National PBM Drug Monograph

ABATACEPT (ORENCIA®)

FDA Approved: December 2005

VHA Pharmacy Benefits Management Strategic Healthcare Group and Medical Advisory Panel

The following recommendations are based on current medical evidence and expert opinion from clinicians. The content of the document is dynamic and will be revised as new clinical data becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. The clinician should utilize this guidance and interpret it in the clinical context of the individual patient.

EXECUTIVE SUMMARY

Mode of Action:
The fusion protein abatacept binds to CD80 and CD86 receptors on antigen presenting cells, thereby preventing their interaction with the CD28 receptor on T-cells, which results in an inhibition of T-cell proliferation and cytokine release.

FDA-Approved Indication:
Abatacept is indicated for reducing signs and symptoms, inducing major clinical response, slowing the progression of structural damage, and improving physical function in adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response to ≥1 disease modifying anti-rheumatic drugs (DMARDs), such as methotrexate (MTX) or tumor necrosis factor (TNF) antagonists .

Dosage and Route:
Abatacept should be administered as a 30-minute intravenous infusion according to the specified dose schedule based on weight (500mg for < 60 kg; 750 mg for 60 kg-100 kg; and 1 gram for > 100 kg). After the initial administration, abatacept should be given at 2 and 4 weeks after the first infusion, then every 4 weeks thereafter. Abatacept can be used as monotherapy or in combination with DMARDs *other than TNF antagonists*. Abatacept is not recommended for use concomitantly with anakinra.

Efficacy:
The approval of abatacept was based on data from five clinical trials that suggested clinical activity of abatacept for the treatment of patients with moderately to severely active RA who have had an inadequate response to ≥1 DMARDs, including TNF antagonists. The studies included 3 adequate and well-controlled studies and additional Phase 2 trials. Abatacept demonstrated effects on signs and symptoms of RA, including inducing major clinical response, delaying structural damage, and improving physical function. Four of these trials are published, and one is in abstract form.

Safety:
There was a higher rate of serious infections in patients treated with abatacept, especially with patients receiving concomitant TNF-blocking agents. Overall malignancy rates were not substantially different between abatacept (1.5%) and placebo (1.1%) treated patients. However, abatacept treated patients had more cases of lung cancer and a higher rate of lymphomas when compared to the general US population. Infusion-related reactions were observed including hypersensitivity reactions and 2 cases of anaphylaxis. Patients with chronic obstructive pulmonary disease (COPD) treated with abatacept had a higher incidence of adverse events and serious adverse events, especially respiratory disorders.

Conclusions:
No comparative studies are available comparing abatacept with other DMARDs for the treatment of RA. Therefore, it is difficult to extrapolate superiority of one over the other. Abatacept has demonstrated efficacy in patients with RA that have not responded to DMARDs, including MTX and TNF antagonists. Abatacept can be taken alone or with other DMARDs, except TNF antagonists or anakinra. Evidence shows increased frequency of infections and serious infections with no added clinical benefit when abatacept was combined with a TNF inhibitor. Safety and efficacy of abatacept has not been evaluated in concomitant use with anakinra. Cost of abatacept is higher compared to other biologic agents when dosed for patients less than 60kg and has the potential to increase with higher doses based on patients' weight.

Recommendations:
ABATACEPT should remain a non-formulary agent and be added to the **Criteria for Use.** Use should be reserved for patients refractory to other RA treatment, may not be candidates for the other agents, or unable to tolerate the other agents. Also, there is a potential for dosing variability depending on patient's weight that is associated with a significant cost difference.

INTRODUCTION

The purposes of this monograph are to:

1. Evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating abatacept for possible addition to the VA National Formulary;
2. Define role of abatacept in therapy for rheumatoid arthritis (RA);
3. Identify parameters for rational use of abatacept in the VA.

PHARMACOLOGY/PHARMACOKINETICS [1, 2]

Abatacept is a soluble chimeric protein consisting of the extracellular domain of human CD152 and a fragment (hinge, CH2 and CH3 domains) of the Fc portion of human IgG1. It binds to B7-1 (CD80) and B7-2 (CD86) molecules on antigen presenting cells, thus blocking the CD-28-mediated costimulary signal for T-cell activation.

Parameter	Healthy Subjects (After 10mg/kg Single Dose) N=13	RA Patients (After 10mg/kg Multiple Doses*) N=14
Peak Concentration (Cmax) [mcg/mL]	292 (175-427)	295 (171-398)
Terminal half-life (t1/2) [days]	16.7 (12-23)	13.1 (8-25)
Systemic Clearance (CL) [mL/h/kg]	0.23 (0.16-0.30)	0.22 (0.13-0.47)
Volume of distribution (Vss) [L/kg]	0.09 (0.06-0.13)	0.07 (0.02-0.13)

* Multiple intravenous infusions were administered at days 1, 15, 30, and monthly thereafter.

No systemic accumulation of abatacept occurred after continued repeated administration with 10mg/kg at monthly intervals in RA patients. There was a trend towards higher clearance of abatacept with increasing body weight. Age and gender (when corrected for body weight) did not affect clearance. Concomitant methotrexate (MTX), nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and tumor necrosis factor (TNF) blocking agents did not influence abatacept clearance.

FDA APPROVED INDICATIONS [1]

- For use in adult patients with moderately to severely active RA that have an inadequate response to ≥1 DMARDs, such as MTX or TNF antagonists
  - Reducing signs and symptoms
  - Inducing major clinical response
  - Slowing the progression of structural damage
  - Improving physical function
- For use as monotherapy or combination therapy with DMARDs (other than TNF antagonists)

CURRENT VA NATIONAL FORMULARY ALTERNATIVES

	Infliximab (Remicade®)	Etanercept (Enbrel®)	Anakinra (Kineret®)	Adalimumab (Humira®)	Rituximab (Rituxan®)
Formulary					X – *Restricted to oncology*
Non-formulary	X	X	X	X	

DOSAGE AND ADMINISTRATION [1]

Body Weight of Patient	Dose	Number of Vials*
< 60 kg	500 mg	2
60 – 100 kg	750 mg	3
> 100 kg	1 gram	4

**Each vial provides 250 mg of abatacept for administration.*

Abatacept should be administered as a 30-minute intravenous infusion according to the specified dose schedule based on weight as depicted above.

After the initial administration, abatacept should be given at 2 and 4 weeks after the first infusion, then every 4 weeks thereafter.

Abatacept can be used as monotherapy or in combination with DMARDs other than TNF antagonists.

Abatacept is provided as a lyophilized powder for intravenous infusion in an individually packaged, single-use vial with a silicone-free disposable syringe. The powder must be protected from light and refrigerated at 2º-8º Celsius. The abatacept powder in each vial must be reconstituted with 10mL of Sterile Water for Injection, USP, using ONLY the SILICONE-FREE DISPOSABLE SYRINGE PROVIDED WITH EACH VIAL and an 18-21 gauge needle. The solution may develop translucent particulate matter if accidentally reconstituted with a siliconized syringe.

The infusion of the entire, fully diluted abatacept solution must be completed within 24 hours of reconstitution of the abatacept vials. The fully diluted solution may be stored at room temperature or refrigerated at 2º-8º Celsius before use.

EFFICACY [3, 4, 5, 6, 7]

- **EFFICACY MEASURES**
  Three endpoints addressing clinical outcomes have been validated and used to determine efficacy of abatacept in the treatment of RA in published clinical trials.
  1. The proportion of subjects achieving a >20% improvement in the American College of Rheumatology (ACR) criteria at 6 months, which is defined as:
     - ≥20% improvement in Tender Joint Count
     - ≥20% improvement in Swollen Joint Count
     - ≥20% improvement in 3 of the following 5:
       - Patient pain assessment
       - Patient global assessment
       - Physician global assessment
       - Patient self-assessed disability (disability index of the Health Assessment Questionnaire [HAQ])
       - Acute phase reactant (C-reactive protein [CRP])
  2. Improvement in the Disability Index of the Health Assessment Questionnaire [HAQ] at time of evaluation compared to baseline to assess improvement in physical function.
  3. Radiographic changes per the Genant-modified Sharp method for x-ray scoring, where radiographs of hands, wrists, and feet are scored to assess the amount of change in radiographic damage from baseline and time of evaluation.

- **SUMMARY OF EFFICACY FINDINGS**
  - ***PUBLISHED TRIALS***
    - A dose-finding, placebo-controlled trial evaluated 214 RA patients treated unsuccessfully with at least 1 DMARD, including etanercept. Patients received 4 infusions of abatacept (0.5, 2, or 10mg/kg) on days 1, 15, 29, and 57, and were evaluated on day 85. Patients discontinued any DMARD or etanercept treatment through day 85. ACR 20 responses on day 85 occurred in a dose-dependent manner (23%, 44%, and 53% respectively for 0.5, 2, and 10mg/kg groups) compared to 31% of placebo-treated patients. [3]
    - A 12-month, randomized, double-blind, placebo-controlled study compared 2mg/kg abatacept, 10mg/kg abatacept, or placebo in 339 patients with active RA despite MTX therapy. Patients received concomitant MTX treatment. After 12 months, greater percentages of patients treated with 10mg/kg abatacept compared to placebo achieved ACR 20 (62.6% versus 36.1%), ACR 50 (41.7% versus 20.2%), and ACR 70 (20.9%

versus 7.6%) responses. Patients treated with 10mg/kg of abatacept also had clinically important improvement in HAQ scores compared with placebo (49.6% versus 27.7%). No significant differences in ACR20 responses or improvements in physical function were observed in the 2mg/kg abatacept group compared to placebo. [4]

- A 6-month, randomized, double-blind, placebo-controlled, phase 3 trial compared abatacept 10mg/kg with placebo in patients with active RA that had an inadequate response to TNF inhibitors. Current or former users of TNF inhibitors were washed-out of their TNF therapy prior to randomization. Background DMARDs or anakinra were allowed. After 6 months, greater responses were seen in the abatacept group compared to placebo regarding ACR 20 (50.4% versus 19.5%), ACR 50 (20.3% versus 3.8%), ACR 70 (10.2% versus 1.5%), and clinically meaningful improvements in physical function (47.3% versus 23.3%). [5]
- A 1-year, randomized, double-blind, placebo-controlled, phase 3 trial compared abatacept 10mg/kg with placebo in 652 patients with an inadequate response to MTX. Patients continued treatment with MTX. At 6 months, the mHAQ summary score improved 41% for patients in the abatacept group compared to 14% for patients in the placebo group. At 1 year, greater responses were seen in abatacept-treated patients compared to placebo regarding ACR 20 (73.1% versus 39.7%), ACR 50 (48.3% versus 18.2%), and ACR 70 (28.8% versus 6.1%). [6]

o ***UNPUBLISHED TRIALS***

- The **A**batacept **S**tudy of **S**afety in **U**se with other **R**heumatoid Arthritis Th**E**rapies (ASSURE) trial assessed the safety of abatacept compared to placebo as add-on therapy with one or more non-biologic DMARDs and/or biologic DMARDs in patients with active RA. A total of 1441 patients were treated during 1 year. Improvements from baseline were seen in patient-reported outcomes for abatacept-treated patients, with greatest benefits over placebo occurring in patients receiving non-biologic background DMARDs. [7]

For further details on the efficacy results of the clinical trials, refer to *APPENDIX: CLINICAL TRIALS.*

ADVERSE EVENTS (SAFETY DATA) [7, 8]

Adverse Event	Abatacept (N=1955)[a] Percentage	Placebo (N=989)[b]
Headache	18	13
Nasopharyngitis	12	9
Dizziness	9	7
Cough	8	7
Back Pain	7	6
Hypertension	7	4
Dyspepsia	6	4
Urinary tract infection	6	5
Rash	4	3
Pain in extremity	3	2

[a] Includes 204 patients on concomitant biologic DMARDs (adalimumab, anakinra, etanercept, or infliximab).
[b] Includes 134 patients on concomitant biologic DMARDs (adalimumab, anakinra, etanercept, or infliximab).

- **TOLERABILITY**

	Abatacept (N 1955) % (n)	Placebo (N 989) % (n)
Discontinuations due to SAEs	2.7 (53)	1.6 (16)
Discontinuations due to AEs	5.5 (107)	3.9 (39)
Adverse Events (AEs)	88.8 (1736)	84.9 (840)

- **OVERALL SAFETY**

	Abatacept (N 1955) % (n)	Placebo (N 989) % (n)
Death	0.5 (9)	0.6 (6)
Serious Adverse Events (SAEs)	13.6 (266)	12.3 (122)
Adverse Events (AEs)	88.8 (1736)	84.9 (840)
Most Commonly Reported AEs:		
Headache	18.2 (356)	12.6 (125)
Upper Respiratory Tract Infection	12.7 (248)	12.0 (119)
Nausea	11.5 (224)	10.6 (105)
Nasopharyngitis	11.5 (225)	9.1 (90)
Most Seriously Reported AEs:		
Infection	53.8 (1051)	48.3 (478)
Serious Infection	3.0 (58)	1.9 (19)
Malignant Neoplasms	1.2 (24)	1.0 (10)

- **SAFETY SPLIT BY BACKGROUND THERAPY**

	Abatacept + biologic background therapy (N=204) %(n)	Placebo + biologic background therapy (N=134) %(n)	Abatacept + non biologic background therapy (N=1755) %(n)	Placebo + non biologic background therapy (N=855) %(n)
SAEs	19.6 (40)	9.0 (12)	12.9 (226)	12.9 (110)
AEs	94.1 (192)	84.3 (113)	88.2 (1544)	85.0 (727)
Infections	63.7 (130)	43.3 (58)	52.6 (921)	49.1 (420)
Serious Infections	4.4 (9)	1.5 (2)	2.8 (49)	2.0 (17)

- **INFUSION RELATED REACTIONS AND HYPERSENSITIVITY REACTIONS**
  - Acute infusion reactions within 1 hour post-infusion
    - 9% abatacept-treated patients vs. 6% placebo-treated patients
    - Most frequently reported events (1-2%)
      - Dizziness
      - Headache
      - Hypertension
  - Less commonly reported events (>0.1% and ≤1%)
    - Cardiopulmonary symptoms (hypotension, increased blood pressure, dyspnea)
    - Other symptoms (nausea, flushing, urticaria, cough, hypersensitivity, pruritis, rash, and wheezing)
  - Fewer than 1% of abatacept-treated patients discontinued due to an acute infusion-related event
  - Anaphylaxis – 2 cases in patients receiving abatacept

For further details on the safety results of the clinical trials, refer to *APPENDIX: CLINICAL TRIALS.*

PRECAUTIONS/CONTRAINDICATIONS [1]

- **PRECAUTIONS**
  - Concomitant use with TNF antagonists – greater risk of infection with no demonstrated enhancement of efficacy
  - Live vaccines should not be given concurrently with abatacept or within 3 months of its discontinuation – may blunt the effectiveness of some immunizations

- New infections, malignancies – potential to exacerbate as T cells mediate their response
- History of recurrent infections, underlying conditions which may predispose to infections, or chronic, latent, or localized infections – exacerbation of infection
- Patients should be screened for latent tuberculosis infection with a tuberculin skin test – safety of abatacept in individuals with latent tuberculosis infection is unknown
- Monitor COPD patients for worsening of their respiratory status – COPD patients treated with abatacept developed adverse events more frequently than those treated with placebo, including COPD exacerbations, cough, rhonchi, and dyspnea.
- The frequency of serious infection and malignancy among abatacept-treated patients over age 65 was higher than for those under age 65.
- Pregnancy Category C
- Nursing mothers – animal studies show abatacept present in rat milk.

- **CONTRAINDICATIONS**
  - Hypersensitivity to abatacept or any of its components

LOOK-ALIKE/SOUND-ALIKE ERROR RISK POTENTIAL

The VA PBM and Center for Medication Safety is conducting a pilot program which queries a multi-attribute drug product search engine for similar sounding and appearing drug names based on orthographic and phonologic similarities, as well as similarities in dosage form, strength, and route of administration. Based on similarity scores and clinical judgment, the following drug names may be potential sources of drug name confusion:

LA/SA for abatacept	LA/SA for Orencia®
Aricept®	Aredia®
Abelcet®	Oretic®
Alefacept	Iressa®
Atrosept®	Auranofin
Etanercept	Orfro®
	Anexsia®

DRUG INTERACTIONS [1]

- No formal drug interaction studies have been conducted with abatacept.
- MTX, NSAIDs, corticosteroids, and TNF blocking agents did not influence abatacept clearance.
- Concomitant administration of a TNF antagonist with abatacept ahs been associated with an increased risk of serious infections and no significant additional efficacy over use of the TNF antagonists alone.
- Concurrent use with anakinra is not recommended due to insufficient experience to assess safety and efficacy.
- Live vaccines should not be given concurrently with abatacept or within 3 months of its discontinuation.

PHARMACOECONOMIC ANALYSIS

No data exists in the published literature regarding the pharmacoeconomics of abatacept.

For further details on the pharmacoeconomic analyses of other biologic agents, refer to *CRITERIA FOR USE FOR LEFLUNOMIDE AND THE BIOLOGIC DMARDs IN THE TREATMENT OF MODERATE TO SEVERE RA.*

ACQUISITION COSTS

**** Costs as reported below reflect current pricing only. Please refer to the PBM website (vaww.pbm.med.va.gov or www.vapbm.org) for updated cost information.***

Product	Dose	Schedule	Cost/Dispensing Unit	Cost/ Patient /Year ($)
Abatacept ◊ (Orencia ®)	500mg (<60 kg) 750mg (60-100 kg) 1 gram (>100 kg)	Once every 4 weeks	$336.84/15ml vial (250mg/15ml vial)	<60 kg: $10,105.20 60-100kg: $15,157.80 >100kg: $20,210.40
Rituximab (Rituxan ®)	1000mg	IV infusions twice, 2 weeks apart	$1,646.28/50ml vial (10mg/ml Inj, 50 ml vial)	$6,585.12
Adalimumab (Humira®)	40 mg	Every other week	$687.74/2 single-use syringes (40mg/1ml syringe)	$8,940.62
Adalimumab (Humira®)	40 mg	Weekly	$687.74/2 single-use syringes (40mg/1ml syringe)	$17,881.24
Anakinra (Kineret®)	100 mg	Once daily	$824.44/28 single-use syringes (100mg/1ml syringe)	$10,717.72
Etanercept (Enbrel®)	25mg	Twice weekly	$360.06/4 SDV (25mg/vial)	$9,361.56
Etanercept (Enbrel®)	50mg	Once weekly	$720.12/4 SDV (50mg/vial)	$9,361.56
Infliximab (Remicade®) ‡	3 mg/kg	Once every 8 weeks	$392.81/20ml vial (100mg/20ml vial)	<70kg $7,070.58 - $10,605.87 >70kg $10,605.87 - $14,141.16
Infliximab (Remicade®)‡	10 mg/kg	Once every 8 weeks	$392.81/20ml vial (100mg/20ml vial)	<70kg $21,211.74 - $24,747.03 >70kg $24,747.03 - $28,282.32
Leflunomide (Arava®)	100 mg; 20mg	Once daily for 3 days (loading dose); Once daily	$169.96/ 30 tablets (20mg/tablet)	$2,147.16
Leflunomide (Arava®)	10 mg	Once daily (not including loading dose)	$170.06/30 tablets (10mg/tablet)	$2,063.39
Leflunomide (Generic)	100 mg; 20mg	Once daily for 3 days (loading dose); Once daily	$ 43.00/ 30 tablets (20mg/tablet)	$543.23
Leflunomide (Generic)	10 mg	Once daily (not including loading dose)	$43.00/30 tablets (10mg/tablet)	$521.73
Methotrexate †	25 mg	Weekly	$0.16 - $0.70 per tablet (2.5 mg tabs)	$83.20 - $364.00

SDV = single dose vials

◊ Costs include infusion at weeks 0, 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52;
<60kg = 2 vials; 60-100kg = 3 vials; >100kg = 4 vials

‡ Costs include infusion at weeks 0, 2, 6, 14, 22, 30, 38, 46, 54;
3mg/kg: <70kg 2-3 vials, >70kg 3-4 vials; 10mg/kg: <70kg 6-7 vials, >70kg 7- 8 vials

† Methotrexate included to calculate combination therapy costs

CONCLUSIONS

No comparative studies are available comparing abatacept with other DMARDs for the treatment of RA. Therefore, it is difficult to extrapolate superiority of one over the other. Abatacept has demonstrated efficacy in patients with RA that have not responded to DMARDs, including MTX and TNF antagonists. Abatacept can be taken alone or with other DMARDs, except TNF antagonists or anakinra. Evidence shows increased frequency of infections and

serious infections with no added clinical benefit when abatacept was combined with a TNF inhibitor. Safety and efficacy of abatacept has not been evaluated in concomitant use with anakinra. Cost of abatacept is higher compared to other biologic agents when dosed for patients less than 60kg and has the potential to increase with higher doses based on patients' weight. Due to limited safety data, use should be reserved for patients refractory to other RA treatment, may not be candidates for the other agents, or unable to tolerate the other agents. Also, there is a potential for dosing variability depending on patient's weight that is associated with a significant cost difference.

RECOMMENDATIONS

It is recommended that ABATACEPT remain a non-formulary agent and be added to the **Criteria for Use for Leflunomide and the Biologic DMARDs for the Treatment of Moderate to Severe Rheumatoid Arthritis** located at http://www.pbm.va.gov/criteria/Criteria%20for%20Use%20for%20Leflunomide%20and%20Biologic%20DMARDs.pdf .

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8. Moreland L, Kaine J, Espinoza L, et al. Safety of abatacept in rheumatoid arthritis patients in five double-blind, placebo-controlled trials [presentation 886]. Annual meeting of the American College of Rheumatology; November 13-17, 2005; San Diego, CA.

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APPENDIX: CLINICAL TRIALS

Citation Design Analysis Type Setting	Eligibility Criteria	Interventions	Patient Population Profile
Moreland et al. (2002) Phase II, MC, RCT, DB, PC, pilot, dose-finding multi-national setting	INCLUSION: 18-65 years of age; RA < 7 yrs; ≥10 SJ, ≥12 TJ;, ESR ≥28 mm/hr or morning stiffness ≥ 45 min; treated unsuccessfully with at least 1 classic DMARD, including MTX, oral/parenteral gold, Sulfasalazine, Chloroquine, D-penicillamine, azathioprine, leflunomide, cyclosporine, or etanercept . Labs = Hgb ≥ 8.5gm/dL, PLT ≥ 125,000 mm3, WBC ≥ 3000/mm3, SCr ≤ 2x ULN, LFTs ≤2x ULN, negative PPD within last 6 months or if positive PPD then Calmette-Guerin Immunization or completion of a course of adequate chemoprophylaxis of TB has to be documented All pts had to use medically accepted form of contraception; women had to have negative result on serum or urine pregnancy test within 72 hours	CTLA4-Ig: 0.5 mg/kg, 2.0 mg/kg, 10.0 mg/kg LEA29Y: 0.5 mg/kg, 2.0 mg/kg, 10.0 mg/kg Placebo Study med was given on days 1, 15, 29, 57; Days 1-85 = tx period; f/u thru Day 169 4 injections over a 2 month period	Female = 75%; Male = 25% Race White = 91% Black = 4% Other = 5% Age = 48.4 ± 11.3 yrs , range 21-66 Weight = 71.0 ± 14.6 kg, range 39-101 RA duration = 3.4 ± 2.0 yrs, range 0.0-7.6 Prior meds MTX = 79% Other DMARDs = 84% Corticosteroids = 90% NSAIDs = 83%

Efficacy Results

N=214 (abatacept pts = 90; LEA29Y pts = 92; Placebo = 32)

	PBO	CTLA4-Ig dose (mg/kg)			LEA29Y dose (mg/kg)		
		0.5	2.0	10.0	0.5	2.0	10.0
ACR 20 (%)	31	23	44	53	34	45	61
ACR 50 (%)	7	0	19	16	6	10	12
ACR 70 (%)	0	0	12	6	0	4	3
100% improvement in both TJ & SJ	0	0	16	9	3	10	0

% Improvement	PBO	CTLA4-Ig dose (mg/kg)			LEA29Y dose (mg/kg)		
		0.5	2.0	10.0	0.5	2.0	10.0
TJC	29.3	26.1	49.0	54.6	40.8	43.5	47.8
SJC	32.1	15.4	41.6	40.7	32.6	40.7	61.3
Pain Score	4.6	5.1	25.6	28.1	15.0	15.2	23.7
Pt Global Assessment	3.3	8.0	24.3	30.9	10.8	20.6	30.6
MD Global Assessment	14.4	10.5	25.7	28.2	20.3	22.3	31.8
Function score	5.1	0.7	11.8	20.3	8.8	18.3	24.5
CRP mg/dL	0.7	0.0	13.7	54.6	-10.0	46.6	71.4
ESR mm/hr	-8.3	-11.1	25.0	18.3	13.0	23.5	41.7
AM stiffness (minutes)	-3.0	13.0	40.5	42.9	29.2	63.3	51.4

Safety Results

% Withdrawals before day 85	PBO	CTLA4-Ig dose (mg/kg)			LEA29Y dose (mg/kg)		
		0.5	2.0	10.0	0.5	2.0	10.0
Total	38	32	27	13	6	8	14
Worsening RA	31	19	12	9	3	3	6
Adverse Events	0.5	8	7	10	3	4	7

AEs occurring up to day 85 N (%)	PBO (n=32)	CTLA4-Ig (n=90)	LEA29Y (n=92)
Total with AEs	24 (75)	73 (81.1)	76 (82.6)
D/C due to AEs	0 (0)	4 (4.4)	1 (1.1)
Most frequent AEs			
HA	1 (3.1)	8 (8.9)	5 (5.4)
N/V	2 (6.3)	5 (5.6)	5 (5.4)
Fatigue	1 (3.1)	4 (4.4)	7 (7.6)
Arthritis	3 (9.4)	4 (4.4)	4 (4.3)
Hypotension	2 (6.3)	3 (3.3)	1 (1.1)
Serious AEs	4 (12.5)	4 (4.4)	4 (4.3)
Serious AEs related to the drug study	0 (0)	0 (0)	0 (0)

No notable renal, hepatic, or hematologic adverse events
173/214 (81%) reported adverse events (518 events) during tx period
129 (60%) reported adverse events (256 events) during f/u
117 peri-infusional events occurred = 29% CTLA4-Ig; 34% LEA29Y; 31% PBO

Most common peri-infusional adverse events (vs. PBO) =
N/V CTLA4-Ig 7% vs. 3% PBO
HA LEA29Y 8% vs. 3% PBO

4% pts tx'd with active med had serious adverse events vs. 13% PBO

5 pts withdrew	
CTLA4Ig	
0.5 mg/kg	1 pt with worsening RA 1 pt with breast CA dx'd on day 57 after 4th infusion
2 mg/kg	1 pt with worsening RA 1 pt with anxiety attack; sx resolved
LEA29Y	1 pt with upper respiratory infection; sx resolved

prior to receiving study med

EXCLUSION:
Nursing women

Kremer et al. (2005) Phase IIb, 12-month, MC, RCT, DB, PC	INCLUSION: 18-65 yrs of age; ACR criteria for RA and were in functional class I, II, or III; active RA: ≥10 SJ, ≥12 TJ, CRP levels of at least 1 mg/dL (ULN, 0.4); treated with MTX (10-30mg weekly) for at least 6 months and received a stable dose for 28 days before enrollment; leflunomide and infliximab were d/c'd at least 60 days before enrollment, and other DMARDs were d/c'd at least 28 days before enrollment; stable low-dose corticosteroids (≤10 mg/day) and NSAIDs were permitted EXCLUSION: Women who were nursing or pregnant	Abatacept 2mg/kg, abatacept 10mg/kg, or placebo was infused intravenously over a 30-minute period on days 1, 15, and 30 and every 30 days thereafter MTX 10-30mg/wk for the first 180 days of the trial with no adjustments except for hepatotoxicity. Between days 180-360, changes allowed based on clinical judgment: 1) change in MTX dose provided that dosage was < 30mg/wk; 2) the addition of another DMARD (hydroxychloroquine, sulfasalazine, gold, or azathioprine); and 3) adjustment in corticosteroids equivalent to ≤ 10mg/day prednisone	Age = 54.4-55.8 Weight = 77.8-79.9 Female = 63-75% Race = White – 91-104% Black – 0-6% Other – 9-14% Disease duration = 8.9-9.7 years TJ = 28.2-30.8 SJ = 20.2-21.8 Pain (VAS) = 62.1-65.2 MHAQ = 1.0 Pt global assessment = 59.4-62.8 MD global assessment= 61.0-63.3 CRP mg/dL = 2.9-3.2 DAS28 = 5.4-5.5 Meds prior to enrollment (%) = MTX- 98.1-99.2 Other DMARDs- 16.5-21.0	N=339 (abatacept 10mg/kg, N=115; abatacept 2mg/kg, N=105; placebo, N=119) 6 months ACR response rate (%) / PBO + MTX (N=119) / 2mg/kg + MTX (N=105) / 10mg/kg + MTX (N=115) ACR 20 / 35.3 / 41.9 / 60.0 P<0.001 ACR 50 / 11.8 / 22.9 P<0.05 / 36.5 P<0.001 ACR 70 / 1.7 / 10.5 P<0.05 / 16.5 P<0.001 *p-value for comparison with group given PBO + MTX 12 months ACR response rate (%) / PBO + MTX (N=71) / 2mg/kg + MTX (N=74) / 10mg/kg + MTX (N=90) ACR 20 / 35.5 / 41.9 / 62.6 P<0.001 ACR 50 / 19.5 / 22.9 / 41.7 P<0.001 ACR 70 / 7.5 / 12.5 / 20.9 P=0.003 Remission rate (%) / PBO + MTX / 10mg/kg + MTX 3 months / 7.6 / 17.4 6 months / 9.2 / 26.1 12 months / 10.1 / 34.8 Significant remission rates seen in abatacept 10mg/kg vs. PBO groups (p<0.001 vs. PBO) Low Disease Activity (%) / PBO + MTX / 10mg/kg + MTX 3 months / 18.5 / 29.6 6 months / 19.3 / 40 12 months / 21.9 / 49.6 Statistically significant rates bt abatacept 10mg/kg vs. PBO (P<0.05 at all time points) Physical function/M-HAQ / PBO + MTX / 10mg/kg + MTX 6 months / 33.6 / 58.3 12 months / 27.7 / 49.6 Statistically significant rates bt abatacept 10mg/kg vs. PBO (P<0.001)	D/C's = placebo - 48 2mg/kg abatacept - 31 10mg/kg abatacept - 25 Significant difference in d/c rates bt 10mg/kg abatacept & PBO (p<0.01) Significant difference in d/c rates for lack of efficacy (p<0.01) No significant difference bt 10mg/kg abatacept & PBO groups in d/c rate due to AEs Most frequently reported AEs in 10mg/kg + 2mg/kg (≥5% of pts) % / PBO + MTX / 2mg/kg + MTX / 10mg/kg + MTX Nasopharyngitis / / 18.1 / 14.8 HA / / 16.2 / 14.8 N / / 11.4 / 13.9 Arthralgia / / 16.2 / Serious AEs (%) / PBO + MTX / 2mg/kg + MTX / 10mg/kg + MTX Chest pain / 0 / 3.8 / 0.9 MI / 0.8 / 0 / 0.9 GI Disorder / 0 / 0 / 0.9 No deaths, cancers, opportunistic infections Malignancies = in 10mg/kg group 1 bladder carcinoma 2 basal cell carcinoma 1 neoplasm IMMUNOGENICITY No pts seroconverted for abatacept antibodies to whole molecule 2 pts produced antibodies to CTLA-4Ig portion

10 mg/kg	

SAEs – 15 during tx period – most were worsening RA needing hospitalization
1 pt with septic arthritis on CTLA4Ig 2mg/kg – hospitalized 88 days after last dose for staph aureus septic arthritis of the elbow

No antibodies to the meds were detectable at any time point

			Corticosteroids-60.0-67.6 MTX dosage during study (mg/wk) 15.0-15.8			
Genovese et al. (2005) 6-month, RCT, DB, PC, Phase III ATTAIN Trial	INCLUSION: ACR criteria for RA; ≥18 years of age; RA ≥ 1 year; inadequate response to anti-TNF therapy with etanercept, infliximab, or both after ≥3 months treatment (study initiated before adalimumab use widespread); ≥ 10 SJ; ≥ 12 TJ; CRP ≥ 1mg/dL (ULN, 0.5mg/dL); oral DMARD or anakinra for at least 3 months @ stable dose X 28 days; use of ≤10mg corticosteroids allowed if dose stable x 28 days	10mg/kg abatacept or placebo plus DMARDs < 60 kg = 500 mg of abatacept; 60-100 kg = 750mg of abatacept; >100 kg = > 1000 mg of abatacept Med administered in a 30-min IV infusion on Days 1, 15, 29, and Q 28 days thereafter, up to and including day 141 All users were required to stop taking etanercept or infliximab for at least 28 or 60 days, respectively, before undergoing randomization. Pts had to be taking an oral DMARD or anakinra for at least 3 months, and dose had to have been stable for at least 28 days. Use of oral corticosteroids (≤10mg of prednisone or its equivalent per day) if dose stable for 28 days Changes in dosages of background DMARDs were not permitted except to avoid adverse effects	Female = 77.1-79.7 Race, (%) = White – 93.2-96.1 Black – 3.5-3.8 Other – 0.4-3.0 Duration of RA = 34-69 years Use of anti-TNF therapy - (%) Current – 38.0-41.4 Former – 58.6-62.0 Anti-TNF therapy = Etanercept – 32.2-39.8 Infliximab – 60.2-67.8 Adalimumab – 1.5-2.3 Meds at randomization (%) = MTX – 75.6 82.0 AZA – 2.3-2.7 Penicillamine – 0-0.4 Gold – 0-0.8 HCQ – 8.9-9.0 Chloroquine – 0-0.8 Leflunomide – 8.3-8.9 SSZ – 7.0-9.8 Anakinra – 2.3-2.7 NSAIDs – 70.2-71.4	N= 393 (abatacept + DMARDs = 258; placebo + DMARDs = 133; 2 did not meet eligibility criteria and were not treated) Among both current and former users of anti-TNFα therapy, ACR 20 responses were significantly higher in the abatacept group than in the placebo group (P<0.001 for both comparisons). @ 6 months, that abatacept group also had greater mean improvements from baseline in HAQ disability index (0.45 vs. 0.11, P<0.001) Abatacept also had significant improvements in the physical component and mental component summary scores (P<0.001 & p<0.01, respectively)	Infections more frequently in abatacept group (37.6%) vs. placebo group (32.3%). P = 0.30 Most frequently reported infections = nasopharyngitis, sinusitis, upper respiratory infection Rates of D/C due to infection = 0.8% abatacept group; 1.5% placebo group; P=0.61. Deaths – 1 pt died of MI and CHF thought unrelated to drug Immunogenicity = 3/234 patients (1.3%)

%	Abatacept + DMARDs	Placebo + DMARDs	p-value
ACR 20	50.4	19.5	<0.001
ACR 50	20.3	3.8	<0.001
ACR 70	10.2	1.5	=0.003
Remission (DAS < 2.6)	10.0	0.8	<0.001
Low level of Dz (DAS ≤ 3.2)	17.1	3.1	<0.001
↑ in physical function (≥0.3 ↑ in HAQ)	47.3	23.3	<0.001

%	Abatacept + DMARDs	Placebo + DMARDs	p-value
Acute infusion reactions	5.0	3.0	P=0.35
Dizziness	1.6	0	P=0.30
Headache	1.2	0.8	P=1.0

Adverse Event N (%)	Abatacept (N = 258)	Placebo (N = 113)	p-value
Death	1 (0.4)	0	1.0
Serious Adverse Events	27 (10.5)	15 (11.3)	0.81
Serious Infections	6 (2.3)	3 (2.3)	0.97
Limb abscess	1 (0.4)	0	1.0
Diverticulitis	1 (0.4)	0	1.0
Peridiverticular abscess	1 (0.4)	0	1.0
Pneumonia	1 (0.4)	0	1.0
Bacterial pneumonia	1 (0.4)	0	1.0
Influenzal pneumonia	1 (0.4)	0	1.0
Streptococcal sepsis	1 (0.4)	0	1.0
Acute sinusitis	0	1 (0.8)	0.34

			Corticosteroids – 64.7-70.2 MTX dose at baseline – mg/wk = 14.4-15.2 Median corticosteroid dose at baseline (mg/day) = 5.0 # TJ = 31.2-32.8 # SJ = 22.0 22.3 Pain score = 69.9-70.8 Physical-function score = 1.8 Global assessment of disease: PT = 69.2-69.7 MD = 67.3-68.8 DAS28 = 6.5 CRP mg/dL = 4.0-4.6 +RF - # (%) = 72.9-73.3				

Osteomyelitis	0	1 (0.8)	0.34
Pharyngitis	0	1 (0.8)	0.34
Sepsis	0	1 (0.8)	0.34
Staphylococcal abscess	0	1 (0.8)	0.34
Any adverse event	205 (79.5)	95 (71.4)	0.08
Most frequent adverse events			
HA	32 (12.4)	7 (5.3)	0.03
Nasopharyngitis	20 (7.8)	8 (6.0)	0.53
Nausea	17 (6.6)	9 (6.8)	0.95
Sinusitis	16 (6.2)	5 (3.8)	0.31
Upper respiratory tract infection	15 (5.8)	10 (7.5)	0.51
Diarrhea	15 (5.8)	7 (5.3)	0.82
Bronchitis	15 (5.8)	6 (4.5)	0.59
Back pain	13 (5.0)	7 (5.3)	0.92
D /C's	35 (13.6)	34 (25.6)	0.003
Adverse events Serious	9 (3.5) 7 (2.7)	5 (3.8) 2 (1.5)	0.89
Lack of efficacy	14 (5.4)	27 (20.3)	<0.001
Withdrawal of consent	5 (1.9)	2 (1.5)	1.0
Lost to follow-up	5 (1.9)	0	0.17
Other	2 (0.8)	0	0.55
Death	0	0	-----

Kremer et al. (2005) AIM Trial 1-year, RCT, DB, PC, MC,	INCLUSION: >/= 18 years of age; RA >/= 1 year duration; American Rheumatism Assoc. criteria for RA; active RA despite MTX tx; MTX>/= 15 mg/wk x >/= 3 months with stable dose x 28 days	Fixed dose abatacept 10mg/kg (<60kg = 500mg; 60-100mg = 750mg; >100kg = 1000mg) vs. placebo with background MTX. Study med administered by IVF over 30 minutes on Days 1, 15, 29, and Q 28 days thereafter. No premedication required. All pts to	Age = 50.4-51.5 years; Weight = 70.2 – 72.3 kg; Women = 77.8-81.7%; White = 87.5-88.1%;	N = 652

N (%)	Abatacept	Placebo	P-value
Received tx	433	219	
Completed Study	385 (88.9%)	162 (74.0%)	
6 MONTHS			
ACR 20	288 (68%)	85 (40%)	<0.001 vs. placebo + MTX
ACR 50	169 (40%)	36 (17%)	<0.001 vs. placebo + MTX
ACR 70	84 (20%)	14 (7%)	<0.001 vs.

ADVERSE EVENT n (%)	Abatacept + MTX (N=433)	PBO + MTX (N=219)
Death	1 (0.2)	1 (0.5)
Total Adverse Events Related to study drug D/C due to AEs	378 (87.3) 214 (49.4) 18 (4.2)	184 (84.0) 104 (47.5) 4 (1.8)
Most frequently reported AEs (>5%) HA Nasopharyngitis Nausea	 76 (17.6) 66 (15.2) 52 (12.0)	 26 (11.9) 25 (11.4) 24 (11.0)

Phase III trial	before enrollment; washout of all other DMARDs at least 28 days prior to randomization; corticosteroid use</= 10 mg/day with dose stable x 25 days before enrollment; >/= 10 SJ; >/= 12 TJ; CRP > 10mg/L (normal 1.0 mg/L-4.0 mg/L); TB skin test (excluded + TB skin test unless completed treatment for latent TB before enrollment)	receive MTX >/= 15mg/wk or = 10mg/wk if h/o toxicity. No adjustment in MTX dose for the first 6 months except for toxicity. Adjustment in meds allowed between 6-12 months for: 1)Adjustment in MTX dose…2) Addition of 1 other DMARD (HCQ, SSZ, gold, or AZA)… or 3) adjustment of corticosteroid dose = 10mg of prednisone or less/day	Disease Duration = 8.5-8.9 years; MTX dose = 15.7-16.1 mg/wk; TJ = 31.0 – 32.3; SJ = 21.4 – 22.1; Pain (100-mm VAS) = 63.3 – 65.9; Physical fxn (HAQ-DI) = 1.7; Pt global assessment = 62.7-62.8; MD global assessment = 67.4-68.0; CRP 28-33 mg/L; RF – 78.5 – 81.8; Baseline radiographic score: Erosion = 21.7 21.8 JSN = 22.8-23.0 Total score = 44.5-44.9; Antirheumatic medications at enrollment: MTX = 100% Other DMARDs = 8.7-12.2% Biologics = 0.2% Corticosteroids 68.5-72.1%

			placebo + MTX
12 MONTHS			
ACR 20	310 (73.1%)	88 (39.7%)	<0.001 vs. placebo + MTX
ACR 50	205 (48.3%)	39 (18.2%)	<0.001 vs. placebo + MTX
ACR 70	122 (28.8%)	13 (6.1%)	<0.001 vs. placebo + MTX
MAJOR CLINICAL RESPONSE @ 1 YEAR (Abatacept+MTX N=424; PBO+MTX = 214)	60 (14%)	4 (2%)	<0.001 vs. placebo + MTX
EXTENDED MAJOR CLINICAL RESPONSE @ 1 YEAR (Abatacept+MTX N=424; PBO+MTX = 214)	26 (6%)	1 (<1%)	<0.002 vs. placebo + MTX
Physical Fxn Improvement @ 1 year	63.7%	39.3%	<0.001

No differences in response in patients with recent-onset vs. more established disease. Statistical comparisons between abatacept- and placebo- treated patients were not performed on the post-hoc analysis

RADIOGRAHIC PROGRESSION	Abatacept (N=391)	Placebo (N=195)	P-value
Median change from baseline			
Erosion score	0.0	0.27	0.029
Joint-space narrowing score	0.0	0.0	0.009
Total Score	0.25	0.53	0.012
Mean change from baseline			
Erosion score	0.63	1.14	
Joint-space narrowing score	0.53	1.18	
Total score	1.21	2.32	

At 1 year, abatacept pts demonstrated statistically significant slowing of structural damage progression compared with placebo with approx 50% reduction in change from baseline in Sharp score compared with placebo

DAS	Abatacept	Placebo	P-value
6 MONTHS			
DAS 28 </= 3.2	30.1%	10.0%	<0.001
DAS 28 < 2.6	14.8%	2.8%	<0.001
12 MONTHS			

Diarrhea	47 (10.9)	21 (9.6)
URI	47 (10.9)	21 (9.6)
Dizziness	40 (9.2)	16 (7.3)
Back Pain	40 (9.2)	12 (5.5)
Influenza	31 (7.2)	12 (5.5)
Cough	29 (6.7)	13 (5.9)
Dyspepsia	27 (6.2)	10 (4.6)
Pharyngitis	26 (6.0)	10 (4.6)
HTN	24 (5.5)	3 (1.4)
Fatigue	23 (5.3)	15 (6.8)
UTI	22 (5.1)	11 (5.0)
Upper abdominal pain	19 (4.4)	13 (5.9)
Sinusitis	18 (4.2)	15 (6.8)
Bronchitis	18 (4.2)	12 (5.5)

SERIOUS AND INFUSIONAL ADVERSE EVENTS AND SERIOUS INFECTIONS n (%)	Abatacept + MTX (N=433)	PBO + MTX (N=219)
Serious Adverse Events	65 (15.0)	26 (11.9)
Related to study drug	15 (3.5)	1 (0.5)
D/Cs due to SAEs	10 (2.3)	3 (1.4)
Musculoskeletal and connective tissue disorders	20 (4.6)	10 (4.6)
Infections	17 (3.9)	5 (2.3)
Nervous System Disorders	6 (1.4)	4 (1.8)
Cardiac Disorders	4 (0.9)	2 (0.9)
Neoplasms (benign, malignant, and unspecified)	4 (0.9)	2 (0.9)
Acute infusional adverse events	38 (8.8)	9 (4.1)
Peri-infusional adverse events	106 (24.5)	37 (16.9)
Serious infections (prespecified)	11 (2.5)	2 (0.9)
Pneumonia	4 (0.9)	1 (0.5)
Bronchopneumonia	2 (0.5)	0
Cellulitis	1 (0.2)	1 (0.5)
Sepsis	1 (0.2)	1 (0.5)
Abscess	1 (0.2)	0
Bacterial arthritis	1 (0.2)	0
Bronchopulmonary Aspergillosis	1 (0.2)	0
Acute pyelonephritis	1 (0.2)	0
Tuberculosis	1 (0.2)	1 (0.5)
Limb abscess	0	1 (0.5)

Most frequently reported AEs (>5% in either group) = HA, Nasopharyngitis, N

More pts d/c'd due to AEs in the abatacept group than in the placebo group (4.2% vs. 1.8%)

Most frequently reported SAEs = musculoskeletal, primarily related to hospitalizations for RA flares or elective surgery for RA

Incidence of infection higher with abatacept [2 d/c (5%) for abatacept vs. 1 d/c (0.5%) for placebo]

Increased cases of pneumonia with abatacept vs. placebo

TB = abatacept group – 1 pt with enlarged lymph node with biopsy compatible with

			NSAIDs = 82.6-85.5 Other = 0.2% Mean baseline DAS = 6.4	DAS 28 </= 3.2	42.5%	9.9%	<0.001
				DAS 28 < 2.6	23.8%	1.9%	<0.001

possible TB; placebo group – 1 unconfirmed case

Deaths = abatacept group – 1 pt with pulmonary disease; placebo group – 1 pt with P. aeuroginosa pneumonia, sepsis, multiorgan failure

Neoplasms = abatacept group – 1 pt with B-cell lymphoma of thyroid with background Hashimoto's thyroiditis; placebo group – 1 pt with endometrial cancer

No major autoimmune disorder

Infusion reactions – 2 pts d/c'd due to severe infusion reactions = 1 after the 2nd infusion – rash and chest pain; 1 during the 4th infusion – hypotension. Both resolved after stopping the infusions

Immunogenicity – 6 pts (1.4%) demonstrated antibody reactivity to abatacept

*Combe et al. (2005)

ASSURE trial

INCLUSION:

Active RA receiving non-biologic or biologic DMARDs

Fixed dose of abatacept (10mg/kg) or placebo in combination with non-biologic or biologic DMARDs

Most were on combination therapy with non-biologic DMARDs;

A much smaller group received background biologic DMARDs

N = 1441

% improvement from baseline at 1 year	Abatacept/ non-biologic (N = 848)	Placebo/ non-biologic (N=418)	Abatacept/ biologic (N = 100)	Placebo/ biologic (N=59)
Patient physical function (HAQ)	30.12 (1.8)	9.03 (5.4)	22.45 (4.6)	14.91 (5.5)
Patient global assessment of disease activity (VAS)	41.17 (1.7)	20.64 (3.4)	35.74 (4.4)	26.49 (6.8)
Patient global assessment of pain (VAS)	37.23 (2.6)	18.55 (3.4)	33.52 (5.1)	22.43 (5.5)

N (%)	Abatacept/ non-biologic (N = 856)	Placebo/ non-biologic (N=418)	Abatacept/ biologic (N = 103)	Placebo/ biologic (N=64)
Total adverse events	768 (89.7)	360 (86.1)	98 (95.1)	57 (89.1)
Discontinuations due to adverse events	43 (5.0)	18 (4.3)	9 (8.7)	2 (3.1)
Serious adverse events	100 (11.7)	51 (12.2)	23 (22.3)	8 (12.5)
Neoplasms (benign and malignant)	27 (3.2)	16 (3.8)	7 (6.8)	1 (1.6)
Infections (all pre-specified)	75 (8.8)	36 (8.6)	20 (19.4)	4 (6.3)
Serious infections (pre-specified)	13 (1.5)	4 (1.0)	4 (3.9)	1 (1.6)

* ABSTRACT