

# **OREXIGEN(TM) THERAPEUTICS REPORTS POSITIVE PHASE II RESULTS FOR EXCALIA(TM) COMBINATION-THERAPY TO TREAT OBESITY**

Orexigen Therapeutics

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OREXIGEN(TM) Therapeutics, Inc., a privately held clinical-stage neuroscience company developing novel strategic approaches to the treatment of obesity, announced that Excalia(TM), a combination of two centrally-acting medications intended to provide and sustain clinically important weight loss, demonstrated significant weight loss in a six month, double-blind, phase IIa clinical study. The magnitude of weight reduction exceeded that seen with placebo. The findings showed that patients completing the blinded 24-week phase lost on average 9.2% of their weight from baseline using Excalia compared to an average of 0.4% weight loss from baseline for patients using placebo. The study results further demonstrate that weight loss continued through an additional 24 week open-label period achieving an average weight loss of 12% from baseline by 48 weeks. These top line phase IIa data for Excalia were presented at the annual meeting of the North American Association for the Study of Obesity (NAASO) in Boston.

"Excalia is designed to achieve an aggressive weight loss trajectory and then to delay the typical weight loss 'plateau' by offsetting one of the body's natural compensatory pathways. These phase II data suggest a level of efficacy that exceeded our expectations in relation to existing approaches," said Gary Tollefson, M.D., Ph.D., OREXIGEN president and CEO. "Excalia is designed to act on a specific reciprocally paired group of hypothalamic neurons that we believe will yield a clinically meaningful weight loss trajectory among significantly overweight individuals. We believe that these positive data support our theoretical approach."

Excalia is a proprietary combination of bupropion, a dopamine and norepinephrine reuptake inhibitor, plus zonisamide, an approved anticonvulsant medication. OREXIGEN's preclinical research suggests that combining these two central nervous system drugs acts on a complex of neurons in the hypothalamus, the area of the brain contributing to the regulation of appetite, energy output and maintaining body weight. The compound was tested in a double-blind, placebo-controlled, randomized, proof-of-concept phase II clinical study of 127 non-smokers with body mass indices (BMI's) between 30 and 40. At the end of the primary treatment interval Excalia was associated with advantages over both the individual components and placebo (see table below). Study completers had lost in excess of 9% of their baseline body weight by week 24.

On categorical measures of response nearly three quarters (73%) of those who completed the study demonstrated a 5% weight loss, and half (50%) demonstrated a 10% weight loss at 24 weeks. After 24 weeks patients were re-randomized for the extension phase of the study. Those staying on their same dose of active therapy lost, [on average], an additional 3% from the start of the study. Approximately one-third of subjects discontinued early due to an adverse event consistent with the existing package insert for zonisamide. In light of this rate, the company has implemented a strategy that it believes will result in improved tolerability in current and forthcoming trials for Excalia.

Separately, the company reported that the first cohort of patients testing its other obesity compound, Contrave, continued to lose weight without an indication of the common diet "plateau" as they reached the 36 week mark of a phase III, multi-center clinical trial. Contrave is a combination of naltrexone and bupropion intended to provide a steady, sustained weight loss trajectory with a mechanism of action differing from Excalia. Contrave was rationally designed to block the compensatory effect of beta-endorphin, a key component of the POMC pathway, a central nervous system pathway that stimulates energy expenditure and reduces hunger. Beta-endorphin has been reported to limit POMC and in turn, weight loss. In September, OREXIGEN reported positive 24-week results for Contrave ([www.orexigen.com/news](http://www.orexigen.com/news)). The company believes that the new nine month data further validate the scientific hypothesis underlying the development of Contrave.