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 costimulatory signal for T-cell activation.

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

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

<table>
<thead>
<tr>
<th>Infliximab (Remicade®)</th>
<th>Etanercept (Enbrel®)</th>
<th>Anakinra (Kineret®)</th>
<th>Adalimumab (Humira®)</th>
<th>Rituximab (Rituxan®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulary</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X – Restricted to oncology</td>
</tr>
<tr>
<td>Non-formulary</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DOSAGE AND ADMINISTRATION 1

<table>
<thead>
<tr>
<th>Body Weight of Patient</th>
<th>Dose</th>
<th>Number of Vials*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 60 kg</td>
<td>500 mg</td>
<td>2</td>
</tr>
<tr>
<td>60 – 100 kg</td>
<td>750 mg</td>
<td>3</td>
</tr>
<tr>
<td>&gt; 100 kg</td>
<td>1 gram</td>
<td>4</td>
</tr>
</tbody>
</table>

*Each vial provides 250 mg of abatacept for administration.

March 2006
Updated versions may be found at http://www.pbm.va.gov or http://vaww.pbm.va.gov
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.  

- 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 (30.4% 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%).

- 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%).

**UNPUBLISHED TRIALS**

- The Abatacept Study of Safety in Use with other Rheumatoid Arthritis Therapies (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.

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

**ADVERSE EVENTS (SAFETY DATA)**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Abatacept (N=1955)^a Percentage</th>
<th>Placebo (N=989)^b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>18</td>
<td>13</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>12</td>
<td>9</td>
</tr>
<tr>
<td>Dizziness</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>Cough</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Back Pain</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Hypertension</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Rash</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

^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**

<table>
<thead>
<tr>
<th></th>
<th>Abatacept (N 1955)</th>
<th>Placebo (N 989)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinuations due to SAEs</td>
<td>2.7 (53)</td>
<td>1.6 (16)</td>
</tr>
<tr>
<td>Discontinuations due to AEs</td>
<td>5.5 (107)</td>
<td>3.9 (39)</td>
</tr>
<tr>
<td>Adverse Events (AEs)</td>
<td>88.8 (1736)</td>
<td>84.9 (840)</td>
</tr>
</tbody>
</table>
• **OVERALL SAFETY**

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

• **SAFETY SPLIT BY BACKGROUND THERAPY**

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

• **INFUSION RELATED REACTIONS AND HYPERSENSITIVITY REACTIONS**
  
  o 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
  o 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)
  o Fewer than 1% of abatacept-treated patients discontinued due to an acute infusion-related event
  o 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**

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

*March 2006*

*Updated versions may be found at [http://www.pbm.va.gov](http://www.pbm.va.gov) or [http://vaww.pbm.va.gov](http://vaww.pbm.va.gov)*
o New infections, malignancies – potential to exacerbate as T cells mediate their response
o History of recurrent infections, underlying conditions which may predispose to infections, or chronic, latent, or localized infections – exacerbation of infection
o Patients should be screened for latent tuberculosis infection with a tuberculin skin test – safety of abatacept in individuals with latent tuberculosis infection is unknown
o 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.
o The frequency of serious infection and malignancy among abatacept-treated patients over age 65 was higher than for those under age 65.
o Pregnancy Category C
o Nursing mothers – animal studies show abatacept present in rat milk.

- CONTRAINDICATIONS
  o 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:

<table>
<thead>
<tr>
<th>LA/SA for abatacept</th>
<th>LA/SA for Orencia®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aricept®</td>
<td>Aredia®</td>
</tr>
<tr>
<td>Abelcet®</td>
<td>Oretic®</td>
</tr>
<tr>
<td>Alefacept</td>
<td>Iressa®</td>
</tr>
<tr>
<td>Atrosept®</td>
<td>Auranofin</td>
</tr>
<tr>
<td>Etanercept</td>
<td>Orfro®</td>
</tr>
<tr>
<td></td>
<td>Anexsia®</td>
</tr>
</tbody>
</table>

DRUG INTERACTIONS

1. No formal drug interaction studies have been conducted with abatacept.
2. MTX, NSAIDs, corticosteroids, and TNF blocking agents did not influence abatacept clearance.
3. Concomitant administration of a TNF antagonist with abatacept has been associated with an increased risk of serious infections and no significant additional efficacy over use of the TNF antagonists alone.
4. Concurrent use with anakinra is not recommended due to insufficient experience to assess safety and efficacy.
5. 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.
**Abatacept Monograph**

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

**SDV = single dose vials**
- Costs include infusion at weeks 0, 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52;
- Costs include infusion at weeks 0, 2, 6, 14, 22, 30, 38, 46, 54;
- 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

March 2006

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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

REFERENCES


pilot, dose-finding, double-blind, placebo-controlled clinical trial evaluating CTLA-4Ig and LEA29Y eighty-five

modulator abatacept: Twelve month results of a phase IIb, double-blind, randomized, placebo controlled trial.


7. Combe B, Weinblatt M, Birbara C, et al. Safety and patient-reported outcomes associated with abatacept in the
treatment of rheumatoid arthritis patients receiving background disease modifying anti-rheumatic drugs (DMARDs):
The ASSURE trial [presentation 1918]. Annual meeting of the American College of Rheumatology; November 13-
17, 2005; San Diego, CA.

placebo-controlled trials [presentation 886]. Annual meeting of the American College of Rheumatology; November
13-17, 2005; San Diego, CA.

Prepared by: M. Sales, Pharm.D.
Date: March 2006
APPENDIX: CLINICAL TRIALS

Citation: Moreland et al. (2002)

Eligibility Criteria:
- 18-65 years of age
- RA < 7 yrs; ≥ 10 SJ
- DBPC, Phase II, Setting: Type 1a
- Unsuccessful treatment with previous DMARDs
- ≤ 65 yrs
- Weight ≤ 14.6 kg, range 21-66
- White = 91%
- Black = 8%
- Other = 1%
- Age = 48.4 ± 11.3 yrs, range 21-66
- MTX, Placebo
- Cyclosporine, Leflunomide
- Infliximab, Abatacept
- African American
- Female
- Male
- N = 214

Interventions:
- CTLA4-Ig: 1 mg/kg
- LEA29Y: 0.5 mg/kg

Patient Population Profile:
- RA duration = 3.4 ± 2 yrs, range 0-7.6
- DMARDs = 84%
- Corticosteroids = 90%
- NSAIDs = 83%
- Labs = Hbg ≥ 8.4 g/dL, FET ≥ 125 000 mm3, BWC ≥ 3000 mm3, SCR ≤ 2x ULN, LFTs ≤ 2x ULN, negative PPD
- Immunosuppression or completion of a course of adequate chemotherapy
- All pts had to be treated with methotrexate or etanercept

Efficacy Results:
- % Improvement:
  - PBO: 0.5
  - CTLA4-Ig: 2.0, 10.0
  - LEA29Y: 0.5, 2.0
- ACR 20 (%):
  - PBO: 31
  - CTLA4-Ig: 23
  - LEA29Y: 23
- ACR 50 (%):
  - PBO: 7
  - CTLA4-Ig: 19
  - LEA29Y: 19
- ACR 70 (%):
  - PBO: 0
  - CTLA4-Ig: 12
  - LEA29Y: 6
- CRP mg/dL:
  - PBO: 0.7
  - CTLA4-Ig: 0.0
  - LEA29Y: 0.0
- ESR mm/hr:
  - PBO: 8.3
  - CTLA4-Ig: 11.1
  - LEA29Y: 11.1
- AM stiffness (minutes):
  - PBO: 3.0
  - CTLA4-Ig: 13.0
  - LEA29Y: 40.5

Safety Results:
- % Withdrawals before day 85:
  - PBO: 0.5
  - CTLA4-Ig: 2.0
  - LEA29Y: 10.0
- % Total:
  - PBO: 38
  - CTLA4-Ig: 32
  - LEA29Y: 27
- % Worse:
  - PBO: 13
  - CTLA4-Ig: 12
  - LEA29Y: 9
- % Adverse Events:
  - PBO: 8
  - CTLA4-Ig: 7
  - LEA29Y: 4

AEs occurring up to day 85:
- N (%):
  - PBO (n=32): 24 (75)
  - CTLA4-Ig (n=90): 73 (81.1)
  - LEA29Y (n=92): 76 (82.6)
- D/C due to AEs:
  - PBO: 0 (0)
  - CTLA4-Ig: 4 (4.4)
  - LEA29Y: 1 (1.1)

Most frequent AEs:
- HA:
  - PBO: 1 (3.1)
  - CTLA4-Ig: 2 (6.3)
  - LEA29Y: 2 (6.3)
- Fatigue:
  - PBO: 1 (3.1)
  - CTLA4-Ig: 4 (4.4)
  - LEA29Y: 7 (7.6)
- Arthritis:
  - PBO: 3 (9.4)
  - CTLA4-Ig: 4 (4.4)
  - LEA29Y: 4 (4.3)
- Hypotension:
  - PBO: 2 (6.3)
  - CTLA4-Ig: 3 (3.3)
  - LEA29Y: 1 (1.1)
- Serious AEs:
  - PBO: 4 (12.5)
  - CTLA4-Ig: 4 (4.4)
  - LEA29Y: 4 (4.3)
- Serious AEs related to the drug study:
  - PBO: 0 (0)
  - CTLA4-Ig: 0 (0)
  - LEA29Y: 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 follow-up
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:
- CTLA4-Ig:
  - 0.5 mg/kg
  - 1 pt with worsening RA
- 2 mg/kg
  - 1 pt with breast CA dx’d on day 57 after 4th infusion
- LEA29Y
  - 1 pt with upper respiratory infection; sx resolved

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February 2006
### Abatacept Monograph

#### Objectives

- **2 mg/kg abatacept vs placebo** at 180 mg/(m²·d) in patients receiving MTX 10 mg/kg wk for at least 6 months
- **10 mg/kg abatacept** at 180 mg/(m²·d) in patients receiving MTX 10 mg/kg wk for at least 6 months

#### Clinical Studies

- **Phase II, 12-month**, Kremer et al., 2005
  - **Inclusion**: women who were nursing or pregnant, received MTX (10-30mg weekly) for at least 6 months and were on 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

- **Inclusion**: 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

#### Abatacept Monograph

<table>
<thead>
<tr>
<th>Age</th>
<th>Weight</th>
<th>Disease duration</th>
<th>Pain (VAS)</th>
<th>Remission</th>
<th>MHAQ</th>
<th>Pt global assessment</th>
<th>CRP mg/dL</th>
<th>DAS28</th>
<th>Meds prior to enrollment (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>54.4-55.8</td>
<td>77.8-79.9</td>
<td>8.9-9.7 years</td>
<td>28.2-30.8</td>
<td>62.1-65.2</td>
<td>59.4-62.8</td>
<td>2.9-3.2</td>
<td>5.4-5.5</td>
<td>5.5-6.5</td>
<td>98.1-99.2</td>
</tr>
</tbody>
</table>

#### Significant rates seen in abatacept

- **Remission rates seen in abatacept 10mg/kg vs. PBO (p<0.0001 vs. PBO)**

#### Clinical Response

- **ACR response rate** (%)
  - **ACR 20**: 35.3
  - **ACR 20**: 9.2

#### Disease Activity

- **Disease Activity (N=71)**
  - **Low Disease Activity** (N=119)
    - **ACR 20**: 35.3
    - **ACR 20**: 9.2

#### Safety

- **SAEs**—15 during tx period—most were worsening RA needing hospitalization 1 pt with septic arthritis on CTLA4lg 2mg/kg — hospitalized 88 days after last dose for staph aureus septic arthritis of the elbow

No Antibodies to the mAbs were detectable at any time point

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 CTLA4lg portion

### References

[Kremer et al. (2005)](http://www.pbm.va.gov)
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**Abatacept Monograph**

### Contraindication

**Corticosteroids**

60.0-67.6%

MTX dosage during study

15.0-15.8%

### Genovese et al. (2005)

**INCLUSION:**

ACR criteria for RA; ≥ 8 years of age; RA ≥ 1 year; inadequate response to anti-TNF therapy with etanercept, infliximab, or abatacept after ≥ 3 months treatment (study initiated before adalimumab use widespread); ≥ 10 SJC; ≥ 12 TJC; 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

<table>
<thead>
<tr>
<th>N= 393</th>
<th>Abatacept + DMARDs</th>
<th>Placebo + DMARDs</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR 20</td>
<td>50.4</td>
<td>19.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ACR 50</td>
<td>20.3</td>
<td>3.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ACR 70</td>
<td>10.2</td>
<td>1.5</td>
<td>&lt;0.003</td>
</tr>
<tr>
<td>Remission (DAS &lt; 2.6)</td>
<td>10.0</td>
<td>0.8</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

### Use of anti-TNF therapy (%)

Current – 38.0-41.4

Former – 58.6-62.0

### Anti-TNF therapy

Infliximab – 60.2-67.8

Adalimumab – 1.5-2.3

### Meds at randomization (%)

MTX – 75.6

AZA – 2.3-2.7

Penicillamine – 0.4

Gold – 0.8

HCQ – 8.9-9.0

Chloroquine – 0.8

Leflunomide – 8.3-8.9

SSZ – 7.0-9.8

Anakinra – 2.3-2.7

NSAIDs – 70.2-71.4

### Adverse Events

**N (%)**

### Deaths

1.0

### Serious Adverse Events

27 (10.5)

### Infections

3/234 patients (1.3%)

### Footnotes:

@: 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)

### Abbreviations:

**ACR:** American College of Rheumatology

**ACR 20:** American College of Rheumatology 20%

**HAQ:** Health Assessment Questionnaire

**DAS:** Disease Activity Score

**D/C:** Discontinued

**MTX:** Methotrexate

**NSAIDs:** Nonsteroidal Anti-Inflammatory Drugs

**Placebo:** Dose adjusted to match Abatacept

**Randomization:**

**SJC:** swollen joint count

**TJC:** tender joint count

**US:** United States

**VHA:** Veterans Health Administration

**CM:** Clinical Management

**N:** N = 393

**%:** Percent

**P:** p-value

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**Abatacept Monograph**

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo</th>
<th>Abatacept</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
<td>0.08</td>
</tr>
<tr>
<td>D/C’s</td>
<td>35 (13.6)</td>
<td>34 (25.6)</td>
<td>0.003</td>
</tr>
<tr>
<td>Adverse events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious</td>
<td>9 (3.5)</td>
<td>7 (2.7)</td>
<td>0.89</td>
</tr>
<tr>
<td>Lack of efficacy</td>
<td>14 (5.4)</td>
<td>27 (20.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Withdrawal of consent</td>
<td>5 (1.9)</td>
<td>2 (1.5)</td>
<td>1.0</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>5 (1.9)</td>
<td>0</td>
<td>0.17</td>
</tr>
<tr>
<td>Other</td>
<td>2 (0.8)</td>
<td>0</td>
<td>0.55</td>
</tr>
</tbody>
</table>

**ADVERSE EVENT n (%)**

<table>
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<th>Placebo</th>
<th>Abatacept</th>
<th>PBO</th>
<th>MTX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>1 (0.2)</td>
<td>1 (0.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Adverse Events</td>
<td>378 (8.7)</td>
<td>214 (4.9)</td>
<td>184 (4.5)</td>
<td>104 (4.7)</td>
</tr>
<tr>
<td>Related to study drug</td>
<td>184 (4.5)</td>
<td>4.9</td>
<td>104 (4.7)</td>
<td>4.18</td>
</tr>
<tr>
<td>Most frequently reported AEs (&gt;5%)</td>
<td>76 (17.6)</td>
<td>26 (11.9)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**MC, DB, RCT, 1-year, AIM Trial**

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<td>0</td>
<td>0.55</td>
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**Age**

- N = 652
- Age = 50.4-70.2
- Median age = 51.5 years
- Age >60 kg: 70.2-72.3 kg
- Age <60 kg: 70.2-72.3 kg

**Corticosteroids**

- 64.7-70.2

**MTX dose at baseline**

- mg/wk = 14.4-15.2
- Median corticosteroid dose at baseline (mg/day) = 5.0

**INCLUSION**

- Active RA for >1 year
- With background MTX
- Study medicated by IVF over 30 minutes
- On Days 1, 15, 29, and 37
- Q 28 days thereafter:
  - No premedication
  - All pts

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**Abatacept Monograph**

**Phase III trial**

- **before enrollment:**
  - washout of all other DMARDs at least 28 days prior to randomization;
  - corticosteroid use for 10 mg/day with dose stable x 25 days before enrollment; >10 mg/day for latent TB before enrollment

  - receive MTX =< 15 mg/wk or = 10 mg/wk if f/t 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 = 10 mg prednisone or less/day

  - Disease Duration = 8.5-8.9 years;

  - MTX dose = 15.7-16.1 mg/wk;

  - TII = 31.0 – 32.3;

  - SJ = 21.4 – 22.1;

  - Pain (100-mm VAS) = 63.3 – 65.9;

  - Physical fnx (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
    - JSN = 22.8
    - Total score = 44.5-44.9;

  - Antihyperemic medications at enrollment:
    - MTX = 100%
    - Other DMARDs = 8.7-12.2%
    - Biologics = 0.2%
    - Corticosteroids = 68.5-72.1%

  - 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

  - 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

  - **Radiographic progression**
    - **Abatacept** (N=391)
    - **Placebo** (N=195)
    - **P-value**

    | Metric | Abatacept | Placebo | P-value |
    |--------|-----------|---------|---------|
    | Median change from baseline | 0.0 | 0.27 | 0.029 |
    | Erosion score | 0.0 | 0.0 | 0.009 |
    | Joint-space narrowing score | 0.0 | 0.0 | 0.009 |
    | Total score | 0.36 | 0.50 | 0.010 |
    | Mean change from baseline | 0.63 | 0.52 | 0.405 |
    | Erosion score | 0.63 | 0.14 | 0.009 |
    | Joint-space narrowing score | 0.53 | 0.18 | 0.001 |
    | Total score | 1.20 | 2.30 | 0.001 |

  - **DAS**
    - **Abatacept**
    - **Placebo**
    - **P-value**

    | Metric | Abatacept | Placebo | P-value |
    |--------|-----------|---------|---------|
    | 6 MONTHS | | | |
    | DAS 28 = 12 | 30.1% | 10.0% | <0.001 |
    | DAS 28 > 12 | 14.8% | 2.8% | <0.001 |

  - **12 MONTHS**
    - **Abatacept**
    - **Placebo**
    - **P-value**

    | Metric | Abatacept | Placebo | P-value |
    |--------|-----------|---------|---------|

  - **SERIOUS AND INFUSIONAL ADVERSE EVENTS AND SERIOUS INFECTIONS (%)**

    | Event | Abatacept + MTX (N=433) | Placebo + MTX (N=219) |
    |-------|-------------------------|------------------------|
    | 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) |
    | Simmsitis | 18 (4.2) | 15 (6.8) |
    | Bronchitis | 18 (4.2) | 12 (5.5) |

  - **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) |

  - **Bacterial pneumonia**
    - 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 polyneuropathy**
    - 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

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**Abatacept Monograph**

<table>
<thead>
<tr>
<th>NSAIDs = 82.6-85.5</th>
<th>Other = 0.2%</th>
<th>Mean baseline DAS = 6.4</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAS 28 =&lt; 3.2</td>
<td>42.5%</td>
<td>9.9%</td>
</tr>
<tr>
<td>DAS 28 =&lt; 2.6</td>
<td>23.8%</td>
<td>1.9%</td>
</tr>
</tbody>
</table>

possible TB; placebo group – 1 unconfirmed case

Deaths – abatacept group – 1 pt with pulmonary disease; placebo group – 1 pt with P. aeruginosa 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

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### *Combe et al. (2005) ASSURE trial*

<table>
<thead>
<tr>
<th>INCLUSION:</th>
<th>Fixed dose of abatacept (10mg/kg) or placebo in combination with non-biologic or biologic DMARDs</th>
<th>Most were on combination therapy with non-biologic DMARDs; a much smaller group received background biologic DMARDs</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 1441</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>% improvement from baseline at 1 year</th>
<th>Abatacept/ non-biologic (N = 848)</th>
<th>Placebo/ non-biologic (N=418)</th>
<th>Abatacept/ biologic (N = 100)</th>
<th>Placebo/ biologic (N=59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient physical function (HAQ)</td>
<td>30.12 (1.8)</td>
<td>9.03 (5.4)</td>
<td>24.25 (4.6)</td>
<td>14.91 (5.5)</td>
</tr>
<tr>
<td>Patient global assessment of disease activity (VAS)</td>
<td>41.17 (1.7)</td>
<td>20.64 (3.4)</td>
<td>35.74 (4.4)</td>
<td>26.49 (6.8)</td>
</tr>
<tr>
<td>Patient global assessment of pain (VAS)</td>
<td>37.23 (2.6)</td>
<td>18.55 (3.4)</td>
<td>33.52 (5.1)</td>
<td>22.43 (5.5)</td>
</tr>
</tbody>
</table>

### N (%)

<table>
<thead>
<tr>
<th>Abatacept/ non-biologic (N = 856)</th>
<th>Placebo/ non-biologic (N=418)</th>
<th>Abatacept/ biologic (N = 103)</th>
<th>Placebo/ biologic (N=64)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total adverse events</td>
<td>768 (89.7)</td>
<td>360 (80.1)</td>
<td>98 (95.1)</td>
</tr>
<tr>
<td>Discontinuations due to adverse events</td>
<td>43 (5.0)</td>
<td>18 (4.3)</td>
<td>9 (8.7)</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>100 (11.7)</td>
<td>51 (12.2)</td>
<td>23 (22.3)</td>
</tr>
<tr>
<td>Neoplasms (benign and malignant)</td>
<td>27 (3.2)</td>
<td>16 (3.8)</td>
<td>7 (6.8)</td>
</tr>
<tr>
<td>Infections (all pre-specified)</td>
<td>75 (8.8)</td>
<td>36 (8.6)</td>
<td>20 (19.4)</td>
</tr>
<tr>
<td>Serious infections (pre-specified)</td>
<td>13 (1.5)</td>
<td>4 (1.0)</td>
<td>4 (3.9)</td>
</tr>
</tbody>
</table>

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* ABSTRACT

February 2006

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