YUFLYMA®
Adalimumab

PRODUCT NAME
Adalimumab solution for injection in pre-filled pen

Trade Name
Yuflyma®

Yuflyma (adalimumab) is a recombinant human immunoglobulin (IgG1) monoclonal antibody produced in Chinese Hamster Ovary cells.

Yuflyma is supplied as a sterile, preservative-free solution of adalimumab for subcutaneous administration. The solution of Yuflyma is clear to slightly opalescent and colorless to pale brown. The drug product is supplied as a single-use pre-filled Pen (Yuflyma Pen). Enclosed within the Pen is a single-use, 1 mL pre-filled glass syringe.

Inactive ingredients for Yuflyma 40 mg per 0.4 mL (100 mg/mL) include: acetic acid, sodium acetate trihydrate, glycine, polysorbate 80, and water for injection.

CLINICAL PHARMACOLOGY

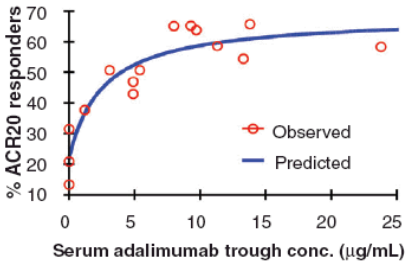
General
Adalimumab binds specifically to TNF and neutralizes the biological function of TNF by blocking its interaction with the p55 and p75 cell surface TNF receptors. TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Elevated levels of TNF are found in the synovial fluid of rheumatoid arthritis, including juvenile idiopathic arthritis, psoriatic arthritis and ankylosing spondylitis patients and play an important role in both the pathologic inflammation and the joint destruction that are hallmarks of these diseases. Increased levels of TNF are also found in hidradenitis suppurativa (HS) lesions. The relationship between these pharmacodynamic activities and the mechanism(s) by which adalimumab exerts its clinical effects is unknown.

Adalimumab also modulates biological responses that are induced or regulated by TNF, including changes in the levels of adhesion molecules responsible for leukocyte migration (ELAM-1, VCAM-1, and ICAM-1 with an IC_{50} of 1-2 X 10^{-10}M).

Pharmacodynamics
After treatment with adalimumab, a rapid decrease in levels of acute phase reactants of inflammation (C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)) and serum cytokines (IL-6) was observed compared to baseline in patients with RA. A decrease in CRP levels was also observed in patients with JIA, Crohn's disease, ulcerative colitis and hidradenitis suppurativa as well as a significant reduction in the expression of the TNF and inflammatory markers such as human leucocyte antigen (HLA-DR) and myeloperoxidase (MPO) in the colon of patients with Crohn's disease. Serum levels of matrix metalloproteinases (MMP-1 and MMP-3) that produce tissue remodeling responsible for cartilage destruction were also decreased after adalimumab administration. Patients with RA, PsA and AS often experience mild to moderate anemia and decreased lymphocyte counts, as well as elevated neutrophil and platelet counts. Patients treated with adalimumab usually experienced improvement in these hematological signs of chronic inflammation.

The serum adalimumab concentration-efficacy relationship as measured by the American College of Rheumatology response criteria (ACR 20) appears to follow the Hill E_{max} equation as shown below:

Figure 1: Concentration- Efficacy Relationship



EC_{50} estimates ranging from 0.8 to 1.4 mcg/mL were obtained through pharmacokinetic / pharmacodynamic modeling of swollen joint count, tender joint count and ACR 20 response from patients participating in Phase II and III trials.

Pharmacokinetics
Absorption
Following a single 40 mg subcutaneous (SC) administration of adalimumab to 59 healthy adult subjects, absorption and distribution of adalimumab was slow, with mean peak serum concentration being reached about five days after administration. The average absolute bioavailability of adalimumab estimated from three studies following a single 40 mg subcutaneous dose was 64%.

Distribution and Elimination
The single dose pharmacokinetics of adalimumab were determined in several studies with intravenous doses ranging from 0.25 to 10 mg/kg. The distribution volume (V_{ss}) ranged from 4.7 to 6.0 L, indicating that adalimumab distributes approximately equally between the vascular and extravascular fluids. Adalimumab is slowly eliminated, with clearances typically under 12 mL/h. The mean terminal phase half-life was approximately two weeks, ranging from 10 to 20 days across studies. The clearance and half-life were relatively unchanged over the studied dose range, and the terminal half-life was similar after IV and SC administration. Adalimumab concentrations in the synovial fluid from several RA patients ranged from 31 to 96% of those in serum.

Steady-state pharmacokinetics
Accumulation of adalimumab was predictable based on the half-life following SC administration of 40 mg of adalimumab every

other week to patients with RA, with mean steady-state trough concentrations of approximately 5 mcg/mL (without concomitant methotrexate (MTX)) and 8 to 9 mcg/mL (with concomitant MTX), respectively. The serum adalimumab trough levels at steady state increased approximately proportionally with dose following 20, 40 and 80 mg every other week and every week SC dosing. In long-term studies with dosing more than two years, there was no evidence of changes in clearance over time.

In patients with psoriasis, the mean steady-state trough concentration was 5 mcg/mL during adalimumab 40 mg eow without concomitant MTX treatment.

In patients with hidradenitis suppurativa, a dose of 160 mg adalimumab on Week 0 followed by 80 mg on Week 2 achieved serum adalimumab trough concentrations of approximately 7 to 8 mcg/mL at Week 2 and Week 4. The mean steady-state trough concentration at Week 12 through Week 36 were approximately 8 to 10 mcg/mL during adalimumab 40 mg every week treatment.

In patients with uveitis, a loading dose of 80 mg adalimumab on Week 0 followed by 40 mg adalimumab every other week starting at Week 1, resulted in mean steady-state concentrations of approximately 8 to 10 mcg/mL.

Population pharmacokinetic and pharmacokinetic/pharmacodynamic modelling and simulation predicted comparable adalimumab exposure and efficacy in patients treated with 80 mg every other week when compared with 40 mg every week (including adult patients with RA, HS, UC, CD or Ps, adolescent patients with HS, and pediatric patients ≥ 40 kg with CD and UC).

Population pharmacokinetic analyses with data from over 1200 patients revealed that co-administration of MTX had an intrinsic effect on adalimumab apparent clearance (CL/F) (see **DRUG INTERACTIONS**). As expected, there was a trend toward higher apparent clearance of adalimumab with increasing body weight and in the presence of anti-adalimumab antibodies.
Other more minor factors were also identified; higher apparent clearance was predicted in patients receiving doses lower than the recommended dose, and in patients with high rheumatoid factor or CRP concentrations. These factors are not likely to be clinically important.

In patients with Crohn's disease, the loading dose of 80 mg adalimumab on Week 0 followed by 40 mg adalimumab on Week 2 achieves serum adalimumab trough levels of approximately 5.5 mcg/mL during the induction period. A loading dose of 160 mg adalimumab on Week 0 followed by 80 mg adalimumab on Week 2 achieves serum adalimumab trough levels of approximately 12 mcg/mL during the induction period. Mean steady-state trough levels of approximately 7 mcg/mL were observed at Week 24 and Week 56 in Crohn's disease patients after receiving a maintenance dose of 40 mg adalimumab every other week.

In patients with ulcerative colitis, a loading dose of 160 mg adalimumab on Week 0 followed by 80 mg adalimumab on Week 2 achieves serum adalimumab trough concentrations of approximately 12 mcg/mL during the induction period. Mean steady-state trough levels of approximately 8 mcg/mL were observed in ulcerative colitis patients who received a maintenance dose of 40 mg adalimumab every other week.

Special Populations
Pharmacokinetics in special populations were investigated using population pharmacokinetic analyses.

Geriatrics
Age appeared to have a minimal effect on adalimumab apparent clearance. From the population analyses, the mean weight-adjusted clearances in patients 40 to 65 years (n=850) and ≥65 years (n=287) were 0.33 and 0.30 mL/h/kg, respectively.

Pediatrics
Following the administration of 24 mg/m^2 (up to a maximum of 40 mg) subcutaneously every other week to patients with polyarticular juvenile idiopathic arthritis (JIA) who were 4 to 17 years, the mean trough steady-state (values measured from Week 20 to 48) serum adalimumab concentration was 5.6 ± 5.6 µg/mL (102% CV) for adalimumab without concomitant MTX and 10.9 ± 5.2 µg/mL (47.7% CV) with concomitant MTX. The mean steady-state trough serum adalimumab concentrations for patients weighing <30 kg receiving 20 mg adalimumab subcutaneously every other week without concomitant MTX or with concomitant MTX were 6.8 µg/mL and 10.9 µg/mL, respectively. The mean steady-state trough serum adalimumab concentrations for patients weighing ≥30 kg receiving 40 mg adalimumab subcutaneously every other week without concomitant MTX or with concomitant MTX were 6.6 µg/mL and 8.1 µg/mL, respectively. In patients with polyarticular JIA who were 2 to <4 years old or aged 4 and above weighing <15 kg dosed with adalimumab 24 mg/m^2, the mean trough steady-state serum adalimumab concentrations was 6.0 ± 6.1 µg/mL (101% CV) for adalimumab without concomitant MTX and 7.9 ± 5.6 µg/mL (71.2% CV) with concomitant MTX.

Following the administration of 24 mg/m^2 (up to a maximum of 40 mg) subcutaneously every other week to patients with enthesitis-related arthritis, the mean trough steady-state (values measured at Week 24) serum adalimumab concentrations were 8.8 ± 6.6 µg/mL for adalimumab without concomitant methotrexate and 11.8 ± 4.3 µg/mL with concomitant methotrexate.

In pediatric patients with moderately to severely active Crohn's disease, the open-label adalimumab induction dose was 160/80 mg or 80/40 mg at Weeks 0 and 2, respectively, dependent on a body weight cut-off of 40 kg. At Week 4, patients were randomized 1:1 to either the Standard Dose (40/20 mg eow) or Low Dose (20/10 mg eow) maintenance treatment groups based on their body weight. The mean (±SD) serum adalimumab trough concentrations achieved at Week 4 were 15.7±6.6 μ/mL for patients ≥40 kg (160/80 mg) and 10.6±6.1 μ/mL for patients <40 kg (80/40 mg).

For patients who stayed on their randomized therapy, the mean (±SD) adalimumab trough concentrations at Week 52 were 9.5±5.6 µg/mL for the Standard Dose group and 3.5±2.2 µg/mL for the Low Dose group. The mean trough concentrations were maintained in patients who continued to receive adalimumab treatment eow for 52 weeks. For patients who dose escalated from eow to weekly regimen, the mean (±SD) serum concentrations of adalimumab at Week 52 were 15.3±11.4 µg/mL (40/20 mg, weekly) and 6.7±3.5 µg/mL (20/10 mg, weekly).

Following the administration of 0.8 mg/kg (up to a maximum of 40 mg) subcutaneously every other week to pediatric patients with chronic plaque psoriasis, the mean ± SD steady-state adalimumab trough concentration was approximately 7.4 ± 5.8 µg/mL (79% CV).

Adalimumab exposure in adolescent hidradenitis suppurativa (HS) patients was predicted using population pharmacokinetic modeling and simulation based on cross-indication pharmacokinetics in other pediatric patients (pediatric psoriasis, juvenile idiopathic arthritis, pediatric Crohn's disease, and enthesitis-related arthritis). The recommended adolescent HS dosing schedule

of 40 mg every other week is predicted to provide serum adalimumab exposure similar to that observed in adult HS patients receiving the recommended adult dose of 40 mg every week.
Adalimumab exposure in paediatric uveitis patients was predicted using population pharmacokinetic modelling and simulation based on cross-indication pharmacokinetics in other paediatric patients (paediatric psoriasis, juvenile idiopathic arthritis, paediatric Crohn's disease, and enthesitis-related arthritis). No clinical exposure data are available on the use of a loading dose in children < 6 years. The predicted exposures indicate that in the absence of methotrexate, a loading dose may lead to an initial increase in systemic exposure.

Following the subcutaneous administration of body weight-based dosing of 0.6 mg/kg (maximum of 40 mg) every other week to pediatric patients with ulcerative colitis, the mean trough steady-state serum adalimumab concentration was 5.01±3.28 µg/mL at Week 52. For patients who received 0.6 mg/kg (maximum of 40 mg) every week, the mean (±SD) trough steady-state serum adalimumab concentration was 15.7±5.60 µg/mL at Week 52.

Gender
No gender-related pharmacokinetic differences were observed after correction for a patient's body weight.

Race
No differences in immunoglobulin clearance would be expected among races. From limited data in non-Caucasians, no important kinetic differences were observed for adalimumab.

Hepatic and Renal Insufficiency
No pharmacokinetic data are available in patients with hepatic or renal impairment.

Disease States
Healthy volunteers and patients with RA displayed similar adalimumab pharmacokinetics.

Interchangeability
Yuflyma is a biosimilar medicinal product. The prescribing physician should be involved in any decision regarding its interchangeability

CLINICAL STUDIES

ADULTS
Rheumatoid Arthritis Clinical Studies
Adalimumab was evaluated in over 3000 patients in all rheumatoid arthritis clinical trials. The efficacy and safety of adalimumab were assessed in five randomized, double-blind and well-controlled studies. Some patients were treated for up to 120 months duration. Injection site pain of adalimumab 40 mg/0.4 mL compared to adalimumab 40 mg/0.8 mL was assessed in two randomized, active control, single-blind, two period crossover studies.

RA Study I (DE009) evaluated 271 patients with moderately to severely active RA who were ≥18 years old, had failed therapy with at least one but no more than four disease-modifying anti-rheumatic drugs (DMARDs) (e.g., hydroxychloroquine, oral or injectable gold, azathioprine, D-penicillamine, sulfasalazine), and had insufficient efficacy with MTX at doses of 12.5 to 25 mg (10 mg if MTX-intolerant) every week and whose MTX dose remained constant at 10 to 25 mg every week. Patients had ≥6 swollen joints and ≥9 tender joints and RA diagnosed according to ACR criteria. Doses of 20, 40 or 80 mg of adalimumab or placebo were given every other week for 24 weeks.

RA Study II (DE011) evaluated 544 patients with moderately to severely active RA who were ≥18 years old and had failed therapy with at least one DMARD (e.g., MTX, sulfasalazine, hydroxychloroquine, oral or injectable gold, D-penicillamine, azathioprine). Patients had ≥10 swollen joints and ≥12 tender joints and were also diagnosed according to ACR criteria. Doses of 20 or 40 mg of adalimumab were given by SC injection every other week with placebo on alternative weeks or every week for 26 weeks; placebo was given every week for the same duration.

RA Study III (DE019) evaluated 619 patients with moderately to severely active RA who were ≥18 years old, had insufficient efficacy to MTX at doses of 12.5 to 25 mg (10 mg if MTX-intolerant) every week and whose MTX dose remained constant at 12.5 to 25 mg every week. Unlike RA Study I, patients in RA Study III were not required to have failed therapy with any DMARDs other than MTX. Patients had ≥6 swollen joints and ≥9 tender joints and RA diagnosed according to ACR criteria. There were three groups in this study. The first received placebo injections every week for 52 weeks. The second received 20 mg of adalimumab every week for 52 weeks. The third group received 40 mg of adalimumab every other week with placebo injections on alternate weeks. Upon completion of the first 52 weeks, 457 patients enrolled in an open-label extension phase in which 40 mg of adalimumab/MTX was administered every other week up to 10 years.

RA Study IV (DE031) assessed 636 patients with moderately to severely active RA who were ≥18 years old. These patients met the ACR criteria for diagnosis of RA for at least three months and had at least 6 swollen joints and 9 tender joints. Patients were permitted to be either DMARD-naive or to remain on their pre-existing rheumatologic therapy provided that therapy was stable for a minimum of 28 days. Patients were randomized to 40 mg of adalimumab or placebo every other week for 24 weeks.
RA Study V (DE013) evaluated 799 methotrexate-naive, adult patients with moderately to severely active early rheumatoid arthritis (mean disease duration less than 9 months). This study evaluated the efficacy of adalimumab 40 mg every other week/methotrexate combination therapy, adalimumab 40 mg every other week monotherapy and methotrexate monotherapy in reducing the signs and symptoms and rate of progression of joint damage in rheumatoid arthritis for 104 weeks. Upon completion of the first 104 weeks, 497 patients enrolled in an open-label extension phase in which 40 mg of adalimumab was administered every other week up to 10 years.

RA Studies VI and VII each evaluated 60 patients with moderately to severely active rheumatoid arthritis who were ≥ 18 years old. Enrolled patients were either current users of adalimumab 40 mg/0.8 mL and rated their average injection site pain as at least 3 cm (on a 0-10 cm VAS) or were biologic-naïve subjects who were starting adalimumab 40 mg/0.8 mL. Patients were randomized to receive a single dose of adalimumab 40 mg/0.8 mL or adalimumab 40 mg/0.4 mL, followed by a single injection of the opposite treatment at their next dose.

Results of all RA Study I-V were expressed in percentage of patients with improvement in RA using ACR response criteria. The primary end point in RA Studies I, II and III and the secondary endpoint in RA Study IV was the percent of patients who achieved an ACR 20 response at Week 24 or 26. The primary endpoint in RA Study V was the percent of patients who achieved an ACR 50 response at Week 52. RA Study III and V had an additional primary endpoint at 52 weeks of retardation of disease progression (as detected by x-ray results). RA Study III also had a primary endpoint of changes in quality of life. The primary endpoint in RA studies VI and VII was injection site pain immediately after injection as measured by a 0-10 cm VAS.

Clinical Response

RA Studies I, II and III

The percent of adalimumab treated patients achieving ACR 20, 50 and 70 responses was consistent across all three trials. The results of the three trials are summarized in Table 1.

Table 1: ACR Responses in Placebo-Controlled Trials (Percent of Patients)

Response	RA Study I[a]*		RA Study II[a]*		RA Study III[a]*	
	Placebo/ MTX n=60	Adalimumab[b]/ MTX n=63	Placebo n=110	Adalimumab[b] n=113	Placebo/ MTX n=200	Adalimumab[b]/ MTX n=207
ACR 20						
6 months	13.3%	65.1%	19.1%	46.0%	29.5%	63.3%
12 months	NA	NA	NA	NA	24.0%	58.9%
ACR 50						
6 months	6.7%	52.4%	8.2%	22.1%	9.5%	39.1%
12 months	NA	NA	NA	NA	9.5%	41.5%
ACR 70						
6 months	3.3%	23.8%	1.8%	12.4%	2.5%	20.8%
12 months	NA	NA	NA	NA	4.5%	23.2%

a RA Study I at 24 weeks, RA Study II at 26 weeks, and RA Study III at 24 and 52 weeks
b 40 mg adalimumab administered every other week
* p<0.01. Adalimumab vs. placebo at all timepoints for ACR 20, 50, 70

Patients receiving adalimumab 40 mg every week in RA Study II also achieved statistically significant ACR 20, 50 and 70 response rates of 53.4%, 35.0% and 18.4%, respectively, at six months.

The results of the components of the ACR response criteria for RA Study III are shown in Table 2. The results depicted below are generally representative of each trial conducted.

In the open-label extension for RA Study III, most patients who were ACR responders maintained response when followed for up to 10 years. Of 207 patients who were randomized to adalimumab 40 mg every other week, 114 patients continued on adalimumab 40 mg every other week for 5 years. Among those, 86 patients (75.4%) had ACR 20 responses; 72 patients (63.2%) had ACR 50 responses; and 41 patients (36%) had ACR 70 responses. Of 207 patients, 81 patients continued on adalimumab 40 mg every other week for 10 years. Among those, 64 patients (79.0%) had ACR 20 responses; 56 patients (69.1%) had ACR 50 responses; and 43 patients (53.1%) had ACR 70 responses.

Table 2: Components of ACR Response in RA Study III

Parameter (median)	Placebo/MTX (N=200)			Adalimumab[a]/MTX (N=207)		
	Baseline	Week 24	Week 52	Baseline	Week 24	Week 52
Number of tender joints (0-68)	26.0	15.0	15.0	24.0	8.0*	6.0*
Number of swollen joints (0-66)	17.0	11.0	11.0	18.0	5.0*	4.0*
Physician global assessment disease activity[b]	63.0	35.0	38.0	65.0	20.0*	16.0*
Patient global assessment disease activity[b]	53.5	39.0	43.0	52.0	20.0*	18.0*
Pain[b]	59.5	38.0	46.0	58.0	21.0*	19.0*
Disability index (HAQ)[c]	1.50	1.25	1.25	1.50	0.75*	0.75*
CRP (mg/L)	10.0	9.0	9.0	10.0	4.0*	4.0*

a 40 mg adalimumab administered every other week
b Visual analogue scale; 0 = best, 100 = worst
c Disability Index of the Health Assessment Questionaire; 0 = best, 3 = worst, measures the patient's ability to perform the following: dress/groom, arise, eat, walk, reach, grip, maintain hygiene, and maintain daily activity
* p<0.01. Adalimumab vs. placebo, based on mean change from baseline

In RA Study III, 84.7% of patients with ACR 20 responses at Week 24 maintained the response at 52 weeks. The following figures illustrate the durability of ACR 20 responses to adalimumab in RA Studies III and II.

Figure 2: RA Study III ACR 20 Responses over 52 Weeks

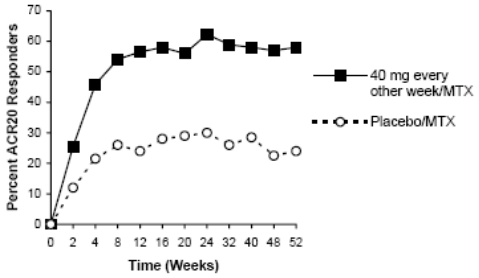
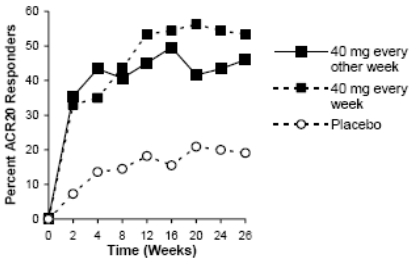


Figure 3: RA Study II ACR 20 Responses over 26 Weeks



RA Study IV

The ACR 20 response of patients treated with adalimumab plus standard of care was statistically significantly better than patients treated with placebo plus standard of care (p<0.001). No unique adverse reactions related to the combination of adalimumab and other DMARDs were observed.

In RA Studies I-IV, adalimumab treated patients achieved ACR 20, 50 and 70 responses faster and more often than placebo-treated patients. In RA Study I, there was a statistically significant difference in ACR 20 responses at week one (first study

visit) between patients treated with adalimumab (26.0%) and placebo (5.0%). Statistically significant differences in ACR 20 responses were also seen in RA Studies II, III and IV at week two (first study visit) between patients treated with adalimumab (36.4%, 29.1% and 33.7%, respectively) and placebo (7.3%, 13.0% and 8.6%, respectively). A similar pattern of the time to first ACR 50 and 70 responses was noted in all four studies.

Some patients not taking concomitant MTX may derive additional benefit from increasing the dosing frequency of adalimumab to 40 mg every week. This was confirmed in a long-term open label study where patients with an incomplete response increased their dosing frequency from 40 mg every other week to 40 mg weekly.

RA Study V

In RA Study V with early rheumatoid arthritis patients who were methotrexate naive, combination therapy with adalimumab and methotrexate led to faster and significantly greater ACR responses than methotrexate monotherapy and adalimumab monotherapy at Week 52 and responses were sustained through Week 104 (see Table 3).

At Week 52 all individual components of the ACR response criteria improved with adalimumab/methotrexate therapy and improvements were maintained to Week 104.

Over the two-year study, 48.5% of patients who received adalimumab/methotrexate combination therapy achieved a major clinical response (ACR 70 for six continuous months) compared to 27.2% of patients who received methotrexate monotherapy (p<0.001) and 24.5% of patients who received adalimumab monotherapy (p<0.001).

Table 3: ACR Response in RA Study V (Percent of Patients)

Response	MTX[b] N=257	Adalimumab N=274	Adalimumab/MTX N=268
ACR 20			
Week 52	63%	54%	73%
Week 104	56%	49%	69%
ACR 50			
Week 52	46%	41%	62%
Week 104	43%	37%	59%
ACR 70			
Week 52	27%	26%	46%
Week 104	28%	28%	47%
Major Clinical Response[a]			
Week 104	28%	25%	49%

a Major clinical response is defined as achieving an ACR 70 response for a continuous six month period
b p<0.05, adalimumab/MTX vs. MTX for ACR 20
p<0.001, adalimumab/MTX vs. MTX for ACR 50 and 70, and Major Clinical Response
c p<0.001, adalimumab/MTX vs. adalimumab

In the open-label extension for RA study V, ACR response rates were maintained when followed for up to 10 years. Of 542 patients who were randomized to adalimumab 40 mg every other week, 170 patients continued on adalimumab 40 mg every other week for 10 years. Among those, 154 patients (90.6%) had ACR 20 responses; 127 patients (74.7%) had ACR 50 responses; and 102 patients (60.0%) had ACR 70 responses.

At Week 52, 42.9% of patients who received adalimumab/methotrexate combination therapy achieved clinical remission (Disease Activity Score (DAS28)-CRP <2.6) compared to 20.6% of patients receiving methotrexate monotherapy and 23.4% of patients receiving adalimumab monotherapy. adalimumab/methotrexate combination therapy was statistically and clinically superior to methotrexate (p<0.001) and adalimumab monotherapy (p<0.001) in achieving a low disease state in patients with recently diagnosed moderate to severe rheumatoid arthritis (see Table 4). Of 342 subjects originally randomized to adalimumab monotherapy or adalimumab/methotrexate combination therapy who entered the open-label extension study, 171 subjects completed 10 years of adalimumab treatment. Among those, 109 subjects (63.7%) were reported to be in remission at 10 years.

Table 4: DAS28 Responses in RA Study V

DAS28 Response	MTX N=257	Adalimumab N=274	Adalimumab/MTX N=268
Week 52			
Baseline (Mean)	6.3	6.4	6.3
Mean Change from Baseline (Mean ± SD)	-2.8 ± 1.4[a]	-2.8 ± 1.5[b]	-3.6 ± 1.3
Percent of Patients in Remission (DAS28<2.6)	20.6%[a]	23.4%[b]	42.9%*
Week 104			
Baseline (Mean)	6.3	6.3	6.3
Mean Change from Baseline (Mean ± SD)	-3.1 ± 1.4[a]	-3.2 ± 1.4[b]	-3.8 ± 1.3

a p<0.001, adalimumab/methotrexate *vs*. methotrexate
b p<0.001, adalimumab/methotrexate *vs*. adalimumab

Radiographic Response

In RA Study III, where adalimumab treated patients had a mean duration of rheumatoid arthritis of approximately 11 years, structural joint damage was assessed radiographically and expressed as change in modified total Sharp score and its components, the erosion score and joint space narrowing score (JSN). Radiographs of hands/wrists and forefeet were read at baseline, 6 months and 12 months. The 12-month results are shown in Table 5. A statistically significant difference for change in modified total Sharp score (TSS) and the erosion score was observed at 6 months and maintained at 12 months. Adalimumab/MTX treated patients demonstrated less radiographic progression than patients receiving MTX alone at 52 weeks. The inhibition of progression of structural damage was maintained through 104 weeks.

Table 5: Radiographic Change Over 12 Months in RA Study III With Background MTX				
	Placebo N=200	Adalimumab[a] N=207	Difference Between Adalimumab [a] and Placebo	p-value
Change in Modified Total Sharp Score (mean)	2.7	0.1	-2.6	<0.001[b]
Change in Erosions (mean)	1.6	0.0	-1.6	<0.001
No New Erosions (% of Patients)	46.2	62.9	16.7	<0.001
Change in JSN Score (mean)	1.0	0.1	-0.9	0.002
a 40 mg adalimumab administered every other week b Based on analysis of ranked ANCOVA				

In the open-label extension of RA Study III, the reduction in rate of progression of structural damage is maintained for 8 and 10 years in a subset of patients. At 8 years, 81 of 207 patients originally treated with adalimumab 40 mg every other week were evaluated radiographically. Among those, 48 patients showed no progression of structural damage defined by a change from baseline in the mTSS of 0.5 or less. At 10 years, 79 of 207 patients originally treated with adalimumab 40 mg every other week were evaluated radiographically. Among those, 40 patients showed no progression of structural damage defined by a change from baseline in the mTSS of 0.5 or less.

In RA Study V, structural joint damage was assessed as in RA Study III. Greater inhibition of radiographic progression, as assessed by changes in TSS, erosion score and JSN was observed in the adalimumab/MTX combination group as compared to either the MTX or adalimumab monotherapy group at Week 52 as well as at Week 104 (see Table 6).

Table 6: Change in Modified Total Sharp Score from Baseline at Weeks 52 and 104 (All Randomized Subjects) in RA Study V					
	MTX N=257	Adalimumab N=274	Adalimumab + MTX N=268	p-value[a]	p-value[b]
Week 52					
Baseline (mean)	21.8 ± 22.2	18.8 ± 19.0	18.1 ± 20.1		
Week 52 (mean)	27.6 ± 24.6	21.8 ± 19.7	19.4 ± 19.9	<0.001	0.002
Change at Week 52 (mean ± SD)	5.7 ± 12.7	3.0 ± 11.2	1.3 ± 6.5		
Week 104					
Baseline (mean)	21.8 ± 22.2	18.8 ± 19.0	18.1 ± 20.1		
Week 104 (mean)	32.3 ± 30.0	24.3 ± 23.2	20.0 ± 20.5	<0.001	<0.001
Change at Week 104 (mean ± SD)	10.4 ± 21.7	5.5 ± 15.8	1.9 ± 8.3		

Note: Primary analysis imputation used for missing data.
a. P-value is from the pairwise comparison of MTX monotherapy and adalimumab + MTX combination therapy using the Mann-Whitney U test.
b. P-value is from the pairwise comparison of adalimumab monotherapy and adalimumab + MTX combination therapy using the Mann-Whitney U test.

Following 52 weeks and 104 weeks of treatment, the percentage of patients without progression (change from baseline in modified total Sharp score <0.5) was significantly higher with adalimumab/MTX combination therapy (63.8% and 61.2% respectively) compared to methotrexate monotherapy (37.4% and 33.5% respectively, p<0.001) and adalimumab monotherapy (50.7%, p<0.002 and 44.5%, p<0.001 respectively).

In the open-label extension of RA study V, the mean change from baseline at Year 10 in the modified Total Sharp Score was 10.8, 9.2 and 3.9 in patients originally randomized to methotrexate monotherapy, adalimumab monotherapy and adalimumab/methotrexate combination therapy, respectively. The corresponding proportions of patients with no radiographic progression were 31.3%, 23.7% and 36.7% respectively.

Quality of Life and Physical Function

Health-related quality of life was assessed using the disability index of the Health Assessment Questionnaire (HAQ) in the four original adequate and well-controlled trials, which was a pre-specified primary endpoint at Week 52 in RA Study III. All doses/schedules of adalimumab in all four studies showed statistically significantly greater improvement in the disability index of the HAQ from baseline to Month 6 compared to placebo. In RA Study III, the mean (CI) improvement in HAQ from baseline at week 52 was -0.60 (-0.65, -0.55) for the adalimumab/MTX patients and -0.25 (-0.33, -0.17) for placebo/MTX (p<0.001) patients. Sixty- three percent of adalimumab/MTX-treated patients achieved a 0.5 or greater improvement in HAQ at week 52 in the double-blind portion of the study. Most subjects who achieved improvement in physical function and continued treatment maintained improvement through week 520 (10 years) of open-label treatment. Improvement in quality of life as measured by SF 36 was assessed up to Week 156 (36 months) and improvement was maintained through that time.

The Short Form Health Survey (SF 36) was also used to assess general health-related quality of life in all four adequate and well-controlled trials. All doses/schedules of adalimumab in all four studies showed statistically significantly greater improvement in SF 36 physical component summary scores from baseline to Month 6 compared to placebo, and this was maintained at Week 52 in RA Study III. Mean improvement in the SF 36 was also maintained through the end of measurement at week 156 (36 months). The SF 36 mental component summary scores in RA Studies II and IV were also statistically significantly greater at Month 6 for adalimumab vs. placebo. The pain and vitality domain scores of the SF 36 showed statistically significantly greater improvement from baseline to Month 6 in all four studies for the 40 mg every other week dose of adalimumab compared to placebo. These findings were supported by functional assessment of chronic illness therapy (FACIT) scores that showed a statistically significant decrease in fatigue at Month 6 in all three studies analyzed that was maintained at Week 52 in RA Study III.

In RA Study V the improvement in the HAQ disability index and the physical component of the SF 36 was greater for the adalimumab/methotrexate combination therapy group versus both methotrexate and adalimumabmonotherapy groups (p<0.001) at Week 52; this improvement was maintained through Week 104. Among the 250 subjects who completed the open-label extension study, improvements in physical function were maintained through 10 years of treatment.

Injection Site Pain

For the pooled crossover RA studies VI and VII, a statistically significant difference for injection site pain immediately after dosing was observed between adalimumab 40 mg/0.8 mL and adalimumab 40 mg/0.4 mL (mean VAS of 3.7 cm versus 1.2

cm, scale of 0-10 cm, P < 0.001). This represented an 84% median reduction in injection site pain.

Psoriatic Arthritis Clinical Studies
The safety and efficacy of adalimumab was assessed in two randomized, double-blind, placebo controlled studies in 413 patients with psoriatic arthritis. PsA Study I (M02-518) enrolled 313 adult patients with moderately to severely active psoriatic arthritis (>3 swollen and >3 tender joints) who had an inadequate response to NSAID therapy in one of the following forms: (1) distal interphalangeal (DIP) involvement (N=23); (2) polyarticular arthritis (absence of rheumatoid nodules and presence of psoriasis) (N=210); (3) arthritis mutilans (N=1); (4) asymmetric psoriatic arthritis (N=77); or (5) ankylosing spondylitis-like (N=2). Patients on MTX therapy (158 of 313 patients) at enrollment (stable dose of <30 mg/week for >1 month) could continue MTX at the same dose. Doses of adalimumab 40 mg or placebo every other week were administered during the 24-week double-blind period of the study. PsA Study II (M02-570) with 12-week duration, treated 100 patients who had an inadequate response to DMARD therapy. Upon completion of both studies, 383 patients enrolled in an open-label extension study, in which 40 mg adalimumab was administered eow.

ACR and PASI Response
Compared to placebo, treatment with adalimumab resulted in improvements in the measures of disease activity (see Tables 7 and 8). Among patients with psoriatic arthritis who received adalimumab, the clinical responses were apparent in some patients at the time of the first visit (two weeks). Similar responses were seen in patients with each of the subtypes of psoriatic arthritis, although few patients were enrolled with the arthritis mutilans and ankylosing spondylitis-like subtypes. Responses were similar in patients who were or were not receiving concomitant MTX therapy at baseline.

Patients with psoriatic involvement of at least three percent body surface area (BSA) were evaluated for Psoriatic Area and Severity Index (PASI) responses. At 24 weeks, the proportions of patients achieving a 75% or 90% improvement in the PASI were 59% and 42% respectively, in the adalimumab group (N=69), compared to 1% and 0% respectively, in the placebo group (N=69) (p<0.001). PASI responses were apparent in some patients at the time of the first visit (two weeks). Responses were similar in patients who were or were not receiving concomitant MTX therapy at baseline.

Table 7: ACR Response in PsA Study I (Percent of Patients)

Response	Placebo N=162	Adalimumab N=151
ACR 20		
Week 12	14%	58%*
Week 24	15%	57%*
ACR 50		
Week 12	4%	36%*
Week 24	6%	39%*
ACR 70		
Week 12	1%	20%*
Week 24	1%	23%*

* p<0.001 for all comparisons between adalimumab and placebo

Table 8: Components of Disease Activity in PsA Study I

	Placebo N=162		Adalimumab* N=151	
Parameter: median	Baseline	24 Weeks	Baseline	24 Weeks
Number of tender joints [a]	23.0	17.0	20.0	5.0
Number of swollen joints [b]	11.0	9.0	11.0	3.0
Physician global assessment [c]	53.0	49.0	55.0	16.0
Patient global assessment [c]	49.5	49.0	48.0	20.0
Pain [c]	49.0	49.0	54.0	20.0
Disability index (HAQ) [d]	1.0	0.9	1.0	0.4
CRP (mg/dL) [e]	0.8	0.7	0.8	0.2

* p<0.001 for Adalimumab vs. placebo comparisons based on median changes.
a Scale 0-78
b Scale 0-76
c Visual analog scale; 0=best, 100=worst
d Disability Index of the Health Assessment Questionaire; 0=best, 3=worst, measures the patient's ability to perform the following: dress/groom, arise, eat, walk, reach, grip, maintain hygiene, and maintain daily activity.

Similar results were seen in an additional, 12-week study in 100 patients with moderate to severe psoriatic arthritis who had suboptimal response to DMARD therapy as manifested by >3 tender joints and >3 swollen joints at enrolment.

Radiographic Response
Radiographic changes were assessed in the psoriatic arthritis studies. Radiographs of hands, wrists and feet were obtained at baseline and Week 24 during the double-blind period when patients were on adalimumab or placebo and at Week 48 when all patients were on open-label adalimumab. A modified Total Sharp Score (mTSS), which included distal interphalangeal joints (i.e., not identical to the TSS used for rheumatoid arthritis), was used.

Adalimumab treatment reduced the rate of progression of peripheral joint damage compared with placebo treatment as measured by change from baseline in mTSS score (mean ± SD) 0.8 ± 2.5 in the placebo group (at week 24) compared with 0.0 ± 1.9 in the adalimumab group (at week 48) (p < 0.001).

In subjects treated with adalimumab with no radiographic progression from baseline to Week 48 (n = 102), 84% continued to show no radiographic progression through 144 weeks of treatment.

Quality of Life and Physical Function
Adalimumab treated patients demonstrated statistically significant improvement in physical function as assessed by HAQ and Short Form Health Survey (SF 36) compared to placebo at week 24. Improved physical function continued during the open

label extension up to week 136.

Ankylosing Spondylitis Clinical Studies
The safety and efficacy of adalimumab 40 mg fortnightly was assessed in 393 adult patients in two randomized, 24-week double- blind, placebo-controlled studies in patients with active ankylosing spondylitis (AS). The larger study (AS Study I or M03-607) enrolled 315 adult patients with active AS (defined as fulfilling at least two of the following three criteria: (1) a Bath AS disease activity index (BASDAI) score ≥ 4 cm, (2) a visual analog score (VAS) for total back pain ≥ 40 mm, (3) morning stiffness ≥ 1 hour, who had an inadequate response to conventional therapy. Seventy-nine (20.1%) patients were treated concomitantly with disease modifying anti-rheumatic drugs, and 37 (9.4%) patients with glucocorticoids. The blinded period was followed by an open label period during which patients receive adalimumab every other week subcutaneously for up to an additional 236 weeks. Subjects (N=215, 54.7%) who failed to achieve ASAS 20 at Weeks 12, or 16 or 20 received early escape open-label adalimumab 40mg fortnightly SC and were subsequently treated as non-responders in double-blind statistical analyses.

Results showed statistically significant improvement of signs and symptoms of AS in patients treated with adalimumab compared to placebo. Significant improvement in measures of disease activity was first observed at Week 2 and maintained through 24 weeks as shown in Figure 4 and Table 9.

Patients with total spinal ankylosis were included in the larger study (n=11). Responses of these patients were similar to those without total ankylosis.

Figure 4. ASAS 20 Response By Visit

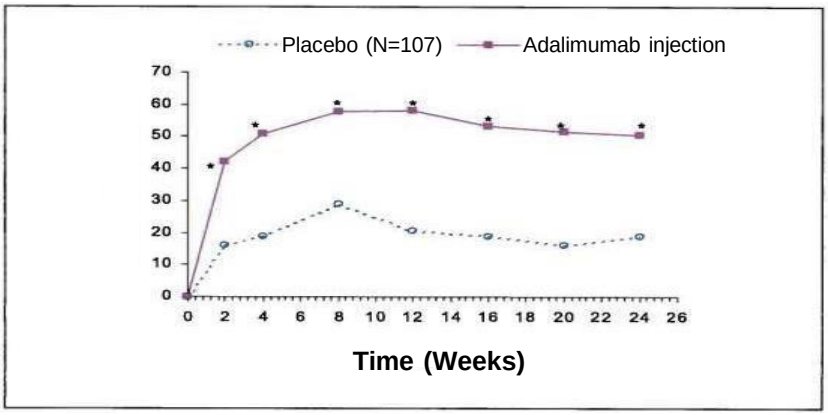


Table 9: Efficacy Responses in Placebo-Controlled AS Study I		
Response	Placebo N=107	Adalimumab N=208
ASAS[a] 20		
Week 2	16%	42%*
Week 12	21%	58%*
Week 24	19%	51%*
ASAS 50		
Week 2	3%	16%*
Week 12	10%	38%*
Week 24	11%	35%*
ASAS 70		
Week 2	0%	7%**
Week 12	5%	23%*
Week 24	8%	24%*
BASDAI[b] 50		
Week 2	4%	20%*
Week 12	16%	45%*
Week 24	15%	42%*

*, ** Statistically significant at p<0.001, <0.01 for all comparisons between adalimumab and placebo at Weeks 2, 12 and 24

a Assessments in Ankylosing Spondylitis
b Bath Ankylosing Spondylitis Disease Activity Index

A low level of disease activity (defined as a value <20 [on a scale of 0-100mm] in each of the four ASAS response parameters) was achieved at 24 weeks in 22% of adalimumab-treated patients vs. 6% in placebo-treated patients (p<0.001).

Table 10: Components of Ankylosing Spondylitis Disease Activity				
	Placebo N=107		Adalimumab N=208	
	Baseline mean	Week 24 mean	Baseline mean	Week 24 mean
ASAS 20 Response Criteria*				
Patient's Global Assessment of Disease Activity[a] *	65	60	63	38
Total back pain*	67	58	65	37
Inflammation[b] *	6.7	5.6	6.7	3.6
BASFI[c] *	56	51	52	34
BASDAI[d] score*	6.3	5.5	6.3	3.7
BASMI[e] score*	4.2	4.1	3.8	3.3
Tragus to wall (cm)	15.9	15.8	15.8	15.4
Lumbar flexion (cm)	4.1	4.0	4.2	4.4
Cervical rotation (degrees)	42.2	42.1	48.4	51.6
Lumbar side flexion (cm)	8.9	9.0	9.7	11.7
Intermalleolar distance (cm)	92.9	94.0	93.5	100.8
CRP[f] *	2.2	2.0	1.8	0.6

a Percent of subjects with at least a 20% and 10-unit improvement measured on a Visual Analog Scale (VAS) with 0 = "none" and 100 = "severe"
b Mean of questions 5 and 6 of BASDAI (defined in 'd')
c Bath Ankylosing Spondylitis Functional Index
d Bath Ankylosing Spondylitis Disease Activity Index
e Bath Ankylosing Spondylitis Metrology Index
f C-Reactive Protein (mg/dL)
* Statistically significant for all comparisons between adalimumab and placebo at Week 24

Similar trends (not all statistically significant) were seen in the smaller randomized, double-blind, placebo-controlled study (AS Study II or M03-606) of 82 patients with active ankylosing spondylitis.

Patient Reported Outcomes were assessed in both ankylosing spondylitis studies using the generic health status questionnaire SF-36 and the disease specific Ankylosing Spondylitis Quality of Life Questionnaire (ASQoL). The adalimumab-treated patients had significantly greater improvement in SF-36 Physical Component Score (mean change: 6.93) compared to placebo-treated patients (mean change: 1.55; p<0.001) at Week 12, which was maintained through Week 24 (mean change 7.44 vs 1.85).

Results from the ASQoL support these findings demonstrating improvement in overall quality of life. The adalimumab-treated patients had statistically significant improvement (mean change: - 3.15) compared to placebo-treated patients (mean change: - 0.95; p<0.001) at Week 12, which was maintained through Week 24 (mean change –3.58 vs –1.06).

Adult Crohn's Disease Clinical Studies
The safety and efficacy of multiple doses of adalimumab were assessed in over 1400 patients with moderately to severely active Crohn's disease (Crohn's Disease Activity Index (CDAI) ≥220 and ≤450) in randomized, double-blind, placebo controlled studies. Concomitant stable doses of aminosalicylates, corticosteroids, and/or immunomodulatory agents were permitted and 79% of patients continued to receive at least one of these medications.

Induction of clinical remission (defined as CDAI <150) was evaluated in two studies. In CD Study I (M02-403, CLASSIC I), 299 TNF-antagonist naïve patients were randomized to one of four treatment groups; the placebo group received placebo at weeks 0 to 2, the 160/80 group received 160mg adalimumab at Week 0 and 80mg at Week 2, the 80/40 group received 80mg at Week 0 and 40mg at Week 2, and the 40/20 group received 40mg at Week 0 and 20mg at Week 2. Clinical results were assessed at Week 4.

In the second induction study, CD Study II (M04-691, GAIN), 325 patients who had lost response or were intolerant to, previous infliximab were randomized to receive either 160mg adalimumab at Week 0 and 80mg at Week 2, or placebo at Weeks 0 and 2. Clinical results were assessed at Week 4.

Maintenance of clinical remission was evaluated in CD Study III (M02-404, CHARM). In this study, 854 patients with active disease received open-label 80 mg adalimumab at Week 0 and 40 mg at Week 2. Patients were then randomized at Week 4 to 40 mg adalimumab every other week, 40 mg adalimumab every week or placebo with a total study duration of 56 weeks. Patients in clinical response (CR-70 = decrease in CDAI ≥70) at Week 4 were stratified and analysed separately from those not in clinical response at Week 4. Corticosteroid taper was permitted after Week 8.

Clinical Results
Induction of Clinical Remission
A statistically significantly greater percentage of the patients treated with 160/80mg adalimumab achieved induction of clinical remission versus placebo at Week 4 regardless of whether the patients were TNF antagonist naïve (CD Study I), or had been previously exposed to infliximab (CD Study II) (see Table 11)

Table 11: Induction of Clinical Remission and Response (Percent of Patients)				
	CD Study I		CD Study II	
	Placebo N = 74	Adalimumab160/80 mg N = 76	Placebo N = 166	Adalimumab160/80 mg N = 159
Week 4				
Clinical remission	12%	36%*	7%	21%*
Clinical response (CR-100)	24%	49%**	25%	38%**
Clinical response (CR-70)	34%	58%**	34%	52%**

Clinical remission is CDAI score <150; clinical response (CR-100) is decrease in CDAI ≥ 100 points; clinical response (CR-70) is decrease in CDAI ≥ 70 points. All p-values are pairwise comparisons of proportions for adalimumab vs. placebo
* p<0.001
** p<0.01

Maintenance of Clinical Remission
In CD Study III, at Week 4, 58% (499/854) patients were in clinical response (decrease in CDAI ≥ 70 points) and were assessed in the primary analysis. Of those in clinical response at Week 4, 48% had been previously exposed to other anti-TNF therapy. At Weeks 26 and 56, statistically significantly greater proportions of patients who were in clinical response at Week 4 achieved clinical remission in the adalimumab maintenance group compared to patients in the placebo maintenance group. Additionally, statistically significantly greater proportions of patients receiving concomitant corticosteroids at baseline were in clinical remission and were able to discontinue corticosteroid use for at least 90 days in the adalimumab maintenance groups compared to patients in the placebo maintenance group at Weeks 26 and 56 (see Table 12). The group that received adalimumab every week did not show significantly higher remission rates than the group that received adalimumab every other week.

Clinical remission results presented in Table 12 remained relatively constant irrespective of previous TNF antagonist exposure.

Table 12: Maintenance of Clinical Remission and Response (Percent of Patients)

	Placebo	**40 mg adalimumab every other week**	**40 mg adalimumab every week**
Week 26	**N = 170**	**N = 172**	**N = 157**
Clinical remission	17%	40%*	47%*
Clinical response (CR-100)	27%	52%*	52%*
Clinical response (CR-70)	28%	54%*	56%*
Patients in steroid-free remission for ≥ 90 days[a]	3% (2/66)	19% (11/58)**	15% (11/74)**
Week 56	**N = 170**	**N = 172**	**N = 157**
Clinical remission	12%	36%*	41%*
Clinical response (CR-100)	17%	41%*	48%*
Clinical response (CR-70)	18%	43%*	49%*
Patients in steroid-free remission for ≥ 90 days[a]	5% (3/66)	29%(17/58)*	20% (15/74)**

Clinical remission is CDAI score <150; clinical response (CR-100) is decrease in CDAI ≥ 100 points; clinical response (CR-70) is decrease in CDAI ≥ 70 points
* p<0.001 for adalimumab vs. placebo pairwise comparisons of proportions
** p<0.02 for adalimumab vs. placebo pairwise comparisons of proportions
a Of those receiving corticosteroids at baseline

Of those in response at Week 4 who attained remission during the study, patients in adalimumab maintenance groups maintained remission for a significantly longer time than patients in the placebo maintenance group. Disease-related hospitalizations and surgeries were statistically significantly reduced with adalimumab compared with placebo at Week 56.

Among patients who were not in response by Week 12, therapy continued beyond 12 weeks did not result in significantly more responses.

117/276 patients from CD study I and 272/777 patients from CD studies II and III were followed through at least 3 years of open-label adalimumab therapy. 88 (75.2%) and 189 (69.5%) patients, respectively, continued to be in clinical remission. Clinical response (CR-70) was maintained in 107 (91.5%) and 248 (91.2%) patients, respectively.

An endoscopy study (M05-769, EXTEND), which enrolled 135 patients, with moderate to severe Crohn's disease, indicated an effect of adalimumab on mucosal healing. 27.4% of patients treated with adalimumab had mucosal healing at Week 12 compared to 13.1% of patients given placebo (p=0.056), and 24.2% of patients treated with adalimumab had mucosal healing at Week 52 compared to 0% of patients given placebo (p<0.001).

Quality of Life
In CD Study I and CD Study II, statistically significant improvement in the disease-specific inflammatory bowel disease questionnaire (IBDQ) total score was achieved at week 4 in patients randomized to adalimumab 80/40 mg and 160/80 mg compared to placebo and was seen at weeks 26 and 56 in CD study III as well among the adalimumab treatment groups compared to the placebo group.

Ulcerative Colitis Clinical Studies
The safety and efficacy of multiple doses of adalimumab were assessed in adult patients with moderately to severely active ulcerative colitis (Mayo score 6 to 12 with endoscopy subscore of 2 to 3 points) in two randomized, double-blind, placebo- controlled studies. Concomitant stable doses of aminosalicylates, corticosteroids, and/or immunomodulatory agents were permitted.

Induction of clinical remission (defined as Mayo ≤ 2 with no subscore > 1) was evaluated in Study UC-I. In Study UC-I, 390 TNF-antagonist naïve patients were randomized to receive either placebo at Weeks 0 and 2, 160 mg adalimumab at Week 0 followed by 80 mg at Week 2, or 80 mg adalimumab at Week 0 followed by 40 mg at Week 2. After Week 2, patients in both adalimumab arms received 40 mg every other week. Clinical remission was assessed at Week 8.

In study UC-II, 248 patients received 160 mg of adalimumab at Week 0, 80 mg at Week 2 and 40 mg eow thereafter, and 246 patients received placebo. Clinical results were assessed for induction of remission at Week 8 and for maintenance of remission at Week 52.

Subjects induced with 160/80 mg adalimumab achieved clinical remission versus placebo at Week 8 in statistically significantly greater percentages in study UC-I (18% vs. 9% respectively, p=0.031) and study UC-II (17% vs. 9% respectively, p=0.019). In study UC-II, among those treated with adalimumab who were in remission at Week 8, 21/41 (51%) were in remission at Week 52.

Results for both the overall UC-II study population and for patients who had responded at Week 8 of treatment per the full Mayo score are shown in Table 13.

Table 13: Response, Remission and Mucosal Healing in Study UC-II (Percent of Patients)

	Placebo	Adalimumab40 mg every other week	Adalimumab160/80/40 mg Week 8 Responders
	N=246	N=248	N=125
Week 52			
Clinical Response	18%	30%*	47%
Clinical Remission	9%	17%*	29%
Mucosal Healing	15%	25%*	41%
Steroid-free remission for ≥ 90 days [a]	6% (N=140)	13%* (N=150)	20% (N=90)
Week 8 and 52			
Sustained Response	12%	24%**	-
Sustained Remission	4%	8%*	-
Sustained Mucosal Healing	11%	19%*	-

Clinical remission is Mayo score ≤ 2 with no subscore > 1;
*p<0.05 for adalimumab *vs.* placebo pairwise comparison of proportions
**p<0.001 for adalimumab *vs.* placebo pairwise comparison of proportions
[a] Of those receiving corticosteroids at baseline

Approximately 40% of patients in study UC-II had failed prior anti-TNF treatment with infliximab. The efficacy of adalimumab in those patients was reduced compared to that in anti-TNF naïve patients. Among patients who had failed prior anti-TNF treatment, Week 52 remission was achieved by 3% on placebo and 10% on adalimumab.

The effectiveness of adalimumab has not been established in patients who have lost response to or were intolerant to TNF blockers.

In the subgroup of patients in Study UC-II with prior TNF-blocker use, the treatment difference for induction of clinical remission appeared to be lower than that seen in the whole study population, and the treatment differences for sustained clinical remission and clinical remission at Week 52 appeared to be similar to those seen in the whole study population. The subgroup of patients with prior TNF-blocker use achieved induction of clinical remission at 9% (9/98) in the adalimumab group versus 7% (7/101) in the placebo group, and sustained clinical remission at 5% (5/98) in the adalimumab group versus 1% (1/101) in the placebo group. In the subgroup of patients with prior TNF-blocker use, 10% (10/98) were in clinical remission at Week 52 in the adalimumab group versus 3% (3/101) in the placebo group.

Patients from UC studies I and II had the option to roll over into an open-label long-term extension study (UC-III). Following 3 years of adalimumab therapy, 75% (301/402) continued to be in clinical remission per partial Mayo score, and of those who had received at least 4 years of adalimumab therapy, 77% (245/320) were in clinical remission per partial Mayo score. Patients, who lost response after one year of treatment or beyond, could benefit from an increase of dosing frequency to 40 mg weekly.

Hospitalisation Rates
During 52 weeks of studies UC-I and UC-II, lower rates of all-cause hospitalisations and UC-related hospitalisations were observed for the adalimumab-treated arm compared to the placebo arm. The number of all cause hospitalisations in the adalimumab treatment group was 0.18 per patient year *vs.* 0.26 per patient year in the placebo group and the corresponding figures for UC-related hospitalisations were 0.12 per patient year *vs.* 0.22 per patient year.

Quality of Life
In UC Study II, improvement in the disease-specific inflammatory bowel disease questionnaire (IBDQ) total score was achieved at Week 52 in patients randomized to adalimumab 160/80 mg compared to placebo (p=0.007).

Plaque Psoriasis Clinical Studies
The safety and efficacy of adalimumab were assessed in over 1,600 patients 18 years of age or older with moderate to severe chronic plaque psoriasis who were candidates for systemic therapy or phototherapy in randomized, double-blind, well-controlled studies.

The safety and efficacy of adalimumab were also studied in adult patients with moderate to severe chronic plaque psoriasis with concomitant hand and/or foot psoriasis who were candidates for systemic therapy in a randomized double-blind study (Ps Study IV).

Ps Study I (M03-656, REVEAL) evaluated 1212 patients with chronic plaque psoriasis with ≥ 10% BSA involvement and Psoriasis Area and Severity Index (PASI) ≥ 12 within three treatment periods. In period A, patients received placebo or adalimumab subcutaneously at an initial dose of 80 mg at Week 0 followed by a dose of 40 mg every other week starting at Week 1. After 16 weeks of therapy, patients who achieved at least a PASI 75 response at Week 16, defined as a PASI score improvement of at least 75% relative to baseline, entered period B and received open label 40 mg adalimumab every other week. After 17 weeks of open label therapy, patients who maintained at least a PASI 75 response at Week 33 and were originally randomized to active therapy in Period A were re-randomized in period C to receive 40 mg adalimumab every other week or placebo for an additional 19 weeks. Across all treatment groups the mean baseline PASI score was 18.9 and the baseline Physician's Global Assessment (PGA) score ranged from "moderate" (52.6%) to "severe" (41.3%) to "very severe" (6.1%).

Ps Study II (M04-716, CHAMPION) compared the efficacy and safety of adalimumab versus methotrexate and placebo in 271 patients with 10% BSA involvement and PASI ≥ 10. Patients received placebo, an initial dose of MTX 7.5 mg and thereafter dose increases up to Week 12, with a maximum dose of 25 mg or an initial dose of 80 mg adalimumab followed by 40 mg every other week (starting one week after the initial dose) for 16 weeks. There are no data available comparing adalimumab and MTX beyond 16 weeks of therapy. Patients receiving MTX who achieved a ≥PASI 50 response at Week 8 and/or 12 did

not receive further dose increases. Across all treatment groups, the mean baseline PASI score was 19.7 and the baseline PGA score ranged from “mild” (<1%) to “moderate” (48%) to “severe” (46%) to “very severe” (6%).

Ps Study III (M02-528) evaluated 148 patients with chronic plaque psoriasis with ≥ 5% BSA involvement for at least 1 year. Patients received placebo or adalimumab subcutaneously at a dose of 40 mg every other week starting at Week 1 after an initial dose of 80 mg at Week 0 or adalimumab at an initial dose of 80 mg at Week 0 followed by a dose of 40 mg weekly.

Patients participating in all Phase 2 and Phase 3 psoriasis studies were eligible to enroll into an open-label extension trial (M03-658), where adalimumab was given for at least an additional 108 weeks.

Clinical Results

In Ps Studies I, II and III, the primary endpoint was the proportion of patients who achieved a reduction in PASI score of at least 75% (PASI 75) from baseline at Week 16 for studies I and II and Week 12 for Study III. Other evaluated outcomes in Ps Studies I, II, and III included the PGA and other PASI measures. Ps Study I had an additional primary endpoint of loss of adequate response after Week 33 and on or before Week 52. Loss of adequate response is defined as a PASI score after Week 33 and on or before Week 52 that resulted in a <PASI 50 response relative to baseline with a minimum of a 6-point increase in PASI score relative to Week 33.

In Ps Studies I and II, more patients randomized to adalimumab than to placebo achieved at least a 75% reduction from baseline of PASI score at Week 16. Other relevant clinical parameters including PASI 100 (i.e. complete clearance of psoriasis skin signs) and PGA of “clear or minimal” were also improved over placebo. In Ps Study II, superior results were achieved for PASI 75, PASI 100 and PGA of "clear or minimal" in patients randomized to the adalimumab treatment group versus those randomized to receive methotrexate (see Tables 14 and 15).

Improvements in signs and symptoms in patients with moderate to severe psoriasis were maintained for up to 1 year (pivotal study M03-656) and for up to 3 years.

Table 14: Ps Study I (M03-656)
Efficacy Results at 16 Weeks (Percent of Patients)

	Placebo N=398	Adalimumab40 mg eow N=814
≥PASI 75	6.5	70.9[a]
PASI 100	0.8	20.0[a]
PGA: Clear/minimal	4.3	62.2[a]

[a] p<0.001, adalimumab vs. placebo

Table 15: Ps Study II (M04-716)
Efficacy Results at 16 Weeks (Percent of Patients)

	Placebo N=53	MTX N=110	Adalimumab40 mg eow N=108
≥PASI 75	18.9	35.5	79.6 [a, b]
PASI 100	1.9	7.3	16.7 [c,d]
PGA: Clear/minimal	11.3	30.0	73.1 [a, b]

[a] p<0.001, adalimumab vs. placebo
[b] p<0.001 adalimumab vs. methotrexate
[c] p< 0.01 adalimumab vs. placebo
[d] p< 0.05 adalimumab vs. methotrexate

In Psoriasis Study I, 28% of patients who were PASI 75 responders and were re-randomized to placebo at week 33 compared to 5% continuing on adalimumab, p<0.001, experienced “loss of adequate response” (PASI score after week 33 and on or before week 52 that resulted in a <PASI 50 response relative to baseline with a minimum of a 6-point increase in PASI score relative to week 33). Of the patients who lost adequate response after re-randomization to placebo who then enrolled into the open- label extension trial, 38% (25/66) and 55% (36/66) regained PASI 75 response after 12 and 24 weeks of re-treatment, respectively.

A total of 233 PASI 75 responders at Week 16 and Week 33 received continuous adalimumab therapy for 52 weeks in Psoriasis Study I, and continued adalimumab in the open-label extension trial. PASI 75 and PGA of clear or minimal response rates in these patients were 74.7% and 59.0%, respectively, after an additional 108 weeks of open-label therapy (total of 160 weeks).

A total of 94 patients were randomized to adalimumab therapy in Psoriasis Study II, and continued adalimumab in the open label extension trial. PASI 75 and PGA clear or minimal response rates in these patients were 58.1% and 46.2%, respectively, after an additional 108 weeks of open-label therapy (total of 124 weeks).

A total of 347 stable responders participated in a withdrawal and retreatment evaluation in an open-label extension study. Median time to relapse (decline to PGA “moderate” or worse) was approximately 5 months. None of these patients experienced rebound during the withdrawal period. A total of 76.5% (218/285) of patients who entered the retreatment period had a response of PGA “clear” or “minimal” after 16 weeks of retreatment, irrespective of whether they relapsed during withdrawal (69.1% [123/178] and 88.8% [95/107] for patients who relapsed and who did not relapse during the withdrawal period, respectively).

Significant improvements at Week 16 from baseline compared to placebo (Studies I and II) and MTX (Study II) were demonstrated in the DLQI (Dermatology Life Quality Index). In Study I, improvements in the physical and mental component summary scores of the SF-36 were also significant compared to placebo.

In an open-label extension study, for patients whose dose escalated from 40 mg every other week to 40 mg weekly due to a PASI response below 50%, 26.4% (92/349) and 37.8% (132/349) of patients achieved PASI 75 response at Week 12 and 24, respectively.

Psoriasis Study III (REACH) compared the efficacy and safety of adalimumab *versus* placebo in 72 patients with moderate to severe chronic plaque psoriasis and hand and/or foot psoriasis. Patients received an initial dose of 80 mg adalimumab followed by 40 mg every other week (starting one week after the initial dose) or placebo for 16 weeks. At Week 16, a statistically significantly greater proportion of patients who received adalimumab achieved PGA of 'clear' or 'almost clear' for the hands and/or

feet compared to patients who received placebo (30.6% versus 4.3%, respectively [P = 0.014]).

Psoriasis Study IV compared the efficacy and safety of adalimumab versus placebo in 217 adult patients with moderate to severe nail psoriasis. Patients received an initial dose of 80 mg adalimumab followed by 40 mg every other week (starting one week after the initial dose) or placebo for 26 weeks followed by open-label adalimumab treatment for an additional 26 weeks. Nail psoriasis was assessed using the Modified Nail Psoriasis Severity Index (mNAPSI) and the Physician's Global Assessment of Fingernail Psoriasis (PGA-F). A statistically significantly higher proportion of patients randomized to adalimumab achieved at least a 75% improvement in mNAPSI (mNAPSI 75) at Week 26, as compared with patients randomized to placebo (see Table 16). The percent improvement in NAPSI was statistically significantly greater in adalimumab patients compared with placebo at Week 16 (44.2% vs 7.8%) and at Week 26 (56.2% vs 11.5%).

A statistically significant higher proportion of patients in the adalimumab group achieved a PGA-F of "clear" or "minimal" with at least a 2-grade improvement from Baseline at Week 26 compared with placebo. In this study, adalimumab demonstrated a treatment benefit in nail psoriasis patients with different extents of skin involvement (BSA≥10% and BSA<10% and ≥5%) and a statistically significant improvement in scalp psoriasis compared with placebo.

Table 16: Efficacy Results at 26 Weeks

Endpoint	Placebo N=108	Adalimumab 40 mg eow N=109
≥ mNAPSI 75 (%)	3.4	46.6[a]
PGA-F clear/minimal and ≥2-grade improvement (%)	6.9	48.9[a]
Percent Change in Total Fingernail NAPSI (%)	-11.5	-56.2[a]
mNAPSI = 0 (%)	0	6.6[b]
Change in Nail Pain Numeric Rating Scale	-1.1	-3.7[a]
Change in Nail Psoriasis Physical Functioning Severity score	-0.8	-3.7[a]
B-SNIPI 50 Scalp (%)	N=12 0.4	N=18 58.3[b]

[a] p<0.001, adalimumab *vs.* placebo
[b] p<0.05, adalimumab *vs.* placebo

B-SNIPI 50: At least a 50% reduction in scalp component of Brigham Scalp Nail Inverse Palmo-Plantar Psoriasis index (B-SNIPI) among subjects with Baseline scalp score of 6 or greater).

Of those who continued to receive adalimumab treatment until Week 52, 65.0% achieved mNAPSI 75 response and 61.3% achieved PGA-F response. adalimumab treated patients showed statistically significant improvements at Week 26 from baseline compared with placebo in the DLQI (Dermatology Life Quality Index). The mean decrease (improvement) from baseline at Week 26 was 8.0 in the adalimumab group (N=94) and 1.9 in the placebo group (N=93).

Results from Ps Study III supported the efficacy demonstrated in Ps Studies I and II.

In Ps Study I, patients who were PASI 75 responders and were re-randomized to continue adalimumab therapy at Week 33 were less likely to experience a loss of adequate response on or before Week 52 than the PASI 75 responders who were re- randomized to placebo at Week 33 (4.9% versus 28.4%, p<0.001).

Quality of Life

Patient Reported Outcomes (PRO) were evaluated by several measures. Quality of Life was assessed using the disease-specific Dermatology Life Quality Index (DLQI) in Ps Study I and Ps Study II. In Ps Study I, patients receiving adalimumab demonstrated clinically meaningful improvement in the DLQI total score, disease severity, pain, and pruritus compared to the placebo group at both Weeks 4 & 16. The DLQI result was maintained at Week 52. In Ps Study II, patients receiving adalimumab demonstrated clinically meaningful improvement in the DLQI total score, disease severity, and pruritus compared to the placebo and methotrexate groups at Week 16, and clinically meaningful improvement in pain compared to the placebo group at Week 16.

The Short Form Health Survey (SF-36) was used to assess general health-related quality of life in Ps Study I. The adalimumab-treated patients had significantly greater improvement in the SF-36 Physical Component Summary (PCS) and Mental Component Summary (MCS) scores.

Hidradenitis Suppurativa Clinical Studies

The safety and efficacy of adalimumab were assessed in randomized, double-blind, placebo-controlled studies and an open-label extension study in adult patients with moderate to severe hidradenitis suppurativa (HS) who were intolerant, had a contraindication or an inadequate response to systemic antibiotic therapy. The patients in Studies HS-I and HS-II had Hurley Stage II or III disease with at least 3 abscesses or inflammatory nodules.

Study HS-I (M11-313) evaluated 307 patients with 2 treatment periods. In Period A, patients received placebo or adalimumab at an initial dose of 160 mg at Week 0, 80 mg at Week 2, and 40 mg every week starting at Week 4 to Week 11. Concomitant antibiotic use was not allowed during the study. After 12 weeks of therapy, patients who had received adalimumab in Period A were re-randomized in Period B to 1 of 3 treatment groups (adalimumab 40 mg every week, adalimumab40 mg every other week, or placebo from Week 12 to Week 35). Patients who had been randomized to placebo in Period A were assigned to receive adalimumab 40 mg every week in Period B.

Study HS-II (M11-810) evaluated 326 patients with 2 treatment periods. In Period A, patients received placebo or adalimumab at an initial dose of 160 mg at Week 0 and 80 mg at Week 2 and 40 mg every week starting at Week 4 to Week 11. 19.3% of patients had continued baseline oral antibiotic therapy during the study. After 12 weeks of therapy, patients who had received adalimumab in Period A were re-randomized in Period B to 1 of 3 treatment groups (adalimumab40 mg every week, adalimumab 40 mg every other week, or placebo from Week 12 to Week 35). Patients who had been randomized to placebo in Period A were assigned to receive placebo in Period B.

Patients participating in Studies HS-I and HS-II were eligible to enroll into an open-label extension study in which adalimumab 40mg was administered every week. Mean exposure in all adalimumab population was 762 days. Throughout all 3 studies patients used topical antiseptic wash daily.

Clinical Response

Reduction of inflammatory lesions and prevention of worsening of abscesses and draining fistulas was assessed using Hidradenitis Suppurativa Clinical Response (HiSCR; at least a 50% reduction in total abscess and inflammatory nodule count with no increase in abscess count and no increase in draining fistula count relative to Baseline). Reduction in HS-related skin pain was assessed using a Numeric Rating Scale in patients who entered the study with an initial baseline score of 3 or greater on a 11 point scale.

At Week 12, a significantly higher proportion of patients treated with adalimumab versus placebo achieved HiSCR. At Week 12, a significantly higher proportion of patients in Study HS-II experienced a clinically relevant decrease in HS-related skin pain (see Table 17). Patients treated with adalimumab had significantly reduced risk of disease flare during the initial 12 weeks of treatment.

Table 17: Efficacy Results at 12 Weeks, HS Studies I and II

	HS Study I		HS Study II	
Endpoint	**Placebo**	**Adalimumab 40 mg Weekly**	**Placebo**	**Adalimumab 40 mg Weekly**
Hidradenitis Suppurativa Clinical Response (HiSCR)[a]	N = 154 40 (26.0%)	N = 153 64 (41.8%)*	N=163 45 (27.6%)	N=163 96 (58.9%)***
≥30% Reduction in Skin Pain[b]	N = 109 27 (24.8%)	N = 122 34 (27.9%)	N=111 23 (20.7%)	N=105 48 (45.7%)***

* $P < 0.05$, *** $P < 0.001$, adalimumab versus placebo

[a] Among all randomized patients.

[b] Among patients with baseline HS-related skin pain assessment ≥ 3, based on Numeric Rating Scale 0 – 10; 0 = no skin pain, 10 = skin pain as bad as you can imagine.

Among patients who were randomized to adalimumab continuous weekly dosing, the overall HiSCR rate at Week 12 was maintained through Week 96. Longer term treatment with adalimumab 40 mg weekly for 96 weeks identified no new safety findings.

Greater improvements at Week 12 from baseline compared to placebo were demonstrated in skin-specific health-related quality of life, as measured by the Dermatology Life Quality Index (DLQI; Studies HS-I and HS-II), patient global satisfaction with medication treatment as measured by the Treatment Satisfaction Questionnaire - medication (TSQM; Studies HS-I and HS-II) and physical health as measured by the physical component summary score of the SF-36 (Study HS-I).

Uveitis Clinical Studies

The safety and efficacy of adalimumab were assessed in adult patients with non-infectious intermediate, posterior, and panuveitis (also known as “non-infectious uveitis affecting the posterior segment”), excluding patients with isolated anterior uveitis, in two randomized, double-masked, placebo-controlled studies (UV Study I (M10-877) and UV Study II (M10-880)). Patients received placebo or adalimumab at an initial dose of 80 mg followed by 40 mg every other week starting one week after the initial dose. Concomitant stable doses of non-biologic immunosuppressants were permitted. The primary efficacy endpoint in both studies was ´time to treatment failure´. Following initial control of disease, a prolongation in time to treatment failure will result in reduced risk of disease flares, inflammation and vision loss.

Treatment failure was defined by a multi-component outcome based on inflammatory chorioretinal and/or inflammatory retinal vascular lesions, anterior chamber (AC) cell grade, vitreous haze (VH) grade and best corrected visual acuity (BCVA).

UV Study I evaluated 217 patients with active uveitis despite treatment with corticosteroids (oral prednisone at a dose of 10 to 60 mg/day). All patients received a standardized dose of prednisone 60 mg/day at study entry followed by a mandatory taper schedule, with complete corticosteroid discontinuation by Week 15.

UV Study II evaluated 226 patients with inactive uveitis requiring chronic corticosteroid treatment (oral prednisone 10 to 35 mg/day) at baseline to control their disease. Patients subsequently underwent a mandatory taper schedule, with complete corticosteroid discontinuation by Week 19.

Clinical Response

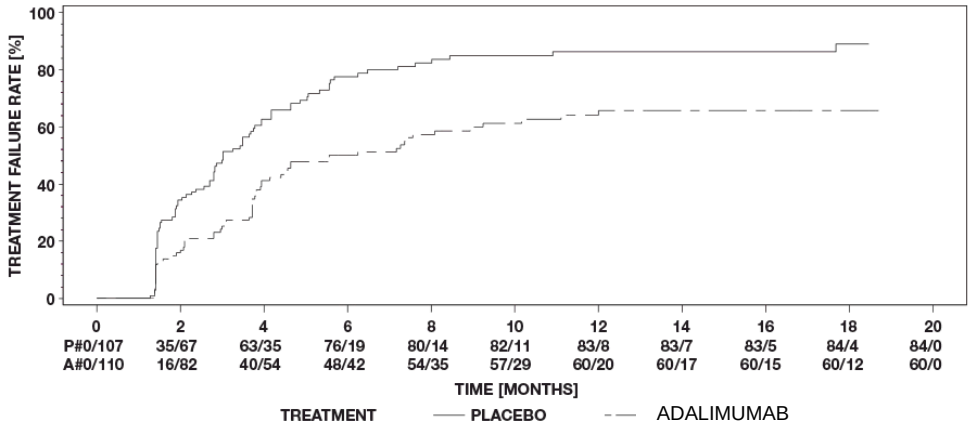
Results from both studies demonstrated statistically significant reduction of the risk of treatment failure in patients treated with adalimumab versus patients receiving placebo (See Table 18). Both studies demonstrated an early and sustained effect of adalimumab on the treatment failure rate versus placebo (see Figure 5).

Table 18: Time to Treatment Failure in UV Studies I and II

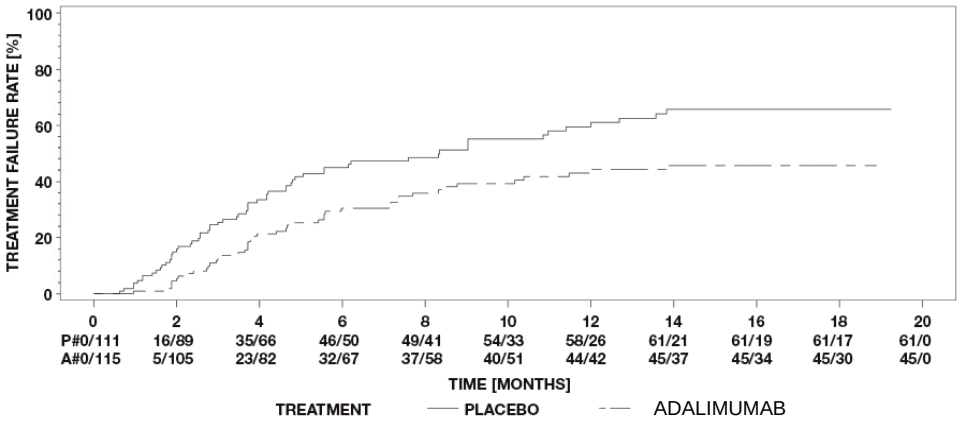
Analysis Treatment	**N**	**Failure N (%)**	**Median Time to Failure (months)**	**HR[a]**	**CI 95% for Hr[a]**	***P* Value[b]**
Time to Treatment Failure At or After Week 6 in UV Study I						
Primary analysis (ITT)						
Placebo	107	84 (78.5)	3.0	--	--	--
Adalimumab	110	60 (54.5)	5.6	0.50	0.36, 0.70	< 0.001
Time to Treatment Failure At or After Week 2 in UV Study II						
Primary analysis (ITT)						
Placebo	111	61 (55.0)	8.3	--	--	--
Adalimumab	115	45 (39.1)	Ne[c]	0.57	0.39, 0.84	0.004

Note: Treatment failure at or after Week 6 (UV Study I), or at or after Week 2 (UV Study II), was counted as event. Drop outs due to reasons other than treatment failure were censored at the time of dropping out.

a. HR of adalimumab vs placebo from proportional hazards regression with treatment as factor.
b. 2-sided *P* Value from log rank test.
c. NE = not estimable. Fewer than half of at-risk subjects had an event.



Study UV I



Study UV II

Figure 5: Kaplan-Meier Curves Summarizing Time to Treatment Failure on or after Week 6 (UV Study I) or Week 2 (UV Study II)

In both studies, all components of the primary endpoint contributed cumulatively to the overall difference between adalimumab and placebo groups (Table 19).

Table 19: Treatment Failure Components in UV Studies I and II

	UV I			UV II		
Component of Time-to-Treatment Failure	**HR[a]**	**CI 95%**	***p Value*[b]**	**HR[a]**	**CI 95%**	***p Value*[b]**
New Active Inflammatory Lesions	0.38	(0.21- 0.69)	*0.001*	0.55	(0.26-1.15)	*0.105*
Anterior Chamber Cells Grade	0.51	(0.30- 0.86)	*0.01*	0.7	(0.42- 1.18)	*0.18*
Vitreous Haze Grade	0.32	(0.18- 0.58)	*<0.001*	0.79	(0.34- 1.81)	*0.569*
Best Corrected Visual Acuity	0.56	(0.32- 0.98)	*0.04*	0.33	(0.16- 0.70)	*0.002*

Note: Treatment failure at or after Week 6 (UV Study I), or at or after Week 2 (UV Study II), was counted as event. Drop outs due to reasons other than treatment failure were censored at the time of dropping out.

a. HR of adalimumab vs placebo from proportional hazards regression with treatment as factor.
b. 2-sided *P* value from log rank test.

Additionally, in UV Study I, statistically significant differences in favor of adalimumab versus placebo were observed for changes in AC cell grade, vitreous haze grade, and logMAR BCVA (mean change from best state prior to Week 6 to the final visit; *P* Values: 0.011, <0.001 and 0.003, respectively).

Of the 417 subjects included in the uncontrolled long-term extension of Studies UV I and UV II, 46 subjects were regarded ineligible (e.g. developed complications secondary to diabetic retinopathy, due to cataract surgery or vitrectomy) and were excluded from the primary analysis of efficacy. Of the 371 remaining patients, 276 evaluable patients reached 78 weeks of

open-label adalimumab treatment. Based on the observed data approach, 222 (80.4%) were in quiescence (no active inflammatory lesions, AC cell grade ≤ 0.5+, VH grade ≤ 0.5+) with a concomitant steroid dose ≤ 7.5 mg per day, and 184 (66.7 %) were in steroid-free quiescence. BCVA was either improved or maintained (< 5 letters deterioration) in 88.4% of the eyes at week 78. Among the patients who discontinued the study prior to week 78, 11% discontinued due to adverse events, and 5% due to insufficient response to adalimumab treatment.

Quality of Life
In UV Study 1, treatment with adalimumab resulted in maintenance of vision-related functioning and health-related quality of life, as measured by the NEI VFQ-25.

PEDIATRICS
Juvenile Idiopathic Arthritis Clinical Studies

Polyarticular Juvenile Idiopathic Arthritis (pJIA)
The safety and efficacy of adalimumab was assessed in two studies (pJIA I and II) in children with active polyarticular or polyarticular course juvenile idiopathic arthritis, who had a variety of JIA onset types (most frequently rheumatoid-factor negative or positive polyarthritis and extended oligoarthritis).

pJIA I
The safety and efficacy of adalimumab were assessed in a multicenter, randomized, double-blind, parallel-group study in 171 children (4 to 17 years old) with polyarticular juvenile idiopathic arthritis (JIA). In the open-label lead in phase (OL LI), patients were stratified into two groups, MTX (methotrexate)-treated or non-MTX-treated. Patients who were in the non-MTX stratum were either naïve or had been withdrawn from MTX at least two weeks prior to study drug administration. Patients remained on stable doses of NSAIDs and or prednisone (≤0.2 mg/kg/day or 10 mg/day maximum). In the OL LI phase, all patients received 24 mg/m^2 up to a maximum of 40 mg of adalimumabevery other week for 16 weeks. The distribution of patients by age and minimum, median and maximum dose received during the OL LI phase is presented in Table 20.

Table 20: Distribution of patients by age and adalimumab dose received during the OL LI phase

Age Group	Number of patients at Baseline n (%)	Minimum, median and maximum dose
4 to 7 years	31 (18.1)	10, 20 and 25mg
8 to 12 years	71 (41.5)	20, 25 and 40mg
13 to 17 years	69 (40.4)	25, 40 and 40mg

Patients demonstrating a Pediatric ACR 30 response at week 16 were eligible to be randomized into the double blind (DB) phase and received either adalimumab 24 mg/m^2 up to a maximum of 40 mg, or placebo every other week for an additional 32 weeks or until disease flare. Disease flare criteria was defined as a worsening of ≥30% from baseline in ≥3 of 6 Pediatric ACR core criteria, ≥2 active joints, and improvement of >30% in no more than 1 of the 6 criteria. After 32 weeks or at disease flare, patients were eligible to enroll into the open label extension phase.

Table 21: Ped ACR Responses in the JIA Study

Stratum	MTX		Without MTX	
Phase				
OL-LI 16 week				
Ped ACR 30 response (n/N)	94.1% (80/85)		74.4% (64/86)	
Double Blind	Adalimumab (n = 38)	Placebo (n = 37)	Adalimumab (n= 30)	Placebo (n = 28)
Disease flares at the end of 32 weeks[a] (n/N)	36.8% (14/38)	64.9% (24/37)[b]	43.3% (13/30)	71.4% (20/28)[c]
Median time to disease flare	> 32 weeks	20 weeks	> 32 weeks	14 weeks

[a] Ped ACR 30/50/70 responses week 48 significantly greater than those of placebo treated patients
[b] p = 0.015
[c] p = 0.031

Among those who responded at week 16 (n=144), the Pediatric ACR 30/50/90 responses were maintained for up to two years in the OLE phase in patients who received adalimumab throughout the study.

Overall responses were generally better and fewer patients developed antibodies when treated with the combination of adalimumab and MTX compared to adalimumab alone. Taking these results into consideration, adalimumab is recommended for use in combination with MTX and for use as monotherapy in patients for who MTX use is not appropriate.

pJIA II
The safety and efficacy of adalimumab was assessed in an open-label, multicenter study in 32 children (2 to <4 years old or aged 4 and above weighing <15 kg) with moderately to severely active polyarticular JIA. The patients received 24 mg/m^2 body surface area (BSA) of adalimumab up to a maximum of 20 mg every other week as a single dose via SC injection for at least 24 weeks. During the study, most subjects used concomitant MTX, with fewer reporting use of corticosteroids or NSAIDs.

At Week 12 and Week 24, Pediatric ACR 30 response was 93.5% and 90.0%, respectively, using the observed data approach. The proportions of subjects with Pediatric ACR 50/70/90 at Week 12 and Week 24 were 90.3%/61.3%/38.7% and 83.3%/73.3%/36.7%, respectively. Amongst those who responded (Pediatric ACR 30) at Week 24 (n=27 out of 30 patients), the Pediatric ACR 30 responses were maintained for up to 60 weeks in the OLE phase in patients who received adalimumab throughout this time period. Overall, 20 subjects were treated for 60 weeks or longer.

Enthesitis-Related Arthritis
The safety and efficacy of adalimumab were assessed in a multicenter, randomized, double-blind study in 46 pediatric patients (6 to 17 years old) with enthesitis-related arthritis. Patients were randomized to receive either 24 mg/m^2 body surface area (BSA) of adalimumab up to a maximum of 40 mg, or placebo every other week for 12 weeks. The double-blind period is followed by an open- label (OL) period during which patients received 24 mg/m^2 BSA of adalimumab up to a maximum of 40 mg every other week subcutaneously for up to an additional 192 weeks. The primary endpoint was the percent change from Baseline to

Week 12 in the number of active joints with arthritis (swelling not due to deformity or joints with loss of motion plus pain and/or tenderness), which was achieved (p=0.039) with mean percent decrease of -62.6% in patients in the adalimumab group compared to -11.6% in patients in the placebo group. Improvement in number of active joints with arthritis was maintained during the open label period through Week 156. The majority of patients demonstrated clinical improvement in secondary endpoints such as number of sites of enthesitis, tender joint count (TJC), swollen joint count (SJC), Pediatric ACR 30 response, Pediatric ACR 50 response, and Pediatric ACR 70 response and maintained these improvements during the open label period through Week 156 of the study.

Pediatric Crohn's Disease Clinical Study
Adalimumab was assessed in a multicenter, randomized, double-blind clinical trial designed to evaluate the efficacy and safety of induction and maintenance treatment with doses dependent on body weight (< 40 kg or ≥ 40 kg) in 192 pediatric subjects between the ages of 6 and 17 (inclusive) years, with moderate to severe Crohn´s disease (CD) defined as Pediatric Crohn's Disease Activity Index (PCDAI) score > 30. Subjects had to have failed conventional therapy (including a corticosteroid and/or an immunomodulator) for CD. Subjects may also have previously lost response or been intolerant to infliximab.

All subjects received open-label induction therapy at a dose based on their Baseline body weight: 160 mg at Week 0 and 80 mg at Week 2 for subjects ≥ 40 kg, and 80 mg and 40 mg, respectively, for subjects < 40 kg.
At Week 4, subjects were randomized 1:1 based on their body weight at the time to either the Low Dose or Standard Dose maintenance regimens as shown in Table 22.

Table 22: Maintenance Regimen

Patient Weight	Low Dose	Standard Dose
< 40 kg	10 mg eow	20 mg eow
≥ 40 kg	20 mg eow	40 mg eow

Efficacy Results
The primary endpoint of the study was clinical remission at Week 26, defined as PCDAI score ≤ 10.
Clinical remission and clinical response (defined as reduction in PCDAI score of at least 15 points from Baseline) rates are presented in Table 23. Rates of discontinuation of corticosteroids or immunomodulators are presented in Table 24.

Table 23: Pediatric CD Study PCDAI Clinical Remission and Response

	Standard Dose 40/20 mg eow N = 93	Low Dose 20/10 mg eow N = 95	P value*
Week 26			
Clinical remission	38.7%	28.4%	0.075
Clinical response	59.1%	48.4%	0.073
Week 52			
Clinical remission	33.3%	23.2%	0.100
Clinical response	41.9%	28.4%	0.038

* p value for Standard Dose *versus* Low Dose comparison.

Table 24: Pediatric CD Study
Discontinuation of Corticosteroids or Immunomodulators and Fistula Remission

	Standard Dose 40/20 mg eow	Low Dose 20/10 mg eow	P value[1]
Discontinued corticosteroids	**N= 33**	**N=38**	
Week 26	84.8%	65.8%	0.066
Week 52	69.7%	60.5%	0.420
Discontinuation of Immunomodulators[2]	**N=60**	**N=57**	
Week 52	30.0%	29.8%	0.983
Fistula remission[3]	**N=15**	**N=21**	
Week 26	46.7%	38.1%	0.608
Week 52	40.0%	23.8%	0.303

[1] p value for Standard Dose *versus* Low Dose comparison.
[2] Immunosuppressant therapy could only be discontinued at or after Week 26 at the investigator's discretion if the subject met the clinical response criterion
[3] Defined as a closure of all fistulas that were draining at Baseline for at least 2 consecutive post-Baseline visits

Statistically significant increases (improvement) from Baseline to Week 26 and 52 in Body Mass Index and height velocity were observed for both treatment groups. Statistically and clinically significant improvements from Baseline were also observed in both treatment groups for quality of life parameters (including IMPACT III).

Pediatric Plaque Psoriasis Clinical Study
The efficacy of adalimumab was assessed in a randomized, double-blind, controlled study of 114 pediatric patients from 4 years of age with severe chronic plaque psoriasis (as defined by a PGA ≥ 4 or > 20% BSA involvement or > 10% BSA involvement with very thick lesions or PASI ≥ 20 or ≥ 10 with clinically relevant facial, genital, or hand/ foot involvement) who were inadequately controlled with topical therapy and heliotherapy or phototherapy.

Patients received adalimumab 0.8mg/kg eow (up to 40 mg), 0.4 mg/kg eow (up to 20 mg), or methotrexate 0.1 – 0.4 mg/kg weekly (up to 25 mg). At week 16, more patients randomized to adalimumab 0.8 mg/kg had positive efficacy responses (e.g.,PASI 75) than those randomized to MTX.

Table 25: Pediatric Plaque Psoriasis Efficacy Results at 16 Weeks

	MTX[a] N=37	Adalimumab 0.8mg/kg eow N=38
PASI 75[b]	12 (32.4%)	22 (57.9%)
PGA: Clear/minimal[c]	15 (40.5%)	23 (60.5%)

a MTX = methotrexate
b P=0.027, adalimumab0.8 mg/kg versus MTX c P=0.083, Adalimumab0.8 mg/kg

Patients who achieved PASI 75 and PGA clear or minimal were withdrawn from treatment for up to 36 weeks and monitored for

loss of disease control (loss of PGA response). Patients were then re-treated with adalimumab 0.8 mg/kg eow for an additional 16 weeks and responses observed during retreatment were similar to the previous double-blind period: PASI 75 response of 78.9% (15 of 19 subjects) and PGA clear or minimal of 52.6% (10 of 19 subjects).

In the open label period of the study, PASI 75 and PGA clear or minimal responses were maintained for up to an additional 52 weeks with no new safety findings.

Adolescent Hidradenitis Suppurativa
There are no clinical trials with adalimumab in adolescent patients with hidradenitis suppurativa (HS). Efficacy of adalimumab for the treatment of adolescent patients with HS is predicted based on the demonstrated efficacy and exposure-response relationship in adult HS patients and the likelihood that the disease course, pathophysiology, and drug effects are substantially similar to that of adults at the same exposure levels. The recommended adolescent HS dosing schedule of 40 mg every other week is predicted to provide similar efficacy to that observed in adult HS patients receiving the recommended adult dose of 40 mg every week. Safety of the recommended adalimumab dose in the adolescent HS population is based on cross-indication safety profile of adalimumab in both adults and pediatric patients at similar or more frequent doses.

Pediatric Uveitis Clinical Study
The safety and efficacy of adalimumab was assessed in a randomized, double-masked, controlled study of 90 pediatric patients from 2 to < 18 years of age with active JIA-associated noninfectious anterior uveitis who were refractory to at least 12 weeks of methotrexate treatment. Patients received either placebo or 20 mg adalimumab (if < 30 kg) or 40 mg adalimumab (if ≥ 30 kg) every other week in combination with their baseline dose of methotrexate.

The primary endpoint was 'time to treatment failure.' The criteria determining treatment failure were worsening, or sustained non-improvement in ocular inflammation, or partial improvement with development of sustained ocular co-morbidities, or worsening of ocular co-morbidities, non-permitted use of concomitant medications, and suspension of treatment for an extended period of time.

Clinical Response
Adalimumab significantly delayed the time to treatment failure, as compared to placebo (See Figure 6, P < 0.0001 from log rank test). The median time to treatment failure was 24.1 weeks for subjects treated with placebo, whereas the median time to treatment failure was not estimable for subjects treated with adalimumab because less than one-half of these subjects experienced treatment failure. Adalimumab significantly decreased the risk of treatment failure by 75% relative to placebo, as shown by the hazard ratio (HR = 0.25 [95% CI: 0.12, 0.49]).

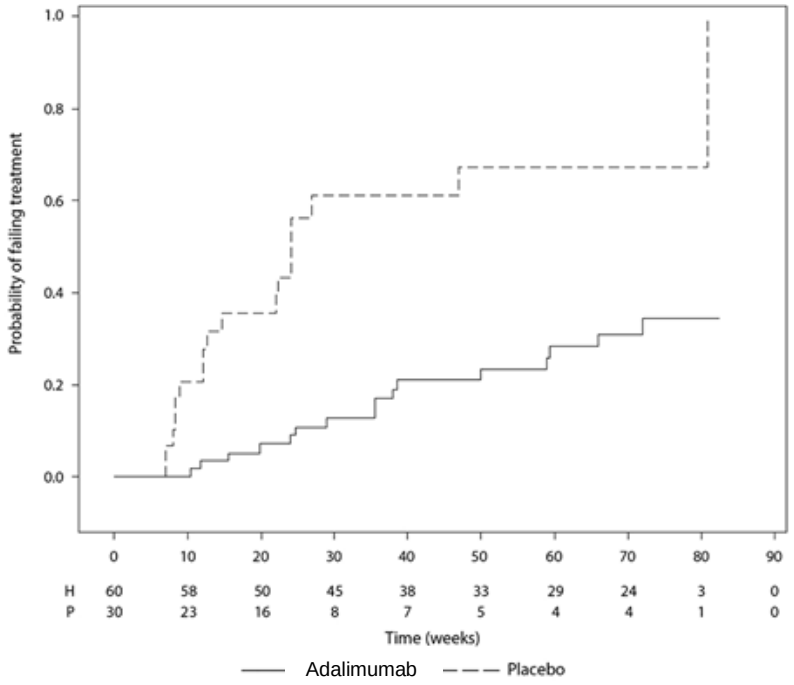


Figure 6: Kaplan-Meier Curves Summarizing Time to Treatment Failure in the Pediatric UV Study

Pediatric Ulcerative Colitis
The safety and efficacy of adalimumab was assessed in a multicenter, randomized, double-blind, trial in 93 pediatric patients from 5 to 17 years of age with moderate to severe ulcerative colitis (Mayo score 6 to 12 with endoscopy subscore of 2 to 3 points, confirmed by centrally read endoscopy) who had an inadequate response or intolerance to conventional therapy. Approximately 16% of patients in the study had failed prior anti-TNF treatment. Patients who received corticosteroids at enrollment were allowed to taper their corticosteroid therapy after Week 4.

In the induction period of the study, 77 patients were randomized 3:2 to receive double-blind treatment with adalimumab at an induction dose of 2.4 mg/kg (maximum of 160 mg) at Week 0 and Week 1, and 1.2 mg/kg (maximum of 80 mg) at Week 2; or an induction dose of 2.4 mg/kg (maximum of 160 mg) at Week 0, placebo at Week 1, and 1.2 mg/kg (maximum of 80 mg) at Week 2. Both groups received 0.6 mg/kg (maximum of 40 mg) at Week 4 and Week 6. Following an amendment to the study design, the remaining 16 patients who enrolled in the induction period received open-label treatment with adalimumab at the induction dose of 2.4 mg/kg (maximum of 160 mg) at Week 0 and Week 1, and 1.2 mg/kg (maximum of 80 mg) at Week 2.

At Week 8, 62 patients who demonstrated clinical response per Partial Mayo Score (PMS; defined as a decrease in PMS ≥ 2 points and ≥ 30% from Baseline) were randomized equally to receive double-blind maintenance treatment at a dose of 0.6 mg/kg (maximum of 40 mg) every week (ew), or a maintenance dose of 0.6 mg/kg (maximum of 40 mg) every other week (eow). Prior to an amendment to the study design, 12 additional patients who demonstrated clinical response per PMS were

randomized to receive placebo but were not included in the confirmatory analysis of efficacy.

Disease flare was defined as an increase in Partial Mayo Score (PMS) of at least 3 points (for patients with PMS of 0 to 2 at Week 8), at least 2 points (for patients with PMS of 3 to 4 at Week 8), or at least 1 point (for patients with PMS of 5 to 6 at Week 8).

Patients who met criteria for disease flare at or after Week 12 were randomized to receive a re-induction dose of 2.4 mg/kg (maximum of 160 mg) or a dose of 0.6 mg/kg (maximum of 40 mg) and continued to receive their respective maintenance dose regimen afterwards.

Efficacy Results

The co-primary endpoints of the study were clinical remission per PMS (defined as PMS ≤ 2 and no individual subscore > 1) at Week 8, and clinical remission per FMS (Full Mayo Score) (defined as a Mayo Score ≤ 2 and no individual subscore > 1) at Week 52 in patients who achieved clinical response per PMS at Week 8.

Clinical remission rates per PMS at Week 8 for patients in each of the adalimumab double-blind induction groups are presented in Table 26.

Table 26: Clinical Remission per PMS at 8 Weeks

	Adalimumab[a] Maximum of 160 mg at Week 0 / Placebo at Week 1	**Adalimumab[b, c] Maximum of 160 mg at Week 0 and Week 1**
Clinical remission	13/30 (43.3%)	28/47 (59.6%)
[a] Adalimumab2.4 mg/kg (maximum of 160 mg) at Week 0, placebo at Week 1, and 1.2 mg/kg (maximum of 80 mg) at Week 2 [b] Adalimumab2.4 mg/kg (maximum of 160 mg) at Week 0 and Week 1, and 1.2 mg/kg (maximum of 80 mg) at Week 2 [c] Not including open-label Induction dose of adalimumab2.4 mg/kg (maximum of 160 mg) at Week 0 and Week 1, and 1.2 mg/kg (maximum of 80 mg) at Week 2		
Note 1: Both induction groups received 0.6 mg/kg (maximum of 40 mg) at Week 4 and Week 6 Note 2: Patients with missing values at Week 8 were considered as not having met the endpoint		

At Week 52, clinical remission per FMS in Week 8 responders, clinical response per FMS (defined as a decrease in Mayo Score ≥ 3 points and ≥ 30% from Baseline) in Week 8 responders, mucosal healing (defined as Mayo endoscopy subscore ≤ 1) in Week 8 responders, clinical remission per FMS in Week 8 remitters, and the proportion of subjects in corticosteroid-free remission per FMS in Week 8 responders were assessed in patients who received adalimumab at the double-blind maximum 40 mg eow (0.6 mg/kg) and maximum 40 mg ew (0.6 mg/kg) maintenance doses (Table 27).

Table 27: Efficacy Results at 52 Weeks

	Adalimumab[a] Maximum of 40 mg eow	**Adalimumab[b] Maximum of 40 mg ew**
Clinical remission in Week 8 PMS responders	9/31 (29.0%)	14/31 (45.2%)
Clinical response in Week 8 PMS responders	19/31 (61.3%)	21/31 (67.7%)
Mucosal healing in Week 8 PMS responders	12/31 (38.7%)	16/31 (51.6%)
Clinical remission in Week 8 PMS remitters	9/21 (42.9%)	10/22 (45.5%)
Corticosteroid-free remission in Week 8 PMS responders[c]	4/13 (30.8%)	5/16 (31.3%)
[a] Adalimumab 0.6 mg/kg (maximum of 40 mg) every other week [b] Adalimumab 0.6 mg/kg (maximum of 40 mg) every week [c] In patients receiving concomitant corticosteroids at baseline Note: Patients with missing values at Week 52 or who were randomized to receive re-induction or maintenance treatment were considered non-responders for Week 52 endpoints		

Additional exploratory efficacy endpoints included clinical response per the Pediatric Ulcerative Colitis Activity Index (PUCAI) (defined as a decrease in PUCAI ≥ 20 points from Baseline) and clinical remission per PUCAI (defined as PUCAI < 10) at Week 8 and Week 52 (Table 28).

Table 28: Exploratory Endpoints Results per PUCAI

	Week 8	
	Adalimumab[a] Maximum of 160 mg at Week 0 / Placebo at Week 1	**Adalimumab[b,c] Maximum of 160 mg at Week 0 and Week 1**
Clinical remission per PUCAI	10/30 (33.3%)	22/47 (46.8%)
Clinical response per PUCAI	15/30 (50.0%)	32/47 (68.1%)
	Week 52	
	Adalimumab[d] Maximum of 40 mg eow	**Adalimumab[e] Maximum of 40 mg ew**
Clinical remission per PUCAI in Week 8 PMS responders	14/31 (45.2%)	18/31 (58.1%)
Clinical response per PUCAI in Week 8 PMS responders	18/31 (58.1%)	16/31 (51.6%)
[a] Adalimumab 2.4 mg/kg (maximum of 160 mg) at Week 0, placebo at Week 1, and 1.2 mg/kg (maximum of 80 mg) at Week 2 [b] Adalimumab 2.4 mg/kg (maximum of 160 mg) at Week 0 and Week 1, and 1.2 mg/kg (maximum of 80 mg) at Week 2 [c] Not including open-label Induction dose of Adalimumab 2.4 mg/kg (maximum of 160 mg) at Week 0 and Week 1, and 1.2 mg/kg (maximum of 80 mg) at Week 2 [d] Adalimumab 0.6 mg/kg (maximum of 40 mg) every other week [e] Adalimumab 0.6 mg/kg (maximum of 40 mg) every week Note 1: Both induction groups received 0.6 mg/kg (maximum of 40 mg) at Week 4 and Week 6 Note 2: Patients with missing values at Week 8 were considered as not having met the endpoints Note 3: Patients with missing values at Week 52 or who were randomized to receive reinduction or maintenance treatment were considered non-responders for Week 52 endpoints		

Of the adalimumab-treated patients who received re-induction treatment during the maintenance period, 2/6 (33%) achieved clinical response per FMS at Week 52.

Quality of Life
Improvements from Baseline were observed in IMPACT III and the caregiver Work Productivity and Activity Impairment (WPAI) scores for the groups treated with adalimumab.

Increases (improvement) from Baseline in height velocity were observed for the groups treated with adalimumab, and increases (improvement) from Baseline in Body Mass Index were observed for subjects on the adalimumab maintenance dose of maximum 40 mg (0.6 mg/kg) ew.

Immunogenicity
Formation of anti-adalimumab antibodies is associated with increased clearance and reduced efficacy of adalimumab. There is no apparent correlation between the presence of anti-adalimumab antibodies and adverse events.

Because immunogenicity analyses are product-specific, comparison of antibody rates with those from other products is not appropriate.

Adults
Patients in rheumatoid arthritis studies I, II and III were tested at multiple time points for anti-adalimumab antibodies during the 6 to 12 month period. In the pivotal trials, anti-adalimumab antibodies were identified in 5.5% (58/1053) of patients treated with adalimumab, compared to 0.5% (2/370) on placebo. In patients not given concomitant methotrexate, the incidence was 12.4%, compared to 0.6% when adalimumab was used as add-on to methotrexate.

In patients with psoriatic arthritis, anti-adalimumab antibodies were identified in 10% (38/376) of patients treated with adalimumab.

In patients not given concomitant methotrexate, the incidence was 13.5% (24/178), compared to 7% (14/198) when adalimumab was used as add-on to methotrexate.

In patients with ankylosing spondylitis anti-adalimumab antibodies were identified in 8.3% (17/204) of patients treated with adalimumab. In patients not given concomitant methotrexate, the incidence was 8.6% (16/185), compared to 5.3% (1/19) when adalimumab was used as add-on to methotrexate.

In patients with Crohn's disease, anti-adalimumab antibodies were identified in 2.6% (7/269) of patients treated with adalimumab.

In patients with moderately to severely active ulcerative colitis, the rate of anti-adalimumab antibody development in patients treated with adalimumab was 5.0%.

In patients with psoriasis, anti-adalimumab antibodies were identified in 8.4% (77/920) of patients treated with adalimumab without concomitant methotrexate. In plaque psoriasis patients on long term adalimumab without concomitant methotrexate who participated in a withdrawal and retreatment study, the rate of anti-adalimumab antibodies after retreatment was 2.3%, and was similar to the rate observed prior to withdrawal 1.9%.

In patients with moderate to severe hidradenitis suppurativa, anti-adalimumab antibodies were identified in 10.1% (10/99) of patients treated with adalimumab.

In patients with non-infectious uveitis, anti-adalimumab antibodies were identified in 4.8% (12/249) of patients treated with adalimumab.

Pediatrics
In patients with polyarticular juvenile idiopathic arthritis who were 4 to 17 years, anti-adalimumab antibodies were identified in 16.0% (27/171) of patients treated with adalimumab. In patients not given concomitant methotrexate, the incidence was 26.0% (22/86), compared to 6.0% (5/85) when adalimumab was used as add-on to methotrexate. In patients with polyarticular juvenile idiopathic arthritis who were 2 to <4 years old or aged 4 and above weighing <15 kg, anti-adalimumab antibodies were identified in 7.0% (1/15) of patients, and the one patient was receiving concomitant methotrexate.

In patients with enthesitis-related arthritis, anti-adalimumab antibodies were identified in 11% (5/46) of patients treated with adalimumab. In patients not given concomitant methotrexate, the incidence was 14% (3/22), compared to 8% (2/24) when adalimumab was used as add-on to methotrexate.

In patients with moderately to severely active pediatrics Crohn's disease, the rate of anti-adalimumab antibody development in patients receiving adalimumab was 3.3% (6/182).

In patients with pediatric psoriasis, anti-adalimumab antibodies were identified in 13% (5/38) of subjects treated with 0.8 mg/kg adalimumab monotherapy.

In patients with moderately to severely active pediatric ulcerative colitis, the rate of anti-adalimumab antibody development in patients receiving adalimumab was 3%.

COMPARATIVE CLINICAL TRIALS

Comparative Trial Design and Study Demographics

Clinical Studies conducted to support similarity between Yuflyma and the reference biologic drug included:

- A comparative pharmacokinetic (PK) clinical Phase I study CT-P17 1.1 in healthy subjects
- A comparative efficacy and safety clinical Phase III study CT-P17 3.1 in patients with moderate to severe RA

An overview of the study design and demographic characteristics of patients enrolled in each clinical study are presented in Table 29

Table 29: Summary of Trial Design and Patient Demographics

Study Number	Study Design	Dosage, Route of Administration and Duration	Study Subjects (n)	Mean Age (years; range)	Gender
CT-P17 1.1	Phase 1, randomized, double-blind, three-arm, parallel group, single-dose study in healthy male and female subjects	Yuflyma, EU-Humira, or US-Humira; Single dose 40 mg, Subcutaneous injection; Total duration 10 weeks	308 healthy subjects Yuflyma (n=102) EU-Humira (n=104) US-Humira (n=102)	28.3 (19, 54) Yuflyma 27.0 (19, 51) EU-Humira 28.8 (19, 54) US-Humira 29.1 (19, 53)	M 264 (85.7%), F 44 (14.3%) Yuflyma M 87 (85.3%) F 15 (14.7%) EU-Humira M 89 (85.6%) F 15 (14.4%) US-Humira M 88 (86.3%) F 14 (13.7%)
CT-P17 3.1	Phase 3, randomized, active-controlled, double-blind , multicenter study in patients with moderate to severe active RA	Yuflyma or EU-Humira; 40 mg every other week; Subcutaneous injection; Total duration 52 weeks	648 RA patients Yuflyma (n=324) EU-Humira (n=324)	51.9 (18, 75) Yuflyma 52.0 (18, 75) EU-Humira 51.8 (19, 75)	M 134 (20.7%), F 514 (79.3%) Yuflyma M 75 (23.1%) F 249 (76.9%) EU-Humira M 59 (18.2%) F 265 (81.8%)

Study CT-P17 3.1 was a phase 3, randomized, active-controlled, double-blind, multicenter study designed to evaluate efficacy, PK, PD, usability, overall safety and immunogenicity of multiple single- doses (40 mg) of either Yuflyma or EU-Humira administered via PFS in combination with MTX in patients with moderate to severe active RA. The study period for up to 52 weeks after 1st randomization includes 48 weeks of treatment and 4 weeks of safety follow-up. Prior to dosing at Week 26, all patients underwent the 2nd randomization process. Patients who were initially randomly assigned to EU-Humira were randomized again in a ratio of 1:1 to either continue EU-Humira or undergo transition to Yuflyma. The primary endpoint, ACR20 at Week 24, met with 95% CI falling within the margin of -15% to +15%.

Comparative Study Results

Comparative Bioavailability Studies

Pharmacokinetics

Comparative Pharmacokinetic Study CT-P17 1.1

Table 30: Study CT-P17 1.1: Analysis of Primary PK parameters

(a) CT-P17 to EU-Humira®

PK Parameters (Units)	Treatment	Mean (%CV)	Geometric LS Means[1]	Ratio (%) of Geometric LS Means	90% CIs[1]
C_{max} (µg/mL)	CT-P17	3.619 (37.4)	3.008	100.05	(93.69, 106.85)
	EU-Humira®	3.660 (33.4)	3.006		
$AUC_{0\text{-}inf}$ (h•µg/mL)	CT-P17	2656.5 (43.3)	2165.0	98.00	(90.06, 106.63)
	EU-Humira®	2690.6 (35.1)	2209.3		
$AUC_{0\text{-}last}$ (h•µg/mL)	CT-P17	2372.7 (40.2)	1949.2	100.79	(92.42, 109.92)
	EU-Humira®	2394.7 (36.2)	1933.9		

(b) CT-P17 to US-Humira®

PK Parameters (Units)	Treatment	Mean (%CV)	Geometric LS Means[1]	Ratio (%) of Geometric LS Means	90% CIs[1]
C_{max} (µg/mL)	CT-P17	3.619 (37.4)	3.008	101.89	(95.33, 108.89)
	US-Humira®	3.556 (33.7)	2.952		
$AUC_{0\text{-}inf}$ (h•µg/mL)	CT-P17	2656.5 (43.3)	2165.0	105.79	(97.19, 115.16)
	US-Humira®	2469.7 (37.2)	2046.5		
$AUC_{0\text{-}last}$ (h•µg/mL)	CT-P17	2372.7 (40.2)	1949.2	107.30	(98.29, 117.13)
	US-Humira®	2185.0 (36.4)	1816.6		

[1] The LS mean differences and 90% CIs for the differences were exponentiated to provide estimates of the ratio of geometric LS means and 90% CIs for the ratios.
%CV: Percent coefficient of variation, ANCOVA: Analysis of covariance, CIs: Confidence intervals, LS: Least squares

Comparative Safety and Efficacy
Efficacy

Adult Rheumatoid Arthritis Study CT-P17 3.1
The number of patients who achieved ACR20 response at Week 24 was equal between the Yuflyma and EU-Humira treatment groups in the ITT population. A total of 268 (82.72%) patients achieved ACR20 response at Week 24 in each of the treatment groups. The 95% CI of the treatment difference was [-5.94, 5.94], which was within the pre-defined equivalence margin of [-15%, 15%] (Table 31).

Table 31: Exact Test for Proportion of Patients Achieving Response According to ACR20 Criteria in Study CT-P17 3.1 at Week 24 (ITT, PP Population)

Treatment	n/N	(%)	Estimated Difference (%)[1]	95% CI
ITT population				
Yuflyma	268/324	(82.72)	0.00	(-5.94, 5.94)
EU-Humira	268/324	(82.72)		
PP population				
Yuflyma	248/285	(87.02)	0.06	(-5.60, 5.78)
EU-Humira	240/276	(86.96)		

[1] Estimate of the difference in proportion and 95% confidence interval between the two treatment groups are estimated using the exact binomial method using a Farrington-Manning score method.
Note: Patients who were terminated from the study prior to the week of interest, who continued the study/study treatment but did not visit the site for the evaluation of ACR20 at the week of interest, and with incomplete data for evaluation of ACR20 criteria at the week of interest are considered as non-responder.
N: number of patients in the full analysis set, n: number of responders

Safety

The types, frequency and severity of adverse events were comparable between the biosimilar and the reference biologic drug.

Immunogenicity

Immunogenicity (Healthy Subjects)
The immunogenicity was evaluated in 308 healthy subjects in Study CT-P17 1.1. The blood samples were collected at Day 1 (pre-dose), Day 15, Day 29, Day 57 and Day 71. The proportions of subjects who had post-treatment ADA/NAb positive results up to Day 71 was similar amongst the three treatment groups.

Immunogenicity (RA)
The incidence of RA patients with ADA/NAb positive was comparable between the treatment groups up to Week 52 in Study CT-P17 3.1 (Table 32).

Table 32: Frequency of Positive ADA/NAb in Study CT-P17 3.1

Visit	Parameter	Yuflyma(N=324)	EU-Humira(N=324)
		n/N (%)	
Treatment Period I (Safety population)			
Week 0 (Pre-dose)	ADA	11/324 (3.4%)	6/324 (1.9%)
	NAb	4/11 (36.4%)	1/6 (16.7%)
Week 24	ADA	93/324 (28.7%)	116/324 (35.8%)
	NAb	83/93 (89.2%)	103/116 (88.8%)

Visit	Parameter	Yuflyma Maintenance (N=303)	EU-Humira Maintenance (N=152)	Switched to Yuflyma (N=152)
Treatment Period II (Safety population – Treatment Period II Subset)				
Week 26	ADA	74/303 (24.4%)	44/152 (28.9%)	52/152 (34.2%)
	NAb	71/74 (95.9%)	42/44 (95.5%)	47/52 (90.4%)
Week 52	ADA	86/303 (28.4%)	41/152 (27.0%)	43/152 (28.3%)
	NAb	75/86 (87.2%)	37/41 (95.5%)	40/43 (93.0%)

Note: The proportion of ADA positive patients was calculated using the number of patients in the safety population.
The proportion of NAb positive patients was re-calculated using ADA positive patients as a denominator. n: number of patients with the event, N: number of patients in each treatment group

INDICATIONS

ADULTS
Rheumatoid Arthritis
Yuflyma is indicated for reducing signs and symptoms and inhibiting the progression of structural damage and improving physical function in adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more DMARDs. Yuflyma can be used alone or in combination with methotrexate or other DMARDs.

Yuflyma, in combination with MTX, can also be used in the treatment of patients with recently diagnosed moderate to severely active rheumatoid arthritis who have not received methotrexate.

Psoriatic Arthritis
Yuflyma is indicated for reducing signs and symptoms of active arthritis in adult patients with moderate to severe psoriatic arthritis when the response to previous DMARD therapy has been inadequate. Yuflyma has been shown to reduce the rate of progression of peripheral joint damage as measured by X-ray in patients with polyarticular symmetrical subtypes of the disease and to improve physical function.

Yuflyma can be used alone or in combination with DMARDs.

Ankylosing Spondylitis
Yuflyma is indicated for reducing signs and symptoms in adult patients with active ankylosing spondylitis who have had an inadequate response to conventional therapy.

Crohn's Disease
Yuflyma is indicated for the treatment of moderate to severe active Crohn's disease in adults to reduce the signs and symptoms of the disease and to induce and maintain clinical remission in patients who have had an inadequate response to conventional therapies, or who have lost response to or are intolerant of infliximab. For induction treatment, Yuflyma should be given in combination with corticosteroids. Yuflyma can be given as monotherapy in case of intolerance to corticosteroids or when continued treatment with corticosteroids is inadequate.

Ulcerative Colitis
Yuflyma is indicated for treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy including corticosteroids and/or 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.

Plaque Psoriasis
Yuflyma is indicated for the treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy and when other systemic therapies are medically less appropriate.

Hidradenitis Suppurativa
Yuflyma is indicated for the treatment of active moderate to severe hidradenitis suppurativa (acne inversa) in adult patients with an inadequate response to conventional systemic HS therapy.

Uveitis
Yuflyma is indicated for the treatment of non-infectious intermediate, posterior and panuveitis in adult patients who have had an inadequate response to corticosteroids, in patients in need of corticosteroid-sparing, or in whom corticosteroid treatment is inappropriate.

PEDIATRICS
Juvenile Idiopathic Arthritis

Polyarticular Juvenile Idiopathic Arthritis
Yuflyma in combination with methotrexate is indicated for the treatment of active polyarticular juvenile idiopathic arthritis (pJIA), in patients 2 years of age and older, who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDS). Yuflyma can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate (for the efficacy in monotherapy see **CLINICAL STUDIES**). Yuflyma has not been studied in patients aged less than 2 years.

Enthesitis-Related Arthritis
Yuflyma is indicated for the treatment of active enthesitis-related arthritis in patients, 6 years of age and older, who have had an inadequate response to, or who are intolerant of, conventional therapy.

Pediatric Crohn's Disease
Yuflyma is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients, 6 years of age and older, with moderately to severely active Crohn's disease who have had an inadequate response to

conventional therapy.

Pediatric Plaque Psoriasis
Yuflyma is indicated for the treatment of severe chronic plaque psoriasis in children and adolescents from 4 years of age who have had an inadequate response to or are inappropriate candidates for topical therapy and phototherapy.

Adolescent Hidradenitis Suppurativa
Yuflyma is indicated for the treatment of active moderate to severe hidradenitis suppurativa (acne inversa) in adolescents from 12 years of age with an inadequate response to conventional systemic hidradenitis suppurativa (HS) therapy.

Pediatric Uveitis
Yuflyma is indicated for the treatment of chronic non-infectious anterior uveitis in pediatric patients 2 years of age and older who have had an inadequate response to or are intolerant to conventional therapy, or in whom conventional therapy is inappropriate.

Pediatric Ulcerative Colitis
Yuflyma is indicated for inducing and maintaining clinical remission in pediatric patients 5 years of age or older with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy including corticosteroids and/or 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies.

CONTRAINDICATIONS
Yuflyma should not be administered to patients with known hypersensitivity to Yuflyma or any of its excipients.
Active tuberculosis or other severe infections such as sepsis, abscesses, and opportunistic infections (see **WARNINGS AND PRECAUTIONS**).
Moderate to severe heart failure (NYHA class III/IV) (see **WARNINGS AND PRECAUTIONS**).

WARNINGS AND PRECAUTIONS
In order to improve traceability of biological medicinal products, the tradename and the batch number of the administered product should be clearly recorded.

Infections
Serious infections, due to bacterial, mycobacterial, invasive fungal (disseminated or extrapulmonary histoplasmosis, aspergillosis, coccidioidomycosis) viral, parasitic or other opportunistic infections have been reported in patients receiving TNF-blocking agents. Sepsis, rare cases of tuberculosis, candidiasis, listeriosis, Legionellosis and pneumocystis have also been reported with the use of TNF antagonists, including Yuflyma. Other serious infections seen in clinical trials include pneumonia, pyelonephritis, septic arthritis and septicaemia. Hospitalization or fatal outcomes associated with infections have been reported. Many of the serious infections have occurred in patients on concomitant immunosuppressive therapy that, in addition to their underlying disease could predispose them to infections.

Treatment with Yuflyma should not be initiated in patients with active infections including chronic or localized infections until infections are controlled. In patients who have been exposed to tuberculosis, and patients who have traveled in areas of high risk of tuberculosis or endemic mycoses, such as histoplasmosis, coccidioidomycosis, or blastomycosis, the risk and benefits of treatment with Yuflyma should be considered prior to initiating therapy (see **Other Opportunistic Infections**).

As with other TNF antagonists, patients should be monitored closely for infections, including tuberculosis before, during and after treatment with Yuflyma.

Patients who develop a new infection while undergoing treatment with Yuflyma should be monitored closely and undergo a complete diagnostic evaluation. Administration of Yuflyma should be discontinued if a patient develops a new serious infection or sepsis, and appropriate antimicrobial or antifungal therapy should be initiated until infections are controlled.

Physicians should exercise caution when considering the use of Yuflyma in patients with a history of recurrent infection or with underlying conditions which may predispose patients.

Tuberculosis
Tuberculosis including reactivation and new onset of tuberculosis, has been reported in patients receiving adalimumab.
Reports included cases of pulmonary and extrapulmonary (i.e.disseminated).

Before initiation of therapy with Yuflyma, all patients should be evaluated for both active and inactive ("latent") tuberculosis infection. The evaluation should include a detailed medical assessment of patient history of tuberculosis or possible previous exposure to people with active tuberculosis and previous and/or current immunosuppressive therapy. Appropriate screening tests (e.g. chest x-ray and tuberculin skin test) should be performed in accordance with local recommendations. Treatment of latent tuberculosis should be initiated prior to therapy with Yuflyma.

The possibility of undetected latent tuberculosis should be considered especially in patients who have immigrated from or traveled to countries with a high prevalence of tuberculosis or who had close contact with a person with active tuberculosis.

If active tuberculosis is diagnosed, Yuflyma therapy must not be initiated.

If latent tuberculosis is diagnosed, appropriate treatment must be started with anti-tuberculosis prophylactic treatment before initiation of Yuflyma and in accordance with local recommendations. Use of anti-tuberculosis prophylactic treatment should also be considered before initiation of Yuflyma in patients with several or significant risk factors for tuberculosis despite a negative test for tuberculosis and in patient with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed. The decision to initiate anti-tuberculosis therapy in these patients should only be made after taking into account both the risk for latent tuberculosis infection and the risks of anti-tuberculosis therapy. If necessary, consultation should occur with a physician with expertise in the treatment of tuberculosis.

Anti-tuberculosis treatment of patients with latent tuberculosis infection reduces the risk of reactivation in patients receiving treatment with adalimumab. Despite prophylactic treatment for tuberculosis, cases of reactivated tuberculosis have occurred in patients treated with adalimumab. Also, active tuberculosis has developed in patients receiving adalimumab whose screening for latent tuberculosis infection was negative, and some patients who have been successfully treated for active tuberculosis have redeveloped tuberculosis while being treated with TNF blocking agents.

Patients receiving Yuflyma should be monitored for signs and symptoms of active tuberculosis, particularly because tests for latent tuberculosis infection may be falsely negative. The risk of false negative tuberculin skin test results should be considered especially in patients who are severely ill or immunocompromised.

Patients should be instructed to seek medical advice if signs/symptoms suggestive of a tuberculosis infection (e.g., persistent cough, wasting/weight loss, low grade fever, listlessness) occur during or after therapy with Yuflyma.

Other Opportunistic Infections
Opportunistic infections, including invasive fungal infections, have been observed in patients receiving adalimumab. These infections are not consistently recognized in patients taking TNF- blockers and this has resulted in delays in appropriate treatment, sometimes resulting in fatal outcomes.

Patients taking TNF-blockers are more susceptible to serious fungal infections such as histoplasmosis, coccidioidomycosis, blastomycosis, aspergillosis, candidiasis, and other opportunistic infections. Those who develop fever, malaise, weight loss, sweats, cough, dyspnea, and/or pulmonary infiltrates, or other serious systemic illness with or without concomitant shock should promptly seek medical attention for a diagnostic evaluation.

For patients who reside or travel in regions where mycoses are endemic, invasive fungal infections should be suspected if they develop the signs and symptoms of possible systemic fungal infection. Patients are at risk of histoplasmosis and other invasive fungal infections and hence clinicians should consider empiric antifungal treatment until the pathogen(s) are identified. Antigen and antibody testing for histoplasmosis may be negative in some patients with active infection. When feasible, the decision to administer empiric antifungal therapy in these patients should be made in consultation with a physician with expertise in the diagnosis and treatment of invasive fungal infections and should take into account both the risk for severe fungal infection and the risks of antifungal therapy. Patients who develop a severe fungal infection are also advised to stop the TNF-blocker until infections are controlled.

Hepatitis B Reactivation
Use of TNF blockers has been associated with reactivation of hepatitis B virus (HBV) in patients who are chronic carriers of this virus. In some instances, HBV reactivation occurring in conjunction with TNF blocker therapy has been fatal. The majority of these reports have occurred in patients concomitantly receiving other medications that suppress the immune system, which may also contribute to HBV reactivation. Patients at risk for HBV infection should be evaluated for prior evidence of HBV infection before initiating TNF blocker therapy. Prescribers should exercise caution in prescribing TNF blockers for patients identified as carriers of HBV. Patients who are carriers of HBV and require treatment with TNF blockers should be closely monitored for signs and symptoms of active HBV infection throughout therapy and for several months following termination of therapy. Adequate data are not available on the safety or efficacy of treating patients who are carriers of HBV with anti-viral therapy in conjunction with TNF blocker therapy to prevent HBV reactivation. In patients who develop HBV reactivation, Yuflyma should be stopped and effective anti-viral therapy with appropriate supportive treatment should be initiated.

Neurologic Events
TNF-antagonists, including adalimumab, have been associated in rare cases with new onset or exacerbation of clinical symptoms and/or radiographic evidence of central nervous system demyelinating disease, including multiple sclerosis, optic neuritis and peripheral demyelinating disease, including Guillain Barré syndrome. Prescribers should exercise caution in considering the use of Yuflyma in patients with preexisting or recent-onset central or peripheral nervous system demyelinating disorders; discontinuation of Yuflyma should be considered if any of these disorders develop.

There is a known association between intermediate uveitis and central demyelinating disorders. Neurologic evaluation should be performed in patients with non-infectious intermediate uveitis prior to the initiation of Yuflyma therapy to assess for pre-existing central demyelinating disorders.

Malignancies

In the controlled portions of clinical trials of TNF-antagonist, including adalimumab, more cases of malignancies including lymphoma have been observed among patients receiving a TNF-antagonist compared with control patients. In the post marketing setting, cases of leukemia have been reported in patients treated with a TNF-antagonist. It should be noted that there is an increased background lymphoma risk in rheumatoid arthritis patients with long-standing, highly active, inflammatory disease, which complicates the risk estimation. During the long-term open label trials with adalimumab, the overall rate of malignancies was similar to what would be expected for an age, gender and race matched general population. With the current knowledge, a possible risk for the development of lymphomas, leukemia or other malignancies in patients treated with a TNF-antagonist cannot be excluded.

Malignancies, some fatal, have been reported among children and adolescents who received treatment with TNF-blocking agents. Approximately half the cases were lymphomas, including Hodgkin's and non-Hodgkin's lymphoma. The other cases represented a variety of different malignancies and included rare malignancies usually associated with immunosuppression. The malignancies occurred after a median of 30 months of therapy. Most of the patients were receiving concomitant immunosuppressants. These cases were reported post-marketing and are derived from a variety of sources including registries and spontaneous postmarketing reports. A risk for the development of malignancies in children and adolescents treated with TNF-antagonists cannot be excluded.

Rare postmarketing reports of hepatosplenic T-cell lymphoma (HSTCL), a rare aggressive lymphoma that is often fatal, have been identified in patients treated with adalimumab. Most of the patients had prior infliximab therapy as well as concomitant azathioprine or 6-mercaptopurine used for inflammatory bowel disease. The potential risk with the combination of azathioprine or 6-mercaptopurine and Yuflyma should be carefully considered. The causal association of HSTCL with adalimumab is not clear. A risk for the development of hepatosplenic T-cell lymphoma in patients treated with Yuflyma cannot be excluded.

No studies have been conducted that include patients with a history of malignancy or that continue treatment in patients who develop malignancy while receiving adalimumab. Thus additional caution should be exercised in considering Yuflyma treatment of these patients.

All patients, and in particular patients with a medical history of extensive immunosuppressant therapy or psoriasis patients with a history of PUVA treatment should be examined for the presence of non-melanoma skin cancer prior to and during treatment with Yuflyma. Melanoma and Merkel cell carcinoma have also been reported in patients treated with TNF-antagonists including adalimumab.

Cases of acute and chronic leukemia have been reported in association with postmarketing TNF blocker use in rheumatoid arthritis and other indications. Patients with rheumatoid arthritis may be at a higher risk (up to 2-fold) than the general

population for the development of leukemia, even in the absence of TNF-blocking therapy.

With current data it is not known if adalimumab treatment influences the risk for developing dysplasia or colon cancer. All patient with ulcerative colitis who are at increased risk for dysplasia or colon carcinoma (for example, patients with long-standing ulcerative colitis or primary sclerosing cholangitis), or who had a prior history of dysplasia or colon carcinoma should be screened for dysplasia at regular intervals before therapy and throughout their disease course. This evaluation should include colonoscopy and biopsies per local recommendations.

Allergic
Serious allergic reactions associated with adalimumab were rare during clinical trials. In post-marketing reports, cases of serious allergic reactions including anaphylaxis have been received following adalimumab administration. If an anaphylactic reaction or other serious allergic reaction occurs, administration of Yuflyma should be discontinued immediately and appropriate therapy initiated.

Surgery
There is limited safety experience of surgical procedures in patients treated with adalimumab. The long half-life of adalimumab should be taken into consideration if a surgical procedure is planned. A patient who requires surgery while on Yuflyma should be closely monitored for infections, and appropriate actions should be taken. There is limited safety experience in patients undergoing arthroplasty while receiving adalimumab.

Hematologic Events
Rare reports of pancytopenia including aplastic anemia have been reported with TNF blocking agents. Adverse events of the hematologic system, including medically significant cytopenia (e.g. thrombocytopenia, leukopenia) have been reported with adalimumab. The causal relationship of these reports to adalimumab remains unclear. All patients should be advised to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias (e.g. persistent fever, bruising, bleeding, pallor) while on Yuflyma. Discontinuation of Yuflyma therapy should be considered in patients with confirmed significant hematologic abnormalities.

Concurrent administration of biologic DMARDs or TNF-antagonists
Serious infections were seen in clinical studies with concurrent use of anakinra and another TNF-antagonist, etanercept, with no added clinical benefit compared to etanercept alone. Because of the nature of the adverse events seen with the combination of etanercept and anakinra therapy, similar toxicities may also result from the combination of anakinra and other TNF-antagonists. Therefore, the combination of adalimumab and anakinra is not recommended.

Concomitant administration of adalimumab with other biologic DMARDS (e.g., anakinra and abatacept) or other TNF antagonists is not recommended based upon the possible increased risk for infections and other potential pharmacological interactions.

Immunosuppression
In a study of 64 patients with RA that were treated with adalimumab, there was no evidence of depression of delayed-type hypersensitivity, depression of immunoglobulin levels, or change in enumeration of effector T- and B-cells and NK-cells, monocyte/macrophages, and neutrophils.

Vaccinations
Similar antibody responses to the standard 23-valent pneumococcal vaccine and the influenza trivalent virus vaccination were observed in a study in 226 adult subjects with rheumatoid arthritis who were treated with adalimumab or placebo. No data are available on the secondary transmission of infection by live vaccines in patients receiving vaccination.

It is recommended that pediatric patients, if possible, be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating Yuflyma therapy.

Patients on Yuflyma may receive concurrent vaccinations, except for live vaccines.

Administration of live vaccines to infants exposed to adalimumab in utero is not recommended for 5 months following the mother's last adalimumab injection during pregnancy.

Congestive Heart Failure
Adalimumab has not been formally studied in patients with congestive heart failure (CHF) however, in clinical studies with another TNF antagonist, a higher rate of serious CHF-related adverse events was observed. Cases of worsening CHF have also been reported in patients receiving adalimumab. Physicians should exercise caution when using Yuflyma in patients who have heart failure and monitor them carefully. Yuflyma should be used with caution in patients with mild heart failure (NYHA class I/II). Yuflyma is contraindicated in moderate to severe heart failure (see **CONTRAINDICATIONS**). Treatment with Yuflyma must be discontinued in patients who develop new or worsening symptoms of congestive heart failure.

Autoimmune Processes
Treatment with Yuflyma may result in the formation of autoantibodies, and, rarely, in the development of a lupus-like syndrome. The impact of long-term treatment with adalimumab on the development of autoimmune diseases is unknown. If a patient develops symptoms suggestive of a lupus-like syndrome following treatment with Yuflyma, treatment should be discontinued (see **Adverse Reactions, Autoantibodies**).

Geriatric Use
The frequency of serious infection among adalimumab treated subjects over 65 years of age was higher than for those under 65 years of age. Of the total number of subjects in clinical studies of adalimumab, 9.4% were 65 years and over, while approximately 2.0% were 75 and over. Because there is a higher incidence of infections in the elderly population in general, caution should be used when treating the elderly.

DRUG INTERACTIONS
When adalimumab was administered to 21 RA patients on stable MTX therapy, there were no statistically significant changes in the serum MTX concentration profiles. In contrast, after single and multiple dosing, MTX reduced adalimumab apparent clearances by 29% and 44% respectively. The data do not suggest the need for dose adjustment of either adalimumab or MTX.

Interactions between adalimumab and drugs other than MTX have not been evaluated in formal pharmacokinetic studies. In clinical trials, no interactions have been observed when adalimumab was administered with commonly used DMARDs

(sulfasalazine, hydrochloroquine, leflunomide and parenteral gold), glucocorticoids, salicylates, nonsteroidal anti-inflammatory drugs or analgesics.

Drug/Laboratory Test Interaction
There is no known interference between adalimumab and laboratory tests.

PRE-CLINICAL SAFETY DATA
Preclinical data reveal no special hazard for humans based on studies of single dose toxicity, repeated dose toxicity, and genotoxicity.

Carcinogenesis, Mutagenesis, and Impairment of Fertility
Long-term animal studies of adalimumab have not been conducted to evaluate the carcinogenic potential or its effect on fertility. No clastogenic or mutagenic effects of adalimumab were observed in the in vivo mouse micronucleus test or the Salmonella-Escherichia coli (Ames) assay, respectively.

PREGNANCY AND LACTATION
Pregnancy
An embryo-fetal perinatal developmental toxicity study has been performed in cynomolgus monkeys at dosages up to 100 mg/kg (373 times human AUC when given 40 mg SC) and has revealed no evidence of harm to the fetuses due to adalimumab.

Limited clinical data on pregnant women exposed to adalimumab are available. In a prospective cohort pregnancy exposure registry, 257 women with RA or CD treated with adalimumab at least during the first trimester and 120 women with RA or CD not treated with adalimumab were enrolled.

There were no significant differences in the overall rates for the primary endpoint of major birth defects (adjusted Odds Ratio 0.84, 95% Confidence Interval (CI) 0.34, 2.05) as well as the secondary endpoints which included minor birth defects, spontaneous abortion, preterm delivery, low birth weight, and serious or opportunistic infections. No stillbirths or malignancies were reported.

Although the registry has methodological limitations, including small sample size and non-randomized study design, the data show no increased risk of adverse pregnancy outcomes in women with RA or CD treated with adalimumab in comparison to women with RA or CD not treated with adalimumab. In addition, data from post-marketing surveillance does not establish the presence of a drug-associated risk. Even then, there are no adequate and well-controlled studies in pregnant women and therefore Yuflyma should only be used during pregnancy if clearly needed.

Adalimumab may cross the placenta into the serum of infants born to women treated with adalimumab during pregnancy. Consequently, these infants may be at increased risk for infection. Administration of live vaccines to infants exposed to adalimumab in utero is not recommended for 5 months following the mother's last adalimumab injection during pregnancy.

Women of child-bearing potential should be advised not to get pregnant during Yuflyma therapy.

Labor and Delivery
There are no known effects of Yuflyma on labor or delivery.

Nursing Mothers
Limited information from the published literature indicates that adalimumab is excreted in breast milk at very low concentrations with the presence of adalimumab in human milk at concentrations of 0.1% to 1% of the maternal serum level. Given orally ingested immunoglobulin G proteins undergo intestinal proteolysis and have poor bioavailability, systemic effects of adalimumab in a breast fed infant are unlikely. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for adalimumab and any potential adverse effects on the breastfed child from adalimumab or from the underlying maternal condition.

ADVERSE REACTIONS

Clinical Trials
Adalimumab was studied in 9506 patients in pivotal controlled and open label trials for up to 60 months or more. These trials included rheumatoid arthritis patients with short term and long term disease, juvenile idiopathic arthritis (polyarticular juvenile idiopathic arthritis and enthesitis-related arthritis) as well as psoriatic arthritis, axial spondyloarthritis (ankylosing spondylitis and non-radiographic axial spondyloarthritis), Crohn's disease, ulcerative colitis, psoriasis, hidradenitis suppurativa and uveitis patients. The controlled pivotal studies involved 6089 patients receiving adalimumab and 3801 patients receiving placebo or active comparator during the controlled period.

The proportion of patients who discontinued treatment due to adverse events during the double-blind, controlled portion of pivotal studies was 5.9% for patients taking adalimumab and 5.4% for control treated patients. Overall discontinuation rates in the RA trials were 12.7% for patients taking adalimumab and 16.8% for placebo treated patients. The most common reasons in the RA trials for discontinuation with adalimumab were adverse events (6.6%), lack of efficacy (2.4%) and withdrawal of consent (1.9%).
Approximately 13% of patients can be expected to experience injection site reactions, based on one of the most common adverse events with adalimumab in controlled clinical studies.

Adverse events at least possibly causally-related to adalimumab, both clinical and laboratory, are displayed by system organ class and frequency (very common ≥1/10; common ≥1/100 to <1/10; uncommon ≥1/1000 to <1/100; rare ≥ 1/10,000 to <1/1000) in Table 29 below. The highest frequency seen among the various indications has been included. An asterisk (*) appears in the SOC column if further information is found elsewhere in sections **CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS** and **ADVERSE REACTIONS**.

Table 33: Adverse Reactions in Clinical Studies		
System Organ Class	**Frequency**	**Adverse Reaction**

Infections and infestations*	Very Common	respiratory tract infections (including lower and upper respiratory tract infection, pneumonia, sinusitis, pharyngitis, nasopharyngitis and pneumonia herpes viral)
	Common	systemic infections (including sepsis, candidiasis and influenza), intestinal infections (including gastroenteritis viral), skin and soft tissue infections (including paronychia, cellulitis, impetigo, necrotizing fasciitis and herpes zoster), ear infections, oral infections (including herpes simplex, oral herpes and tooth infections), reproductive tract infections (including vulvovaginal mycotic infection), urinary tract infections (including pyelonephritis), fungal infections, joint infections
	Uncommon	opportunistic infections and tuberculosis (including coccidioidomycosis, histoplasmosis and mycobacterium avum complex infection), neurological infections (including viral meningitis), eye infections, bacterial infections
Neoplasms benign, malignant and unspecified (including cysts and polyps)*	Common	benign neoplasm, skin cancer excluding melanoma (including basal cell carcinoma and squamous cell carcinoma)
	Uncommon	lymphoma**, solid organ neoplasms (including breast cancer, lung neoplasm and thyroid neoplasm), melanoma**
Blood and the lymphatic system disorders*	Very Common	leucopenia (including neutropenia and agranulocytosis), anemia
	Common	thrombocytopenia, leucocytosis
	Uncommon	idiopathic thrombocytopenic purpura
	Rare	pancytopenia
Immune system disorders*	Common	hypersensitivity*, allergies (including seasonal allergy)
Metabolism and nutrition disorders	Very Common	lipids increased
	Common	hypokalemia, uric acid increased, blood sodium abnormal, hypocalcemia, hyperglycemia, hypophosphotemia, dehydration
Psychiatric disorders	Common	mood alterations (including depression), anxiety, insomnia
Nervous system disorders*	Very Common	headache
	Common	paraesthesias (including hypoesthesia) migraine, nerve root compression
	Uncommon	tremor, neuropathy
	Rare	multiple sclerosis
Eye disorders	Common	visual impairment, conjunctivitis, blepharitis, eye swelling
	Uncommon	diplopia
Ear and labyrinth disorders	Common	vertigo
	Uncommon	deafness, tinnitus
Cardiac disorders*	Common	tachycardia
	Uncommon	arrhythmia, congestive heart failure
	Rare	cardiac arrest
Vascular disorders	Common	Hypertension, flushing, haematoma
	Uncommon	vascular arterial occlusion, thrombophlebitis, aortic aneurysm
Respiratory, thoracic and mediastinal disorders*	Common	cough, asthma, dyspnoea
	Uncommon	chronic obstructive pulmonary disease, interstitial lung disease, pneumonitis
Gastrointestinal disorders	Very Common	abdominal pain, nausea and vomiting
	Common	GI hemorrhage, dyspepsia, gastroesophageal reflux disease, sicca syndrome
	Uncommon	pancreatitis, dysphagia, face edema
Hepato-biliary disorders*	Very Common	liver enzymes elevated
	Uncommon	cholecystitis and cholelithiasis, bilirubin increased, hepatic steatosis
Skin and subcutaneous tissue disorders	Very Common	rash (including exfoliative rash)
	Common	pruritis, urticaria, bruising (including purpura), dermatitis (including eczema), onychoclasis, hyperhydrosis
	Uncommon	night sweats, scar

Musculoskeletal and connective tissue disorders	Very Common Common Uncommon	musculoskeletal pain muscle spasms (including blood creatinine phosphokinase increased) rhabdomyolysis, systemic lupus erythematosus
Renal and urinary disorders	Common Uncommon	haematuria, renal impairment nocturia
Reproductive system and breast disorders	Uncommon	erectile dysfunction
General disorders and administration site conditions*	Very Common Common Uncommon	injection site reaction (including injection site erythema) chest pain, edema inflammation
Investigations	Common	coagulation and bleeding disorders (including activated partial thromboplastin time prolonged), autoantibody tests positive (including double stranded DNA antibody), blood lactate dehydrogenase increased
Injury, poisoning and procedural complications*	Common	impaired healing

* Further information found in CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS.
** Includes open label extension studies

Hidradenitis Suppurativa
The safety profile for patients with hidradenitis suppurativa treated with adalimumab weekly was consistent with the known safety profile of adalimumab.

Uveitis
The safety profile for patients with non-infectious uveitis treated with adalimumab was consistent with the known safety profile of adalimumab.

Pediatric Population
In general, the adverse reactions in pediatric patients were similar in frequency and type to those seen in adult patients.

Injection Site Reactions
In the pivotal controlled trials in adults and children, 12.9% of patients treated with adalimumab developed injection site reactions (erythema and/or itching, hemorrhage, pain or swelling), compared to 7.2% of patients receiving control treatment. Most injection site reactions were described as mild and generally did not necessitate drug discontinuation.

Infections
In the pivotal controlled trials in adults and children, the rate of infection was 1.51 per patient year in the adalimumab treated patients and 1.46 per patient year in the control-treated patients. The incidence of serious infections was 0.04 per patient year in adalimumab treated patients and 0.03 per patient year in control-treated patients. The infections consisted primarily of nasopharyngitis, upper respiratory tract infections and sinusitis. Most patients continued on adalimumab after the infection resolved.

In the controlled and open label adult and pediatric studies with adalimumab, serious infections (including fatal infections, which occurred rarely) have been reported, which include reports of tuberculosis (including miliary and extrapulmonary locations) and invasive opportunistic infections (e.g., disseminated histoplasmosis, pneumocystis carinii pneumonia, aspergillosis and listeriosis). Most of the cases of tuberculosis occurred within the first eight months after initiation of therapy and may reflect recrudescence of latent disease.

Malignancies and Lymphoproliferative Disorders
No malignancies were observed in 249 pediatric patients with an exposure of 655.6 patient-years during adalimumab trials in patients with juvenile idiopathic arthritis (polyarticular juvenile idiopathic arthritis and enthesitis-related arthritis).

In addition, no malignancies were observed in 192 pediatric patients with an exposure of 498.1 patient years during an adalimumab trial in pediatric patients with Crohn's disease.

No malignancies were observed in 77 pediatric patients with an exposure of 80.0 patient years during an adalimumab trial in pediatric patients with plaque psoriasis.

No malignancies were observed in 60 pediatric patients with an exposure of 58.4 patient years during an adalimumab trial in pediatric patients with uveitis.

No malignancies were observed in 93 pediatric patients with an exposure of 65.3 patient years during an adalimumab trial in pediatric patients with ulcerative colitis.

During the controlled portions of pivotal adalimumab trials in adults at least 12 weeks in duration in patients with moderately to severely active rheumatoid arthritis, psoriatic arthritis, axial spondyloarthritis (ankylosing spondylitis and non-radiographic axial spondyloarthritis), Crohn's disease, ulcerative colitis, hidradenitis suppurativa, psoriasis and uveitis, malignancies, other than lymphoma and non-melanoma skin cancer, were observed at a rate (95% confidence interval) of 6.8 (4.4, 10.5) per 1000 patient-years among 5291 adalimumab treated patients versus a rate of 6.3 (3.4, 11.8) per 1000 patient-years among 3444 control patients (median duration of treatment was 4.0 months for adalimumab and 3.8 months for control-treated patients.

The rate (95% confidence interval) of non-melanoma skin cancers was 8.8 (6.0, 13.0) per 1000 patient-years among adalimumab- treated patients and 3.2 (1.3, 7.6) per 1000 patient-years among control patients. Of these skin cancers, squamous cell carcinomas occurred at rates (95% confidence interval) of 2.7 (1.4, 5.4) per 1000 patient-years among adalimumab-treated patients and 0.6 (0.1, 4.5) per 1000 patient-years among control patients.

The rate (95% confidence interval) of lymphomas was 0.7 (0.2, 2.7) per 1000 patient-years among adalimumab-treated patients and 0.6 (0.1, 4.5) per 1000 patient-years among control patients.

The observed rate of malignancies, other than lymphoma and non-melanoma skin cancers, is approximately 8.5 per 1000 patient years in the controlled portion of clinical trials and in ongoing and completed open label extension studies. The observed rate of non-melanoma skin cancers is approximately 9.6 per 1000 patient years, and the observed rate of lymphomas is approximately 1.3 per 1000 patient years. The median duration of these studies is approximately 3.3 years and included 6427 patients who were on adalimumab for at least 1 year or who developed a malignancy within a year of starting therapy, representing over 26439.6 patient years of therapy.

In post-marketing experience from January 2003 to December 2010, predominately in patients with rheumatoid arthritis, the reported rate of malignancies is approximately 2.7 per 1000 patient years. The reported rates for non-melanoma skin cancers and lymphomas are approximately 0.2 and 0.3 per 1000 patient years, respectively.

Rare post-marketing cases of hepatosplenic T-cell lymphoma have been reported in patients treated with adalimumab (see **WARNINGS AND PRECAUTIONS**).

Autoantibodies
Patients had serum samples tested for autoantibodies at multiple time points in RA Studies I−V. In these adequate and well-controlled trials, 11.9% of patients treated with adalimumab and 8.1% of placebo and active control−treated patients that had negative baseline anti-nuclear antibody titers reported positive titers at week 24.

Two patients out of 3989 treated with adalimumab in all RA, PsA and AS studies developed clinical signs suggestive of new-onset lupus-like syndrome. The patients improved following discontinuation of therapy. No patients developed lupus nephritis or central nervous system symptoms. The impact of long-term treatment with adalimumab on the development of autoimmune diseases is unknown.

Psoriasis: New onset and Worsening
Cases of new onset psoriasis, including pustular psoriasis and palmoplantar psoriasis, and cases of worsening of pre-existing psoriasis have been reported with the use of TNF blockers, including adalimumab. Many of these patients were taking concomitant immunosuppresants (e.g. MTX, corticosteroids). Some of these patients required hospitalization. Most patients had improvement of their psoriasis following discontinuation of their TNF blocker. Some patients have had recurrences of the psoriasis when they were re-challenged with a different TNF blocker. Discontinuation of adalimumab should be considered for severe cases and those that do not improve or that worsen despite topical treatments.

Liver Enzyme Elevations
In controlled Phase 3 trials of adalimumab (40 mg SC every other week), in patients with RA and PsA with a control period duration ranging from 4 to 104 weeks, ALT elevations ≥ 3 x ULN occurred in 3.7% of adalimumab -treated patients and 1.6% of control- treated patients. Since many of the patients in these trials were also taking medications that cause liver enzyme elevations (e.g. NSAIDS, MTX), the relationship between adalimumab and the liver enzyme elevations is not clear. In controlled Phase 3 trials of adalimumab (initial doses of 160 mg and 80 mg, or 80 mg and 40 mg on Days 1 and 15, respectively, followed by 40 mg every other week), in patients with Crohn's disease with a control period duration ranging from 4 to 52 weeks. ALT elevations ≥ 3 x ULN occurred in 0.9% of adalimumab-treated patients and 0.9% of control-treated patients. In controlled Phase 3 trials of adalimumab (initial doses of 160 mg and 80 mg on Days 1 and 15 respectively, followed by 40 mg every other week), patients with ulcerative colitis with a control period duration ranging from 1 to 52 weeks, ALT elevations ≥ 3 x ULN occurred in 1.5% of a dalimumab -treated patients and 1.0% of control-treated patients. In controlled Phase 3 trials of adalimumab (initial dose of 80 mg then 40 mg every other week), in patients treated with plaque psoriasis with a control period duration ranging from 12 to 24 weeks. ALT elevations ≥ 3 x ULN occurred in 1.8% of adalimumab -treated patients and 1.8% of control-treated patients.

In controlled trials of adalimumab (initial doses of 160 mg at Week 0 and 80 mg at Week 2, followed by 40 mg every week starting at Week 4), in patients with hidradenitis suppurativa with a control period duration ranging from 12 to 16 weeks, ALT elevations ≥ 3 x ULN occurred in 0.3% of adalimumab -treated patients and 0.6% of control-treated patients.

In controlled Phase 3 trials of adalimumab (40 mg every other week), in patients with ankylosing spondylitis with a control period of 12 to 24 weeks, ALT elevations ≥ 3 x ULN occurred in 2.44% of adalimumab-treated patients and 0.66% of control-treated patients.

In controlled Phase 3 trials of adalimumab in patients with polyarticular juvenile idiopathic arthritis who were 4 to 17 years and enthesitis-related arthritis who were 6 to 17 years, ALT elevations ≥ 3 x ULN occurred in 6.1% of adalimumab -treated patients and 1.3% of control-treated patients. Most ALT elevations occurred with concomitant methotrexate use. No ALT elevations ≥ 3 x ULN occurred in the Phase 3 trial of adalimumab in patients with polyarticular juvenile idiopathic arthritis who were 2 to <4 years.

In the Phase 3 trial of adalimumab in patients with pediatric Crohn's disease which evaluated efficacy and safety of two body weight adjusted maintenance dose regimens following body weight adjusted induction therapy up to 52 weeks of treatment, ALT elevations ≥ 3 X ULN occurred in 2.6% (5/192) of patients, of whom 4 were receiving concomitant immunosuppressants at baseline.

In controlled trials of adalimumab (initial doses of 80 mg at Week 0 followed by 40 mg every other week starting at Week 1) in patients with uveitis with an exposure of 165.4 PYs and 119.8 PYs in adalimumab-treated and control-treated patients, respectively, ALT elevations ≥ 3 x ULN occurred in 2.4% of adalimumab-treated patients and 2.4% of control-treated patients.

In the controlled Phase 3 trial of adalimumab in patients with pediatric ulcerative colitis (N=93) which evaluated efficacy and safety of a maintenance dose of 0.6 mg/kg (maximum of 40 mg) every other week (N=31) and a maintenance dose of 0.6 mg/kg (maximum of 40 mg) every week (N=32), following body weight adjusted induction dosing of 2.4 mg/kg (maximum of 160 mg) at Week 0 and Week 1, and 1.2 mg/kg (maximum of 80 mg) at Week 2 (N=63), or an induction dose of 2.4 mg/kg (maximum of 160 mg) at Week 0, placebo at Week 1, and 1.2 mg/kg (maximum of 80 mg) at Week 2 (N=30), ALT elevations ≥ 3 X ULN occurred in 1.1% (1/93) of patients.

No ALT elevations ≥ 3 X ULN occurred in the Phase 3 trial of adalimumab in pediatric patients with plaque psoriasis.

Across all indications in clinical trials patients with raised ALT were asymptomatic and in most cases elevations were transient and resolved on continued treatment. However, there have been very rare postmarketing reports of severe hepatic reactions including liver failure in patients receiving TNF blockers, including adalimumab. The causal relationship to adalimumab treatment remains unclear.

Concurrent Treatment with Azathioprine/6-Mercaptopurine
In adult Crohn's disease studies, higher incidences of malignant and serious infection-related adverse events were seen with the combination of adalimumab and azathioprine/6-mercaptopurine compared with adalimumab alone.

Additional Adverse Reactions from Postmarketing Surveillance or Phase IV Clinical Trials
Adverse events have been reported during post-approval use of adalimumab. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to adalimumab exposure.

Table 34: Additional Adverse Reactions from Postmarketing Surveillance or Phase IV Clinical Trials

Infections and infestations	Diverticulitis
Neoplasms benign, malignant and unspecified (including cysts and polyps)*	Hepatosplenic T-cell lymphoma, leukemia, Merkel Cell Carcinoma (neuroendocrine carcinoma of the skin)
Immune system disorders*	Anaphylaxis, angioneurotic edema, sarcoidosis
Nervous system disorders*	Demyelinating disorders (e.g. optic neuritis, Guillain-Barré syndrome), cerebrovascular accident
Respiratory, thoracic and mediastinal disorders	Pulmonary embolism, pleural effusion, pulmonary fibrosis
Hepatobiliary disorders*	Reactivation of hepatitis B, liver failure, hepatitis, autoimmune hepatitis
Gastrointestinal disorders*	Intestinal perforation
Skin and subcutaneous tissue disorders	Stevens-Johnson syndrome, angioedema, new onset or worsening of psoriasis (including palmoplantar pustular psoriasis), cutaneous vasculitis, erythema multiforme, alopecia, lichenoid skin reaction**
Musculoskeletal and connective tissue disorders	Lupus-like syndrome
Cardiac disorders	Myocardial infarction
General disorders and administration site conditions	Pyrexia
* further information is found in CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS. ** occurring in patients receiving a TNF-antagonist including adalimumab	

INCOMPATIBILITIES
There are no known reports of any incompatibilities.

OVERDOSAGE
The maximum tolerated dose of adalimumab has not been established in humans. No dose-limiting toxicities have been observed during clinical trials with adalimumab. Multiple doses up to 10 mg/kg have been administered to patients in clinical trials without evidence of dose-limiting toxicities. In case of overdosage, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions or effects and appropriate symptomatic treatment instituted immediately.

DOSAGE AND ADMINISTRATION

ADULTS

Rheumatoid Arthritis, Psoriatic Arthritis and Ankylosing Spondylitis
The recommended dose of Yuflyma for adult patients with rheumatoid arthritis, psoriatic arthritis, or ankylosing spondylitis is 40 mg administered every other week as a single dose via subcutaneous injection. Methotrexate, glucocorticoids, salicylates, nonsteroidal anti-inflammatory drugs, analgesics or other DMARDs may be continued during treatment with Yuflyma.

In rheumatoid arthritis, some patients not taking concomitant MTX may derive additional benefit from increasing the dosage of Yuflyma to 40 mg every week or 80 mg every other week.

Crohn's Disease

	Dose	Frequency
Induction	80mg	Initial dose (Day 0)
	40mg	Second dose (Day 14)
Maintenance	40mg	Starting Day 28 and continuing fortnightly

In case there is a need for a more rapid response to therapy, the regimen 160 mg at week 0 (given as 160 mg in one day or as 80 mg per day for two consecutive days), 80 mg at week 2, can be used with the awareness that the risk for adverse events is higher during induction.

Some patients who experience a decrease in their response may benefit from an increase in dosage to 40 mg Yuflyma every week or 80mg every other week.

Aminosalicylates, corticosteroids, and/or immunomodulatory agents (e.g., 6-mercaptopurine and azathioprine) may be continued during treatment with Yuflyma.

Patients usually respond within the induction phase. However, if a patient does not show any response, available data do not sufficiently support further Yuflyma treatment.

Ulcerative Colitis
The recommended Yuflyma induction dose regimen for adult patients with moderate to severe ulcerative colitis is 160 mg at Week 0 (given as 160 mg in one day or as 80 mg per day for two consecutive days) and 80 mg at Week 2. After induction treatment, the recommended dose is 40 mg every other week via subcutaneous injection. Aminosalicylates, corticosteroids, and/or immunomodulatory agents (e.g., 6-mercaptopurine and azathioprine) may be continued during treatment with Yuflyma.

During maintenance treatment, corticosteroids may be tapered in accordance with clinical practice guidelines.

Some patients who experience decrease in their response may benefit from an increase in dosage to 40 mg Yuflyma every week or 80 mg every other week.

Available data suggest that clinical response is usually achieved within 2-8 weeks of treatment. Adalimumab should only be continued in patients who have responded during the first 8 weeks of therapy.

Plaque Psoriasis
The recommended dose of Yuflyma for adult patients with plaque psoriasis is an initial dose of 80 mg, followed by 40 mg given every other week starting one week after the initial dose. Continued therapy beyond 16 weeks should be carefully reconsidered in a patient not responding within this time period.

Beyond 16 weeks, patients with inadequate response may benefit from an increase in dosage to 40 mg every week or 80 mg every other week. Response should be periodically evaluated (for example, every 12 weeks). Patients with continued inadequate response should discontinue treatment. If an adequate response is achieved with an increased dosage, the dose may subsequently be reduced to 40mg fortnightly.

Hidradenitis Suppurativa
The recommended Yuflyma dose regimen for adult patients with hidradenitis suppurativa (HS) is 160 mg initially at Day 1 (given as 160 mg in one day or as 80 mg per day for two consecutive days), followed by 80 mg two weeks later at Day 15. Two weeks later (Day 29) continue with a dose of 40 mg every week or 80 mg every other week. Antibiotics may be continued during treatment with Yuflyma if necessary. It is recommended that the patient should use a topical antiseptic wash on their HS lesions on a daily basis during treatment with Yuflyma.

Should treatment need to be interrupted, Yuflyma 40 mg every week may be re-introduced.

In patients without any benefit after 12 weeks of treatment, continued therapy should be reconsidered.

Uveitis
Ophthalmologists are advised to consult with an appropriate specialist before initiation of treatment with Yuflyma.

The recommended dose of Yuflyma for adult patients with uveitis is an initial dose of 80 mg, followed by 40 mg given every other week starting one week after the initial dose. There is limited experience in the initiation of treatment with Yuflyma alone. Treatment with Yuflyma can be initiated in combination with corticosteroids and/or with other non-biologic immunomodulatory agents. Concomitant corticosteroids may be tapered in accordance with clinical practice starting two weeks after initiating treatment with Yuflyma.

It is recommended that the benefit and risk of continued long-term treatment should be evaluated on a yearly basis.

PEDIATRICS
Juvenile Idiopathic Arthritis

Polyarticular Juvenile Idiopathic Arthritis

The recommended dose of Yuflyma for patients from 2 years of age with polyarticular juvenile idiopathic arthritis (JIA) is based on body weight (Table 35). MTX, glucocorticoids, NSAIDs, and/or analgesics may be continued during treatment with Yuflyma.

Table 35: Yuflyma Dose for Patients with Polyarticular Juvenile Idiopathic Arthritis

Patient Weight	Dosing Regimen
10 kg to < 30 kg	-
≥ 30 kg	40 mg every other week

Note: Yuflyma is only available as 40 mg pre-filled pen. Thus, it is not possible to administer Yuflyma to patients that require less than a full 40 mg dose. If an alternate dose is required, other adalimumab products offering such an option should be used.

Yuflyma has not been studied in patients with polyarticular juvenile idiopathic arthritis less than 2 years of age or in patients with a weight below 10kg.

Available data suggest that clinical response is usually achieved within 12 weeks of treatment. Continued therapy should be carefully reconsidered in a patient not responding within this time period.

There is no relevant use of Yuflyma in children aged less than 2 years in this indication.

Enthesitis-Related Arthritis
The recommended dose of Yuflyma for patients from 6 years of age with enthesitis-related arthritis is based on body weight (Table 36).

Table 36: Adalimumab Dose for Patients with Enthesitis-Related Arthritis

Patient Weight	Dosing Regimen
15 kg to < 30 kg	-
≥ 30 kg	40 mg every other week

Note: Yuflyma is only available as 40 mg pre-filled pen. Thus, it is not possible to administer Yuflyma to patients that require less than a full 40 mg dose. If an alternate dose is required, other adalimumab products offering such an option should be used.

Yuflyma has not been studied in patients with enthesitis-related arthritis aged less than 6 years.

Pediatric Crohn's Disease
The recommended dose of Yuflyma for patients from 6 to 17 years of age with Crohn's disease is based on body weight (Table 37). Yuflyma is administered via subcutaneous injection.

Table 37: Yuflyma Dose for Pediatric Patients with Crohn's disease

Patient Weight	Induction Dose	Maintenance Dose Starting at Week 4
≥ 40 kg	• 80 mg at week 0 and 40 mg at week 2 In case there is a need for a more rapid response to therapy with the awareness that the risk for adverse events may be higher with use of the higher induction dose, the following dose may be used: • 160 mg at week 0 and 80 mg at week 2	40 mg every other week

Patients who experience insufficient response may benefit from an increase in dosage:
- ≥ 40 kg: 40 mg every week or 80mg every other week

Note: Yuflyma is only available as 40 mg pre-filled pen. Thus, it is not possible to administer Yuflyma to patients that require less than a full 40 mg dose. If an alternate dose is required, other adalimumab products offering such an option should be used.

Adalimumab has not been studied in children with Crohn's disease aged less than 6 years.

Pediatric Plaque Psoriasis
The recommended Yuflyma dose for patients from 4 to 17 years of age with plaque psoriasis is based on body weight (Table 38). Yuflyma is administered via subcutaneous injection.

Table 38. Yuflyma Dose for Paediatric Patients with Plaque Psoriasis

Patient Weight	Dosing Regimen
15 kg to < 30 kg	-
≥ 30 kg	Initial dose of 40 mg, followed by 40 mg given every other week starting one week after the initial dose

Note: Yuflyma is only available as 40 mg pre-filled pen. Thus, it is not possible to administer Yuflyma to patients that require less than a full 40 mg dose. If an alternate dose is required, other adalimumab products offering such an option should be used.

Continued therapy beyond 16 weeks should be carefully considered in a patient not responding within this time period. If retreatment with Yuflyma is indicated, the above guidance on dose and treatment duration should be followed.

There is no relevant use of Yuflyma in children aged less than 4 years in this indication.

Adolescent hidradenitis suppurativa
There are no clinical trials with Yuflyma in adolescent patients with hidradenitis suppurativa (HS). The posology of Yuflyma in these patients has been determined from pharmacokinetic modeling and simulation.

The recommended Yuflyma dose in adolescent patients from 12 years of age weighing at least 30 kg with hidradenitis suppurativa is 80 mg at Week 0 followed by 40 mg every other week starting at Week 1 via subcutaneous injection.

In adolescent patients with inadequate response to Yuflyma 40 mg every other week, an increase in dosage to 40 mg every week or 80 mg every other week may be considered.

Antibiotics may be continued during treatment with Yuflyma if necessary. It is recommended that the patient should use a topical antiseptic wash on their HS lesions on a daily basis during treatment with Yuflyma.

Continued therapy beyond 12 weeks should be carefully reconsidered in a patient with no improvement within this time period. Should treatment be interrupted, Yuflyma may be re-introduced as appropriate.
The benefit and risk of continued long-term treatment should be periodically evaluated. There is no relevant use of Yuflyma in children aged less than 12 years in this indication.

Pediatric Uveitis
The recommended dose of Yuflyma for pediatric patients 2 years of age and older with chronic non-infectious anterior uveitis is based on body weight (Table 39). Yuflyma is administered via subcutaneous injection. In paediatric uveitis, there is no experience in the treatment with Yuflyma without concomitant treatment with methotrexate.

Table 39. Yuflyma Dose for Paediatric Patients with Uveitis

Patient Weight	Dosing Regimen
< 30 kg	-
≥ 30 kg	40 mg every other week in combination with methotrexate

Note: Yuflyma is only available as 40 mg pre-filled pen. Thus, it is not possible to administer Yuflyma to patients that require less than a full 40 mg dose. If an alternate dose is required, other adalimumab products offering such an option should be used.

When Yuflyma is initiated, a loading dose of 40 mg for patients <30 kg or 80 mg for patients ≥30 kg may be administered one week prior to the start of maintenance therapy. No clinical data are available on the use of a Yuflyma loading dose in children < 6 years of age (see section Pharmacokinetics).

There is no relevant use of Yuflyma in children aged less than 2 years in this indication. It is recommended that the benefit and risk of continued long-term treatment should be evaluated on a yearly basis.

Pediatric Ulcerative Colitis
The recommended dose of Yuflyma for patients from 5 to 17 years of age with ulcerative colitis is based on body weight (Table 40). Yuflyma is administered via subcutaneous injection.

Table 40. Yuflyma Dose for Pediatric Ulcerative Colitis

Patient Weight	Induction Dose	Maintenance Dose Starting at Week 4*
< 40 kg	• 80 mg at Week 0 and • 40 mg at Week 2	• 40 mg every other week or • 20 mg every week**
≥ 40 kg	• 160 mg at Week 0 and • 80 mg at Week 2	• 80 mg every other week or • 40 mg every week

* Pediatric patients who turn 18 years of age while on Yuflyma should continue their prescribed maintenance dose.
** Yuflyma is only available as 40 mg pre-filled pen. Thus, it is not possible to administer Yuflyma to patients that require less than a full 40 mg dose. If an alternate dose is required, other adalimumab products offering such an option should be used.

Continued therapy beyond 8 weeks should be carefully considered in patients not showing signs of response within this time period.

There is no relevant use of Yuflyma in children aged less than 5 years in this indication.

Pediatric Use
Adalimumab has not been studied in children less than 2 years of age and there are limited data on adalimumab treatment in children with weight < 10kg. The safety and efficacy of adalimumab in pediatric patients for indications other than juvenile idiopathic arthritis (polyarticular juvenile idiopathic arthritis and enthesitis-related arthritis), pediatric Crohn's disease, pediatric plaque psoriasis, adolescent hidradenitis suppurativa, pediatric uveitis and pediatric ulcerative colitis have not been established.

Geriatric Use
Of the total number of subjects in clinical studies of adalimumab, 9.4% were 65 years and over, while approximately 2.0% were 75 and over. No overall differences in effectiveness were observed between these subjects and younger subjects. No dose adjustment is needed for this population.

Preparation of Yuflyma
Yuflyma is intended for use under the guidance and supervision of a physician. Patients may self-inject Yuflyma if their physician determines that it is appropriate and with medical follow-up, as necessary, after proper training in injection technique.

Sites for self-injection include thigh or abdomen. Injection sites should be rotated. New injections should never be given into areas where the skin is tender, bruised, red or hard.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Yuflyma should not be mixed in the same syringe with any other medicine.

Any unused product or waste material should be disposed of in accordance with local requirements.

STORAGE
Store at 2° C to 8° C (36° F to 46° F) (in a refrigerator) and store the pen in the outer carton in order to protect from light. Do not freeze.

Alternative Storage for Yuflyma 40 mg/0.4 mL:
A Yuflyma pre-filled Pen may be stored at temperatures up to a maximum of 25°C (77°F) for a single period of up to 30 days.
The pre-filled pen must be protected from light, and discarded if not used within the 30-day period.

Do not use beyond the expiration date.

HOW SUPPLIED
Yuflyma solution for injection is supplied as a sterile solution for parenteral administration in the following packaging configurations:

Yuflyma 40 mg per 0.4 mL for injection in a single-use pre-filled Pen:
- Carton containing 2 alcohol pads, each containing 1 pre-filled Pen.
- Carton containing 2 alcohol pads, each containing 2 pre-filled Pens.

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