# Weight Loss Drug Combo May Improve QOL

BY MIRIAM E. TUCKER

FROM THE ANNUAL MEETING OF THE AMERICAN ASSOCIATION OF DIABETES EDUCATORS

LAS VEGAS – The investigational, controlled-release phentermine/topiramate combination produced significant weight loss that was associated with significantly improved quality of life in two studies of overweight and obese individuals.

Vivus Inc., which sponsored the studies, is developing the once-daily oral, controlled-release formulation of low-dose phentermine plus topiramate under the name Qnexa. Designed to decrease appetite and increase satiety, the combination treatment has completed phase III clinical trials for the treatment of obesity and is currently under evaluation by the Food and Drug Administration for that indication. It also is in phase II trials for the treatment of type 2 diabetes and obstructive sleep apnea, according to a company statement.

Ronette L. Kolotkin, Ph.D., summarized the 56-week weight loss data at the meeting and presented new findings on quality of life from two phase III, double-blind, placebo-controlled trials. One study (EQUIP) enrolled 1,267 subjects with body mass indexes of 35 kg/m$^2$ or greater. The other (CONQUER) enrolled 2,487 patients who had BMIs of 27-45 plus two or more comorbidities, such as diabetes, dyslipidemia, or hypertension.

In the EQUIP trial, subjects were randomized to 3.75 mg phentermine/23 mg topiramate, 15 mg phentermine/92 mg topiramate, or placebo. They were mostly women (83%), with a mean age of 43 years and mean BMI of 42. Among those who completed 56 weeks of treatment, the percentage of weight loss was 3% for placebo, 7% for the lower dose, and 15% for the higher dose. In the intent-to-treat (ITT) analysis with the last observation carried forward (LOCF), the weight loss percentages were 2%, 5%, and 11%, respectively, said Dr. Kolotkin, a clinical psychologist, researcher, and consultant with Obesity and Quality of Life Consulting, Durham, N.C.

In the CONQUER trial, two-thirds of the patients were women, with a mean age of 51 years and a mean BMI of 37. They were randomized to 7.5 mg phentermine/46 mg topiramate, 15 mg phentermine/92 mg topiramate, or placebo. At 56 weeks, the completers had lost 2% of their body weight with placebo, 11% with the lower dose, and 13% with the higher dose. In the ITT/LOCF analysis, the weight loss percentages were 1%, 8%, and 10%, respectively. In both studies, weight loss was statistically significant for both drug doses but not for placebo, Dr. Kolotkin said.

**VITALS**

**Major Finding:** The proportions of patients achieving a meaningful change in weight-related quality of life ranged from 30%-36% with placebo, 37%-52% with the lower phentermine/topiramate dose, and 49%-52% with the higher dose.

**Data Source:** One randomized study (EQUIP) enrolled 1,267 subjects with BMIs of 35 or greater. The other randomized study (CONQUER) enrolled 2,487 patients who had BMIs of 27-45 plus two or more comorbidities.

**Disclosures:** All studies were funded by Vivus. Dr. Kolotkin and Ms. Rueger reported having no further disclosures.

Two measures were used to assess health-related quality of life (HRQOL). One, the Impact of Weight on Quality of Life–Lite (IWQOL-Lite), is a 31-item survey, each beginning with the phrase "Because of my weight…" with five possible responses ranging from "Never true" to "Always true." Domains include physical function ("…I have trouble tying my shoe"), self-esteem ("I'm afraid of being rejected"), sexual life ("I do not enjoy sexual activity"), public distress ("I experience ridicule, teasing, etc."), and work ("I am less productive than I could be"). Scoring is on a 0-100 scale, with a higher score signifying better HRQOL.

The other measure, the Study Short Form–36 (SF-36), assesses general HRQOL with a 36-item survey pertaining to physical and mental/psychosocial health, each with four health domains. Scoring is also on a 0-100 scale, with higher being better.

At 56 weeks in the ITT-LOCF analysis, IWQOL score changes were significantly better for both treatment groups than for placebo. With the higher dose, score increases ranged from 7 for work to 16 for self-esteem in EQUIP and from 8 for public distress to 16 for self-esteem in CONQUER.

On the SF-36, in CONQUER there were statistically significant increases from baseline to 56 weeks in the areas of physical functioning, physical role functioning, bodily pain, general health, vitality, and the overall physical component summary score. However, changes in the overall mental component, social functioning, emotional role functioning, and mental health were not significant, Dr. Kolotkin reported.

Further evaluation assessed the degree to which the changes were meaningful, with the definition of "meaningful" on the IWQOL-Lite total score as an increase of 8-12 points, depending on score severity at baseline (J. Clin. Epidemiol. 2004;57:1153-60).

In EQUIP, the proportions of patients achieving a meaningful change in weight-related quality of life were 30% with placebo, 37% with the lower phentermine/topiramate dose, and 49% with the higher dose.

In CONQUER, meaningful improvement on IWQOL-Lite occurred in 36% of the placebo patients, compared with 52% of each of the two doses of phentermine/topiramate. Similar results in CONQUER were seen with the SF-36, for which meaningful improvement was defined as an increase of 2.5 or more points. Those percentages were 36% for placebo, 55% for the lower dose, and 53% for the higher dose, she reported.

Not surprisingly, improvement in quality of life was directly related to amount of weight lost. In EQUIP, those losing less than 5% of their body weight had a mean change of 5 points on the IWQOL-Lite at 56 weeks, compared with 17 points for those who lost 10% or more of their body weight. Similar results were seen on the IWQOL-Lite in CONQUER (from 6 vs. 18 points, respectively), and on the SF-36 in CONQUER (2 vs. 6 points).

Separately, Miriam M. Rueger, R.N., a certified diabetes educator at the University of Alabama at Birmingham, and her associates presented data showing sustained weight loss among the CONQUER patients in a 52-week extension trial (SEQUEL).

In the double-blind, placebo-controlled extension study of subjects who completed 56 weeks of treatment in CONQUER and enrolled in SEQUEL, the original randomization was maintained in a total of 675 patients for an additional 52 weeks, with 227 continuing to receive placebo, 153 the lower phentermine/topiramate dose, and 295 the higher dose.

In the ITT-LOCF analysis conducted at 108 weeks, significantly greater weight loss was achieved with both the lower and higher drug doses, compared with placebo (9% and 11%, respectively, compared with 2%). The proportions of those achieving a body weight loss of 10% or more were 54% and 50% for the higher and lower doses, respectively, vs. just 12% with placebo, said Ms. Rueger.

The proportion of patients who discontinued the study because of adverse events was low and did not differ between groups, ranging from 3% with placebo to 5% with the lower drug dose, they said. ■

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## Blognosis

# Money Is Only Part of the Conflict Story

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"Any senior scientist will tell you that the biggest conflict of interest he or she has doesn't have anything to do with the [corporate or other] interests that they list on their PowerPoints or at the end of their publications," Dr. Paul M. Ridker said during his presentation on the inflammatory hypothesis of atherosclerosis at the annual meeting of the International Society on Hypertension in Blacks in Boston. "It has to do with our individual belief in the biology of what we're doing."

For this reason, the lengthy disclosure slide that served as the backdrop to his talk was less relevant, he said, than his fundamental bias, which is his belief that inflammation is "part and parcel, if not the cause of, atherosclerosis."

That type of bias, not industry support, "is what drives my work, and it is what drives most scientists," stressed Dr. Ridker, the Eugene Braunwald professor of medicine at Harvard University and director of the Center for Cardiovascular Disease Prevention of Brigham and Women's Hospital in Boston.

Dr. Ridker's contention is likely a nod to the diatribe that followed the publication of results from the 2008 JUPITER trial on the effects of rosuvastatin (Crestor) in which he and his co-investigators attributed a 44% reduction in cardiovascular events to the agent's ability to both lower LDL cholesterol and reduce C-reactive protein (CRP) levels (N. Engl. J. Med. 2008;359:2195-207).

Following the publication of the findings, his colleagues questioned the interpretation and veracity of the data in the face of what they deemed to be an unacceptable degree of commercial bias. They were referring not only to the fact that the study was funded by AstraZeneca, the drug's manufacturer, and that 9 of the 14 authors disclosed financial ties to the company, but also that Dr. Ridker holds the legal patent on CRP testing technology. Without question, the skeptics argued, Dr. Ridker had much to gain from the acceptance of his research (Arch Intern Med. 2010;170:1032-6).

For his part, Dr. Ridker vigorously defended and continues to defend the quality of the JUPITER data. He has also introduced a salient argument, that the conflicts of interest that have the most potential to bias research are not the tangible ones that are listed at the end of a paper.

They are, instead, the intellectual and emotional ones that defy enumeration. He doesn't argue against financial disclosures, but he does warn that they don't tell the "whole story." ■

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