

# Gout Treatment Pipeline Includes Cherry Juice

BY BRUCE JANCIN

FROM THE ANNUAL EUROPEAN CONGRESS OF RHEUMATOLOGY

ROME – Last year's approval of febuxostat as the first new gout medication in over 40 years appears to have triggered a sharp uptick in drug development for a disease many physicians consider long neglected. The recent approval of pegloticase is proof of the pudding.

Novel gout therapies in the developmental pipeline range from the high tech – a fully human monoclonal antibody to interleukin-1beta – to the low tech, as in cherry juice.

"I've got more than 100 gout patients in my practice on cherry juice concentrate," Dr. Naomi Schlesinger said in an interview with RHEUMATOLOGY NEWS.

Her small retrospective study showed that consumption of 1 tablespoon of Brownwood Acres tart cherry juice con-



**As a result of its anti-inflammatory effect, cherry juice concentrate halves levels of interleukin-1-beta and TNF-alpha.**

DR. SCHLESINGER

centrate twice daily – equivalent to eating 90-120 cherries – led to a 50% or greater reduction in acute gout attacks in 92% of treated patients, with no side effects. Prophylaxis with cherry juice concentrate is worth considering as an adjunct to urate-lowering therapy, said Dr. Schlesinger, chief of the division of rheumatology and connective tissue research at Robert Wood Johnson Medical School, New Brunswick, N.J.

Many patients over the years had told her they loved to eat cherries and thought they might be helpful. Eventually she came across a small 1950 study suggesting a preventive effect.

"I've looked at pomegranate juice, too. It didn't work," she added.

The mechanism of benefit for cherry juice concentrate is an anti-inflammatory effect, the rheumatologist said. Her in vitro studies showed that cherry juice concentrate reduced by up to half interleukin-1-beta and tumor necrosis factor-alpha secretion by monocytes exposed to monosodium urate crystals.

In gout patients, cherry juice concentrate didn't lower serum urate levels; indeed, more than one-third of patients not on urate-lowering therapy who had averaged close to one attack per month remained attack free during 4-6 months on cherry juice concentrate despite an average serum urate level of 7.8 mg/dL.

Other novel gout therapies subjected to studies presented at the European congress included the anti-interleukin-1-beta monoclonal antibody canakinumab, a uricosuric drug known for now as RDEA594, and tranilast, which has been licensed in Japan for several decades as an oral mast cell inhibitor for treatment of

asthma and allergic rhinitis.

Tranilast also has a potent serum uric acid-lowering effect, making it a potential therapy for chronic management of hyperuricemia in gout patients – one that already has a well-established track record for safety, according to Dr. Michael Kitt, executive vice president and chief medical officer at Nuon Therapeutics Inc., San Mateo, Calif.

He presented a preliminary study in

which 49 healthy subjects who received 7 days of tranilast at 300, 600, or 900 mg daily showed dose-dependent 1.1- to 3.3-mg/dL reductions in serum uric acid. A phase-IIa study in hyperuricemic patients should be completed in time for presentation later this year at the American College of Rheumatology meeting, and a phase IIb study of tranilast plus allopurinol is just starting in gout patients. When commercialized, tranilast will be

combined with allopurinol in a single tablet, Dr. Kitt said in an interview.

Dr. Schlesinger also presented a large phase II clinical trial in which canakinumab, the fully human anti-interleukin-1-beta monoclonal antibody, outperformed colchicine for the reduction of flares in gout patients starting allopurinol therapy.

The double-blind, multicenter, 24-week study included 432 gout patients starting allopurinol who were random-

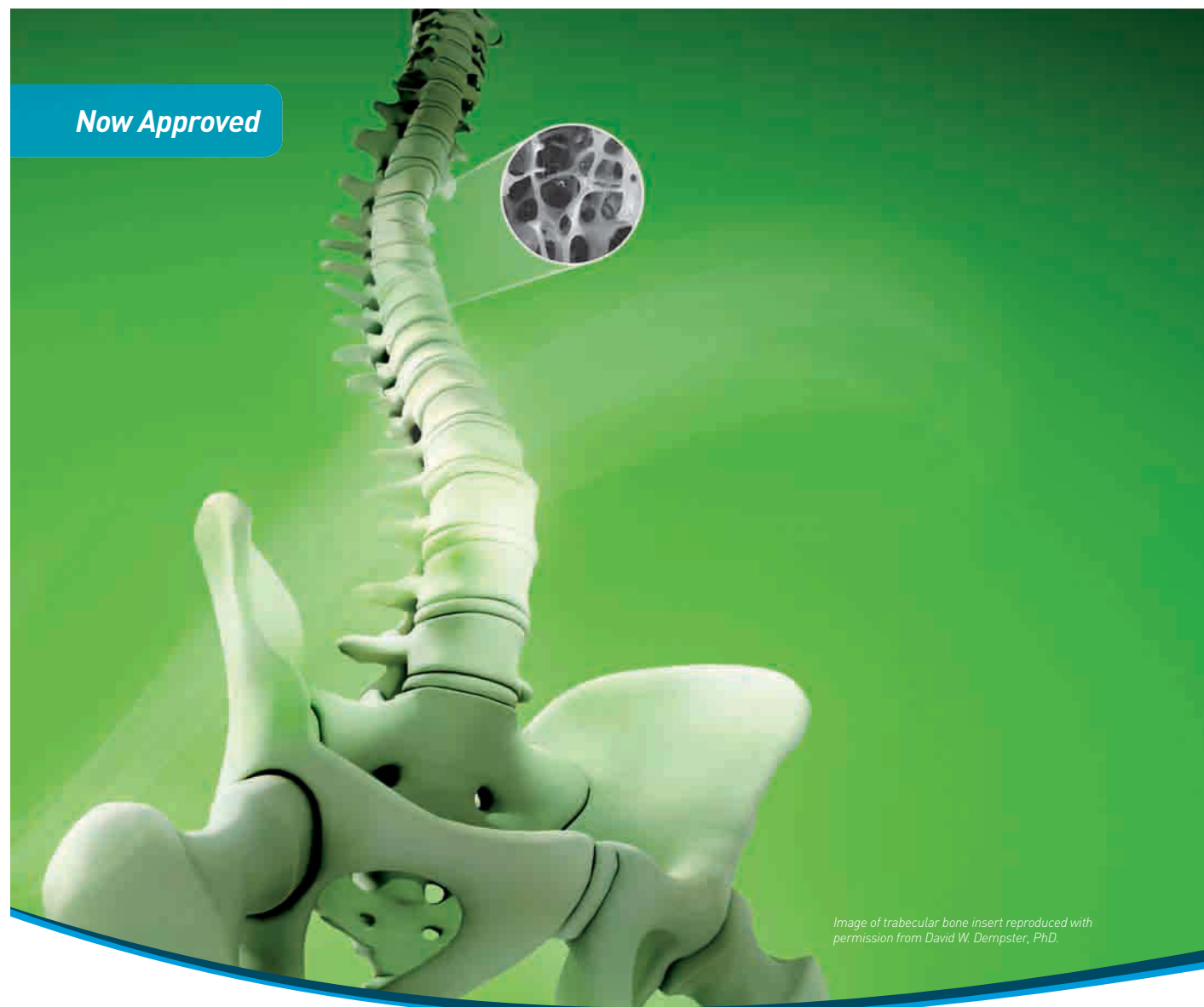


Image of trabecular bone insert reproduced with permission from David W. Dempster, PhD.

## INDICATION

**Prolia™ is indicated for the treatment of postmenopausal women with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy. In postmenopausal women with osteoporosis, Prolia™ reduces the incidence of vertebral, nonvertebral, and hip fractures.**

## IMPORTANT SAFETY INFORMATION

**Hypocalcemia:** Prolia™ is contraindicated in patients with hypocalcemia. Pre-existing hypocalcemia must be corrected prior to initiating Prolia™. Hypocalcemia may worsen, especially in patients with severe renal impairment. In patients predisposed to hypocalcemia and disturbances of mineral metabolism, clinical monitoring of calcium and mineral levels is highly recommended. Adequately supplement all patients with calcium and vitamin D.

**Serious Infections:** In a clinical trial (N = 7808), serious infections leading to hospitalization were reported more frequently in the Prolia™ group than in the placebo group. Serious skin infections, as well as infections of

the abdomen, urinary tract and ear, were more frequent in patients treated with Prolia™. Endocarditis was also reported more frequently in Prolia™-treated subjects. The incidence of opportunistic infections was balanced and the overall incidence of infections was similar between the treatment groups. Advise patients to seek prompt medical attention if they develop signs or symptoms of severe infection, including cellulitis.

Patients on concomitant immunosuppressant agents or with impaired immune systems may be at increased risk for serious infections. In patients who develop serious infections while on Prolia™, prescribers should assess the need for continued Prolia™ therapy.

**Dermatologic Adverse Reactions:** Epidermal and dermal adverse events such as dermatitis, eczema and rashes occurred at a significantly higher rate in the Prolia™ group compared to the placebo group. Most of these events were not specific to the injection site. Consider discontinuing Prolia™ if severe symptoms develop.

**Osteonecrosis of the Jaw (ONJ):** ONJ, which can occur spontaneously, is generally associated with tooth extraction and/or local infection with delayed healing, and has been reported in patients receiving Prolia™. An oral exam should

ized to 16 weeks of colchicine at 0.5 mg/day, a single subcutaneous injection of canakinumab at 25, 50, 100, 200, or 300 mg, or monthly canakinumab injections at 50, 50, 25, and 25 mg.

The canakinumab regimens reduced the risk of one or more urate-lowering therapy-induced flares by 61%-80% compared with colchicine. Canakinumab also reduced the overall rate of flares by 48%-75% relative to colchicine.

Phase III studies are underway, and Novartis plans to file for marketing approval of canakinumab for the treatment and prevention of acute gout attacks by

year's end. The monoclonal antibody is licensed as Ilaris for treatment of cryopyrin-associated periodic syndromes.

Dr. Fernando Perez-Ruiz presented a phase II study of RDEA594, a uricosuric drug that normalizes gout patients' underexcretion of uric acid by a novel mechanism: inhibition of reabsorption of uric acid in the proximal tubule of the kidney.

The study involved 123 hyperuricemic gout patients randomized to 4 weeks of RDEA594 at 200, 400, or 600 mg/day or placebo. All were on colchicine at 0.5-0.6 mg/day to reduce the rate of gout flares.

The primary end point – reduction of

serum uric acid to less than 6 mg/dL after 4 weeks of treatment – was achieved in 45% of patients on the highest dose of RDEA594 and 0% of those on placebo. The median reduction in serum uric acid in patients on the highest dose was 38%, versus a 1% increase in the placebo arm.

Among the subset of patients with a baseline serum uric level below 10 mg/dL, as is the case for a large majority of gout patients seen in clinical practice, the response rate to the highest dose of RDEA594 was 58%. The side effect profile of RDEA594 was comparable to placebo, added Dr. Perez-Ruiz of

Hospital de Cruces in Vizcaya, Spain.

Ardea Biosciences, San Diego, which is developing RDEA594, has not decided whether to take the drug into phase III trials as monotherapy or in combination with febuxostat, with which RDEA594 has shown synergistic effects, a company official said in an interview with RHEUMATOLOGY NEWS. ■

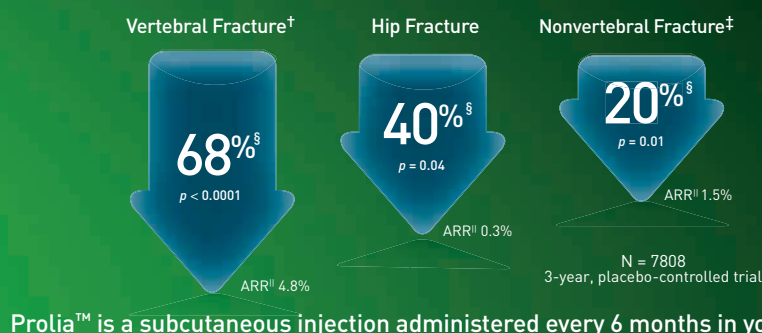
**Disclosures:** Dr. Schlesinger has received research grants from Brownwood Acres and Novartis. Dr. Kitt is employed by Nuon Therapeutics Inc. Dr. Perez-Ruiz is a consultant to Ardea Biosciences.

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Prolia™ significantly reduced fracture risk at key sites in a phase 3 trial<sup>\*1,2</sup>



Prolia™ is a subcutaneous injection administered every 6 months in your office<sup>1</sup>



Please see Brief Summary of Prescribing Information on the following page.

be performed by the prescriber prior to initiation of Prolia™. A dental examination with appropriate preventive dentistry should be considered prior to treatment in patients with risk factors for ONJ. Good oral hygiene practices should be maintained during treatment with Prolia™.

For patients requiring invasive dental procedures, clinical judgment should guide the management plan of each patient. Patients who are suspected of having or who develop ONJ should receive care by a dentist or an oral surgeon. Extensive dental surgery to treat ONJ may exacerbate the condition. Discontinuation of Prolia™ should be considered based on individual benefit-risk assessment.

**Suppression of Bone Turnover:** Prolia™ resulted in significant suppression of bone remodeling as evidenced by markers of bone turnover and bone histomorphometry. The significance of these findings and the effect of long-term treatment are unknown. Monitor patients for consequences, including ONJ, atypical fractures, and delayed fracture healing.

**Adverse Reactions:** The most common adverse reactions (> 5% and more common than placebo) are back pain, pain in extremity, musculoskeletal pain, hypercholesterolemia, and cystitis. Pancreatitis has been reported with Prolia™.

The overall incidence of new malignancies was 4.3% in the placebo and 4.8% in the Prolia™ groups. A causal relationship to drug exposure has not been established. Denosumab is a human monoclonal antibody. As with all therapeutic proteins, there is potential for immunogenicity.

### Prolia™ Postmarketing Active Safety Surveillance Program:

The Prolia™ Postmarketing Active Safety Surveillance Program is available to collect information from prescribers on specific adverse events. Please go to [www.proliasafety.com](http://www.proliasafety.com) or call 1-800-772-6436 for more information about this program.

\* Key sites: vertebral, hip, and nonvertebral.<sup>1,2</sup>  
<sup>†</sup> Includes 7393 patients with a baseline and at least one post-baseline radiograph.<sup>1,2</sup>  
<sup>‡</sup> Composite measurement excluding pathological fractures and those associated with severe trauma, fractures of the vertebrae, skull, face, mandible, metacarpals, fingers, and toes.<sup>1,2</sup>  
<sup>§</sup> RRR = relative risk reduction.  
<sup>||</sup> ARR = absolute risk reduction.

References: 1. Prolia™ (denosumab) prescribing information, Amgen. 2. Cummings SR, San Martin J, McClung MR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *N Engl J Med.* 2009;361:756-765.

For more information, visit [www.ProliaHCP.com/RH](http://www.ProliaHCP.com/RH)

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