (Ae_{0-24}), half-life associated with the terminal elimination phase of the plasma concentration-time profile ($t_{½}$), apparent volume of distribution following oral administration (Vd/F), oral clearance (CL/F), renal clearance (CL_R), area under the plasma concentration-time profile from time zero to infinity (AUC_{0-inf}), and fraction of systemically available drug excreted unchanged in urine from time zero to 24 hours (fe_{0-24}).

Pharmacodynamics:

PD were assessed using biomarkers including the urine leukotriene E4 (LTE_4)/urine creatinine ratio and urine prostaglandin E2 metabolite (PGE-M)/urine creatinine ratio.

Efficacy:

Efficacy was assessed by:

- Patient global assessment of arthritis (GAA) using visual analogue scale (VAS);
- Patient assessment of arthritis pain using VAS;
- Acute phase reactant (C-reactive protein [CRP]); and
- Erythrocyte sedimentation rate (ESR).

Safety and tolerability:

Safety and tolerability were assessed by medical history, reviews of pre-study and concomitant medications, urine pregnancy test (for women of childbearing potential), serology (hepatitis B surface antigen [HBsAg] and hepatitis C virus [HCV]), physical examination, 12-lead electrocardiogram (ECG), vital signs (sitting and supine blood pressure [BP], heart rate [HR], respiration rate [RR], and body temperature), adverse events (AEs) monitoring, clinical laboratory test results (haematology, clinical chemistry, urinalysis, urine DOA, and bleeding time assessment).

Statistical Methods:

Demographics and baseline characteristics were summarised using descriptive statistics.

Efficacy analyses were performed on the Intent-to-Treat (ITT) population and the Per Protocol Set (PPS) population and were summarised descriptively by treatment group and by Days 8, 15, and 22, which correspond to AK106-001616 doses of 200 mg, 400 mg, and 600 mg bid, respectively.

Comparisons were between the AK106-001616 and placebo treatment groups in summaries of Patient GAA and the change from baseline in Patient GAA; summaries of Patient Assessment of Arthritis Pain and the change from baseline in Patient Assessment of Arthritis Pain; summaries of CRP and change from baseline in CRP; and summaries of ESR and the change from baseline in ESR.

Pharmacokinetic analyses were performed on the PK population.

PK parameters for AK106-001616 (and the metabolite AK106-001640) were summarised descriptively by study day. The C_{max}, t_{max}, AUC_{0-t}, and C_{min} were determined for 200, 400, and 600 mg bid.

Additionally, an assessment of the dose proportionality of AK106-001616 (and AK106-001640) among the 200, 400, and 600 mg doses was performed for the C_{max} and $AUC_{0-t.}$

Dose-normalised PK parameters for MTX (and the metabolite 7-hydroxy MTX) were summarised descriptively by treatment group and by study day. The C_{max}, t_{max}, AUC_{0-t}, AUC_{0-24}, $t_{½}$, Vd/F, CL/F, CL_R, AUC_{0-inf}, and fe_{0-24}

were summarised. The C_{max} and AUC_{0-t} were statistically compared using the 90% CIs for the geometric mean ratio between Day 1 and Day 8, 15, and 22 to investigate whether there was a drug-drug interaction between AK106-001616 and MTX.

A blinded interim PK analysis was planned and performed to investigate whether there was a drug-drug interaction between AK106-001616 and MTX, to determine whether Part 2 of the study would be conducted, and if so, to select the dose level for Part 2.

Additional PK analysis of MTX in the placebo group was performed to compare with the AK106-001616 group. This analysis was not planned per protocol; accordingly, it was described in the cover letter entitled, "Declaration of End of Clinical Trial Form," dated 14 December 2009.

Pharmacodynamic analyses were performed on the PD population. These included a summary of the urine LTE_4/urine creatinine ratio and of the percentage change from baseline in urine LTE_4/urine creatinine and a summary of the urine PGE-M/urine creatinine ratio and of the percentage change from baseline in urine PGE-M/urine creatinine. These were summarised descriptively by treatment group and time point.

Safety analyses were performed on the Safety population and were summarised descriptively; the following summary statistics were given for continuous variables: count (n), arithmetic mean, standard deviation (SD), coefficient of variation expressed as a percentage (CV[%]), median, minimum and maximum. For categorical variables, summary data of count and percentages were given.

Pre-study and concomitant medications and changes in clinical laboratory parameters (biochemistry, haematology and urinalysis) from pre-treatment (screening visit) to follow-up visit were summarised descriptively. Individual vital sign values of systolic BP, diastolic BP (sitting and supine), HR, and RR and temperature were summarised descriptively for each treatment by assessment time. Descriptive statistics (absolute and change from baseline) by treatment group and by time point were presented for physical examination and for ECG parameters (HR, PR interval [PR], QRS complex [QRS], and QTc interval Bazett's formula [QTcB]). Descriptive statistics by treatment group and by day are presented for bleeding time assessment.

Adverse events (AEs) were coded to body systems and preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA), version 11.1. AEs were regarded as pre-dose AE events if they occurred between screening and the time of first dose of MTX in Part 1. All other AEs were considered treatment-emergent. However, if a pre-treatment AE worsened during the treatment phase, it was counted as a treatment-emergent adverse event (TEAE). An overall summary of AEs is presented.

The correlation between elevation of MTX plasma level and safety is also discussed.

Summary Results and Conclusions:

Pharmacokinetic Results and Conclusions:

- An interaction between MTX and AK106-001616 was indicated, since systemic exposure to MTX after repeated administration of AK106-001616 was higher compared with baseline values. The geometric mean ratio of C_{max} and AUC_{0-t} for MTX administered AK106-001616 to MTX administered alone exceeded 1. The upper limit of 90% CIs for the geometric mean ratio of C_{max} for MTX administered AK106-001616 400 mg to the geometric mean ratio of AUC_{0-t} for MTX administered AK106-001616 400 mg and 600 mg to MTX alone exceed 1.25. Additionally, MTX C_{max} increased by more than 50% in 2 or more patients and by more than 75% in 2 patients across the AK106-001616 dose levels studied. Therefore, the study did not progress from Part 1 to Part 2.
- Systemic exposure to 7-hydroxy MTX after repeated administration of AK106-001616 was lower compared with baseline values.

- In the placebo group, the geometric mean of the MTX C_{max} and AUC_{0-t} for Days 8, 15, and 22 decreased. The range of MTX C_{max} and AUC_{0-t} for Days 8, 15, and 22 remained essentially the same between the AK106-001616 group and the placebo group.
- However, the observed increase in mean C_{max} and AUC_{0-t} values may not be significant, since the geometric mean ratio for the C_{max} and AUC_{0-t} of MTX coadministered with AK106-001616 to MTX alone ranged from 1.1024 to 1.2129. There was no difference in the ranges between the AK106-001616 group and the placebo group on Days 1, 8, 15, and 22 and the ranges on Days 8, 15, and 22 were similar.
- There was a greater than dose-proportional increase for C_{min} and AUC_{0-t} of AK106-001616 and AK106-001640. Additionally, dose-proportionality may be indicated for C_{max} of AK106-001616 and AK106-001640.
- AK106-001616 trough levels reached the tentative effective concentration level (100 ng/mL) even at AK106-001616 200 mg bid.
- There was wide inter-patient variability in the plasma concentrations of AK106-001616 at all 3 dose levels.
- A gender effect was indicated for AK106-001616 and AK106-001640 with exposure, on average, higher in females; this is consistent with the results of Phase I study AK 106 I-02.
- No apparent relationship emerged between the C_{max} and AUC_{0-t} of MTX on the C_{max} of AK106-001616 or the MTX ratio of C_{max} or AUC_{0-t} on Days 8, 15, and 22 to C_{max} or AUC_{0-t} on Day 1 on the C_{max} of AK106-001616.

Pharmacodynamic Results and Conclusions:

- AK106-001616 appeared to inhibit urinary PGE-M and LTE_4; this inhibition effect appears to be saturated at the lower AK106-001616 200 mg bid dose.

Efficacy Results and Conclusions:

- In the patient GAA evaluations, means decreased during the course of the study in the AK106-001616 group, indicating many patients evaluated their symptoms as improved.
- In the summary of patients' assessment of arthritis pain, the change in mean values gradually decreased during the course of the study in the AK106-001616 group, indicating improvement in arthritis pain.
- In 2 markers of inflammation, CRP and ESR, changes from baseline to follow-up were slight and many patients were only mildly symptomatic. No effects were detected in either of these markers.

Safety and Tolerability Results and Conclusions:

- During this study, 14 (45.2%) patients reported TEAEs and 8 (25.8%) patients had treatment-related TEAEs. The most frequently reported TEAE, regardless of relationship to study medication, was headache in 7 (22.6%) patients, most (3 [12.0%] patients) during the AK106-001616 600 mg bid treatment period. There were 2 severe and possibly related TEAEs: nausea during the AK106-001616 200 mg bid treatment period and vomiting during the AK106-001616 600 mg bid treatment period. There was 1 moderate possibly related TEAE (GERD) during the AK106-001616 400 mg bid treatment period. There were 14 TEAEs across the dose periods assessed as mild and considered possibly related to study medication. There was 1 TEAE assessed as probably related to study medication, mild flatulence during the AK106 001616 600 mg bid treatment period.
- During the study, there were 2 severe TEAEs: 1 during the AK106-001616 200 mg bid treatment period and 1 during the AK106-001616 600 mg bid treatment period; 4 moderate TEAEs (3 during the

AK106-001616 400 mg bid treatment period and 1 during the 600 mg bid treatment period); and 24 mild TEAEs, most (9) during the AK106-001616 600 mg bid treatment period.

- TEAEs were approximately evenly divided between not related and possibly related to study medication. The only 1 TEAE considered probably related was mild; 2 severe TEAEs were considered possibly related.
- There were no SAEs and no deaths during the study.
- There were no dose reductions or temporary discontinuations.
- During the AK106-001616 600 mg bid treatment period, 1 patient discontinued the study prematurely due to a TEAE (severe vomiting). There was 1 patient who discontinued the study prematurely due to a protocol deviation (had not been on a stable dose of MTX for 12 weeks).
- Evaluation of changes in vital signs, physical examinations, clinical laboratory tests, and ECGs were unremarkable
- Based upon AEs and laboratory test values, there were no safety concerns, including those which could have been caused by elevations in MTX levels.

Overall Conclusions:

- A total of 31 patients were enrolled in the study; 26 received AK106-001616 and 5 received placebo.
- None of the AK106-001616 doses (200, 400, and 600 mg bid) met the protocol-defined transition criteria; this indicated a PK interaction between AK106-001616 and MTX in Part 1. Therefore, the Sponsor made the decision to not proceed with Part 2 and terminated Study AK106 II-01.
- There was a greater-than-dose-proportional increase in the C_{min} and AUC_{0-t} of AK106-001616 and AK106-001640. AK106-001616 trough levels reached the tentative effective concentration level (100 ng/mL) even at an AK106-001616 200 mg bid dose. At all 3 dose levels, there was wide inter-patient variability in the plasma concentrations of AK106-001616.
- AK106-001616 appeared to inhibit urinary PGE-M and LTE_4; this inhibition effect appears to be saturated at the lower AK106-001616 200 mg bid dose.
- In both VAS assessments (GAA and patients' assessment of arthritis pain), means decreased during the course of the study in the AK106-001616 group, indicating many patients evaluated their symptoms as improved.
- AK106-001616 was safe and well tolerated by patients with RA when administered at dose levels up to 600 mg bid. There were no serious TEAEs reported during the study and only 1 patient was withdrawn during the AK106-001616 600 mg bid treatment period due to severe vomiting. The overall incidence of AEs was low. There was no trend in the frequency of AEs across the dose levels. The majority of AEs were mild in severity and resolved without treatment; the most frequently reported AE, regardless of relationship to study medication, was headache. There were 2 severe AEs (both possibly related, both in the same patient): nausea during the AK106-001616 200 mg bid treatment period and vomiting during the AK106-001616 600 mg bid treatment period. There was 1 moderate AE (GERD) during the AK106-001616 400 mg bid treatment period. There were no SAEs and no deaths during the study. There were no safety concerns (eg, AEs and laboratory test values) including those which could have been caused by an elevation in MTX level. Overall, the safety profile of AK106-001616 showed no negative trends and did not reveal any cause for safety concerns.

Date of Report: 06 Jul 2010