⮕ **TRIAL WATCH**

Novel obesity therapies set to attract spotlight in Q3 2009

Current pharmacotherapies for obesity have limited efficacy and are associated with concerns over side effects. However, in the third quarter of 2009, mid–late-stage clinical data are due to be reported for a new generation of anti-obesity therapies — mainly novel combinations involving drugs approved for other indications — that could reinvigorate the field.

The two new therapies that have resulted in the greatest weight loss include the anti-seizure medications topiramate or zonisamide. Over ~6 months, phentermine plus topiramate (Qnexa; Vivus) and bupropion plus zonisamide (Empatic; Orexigen) reduced body weight by 7.5% (in the Phase III EQUATE trial and a Phase IIb trial, respectively) compared with placebo. If these results hold up in the forthcoming year-long Phase III trial data for phentermine plus topiramate and the Phase IIb trial for bupropion plus zonisamide, the therapies will be on track to meet one of the FDA's two current efficacy criteria: a mean weight loss at least 5% greater than placebo. However, safety will be a crucial factor. Among other issues, anti-seizure medications received a label warning for suicidality this year, and the FDA found topiramate and zonisamide had among the highest relative risks. Phentermine plus topiramate did numerically raise depression events slightly in the EQUATE trial, but also showed significant improvements on a depression scale, with no reports of suicidality. The bupropion component of Empatic is an antidepressant, which could help reduce the risk of suicidality in adults.

Another combination using bupropion, but with naltrexone (Contrave; Orexigen), did not meet the first FDA criterion in an initial Phase III trial, although it may qualify for the second FDA efficacy criterion related to the proportion of subjects who lose at least 5% of baseline body weight in the treatment group in comparison to the proportion in the placebo group. This trial was different from the three that will be reported this quarter (one of which involves patients with diabetes, an important co-morbid population), as patients underwent behavioural modification, leading to higher weight loss in both the treatment and placebo groups (9.3% and 5.1%, respectively).

Phase IIb results are also expected for the combination of pramlintide and metreleptin (developed by Amylin and Amgen) — a combination which reduced body weight by 12.7% from baseline in a previous trial. However, the population was enriched with patients that had previously demonstrated weight loss, and there was no placebo comparator.

Finally, Phase III data are expected for lorcaserin (developed by Arena), which was designed to be a safer version of fenfluramine, popularly combined with phentermine (fen-phen) until cardiac valve deformities led to its removal from the market in 1997. Although the weight loss observed in the first Phase III trial of lorcaserin (mean of 3.6% compared with placebo) is less than for the combination therapies above, it met the second FDA criterion, and some experts have speculated on a future combination with phentermine if it can demonstrate cardiac-valve safety.

Given the new FDA guidelines on assessing cardiovascular risk in diabetes drugs, scrutiny of cardiovascular events will probably be heightened for obesity drugs as well, particularly for an adverse effect on specific vital signs or lipids. For the above drugs, most data reported on risk factors have been positive. Even if these drugs are approved, one survey found that half of payors favoured a higher weight-loss threshold for reimbursement, closer to that seen with surgical treatment. However, this might change if obesity drugs can demonstrate improved cardiovascular outcomes in studies such as a Phase III trial for sibutramine known as SCOUT, for which results are anticipated by the end of the year.

Peter Chang is a BioMedTracker Scientific Analyst at Sagient Research Systems, 3655 Nobel Drive Suite 540, San Diego, California 92122, USA.
e-mail: pchang@SagientResearch.com