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FDA Approves Strattera® for Maintenance of ADHD in Children and Adolescents

First Medication Indicated for Maintenance Treatment for ADHD

INDIANAPOLIS – May 8, 2008 – Eli Lilly and Company (NYSE: LLY) announced today that the United States Food and Drug Administration (FDA) has approved Strattera® (atomoxetine HCI) for maintenance treatment of Attention-Deficit/Hyperactivity Disorder (ADHD) in children and adolescents. Strattera, a selective norepinephrine reuptake inhibitor, is the first FDA-approved non-stimulant to treat ADHD in children, adolescents and adults.

"The approval provides physicians and their patients with the first treatment option that is indicated for maintenance of ADHD" said Thomas J. Spencer, M.D.
Associate Professor of Psychiatry, Harvard Medical School. "This is critical as ADHD may be a life-long disease and effective long-term control of symptoms may mean improved outcomes in children and adolescents."

The safety and efficacy of Strattera in the maintenance of ADHD was demonstrated in one of the largest relapse prevention studies ever conducted in ADHD, which is one of the most common mental health disorders in children and adolescents. [1]

The 18-month trial of about 600 children and adolescents aged six to 15 years, who met DSM-IV (Diagnostic and Statistical Manual of Mental Disorders) criteria for ADHD, showed Strattera was superior to placebo in maintaining continuous efficacy in patients, as measured by the ADHD Rating Scale (ADHD-RS). Additionally, at the end of the trial, patients taking Strattera had lower relapse rates (2.5 percent) as compared to patients taking placebo (12.2 percent).

Strattera provides uninterrupted relief from ADHD symptoms throughout the day into the evening. This is important since the symptoms of ADHD go beyond the work and school day. ADHD

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FDA Approves Symbyax® as First Medication for Treatment-Resistant Depression

New Indication is One of Three FDA Approvals Spanning Lilly Neuroscience Brands

INDIANAPOLIS – March XX, 2009 – The U.S. Food and Drug Administration (FDA) has approved a new indication for Symbyax® (olanzapine and fluoxetine HCl capsules), Eli Lilly and Company (NYSE: LLY) announced today. Symbyax is now the first drug approved by the FDA for the acute treatment of treatment-resistant depression (TRD).

"Living with major depressive disorder is difficult and distressing for anyone, but even more so for patients whose symptoms continue despite treatment," said Lilly Medical Director Dr. Sara Corya. "Until today, there has been no approved medication for treatment-resistant depression. Now, after two failed attempts with other antidepressants, doctors and patients have a new treatment option."

In other actions, the FDA approved two new combination indications for Zyprexa® (olanzapine) and fluoxetine for the acute treatment of bipolar depression and TRD. Lilly originally developed Prozac® (fluoxetine HCl), the branded version of fluoxetine.

Additionally, the format of the product labels was updated according to the Physician's Labeling Rule (PLR), which many consider easier to understand. Additions were also made to the Medication Guides for Symbyax and Prozac, and a new Medication Guide was created for Zyprexa. Medication Guides include information for patients about potential risks associated with a particular product.

"Lilly maintains its commitment to patients by the continued research of Zyprexa, Symbyax, and Prozac," said Dr. Cherri Miner, Lilly neuroscience senior medical director. "Today's new indications confirm that these medications are valuable tools for patients in the fight against severe and disabling mental illness, and expand treatment options for prescribers and patients."

Indication Details:

1. The new Symbyax TRD indication is for acute treatment of adult patients with major depressive disorder who have not responded to two separate trials of different antidepressants of adequate dose and duration in their current episode.
2. Zyprexa, in combination with fluoxetine, is now approved for the acute treatment of TRD in adults.
3. Symbyax was the first drug approved by the FDA for acute treatment of bipolar depression in adults in 2003. Zyprexa, in combination with fluoxetine, is now approved for the same indication.

With these FDA approvals, clinicians in the United States have the choice to use the single pill option (Symbyax), or the two drugs (Zyprexa and fluoxetine) together, allowing physicians to tailor treatment to each patient's needs. Neither Zyprexa nor fluoxetine are indicated as monotherapy for bipolar depression or TRD.

Additional Label Changes

In addition to the new indications, Lilly has updated the Symbyax and Zyprexa labels to include additional information regarding weight gain, hyperglycemia, and hyperlipidemia following the FDA's review of clinical trial data that Lilly submitted to the FDA between August 2007 and July 2008. In the course of this review, Lilly provided data from several large databases, including analyses of placebo-controlled data, comparator-controlled data, long-term data and special populations, including antipsychotic-naïve patients.

Symbyax and Zyprexa in Combination with Fluoxetine Supportive Study Details for TRD

The data package submitted to the FDA supporting the approval of Symbyax for TRD as well as the approval of Zyprexa in combination with fluoxetine for TRD, included one pivotal trial and data from three supportive trials and one inconclusive trial. The TRD-related label language includes efficacy data from three of these clinical studies (n=579). Acute safety information was based on a total of 10 studies. Doses evaluated in these studies ranged from 6-18 mg for olanzapine and 25-50 mg for fluoxetine in fixed combination.

- An eight-week randomized, double-blind, controlled study was conducted to evaluate the efficacy of Symbyax in patients (n=300) who met the fourth edition of "Diagnostic and Statistical Manual of Mental Disorders" (DSM-IV) criteria for major depressive disorder (MDD) and did not respond to two antidepressants of adequate dose and duration in their current episode. Patients who were not responding to an antidepressant in their current episode entered an eight-week open-label fluoxetine lead-in, and then non-responders were randomized (1:1:1) to receive an eight-week trial of Symbyax, olanzapine, or fluoxetine. Symbyax was flexibly dosed between 6/50 mg, 12/50 mg, and 18/50 mg (olanzapine/fluoxetine dose). Results from this study yielded a greater statistically significant reduction in mean total Montgomery Åsberg Depression Rating Scale (MADRS) scores from baseline to endpoint for Symbyax versus fluoxetine and olanzapine alone.
- A second study of 28 patients who met the same criteria for TRD demonstrated statistically significant greater reductions in MADRS scores for Symbyax versus fluoxetine and olanzapine alone.
- A third study demonstrated statistically significant greater reductions in total MADRS scores for Symbyax versus fluoxetine or olanzapine alone, when analyzed in a subpopulation of depressed patients (n=251) who met the same criteria for treatment resistance.
- Although not cited in the approved label, two additional studies were included in the sNDA data package. One of the trials provided statistically significant supporting data for Symbyax in the acute treatment of TRD, while the other trial was inconclusive.

- An integrated analysis of all five studies provided to the FDA yielded a statistically significant greater reduction in mean total MADRS scores from baseline to endpoint in the defined population for patients treated with Symbyax (-12.2) vs. fluoxetine (-8.5, p=0.015) and olanzapine (-7.7, p=0.007) and greater statistically significant remission rates (p=<0.05) for patients treated with Symbyax (25.5 percent), vs. fluoxetine (17.3 percent) and olanzapine (14.0 percent).

Adverse events that were reported in five percent or more of Symbyax-treated patients in these trials and at twice the rate of placebo were weight gain, increased appetite, dry mouth, somnolence and fatigue. This is consistent with the current safety information provided in the Symbyax label.

Pivotal Studies for Bipolar Depression

Approval was based on the results of two identical, eight-week, randomized, double-blind, controlled studies of patients diagnosed with bipolar depression. Zyprexa and fluoxetine in combination (6/25, 6/50, or 12/50 mg/day respectively) were compared to both Zyprexa alone (5 to 20 mg/day) and placebo. The primary outcome was symptom improvement based on the Montgomery-Åsberg Depression Rating Scale (MADRS). Both trials showed that combination therapy with Zyprexa and fluoxetine resulted in a statistically significant greater improvement compared to Zyprexa alone and placebo.

- In one eight-week controlled trial, combination therapy with Zyprexa and fluoxetine (n=42) was superior to both Zyprexa monotherapy (n=169) and placebo (n=174) in the reduction of the MADRS total score.
- In a second eight-week controlled trial, combination therapy with Zyprexa and fluoxetine (n=40) was superior to both Zyprexa monotherapy (n=182) and placebo (n=181) in the reduction of MADRS total score.

About Treatment-Resistant Depression

It is estimated that up to 35 percent of patients with depression – or approximately two percent of the general population – fail to achieve an adequate response to two respective antidepressant drug therapy attempts.[1] The exact causes of depression and why some people do not respond to initial pharmacological therapy is not known.[2]

About Bipolar Depression

Depressive episodes associated with bipolar I disorder (also known as bipolar depression) refers to the depressive phase of bipolar disorder, a complex mental illness characterized by debilitating swings in mood. The swings range from manic episodes, marked by abnormal euphoria, elation and irritability, to episodes of deep depression, marked by extreme sadness and difficulty functioning.[3]

Safety Information for Symbyax and Concomitant Use of Zyprexa and Fluoxetine

Symbyax is indicated in the United States for the acute treatment of bipolar depression and treatment-resistant depression in adults. Treatment-resistant depression is defined as major depressive disorder in adults who do not respond to two separate trials of different antidepressants of adequate dose and duration in the current episode.

Antidepressants can increase suicidal thoughts and behaviors in children, teens and young adults. All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for worsening depression symptoms, unusual changes in behavior or thoughts of suicide. Patients and caregivers should be especially observant within the first few months of treatment or after a change in dose. Symbyax is not approved for children and adolescents.

Symbyax is not approved for the treatment of patients with dementia-related psychosis. Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death.

In addition, compared to elderly patients with dementia-related psychosis taking a placebo, there was a significantly higher incidence of cerebrovascular adverse events in elderly patients with dementia-related psychosis treated with olanzapine, a component of Symbyax.

Symbyax should not be used with a monoamine oxidase inhibitor (MAOI) or within at least 14 days of discontinuing an MAOI. At least five weeks should be allowed after stopping Symbyax before starting an MAOI. Thioridazine should not be given with Symbyax or within at least five weeks after stopping Symbyax. Concomitant use of Symbyax in patients taking pimozide is contraindicated. Symbyax is contraindicated in patients with known hypersensitivity to the product or any component of the product.

As with all antipsychotic medications, a potentially fatal condition known as Neuroleptic Malignant Syndrome (NMS) has been reported with olanzapine. If signs and symptoms appear, immediate discontinuation is recommended. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmia). Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure.

Hyperglycemia, in some cases associated with ketoacidosis, coma, or death, has been reported in patients treated with atypical antipsychotics, including olanzapine alone, as well as olanzapine taken concomitantly with fluoxetine. While relative risk estimates are inconsistent, the association between atypical antipsychotics and increases in glucose levels appears to fall on a continuum and olanzapine appears to have a greater association than some other atypical antipsychotics. Physicians should consider the risks and benefits when prescribing Symbyax to patients with an established diagnosis of diabetes mellitus, or having borderline increased blood glucose level. Patients taking Symbyax should be monitored regularly for worsening of glucose control. Patients starting treatment with Symbyax should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia,

polyuria, palyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment should undergo fasting blood glucose testing.

Undesirable alterations in lipids have been observed with Symbyax use. Clinical monitoring, including baseline and follow-up lipid evaluations in patients using Symbyax, is advised. Clinically significant, and sometimes very high, elevations in triglyceride levels have been observed with Symbyax use. Clinically meaningful increases in total cholesterol have also been seen with Symbyax use.

Potential consequences of weight gain should be considered prior to starting Symbyax. Patients receiving Symbyax should receive regular monitoring of weight.

Development of a potentially life-threatening serotonin syndrome or NMS-like reactions have been reported with serotonin-norepinephrine reuptake inhibitors (SNRIs) and selective serotonin reuptake inhibitors (SSRIs) alone, including Symbyax treatment, but particularly with concomitant use of serotonergic drugs, including triptans, with drugs which impair serotonin metabolism, including MAOIs, or with antipsychotics or other dopamine antagonists. If these events occur, treatment with Symbyax and any concomitant serotonergic or antidopaminergic agents should be discontinued immediately and supportive symptomatic treatment should be initiated.

If rash or other possibly allergic phenomena appear for which an alternative etiology cannot be determined, immediate discontinuation is recommended.

Patients being treated with Symbyax should be screened for bipolar disorder and monitored for mania/hypomania.

As with all antipsychotic treatment, prescribing should be consistent with the need to minimize Tardive Dyskinesia (TD). The risk of developing TD and the likelihood that it will become

irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic increase. The syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn.

Symbyax may induce orthostatic hypotension associated with dizziness, tachycardia, bradycardia, and in some patients, syncope, especially during the initial dose-titration period. Particular caution should be used in patients with known cardiovascular disease, cerebrovascular diseases, or those predisposed to hypotension.

Symbyax should be used cautiously in patients with a history of seizures or with conditions that lower the seizure threshold.

Patients should be cautioned regarding the risk of bleeding associated with the concomitant use of Symbyax with non-steroidal anti-inflammatory drugs (NSAIDs), aspirin, warfarin or other drugs that affect coagulation.

As with other antidepressants, Symbyax has been associated with cases of clinically significant hyponatremia that appeared to be reversible when Symbyax was discontinued.

As with any CNS-active drug, Symbyax has the potential to impair judgment, thinking or motor skills.

As with other drugs that antagonize dopamine receptors, Symbyax elevates prolactin levels, and a modest elevation persists during administration.

Because of the long elimination half-lives of fluoxetine and its major metabolite, changes in dose will not be fully reflected in plasma for several weeks.

Other potentially serious adverse events include body temperature elevation, trouble swallowing and adverse events upon discontinuation of treatment.

The most common (≥5% and at least twice that for placebo) treatment-emergent adverse event associated with Symbyax in placebo-controlled clinical trials were weight gain, increased appetite, dry mouth, somnolence, fatigue, peripheral edema, tremor, sedation, hypersonmia, disturbance in attention, and blurred vision.

Full prescribing information, including boxed warnings, is available at www.symbyax.com, www.zyprexa.com and www.prozac.com.

About Lilly

Lilly, a leading innovation-driven corporation, is developing a growing portfolio of first-in-class and best-in-class pharmaceutical products by applying the latest research from its own worldwide laboratories and from collaborations with eminent scientific organizations. Headquartered in Indianapolis, Ind., Lilly provides answers -- through medicines and information -- for some of the world's most urgent medical needs. Additional information about Lilly is available at www.lilly.com.

This press release contains forward-looking statements about Zyprexa, Prozac, and Symbyax. These statements reflect management's current beliefs; however, as with any pharmaceutical product there are risks and uncertainties in the process of research and development, regulatory review, and commercialization. In addition, there are no guarantees that the products will continue to be commercially successful or will be successful in these new indications. For further discussion of these and other risks and uncertainties, see Lilly's filings with the United States Securities and Exchange Commission. Lilly undertakes no duty to update forward-looking statements.

Symbyax® (olanzapine and fluoxetine HCl capsules, Lilly)

Zyprexa® (olanzapine, Lilly)

Prozac® (fluoxetine HCl capsules, Lilly)

P-LLY

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Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis (CHAMPION)

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Summary

Background Biologic therapies such as adalimumab, a tumour necrosis factor antagonist, are safe and effective in the treatment of moderate to severe chronic plaque psoriasis.

Objectives To compare a biologic agent with methotrexate, a traditional systemic agent, to define clearly the role of biologics in psoriasis.

Methods Patients with moderate to severe plaque psoriasis were randomized to adalimumab (80 mg subcutaneously at week 0, then 40 mg every other week, n = 108), methotrexate (7·5 mg orally, increased as needed and as tolerated to 25 mg weekly; n = 110) or placebo (n = 53) for 16 weeks. The primary efficacy endpoint was the proportion of patients achieving at least a 75% improvement in the Psoriasis Area and Severity Index (PASI 75) after 16 weeks. Safety was assessed at all visits through week 16.

Results After 16 weeks, 79·6% of adalimumab-treated patients achieved PASI 75, compared with 35·5% for methotrexate ($P < 0·001$ vs. adalimumab) and 18·9% for placebo ($P < 0·001$ vs. adalimumab). Statistically significantly more adalimumab-treated patients (16·7%) than methotrexate-treated patients (7·3%) or placebo-treated patients (1·9%) achieved complete clearance of disease. The response to adalimumab was rapid, with a 57% improvement in mean PASI observed at week 4. Adverse events were similar across treatment groups. Adverse events leading to study discontinuation were greatest in the methotrexate group, primarily because of hepatic-related adverse events.

Conclusions After 16 weeks, adalimumab demonstrated significantly superior efficacy and more rapid improvements in psoriasis compared with either methotrexate or placebo.

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Key words
adalimumab, methotrexate, psoriasis, randomized controlled trial, tumour necrosis factor

Conflicts of interest
J.-H.S., G.S., L.D., K.P. and J.-P.O. have served as consultants for Abbott Laboratories. In addition, they have participated in continuing medical education events supported by unrestricted educational grants from Abbott. R.G.L. reports receiving fees as a consultant or advisory board member for Abbott, Amgen, Astellas, Boehringer-Ingelheim, Barrier Therapeutics and Genentech; he has received lecture fees from Abbott, Amgen/Wyeth and Biogen-Idec, and has been the principal investigator and received grants from Abbott, Amgen, Astellas, Centocor, Galderma and Genentech. K.U., M.K. and A.C. are employees of Abbott.

CHAMPION Study Investigators are listed at the end of the report.

Methotrexate has been widely used as an effective systemic therapy for psoriasis for > 40 years.[1–4] Advances in the understanding of the immunological basis of psoriasis in psoriatic plaques—such as the increased expression of tumour necrosis factor (TNF), a proinflammatory cytokine—has led to the advent of newer target-specific biologic agents, including TNF antagonists.[5]

Adalimumab is a fully human IgG1 monoclonal antibody that binds with high affinity and specificity to TNF.[6] The efficacy and safety of adalimumab[7–9] and other biologics[10–15]

have been established in several placebo-controlled trials of psoriasis. However, clinical trials comparing these agents with traditional systemic agents such as methotrexate are needed to clarify and define their place fully in the treatment of psoriasis. A search of the medical literature and clinical trial registries, such as ClinicalTrials.gov, indicates that the CHAMPION study was the first Phase III, randomized, double-blind, placebo-controlled trial to compare the efficacy and safety of a biologic and methotrexate in psoriasis. This study was designed to demonstrate that adalimumab was superior to placebo and not inferior to methotrexate in the treatment of patients with moderate to severe plaque psoriasis.

Materials and methods

Patients

The study protocol was approved by an independent ethics committee or institutional review board at each of the 28 study sites in Europe and Canada. Each patient provided written informed consent before any study-related procedures were initiated. Eligible patients included men and women ≥ 18 years of age with moderate to severe psoriasis, defined as ≥ 10% body surface area (BSA) involvement and a Psoriasis Area and Severity Index (PASI) of ≥ 10. The patients were to have had plaque psoriasis for at least 1 year and stable plaque psoriasis for at least 2 months. Patients were to have been candidates for systemic therapy or phototherapy and to have had active psoriasis despite treatment with topical agents. All patients were to have been naïve to both TNF-antagonist therapy and methotrexate.

Concomitant psoriasis therapies were not permitted during the study, with the exception of shampoos free of corticosteroids; bland emollients; and low-potency topical corticosteroids for the palms, soles, face, inframammary areas and groin only, provided they were not used within 24 h of a study visit. The washout period for prior psoriasis therapies was 2 weeks for topical therapies and phototherapy, 4 weeks for nonbiologic systemic therapies, and 12 weeks for biologic therapies. Prior to enrollment, all patients were evaluated for latent tuberculosis with a purified protein derivative test (≥ 5 mm of induration, 48–72 h after placement) and chest X-ray. Patients with evidence of latent tuberculosis were permitted to enrol if they had received prophylactic treatment for tuberculosis, which had to have been documented, or if prophylactic treatment was initiated before administration of study drug; however, the course of prophylaxis did not need to be completed prior to the initiation of study drug. Patients with a history of clinically significant haematological, renal or liver disease/abnormal laboratory values; with a history of demyelinating disease, cancer, or other lymphoproliferative disease (other than successfully treated nonmetastatic cutaneous squamous cell or basal cell carcinoma and/or localized carcinoma *in situ* of the cervix); or who were immunocompromised were excluded. Women of childbearing potential and all men were required to use contraception. Patients must have been willing to self-administer subcutaneous injections or have a qualified person administer them.

Study design

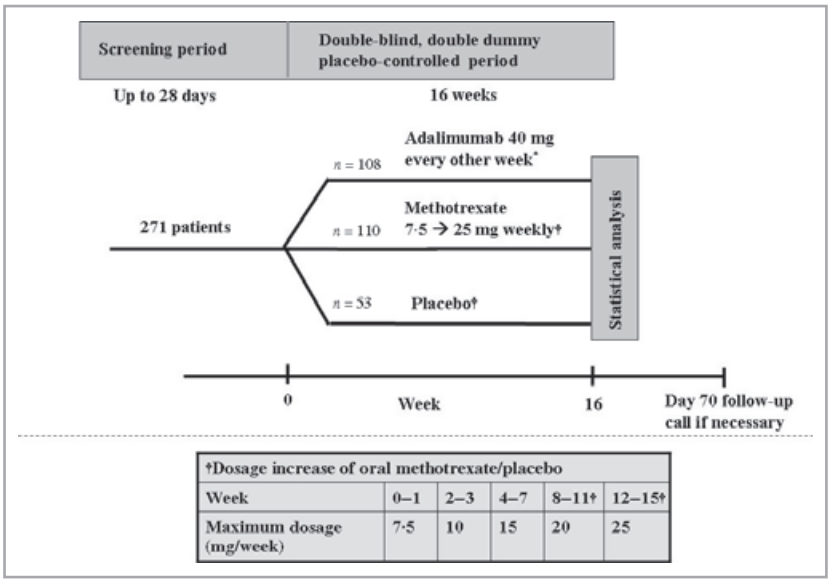
This was a randomized, double-blind, double-dummy, placebo-controlled study to compare adalimumab subcutaneous injections with oral methotrexate and with placebo in patients with moderate to severe psoriasis. Eligible patients were randomized in a 2 : 2 : 1 ratio to receive one of three treatments—adalimumab, methotrexate or placebo—for 16 weeks (Fig. 1). Patients, investigators, study site personnel and Abbott Laboratories (Abbott Park, IL, U.S.A.) were unaware of treatment assignments. Randomization was completed through a central computer-generated scheme stratified by centre, with block sizes of four. Patient numbers were centrally assigned by an interactive voice-response system in consecutive order. Adalimumab (Humira®; Abbott Laboratories) or matching placebo for subcutaneous injection was provided as sterile preservative-free solution in prefilled syringes. Oral methotrexate tablets were supplied by Wyeth Pharma (Münster, Germany), and placebo tablets were supplied by Abbott GmbH & Co. KG (Ludwigshafen, Germany). Both the methotrexate and placebo tablets were administered as capsules (encapsulated tablets) as a single weekly dose. The capsules for both methotrexate and placebo were supplied by Fisher Clinical Services (Basel, Switzerland).

Dosage increase of injected study medication was not permitted. Dosage increase of oral medication (methotrexate or matching placebo) was permitted and is described in Figure 1. The initial methotrexate dosage and the regimen for dosage increase were consistent with the various Summary of Product Characteristics (SmPCs) for methotrexate in the countries where this study was conducted. Each patient received a dietary supplement of oral folate (approximately 5 mg weekly) throughout the study, on any day beginning 48 h after ingestion of oral study medications.

A qualified investigator from each site performed clinical efficacy assessments at each study visit and remained throughout the study, if possible. The investigators remained blinded to all clinical laboratory results and safety data except in the case of a medical emergency. Safety assessors reviewed clinical laboratory tests, physical examination results and adverse event reports, and determined all dosage adjustments for oral study drugs based on safety findings and degree of PASI improvement.

Efficacy assessments

The primary efficacy assessment was the proportion of patients achieving at least a 75% reduction in PASI (PASI 75) at week 16 relative to the baseline score. PASI assesses both the severity of psoriatic lesions in terms of erythema, induration and desquamation at four anatomical sites—head, upper extremities, trunk and lower extremities—and the extent of BSA involvement within a given anatomical site. Scores for PASI



†Dosage increase of oral methotrexate/placebo

Week	0–1	2–3	4–7	8–11†	12–15†
Maximum dosage (mg/week)	7·5	10	15	20	25

Fig 1. Study design and dosing regimens. *Adalimumab (and matching placebo) was administered as 80 mg subcutaneously (two 40-mg injections) at week 0 (baseline), then 40 mg every other week from week 1 through week 15. Two matching placebo injections were also administered at week 0, and then a single placebo injection was administered from week 1 through week 15. Patients receiving oral placebo had simulated dosage increase according to their methotrexate regimens. †Oral methotrexate was administered as a single weekly dose and was initiated at 7·5 mg per week at week 0, increased to 10 mg per week at week 2, and increased to 15 mg per week at week 4 for all patients. At week 8 onward, patients who achieved at least a 50% reduction in Psoriasis Area and Severity Index (PASI 50) response maintained their current dosages (15 mg per week maximum) for the duration of the study. However, at week 8, patients who did not achieve a PASI 50 response had their dosage increased to 20 mg per week. By week 12, only patients not achieving a PASI 50 response and who had a < PASI 50 response at week 8 underwent further dosage increase to 25 mg per week for the duration of the study. Patients who achieved ≥ PASI 50 responses at week 12 maintained their current dosages (20 mg per week maximum) for the duration of the study. Oral medication dosages were also adjusted to alanine aminotransferase, aspartate aminotransferase, serum creatinine and blood cell count between week 2 and week 15, if necessary, and could be withheld or reduced at any time, as deemed appropriate by the safety assessors.

ranged from 0 (no disease) to 72 (severe disease).[16] The proportions of patients achieving at least a 50% reduction in PASI (PASI 50), at least a 90% reduction in PASI (PASI 90) and a 100% reduction (complete clearance) in PASI (PASI 100) were also determined. The physician's global assessment (PGA) of psoriasis, which measures the severity of disease on a six-point scale ranging from 0 (no disease, 'clear') to 5 ('very severe'), was also assessed.[17] PASI and PGA were measured at baseline and at weeks 1, 2, 4, 8, 12 and 16.

Safety assessments

Safety assessments, including adverse events, standard laboratory tests and vital signs, were assessed throughout the study and spanned a period through 70 days after last treatment.

Statistical analysis

The sample size was estimated for the primary efficacy measurement: PASI 75 at week 16. With the assumption of clinical response rates of 62% in the adalimumab group, 60% in the methotrexate group and 4% in the placebo group, approximately 250 patients, randomized in a 2 : 2 : 1 ratio to receive adalimumab, methotrexate or placebo, were needed to achieve more than 95% power to detect the difference between adalimumab and placebo, and approximately 90% power was needed to determine the noninferiority of adalimumab relative to methotrexate with an absolute difference of 20%. In addition, this sample size would provide 80% power to detect a 20% difference between adalimumab and methotrexate.

Baseline demographics and clinical characteristics were summarized descriptively. All efficacy analyses were performed in the intention-to-treat (ITT) population, which included all randomized patients. Nonresponder imputation was used for the primary efficacy analysis. For secondary efficacy analyses, nonresponder imputation (the generally more conservative approach for analysing data) was employed for all categorical variables. Last-observation-carried-forward (LOCF) analysis was used for mean percentage PASI improvement, as it was not reasonable to use nonresponder imputation for this continuous variable. LOCF analysis was used for mean percentage PASI improvement, because the study designers considered it excessively conservative to impute a value of zero for missing patients. Differences in the primary efficacy assessment across the treatment arms were tested in a two-step process. The superiority of adalimumab vs. placebo was tested using the Cochrane–Mantel–Haenszel (CMH) test, with stratification by country. After superiority of adalimumab was established via this method, adalimumab and methotrexate were compared by calculating the 95% confidence interval (CI) for the differ-

ence in PASI 75 (week 16) between adalimumab and methotrexate based on the CMH test. By prespecified statistical plan, noninferiority of adalimumab vs. methotrexate would be established if the lower limit of the CI for the difference (adalimumab − methotrexate) were between −0·2 and 0·0 and the upper limit were positive. If the lower limit of the CI were positive, results of the adalimumab group would also be considered superior to results of the methotrexate group.

Summary statistics were provided for all secondary efficacy variables. In addition, appropriate statistical tests and CIs were provided for the comparison of adalimumab vs. placebo and vs. methotrexate. All statistical tests were two-sided with a significance level of 0·05.

The safety analyses included all patients who received at least one dose of study drug. Statistical analyses were performed using SAS® (SAS Institute Inc., Cary, NC, U.S.A.).

Role of the funding source

Abbott Laboratories funded this study and participated in the study design, data collection, data management, data analysis and preparation of the manuscript. The corresponding author had full access to all of the data and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors were involved in the decision to submit the manuscript for publication.

Results

Patients

In total, 334 patients were screened for the study, 271 of whom underwent randomization (ITT population). Fifteen (5·5%) patients discontinued the study, including four (3·7%) in the adalimumab group (one because of an adverse event, two because of withdrawal of consent, one for other reasons), six (5·5%) in the methotrexate group (all because of adverse events) and five (9·4%) in the placebo group (one because of an adverse event and four because of lack of efficacy). Treatment groups were well-balanced with respect to baseline demographics, clinical characteristics and disease severity (Table 1). At baseline, the mean duration of psoriasis for the entire study population was 18·5 years, the mean score for PASI was 19·7, and the mean affected BSA was 32·1%. Approximately 86% of patients had previously received systemic therapy or phototherapy.

Treatments

The mean ± SD number of injections in the adalimumab group was 9·8 ± 1·0. The mean ± SD weekly dosages of oral medication in the methotrexate group were 14·2 ± 3·0 mg at week 4, 16·8 ± 3·0 mg at week 8, 18·8 ± 4·8 mg at week 12 and 19·2 ± 4·9 mg at week 15. Eighty-nine of 95 (94%) patients in the methotrexate group received a methotrexate dosage of ≥ 15 mg at week 12. Six patients (6%) received a dosage of < 15 mg at week 12 because of elevations of alanine aminotransferase or aspartate aminotransferase concentrations > 1·5 times the upper limit of normal value, which necessitated decreasing the methotrexate dosage. Treatment compliance (mean ± SD) was high for use of both oral (99·7 ± 2·5%) and injectable (97·2 ± 8·7%) study medications. The use of low-potency (grade VI or VII) topical corticosteroids was roughly balanced between groups (8% placebo, 11% methotrexate and 6% adalimumab). A total of 24 patients received prophylactic treatment for tuberculosis during the study. The mean ± SD duration between the start of prophylaxis and initiation of study drug was 8·4 ± 6·2 days (n = 21). One patient received prophylaxis 56 days after the start of study medication.

Table 1 Baseline demographic and clinical characteristics of all randomized patients (N = 271)[a]

Characteristic	Placebo (n = 53)	Methotrexate (n = 110)	Adalimumab (n = 108)
Age (years)	40·7 ± 11·4	41·6 ± 12·0	42·9 ± 12·6
Age ≥ 65 years (%)	1·9	4·5	5·6
Male (%)	66·0	66·4	64·8
Caucasian (%)	92·5	95·5	95·4
Weight (kg)	82·6 ± 19·9	83·1 ± 17·5	81·7 ± 20·0
Duration of psoriasis (years)	18·8 ± 8·7	18·9 ± 10·2	17·9 ± 10·1
BSA affected by psoriasis (%)	28·4 ± 16·1	32·4 ± 20·6	33·6 ± 19·9
Patients with psoriatic arthritis (%)	20·8	17·3	21·3
Previous systemic and/or phototherapy (%)	90·4	87·2	82·2
PASI (range)	19·2 ± 6·9 (6·5–38·1)	19·4 ± 7·4 (9·3–46·6)	20·2 ± 7·5 (10·4–52·9)
Physician's global assessment (%)			
Very severe psoriasis	3·8	5·5	8·4
Moderate to severe psoriasis	58·5	41·8	43·0
Moderate psoriasis	37·7	52·7	47·7

PASI index ranges from 0 to 72, with 0 indicating no psoriasis and 72 indicating severe disease. [a]Values are mean ± SD unless otherwise noted. BSA, body surface area; PASI, Psoriasis Area and Severity Index.

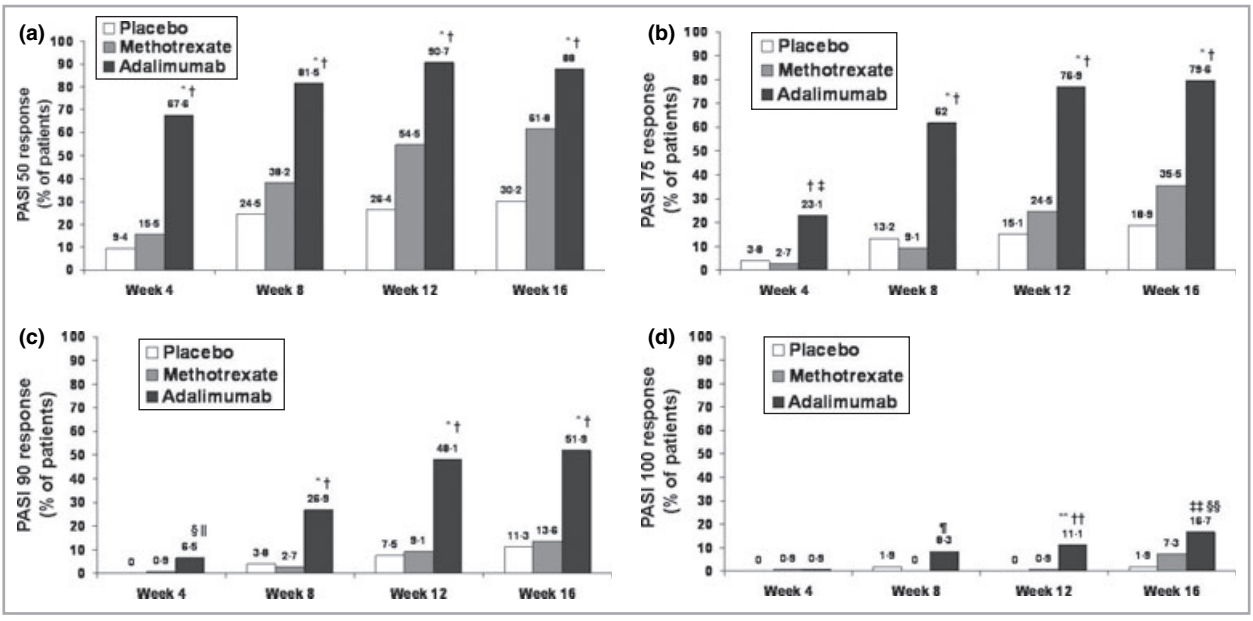


Fig 2. Psoriasis Area and Severity Index (PASI) response rates over 16 weeks. Patients achieving at least a 50% reduction in PASI (PASI 50) (a). Patients achieving at least a 75% reduction in PASI (PASI 75) (b). Patients achieving at least a 90% reduction in PASI (PASI 90) (c). Patients achieving complete clearance of psoriasis (PASI 100) (d). Data based on the intention-to-treat population with missing values imputed as nonresponse. *P < 0·001 vs. placebo; †P < 0·001 vs. methotrexate; ‡P = 0·001 vs. placebo; §P = 0·10 vs. placebo; ‖P = 0·03 vs. methotrexate; ¶P = 0·002 vs. methotrexate; **P = 0·009 vs. placebo; ††P = 0·001 vs. methotrexate; ‡‡P = 0·004 vs. placebo; §§P = 0·04 vs. methotrexate.

Efficacy

At the end of the 16-week treatment period, 79·6% of patients in the adalimumab group, 35·5% in the methotrexate group (risk difference 43·7%; 95% CI 30·8–56·7; P < 0·001 vs. adalimumab) and 18·9% in the placebo group (risk difference 60·5%; 95% CI 44·5–76·6; P < 0·001 vs. adalimumab) achieved PASI 75 (Fig. 2b). Statistically significantly more patients in the methotrexate group than in the placebo group achieved PASI 75 at week 16 (P < 0·05, analysis not prespecified). The differences in the percentages of patients achieving PASI 75 occurred as early as week 2 for adalimumab vs. methotrexate (adalimumab 4·6%; methotrexate 0%; P < 0·05) and as early as week 4 for adalimumab vs. placebo (P = 0·001) (Fig. 2b). Data for 16 patients with missing week 16 assessments for PASI, including the 15 patients who discontinued and one additional patient in the methotrexate group, were imputed as nonresponse. To confirm the results of the primary efficacy analysis, a sensitivity analysis was performed to evaluate PASI 75 response rates with missing data imputed as LOCF. The PASI 75 LOCF results were 79·6%, 36·4% (P < 0·001 vs. adalimumab) and 18·9% (P < 0·001 vs. adalimumab) for the adalimumab, methotrexate and placebo groups, respectively.

By week 16, complete clearance of skin disease (PASI 100) was achieved by 16·7% of adalimumab-treated patients, 7·3% of methotrexate-treated patients (P = 0·04 vs. adalimumab) and 1·9% of placebo patients (P = 0·004 vs. adalimumab) (Fig. 2d). Response to adalimumab was rapid, with a mean percentage PASI improvement of 56·5% as early as week 4, which was statistically significantly different from the responses to methotrexate (22·0%; P < 0·001 vs. adalimumab) and placebo (15·4%; P < 0·001 vs. adalimumab) (Fig. 3a). At week 16, absolute change (mean ± SD) in PASI was −16·7 ± 8·8, −10·9 ± 8·3 (P < 0·001 vs. adalimumab) and −4·6 ± 9·9 (P < 0·001 vs. adalimumab) for the adalimumab, methotrexate and placebo groups, respectively (based on imputation with LOCF).

The percentages of patients achieving PASI 50 (Fig. 2a), PASI 90 (Fig. 2c) and a PGA score of 'clear' or 'minimal' (Fig. 3b) by week 16 consistently demonstrated significant differences between adalimumab- and methotrexate-treated groups and adalimumab- and placebo-treated groups. Of 64 patients in the methotrexate group who achieved a PASI 50 response at week 8 or week 12 and who did not have their weekly methotrexate dosages increased to 25 mg, 37 (57·8%) achieved a PASI 75 response at week 16. For the 46 patients who had a dosage increase from 20 mg to 25 mg at week 12, mean percentage PASI improvement relative to baseline increased by 9·8 percentage points between weeks 12 and 16.

Safety evaluations

The total number of patients who reported adverse events was 79 (73·8%) in the adalimumab group, 89 (80·9%) in the methotrexate group and 42 (79·2%) in the placebo group (Table 2). Most adverse events in each group were mild or moderate. There were no statistically significant differences between groups in the rate of infectious adverse events, and

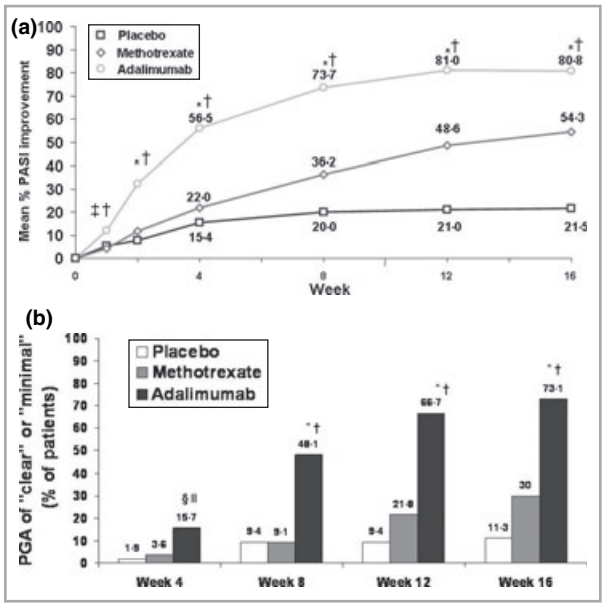


Fig 3. Clinical response to adalimumab treatment compared with methotrexate treatment with placebo controls over 16 weeks. Mean percentage improvement in Psoriasis Area and Severity Index (PASI) (a). Patients who had physician's global assessment (PGA) of 'clear' or 'minimal' (b). *P < 0·001 vs. placebo; †P < 0·001 vs. methotrexate; ‡P = 0·01 vs. placebo; §P = 0·007 vs. placebo; ‖P = 0·003 vs. methotrexate.

no serious infections were reported. Serious adverse events were infrequent: two patients in the adalimumab group reported adverse events (one patient with pancreatitis and one patient with an enlargement of an ovarian cyst), one patient in the methotrexate group reported hepatitis secondary to methotrexate, and one patient in the placebo group had a calculus of the right uretero-pelvic junction. More patients in the methotrexate group (9·1%) had elevated liver enzyme concentrations than did patients in the adalimumab (1·9%) or placebo groups (7·5%) (Table 2). Eight patients discontinued treatment because of an adverse event: one patient in the adalimumab group because of increases in aminotransferase concentrations, six patients in the methotrexate group (one patient with upper abdominal pain, one patient with retrobulbar optic neuritis, one patient with hepatitis and three patients with abnormal liver function tests), and one patient in the placebo group because of an increased hepatic enzyme concentration. There were no reports of tuberculosis, and no deaths occurred during the study.

Discussion

A published international consensus statement recommends that for patients with moderate to severe psoriasis, 'equal consideration' should be given to traditional systemic therapies such as methotrexate, phototherapy, and biologic therapy.[18] However, resistance to using biologics as first-line therapy has rested, in part, on the absence of data demonstrating equivalency or superiority of a biologic to a traditional systemic agent in a direct, comparative clinical trial.

In this trial, adalimumab therapy resulted in significantly superior efficacy and more rapid improvement in psoriasis compared with methotrexate in all measures of clinical

Table 2 Adverse events by treatment group, adverse events that occurred in ≥ 5% of patients in any treatment group, and elevated liver function tests by treatment group

Event	Placebo (n = 53)	Methotrexate (n = 110)	Adalimumab (n = 107)
Total adverse events	42 (79·2%)	90 (81·8%)	79 (73·8%)
Serious adverse events	1 (1·9%)	1 (0·9%)	2 (1·9%)
Serious infections	0	0	0
Adverse events leading to discontinuation	1 (1·9%)	6 (5·5%)	1 (0·9%)
Adverse events			
Infections, nonserious	23 (43·4%)	46 (41·8%)	51 (47·7%)
Nasopharyngitis	11 (20·8%)	26 (23·6%)	30 (28·0%)
Headache	5 (9·4%)	12 (10·9%)	14 (13·1%)
Pruritus	6 (11·3%)	2 (1·8%)	4 (3·7%)
Rhinitis	4 (7·5%)	4 (3·6%)	3 (2·8%)
Nausea	4 (7·5%)	8 (7·3%)	4 (3·7%)
Rhinorrhea	3 (5·7%)	0	3 (2·8%)
Viral infection	1 (1·9%)	6 (5·5%)	0
Arthralgia	1 (1·9%)	5 (4·5%)	6 (5·6%)
Liver function tests			
γ-Glutamyltransferase elevation	3 (5·7%)	0	2 (1·9%)
Alanine aminotransferase > 2·5 times the ULN	1 (1·9%)	4 (3·6%)	0
Aspartate aminotransferase > 2·5 times the ULN	0	2 (1·8%)	0
Total bilirubin > 1·5 times the ULN	0	4 (3·6%)	0

ULN, upper limit of normal.

response, the first time this has been demonstrated with a biologic therapy for psoriasis. Statistically significantly more adalimumab-treated patients achieved the primary endpoint (PASI 75 at week 16) and all secondary efficacy endpoints (including a PGA of 'clear' or 'minimal') compared with methotrexate-treated or placebo-treated patients.

Although adalimumab PASI 75 results (79·6% at week 16) from this study cannot be directly compared with efficacy results from studies with other biologics in moderate to severe psoriasis because they were not assessed in head-to-head comparative trials, current data show PASI 75 rates of 82% at week 24 in studies of infliximab,[10] 33% at any time during the 24-week alefacept study at its recommended dosages,[11] 44% (25 mg twice weekly) to 50% (50 mg twice weekly, then 25 mg twice weekly) at week 24 with etanercept,[12,13] and 44% at week 24 with efalizumab at 1 mg kg^{-1} weekly.[14,15]

At week 16, statistically significantly more adalimumab-treated patients (16·7%) than methotrexate-treated (7·3%) or placebo-treated (1·9%) patients achieved 100% clearance of psoriatic lesions (PASI 100), an outcome that few physicians considered a realistic and sustainable goal for the treatment of psoriasis before widespread use of biologics.[19]

Improvements in health-related quality of life are also important in assessing the overall benefits of new therapies. In this study, the magnitude and direction of patient-reported outcomes achieved with either adalimumab or methotrexate were similar to the clinical findings. To cover this topic fully and meaningfully, comprehensive patient-reported outcomes from the CHAMPION study have been published separately.[20]

There were no differences in rates of adverse events between any of the three treatment groups. Reports of adverse events for adalimumab in this psoriasis study are comparable to rates observed in clinical trials of adalimumab in patients with rheumatoid arthritis.[21–23] Adverse events leading to discontinuation were greatest for the methotrexate group, with three patients discontinuing treatment because of elevations in liver enzyme concentrations and one patient discontinuing because of hepatitis. However, as a 16-week study, our trial was limited in providing data to assess important but uncommon or long-term adverse effects of adalimumab or methotrexate. Large-scale, long-term surveillance studies are needed to assess safety differences between treatments fully, and to provide information critical to the evaluation of treatments used for chronic diseases.

The methotrexate dosing regimen used in this study was derived from the SmPCs of methotrexate for the countries involved in the study. Although some differences in the recommended dosing regimens for psoriasis treatment across countries do exist, a starting dosage of 7·5 mg per week and a maximal dosage of 25 mg per week were most widely recommended. In the absence of a widely accepted consensus on dosage titration, a slow dose increment was chosen to minimize occurrence of methotrexate-related adverse events that might have led to discontinuation from the study, as were reported for an earlier randomized, controlled study of methotrexate vs. ciclosporin in psoriasis.[3] To reduce the incidence of gastrointestinal and haematological adverse effects of methotrexate therapy—effects suggested by a few studies of a small number of patients[2]—all patients received concomitant folic acid. The low rate of withdrawals in the methotrexate-treated group in this study suggest that dosing recommendations of the SmPCs of the countries where this study was conducted are generally practical. In the current study, based on a comparison of methotrexate with the other treatment groups, there was a slight increase in the number of hepatic-related adverse events leading to discontinuation [four of 110 patients (3·6%)] and in the number of patients who had abnormal liver function tests in the methotrexate group, which suggests that intolerance of methotrexate had already occurred in this subset of patients. By contrast, in the previous study, 12 of 43 (27·9%) methotrexate-treated patients discontinued from the study because of hepatic-related adverse events,[3] indicating that the regimen chosen in the current study sustained a sufficient number of patients in the methotrexate group for appropriate ITT analysis. A retrospective study of long-term methotrexate use in psoriasis also suggests that low-dosage methotrexate (< 15–20 mg per week) is an effective therapy for extensive plaque psoriasis that minimizes adverse effects.[4]

The percentage of patients achieving a PASI 75 response in the methotrexate group (35·5%) was low compared with results from the earlier study (60%).[22] Both studies employed ITT analyses. In the current study, PASI response rates (as well as PGA) were calculated in a conservative fashion by assuming that patients with missing data were nonresponders. PASI 75 response rates were also confirmed by a sensitivity analysis that calculated similar PASI 75 results, with missing data imputed as LOCF. In the prior methotrexate study, the method by which missing data were imputed for these efficacy variables was not explicitly stated,[22] which makes comparisons difficult. Potential differences in outcomes may also be attributed to administration of methotrexate as a single dose in this study as compared with three divided doses in the previous study.[3]

Emulating standard clinical practice, the initial dosage of methotrexate was low, then titrated up as indicated and as tolerated. Adalimumab was administered as a greater initial dose (80 mg) and then at a 40-mg, every-other-week maintenance dosage. Although adalimumab efficacy appears to have reached a plateau by week 16 (Fig. 3a), the efficacy of methotrexate continued to increase to week 16, although at a slower rate at later time points. The full effects of methotrexate may not have been achieved, possibly because the 16-week evaluation period was too short or the regimen for methotrexate dosage up-titration was insufficient. Notwithstanding these limitations, this was the first placebo-controlled study to assess the efficacy of methotrexate for its labelled indication in psoriasis. Based on the shape of the response curves, we speculate that methotrexate efficacy might have been marginally greater if the study had continued for another 4–8 weeks. Most methotrexate-treated patients who achieved PASI 50 at week 8 or 12 and, therefore, who were not titrated up to a methotrexate dosage of 25 mg per week, achieved PASI 75 response. Those

patients who did qualify for dosage increase to 25 mg per week experienced an incremental increase in mean percentage PASI improvement. Taken together, these results suggest that a more aggressive upward titration of methotrexate dosing might have marginally increased efficacy but would not have changed overall study results.

The placebo response for PASI 75 in the current study (18·9%), with a primarily European patient population, was greater than it was in previous studies.[7,12,15] There are several factors that may be responsible for this anomalous placebo response. Another multinational study with substantial participation of European countries reported a 13% placebo response rate for PASI 75.[14] These results suggest that the reported response to placebo could be greater in Europe. Also, the placebo response may partly have resulted from the correction of an underlying folate deficiency following folate supplementation, which was mandatory for all study patients. Patients with psoriasis have been reported to have folate deficiency, the magnitude of which correlates with the severity of psoriasis.[24] Previous studies suggest that folate deficiency stimulates the pathogenesis of psoriasis through accumulation of homocysteine[25] and the subsequent release of interleukin-8 and monocyte chemotactic protein-1.[26,27] Nevertheless, these influences are considered to be systematic influences and would be equally applicable to each of the study groups and, therefore, would not be expected to influence the differences in response rates of the groups. Patients with moderate to severe psoriasis who are methotrexate-naïve, which was an inclusion criterion of this study, may have a greater likelihood of natural improvement than is typically observed for patients with psoriasis enrolled in randomized controlled trials of systemic agents.

In conclusion, adalimumab demonstrated significantly superior efficacy and more rapid improvement in psoriasis compared with methotrexate and with placebo in this 16-week study of patients with moderate to severe plaque psoriasis. During the 16-week evaluation period, the incidences of adverse events were similar across treatment groups. The results of this first trial comparing a biologic with a traditional systemic agent will help define the place of biologics in general, and of the TNF-antagonist adalimumab in particular, in the treatment of moderate to severe psoriasis. They should also assist in defining the appropriate dosing for oral methotrexate at the initiation of therapy for moderate to severe psoriasis, as well as for potential new trials comparing methotrexate with a biologic.

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patients can experience frustration, low self-esteem, difficulty with relationships and increased lifestyle risks.

"In the past, our understanding of ADHD treatment was limited to clinical data on short-term use, meaning a few weeks or a couple of months," said A.J. Allen, M.D., Ph.D., Strattera global medical director for Eli Lilly and Company. "For the first time, clinicians have guidance that Strattera is effective for up to a year in patients who respond well to initial treatment."

The long-term, international, multi-center study, which was reviewed by the FDA as part of its decision to grant this approval, employed a treatment discontinuation design (3 months of acute open-label treatment followed by up to 15 months of placebo controlled maintenance treatment) that enabled investigators to test the efficacy of Strattera as maintenance therapy. In the study, 604 patients initially received acute open label treatment with Strattera. After 10-weeks, 69% of patients qualified as responders and were re-randomized to double-blind treatment with either Strattera or placebo for nine months. A second six-month randomization occurred after approximately one year of treatment with 81 patients taking Strattera and 82 patients in the placebo group.

Results of both randomization phases showed that patients treated with Strattera had significantly greater continuous response rates versus patients taking placebo. For child and adolescent ADHD patients with a good initial response to Strattera and who continued to respond well for 1 year, 97.5% maintained response on Strattera vs. 87.8% on placebo (relapse rates 2.5% for Strattera vs. 12.2% for placebo). Additionally, relapse rates for those discontinuing treatment after one year were lower than the relapse rates for patients who discontinued treatment during the 6 months following the open label treatment phase (Strattera, 61/292 [20.9%]; placebo, 46/124 [37.1%]).

Strattera was generally well-tolerated. The most common side effects reported in the study were headache and the common cold (nasopharyngitis). In the study, the mean final dose of Strattera was approximately 1.54 mg/kg/day after 12 months and 18 months treatment. There were no significant differences in standardized height change between groups during the post-randomization period.

About ADHD

ADHD is the most common psychiatric disorder to appear in childhood. If left untreated, ADHD can have long-term effects on a child's emotional well-being and social skills, like making friends or doing well at school or at work.[2] ADHD can also have lifelong consequences, including poor

peer relations, poor academic and work performance and increased risk-taking behaviors, such as substance abuse.[3]

About Strattera

It is not known precisely how Strattera reduces ADHD symptoms, but scientists believe it works by blocking or slowing reabsorption of norepinephrine, a chemical in the brain considered important in regulating attention, impulsivity and activity levels. This keeps more norepinephrine at work in the spaces between neurons in the brain. Improved efficiency in the norepinephrine system is associated with improvement in symptoms of ADHD.[4] Since its first approval in the United States in 2002, more than 5 million patients have taken Strattera worldwide. It has been studied in more than 6,000 patients in clinical trials, some for as long as three years.

Important Safety Information for Strattera® (atomoxetine HCl)

In some children and teens, Strattera increases the risk of suicidal thoughts. A combined analysis of 12 studies of Strattera showed that in children and teens this risk was 0.4% for those taking Strattera compared to none for those taking a sugar pill. A similar analysis in adults treated with Strattera did not reveal an increased risk of suicidal thoughts. **Call your doctor right away if your child has thoughts of suicide or sudden changes in mood or behavior, especially at the beginning of treatment or after a change in dose.**

Strattera should not be taken if you or your child: are taking or have taken within the past two weeks a medicine for depression called a monoamine oxidase inhibitor (MAOI); have an eye problem called glaucoma; are allergic to anything in STRATTERA.

Tell your doctor if you or a family member has a history of high or low blood pressure, increased heart rate, heart or blood vessel disease or structural heart defects. **When on Strattera, tell your doctor right away if you have chest pain, shortness of breath, or fainting, as these may be signs of heart-related conditions that may be life threatening**.

In rare cases, Strattera can cause severe liver problems. Call your doctor right away if you or your child has itching, dark urine, yellow skin/eyes, upper right-side abdominal tenderness, or unexplained "flu-like" symptoms.

Tell the doctor about any family history of or if you or your child: has bipolar illness (manic-depressive illness); or has suicidal thoughts or actions before starting Strattera.

If your child develops new psychological symptoms such as abnormal thoughts/behaviors and/or extreme elevated or irritable moods, while taking Strattera you should report them to your child's doctor right away.

For male patients, call your doctor right away if you or your child experience priapism, a painful or prolonged erection lasting more than 4 hours.

Other rare but serious side effects include: serious allergic reactions including swelling, hives, or other allergic reactions; problems passing urine; and slowing of growth in children. As with all ADHD medications, growth should be monitored during treatment although height and weight data for Strattera measured up to 3 years indicates minimal, if any, long-term effects.

Tell your doctor about all prescription and nonprescription medicines that you or your child takes, including vitamins, and herbal supplements. Do not start any new medicine while taking STRATTERA without talking to your doctor first.

Tell your doctor if you or your child is pregnant, planning to become pregnant, or breastfeeding.

In children, the most common side effects were upset stomach, decreased appetite, nausea or vomiting, tiredness, and drowsiness. In adults, the most common side effects were constipation, dry mouth, nausea, decreased appetite, dizziness, problems sleeping, sexual side effects, problems urinating, and menstrual cramps. Most people in clinical studies who experienced side effects were not bothered enough to stop using Strattera. Strattera has not been tested in children under 6 years of age or in geriatric adults.

For Medication Guide, visit www.Strattera.com.
For full Prescribing Information, including Boxed Warning information, visit http://www.Strattera.com/.

About Eli Lilly and Company
Lilly, a leading innovation-driven corporation, is developing a growing portfolio of first-in-class and best-in-class pharmaceutical products by applying the latest research from its own worldwide laboratories and from collaborations with eminent scientific organizations. Headquartered in Indianapolis, Ind., Lilly provides answers - through medicines and information - for some of the world's most urgent medical needs. Additional information about Lilly is available at www.lilly.com.

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This press release contains forward-looking statements about Strattera for the treatment of ADHD and reflects Lilly's current beliefs. However, as with any pharmaceutical product, there are substantial risks and uncertainties in the process of development and commercialization, including the risk of side effects and other safety concerns. There is no guarantee that the product will continue to be commercially successful. For further discussion of these and other risks and uncertainties, see Lilly's filings with the United States Securities and Exchange Commission. Lilly undertakes no duty to update forward-looking statements.

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[1] National Resource Center on ADHD. "Statistical Prevalance." Available at" http://www.help4ADHD.org/en/about/statistics. Accessed on March 28, 2007.
[2] National Institute of Mental Health. "NIMH research on treatment for attention deficit disorder (ADHD): The multimodal treatment study – questions and answers." Available at: http://www.nimh.nih.gov/childhp/mtaqa.cfm. Accessed on May 2, 2008
[3] Faraone S, Beiderman J, et al. ADHD in adults: an overview. *Biol Psychiatry* 2000; 48:9-20.
[4] Pliszka SR, et al. *Journal of the American Academy of Child and Adolescent Psychiatry*. 1996., 35 (264-272).