

# Rapid and Sustained Improvement in Health-Related Quality of Life and Utility for 72 Weeks in Patients with Ankylosing Spondylitis Receiving Etanercept

ANNELIES BOONEN, VAISHALI PATEL, SHANA TRAINA, CHIUN-FANG CHIOU, ANDREAS MAETZEL, and WAYNE TSUJI

**ABSTRACT. Objective.** To examine the longterm effect of etanercept (ETN) therapy on health-related quality of life (HRQOL) and utility in patients with ankylosing spondylitis.

**Methods.** Patients completing a 24-week placebo-controlled trial were continued on ETN in a 72-week open-label extension study. Short Form-36 (SF-36), EuroQOL-5D (EQ-5D), and EuroQOL visual analog scale (EQ-VAS) scores were collected at open-label baseline and every 12 weeks thereafter. Mental and physical component scores (MCS and PCS) of the SF-36, EQ-5D and SF-6D utility scores, and quality-adjusted life-years (QALY) were calculated.

**Results.** 257 patients [129 previous placebo (PLA) and 128 ETN recipients] enrolled in this open-label extension study, and 85% completed the 72-week followup. PCS, EQ-5D and SF-6D utilities, and EQ-VAS were significantly lower at open-label baseline in the previous PLA group (PLA/ETN group) than in the previous ETN group (ETN/ETN group; all  $p < 0.001$ ). At week 12, PCS and MCS, EQ-5D and SF-6D utility scores, and EQ-VAS were similar in the PLA/ETN and ETN/ETN groups. As expected, mean change in EQ-5D in the PLA/ETN group was significantly greater than that for SF-6D (0.18 vs 0.06;  $p < 0.0001$ ). HRQOL and utility improvements were maintained in both groups for up to 72 weeks. The average 72-week QALY gain per person in the PLA/ETN group was 0.24 and 0.10 for EQ-5D and SF-6D, respectively.

**Conclusion.** Patients continuing ETN therapy sustained HRQOL and utility improvements attained during the original PLA-controlled trial. Patients previously taking PLA showed rapid and sustained improvements in HRQOL and utility and substantial QALY gain with ETN therapy. (First Release Feb 15 2008; J Rheumatol 2008;35:662–7)

*Keyword Indexing Terms:*

ANKYLOSING SPONDYLITIS  
HEALTH-RELATED QUALITY OF LIFE

ETANERCEPT  
UTILITY  
HEALTH RESOURCE UTILIZATION

Ankylosing spondylitis (AS) is a chronic inflammatory disease of the sacroiliac joints that can also affect the longitudinal ligaments of the spine, insertions of tendons, and synovial tissue of peripheral joints<sup>1–3</sup>. Pain and stiffness in the back and joints and limitations of spinal mobility reduce the ability of patients to perform daily activities and negatively affect patient quality of life. Indeed, the disease leaves its mark on patients' ability to perform physical activities, with

pronounced reductions in physical domain scores of the Medical Outcome Study Short Form-36 (SF-36)<sup>4–6</sup>. The disease is also associated with an increased absence from work and increased work disability compared with the general population<sup>7–9</sup>. Fatigue and worries about health, including family relationships, add to the burden experienced by patients<sup>5,10</sup>.

Utility measures are preference-based measures of health-related quality of life (HRQOL), with utility scores representing the values that society assigns to various health states. Studies have shown reduced utility as measured by the EuroQOL-5D (EQ-5D) in patients with AS<sup>11,12</sup>. Algorithms for calculating EQ-5D utility scores were constructed using data collected from members of the general public. Therefore, these utility scores reflect the societal perspective of their corresponding health states<sup>13–16</sup>. More specifically, EQ-5D scores represent the degree to which members of the general public are willing to trade off the given EQ-5D health state for a perfect state of health with a shorter duration. Another utility measure, the Short Form-6D (SF-6D), is a preference-based single index of health

*From the Department of Internal Medicine, Division of Rheumatology, University Hospital Maastricht, Maastricht, The Netherlands; Amgen Inc., Thousand Oaks, California, USA; and Amgen (Europe) GmbH, Zug, Switzerland.*

*Funded by Immunex Corporation, a wholly owned subsidiary of Amgen Inc., and by Wyeth Research.*

*A. Boonen, MD, PhD; Department of Internal Medicine, Division of Rheumatology, University Hospital Maastricht; V. Patel, PharmD; S. Traina, PhD; C-F. Chiou, PhD; W. Tsuji, MD, Amgen Inc.; A. Maetzel, MD, MSc, PhD, Amgen (Europe) GmbH.*

*Address reprints to Dr. A. Boonen, Department of Internal Medicine, Division of Rheumatology, University Hospital Maastricht, PO Box 5800, 6202 AZ Maastricht, The Netherlands. E-mail: aboo@sint.azm.nl*

*Accepted for publication November 8, 2007.*

Personal non-commercial use only. The Journal of Rheumatology Copyright © 2008. All rights reserved.

that is derived from the SF-36, with scores calculated using a published algorithm<sup>17,18</sup>. Health states for the SF-6D are valued by a representative UK population sample applying standard gamble to assess the level of risk that a patient is willing to accept to attain a preferable health state. Utility scores typically range from 0 (death) to 1 (perfect health). Some utility measures such as EQ-5D allow utility scores to be less than 0 to indicate a health state worse than death.

An important application of utility is that it can be used to calculate quality-adjusted life-years (QALY), which is commonly used in cost-effectiveness analyses<sup>13</sup>. For example, 1 year with AS and utility score of 0.5 is only half as good as 1 year in perfect health with a utility score of 1. This is because QALY for this hypothetical patient with AS would be 0.5, whereas the QALY for a person in perfect health would be 1.0.

Etanercept (ETN), a fully human soluble tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) receptor-Fc fusion protein, has demonstrated short- and long-term clinical efficacy in patients with AS<sup>19,21</sup>. Results from a recent analysis of data from 2 trials<sup>19,21</sup> indicate that ETN significantly improves HRQOL scores relative to placebo (PLA) at 16 weeks and relative to baseline at 48 weeks<sup>4</sup>. Longer-term HRQOL and utility data, however, are not available. We describe the long-term effects of ETN therapy on HRQOL and utility from an open-label extension study of ETN in patients with AS and provide an estimate of the QALY gained.

## MATERIALS AND METHODS

**Study design.** This 72-week, multicenter, open-label extension study was designed to evaluate long-term safety, efficacy, and patient-reported outcomes for patients receiving ETN after completing 24 weeks of treatment with ETN or PLA. A detailed description of the study design for both the double-blind phase and the subsequent open-label extension phase has been reported<sup>4,19,20</sup>. Briefly, patients with active AS who met the modified New York criteria were enrolled in the study<sup>22</sup>. A total of 277 patients were randomized in a double-blind fashion to receive either subcutaneous ETN 25 mg or PLA twice weekly for 24 weeks. The study was conducted at 28 sites across North America and Europe and was approved by the Institutional Review Boards or independent ethics committees of all centers. Patients signed informed consent forms before screening and enrollment.

All patients who had (1) completed the double-blind phase of the clinical trial, (2) discontinued because of lack of efficacy after at least 12 weeks but completed follow-up evaluations, or (3) discontinued owing to an adverse event that subsequently resolved were eligible to enroll in the ongoing open-label extension study. All patients received subcutaneous ETN 25 mg twice weekly (or 50 mg weekly) for up to 168 weeks. The data presented in this report on long-term HRQOL and utility represent 72 weeks of open-label treatment.

**Patient-reported outcomes. Short Form-36.** The SF-36 (version 1) was administered at open-label baseline and at 12-week intervals for up to 72 weeks. The SF-36 is a widely used generic HRQOL measure chosen for its multidimensionality, brevity, and previous use in other diseases<sup>23,24</sup>. This 36-item instrument measures 8 domains, 4 of which predominantly reflect physical wellness and are aggregated into a physical component score (PCS; physical functioning, role limitations attributable to physical problems, bodily pain, and general health). The other 4 domains predominantly reflect emotional and social well-being and are aggregated into a mental component score (MCS; vitality, social function, role limitations due to

emotional problems, and mental health). PCS and MCS scores range from 0 to 100, with higher scores indicating better HRQOL. A difference of 5 points on an SF-36 score is considered "clinically and socially relevant"<sup>25</sup>. Normalized scoring was utilized.

**EQ-5D.** EQ-5D and EQ-5D visual analog scale (EQ-VAS) were administered at open-label baseline and at 12-week intervals for up to 72 weeks. EQ-5D utility scores were constructed based on an algorithm using data from preference elicitation by time trade-off from a UK population<sup>26</sup>. Negative utility values were imputed as 0. EQ-VAS scores were reported on a scale of 0 to 100, with the lowest and highest scores labeled "worst imaginable health state" and "best imaginable health state," respectively.

**Short Form-6D.** The SF-6D comprises 10 questions from the SF-36 that encompass 6 domains of health (physical functioning, role limitations, social functioning, pain, mental health, and vitality). SF-6D utilities were calculated using an algorithm based on utility elicitation using standard gamble from healthy individuals in the United Kingdom, and utility scores ranged from 0.30 to 1.00<sup>16,17</sup>. The SF-6D scores were calculated at open-label baseline and at 12-week intervals for up to 72 weeks.

**Analysis methods.** To describe the change in HRQOL and utility over time, last observation carried forward methodology was used to impute values for the remainder of the study period, except for patients who did not complete the first assessment at week 12, who were excluded from the sample. Descriptive statistics were used to summarize SF-36, EQ-5D, and SF-6D scores. Baseline SF-36, EQ-5D, and SF-6D scores were compared between the 2 groups (PLA/ETN and ETN/ETN). Scores at each of the subsequent time points were also compared to evaluate whether HRQOL and utility in the PLA/ETN group achieved levels comparable to those observed in the ETN/ETN group at the same time point and to assess the sustainability of response for both groups. Baseline values and mean change from baseline were calculated and compared for EQ-5D utilities to SF-6D utilities. For SF-36, EQ-5D, and SF-6D, *p* values were calculated using the *t* test comparing the means of each group. QALY over the 72 weeks were calculated based on the EQ-5D and SF-6D utility scores in the previous placebo group (PLA/ETA). It was assumed that the utility score would not have changed if the patients had not received active treatment. Patients who withdrew during the 72-week follow-up were assigned the mean baseline utility score before starting active treatment.

## RESULTS

**Patients.** The disposition and demographics of the patients entering the open-label extension phase of the trial have been published<sup>20</sup>. Of the 277 patients who received treatment and were analyzed in the original randomized trial, 257 [129 previous PLA (PLA/ETN group) and 128 previous ETN (ETN/ETN group)] enrolled in the open-label extension study, and 220 (105 in the PLA/ETN group and 115 in the ETN/ETN group) completed the 72-week open-label extension study (Figure 1). A total of 232 patients (113 in the PLA/ETN group and 119 in the ETN/ETN group) had data at baseline and at week 12 for at least 1 patient-reported outcome, and were included in the analysis. Of these, all had at least 2 assessments of the EQ-5D, and 227 provided 2 assessments of the SF-36 and SF-6D (Figure 1). The PLA/ETN and ETN/ETN groups were similar with respect to baseline demographics and disposition (Table 1).

**Patient-reported outcomes.** The SF-36 was completed at open-label baseline and week 12 by 227 (88%) of 257 patients. At open-label baseline, mean values for the SF-36 PCS were significantly lower for the PLA/ETN group than

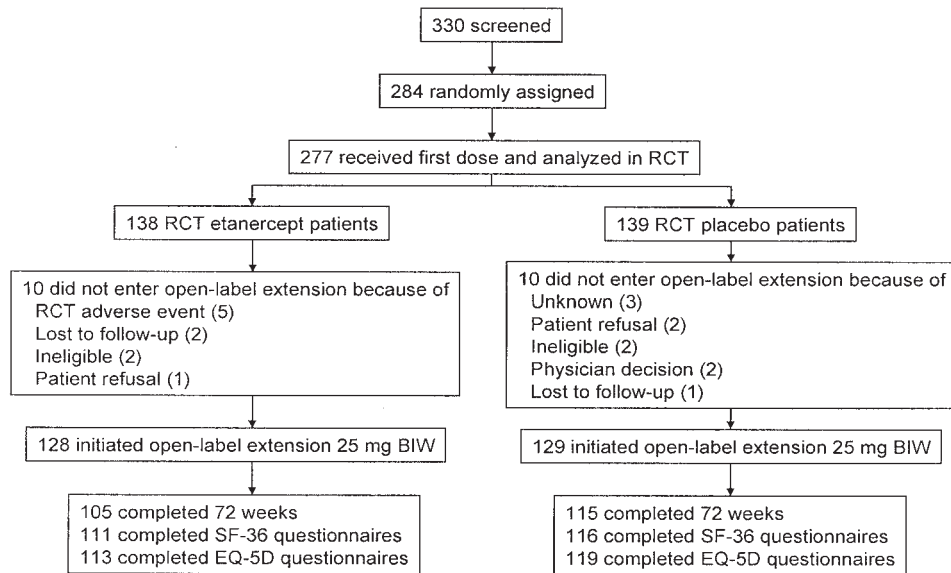


Figure 1. Patient disposition in the open-label trial. Patients who completed EQ-5D and SF-6D questionnaires had a baseline and one followup assessment. BIW: twice weekly; EQ-5D: EuroQOL-5D; RCT: randomized controlled trial; SF-36: Medical Outcome Study Short Form-36.

Table 1. Baseline demographics and disposition for the 232 patients entering the open-label extension phase meeting eligibility criteria for the patient-reported outcomes analyses. Values are mean (SD) unless indicated otherwise.

Characteristic	Open-Label Enrollees	
	Prior ETN, n = 119	Prior PLA, n = 113
Age, yrs	40.90 (9.02)	41.03 (10.92)
Men, n (%)	85 (75.2)	89 (74.8)
Caucasian, n (%)	108 (95.6)	110 (92.4)
Height, cm	173.45 (9.19)	171.46 (10.36)
Weight, kg	82.44 (18.83)	83.34 (20.14)
Disease duration, yrs	10.90 (7.91)	10.75 (8.83)
SF-36 PCS <sup>†</sup>	40.14 (12.15)*	33.71 (10.20)
SF-36 MCS <sup>†</sup>	50.49 (10.70)	47.94 (11.00)
EQ-5D	0.69 (0.20)*	0.49 (0.30)
EQ VAS	66.50 (18.66)	55.93 (20.66)
SF-6D <sup>†</sup>	0.71 (0.13)**	0.65 (0.13)

<sup>†</sup> Patient numbers for the SF-36 and SF-6D analyses were 111 for the prior ETN group and 116 for the prior PLA group. \*  $p < 0.0001$ ; \*\*  $p = 0.0007$ . EQ-5D: EuroQOL-5D; EQ VAS: EuroQOL visual analog scale; ETN: etanercept; MCS: Mental Component Score; PCS: Physical Component Score; PLA: placebo; SF-36: Short-Form-36; SF-6D: Short Form-6D.

the ETN/ETN group (33.7 vs 40.1;  $p < 0.0001$ ; Figure 2A). Mean SF-36 MCS values were also lower in the PLA/ETN group at open-label baseline, but the difference was not statistically significant (47.9 vs 50.5;  $p = 0.08$ ; Figure 2B). Patients in the PLA/ETN group achieved levels similar to the ETN/ETN group on the SF-36 PCS and MCS after 12 weeks of open-label ETN therapy. The levels of SF-36 PCS (Figure 2A) and MCS (Figure 2B) scores in both groups were sustained for 72 weeks.

The EQ-5D was completed at open-label baseline and

week 12 by 232 (90%) of 257 patients. The EQ-5D score at open-label baseline was significantly lower in the PLA/ETN group than in the ETN/ETN group (0.49 vs 0.69;  $p < 0.0001$ ; Figure 3A). The average QALY gain calculated using EQ-5D in the PLA/ETN group over the 72 weeks for all patients was 0.24. The SF-6D analysis had usable data at baseline for 227 (88%) of 257 patients. Mean scores at open-label baseline were significantly lower in the PLA/ETN group than in the ETN/ETN group (0.65 vs 0.71;  $p = 0.0007$ ; Figure 3B). Mean scores at subsequent evaluation points were not significantly different between the 2 groups (Figure 3B). The average QALY gain calculated using SF-6D in the PLA/ETN group over 72 weeks was 0.10. Similarly, the EQ-VAS score in the PLA/ETN group at open-label baseline [completed by 235 (91%) patients] was significantly lower than in the ETN/ETN group (55.9 vs 66.5;  $p < 0.001$ ), but attained similar levels to those in the ETN/ETN group by week 12 and showed sustained benefits through week 72 (data not shown).

For the comparison of SF-6D and EQ-5D scores between the groups at open-label baseline, mean scores for SF-6D were significantly higher than EQ-5D scores in the PLA/ETN group (0.65 vs 0.49;  $p < 0.0001$ ), but not in the ETN/ETN group (0.71 vs 0.69;  $p = 0.3994$ ). For the comparison of mean changes in SF-6D and EQ-5D scores from baseline to week 12, the change in the PLA/ETN group was significantly lower for SF-6D than for the EQ-5D (0.06 vs 0.18;  $p < 0.0001$ ).

## DISCUSSION

The results from our study demonstrate that ETN produces sustained improvement in SF-36 as well as EQ-5D and SF-

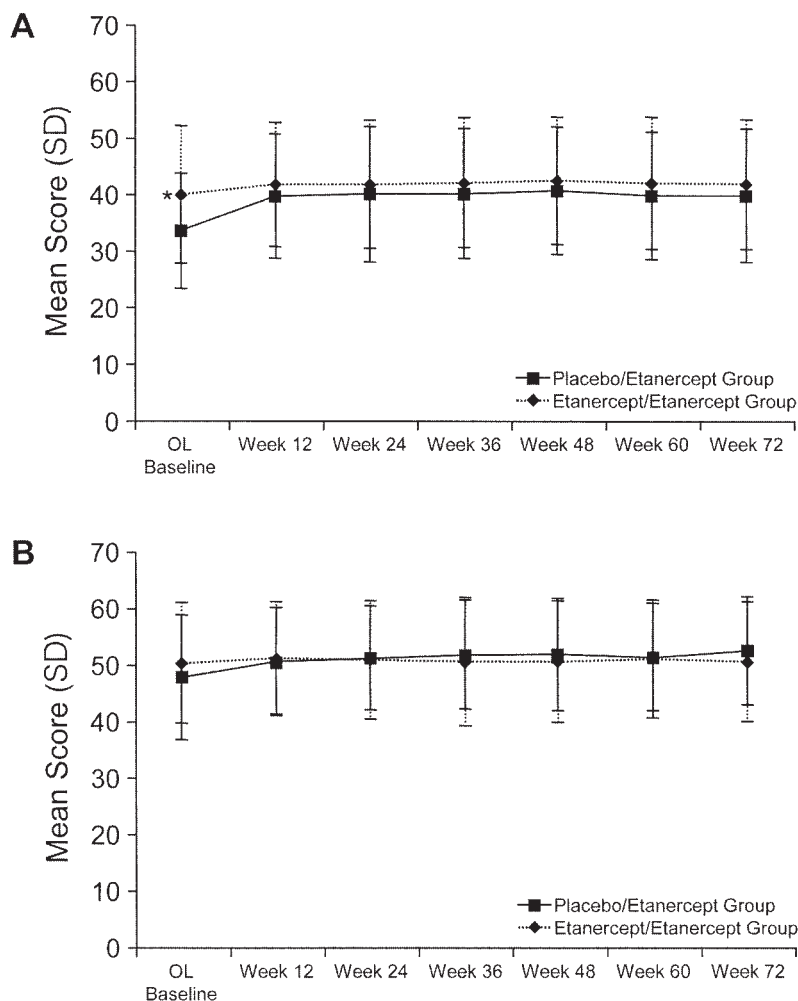


Figure 2. Mean scores over time during open-label extension study for (A) SF-36 Physical Component Scores and (B) SF-36 Mental Component Scores using last observation carried forward method. OL: open label; SD: standard deviation; SF-36: Medical Outcome Study Short Form-36. \* $p < 0.0001$  vs placebo/etanercept.

6D utility scores over a 72-week period. Patients who were assigned to PLA during the first 24 weeks achieved a comparable level of HRQOL and utility after switching to ETN, with a significant improvement of about 0.2 utility points in the course of the first 12 weeks of the open-label extension. The overall QALY gain over the 72-week extension for this group was substantial (0.24 and 0.10 for EQ-5D and SF-6D, respectively). These values translate into considerable QALY gains over 1 year (0.17 and 0.07, respectively, equivalent to an additional 62 and 26 days, respectively, of perfect health). The findings regarding the gain in QALY are important for economic evaluations in AS. Up to now, economic evaluations in AS with TNF- $\alpha$  inhibitors assumed improvement in utility by indirect evidence<sup>27</sup>. These results show that these assumptions are likely valid.

In a separate report from this open-label extension trial, the clinical efficacy and tolerability of ETN in patients with

AS was demonstrated for up to 96 weeks after randomization<sup>19,20</sup>. The short-term initial improvement in domains of the SF-36 has already been observed in PLA-controlled studies of TNF- $\alpha$  inhibitors in patients with AS, and in all of these studies the improvements in the PCS were larger than in the MCS<sup>4,28,29</sup>. Only 1 small ( $n = 52$ ) open-label extension study demonstrated longer-term improvements in SF-36 PCS and MCS with infliximab therapy over 2 years<sup>30</sup>. Our present study demonstrates sustained effects of SF-36 with ETN in a large group of patients.

As expected, the SF-6D utility values were much higher than the EQ-5D utility values in the PLA/ETN group at baseline of open-label treatment. Additionally, the mean changes from baseline in utility values in the PLA/ETN group were much lower for the SF-6D compared with the EQ-5D. As a consequence of this, the average QALY gain calculated using SF-6D is much lower than EQ-5D. This is

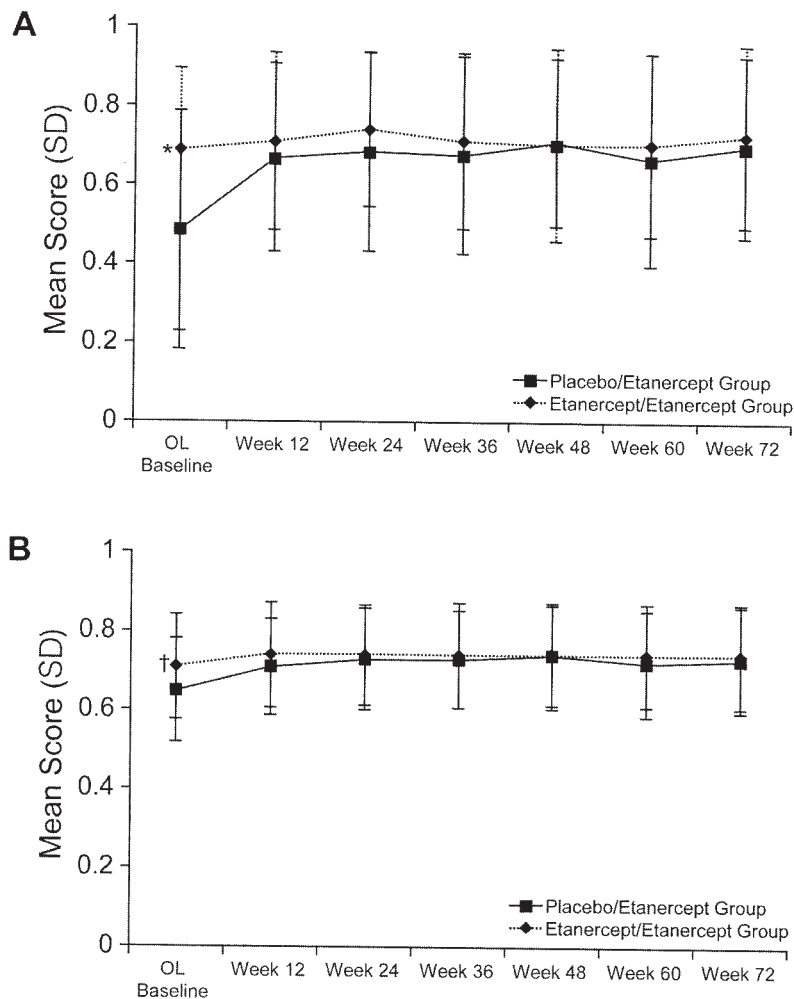


Figure 3. Mean scores over time during the open-label extension study for (A) combined EQ-5D scores and (B) SF-6D scores using last observation carried forward method. EQ-5D: EuroQOL-5D; OL: open label; SD: standard deviation; SF-6D: Short Form-6D. \* $p < 0.0001$  vs placebo/etanercept; † $p = 0.0007$  vs placebo/etanercept.

expected because utility is scored on a narrower range of scale for the SF-6D (0.3–1.0) than for the EQ-5D (0–1). These differences need to be taken into consideration when estimating QALY gains or using QALY for cost-effectiveness calculations.

A limitation of this study is the open-label study design and the absence of data on HRQOL and utility in patients who withdrew from treatment because of adverse events or insufficient efficacy. However, an advantage of this study design is that it likely reflects a more real-life situation, proving that patients experience sustained improvements.

The clinical efficacy and tolerability of ETN in patients with AS are well established<sup>19–21</sup>, with patients experiencing durable clinical benefits for up to 96 weeks. Consistent with these reports of sustained improvements in the signs and symptoms of AS with ETN therapy, ETN showed rapid and sustained improvement in HRQOL and utility in this study,

as well as substantial QALY gain during the 72-week treatment period. These benefits further support the long-term use of ETN in patients with AS.

#### ACKNOWLEDGMENT

The authors thank Rick Davis, MS, RPh, on behalf of Amgen Inc., for help with the preparation of this manuscript.

#### REFERENCES

1. Sieper J, Braun J, Rudwaleit M, Boonen A, Zink A. Ankylosing spondylitis: an overview. *Ann Rheum Dis* 2002;61 Suppl 3:iii8-18.
2. van der Linden S, van der Heijde D, Braun J. Ankylosing spondylitis. In: Harris EJ, Budd R, Firestein GS, Genovese MC, Sargent JS, Sledge CB, editors. *Kelly's textbook of rheumatology*. 7th ed. Philadelphia: Elsevier Saunders; 2005:1125-41.
3. Khan MA. Update on spondyloarthropathies. *Ann Intern Med* 2002;136:896-907.
4. Davis JC, van der Heijde D, Dougados M, Woolley JM. Reductions in health-related quality of life in patients with ankylosing

- spondylitis and improvements with etanercept therapy. *Arthritis Rheum* 2005;53:494-501.
5. Ozgul A, Peker F, Taskaynatan MA, Tan AK, Dincer K, Kalyon TA. Effect of ankylosing spondylitis on health-related quality of life and different aspects of social life in young patients. *Clin Rheumatol* 2006;25:168-74.
  6. Dagfinrud H, Mengshoel AM, Hagen KB, Loge JH, Kvien TK. Health status of patients with ankylosing spondylitis: a comparison with the general population. *Ann Rheum Dis* 2004;63:1605-10.
  7. Zink A, Listing J, Klindworth C, Zeidler H. The national database of the German Collaborative Arthritis Centres: I. Structure, aims, and patients. *Ann Rheum Dis* 2001;60:199-206.
  8. Boonen A, Chorus A, Miedema H, van der Heijde D, van der Tempel H, van der Linden S. Employment, work disability, and work days lost in patients with ankylosing spondylitis: a cross sectional study of Dutch patients. *Ann Rheum Dis* 2001;60:353-8.
  9. Boonen A, van der Heijde D, Landewe R, et al. Work status and productivity costs due to ankylosing spondylitis: comparison of three European countries. *Ann Rheum Dis* 2002;61:429-37.
  10. Ward MM. Health-related quality of life in ankylosing spondylitis: a survey of 175 patients. *Arthritis Care Res* 1999;12:247-55.
  11. Kobelt G, Andlin-Sobocki P, Maksymowych WP. Costs and quality of life of patients with ankylosing spondylitis in Canada. *J Rheumatol* 2006;33:289-95.
  12. Kobelt G, Andlin-Sobocki P, Brophy S, Jonsson L, Calin A, Braun J. The burden of ankylosing spondylitis and the cost-effectiveness of treatment with infliximab (Remicade). *Rheumatology Oxford* 2004;43:1158-66.
  13. Drummond MF, O'Brien B, Stoddart G, Torrence G. Chapter 6: Cost-utility analysis. *Methods for the economic evaluation of health care programmes*. 2nd ed. Oxford, New York: Oxford University Press; 1997:139-204.
  14. Brooks R. EuroQOL: the current state of play. *Health Policy* 1996;37:53-72.
  15. Hurst NP, Jobanputra P, Hunter M, Lambert M, Lochhead A, Brown H. Validity of EuroQOL — a generic health status instrument — in patients with rheumatoid arthritis. *Economic and Health Outcomes Research Group. Br J Rheumatol* 1994;33:655-62.
  16. Boonen A, van der Heijde D, Landewe R, et al. How do the EQ-5D, SF-6D and well-being rating scale compare in patients with ankylosing spondylitis. *Ann Rheum Dis* 2007;66:771-7. Epub 2007 Jan 9
  17. Brazier J, Usherwood T, Harper R, Thomas K. Deriving a preference-based single index from the UK SF-36 Health Survey. *J Clin Epidemiol* 1998;51:1115-28.
  18. Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. *J Health Econ* 2002;21:271-92.
  19. Davis JC, Jr, van der Heijde D, Braun J, et al. Recombinant human tumor necrosis factor receptor (etanercept) for treating ankylosing spondylitis: a randomized, controlled trial. *Arthritis Rheum* 2003;48:3230-6.
  20. Davis JC, van der Heijde DM, Braun J, et al. Sustained durability and tolerability of etanercept in ankylosing spondylitis for 96 weeks. *Ann Rheum Dis* 2005;64:1557-62.
  21. Gorman JD, Sack KE, Davis JC, Jr. Treatment of ankylosing spondylitis by inhibition of tumor necrosis factor alpha. *N Engl J Med* 2002;346:1349-56.
  22. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. *Arthritis Rheum* 1984;27:361-8.
  23. Kosinski M, Keller SD, Hatoum HT, Kong SX, Ware JE Jr. The SF-36 Health Survey as a generic outcome measure in clinical trials of patients with osteoarthritis and rheumatoid arthritis: tests of data quality, scaling assumptions and score reliability. *Med Care* 1999;37 Suppl:MS10-MS22.
  24. Kosinski M, Keller SD, Ware JE, Jr, Hatoum HT, Kong SX. The SF-36 Health Survey as a generic outcome measure in clinical trials of patients with osteoarthritis and rheumatoid arthritis: relative validity of scales in relation to clinical measures of arthritis severity. *Med Care* 1999;37 Suppl:MS23-MS39.
  25. Ware J Jr, Kosinski M, Gandek B. SF-36 Health Survey. Manual and interpretation guide. Lincoln, RI: QualityMetric Inc.; 2000.
  26. EuroQol — A new facility for the measurement of health-related quality of life. The EuroQol Group. *Health Policy* 1990; 16:199-208.
  27. Kobelt G, Andlin-Sobocki P, Maksymowych WP. The cost-effectiveness of infliximab (Remicade) in the treatment of ankylosing spondylitis in Canada. *J Rheumatol* 2006;33:732-40.
  28. van der Heijde D, Dijkmans B, Geusens P, et al. Efficacy and safety of infliximab in patients with ankylosing spondylitis: results of a randomized, placebo-controlled trial (ASSERT). *Arthritis Rheum* 2005;52:582-91.
  29. van der Heijde D, Luo M, Matsumoto A, et al. Adalimumab improves health-related quality of life in patients with active ankylosing spondylitis — the ATLAS trial [abstract 490]. *Arthritis Rheum* 2005;52 Suppl:S211.
  30. Braun J, Brandt J, Listing J, et al. Two year maintenance of efficacy and safety of infliximab in the treatment of ankylosing spondylitis. *Ann Rheum Dis* 2005;64:229-34.