2. CLINICAL STUDY SYNOPSIS

Name of Company: Alder Biopharmaceuticals, Inc.	**Volume:**	(For national authority use only)
Name of Finished Product: ALD518	**Page:**	
Name of Active Ingredient(s): ALD518, a humanized anti-interleukin-6 monoclonal antibody		

Title of Study: A Study to Determine the Safety, Efficacy, and Pharmacokinetics of 80 mg, 160 mg, and 320 mg ALD518 versus Placebo Administered as Multiple Intravenous Infusions to Patients with Active Rheumatoid Arthritis Who Have Had an Inadequate Response to Methotrexate

Protocol Number: ALD518-CLIN-003

Study Period: 8 months **Study Phase:** II

Date of first subject, first visit: 21 Oct 2008

Date of last subject, last visit: 17 Jun 2009

Principal Investigators: 24 in Georgia, Russia, Poland, Serbia, and Canada

Study Center(s): 24 centers in 5 countries

Publication(s): None

Primary Objective: To determine the safety of 2 intravenous (IV) infusions of ALD518 80, 160, and 320 mg in subjects with active rheumatoid arthritis with an inadequate response to methotrexate.

Secondary Objectives: To determine the efficacy, pharmacokinetics (PK), and immunogenicity of 2 IV infusions of ALD518 80, 160, and 320 mg in subjects with active rheumatoid arthritis with an inadequate response to methotrexate.

Study Design: This was a Phase II, parallel-group, double-blind, randomized, placebo-controlled study of ALD518 in subjects with active rheumatoid arthritis (RA) with an inadequate response to methotrexate. Enrolled subjects were screened within a 4-week period (Day -35 to -7). Within a 12-day period (Day -14 to -3) before initial dosing on Day 1, subjects were randomized to 1 of the following 4 treatments groups:

Group A: ALD518 80 mg x 2 doses
Group B: ALD518 160 mg x 2 doses
Group C: ALD518 320 mg x 2 doses
Group D: placebo x 2 doses

In all treatment groups, subjects continued to take a stable dose of methotrexate.
There were a total of 11 visits. Subjects received 1 IV infusion on Day 1 and a second IV infusion at Week 8. All subjects remained in the clinic for at least 4 hours from the time the infusion was started. There were 5 visits between dosing (Weeks 1, 2, 3, 4, and 6) and 3 follow-up visits after the second (final) dose (Weeks 10, 12, and 16). At these visits, safety, efficacy, PK, and immunogenicity assessments were performed. The study was unblinded after the last randomized subject had reached the Week 12 visit.
The total duration of the subject study participation was approximately 16 weeks (excluding the screening period).

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Number of Subjects (planned and analyzed): Approximately 120 subjects (30 per treatment group) with active RA with an inadequate response to methotrexate were to be enrolled at up to 30 centers. 132 subjects were actually randomized, and 127 were dosed (32 subjects in the ALD518 80 mg group, 34 subjects in the ALD518 160 mg group, 28 subjects in the ALD518 320 mg group, and 33 subjects in the placebo group received at least 1 dose); 5 subjects were withdrawn between randomization and dosing (1 subject in the ALD518 80 mg group, 3 subjects in the ALD518 320 mg group, and 1 subject in the placebo group). Overall, 127 subjects were included in the Safety and Modified Intent-to-Treat (MITT) Populations, of whom all received at least 1 dose of study drug and 118 received 2 doses of study drug. A total of 122 subjects were included in the Per Protocol (PP) Population, defined as subjects who were randomized, received at least 1 dose of study drug, did not have any major protocol violations, and received the treatment to which they were randomized.

Diagnosis and Main Criteria for Inclusion: Subjects aged between 18 and 80 years (inclusive) with a diagnosis of active RA (ACR criteria 1987) at least 16 weeks before the Screening visit (excluded if onset prior to 16 years old); an ACR global functional status class of 1 to 3; a minimum of 6 tender and 6 swollen joints on a 68/66 joint analysis at Screening and predose; C-reactive protein (CRP) of ≥ 10 mg/L; and on a stable dose of methotrexate (≥ 10 mg/week) for at least 3 months before study Day 1; did not require disallowed narcotics or any drug for treatment of RA, disease modifying anti-rheumatic drugs (DMARDS) other than methotrexate, within 4 months before Day 1, or any intra-articular, intramuscular, or intravenous glucocorticoids within 4 weeks before Day 1.

Test Product, Dose and Mode of Administration, and Lot Number(s): Two single IV infusions of ALD518 (80, 160, or 320 mg) or placebo, 8 weeks apart. ALD518 was added to normal saline (250 mL) and then infused IV over a period of 1 hour (± 15 minutes).
ALD518 lot numbers:
FIN 0560 (retest dates: Mar 2009 [9 months], Jun 2009 [12 months], Dec 2009 [18 months])
FIN 0561 (retest dates: Jun 2009 [12 months])

Reference Therapy, Dose, and Mode of Administration, and Lot Number(s): Subjects randomized to receive placebo received normal saline (250 mL) infused IV over a period of 1 hour (± 15 minutes).

Duration of Treatment: 8 weeks: 1 IV infusion on Day 1 and a second IV infusion at Week 8

Criteria for Evaluation:

Efficacy:

The primary efficacy endpoint was to evaluate the difference in treatment with ALD518 (defined as Groups A, B, and C) relative to treatment with placebo (defined as Group D) in the proportion of subjects achieving a 20% improvement in ACR response (ACR20) at Week 12.

The secondary efficacy endpoints were:

- To evaluate the difference in treatment with ALD518 relative to treatment with placebo in the proportion of subjects achieving 50% and 70% improvement in their ACR response (ACR50 and ACR70, respectively) at Week 12
- Change from baseline in each separate component of the ACR response: the tender and swollen joint count 68/66; joint pain; patient and physician global assessment of disease activity (VAS); health assessment questionnaire (HAQ) disability index (DI); and acute phase reactant (CRP)
- Change from baseline in the following secondary efficacy parameters:
  - Disease Activity Score (DAS28)
  - Short Form-36 (SF-36)

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  - Morning stiffness
- The evaluation of PK over time: peak plasma concentration (C_{max}), time to peak concentration (T_{max}), area under the concentration-time curve extrapolated to infinity (AUC_{∞}), AUC from time zero to the last plasma sample ($AUC_{0\text{-last}}$), and elimination half life ($t_{½}$)
- Evaluation of anti-ALD518 antibodies

Safety:

The safety endpoints (primary objective) of the study were:

- Incidence and severity of adverse events (AEs) and serious AEs (SAEs) during the study
- Changes in vital signs and 12-lead electrocardiograms (ECGs) during the study
- Changes in physical examination during the study
- Changes in anti-nuclear antibody (ANA) and anti-double strand deoxyribonucleic acid (dsDNA) during the study
- Changes in laboratory assessments (serum chemistry, hematology, and urinalysis) during the study.

Statistical Methods: Study variables were summarized by descriptive statistics (mean, standard deviation [SD], median, minimum, and maximum for continuous variables and frequency and percentage for categorical variables). Unless otherwise stated, all statistical tests were performed using 2-sided tests at 5% significance level.

Efficacy: The proportion of subjects achieving ACR20, at Week 12, stratified by treatment group was evaluated using a test of proportions, Fisher's exact test. Change from baseline in the DAS28, SF-36, and morning stiffness was summarized as descriptive statistics by treatment group and visit. The DAS28 European League Against Rheumatism (EULAR) response was summarized as proportion by treatment group and visit.

Safety: All AEs recorded during the course of the clinical trial were coded according to the Medical Dictionary of Regulatory Activities (MedDRA) system, version 12.0. Treatment-emergent adverse events (TEAEs) were defined as AEs that had first occurred or worsened in severity after initiation of therapy. The frequency of subjects experiencing any TEAE was summarized in each treatment group using counts and percentages by body system, preferred term, relatedness, and severity. Changes in laboratory assessments and vital signs were made from baseline, and presented in change tables and evaluated descriptively.

Pharmacokinetics: Standard PK parameters were derived from the plasma concentration data for ALD518 and tabulated. Pharmacokinetic parameters that were estimated for ALD518 include C_{max}, T_{max}, AUC_{∞}, $AUC_{0\text{-last}}$, and $t_{½}$. Analysis of variance (ANOVA) was used to analyze all PK parameters except for T_{max}. These models took into account variations due to subject, treatment, and period, if necessary.

Efficacy Results:

Subjects who received ALD518 (plus methotrexate) experienced a greater improvement in symptoms starting 2 weeks after the first dose, and lasting for the duration of the 16-week study compared to subjects who received methotrexate only (placebo).

- The study met its primary efficacy endpoint of a statistically significant difference in the proportion of subjects achieving ACR20 at Week 12, with 81.3, 70.6, and 82.1% subjects in the ALD518 80, 160, and 320 mg groups achieving ACR20, respectively, compared to 27.3% in the placebo group ($p \leq 0.0005$ for each comparison to placebo; non-responder imputation). The proportions of subjects achieving ACR20 were similar at Week 16, for each group.

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- Similar results were observed for ACR50 and ACR70 as shown in Table I.

Table I. Percentage of Subjects Achieving ACR20/50/70 at Weeks 12 and 16 (MITT Population; Non-responder Imputation)

	Study Visit	ALD518 80 mg + MTX	ALD518 160 mg + MTX	ALD518 320 mg + MTX	MTX only (Placebo)
		n (%)	n (%)	n (%)	n (%)
ACR20	Week 12	26 (81.3)*	24 (70.6)*	23 (82.1)*	9 (27.3)
	Week 16	24 (75.0)*	22 (64.7)*	23 (82.1)*	12 (36.4)
ACR50	Week 12	11 (34.4)*	9 (26.5)	14 (50.0)*	3 (9.1)
	Week 16	13 (40.6)*	14 (41.2)*	14 (50.0)*	5 (15.2)
ACR70	Week 12	4 (12.5)	4 (11.8)	7 (25.0)*	1 (3.0)
	Week 16	7 (21.9)	6 (17.6)	12 (42.9)*	2 (6.1)

* Difference statistically significant ($p < 0.05$) in comparison with placebo based on Fisher's exact test.

- For the ALD518 groups, there was a notable decrease (improvement) from baseline in each separate component of the ACR response: the mean tender and swollen joint count 68/66, joint pain, patient and physician global assessments of disease activity (VAS), HAQ-DI, and acute phase reactant (CRP), as shown in Table II. C-reactive protein, in particular, decreased significantly in all ALD518 treatment groups, starting 1 week after the first dose, and remained at this suppressed level throughout the study.

Table II. Mean Change from Baseline in ACR Core Set Variables at Week 16 (MITT Population)

ACR Variable	ALD518 80 mg + MTX	ALD518 160 mg + MTX	ALD518 320 mg + MTX	MTX only (Placebo)
Swollen joint count (66)	-13.8	-11.5	-12.8	-5.5
Tender joint count (68)	-16.3	-16.8	-18.9	-8.1
Patient Global VAS (mm)	-31.2	-24.7	-36.6	-13.6
Physician Global VAS (mm)	-44.9	-37.3	-43.4	-22.0
Pain VAS (mm)	-33.2	-29.3	-33.6	-13.8
HAQ-DI	-0.570	-0.576	-0.674	-0.470
CRP (mg/dL)	-3.070	-2.556	-3.040	-0.653

- For the ALD518 groups, there was a notable decrease (improvement) from baseline in the mean DAS28 score. At Week 16, the mean decreases in DAS28 scores were -2.7, -2.7, and -3.2 points in the ALD518 80, 160, and 320 mg groups compared to -1.1 points in the placebo group.
- The percentage of subjects achieving remission (DAS28 $\leq$ 2.6) in the ALD518 groups increased throughout the course of the study, reaching 13.8, 28.1, and 44.0% at Week 16 in the ALD518 80, 160, and 320 mg groups, respectively, compared to no subjects in the placebo group.
- The percentage of subjects achieving a good or moderate EULAR response increased throughout the study, reaching 96.6, 93.8, and 96.0% at Week 16 in the ALD518 80, 160, and 320 mg group,

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respectively, compared to 51.7% of subjects in the placebo group.

- Results for the SF-36 components indicated a notable improvement from baseline for all ALD518 groups in comparison to placebo.
- There was a greater reduction (improvement) in the duration of morning stiffness for the ALD518 groups compared to placebo.
- Mean C_{max} (ranging from 26.068 to 129.985 µg/mL) was observed at approximately 5 hours post-dose (T_{max}) at all doses for both days of treatment. Maximum plasma concentration of ALD518, AUC_{∞}, and $AUC_{0\text{-last}}$ showed higher mean values with increasing dose group, after both infusions; differences between treatment groups for all 3 parameters were statistically significant ($p < 0.0001$). Mean values were also higher in all groups after the second dose (Week 8) compared to the first dose (Day 1). The observed mean values for C_{max}, AUC_{∞}, and $AUC_{0\text{-last}}$ were linear and approximately dose-proportional over all 3 ALD518 doses. Mean $t_{½}$ estimates for plasma ALD518 ranged from 602 hours to 743 hours (25 to 31 days).
- All plasma samples from subjects were negative for antibodies to ALD518.

Safety Results:

ALD518, when administered by IV infusion at doses of 80, 160, and 320 mg on 2 occasions 8 weeks apart, was well-tolerated in RA subjects taking methotrexate.

- No deaths occurred during the study. Overall, 48 subjects (37.8%) experienced at least 1 TEAE during the study, 33 of whom (26.0%) experienced at least 1 TEAE that was considered related to the study drug. The majority of related TEAEs occurred in the ALD518 groups (30 subjects [31.9%]; pooled) compared with the placebo group (3 subjects [9.1%]). Within the ALD518 groups, the majority of related TEAEs occurred in the 320 mg group (15 subjects [51.7%]) followed by the 80 mg group (10 subjects [31.3%]). The most commonly reported related TEAEs in the pooled ALD518 group were increased ALT (18 subjects [19.1%]), increased AST (16 subjects [17.0%]), and increased GGT (6 subjects [6.4%]), although the majority of these were mild or moderate in severity.
- Two subjects experienced SAEs: elevated liver enzymes (Common Toxicity Criteria [CTC] Grade 3 increased ALT/CTC Grade 4 increased AST) in an ALD518 80 mg subject and chronic toxical-allergical hepatitis (manifested as CTC Grade 4 increased GGT) in an ALD518 320 mg subject. Both subjects were discontinued from the study. Two additional subjects were discontinued from the study due to AEs: CTC Grade 2 increased ALT/CTC Grade 3 increased AST in an ALD518 80 mg subject and CTC Grade 1 increased ALT/CTC Grade 1 increased AST/CTC Grade 1 increased GGT in an ALD518 320 mg subject. All of the SAEs and AEs leading to discontinuation were related to LFT abnormalities and all were considered related to the study drug. All of the SAEs were considered severe or life-threatening/disabling. Of the AEs leading to discontinuation, 2 were severe and 3 were mild. There were no serious infusion or infection events reported.
- The following notable laboratory trends over time were observed in the ALD518 groups compared with the placebo group (placebo showed a lesser change or a small change in the opposite direction in all cases):
    a. Decrease from baseline for ALD518 groups in mean platelet count and mean absolute neutrophil count (ANC) over time.
    b. Increase from baseline for ALD518 groups in mean HGB over time.
    c. Increase from baseline for ALD518 groups in mean ALT, AST, GGT, total cholesterol, triglycerides, total and direct bilirubin, and albumin over time.
- Although a notable proportion of subjects experienced shifts in the above laboratory values from normal at baseline to above or below the reference range, the majority (97.7%) of those with an

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associated CTC Grade were reported as CTC Grade 1 or 2.

- The urinalysis tests with notable numbers of subject shifts from normal to abnormal were blood, ketones, and protein. Urinalysis results were reported as AEs for 1 subject (ALD518 320 mg), who experienced the mild AE of glycosuria and 2 mild AEs of hematuria, which were not considered related to the study drug.
- Overall, there were no notable changes in vital signs, 12-lead ECGs, or physical examinations over the course of the study. Three subjects (2 in the ALD518 80 mg group and 1 in the placebo group) experienced treatment related AEs associated with vital sign measures (feeling hot, increased blood pressure, and hypertension).
- There were no notable changes in rheumatoid factor (RF) anti-cyclic citrullinated peptide (anti-CCP), anti-dsDNA, or ANA.

Conclusions:

The results of the analysis of this study support the following conclusions:

- Subjects who received ALD518 (plus methotrexate) experienced a greater improvement in symptoms starting 2 weeks after first dose and lasting for the duration of the 16-week study compared to subjects who received methotrexate only (placebo). The study met its primary efficacy endpoint of a statistically significant difference in the proportion of subjects achieving ACR20 at Week 12.
- C_{max}, AUC_{∞}, and $AUC_{0\text{-last}}$ were linear and approximately dose-proportional over all 3 ALD518 doses. $t_{½}$ estimates for plasma ALD518 ranged from 602 hours to 743 hours (25 to 31 days).
- ALD518 was well-tolerated in RA subjects taking methotrexate. There were no deaths during the study; 2 subjects experienced SAEs and 2 subjects experienced AEs leading to discontinuation. There were no serious infusion or infection events reported.

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