DEAL WATCH

AbbVie invests in pioneering celiac disease therapy

AbbVie and Alvine Pharmaceuticals have teamed up to develop ALV003, which is a novel oral treatment that is currently in Phase II development for patients with celiac disease.

Under the terms of the agreement, AbbVie will make an initial upfront payment of US$70 million for an exclusive option to acquire either the assets relating to ALV003 or the equity of the company upon successful completion of Phase II development. Alvine will also be entitled to receive a milestone payment upon AbbVie's initiation of Phase III development.

Celiac disease is an acquired autoimmune disorder of the small intestine that develops in genetically susceptible individuals after exposure to dietary gluten, causing intestinal inflammation and chronic gastrointestinal symptoms, with potential complications including malabsorption, osteoporosis, anaemia and malignancy. The pathogenesis is complex. "What we know is that all patients have gluten-specific T cells in the small intestinal lamina propria. These T cells respond to gluten-derived peptides bound to the disease-predisposing molecules, human leukocyte antigen DQ2 (HLA-DQ2) or HLA-DQ8, resulting in the production of pro-inflammatory cytokines," explains Frits Koning, Leiden University Medical Center, the Netherlands. "However, most HLA-DQ2- and HLA-DQ8-positive individuals do not develop celiac disease, so there must be additional genetic and environmental factors that trigger disease initiation or affect disease development."

There are currently no approved therapies for the disease, and patients must adhere to a strict lifelong gluten-free diet, which is challenging. "Cereals containing gluten are heavily used in the food industry and products that are naturally gluten-free may become contaminated during food processing," says Koning. "Gluten is also one of the cheapest food proteins and has interesting properties, and so is added to many products, making it difficult to completely avoid."

The development of therapies for the disease is also challenging. "Any therapy would have to be as safe as a strict gluten-free diet. No risk-taking is allowed," says Stefano Guandalini, University of Chicago Celiac Disease Center, Illinois, USA.

ALV003 is composed of two gluten-specific proteases: a modified recombinant version of a *Hordeum vulgare* (barley) cysteine endoprotease and a modified recombinant version of a *Sphingomonas capsulata* prolyl endopeptidase. "Gluten is only partially degraded in the stomach and upper intestine, and the remaining fragments are large enough to bind to HLA-DQ," says Koning. "So the general idea is that taking enzymes that can degrade gluten with a gluten-containing meal could help alleviate the disease-inducing properties of gluten by breaking down gluten further so that the fragments can no longer bind to HLA-DQ."

In a Phase IIa study involving 41 well-controlled patients with celiac disease, in which individuals were randomized to receive oral ALV003 or placebo daily for 6 weeks at the time of ingestion of 2 g of gluten, ALV003 was reported to significantly attenuate gluten-induced intestinal mucosal injury. Importantly, no serious adverse events were reported.

"I was impressed by the conceptual validity of this approach from the early stages of its development," says Guandalini. "The results obtained in rigorous, well-controlled, well-documented investigations so far indicate that the premises are correct." A 500-patient Phase IIb trial is expected to begin later this year.

However, although the approach seems promising, there are limitations, says Koning. "ALV003 is most likely to be safe and its potential to help degrade gluten could benefit patients. However, it is difficult to imagine that it will make it possible for them to completely switch to a normal gluten-containing diet; such enzymatic approaches seem more likely to be used to prevent the deleterious effects of inadvertent gluten exposure and allow patients to eat out."

Koning notes that another gluten-degrading enzyme, a prolyl endoprotease derived from *Aspergillus niger*, is expected to be launched in the USA towards the end of the year as a food supplement. Several other therapeutic strategies are also being investigated, including: inhibition of tissue transglutaminase (the enzyme that modifies gluten so that it can bind to HLA-DQ); enhancing the tightness of the intestinal barrier to prevent the entry of gluten peptides; and the development of vaccines that aim to restore gluten tolerance. "It is a very dynamic and exciting time for investigation into novel treatments for celiac disease," concludes Guandalini.

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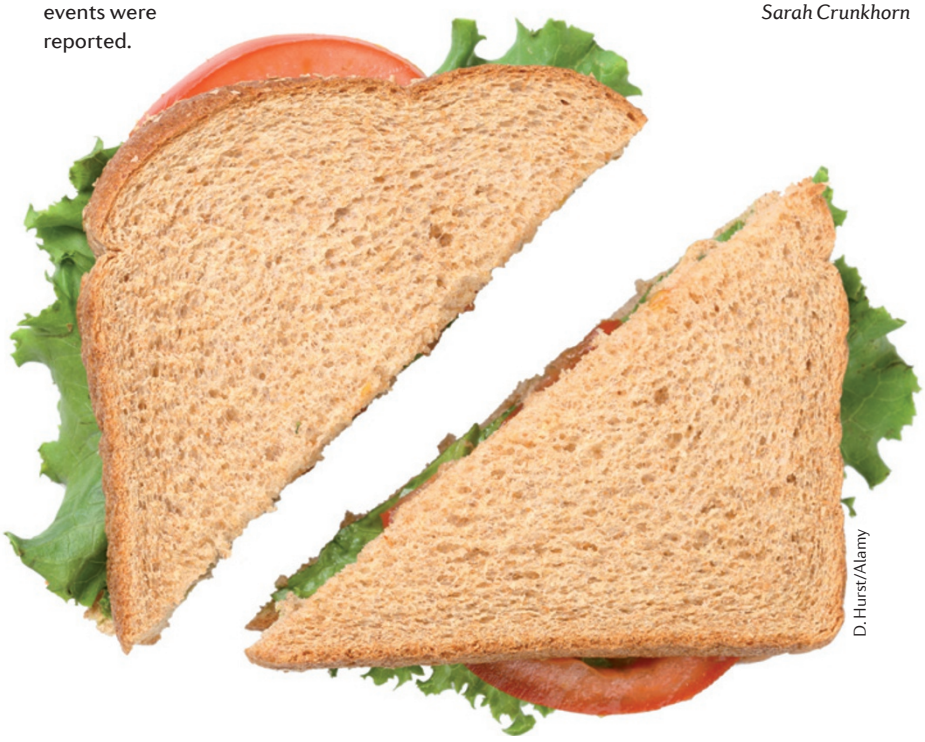

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