TAK-062 effectively digests gluten in the human stomach: results of a phase 1 study

Pultz IS,\textsuperscript{1} Leffler DA,\textsuperscript{2} Liu T,\textsuperscript{2} Winkle P,\textsuperscript{3} Vitanza JM,\textsuperscript{1} Hill M\textsuperscript{1}

\textsuperscript{1}PvP Biologics, Inc., San Diego, CA, USA
\textsuperscript{2}Takeda Pharmaceuticals Inc. Co., Cambridge, MA, USA
\textsuperscript{3}Anaheim Clinical Trials, Anaheim, CA, USA
Conflicts of interest disclosures and funding statement

- Pultz IS and Hill M are employees of PvP Biologics, Inc. and shareholders of the company
- Leffler DA and Liu T are employees of Takeda Pharmaceuticals Inc. Co.
- Winkle P has no conflict of interest to declare
- Vitanza JM has a consulting agreement with PvP Biologics, Inc.

Funding statement
This study was sponsored by PvP Biologics, Inc. and supported by Takeda Pharmaceuticals
Celiac disease

- Celiac disease is an **autoimmune** disorder triggered in genetically predisposed individuals by the ingestion of **dietary gluten**

- Gluten peptides (including gliadin) enter the submucosa of the small intestine and are deamidated by tissue transglutaminase\(^1\)

- Gliadin-specific CD4+ T cells recognize the deamidated gliadin leading to **mucosal inflammation** and **autoantibody formation**\(^1\)

- Consequences of active celiac disease include a variety of gastrointestinal symptoms and extraintestinal manifestations\(^1\)

- A strict gluten-free diet, while the only accepted treatment for celiac disease, is inadequate in a significant proportion of patients who continue to suffer with symptoms and **villous atrophy** due predominantly to **inadvertent gluten exposure**

TAK-062: a potential treatment for celiac disease

- Degradation of undigested immunogenic fractions of gluten peptides in the stomach is expected to decrease the immunogenicity of ingested gluten\(^1\)

- TAK-062 is a highly potent, computationally designed endopeptidase with several advantages compared with previously investigated enzymes:
  - Increased proteolytic activity and substrate specificity
    - > 99% gluten degradation measured in *in vitro* and *in vivo* models\(^2\)
  - Stable over a range of relevant pH levels
  - Resistant to gastric/intestinal proteases (pepsin/trypsin)

- TAK-062 offers the potential to reduce the immune response to gluten in patients with celiac disease

TAK-062 phase 1, single-blind, placebo-controlled, cross-over study: study objectives

- **Primary objectives**
  - Evaluate ability of TAK-062 (liquid and capsule formulations) to degrade gluten in the gastric space of healthy participants
  - Determine effect of PPI pretreatment on ability of TAK-062 (liquid formulation) to degrade gluten

- **Secondary objectives**
  - Evaluate safety, tolerability and gluten degradation ability of the maximum tolerated dose of TAK-062 liquid formulation (900 mg) compared with the maximum feasible dose of TAK-062 capsule formulation (600 mg)
  - Evaluate pharmacokinetics of TAK-062 in healthy participants

PPI, proton pump inhibitor
ClinicalTrials.gov Identifier: NCT03701555
Group 1: gluten digestion using TAK-062 liquid formulation with or without PPI pretreatment

- TAK-062 liquid formulation, 900 mg, N = 14 (treated)

<table>
<thead>
<tr>
<th>Screening (up to 4 weeks)</th>
<th>Randomized to treatment order</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>TAK-062 900 mg</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>TAK-062 900 mg + PPI</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>TAK-062 900 mg</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>TAK-062 900 mg + PPI</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
</tr>
</tbody>
</table>

Final safety visit, followed by anti-drug antibody testing 14 and 28 days after final treatment

PPI, proton pump inhibitor (Nexium, 20 mg, daily for 7 days prior to study drug administration)
ClinicalTrials.gov Identifier: NCT03701555
Group 2: gluten digestion using TAK-062 capsule formulation

- TAK-062 capsule formulation, 600 mg, N = 9 (treated)
Group 3: gluten digestion using TAK-062 liquid formulation with varying doses and gluten amounts

- TAK-062 liquid formulation, 300, 600 or 900 mg, N = 24 (treated)

![Diagram showing randomized treatment orders and gastric aspiration times](image-url)
Methods

- Gastric aspiration: single lumen catheter (nasogastric tube) introduced into the stomach
  - Samples of gastric fluid obtained pretreatment and at specified times post treatment via the nasogastric tube

- Gluten degradation in aspirated gastric samples measured using ELISA based on the monoclonal R5 and G12 antibodies specific for immunogenic fractions of gluten (QQPFP and QPQ-(L/Q)-P-(Y/F) epitopes, respectively)
  - Ridascreen® R5 Competitive ELISA kit from R-Biopharm and G12 competitive ELISA developed using HRP-conjugated anti-gliadin 33-mer monoclonal antibody from Biomedal

- PEG 3350 calibration curve used to correct gluten levels in each gastric sample
  - PEG 3350 1 g combined with standardized study meal
  - PEG 3350 concentration in aspirated gastric samples measured using validated liquid chromatography/mass spectrometric method by Battelle

- Pharmacokinetic analysis
  - Blood samples were collected pretreatment and at several timepoints from 15 minutes to 8 hours after study drug administration
  - Plasma TAK-062 concentrations were determined using a validated ELISA method to evaluate systemic exposure
Standardized 3 g gluten-containing study meal

- Standardized ‘smoothie’ study meal consisting of:
  - Lactose-free vanilla ice cream, 140 g
  - Pasteurized egg whites, 50 g
  - Orange juice, 35 g
  - Whole wheat (gluten-containing) bread, 27.9 g
  - Lime juice, 14 g
  - Vanilla extract, 3 g
  - MiraLAX® (polyethylene glycol), 1 g
- Entire study meal was consumed within 10 minutes of study drug administration

Study meal nutrients

<table>
<thead>
<tr>
<th>3 g gluten-containing study meal</th>
<th>Amount of food (g)</th>
<th>Energy (kcal)</th>
<th>Total fat (g)</th>
<th>Total carbohydrates (g)</th>
<th>Total protein (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>270.9</td>
<td>455.0</td>
<td>16.6</td>
<td>60.4</td>
<td>12.7</td>
</tr>
<tr>
<td>Percentage of total grams</td>
<td>NA</td>
<td>NA</td>
<td>6.13%</td>
<td>22.28%</td>
<td>4.70%</td>
</tr>
<tr>
<td>Percentage of total kcal</td>
<td>NA</td>
<td>NA</td>
<td>3.65%</td>
<td>13.27%</td>
<td>2.80%</td>
</tr>
</tbody>
</table>
Participant disposition and demographics

Participants enrolled
N = 57

Participants treated
n = 47 (82.5%)
- Group 1, n = 14
- Group 2, n = 9
- Group 3, n = 24

Participants completing study
n = 43 (75.4%)

Discontinued
n = 14
- Unable to tolerate nasogastric tube (n = 7)
- Non-compliance (n = 4)
- Positive urine drug screen (n = 2)
- Lost to follow-up (n = 1)

- Age: 18–59 years
- BMI: < 35 kg/m²
- 14 females (29.8%), 33 males (70.2%)
- Mean age: 42 (SD 10.7) years
- Mean BMI: 26.48 (SD 3.1) kg/m²

BMI, body mass index; SD, standard deviation
ClinicalTrials.gov Identifier: NCT03701555
TAK-062 achieved consistently high degradation levels of gluten in the gastric space (up to 99%)

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Gluten degradation (%) measured by R5 ELISA relative to placebo</th>
<th>Gluten degradation (%) measured by G12 ELISA relative to placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAK-062(^a) 900 mg with 3 g gluten meal (n(^*) = 11), Group 1</td>
<td>94.6 (10.95); 97.6</td>
<td>95.4 (8.84); 98.9</td>
</tr>
<tr>
<td>TAK-062(^a) 900 mg + PPI with 3 g gluten meal (n(^*) = 12), Group 1</td>
<td>98.1 (2.99); 99.2</td>
<td>98.8 (1.41); 99.6</td>
</tr>
<tr>
<td>TAK-062(^b) 600 mg with 3 g gluten meal (n(^*) = 9), Group 2</td>
<td>85.6 (21.38); 99.4</td>
<td>86.6 (26.51); 99.7</td>
</tr>
<tr>
<td>TAK-062(^a) 300 mg with 1 g gluten meal (n(^*) = 8), Group 3</td>
<td>97.8 (2.33); 98.6</td>
<td>98.4 (1.17); 98.7</td>
</tr>
<tr>
<td>TAK-062(^a) 600 mg with 1 g gluten meal (n(^*) = 8), Group 3</td>
<td>97.9 (2.06); 98.4</td>
<td>95.7 (5.32); 98.3</td>
</tr>
<tr>
<td>TAK-062(^a) 900 mg with 6 g gluten meal (n(^*) = 8), Group 3</td>
<td>99.0 (0.95); 99.3</td>
<td>99.0 (1.08); 99.4</td>
</tr>
</tbody>
</table>

Absolute measured values differ between R5 and G12 ELISA methods as they measure different epitopes.

*Number of evaluable gluten degradation data sets; gastric aspiration at 35 minutes post dose; \(^a\)liquid formulation; \(^b\)capsule formulation

ELISA, enzyme-linked immunosorbent assay; PPI, proton pump inhibitor; SD, standard deviation

ClinicalTrials.gov Identifier: NCT03701555
3 g gluten degradation by TAK-062 is not affected by pretreatment with a PPI, and liquid and capsule formulations are similarly effective

- TAK-062 600 mg (capsule) and 900 mg (liquid) both degraded 3 g of gluten (median > 97%) in the gastric space within 35 minutes of study drug administration
- The ability of liquid and capsule formulations of TAK-062 to degrade gluten were comparable
- Pretreatment with PPI had no significant effect on gluten degradation by TAK-062 900 mg
- Results were similar for both G12 and R5 ELISA methods

ELISA, enzyme-linked immunosorbent assay; IQR, interquartile range; PEG, polyethylene glycol; PPI, proton pump inhibitor
ClinicalTrials.gov Identifier: NCT03701555
TAK-062 liquid formulation rapidly degrades up to 6 g gluten in healthy adults

- Gluten was degraded > 97% by TAK-062 (liquid formulation) in both 1 g and 6 g standardized gluten-containing study meals.
- The percentage gluten degradation was not significantly different at 20, 35 and 65 minutes post dose.
- At 35 minutes post dose, the mean percentage of gluten degraded relative to placebo was 97.8% (1 g gluten), 97.9% (1 g gluten) and 99.0% (6 g gluten) after administration of TAK-062 300 mg, 600 mg and 900 mg, respectively (as measured by R5 ELISA method).

*Results from R5 ELISA method (data from G12 ELISA were similar)

ELISA, enzyme-linked immunosorbent assay; IQR, interquartile range; PEG, polyethylene glycol; PPI, proton pump inhibitor

ClinicalTrials.gov Identifier: NCT03701555
TAK-062 is well tolerated in adults with a favorable safety profile

- **Pharmacokinetics**
  - TAK-062 was not detected in plasma after administration of any dose in this study (liquid or capsule formulation); hence, there was no evidence of systemic exposure to TAK-062

- **Safety**
  - No TEAEs were reported by > 1 participant and none were assessed as related to study drug
  - No TEAEs were serious or led to discontinuation of study drug or premature withdrawal from the study
  - No apparent clinically meaningful trends in clinical laboratory tests, vital signs, physical examinations, ECGs or anti-drug antibodies were observed

- Safety, tolerability and pharmacokinetics of single ascending doses of TAK-062 in 10 patients with celiac disease were similar to those observed in healthy participants
Summary: liquid and capsule formulations of TAK-062 degrade gluten in healthy adults

- TAK-062 rapidly degrades gluten in standardized gluten-containing study meals (containing up to 6 g gluten) in healthy adults
- The ability of TAK-062 to degrade gluten is similar with or without PPI pretreatment, and with liquid and capsule formulations
- TAK-062 is well tolerated with a favorable safety profile

Conclusion

- Further evaluation of TAK-062 in patients with celiac disease is supported by this study
- Phase 2 studies evaluating the ability of TAK-062 to improve symptoms and small intestinal mucosal injury in patients with celiac disease are planned to begin in late 2020