Asahi Kasei Pharma Corporation

CLINICAL STUDY REPORT

Study Title:	A Phase IIa, Multi-Centre, Randomised, Double-Blind, Comparator-Controlled, Repeated-Dose Study of 2 Dose Levels of AK106-001616 in Patients with Rheumatoid Arthritis
Investigational Product:	AK106-001616
Indication Studied:	Rheumatoid Arthritis
Description of Study:	Phase IIa, multi-centre study with a randomised, double-blind, triple-dummy, 3-arm, parallel-group, comparator-controlled, repeated-dose design
Name of Sponsor:	Asahi Kasei Pharma Corporation
Protocol Number:	AK106 II-02
Development Phase:	IIa
First Subject Enrolled:	7 March 2011
Last Subject Completed:	25 January 2012
Principal Investigator:	Multiple Investigators, see Appendix 16.1.4, Protocol
Sponsor Signatory:	Toshihiko Kayanoki, Manager of Global Project Clinical Development Center Asahi Kasei Pharma Corporation 1-105 Kanda Jinbocho Chiyoda-ku, Tokyo 101-8101, Japan Phone: +81 3 3296 3640 Fax: +81 3 3296 3689 Ian Dews MRCP, FFPM, Director Envestia Limited The Sanderum Centre, 30A Upper High Street, Thame Oxfordshire, OX3 9EX, United Kingdom Phone: +44 1235 227249 Fax: +44 1235 227249
GCP Compliance:	This study was performed in compliance with Good Clinical Practice (GCP), including the archiving of essential documents.
Date of the Report:	6 December 2012

2 SYNOPSIS

<table>
<tr><td colspan="2">Name of Sponsor/Company:
Asahi Kasei Pharma Corporation</td><td rowspan="3">Individual Study Table Referring to Part of the Dossier
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<tr><td colspan="2">Name of Finished Product:
to be decided</td></tr>
<tr><td colspan="2">Name of Active Ingredient:
3-[3-amino-4-(indan-2-yloxy)-5-(1-methyl-1H-indazol-5-yl)-phenyl]-propionic acid</td></tr>
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<tr><td colspan="4">Investigators:
29 investigators, see Appendix 16.1.4</td></tr>
<tr><td colspan="4">Study Centres:
29 study centres in 7 countries (UK, Germany, Hungary, Poland, Czech Republic, Slovakia, and Ukraine), see Appendix 16.1.4</td></tr>
<tr><td colspan="4">Publication (Reference):
None</td></tr>
<tr><td colspan="2">Study Period:
7 March 2011 (First Subject Enrolled) –
25 January 2012 (Last Subject Completed)</td><td colspan="2">Phase of Development:
IIa</td></tr>
<tr><td colspan="4">Objectives:
The primary objectives of the study were:
to investigate the clinically relevant improvement in anti-inflammatory/analgesic activity after multiple doses of AK106-001616 compared with naproxen in patients with rheumatoid arthritis (RA) on background oral methotrexate (MTX), and
to compare the safety of AK106-001616 to that of naproxen in patients with RA on background oral MTX.
The secondary objectives of the study were:
to compare the safety and efficacy of multiple, oral doses of AK106-001616 with those of naproxen in patients with RA on background oral MTX using pharmacodynamic (PD) urinary biomarkers, and
to compare the effect of AK106-001616 on the gastrointestinal (GI) tract to that of naproxen in a subpopulation of RA patients on background oral MTX (based on optional video capsule endoscopy [VCE] assessment).</td></tr>
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Additional objectives of the study were:

- to assess the correlation between the clinical efficacy and PD (urinary prostaglandin E metabolite [PGE-M] and urinary leukotriene E_4 [LTE_4]) effects of AK106-001616 in patients with RA on background oral MTX,
- to compare the effects of multiple, oral doses of AK106-001616 with those of naproxen on serum PD in patients with RA on background oral MTX, and
- to assess the pharmacokinetics (PK) of AK106-001616 and its active metabolite AK106-001640 in patients with RA on background oral MTX.

Methodology:

This was planned as a phase IIa, multi-centre study with a randomised, double-blind, triple-dummy, 3-arm, parallel-group, comparator-controlled, repeated-dose design. The study investigated/compared the efficacy, safety, PK, and PD of 2 dose levels of AK106-001616 in patients with RA to those of naproxen. Patients were required to be on background oral MTX (5 to 25 mg administered as a single weekly dose). Patients were randomly assigned to one of 3 treatment arms:

- AK106-001616 100 mg, matching placebo for AK106-001616 600 mg, and matching placebo for naproxen twice daily (bid) for 4 weeks,
- AK106-001616 600 mg, matching placebo for AK106-001616 100 mg, and matching placebo for naproxen bid for 4 weeks, and
- naproxen 500 mg, matching placebo for AK106-001616 100 mg, and matching placebo for AK106-001616 600 mg bid for 4 weeks.

Number of Subjects (Planned and Analysed):

Planned:

In order for 210 patients to complete the study, it was planned that a total of 240 patients were to be enrolled onto the study (80 patients per treatment arm). VCE was set as an optional assessment.

Analysed:

A total of 253 subjects (85 subjects for AK106-001616 100 mg, 84 subjects for AK106-001616 600 mg, and 84 subjects for naproxen 500 mg) were randomised. The intent-to-treat (ITT) population including 248 subjects (81, 84, and 83 subjects, respectively) and the per protocol set (PPS) population including 245 subjects (80, 82, and 83 subjects, respectively) were analysed for efficacy; the PK population including 165 subjects (81, 84, and 0 subjects, respectively) were analysed for PK; the PD population including 248 subjects (81, 84, and 83

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subjects, respectively) were analysed for PD; the safety population including 253 subjects (85, 84, and 84 subjects, respectively) were analysed for safety; the VCE population including 138 subjects (50, 45, and 43 subjects, respectively) were analysed for VCE.

Diagnosis and Main Criteria for Inclusion:

Patients had to meet all of the following inclusion criteria to participate in the study:

1. was diagnosed with adult-onset RA (as defined by the 1987 American College of Rheumatology [ACR] classification criteria) for at least 3 months;
2. had a Functional Capacity Classification of I to III;
3. had been stable on oral MTX therapy (5 to 25 mg administered as a single weekly dose) for at least 12 weeks;
4. had RA activity at screening and at baseline (Day 1, pre-morning dose), defined as a 28-joint disease activity score (DAS28) of ≥3.2 and an increase in DAS28 from screening to baseline that is >0 and ≤1.2 (baseline minus screening);
5. was between 18 and 65 years of age inclusive;
6. was able to give voluntary written informed consent to participate in this trial;
7. A female patient of childbearing potential had to confirm she had been using adequate contraception since her last menses, and had a negative result on the urine pregnancy test taken before the administration of the study drug. She had to be willing to consent to the continued use of adequate contraception during the study and for 3 months after the study conclusion. Adequate contraception was defined as the use of 2 acceptable methods of birth control (ie, a hormonal contraceptive, intra-uterine device, diaphragm with spermicide, and condom with spermicide). A condom alone was not considered an acceptable method of birth control; and
8. A male patient with a sexual partner of childbearing potential had to confirm that he and his sexual partner agreed to use 2 acceptable methods of birth control (ie, a hormonal contraceptive, intra-uterine device, diaphragm with spermicide, and condom with spermicide) during the study and for 3 months after the study conclusion.

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

AK106-001616 100 or 600 mg was orally administered bid. AK106-001616 was supplied as 100 mg capsules (batch number PLM012) and 200 mg capsules (batch numbers PLQ012 and PLQ013).

Duration of Treatment:

The duration of the treatment period was planned as 28 days (4 weeks).

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

Naproxen 500 mg was orally administered bid. Naproxen was supplied as 500 mg encapsulated tablets (batch numbers E0028E1 and E0084E1). Matching placebo for AK106-001616 (100 mg capsules and 200 mg capsules) and matching placebo for naproxen were also supplied.

Criteria for Evaluation:

Efficacy:

Efficacy assessments included:

- patient global assessment of arthritis (GAA) (visual analogue scale [VAS]),
- patient assessment of arthritis pain (VAS),
- physician GAA (VAS),
- number of tender/painful joints (68 joint count),
- number of swollen joints (66 joint count),
- ACR 20% improvement criteria (ACR20) responder index,
- ACR 50% improvement criteria (ACR50) responder index,
- DAS28,
- European League against Rheumatism (EULAR) response criteria,
- health assessment questionnaire (HAQ) functional disability index,
- acute phase reactant (C-reactive protein [CRP]),
- erythrocyte sedimentation rate (ESR), and
- incidence of withdrawal due to lack of arthritis efficacy.

Pharmacokinetics:

Five plasma samples per patient were collected for analysis of AK106-001616 and AK106-001640 concentrations. Blood samples were collected from each patient on Day 1 (between 1 and 4 hours after the morning dose [preferably more than 2 hours post-dose]), Day 14 (before the morning dose and between 1 and 4 hours after the morning dose [preferably more than 2 hours post-dose]), and Day 28 (before the morning dose and between 6 and 12 hours after the morning dose). For patients who took part in the optional VCE, the second Day 28 sample was taken between 8 and 12 hours after the morning dose. Population PK analyses are planned to be performed for AK106-001616.

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Genetic Analysis:

In consenting patients, an optional blood sample was taken prior to dosing and was genetically analysed for the presence of a set of defined polymorphisms in cytochrome P450 2C8 (CYP2C8), uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1), uridine diphosphate glucuronosyltransferase 1A3 (UGT1A3), and the solute carrier organic anion transporter family member 1B1 (SLCO1B1) gene. Other genetic analyses were able to be performed, if needed, to investigate the relationship among genotype, post-dose plasma concentration of AK106-001616, and adverse events (AEs) during the study. Blood samples were not banked after completion of the study.

Pharmacodynamics:

Urine was collected from all subjects before dosing on Days 1, 7, 14, 21, and 28 (single void prior to morning dose) and at the follow-up visit. In the subgroup of patients who were participating in the optional VCE, additional urine samples were collected on Day 1 (pooled urine: −24 to 0 hours [pre-morning dose]) and Day 28 (pooled urine: 0 to 12 hours, 12 to 24 hours, and 24 to 48 hours post-dose).

The following PD biomarkers were measured:

Efficacy PD biomarkers

- urine LTE_4/urine creatinine, and
- urine PGE-M/urine creatinine.

Safety PD biomarkers

- urine 2,3-dinor 6-keto prostaglandin $F_{1\alpha}$ ($PGF_{1\alpha}$)/urine creatinine,
- urine 6-keto $PGF_{1\alpha}$/urine creatinine,
- urine 11-dehydro thromboxane B_2 (TXB_2)/urine creatinine, and
- urine 11-dehydro TXB_2/urine 2,3-dinor 6-keto $PGF_{1\alpha}$ ratio.

Blood samples were collected from all subjects before dose administration on Days 1, 14, and 28 (prior to the morning dose) for the determination of serum PD biomarkers. The following serum PD biomarkers were measured:

- serum matrix metalloproteinase 3 (MMP3),
- serum cross-linked N-telopeptide of type 1 collagen (NTX),
- serum interleukin-6 (IL-6),
- serum interleukin-10 (IL-10), and

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- serum tumour necrosis factor alpha (TNFα).

Safety and Tolerability:

Safety and tolerability were assessed by physical examination, 12-lead electrocardiogram (ECG), vital signs, AEs, haematology, clinical chemistry and urinalysis, and safety PD biomarkers. In addition, optional VCE was performed using PillCam™ SB2 in a subgroup of patients.

Statistical Methods:

Efficacy Endpoints

Efficacy endpoints were summarised descriptively by treatment group and time point.

Pharmacokinetics

Plasma concentration-time profiles for all patients who received AK106-001616 are planned to be evaluated by population PK analyses.

Pharmacodynamics

PD endpoints were summarised descriptively by treatment group and time point.

Safety Endpoints

AEs, 12-lead ECG data, vital signs, and clinical laboratory parameters were summarised descriptively by treatment group and time point.

Summary – Conclusions:

Efficacy Results:

The anti-inflammatory and analgesic effects of AK106-001616 in the 100 mg and 600 mg groups were comparable to those of naproxen. Results of efficacy analyses are summarised below:

- Mean changes (SD) in patient GAA (VAS) from Visit 2 (Day 1 pre-morning dose) to Visit 6 (Day 28) were −20.7 (21.8) mm in the 100 mg group, −17.6 (20.7) mm in the 600 mg group, and −18.0 (20.6) mm in the naproxen group. Mean changes in patient assessment of arthritis pain (VAS) from Visit 2 (Day 1 pre-morning dose) to Visit 6 (Day 28) were −18.3 (19.2) mm, −15.9 (22.0) mm, and −16.7 (20.6) mm, respectively. Mean changes in physician GAA (VAS) from Visit 2 (Day 1 pre-morning dose) to Visit 6 (Day 28) were −19.6 (16.4) mm, −18.5 (17.7) mm, and −21.1 (22.3) mm, respectively.
- ACR20 response was achieved at Visit 6 (Day 28) in 40 (49.4%) subjects in the 100 mg group, 40 (47.6%) subjects in the 600 mg group, and 41 (49.4%) subjects in the

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naproxen group. ACR50 response was achieved at Visit 6 (Day 28) in 12 (14.8%) subjects in the 100 mg group, 16 (19.0%) subjects in the 600 mg group, and 16 (19.3%) subjects in the naproxen group.

- EULAR response at Visit 6 (Day 28) was good in 12 (14.8%) subjects in the 100 mg group, 10 (11.9%) subjects in the 600 mg group, and 11 (13.3%) subjects in the naproxen group, and was moderate in 45 (55.6%), 40 (47.6%), and 43 (51.8%) subjects, respectively.
- No apparent efficacy was demonstrated for CRP and ESR in any of the three treatment groups.
- No subject was withdrawn due to lack of arthritis efficacy in any of the three treatment groups.
- AK106-001616 was as effective as naproxen in terms of the other efficacy variables in both the 100 mg and 600 mg groups.

Pharmacokinetic Results:

The plasma concentrations of AK106-001616 and its metabolite, AK106-001640, after the administration of AK106-001616 600 mg were higher than those of AK106-001616 100 mg. The plasma concentration of AK106-001640 was much lower than that of AK106-001616. The population PK is planned to be analysed.

Pharmacogenetic Results:

In the genetic analysis, there were no notable findings for any of the CYP2C8, UGT1A1, UGT1A3, and SLCO1B1 genes.

Pharmacodynamic Results:

The production of LTE_4/urine creatinine and PGE-M/urine creatinine was sufficiently suppressed in the 100 mg and 600 mg groups. They were suppressed more strongly in the 600 mg group than in the 100 mg group. The production of PGE-M/urine creatinine was suppressed by naproxen. The production of LTE_4/urine creatinine was not suppressed by naproxen. The urine PD markers for efficacy were analysed separately in the two cohorts (non-VCE and VCE) since a different sampling method was used for each cohort. Results for the non-VCE group are summarised below. The tendency was similar in that for the VCE subgroup.

- For the PD population excluding the VCE subgroup, urine LTE_4/urine creatinine levels decreased in both the 100 mg and 600 mg groups, demonstrating that AK106-001616 suppressed the production of LTE_4, whereas no suppression was demonstrated in the naproxen group. The suppressive effect of AK106-001616 was stronger in the 600 mg

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group than in the 100 mg group.

- For the PD population excluding the VCE subgroup, urine PGE-M/urine creatinine levels decreased in the 100 mg, 600 mg, and naproxen groups, demonstrating that AK106-001616 and naproxen suppressed the production of PGE-M. The suppressive effect of AK106-001616 was stronger in the 600 mg group than in the 100 mg group.
- Analysis of the serum PD markers did not indicate any clear suppressive effect on the production of serum MMP3, NTX, IL-6, IL-10, and TNFα in any of the three treatment groups.
- No clear correlation was observed between suppression of PD markers for efficacy (ie, LTE_4 and PGE-M) and clinical efficacy (ie, patient GAA, patient assessment of arthritis pain, and physician GAA) in any of the three treatment groups.

Safety Results:

The overall incidence of treatment-emergent adverse events (TEAEs) for the 100 mg group was comparable to that for the naproxen group. The incidence of TEAEs for the 600 mg group was higher. Assessments in the VCE subgroup indicated that the total number of mucosal breaks without haemorrhage increased in the 600 mg and naproxen groups to a similar extent, but not in the 100 mg group.

- TEAEs regardless of relationship to the study drug were experienced by 22 (25.9%), 40 (47.6%), and 24 (28.6%) subjects in the 100 mg, 600 mg, and naproxen groups, respectively. There were no deaths during the study. One treatment-emergent serious adverse event (SAE) was reported in 1 subject in the 600 mg group, and was not related to the study drug. No suspected unexpected serious adverse reactions (SUSARs) were reported.
- Accumulation of TEAEs specified as key events by the Safety Monitoring Committee (SMC) did not lead to termination of the entire study or discontinuation of treatment with AK106-001616 600 mg.
- Slight decreases in haemoglobin were observed in the 600 mg group, and no notable differences were observed in mean changes in any other laboratory parameters among the three treatment groups.
- Mean supine blood pressure was 122.6/74.2, 122.5/74.9, and 126.9/76.8 mmHg for the 100 mg, 600 mg, and naproxen groups, respectively at Visit 2 (Day 1 pre-morning dose) and 125.2/76.7, 125.5/76.4, and 127.1/78.0 mmHg at Visit 6 (Day 28), respectively. Mean change (SD) in supine blood pressure from Visit 2 (Day 1 pre-morning dose) to Visit 6 (Day 28) was 2.9 (10.9)/2.8 (9.4), 4.1 (13.3)/1.7 (10.1), and

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1.0 (10.4)/1.4 (8.0) mmHg, respectively. No notable differences were observed in other vital signs among the three treatment groups.

- There were no notable differences in physical measurements or 12-lead ECG among the three treatment groups. Maximum increases in QT interval corrected by Fridericia's formula (QTcF interval) from baseline by >60 ms were reported in 1 subject in the 600 mg (at Visits 4 [Day 14] and 7 [follow-up]) and 2 subjects in the naproxen group (at Visit 2 [Day 1 >2 hours post-dose] and Visit 6 [Day 28], respectively). Maximum increases in QTcF interval from baseline by >60 ms were not experienced by any subject in the 100 mg group.
- In the VCE population, the mean total numbers of mucosal breaks without haemorrhage (SD) were 2.4 (5.8) in the 100 mg group, 2.1 (4.9) in the 600 mg group, and 1.5 (3.9) in the naproxen group at Visit 2 (Day −1) and 2.3 (5.1), 5.4 (7.8), and 5.0 (7.2), respectively at Visit 6 (Day 29). Mean changes in the total number of mucosal breaks without haemorrhage (SD) from Visit 2 (Day −1) to Visit 6 (Day 29) were −0.1 (6.6), 3.4 (7.0), and 3.5 (7.4), respectively. The results of the VCE assessments in the small bowel showed that the 100 mg group demonstrated no change in the number of mucosal breaks without haemorrhage however there was an increase in the naproxen group. The results for the 600 mg group were similar to those for the naproxen group.
- No impact suggestive of safety concern was noted on urine PD markers for safety, ie, urine 2,3-dinor 6-keto $PGF_{1\alpha}$/urine creatinine (potential CV risk indicator), urine 6-keto $PGF_{1\alpha}$/urine creatinine (potential renal function indicator), urine 11-dehydro TXB_2/urine creatinine (potential CV risk indicator), and urine 11-dehydro TXB_2/urine 2,3-dinor 6-keto $PGF_{1\alpha}$ ratio (potential CV risk indicator), in any of the three treatment groups.
- Urine 2,3-dinor 6-keto $PGF_{1\alpha}$/urine creatinine and urine 11-dehydro TXB_2/urine creatinine levels decreased in the 100 mg, 600 mg, and naproxen groups, demonstrating that AK106-001616 and naproxen suppressed the production of urine 2,3-dinor 6-keto $PGF_{1\alpha}$ and urine 11-dehydro TXB_2.
- Urine 6-keto $PGF_{1\alpha}$/urine creatinine levels for the 100 mg, 600 mg, and naproxen groups did not indicate any clear suppressive effect on the production of urine 6-keto $PGF_{1\alpha}$.
- The urine 11-dehydro TXB_2/urine 2,3-dinor 6-keto $PGF_{1\alpha}$ ratio did not increase in any of the 100 mg, 600 mg, or naproxen groups.

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<u>Conclusion</u>: AK106-001616 was efficacious, safe, and well tolerated by patients with RA when administered at dose levels of 100 mg or 600 mg bid, although the frequency of TEAEs, especially TEAEs of GI disorders, was higher in the 600 mg group.		