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# Is Oral XEN-D0501 the Next Obesity Drug Hype?

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XEN-D0501, a transient receptor potential vanilloid 1 (TRPV1) antagonist, is gaining attention for its potential as an oral tablet to treat type 2 diabetes, obesity, and cardiovascular diseases. Dorte X. Gram, PhD, founder of Pila Pharma, a Swedish pharmaceutical company investigating XEN-D0501, first noticed the connection more than 20 years ago as a researcher at Novo Nordisk.

Dorte X. Gram, PhD

"In my very first experiments, I noticed that mice who would normally become diabetic didn't get diabetes at all," she told *Medscape Medical News*.

These surprising observations prompted Gram to investigate further the potential role of the TRPV1 receptor in regulating metabolism, leading her to file a patent and pursue the development of TRPV1 antagonists for obesity and related conditions.

The company has received enough attention from investors that it witnessed a triple-digit percentage gain on the Nasdaq First North stock exchange in 2024.

While XEN-D0501 shows promise, researchers urge caution, as the drug is still in early development. "There is simply no quality human data to say anything about the possibilities for this pathway," said John B. Dixon, PhD, professor at Iverson Health Innovation Research Institute, Swinburne University of Technology, Melbourne, Australia.

John B. Dixon, PhD

## What Is TRPV1 and How Do TRPV1 Modulators Work?

TRPV1 is a homotetrameric receptor with six transmembrane domains expressed primarily in sensory nerve fibers. It is responsible for detecting noxious signals, including heat and chemical irritants — particularly capsaicin, the active component of chili peppers.

TRPV1 mediates the sensation of burning pain, often associated with inflammation and heat exposure. It also helps detect and regulate body temperature and influences the release of inflammatory mediators. In the central nervous system, it affects synaptic function and plasticity.

Given TRPV1's broad physiologic role, its modulation has potential for treating several conditions, including pain disorders, inflammation, and cardiovascular diseases.

Studies have shown that activating TRPV1 can help counter diet-induced obesity by increasing thermogenesis in brown adipose tissue and improving metabolic activity. TRPV1 agonists such as capsaicin have been shown to reduce weight gain in high-fat-diet-induced obese mice, with clinical trials further supporting its potential for decreasing body weight in people with overweight.

For instance, aclinical trial showed that participants with obesity taking capsinoid supplementation for 12 weeks experienced a reduction in body weight compared with those who took a placebo.

While TRPV1 agonists have been more commonly studied for obesity management, most studies involving antagonists have focused on pain relief, inflammation, and conditions like erythromelalgia rather than weight loss.

However, some evidence suggests that TRPV1 antagonism may influence metabolism. For example, in one study, mice lacking TRPV1 were resistant to obesity, "but that is not sufficient [to come to any conclusion]," said Vincenzo Di Marzo, PhD, director of the Joint International Research Unit for the Chemical and Biomolecular Study of the Microbiome in Metabolic Health and Nutrition between

the Consiglio Nazionale delle Ricerche, Italy, and Université Laval, in Quebec City, Quebec, Canada. He was not involved in the study.

Vincenzo Di Marzo, PhD

Gram admits that the picture around the mechanism of action of TRPV1 modulators is unclear. “There is not a consensus in the literature about the effect of this receptor. Should it be agonized or should it be antagonized?” she said.

## What Is XEN-D0501?

XEN-D0501 is a novel selective TRPV1 antagonist, which Pila Pharma is developing for treating erythromelalgia, a rare condition that causes burning pain, redness, and hotness in the skin, especially the feet. It has received orphan-drug status for this indication in the United States.

Initially, the company explored XEN-D0501 for treating overactive bladder, but the development of the drug for this condition has been discontinued. Now, attention has moved to investigating XEN-D0501 for its potential in treating type 2 diabetes, obesity, and cardiovascular disease.

Although phase 2a clinical trials showed that XEN-D0501 is generally well tolerated in healthy participants, it has been associated with several side effects, including hyperthermia and oral discomfort, thought to be due to TRPV1 antagonism at sensory nerve endings in the mouth, in addition to transient urinary retention and postvoiding residual volumes, indicating potential issues with bladder function.

Another phase 2a trial (PP-CT03) is planned to assess the maximum tolerable dose of XEN-D0501 in people with obesity and type 2 diabetes, focusing on safety and potential effects on body weight. Gram said that early data show these populations experience less hyperthermia than healthy participants. However, the mechanism behind it is still not understood. These studies also showed some positive effects on insulin sensitivity and a biomarker for heart failure.

“The company data provided so far for XEN-D0501 are promising but still too preliminary,” said Di Marzo, speaking with *Medscape Medical News.*

The company is now planning a further 3-month-long dose-escalation study in people with obesity and diabetes. “If these studies show that the molecule is as efficacious and safe as we think it is, then it would make life a lot better for a lot of people because it is a tablet, not an injectable,” Gram said.

Also being explored by the company is the potential of the molecule for treating cardiovascular diseases, particularly abdominal aortic aneurysms, and as a potential nonopioid painkiller.

*John B. Dixon, PhD, and Vincenzo Di Marzo, PhD, have disclosed no relevant financial relationships. Dorte X. Gram, PhD, is founder and CSO at Pila Pharma.*

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