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CLINICAL INVESTIGATION

NEWS

Highlights from the latest news and research in Clinical Investigation

Denosumab open-label extension trial shows positive results for osteoporosis treatment

Further evidence supporting the role of denosumab (Prolia®) for the treatment of osteoporosis in postmenopausal women has recently been announced. Positive results from the open-label extension trial has shown a continued increase in bone mineral density over 5 years, with a similar safety profile observed in a pivotal trial.

Osteoporosis is a worldwide concern, becoming more significant as the global population both increases and ages. Termed the 'silent epidemic' by the International Osteoporosis Foundation (IOF), the WHO has officially declared osteoporosis a public health crisis.

Denosumab is the first approved therapy that specifically targets the essential regulator of osteoclasts, RANKL. Data presented at the annual European Congress Osteoporosis and Osteoarthritis (ECCEO11-IOF) in Valencia, Spain, showed new long-term data for postmenopausal women with osteoporosis receiving denosumab treatment. Data showed that during the fourth and fifth years of denosumab treatment, women receiving denosumab had statistically significant, year-over-year increases in lumbar spine and total hip bone mineral density (BMD), a key measurement of bone strength.

The Fracture Reduction Evaluation of Denosumab in Osteoporosis every 6 Months (FREEDOM) study was based on 3 years of data from approximately 7800 postmenopausal women, to establish the efficacy and safety of denosumab. The open-label extension of the FREEDOM study involved 4550 postmenopausal women, to evaluate for long-term (up to 10 years) efficacy and safety of denosumab.

It was announced that in years 4 and 5 respectively, women taking denosumab experienced further 1.9 and 1.7% increases in lumbar spine BMD and further 0.7 and 0.6% increases in total hip BMD (all $p < 0.0001$ compared with extension baseline). The results also showed that the incidences of new osteoporotic fractures for women taking denosumab for 5 years, remained low.

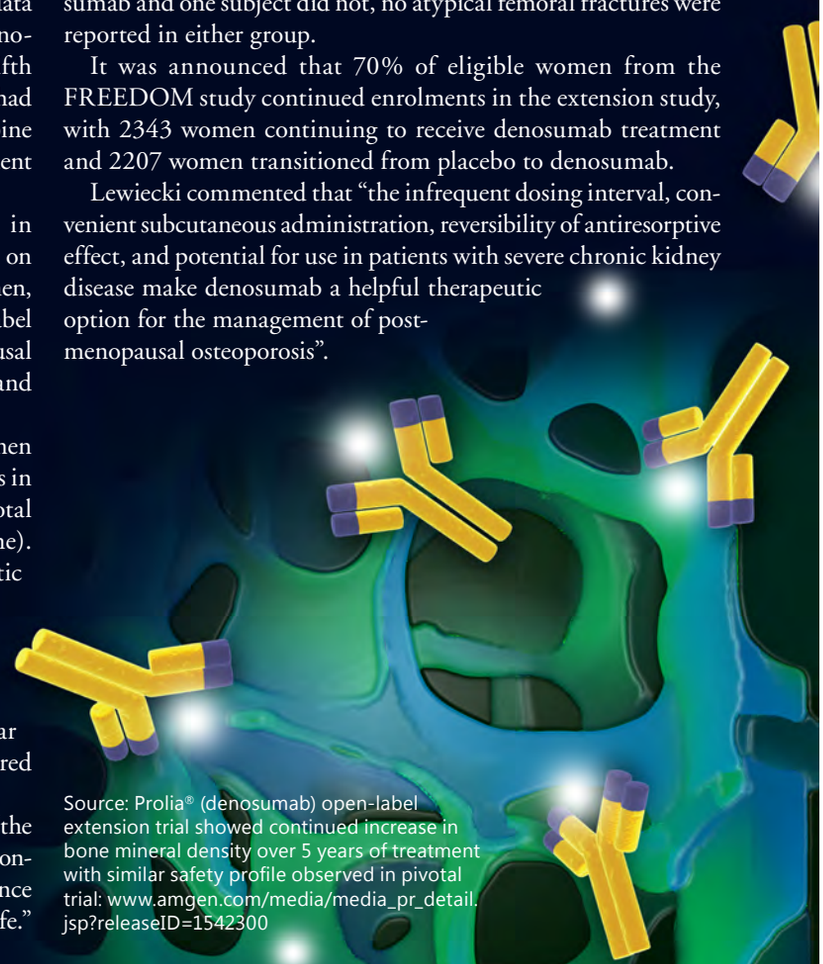
Women who transitioned from placebo to denosumab in the extension study, during the first 2 years of denosumab treatment, showed significant BMD increases of 7.9% in lumbar spine BMD and 4.1% in total hip BMD (all $p < 0.0001$ compared with extension baseline).

Dr Lewiecki, senior editor for *Clinical Investigation*, said: "the continuing increases in lumbar spine and hip BMD, along with continuing favorable reports of safety end points, provide reassurance to physicians that its use for at least 5 years is efficacious and safe."

Adverse event (AE) rates for women who continued on denosumab were 83.4%, for women transitioned from placebo to denosumab AE rates were 82.8%, with serious AE rates 18.9% and 19.4% for the two groups respectively. In the group that transitioned from placebo to denosumab, two subjects had AEs adjudicated to osteonecrosis of the jaw, which healed without further complications. One of these subjects continued denosumab and one subject did not, no atypical femoral fractures were reported in either group.

It was announced that 70% of eligible women from the FREEDOM study continued enrolments in the extension study, with 2343 women continuing to receive denosumab treatment and 2207 women transitioned from placebo to denosumab.

Lewiecki commented that "the infrequent dosing interval, convenient subcutaneous administration, reversibility of antiresorptive effect, and potential for use in patients with severe chronic kidney disease make denosumab a helpful therapeutic option for the management of postmenopausal osteoporosis".



Source: Prolia® (denosumab) open-label extension trial showed continued increase in bone mineral density over 5 years of treatment with similar safety profile observed in pivotal trial: www.amgen.com/media/media_pr_detail.jsp?releaseID=1542300

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EU Clinical Trials Register goes live

For the first time, public access is now available to the EU Clinical Trials Register. The European Medicines Agency (EMA) launched the database in order to make information available on interventional clinical trials for medicines, authorized in the 27 EU Member States as well as Iceland, Liechtenstein and Norway. The database also allows searches for information on clinical trials outside the EU if these trials are part of a pediatric investigation plan.

The EU Clinical Trials Register compiles information from the EU Clinical Trials Database (EudraCT), loaded by the National Medicines Regulatory Authority, who then also add data on the authorization of the clinical trial and the opinion from the relevant ethics committee. Information is provided by the sponsor of both industry and research clinical trials, with it now being a component of the application to conduct a trial. The information listed in the pediatric investigation plan (PIP) on third-country trials is directly provided by the PIP addressee, via the EMA, to the system.

The comprehensive functions of this new register will help the public search for clinical trials by country, age, gender, trial phase and status, allowing patients and healthcare professionals access to vital information on the latest advancements offered by clinical research. Co-chair of the EMA's Working Party with Patients' and Consumers' Organisations, Lise Murphy, commented that the EU Clinical Trials Register "increases transparency of medical research and will make it much easier for patients to find information about clinical trials taking place in Europe".

The EMA has announced that it will continue to work with stakeholders to improve the database, in particular by improving the quality of data and improving the search functionality. Future plans also include publishing summaries of clinical trial results, on which the European Commission have already published for consultation. However, the publication of these trial results summaries will require the existing system to have a major upgrade, which will start depending on the finalization of guidelines and the availability of budget and resources. Murphy stated "we are committed to continue working with the EMA to further develop the system so that it becomes a valuable and useful resource for patients across the EU."

Sources: EU Clinical Trials Register goes live: www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2011/03/news_detail_001228.jsp&murl=menus/news_and_events/news_and_events.jsp&mid=WC0b01ac058004d5c1&jsenabled=true; EuropaBio welcomes the launch of the EU Clinical Trials Register: www.medicalnewstoday.com/articles/220029.php

Marketing authorization for retigabine (Trobalt™) as an adjunctive treatment of partial-onset seizures

GlaxoSmithKline (GSK) and Valeant Pharmaceuticals International, Inc. (NYSE/TSX: VRX) have announced that marketing authorization has been granted by the European Commission for retigabine, with or without secondary generalization in adults >18 years old with epilepsy. Retigabine will be an add-on treatment of partial-onset seizures, which are a form of epilepsy where the seizure begins in one side of the brain in a specific area.

Retigabine, referred to as ezogabine in the US and Canada, is being jointly developed by GSK and Valeant. The European authorization represents the first licence for retigabine, which was supported due to the results of pivotal Phase III studies RESTORE 1 and 2 and Study 205, a Phase IIb study. These results demonstrated that, compared to placebo, more patients with partial onset seizures saw a reduction of >50% in seizure frequency, when a 600, 900 or 1200 mg dose of retigabine was added to current antiepileptic drug (AED) therapy.

Tony Hoos, Senior Vice President of European Medical Affairs at GSK, said that the "European authorization of retigabine is very welcome as it will provide neurologists within Europe with a new therapeutic option for the management of appropriate patients with uncontrolled partial onset seizures."

The EU Prescribing Information recommends that retigabine is used with caution in patients at risk of urinary retention, from results in controlled clinical studies. The EU prescribing information also recommends that an ECG is recorded in patients who are taking any medication that may interfere with QT intervals or who may have congestive heart failure, ventricular hypertrophy, hypokalemia or hypomagnesemia and in patients initiating treatment who are 65 years of age and above, before the initiation of retigabine.

Susan Hall, Head of Research and Development at Valeant, said that "we are very pleased to have reached such an important milestone in the development of retigabine," she continued to say that there is a "significant need for new AEDs and retigabine could potentially play an important role in the management of partial onset seizures in appropriate patients."

Source: GSK and Valeant receive European authorisation for Trobalt (retigabine): www.gsk.com/media/pressreleases/2011/2011-pressrelease-381864.htm

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Joanne Walker,
Commissioning Editor, *Clinical Investigation*
Tel.: +44 (0)20 8371 6080;
E-mail: j.walker@future-science.com

FDA approves ipilimumab for advanced melanoma

The US FDA has announced the approval of ipilimumab (Yervoy™, Bristol-Myers Squibb), the first agent ever proven to improve survival in advanced melanoma, for treatment as a second-line therapy.

Melanoma is the leading cause of death from skin disease. According to the NCI, in 2010 an estimated 68,130 new cases of melanoma were diagnosed in the USA, with approximately 8700 people dying from the disease.

Richard Pazdur, Director of the Office of Oncology Drug Products in the FDA's Center for Drug Evaluation and Research commented that "late-stage melanoma is devastating, with very few treatment options for patients, none of which previously prolonged a patient's life." He contined to say that ipilimumab "is the first therapy approved by the FDA to clearly demonstrate that patients with metastatic melanoma live longer by taking this treatment."

The study of ipilimumab, known as 020, was conducted on previously treated unresectable stage III or stage IV melanoma patients. In the study, patients receiving ipilimumab in addition to a peptide vaccine (glycoprotein 100) had a median survival of 10 months, compared to 6.4 months for patients receiving the vaccine alone ($p < 0.001$). The patients receiving ipilimumab alone had a nearly identical median survival of 10.1 months in the three-group clinical trial ($p < 0.003$).

In the editorial that accompanied the study, Patrick Hwu, from the University of Texas MD Anderson Cancer Center, stated that follow-up from the earliest group of patients who received ipilimumab "shows that ongoing complete responses in some patients with metastatic melanoma can continue past 6 years". He mentions that the response to ipilimumab can be "dramatic", and experts have already predicted a strong patient demand for the new drug.

However, it should be noted that from the 676-patient study that the "best overall response rate" (patients with a complete or partial response) was limited to 10.9% of the ipilimumab recipients. Therefore, a minority of patients respond to the new drug.

Sources: FDA approves ipilimumab for advanced melanoma: www.bms.com/news/press_releases/pages/default.aspx?RSSLink; Hwu P. Treating cancer by targeting the immune system. *N. Engl. J. Med.* 363, 779–781 (2010).

Accelerated approval for oncology drugs comes under question

Agency researchers have published claims that cancer drugs rushed to the market through the US FDA process of accelerated approval, often languish in confirmatory trials.

In the paper 'Accelerated approval of oncology products: the Food and Drug Administration experience' published by the Journal of the National Cancer Institute, researchers stated that out of 47 indications granted fast-track status, benefits are yet to be confirmed in 21. They noted that this was mostly due to trials ongoing.

Established in 1992, the accelerated approval process was set up for drugs that seemed more beneficial than existing therapies for the treatment of life-threatening diseases. Due to the Food, Drug and Cosmetic Act of 2007, the FDA authority can levy penalties of up to US$10 million on pharmaceutical companies for not completing trials for fast-tracked drugs quickly enough.

In their review, the FDA researchers analyzed all of the oncology products fast-tracked between 11 December 1992 and 1 July 2010. They found that a total of 35 products were fast-tracked for 47 new indications and that for 26 indications the benefits were ultimately confirmed. Following the accelerated approval, the median time to official full approval was found at 3.9 years, with a mean time of 4.7 years. The researchers claimed this "represents substantial time savings in terms of earlier availability of drugs to patients".

However, analysis found that in 21 new indications the benefits had not yet been confirmed. Researchers noted that it took approximately 10 years to find that amifostine and gemtuzumab ozogomycin weren't clinically beneficial. When analyzing 18 other indications, trials were still found to be underway in 14, while studies had been completed in four cases but the FDA had not finished its review.

Writing online in the *Journal of the National Cancer Institute* the authors commented that "lack of due diligence in conducting confirmatory trials is a serious concern that has threatened the continuation of the accelerated approval process". Susan Ellenberg, from the University of Pennsylvania (PA, USA), wrote in the editorial to accompany the report that the FDA is "routinely castigated for proceeding too cautiously and slowly, and at the same time, for rushing drugs to market too rapidly without adequate study". She continued that "what some might consider a happy medium will inevitably leave many other scientists, clinicians, and consumers dissatisfied".

Sources: Johnson JR, Ning YM, Farrell A, Justice R, Keegan P, Pazdur R. Accelerated approval of oncology products: the Food and Drug Administration experience *J. Natl. Cancer Inst.* DOI: 10.1093/jnci/djr062 (2011); Ellenberg SS. Accelerated approval of oncology drugs: Can we do better? *J. Natl. Cancer Inst.* DOI: 10.1093/jnci/djr104 (2011).