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

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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.

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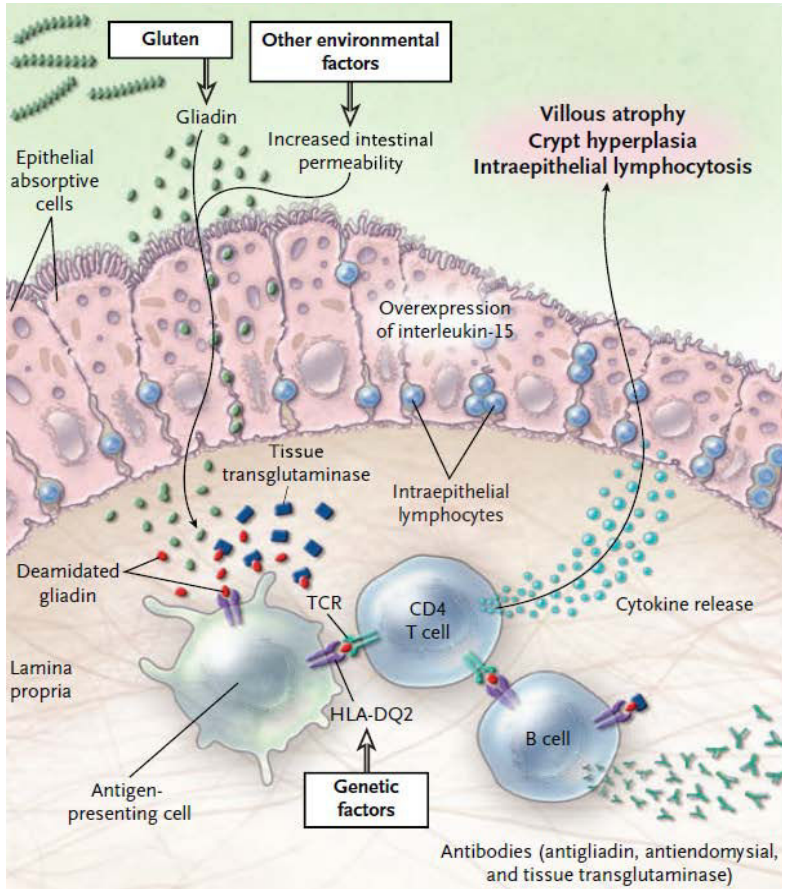
Celiac disease

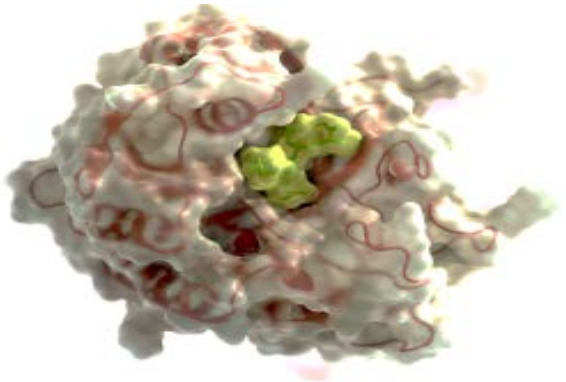


- Celiac disease is an **autoimmune** disorder triggered in genetically predisposed individuals by the ingestion of **dietary gluten**
- Gluten peptides (including gliadin) enter the submucosa of the small intestine and are deamidated by tissue transglutaminase[1]
- Gliadin-specific CD4+ T cells recognize 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**

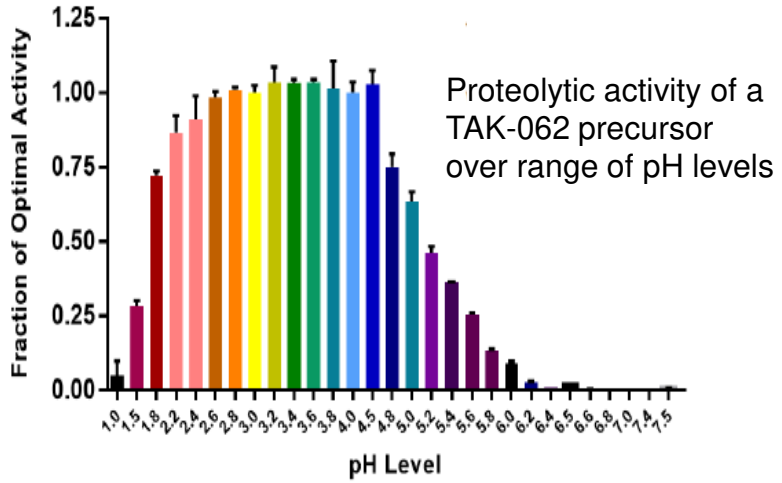
1. Green PH, Cellier C., *N Engl J Med* 2007;357:1731–43.

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



Computer rendered image of TAK-062



Proteolytic activity of a TAK-062 precursor over range of pH levels

1. Tye-Din JA., *Clin Immunol* 2010;134:289–95; 2. Wolf C et al., *JACS* 2015;137:13106–13

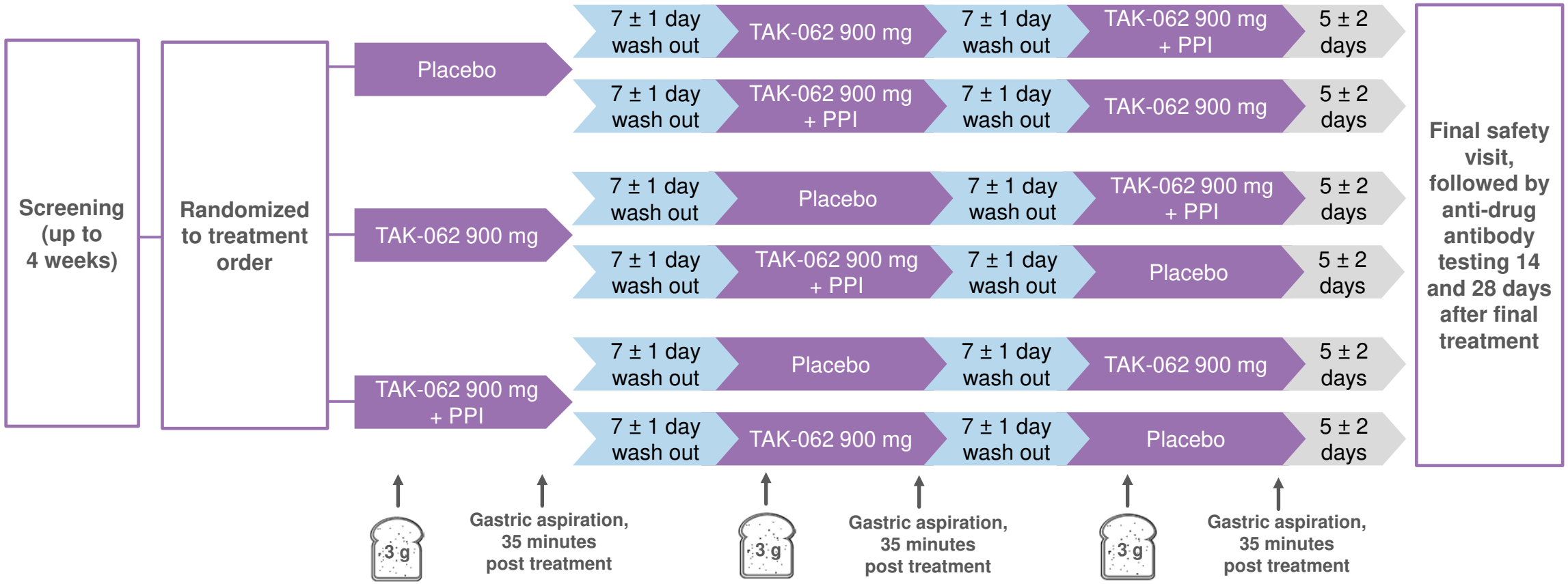
TAK-062 phase 1, single-blind, placebo-controlled, cross-over study: study objectives

- **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

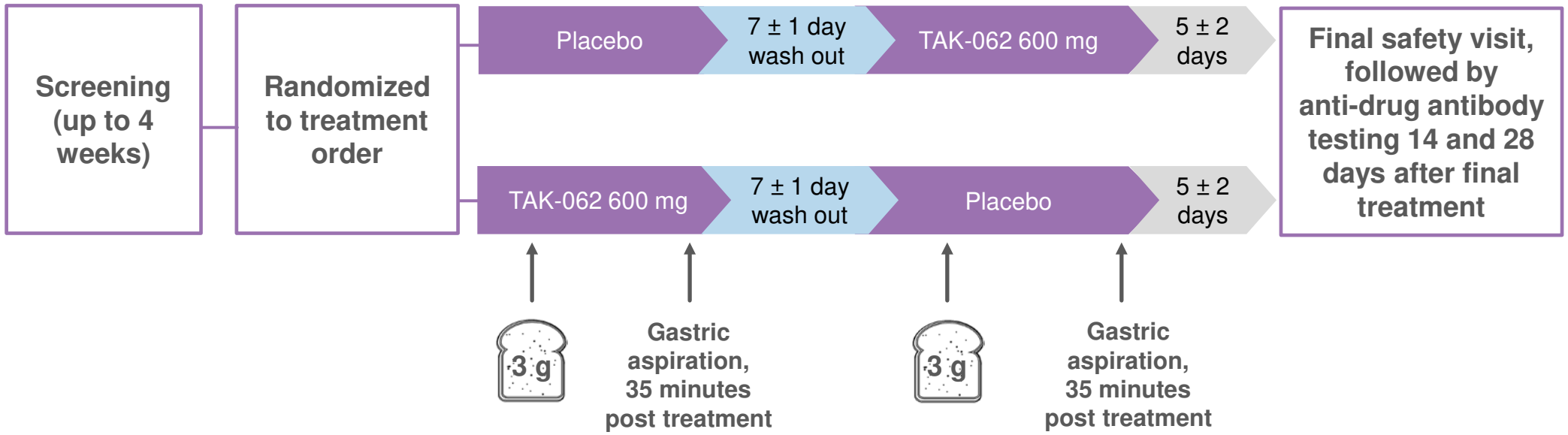
- TAK-062 liquid formulation, 900 mg, N = 14 (treated)



PPI, proton pump inhibitor (Nexium, 20 mg, daily for 7 days prior to study drug administration)
ClinicalTrials.gov Identifier: NCT03701555

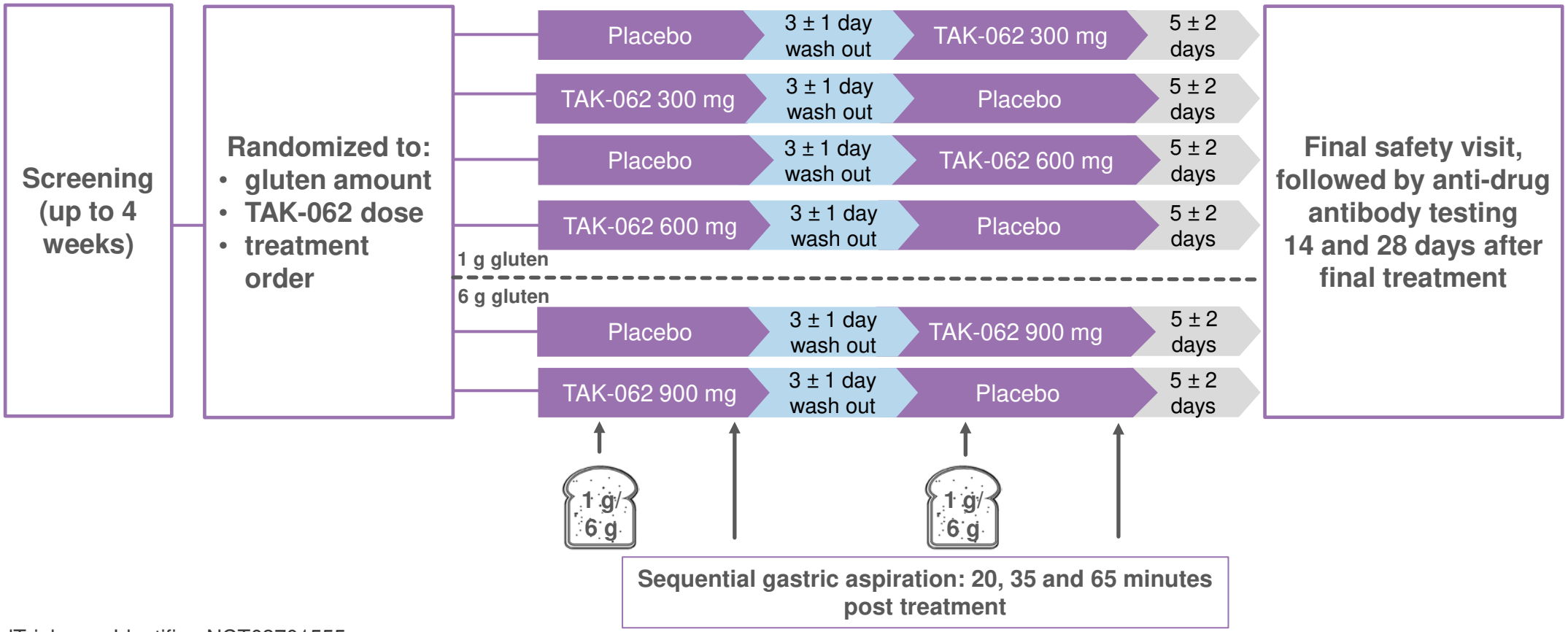
Group 2: gluten digestion using TAK-062 capsule formulation

- 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)



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

ELISA, enzyme-linked immunosorbent assay; HRP, horseradish peroxidase
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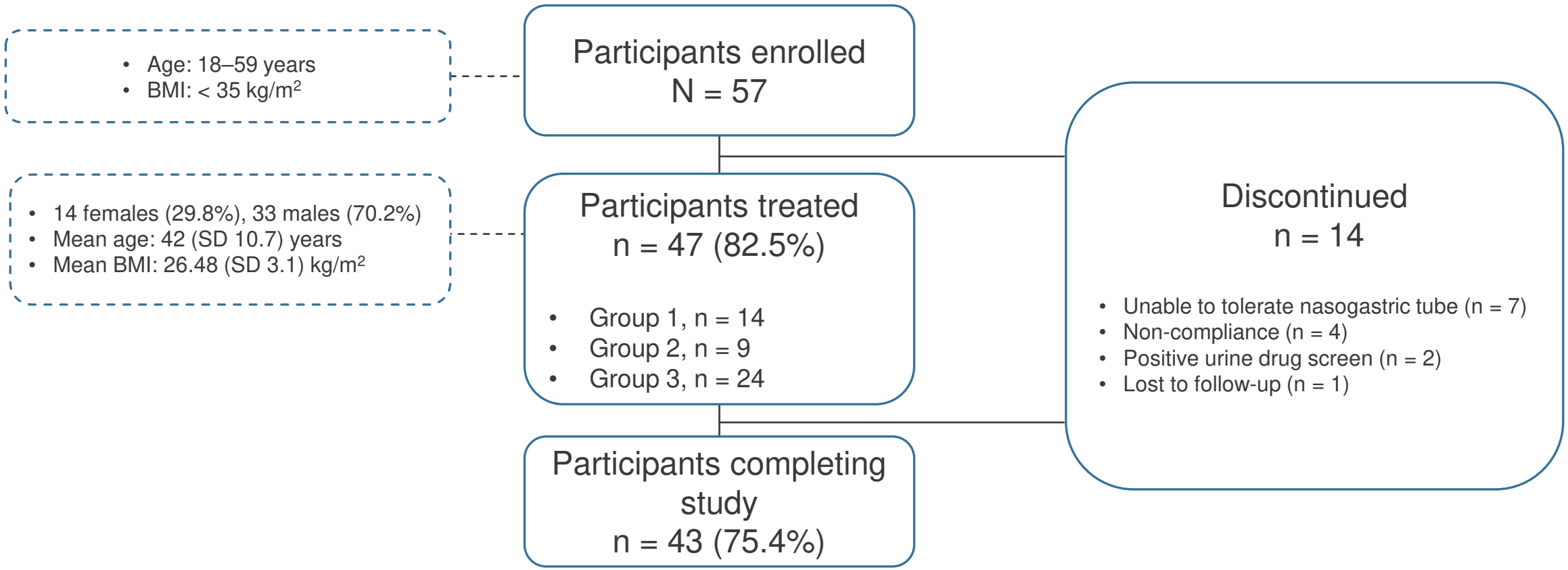
Standardized 3 g gluten-containing study meal

- 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

3 g gluten-containing study meal	Amount of food (g)	Energy (kcal)	Total fat (g)	Total carbohydrates (g)	Total protein (g)
Total	270.9	455.0	16.6	60.4	12.7
Percentage of total grams	NA	NA	6.13%	22.28%	4.70%
Percentage of total kcal	NA	NA	3.65%	13.27%	2.80%

Participant disposition and demographics



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

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

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
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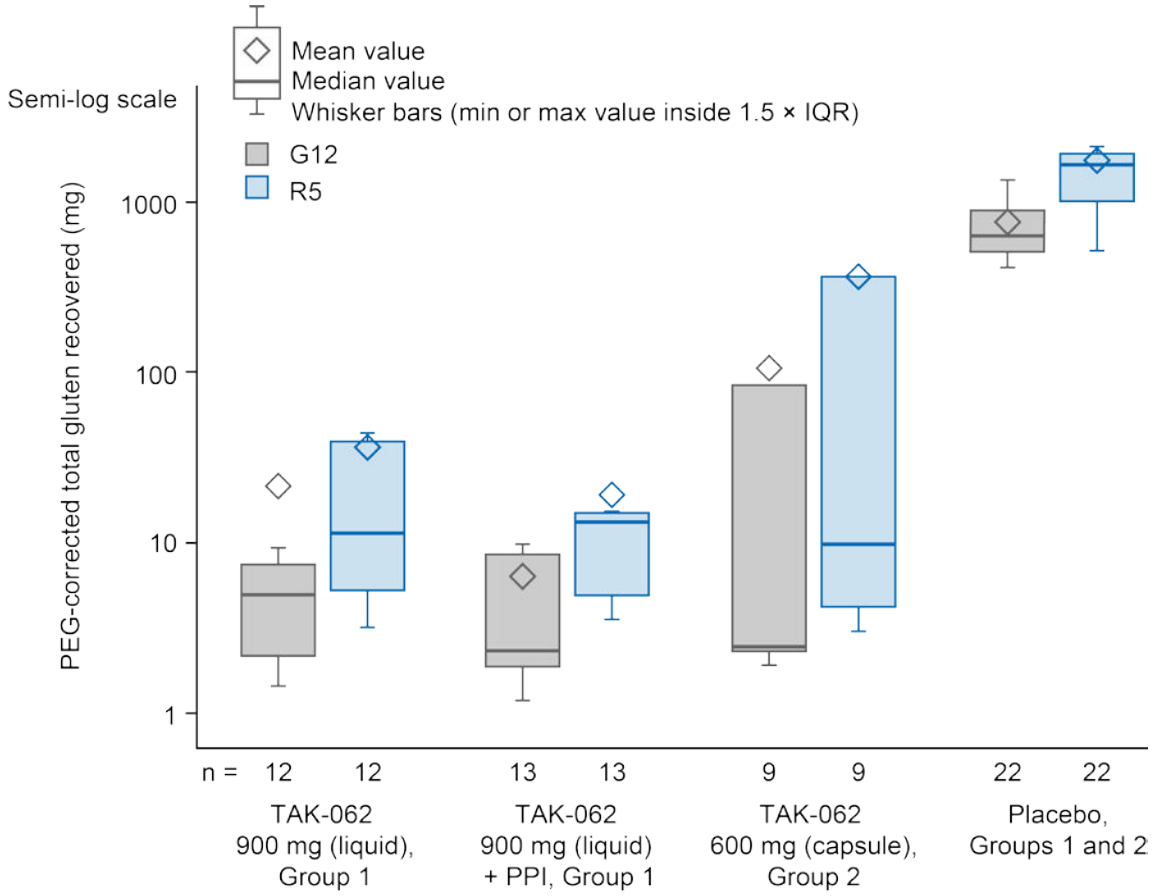
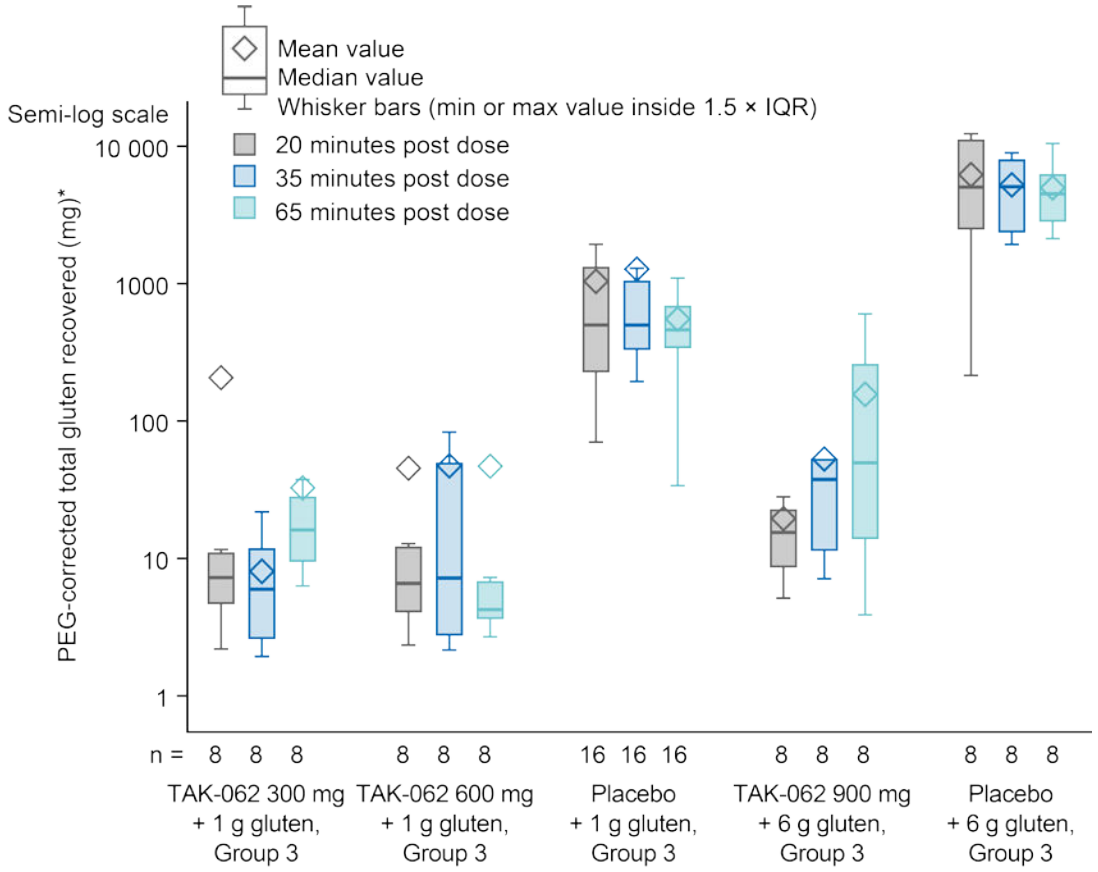
3 g gluten degradation by TAK-062 is not affected by pretreatment with a PPI, and liquid and capsule formulations are similarly effective



- 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

ECG, electrocardiogram; TEAE, treatment emergent adverse event
ClinicalTrials.gov Identifier: NCT03701555

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

PPI, proton pump inhibitor
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