



## Bulletin Board

# Results from the Phase III ORAL Standard and ORAL Step studies demonstrate promise for tofacitinib as a treatment for rheumatoid arthritis

Pfizer have announced top-line results from two pivotal Phase III studies of its investigational, novel oral JAK inhibitor, tofacitinib. Both the ORAL Standard and ORAL Step studies met their primary end points and demonstrated no new safety concerns regarding the use of tofacitinib in patients with active rheumatoid arthritis (RA). ORAL Standard and ORAL Step are the final two pivotal trials in a program designed by Pfizer to study tofacitinib for RA. The program consists of five pivotal trials and a sixth long-term treatment study carried out at more than 350 locations in 35 countries worldwide.

The 12-month ORAL Standard trial enrolled 717 patients with moderate-to-severe active RA who had an inadequate response to methotrexate (MTX). Patients were randomized to receive tofacitinib 5 or 10 mg twice daily, adalimumab 40 mg subcutaneously every other week or placebo, each of which was added to stable background MTX. All primary end points of the study were met, demonstrating statistically significant changes versus placebo in reducing the signs and symptoms of RA as measured by ACR20 response rates at 6 months; in improving physical function, as measured by mean change in HAQ DI at 3 months; and in reaching DAS28-4(ESR) <2.6 at 6 months.

The ORAL Step study was conducted over a 6-month period and enrolled 399 patients with moderate-to-severe active RA who had an inadequate response to a TNF inhibitor. Patients were randomized to receive tofacitinib 5 or 10 mg twice daily or placebo, which were added to stable background MTX. As with the ORAL Standard study, all primary end points of the ORAL Step were met, at both the 5 and

10 mg twice daily doses. Tofacitinib demonstrated statistically significant changes versus placebo in reducing signs and symptoms of RA, as measured by ACR20 response rates; in improving physical function, as measured by mean change in HAQ DI; and in reaching DAS28-4(ESR) <2.6, all assessed at 3 months.

“ORAL Standard and ORAL Step ... demonstrated no new safety concerns regarding the use of tofacitinib...”

A more detailed analysis of the ORAL Standard and ORAL Step efficacy and safety data is likely to be presented at a scientific meeting in the near future.

Source: Pfizer newsroom: [www.pfizer.com/news/press\\_releases/pfizer\\_press\\_releases.jsp#guid=20110428005895en&source=RSS\\_2011&page=1](http://www.pfizer.com/news/press_releases/pfizer_press_releases.jsp#guid=20110428005895en&source=RSS_2011&page=1)



### in the news...

- **Lead story:** Results from the Phase III ORAL Standard and ORAL Step studies demonstrate promise for tofacitinib as a treatment for rheumatoid arthritis [pg 263](#)
- First new therapy for lupus approved by the US FDA since 1955 [pg 264](#)
- Report on the economic impact of autoimmune diseases published to coincide with National Autoimmune Diseases Awareness Month [pg 264](#)
- Study results demonstrate that buprenorphine is superior to placebo in treating opioid-naive patients with moderate-to-severe chronic low back pain [pg 265](#)
- In brief... [pg 265](#)

## First new therapy for lupus approved by the US FDA since 1955

Benlysta® (belimumab), the first in a new class of drugs called B lymphocyte stimulator-specific inhibitors developed by GlaxoSmithKline (Brentford, Middlesex, UK) and Human Genome Sciences Inc. (Rockville, MD, USA) has recently been granted approval from the US FDA (Silver Spring, MD, USA).

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“The FDA’s approval of Benlysta is momentous not only for the new hope it brings to the 300,000 to 1.5 million Americans suffering with lupus but also for the millions of Americans who suffer from many other autoimmune diseases...”

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Benlysta is a new therapy for the treatment of adults with active, autoantibody-positive systemic lupus erythematosus who are receiving standard therapy. In August 2010, the FDA granted Benlysta priority review designation

owing to the potential major advances in treatment offered by the drug.

“The FDA’s approval of Benlysta is momentous not only for the new hope it brings to the 300,000 to 1.5 million Americans suffering with lupus but also for the millions of Americans who suffer from many other autoimmune diseases such as autoimmune hemolytic anemia and autoimmune hepatitis. These diseases, along with lupus, have not seen the development of specific new treatments since the 1950s. Benlysta exemplifies a welcomed interest by today’s biotechnology and pharmaceutical companies to investigate and develop new treatments for orphan and less common diseases”, commented Virginia Ladd, the President and Executive Director of the American Autoimmune Related Diseases Association (East Detroit, MI, USA).

Source: Human Genome Sciences website: [www.hgsi.com/benlysta-belimumab-3.html](http://www.hgsi.com/benlysta-belimumab-3.html)

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## Report on the economic impact of autoimmune diseases published to coincide with National Autoimmune Diseases Awareness Month

To coincide with the National Autoimmune Diseases Awareness Month, the American Autoimmune Related Diseases Association (AARDA; East Detroit, MI, USA) has published a report on the economic impact of autoimmune disease on Americans, their families and the USA called; “The cost burden of autoimmune disease: the latest front in the war on healthcare spending”.

In their report, the AARDA highlighted the need to increase awareness of autoimmune diseases among medical practitioners and the general public. Based on epidemiology studies from the NIH (Bethesda, MD, USA) and patient group data through members of the National Coalition of Autoimmune Patient Groups (MI, USA), the AARDA estimates that

50 million Americans have an autoimmune disease. Autoimmune diseases are one of the top ten causes of death in women below 65 years of age, are the second highest cause of chronic illness and are the top cause of morbidity in women in the USA.

Virginia Ladd, Executive Director of AARDA, commented “it is clear that these chronic illnesses constitute a major component of US healthcare spending, totaling perhaps hundreds of billions of dollars in direct and indirect costs to individual patients, insurance companies and the federal government.”

The AARDA argued that the lack of awareness with regard to autoimmune diseases, combined with an unequal allocation of research funding and a lack of

both coordinated care and diagnostic tests has resulted in the rising economic cost of autoimmune disease in the USA. The total annual cost of the 100 or more autoimmune diseases in the USA has not been calculated, but the cost of seven of the most prevalent diseases has been estimated through epidemiological studies to total from US\$51.8 to 70.6 billion.

The report suggested solutions to several of the problems preventing cost-effective and efficient treatment for patients with autoimmune diseases, including streamlining the diagnosis process and creating a new medical specialist; the autoimmunologist.

Source: American Autoimmune Related Diseases Association publication: [www.aarda.org/pdf/cbad.pdf](http://www.aarda.org/pdf/cbad.pdf)

## Study results demonstrate that buprenorphine is superior to placebo in treating opioid-naïve patients with moderate-to-severe chronic low back pain

Physicians from Purdue Pharma LP (Stamford, Connecticut) have announced results from a 12-week study demonstrating the analgesic efficacy and safety of buprenorphine (Butrans®) for the relief of moderate-to-severe chronic lower back pain in opioid-naïve patients. Buprenorphine is a new treatment for chronic back pain approved by the US FDA in June 2010. Via a transdermal delivery system, it provides systemic delivery of buprenorphine continuously over a 7-day period.

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“...Butrans was superior to placebo in treating opioid-naïve patients with moderate to severe chronic low back pain...”

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The safety and efficacy of buprenorphine was tested in a randomized, double-blind study, where 1024 patients were

treated with buprenorphine during the open-label run-in period. Patients were randomized to buprenorphine 10 and buprenorphine 20, or matching placebos.

“In the open-label run-in period, if Butrans 10 was tolerated but adequate analgesia was not reached, the dose was increased to Butrans 20 for an additional 10 to 12 days” explained Deborah Steiner, medical director at Purdue Pharma. “Patients who achieved adequate analgesia and tolerated Butrans were then randomized to remain on the titrated dose of Butrans (10 or 20) or a matching placebo. To demonstrate adequate analgesia in the open-label run-in period, patients had to have pain scores of less than or equal to 4 on an 11-point scale for 3 consecutive days and at least a 2-point reduction from their screening pain scores”.

The trial’s primary efficacy outcome, the “average pain over the last 24 hours” at week 12, resulted in a statistically

significant treatment difference of -0.58 in favour of buprenorphine over placebo ( $p = 0.0104$ ). The proportions of patients with at least 30% and at least 50% pain score improvements were larger for buprenorphine-treated patients.

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“...the safety profile of Butrans is consistent with that associated with opioid analgesics and transdermal patches...”

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“We were able to demonstrate that Butrans was superior to placebo in treating opioid-naïve patients with moderate to severe chronic low back pain and that the safety profile of Butrans is consistent with that associated with opioid analgesics and transdermal patches” concluded Steiner.

Source: American Academy of Pain Medicine: [www.painmed.org/files/butrans-press-release.pdf](http://www.painmed.org/files/butrans-press-release.pdf)

### in brief...

**Bisphosphonate use and atypical fractures of the femoral shaft.** Schilcher J, Michaëlsson K, Aspenberg P. *N. Engl. J. Med.* 364, 1728–1737 (2011).

A population-based study from Sweden has confirmed a link between atypical fractures of the femoral shaft and bisphosphonate use, although the authors stress that absolute risk is very small. The researchers looked at health records for 1.5 million women. Of the 12,777 women aged over 55 years who suffered a femoral fracture in 2008, 59 were found to have an atypical femoral fracture. Of these, 78% were taking bisphosphonates, compared with 10% of matched controls with fractures in a similar location (multivariable-adjusted odds ratio of 33.3; 95% CI: 14.3–77.8). The increased risk was not related to coexisting conditions or other drugs that affect bone. Longer duration of bisphosphonate use increased the risk. These findings confirm a previous population-based analysis from Canada. However, this small risk of atypical fractures is considered by the authors to be far outweighed by the benefits of bisphosphonates in preventing osteoporotic fractures.

**Levothyroxine dose and risk of fractures in older adults: nested case-control study.** Turner MR, Camacho X, Fischer HD *et al.* *BMJ* 342, d2238 (2011).

It was found that elderly patients receiving medication for underactive thyroid are at increased risk of fractures, particularly those receiving high doses. The study looked at 213,511 people aged over 70 who were prescribed the thyroid drug levothyroxine between 2002 and 2007, and followed these patients until 2008 for fractures using hospital records. In total, 22,236 (10.4%) of the participants suffered a fracture. Each fracture patient was matched with five controls who did not have a fracture. Participants who had a fracture in the study period were divided into current, recent or remote (stopped medication more than 180 days before the start of the study) levothyroxine users. Current levothyroxine users had an increased risk of fracture (adjusted odds ratio 1.88; 95% CI: 1.71–2.05) compared with remote users. Those receiving medium or high cumulative doses were more likely to have a fracture than those receiving low doses. The authors concluded that physicians must monitor levothyroxine dosage regularly, particularly in elderly patients, and ensure that patients are receiving the lowest possible dose.