1. TITLE PAGE

Investigational Drug:	Remicade® (Infliximab) injection
Study No.:	P05645 (Extension study for P04280)
Clinical study title:	Open-Label Extension - A Placebo-controlled, Double-blinded, Randomized Clinical Trial of Anti-TNF Chimeric Monoclonal Antibody (cA2) in Korean Patients with Active Rheumatoid Arthritis Despite Methotrexate Treatment

Indication:	Rheumatoid Arthritis
GCP statement:	This clinical study was conducted in accordance with GCP, written informed consent was obtained from the patient and the all documents related with the results were kept and maintained in archiving room.

The included date of the first patient:	09Aug2006
The completed date of the last patient:	13May2008
The date of report:	05Feb2009
Director on Sponsor:	[redacted], General manager / [redacted] [redacted]
Personnel on Sponsor:	[redacted], Sr.CRA
Sponsor:	Schering-Plough Korea
Coordinating investigator:	[redacted], PhD

2. SYNOPSIS

SPONSOR: SCHERING-PLOUGH KOREA
NAME OF STUDY DRUG: REMICADE® (INFLIXIMAB)
PRINCIPAL INGREDIENT: INFLIXIMAB
TITLE OF STUDY: Open-label Extension - A Placebo-controlled, Double-blinded, Randomized Clinical Trial of Anti-TNF Chimeric Monoclonal Antibody (cA2) in Korean Patients with Active Rheumatoid Arthritis Despite Methotrexate Treatment
COORDINATING INVESTIGATOR: [redacted] [redacted], Korea
CLINICAL STUDY INSTITUTIONS: 6 institutions including [redacted]
PUBLICATION: NA
STUDY PERIOD (MONTHS): 22 months
OBJECTIVE: This extension study is to evaluate long term safety of Infliximab treatment after the completion of double-blind bridging 30 weeks study.
METHODS : After completion of week 30 visits of all patients and code break, additional Infliximab was infused to the patients in placebo group (Group 1) and who received Infliximab-containing regimen (Group 2) showing clinical response at week 30. Patients in group 1 were administered with Infliximab 3 mg/kg at weeks 0, 2, and 6 and every 8 weeks thereafter as an open label, if patients want to receive this treatment and physician‘s decision supports this treatment for patients’ disease status. Patients in group 2 who were treated with Infliximab-containing regimen showing clinical response of at least ACR20 at week 30 continued their treatment with Infliximab at their physicians’ discretion. The patients received Infliximab with methotrexate maintenance until they come up with reasons for drop-out described in section 7.7 “Discontinuation of Study Treatment and Treatment Failure” including congestive heart failure, tuberculosis, lack of efficacy, adverse reactions, and treatment failure OR Infliximab became commercially available. They started Infliximab treatment after signing separate informed consent form.
Quality of Data: This clinical trial was conducted ethically and scientifically in accordance with KGCP and Helsinki Declaration. Participating investigators and trial staffs were trained for the trial’s protocol and whether all trial procedures follow the protocol and relevant regulations during the study was reviewed. CRF records were compared and reviewed with source documents at monitoring and the collected CRFs were repeatedly reviewed until no additional inquiry or inconsistency was made by double record.

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NAME OF STUDY DRUG: REMICADE® (INFLIXIMAB)
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NUMBER OF PATIENTS: Total 92 patients were enrolled in this extension study.
INDICATION, INCLUSION & EXCLUSION CRITERIA: The patient should meet the below criteria in order to receive additional infusions; - does not withdraw informed consent - should have adhered to the study visit schedule and other protocol requirements - must be using adequate birth control measures and continue such precaution for six months after receiving the last infusion - does not meet exclusion criteria 12- 22 (refer to below criteria) exclusion criteria in main study: 12. Had serious infections, such as hepatitis, pneumonia, pyelonephritis in the previous 3 months. 13. Had a chronic infectious disease such as chronic renal infection, chronic chest infection with bronchiectasis or sinusitis. 14. Had active TB. Also excluded patients who had evidence of latent TB (positive PPD skin test or a history of latent TB) without adequate therapy for TB initiated prior to first infusion of study drug. Also excluded patients with evidence of an old or latent TB infection without documented adequate therapy, if they were not treated with anti-tubercular therapy during the trial. Patients with a current close contact with an individual with active TB were also excluded. Additionally, patients who had completed treatment for active TB within the previous 2 years were explicitly excluded from the trial. Patients with a household member who had a history of active pulmonary TB were to have had a thorough evaluation for TB prior to study enrollment as recommended by a local infectious disease specialist or published local guidelines of TB control agencies. Also excluded patients with opportunistic infections, including but not limited to evidence of active cytomegalovirus, active pneumocystis carinii, aspergillosis, or atypical mycobacterial infection, etc, within the previous 6 months. 15. Had current signs or symptoms of severe, progressive or uncontrolled renal, hepatic, hematological, gastrointestinal, endocrine, pulmonary, cardiac, neurologic or cerebral disease. 16. Had a history of lymphoproliferative disease including lymphoma or signs suggestive of possible lymphoproliferative disease, such as lymphadenopathy of unusual size or location (such as nodes in the posterior triangle of the neck, infraclavicular, epitrochlear, or periaortic areas), or splenomegaly. 17. Had any currently known malignancy or history of malignancy within the previous 5 years, except for squamous or basal cell carcinoma of the skin that were to have treated with no evidence of recurrence. 18. Had moderate or severe heart failure (NYHA class III/IV) 19. Were with pre-existing or recent onset of central nervous system demyelinating disorders

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20. Were known to have a recent substance abuse (drug or alcohol).
21. Were unable to undergo multiple venipunctures due to poor tolerability or lack of easy access.
22. Had a known infection with HIV or known active hepatitis B / C infection (including associated chronic active hepatitis).

INVESTIGATIONAL DRUG:	USAGE·DOSE:	LOT NO.:
Remicade 100 mg/vial	3 mg/kg I.V	[redacted]

TREATMENT PERIOD:

Patients who treated with Placebo in main study were administered with Infliximab 3 mg/kg at weeks 0, 2, and 6 and every 8 weeks thereafter as an open label. Patients who treated with Infliximab in main study were administrered at every 8 weeks.

EVALUATION OF DATA:

For safety evaluation, kinds and occurrence rate of adverse experiences, vital signs and change in laboratory values were assessed. All kinds of adverse events were summarized by WHOART system organ class and preferred term.

STATISTICAL METHODOLOGY:

Simple descriptive statistics, such as mean, median, standard deviation, interquartile range, minimum, and maximum for continuous variables, and counts and percentages for categorical variables were used to summarize most data. In addition to statistical analyses, graphical data displays (eg, box plots) and patient listings may also be used to summarize the data. Patients' demographic data (e.g., age, weight, height, and sex) and concomitant medications at baseline were summarized

RESULTS:

Total 92 patients administered with Infliximab for average 61±28.9 weeks until study completed by sponsor in extension period. Eighty six patients (93.5%) continued treatment for 12 weeks, 74 patients (80.4%) continued for 24 weeks, 64 patients (69.6%) continued for 48 weeks and 57 patients (62.0%) continued for 84 weeks until study completed by sponsor. Two hundreds and eighty seven adverse events reported from 76 patients (82.6%), and among this, 24 serious adverse events reported from 12 patients (13.0%). Eighteen patients (19.6%) discontinued study due to adverse events, and 70 infection related events were reported from 41 patients (44.6%). This result has no big difference from existing results. No tuberculosis or malignancy was reported in the study. Unlisted and related adverse events by investigator include Cervical dysplasia, Gastritis, Otitis media, Cystitis, Eye pain.

CONCLUSION

Long term Infliximab treatment in patients who have active RA despite Methotrexate treatment showed favorable safety tolerance. Adverse events profile was similar to previously reported results and there were no prominently increased adverse events.