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CELIAC DISEASE

Latiglutenase Protects the Mucosa and Attenuates Symptom Severity in Patients With Celiac Disease Exposed to a Gluten Challenge

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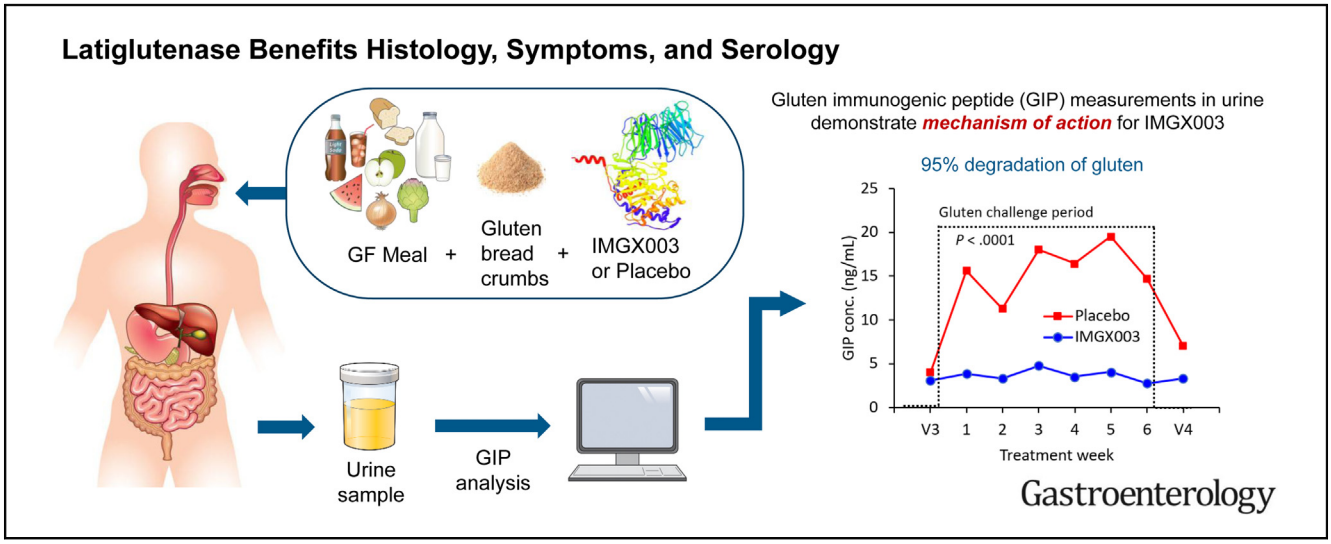

BACKGROUND & AIMS: Gluten ingestion in patients with celiac disease can lead to gastrointestinal symptoms and small intestinal mucosal injury. **METHODS:** This gluten challenge phase 2 trial was double blind and placebo controlled, and it assessed the efficacy and safety of a 1200-mg dose of IMGX003 in patients with celiac disease exposed to 2 g of gluten per day for 6 weeks. The change in the ratio of villus height to crypt depth was the primary endpoint. Secondary endpoints included density of intraepithelial lymphocytes and symptom severity. These endpoints were evaluated by analysis of covariance. Additional endpoints included serology and gluten-immunogenic peptides in urine. **RESULTS:** Fifty patients were randomized, and 43 patients completed the study (IMGX003, n = 21; placebo, n = 22). The mean change in the ratio of villus height to crypt depth (primary endpoint) for IMGX003 vs placebo was −0.04 vs −0.35 (P = .057). The mean change in the density of intraepithelial lymphocytes (secondary endpoint) for IMGX003 vs placebo was 9.8 vs 24.8 cells/mm epithelium (P = .018). The mean change (worsening) in symptom severity in relative units (secondary endpoint) for IMGX003 vs placebo was 0.22 vs 1.63 (abdominal pain, P = .231), 0.96 vs 3.29 (bloating, P = .204), and 0.02 vs 3.20 (tiredness, P = .113). The 3 × 2-week trend line significance values for these symptoms, respectively, were P = .014, .030, and .002. **CONCLUSIONS:** IMGX003 reduced gluten-induced intestinal mucosal damage and symptom severity. (ClinicalTrials.gov, Number: NCT03585478)

Keywords: Morphometry; Inflammation; Treatment.

***Author share co-first authorship.**

Abbreviations used in this paper: **ANCOVA, analysis of covariance; Cd, crypt depth; CDSD, Celiac Disease Symptom Diary; CeD, celiac disease; DGP, deamidated gliadin peptide; DSMB, Data and Safety Monitoring Board; EGD, esophagogastroduodenoscopy; GC, gluten challenge; GFD, gluten-free diet; GI, gastrointestinal; GIP, gluten immunogenic peptide; IEL, intraepithelial lymphocytes; IMGX001, hordein vulgare endoprotease B2 proenzyme enzyme; IMGX002, sphingomonas capsulata prolyl endopeptidase enzyme; IMGX003, latiglutenase; IG, immunoglobulin; ITT, intent to treat; mITT, modified intent to treat; MSM, masked study medication; tTG, tissue transglutaminase; TEAE, treatment-emergent adverse event; VCIEL, blended histology scale for villus height–to–crypt depth ratio and intraepithelial lymphocytes; V, visit; Vh, villus height.**

Most current article

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Celiac disease (CeD), a genetically predisposed chronic small intestinal inflammatory disorder caused by exposure to gluten, affects approximately 1% of most populations.[1–3] The only available treatment is a lifelong gluten-free diet (GFD). Although a GFD can reduce symptoms and intestinal damage, the diet is neither easy nor readily achievable by many patients and, furthermore, can be lacking in essential nutrients.[4,5] The pathologic lesion of villous atrophy in the proximal epithelium of the small intestine is due to an immune response to wheat, rye, or barley. Low levels of gluten exposure can lead to ongoing inflammation that can increase the risk of complications including lymphoma, bowel cancer, osteoporosis, anemia, and malnutrition.[6,7] Nearly 50% of patients with CeD are moderately to severely symptomatic, and this is associated with significant financial and other burdens on them, as well as on their family and friends.[8]

Latiglutenase (IMGX003, formerly ALV003) is an enzyme supplementation therapy comprising 2 enzymes, designed to mitigate the impact of gluten exposure in patients attempting to adhere to a GFD. The treatment has shown success for attenuating gluten-induced mucosal injury in CeD patients in a gluten challenge (GC) study (ALV003-1021)[9] and in reducing multiple gluten-induced symptoms, particularly for serologically positive (tTG-IgA, DGP-IgA, DGP-IgG) patients in a "real-world" trial (ALV003-1221).[10–12]

Pathophysiologically relevant gluten peptides are generally highly resistant to proteolytic activity in the intestine.[13] This resistance accounts for the accumulation of gluten-derived intermediates in the small intestinal lumen, which drives a potent T-cell–dependent response in CeD patients. This would suggest that proteases that target the gluten in ingested food should reduce the bioavailability of immunogenic peptides present after gluten exposure and perhaps provide a pharmacologic basis for managing CeD.[14] Latiglutenase (IMGX003) is delivered orally as a liquid that functions in the stomach during a meal and, hence, is a nonsystemic treatment that works upstream of the CeD autoimmune response.

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

A gluten-free diet is the only available treatment for celiac disease. Latiglutenase (IMGX003) is an investigational dual-enzyme drug candidate that acts to degrade gluten in vivo when consumed with a meal.

NEW FINDINGS

Mucosal and symptom deterioration from gluten ingestion were reduced by latiglutenase relative to placebo. Measurements of gluten-immunogenic peptides (GIP) in urine indicated 95% gluten degradation in the stomach by latiglutenase.

LIMITATIONS

There was no evidence of safety issues relative to placebo; however, this limited-duration phase 2 trial was insufficient to assess long-term effects.

IMPACT

The latiglutenase mechanism of action is degrading gluten in the stomach, as shown by measurements of GIP in urine. Digestive elimination contributes to the favorable safety profile observed in studies to date.

Patients and Methods

Study Design

This was a randomized, double-blind, placebo-controlled GC study in patients with treated CeD in remission to assess the efficacy and safety of a 1200-mg dose of IMGX003 (formerly ALV003). The trial was conducted at the Mayo Clinic. The study protocol was approved by the Mayo Clinic institutional review board. All authors had access to the study data and reviewed and approved the final manuscript.

Screening and Enrollment

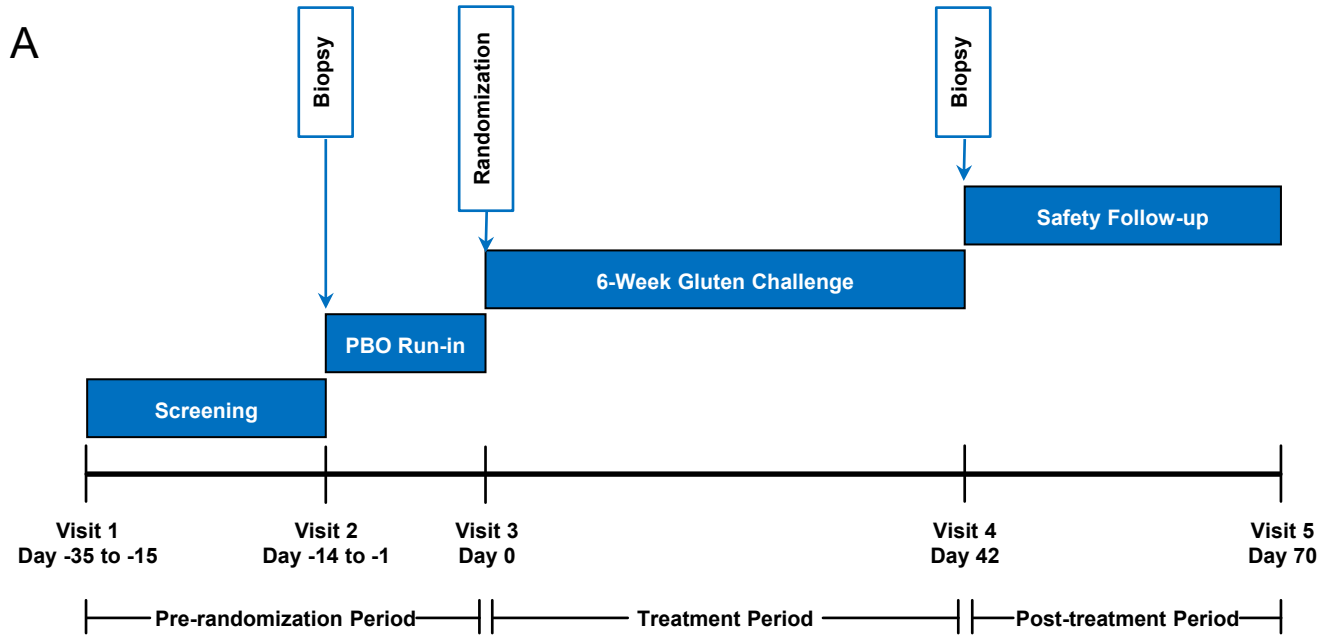
Adult patients (18–80 years) were required to have physician-diagnosed, biopsy-confirmed CeD; to be following a GFD for longer than 1 year; and to have histologically well-controlled disease, as evidenced by a measured ratio of villus height (Vh) to crypt depth (Cd) of $\geq$2.0. A schematic summary and enrollment flow chart of the study is shown in Figure 1. Main inclusion criteria included biopsy-confirmed CeD diagnosis, >1 year on a GFD after diagnosis, being tTG-IgA negative, and a Vh:Cd ratio of $\geq$2.0. Main exclusion criteria included active dermatitis herpetiformis, history of colitis, history of IgE-mediated reactions to wheat (ie, wheat allergy) and type 1 diabetes.

Patients who met the visit (V) 1 protocol enrollment criteria were enrolled and began the screening period. Patients were evaluated for adherence to study criteria, including testing negative for tTG-IgA serology and demonstrating compliance when completing the daily Celiac Disease Symptom Diary (CDSD) patient-reported outcome instrument ($\geq$85% compliance required). At V2, patients underwent an esophagogastroduodenoscopy (EGD) with biopsy, and those with a Vh:Cd of $\geq$2.0 proceeded to the placebo run-in period, including continued daily CDSD patient-reported outcome completion. Patients were dispensed run-in kits containing placebo (only) and instructed to ingest a single dose once daily with their evening meal (eg, dinner) for 14 consecutive days. Reasons for placebo run-in period failure included noncompliance ($\geq$85% compliance requirement for CDSD, GC, masked study medication, etc). Patients who continued to meet eligibility requirements at V3 began the randomized treatment period consistent with the other descriptions already explained as well as with Figure 1*A*. Patients were randomized 1:1 to either placebo or 1200 mg IMGX003. The details of the patients' self-administered treatment are given in the Supplementary Material.

At the end of the treatment period, V4, patients were evaluated via EGD with biopsy, urinalysis, and serology. At the final visit (V5) a serology test was performed. Routine safety laboratory tests (chemistry, hematology, and urinalysis) and physical examination were performed at V1 and V5.

Study Medication, Gluten, and Administration Description

IMGX003 consists of 3 components: 2 enzymes (hordein vulgare endoprotease B2 proenzyme enzyme [IMGX001] and



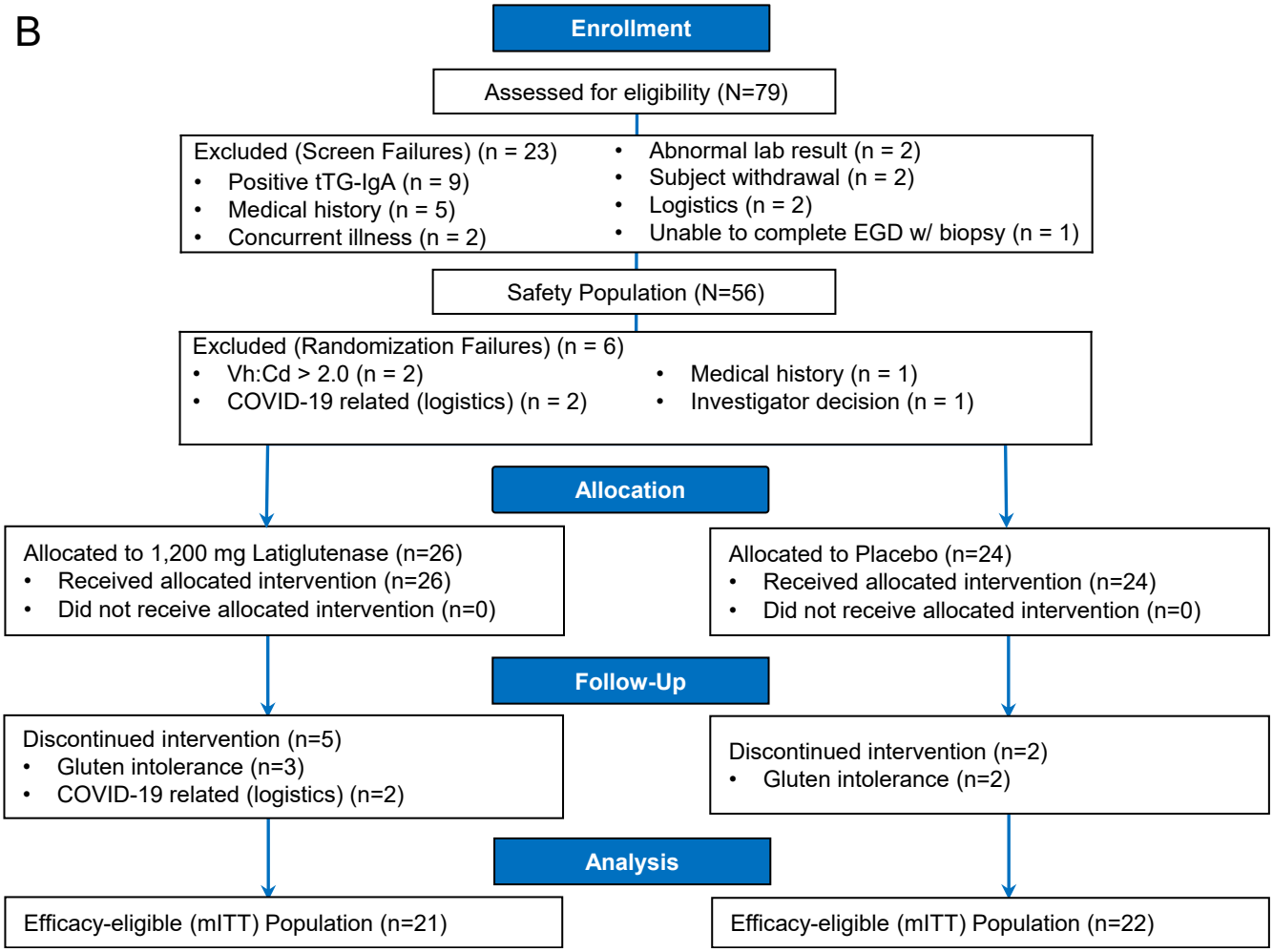


Figure 1. The IMGX003-NCCIH-1721 CeliacShield study (*A*) schematic and (*B*) enrollment flow chart. PBO, placebo.

sphingomonas capsulata prolyl endopeptidase enzyme [IMGX002]) packaged in separate stick packs and a sachet containing flavor (peach/mango) and buffer components. IMGX003, upon dissolution in 6–8 ounces of water, provides a fixed-dose combination glutenase consisting of a 1:1 ratio by weight of the 2 gluten targeting enzymes, which demonstrate complementary substrate sequence and chain length specificity. The properties of IMGX003 have been described previously[9–12] and are briefly presented, along with a description of the gluten samples, in the Supplementary Material.

Masked study medication (MSM) (IMGX003 or placebo) and gluten were orally administered. The order of ingestion of MSM and gluten were as follows: (1) commence MSM ingestion after beginning the evening meal, (2) ingest gluten when approximately one quarter of the way finished with the meal, and (3) complete MSM ingestion by half-way through the meal.

Blinding

The randomization schedule was created by an independent statistician using a random number table with random block size. Randomization assignments were provided to the onsite pharmacy for execution. Only the independent biostatistician and the study pharmacist were unblinded to handle randomization codes and delivery of MSM.

Duodenal Biopsy

The primary endpoint was change in Vh:Cd, and a secondary endpoint was change in intraepithelial lymphocytes (IELs) both measured before (V2) and after (V4) the GC period. EGD biopsy specimens were obtained from the postbulbar duodenum before (at V2) and after (at V4) the GC. Biopsy samples were individually formalin fixed, paraffin embedded, oriented, cut, and then (1) stained with H&E for Vh and Cd measurements and (2) stained with $CD3^+$ for measurements of IEL densities expressed as cells/mm epithelium. At least 4 biopsy samples are taken, with 3–5 cuts per sample.[15] Morphometric analysis of the samples was done using light microscopy by a reference gastrointestinal (GI) pathologist. Measurements included Vh:Cd and population of IELs. IELs are associated with inflammation within the mucosal lining of the GI tract. For reporting, we obtained the ratio of the averages of Vh and Cd for the endoscopy visit whereby the total biopsy reads for Vh and Cd were converted to an average Vh:Cd by the operation of sum(Vh)/sum(Cd). A Vh:Cd value of $\geq$2.0 served as a histologic inclusion criterion. V2 biopsy samples were reread with the V4 biopsy samples in groups of at least 4 pairs of biopsy sets per study participant to ensure minimal intrareader time-lapsed variability and to enable masking of the pathologist to the pairing and sequence of biopsy samples.

Celiac Disease Symptom Diary

The CDSD is a daily diary administered to assess common CeD symptoms (abdominal pain, bloating, tiredness, nausea, diarrhea, and constipation). The presence or absence of each of the symptoms over the previous 24 hours was reported by the participant along with a severity score if a symptom was present.[16] The scoring system for all symptoms is presented in the Supplementary Material.

Weekly severity scores for abdominal pain, bloating, tiredness, and constipation were calculated for each week between V2 and V4, resulting in 8 weekly scores. The 2 weekly scores leading up to V3 (baseline) were averaged to form the baseline score for each participant. Each of the 6 individual postbaseline weekly scores was combined into 3 2-week average severity scores. A 6-week average severity score was similarly calculated.

Celiac Disease Serology

Whole blood for CeD serology was collected and analyzed at V1, V4, and V5. Antibodies (tTG-IgA, DGP-IgA, DGP-IgG) were measured by an enzyme-linked immunosorbent assay (QUANTA Lite h-tTG IgA, QUANTA Lite Gliadin IgA II, QUANTA Lite Gliadin IgG II; INOVA Diagnostics, Inc). Although all 3 titers were measured, the participant exclusion criterion for serology was based only on tTG-IgA positivity.

Gluten Immunogenic Peptides in Urine

Urine samples were collected in the clinic at V3 and V4 (before and after the GC period) and frozen at −20°C. Remote samples were collected and frozen by study patients once a week for 6 weeks during the GC period. Patients were instructed to collect their urine sample 6–12 hours after gluten ingestion with the evening meal. Lateral flow immunochromatographic assay (IVYCHECK GIP Urine) with the IVYCHECK Reader (IVYDAL In Vitro Diagnostics, Biomedal) was used to measure the concentration of gluten immunogenic peptide (GIP) present in each urine sample.[17]

Safety Assessments

Safety assessments included adverse event monitoring, standard laboratory tests (blood chemistry, hematology, and urinalysis), and physical examination including vital signs. All adverse events were followed over the course of the study and presented in a by-participant listing. All treated patients were included in all summaries of adverse events for the safety population. All reported events were coded to the current Medical Dictionary for Regulatory Activities adverse event dictionary. The frequency of each event for each system organ class and preferred term were summarized by severity (mild, moderate, severe) and by relatedness (related, not related) with the study medication, procedure, and GC. Because some patients may have reported the same event several times (headache, for example), the first occurrence of the worst reported case of the event was used for the purpose of analysis.

A treatment-emergent adverse event (TEAE) is an adverse event that begins or worsens after the first dose of study treatment regardless of the suspected cause. Collection of TEAEs occurred during the randomized treatment period of the trial (V3–V4).

All clinical laboratory data were provided as summary statistics for results, and change from baseline values were calculated and presented by treatment and visit. Physical examination and vital sign results were listed for all individual patients in the safety population.

A futility analysis, unblinded to a third-party biostatistics firm, was performed when 20 randomized patients had completed the treatment period. In addition to monitoring

participant safety, the data and safety monitoring board (DSMB) evaluated the futility analysis results and made a recommendation for the trial to proceed.

Study Outcome Measures and Statistical Analysis

The study populations were defined as follows:

- Intent to treat (ITT): This population included all patients who were randomized to study treatment.
- Modified ITT (mITT): This population included all patients who were treated and attended V4 after the GC period.
- Efficacy eligible: This population included all randomized patients who completed at least 6 weeks of treatment and had biopsies at V2 and V4. In this study, the efficacy-eligible and mITT populations are the same, so we use the latter nomenclature henceforth.
- Safety population: The population includes all patients who signed an informed consent at V1 (screening) and received any amount of randomized MSM starting at V3.

Sample size numbers are presented in the enrollment flow chart in Figure 1*B*. A sample size calculation was performed using preexisting clinical study data. We anticipated the need to enroll 80 patients and finished with 79. We anticipated a 37.5% screening period attrition rate to yield 50 patients at randomization for an ITT analysis and finished with 50. We anticipated an additional 16% dropout rate postrandomization to yield 42 patients completing the study for the mITT analysis and finished with 43.

A sample size of 50 ITT patients (25 patients per treatment group) provided 86% power and 2-sided 5% type 1 error to detect a 0.40 difference between the treatment groups in change from baseline Vh:Cd at week 6, assuming a standard deviation of 0.45. Using the same assumptions, the power dropped to 80% for the mITT analysis (43 patients).

Summary tables (descriptive statistics and/or frequency distributions) were developed for baseline variables, efficacy variables, and safety variables. Continuous variables are described by descriptive statistics (n, mean, standard deviation, range, and median). Frequency distributions (counts and percentages) of patients are provided for categorical data. All variables are summarized by treatment group for the efficacy-eligible population unless otherwise indicated.

The histology analysis for Vh:Cd and IELs was carried out on both the change from baseline and the percent change from baseline using the mITT (the same as the efficacy-eligible) population, and comparisons were performed using 2-sided tests at the 5% level of significance. A linear regression model was used for efficacy analysis to compare the distribution of changes and percent changes in Vh:Cd and IEL from V2 (baseline) to V4 (after the GC period) between the 2 treatment groups. The model included baseline Vh:Cd and treatment as covariates (analysis of covariance [ANCOVA]). The change and percent change from baseline were also evaluated within each treatment group using a paired t test.

To confirm the results, a nonparametric Wilcoxon-Mann-Whitney test was run for the sensitivity analyses for the between-group comparison. Similarly, the within-group change and percent change from baseline was evaluated using a Wilcoxon signed-rank test.

The primary analysis for Vh:Cd and analyses for IELs, symptoms, and adverse events were performed using SAS, version 9.4. Other analyses, such as for serology, GIP in urine, and exploratory and sensitivity analyses, were performed using GraphPad Prism 9.1.1 (GraphPad Software) or XLSTAT 2021.1.1 (Addinsoft).

This clinical trial was registered (https://clinicaltrials.gov/ct2/show/NCT03585478), and all authors had access to the study data and reviewed and approved the final manuscript.

Table 1. Demographics—All-Randomized Population

Characteristics	Placebo (n = 24)	IMGX003 (n = 26)	All patients (N = 50)
Age at baseline, *y*			
Mean (SD)	45.0 (13.88)	42.7 (10.88)	43.8 (12.34)
Median	43.9	43.3	43.3
Minimum, maximum	22.8, 66.4	22.2, 62.7	22.2, 66.4
Sex, n (%)			
Male	8 (33.3)	5 (19.2)	13 (26.0)
Female	16 (66.7)	21 (80.8)	37 (74.0)
Ethnicity, n (%)			
Hispanic	1 (4.2)	1 (3.8)	2 (4.0)
Non-Hispanic	23 (95.8)	25 (96.2)	48 (96.0)
Race, n (%)			
American Indian or Alaska Native	0 (0)	0 (0)	0 (0)
Asian	0 (0)	0 (0)	0 (0)
Black or African American	0 (0)	0 (0)	0 (0)
Native Hawaiian or other Pacific Islander	0 (0)	0 (0)	0 (0)
White	24 (100.0)	25 (96.2)	49 (98.0)
Other	0 (0)	1 (3.8)	1 (2.0)

SD, standard deviation.

Results

Study Population

The demographics for this study are summarized in Table 1, and an enrollment flow chart is presented in Figure 1*B*. Of the randomized ITT population of 50 patients (IMGX003, n = 26; placebo, n = 24), 43 patients completed the trial and constitute the mITT population (IMGX003, n = 21; placebo, n = 22). Age ranges were comparable for IMGX003 (mean, 42.7 years) and placebo (mean, 45.0 years). Most of the study population was female (total, 74%; IMGX003, 81%; placebo, 67%). The ethnicity and racial profile of the ITT population was predominantly White (IMGX003, 96%; placebo, 100%). MSM and gluten compliance were measured during the placebo run-in and randomized treatment periods and were above a 90% mean for each separate group and for all patients combined.

Histology

The summary results for histology (Vh:Cd and IELs) are tabulated for the mITT population in Table 2. The detailed mITT participant-specific results are presented in Supplementary Figures 1 and 2. The mean histologic values for V2 (before GC) for IMGX003 and placebo, respectively, were 2.99 and 2.95 for Vh:Cd and 35.0 and 34.6 for IELs.

The post-GC treatment relative to baseline biopsy samples for placebo measured a mean change in Vh:Cd of −0.35 (median, −0.28; $P = .015$) and a mean change in IEL densities of 24.75 cells/mm epithelium (median, 24.8; $P < .001$). The corresponding values for latiglutenase (IMGX003) were a mean change in Vh:Cd of −0.04 (median, −0.05; $P = .671$) and a mean change in IEL densities of 9.79 cells/mm epithelium (median, 7.0; $P < 0.01$). The between-group ANCOVA significance was $P = .057$ for change in Vh:Cd and $P = .018$ for change in IELs (Supplementary Figures 1 and 2). Based on the ratio of the means for both groups, we computed a reduction of worsening for latiglutenase relative to placebo of 88% (median, 83%) and 60% (median, 72%), respectively, for change in Vh:Cd and change in IELs. Other histology outcome measures that blend the Vh:Cd and IEL scales are described below (Supplementary Figures 3 and 4).

Symptoms

Results for the secondary endpoints of changes in symptom severity averaged over the 6-week GC treatment period relative to the 2-week baseline period are shown in Figure 2*A* (and reported in Supplementary Table 1) for abdominal pain, bloating, and tiredness, as well as the retrospective addition of the nonstool gastrointestinal composite, which consists of abdominal pain, bloating, and nausea. The mean changes from baseline in symptom severity in relative units for IMGX003 vs placebo were 0.22 vs 1.63 (abdominal pain, $P = .231$), 0.96 vs 3.29 (bloating, $P = .204$), 0.02 vs 3.20 (tiredness, $P = .113$), and 0.64 vs 2.27 (nonstool composite, $P = .163$). Calculated symptom reduction values based on the ratio of the measured means (Supplementary Table 1) were 93% (abdominal pain), 53% (bloating), 99% (tiredness), and 70% (nonstool composite).

The mean change from baseline was evaluated over 3 2-week periods, and the percent changes (percent worsening) show consistent reduction of symptom worsening for IMGX003 vs placebo groups (Figure 2*B*). Based on the effect size and trend significance, the *P* values (unpaired 2-tailed *t* test) for abdominal pain, bloating, tiredness, and nonstool gastrointestinal composite were .014, .030, .002, and <.001, respectively.

Table 2. Histologic Efficacy Analysis—mITT Population

Vh:Cd ratios	Placebo (n = 22)	IMGX003 (n = 21)
V2 (day −14, baseline)		
Mean (SD)	2.95 (0.473)	2.99 (0.326)
Median	2.93	3.00
Minimum, maximum	2.26, 3.89	2.13, 3.53
V4 (day 42)		
Mean (SD)	2.61 (0.657)	2.95 (0.504)
Median	2.52	2.97
Minimum, maximum	1.62, 3.73	1.99, 4.20
Change from baseline to V4 (day 42)		
Mean (SD)	−0.35 (0.616)	−0.04 (0.466)
Median	−0.28	−0.05
Minimum, maximum	−1.38, 1.01	−1.04, 0.83
Within-group *P* value[a]	.0148	.6713
Between-group *P* value[b]		.0570

IEL densities (cells/mm epithelium)	Placebo (n = 22)	IMGX003 (n = 21)
Visit 2 (day −14, baseline)		
Mean (SD)	34.55 (13.588)	35.05 (17.279)
Median	38.00	33.00
Minimum, maximum	12.00, 62.00	10.00, 82.50
Visit 4 (day 42)		
Mean (SD)	59.30 (23.697)	44.83 (22.592)
Median	54.75	37.50
Minimum, maximum	17.50, 98.50	17.00, 98.50
Change from baseline to visit 4 (day 42)		
Mean (SD)	24.75 (22.941)	9.79 (15.741)
Median	24.75	7.00
Minimum, maximum	−12.50, 66.00	−11.00, 54.00
Within-group *P* value[a]	<.0001	.0099
Between-group *P* value[b]		.0181

[a]*P* value was calculated using a paired *t* test of V4 (day 42) compared to V2 (day −14) values within each treatment arm and indicates if the change at V4 (day 42) is statistically significantly different than 0.
[b]*P* value was calculated using a linear regression model including baseline Vh:Cd and treatment as covariates and indicates if the mean change/percent change from baseline at V4 is different between the treatment arms.

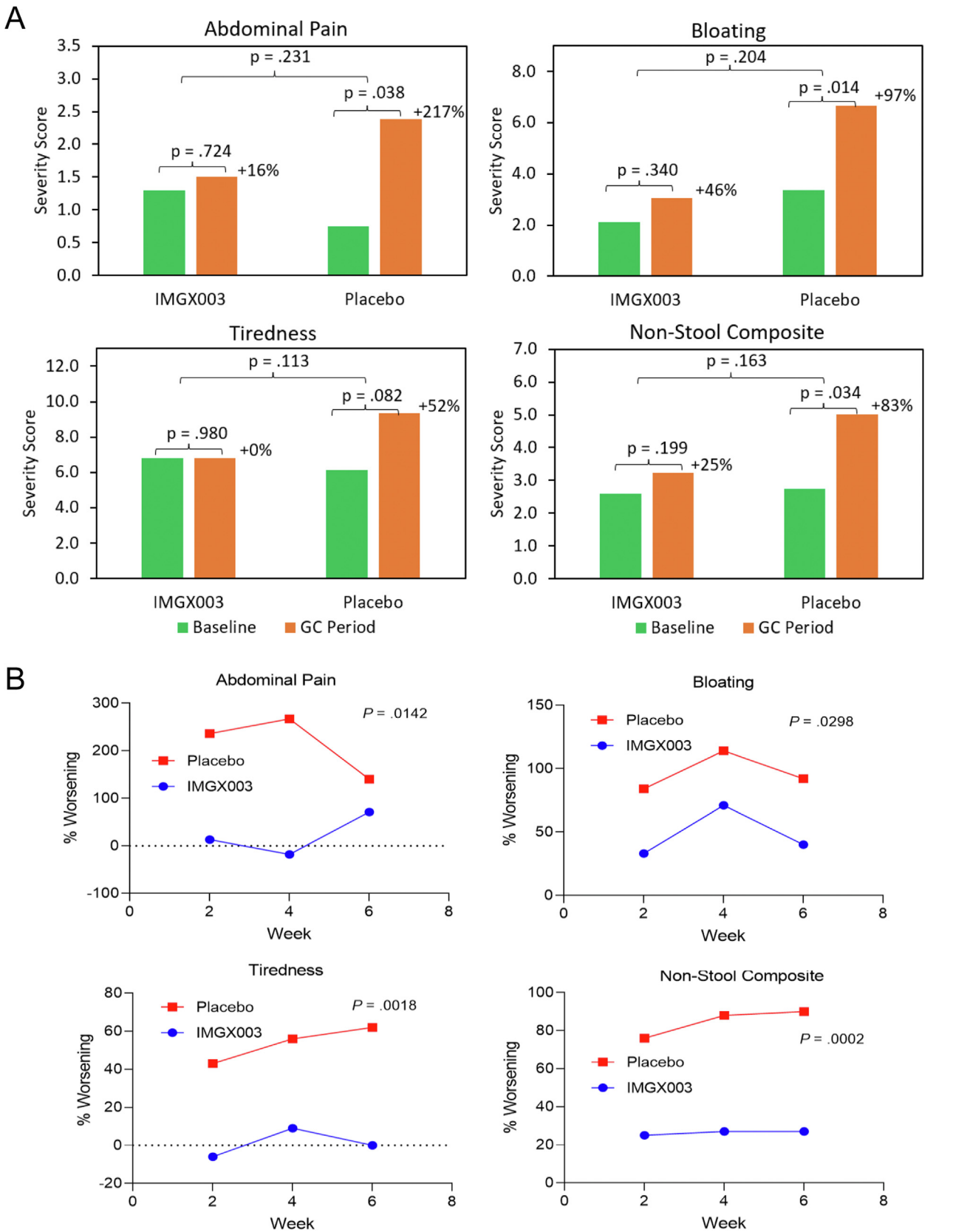


Figure 2. Symptom results for abdominal pain; bloating; tiredness; and nonstool gastrointestinal composite, which includes abdominal pain, bloating, and nausea. (*A*) Absolute severity for baseline and the 6-week GC treatment period for IMGX003 vs placebo groups. Also shown are the magnitude of worsening for baseline vs 6-week GC period. *P* values are by ANCOVA for intergroup and paired *t* test for intragroup results. (*B*) Mean change from baseline (percent worsening) for 3 2-week sequential GC treatment periods for IMGX003 vs placebo. Also shown are the unpaired 2-tailed *t* test *P* values.

Serology

The mean changes for all 3 serology titers (tTG-IgA, DGP-IgA, and DGP-IgG) before and after the GC treatment period were analyzed retrospectively and showed a trend toward worsening for placebo (3.45, 5.65, and 4.39, respectively) and improvement for latiglutenase (−0.83, −1.68, and −0.53, respectively), but none reached statistical significance (Supplementary Figure 5). Despite the magnitude of the effect size, most patients did not show a change in serology and remained below the titer thresholds for CeD gluten-induced antibody activity (Supplementary Figure 5).

Gluten Immunogenic Peptides in Urine

The exploratory (a priori) endpoint for baseline levels of GIP were measurable but at the lower limit of detection (3.4 ng/mL), indicating that both groups were generally compliant with a GFD before the GC treatment period (Figure 3*A*). The mean change in GIP in urine for the 6-week GC period relative to baseline for IMGX003 vs placebo was 0.59 vs 11.53 ($P = .001$) (Figure 3*B* and *C*). Based on the ratio of mean changes, we estimate an efficacy of gluten degradation in vivo of 95%. The individual patient responses pre- and post-GC treatment show wide variability for the placebo-treated group.

Safety

There were no significant differences in adverse events between IMGX003 and placebo. Twenty (76.9%) IMGX003 and 17 (70.8%) placebo patients experienced at least 1 TEAE ($P = .751$ by Fisher exact test) (Table 3). Twenty-six patients (52%) (16 IMGX003 and 10 placebo) experienced at least 1 TEAE of mild severity. Moderate to severe TEAEs occurred in 4 IMGX003 and 7 placebo patients. No serious adverse events were observed. Twenty-eight (56%) patients (16 IMGX003 and 12 placebo) experienced GI disorders, with nausea (18%), abdominal distension (16%), and diarrhea (16%) being the most common. The only other non-GI TEAE that exceeded 10% in all patients was fatigue (14%). There was no meaningful statistical differentiation between IMGX003 and placebo for any adverse events.

Among patients who withdrew, 3 IMGX003 and 2 placebo withdrew because of gluten intolerance. Two other IMGX003 patients discontinued because of COVID-19–related logistical issues (Figure 1*B*).

No significant differences were detected between the IMGX003 and placebo cohorts for chemistry, hematology, and urinalysis measures or for physical examination and vital signs collected at V1 and V5 (before and after the GC period).

Exploratory and Sensitivity Analysis

We also retrospectively applied other accepted methods of assessing histologic change, for example, the conversion of quantitative histology to Marsh-Oberhuber (M-O)–type scoring.[18] Applying a conversion of measured Vh:Cd and IEL values to M-O–like scoring[19,20] gave a calculated reduction in histologic worsening of 75% ($P = .035$) for the change in scale for latiglutenase (IMGX003) vs placebo (Table 4). Assessing the use of other M-O conversion scales[21,22] produced similar results.

We combined Vh:Cd and IEL measurements into a blended histology score, "VCIEL," that retains the general range of the Vh:Cd score but includes IEL changes with equal weighting (Supplementary Material). This analysis led to a reduction of histologic damage of 90% ($P = .010$) for latiglutenase (IMGX003) vs placebo (Table 4 and Supplementary Figure 3). Furthermore, when we applied this blended VCIEL threshold score of <2.0 as an alternate exclusion criterion rather than Vh:Cd of <2.0, we saw a 100% reduction for IMGX003 vs placebo ($P < .001$).

A single placebo-treated patient exhibited healing despite the GC (Supplementary Figures 1 and 2). When we removed the high and low change in Vh:Cd for IMGX003 and placebo, we saw an improved outcome of 90% reduction of histologic damage ($P = .027$).

Discussion

There are several therapeutic candidates for CeD currently in clinical trials.[23] Enzyme-directed therapy in concert with a meal[9–12] and tight junction modulation in the small intestine have undergone post-GC studies.[24,25] Other therapeutic candidates that have completed GC studies include AMG 714, an interleukin 15 inhibitor[26]; TAK-101, a nanoparticle-encased gliadin protein[27]; and ZED1227, a transglutaminase 2 inhibitor.[28] Although some of these trials, including the present study, have reported evidence of histologic protection to GC, no study yet has directly shown evidence of histologic healing in a real-world trial.

Despite strict adherence to a GFD, about half of CeD patients show evidence of persistent small intestinal mucosal injury (Marsh grades II–III).[29] Small bowel mucosal recovery is essential for long-term health and highlights the need for an adjunct treatment to a GFD. This GC study demonstrated the efficacy of a combination enzyme therapeutic candidate in breaking down purposefully ingested gluten-derived immunogenic peptides in the stomach, preventing their absorption in the small intestine and consequent histologic, symptomatic, and serologic effects. The amount of gluten consumed (2 g for a single meal) would likely substantially exceed that accidently occurring while on a GFD,[4] supporting such an approach for management for gluten-triggered symptoms in treated patients.

Composite Histology Scale

The quantitative assessment of histology used in this study and other studies includes the separate measures of villus crypt architecture and IELs; however, they have not been combined. Rostami et al[30] presented arguments for attaching more significance to the range of IEL values for interpreting mucosal condition. We retrospectively combined both measures into a composite endpoint (VCIEL) of mucosal health that could be a useful assessment of interventions as well as for the selection of patients for inclusion in trials that include GC. Patients who have too much disease activity at entry may show healing, perhaps due to a

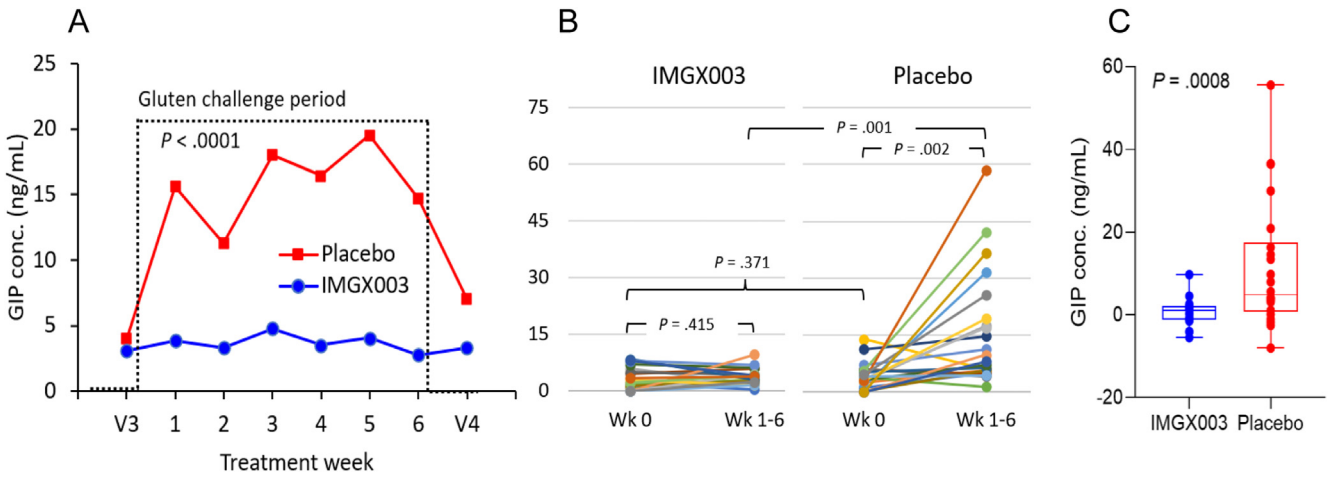


Figure 3. (*A*) Mean GIP concentration in urine before (V3), during (6 weekly readings), and after (V4) the GC treatment period with unpaired 2-tailed *t* test *P* value. (*B*) Participant responses for GIP concentration in urine showing individual participant changes. (*C*) Box-and-whisker plot showing minimum and maximum, first and third quartiles, median, and ANCOVA *P* value. conc., concentration.

Hawthorne effect, despite the GC, which was likely the cause of improvement in histology in a real-life study.[10] Additionally, the sole reliance on Vh:Cd as a primary outcome measure may fail to capture disease-relevant changes embodied in IEL measurements. Indeed, Marsh's original concept of the spectrum of gluten-sensitive enteropathy has incorporated change in IELs as an integral and indeed essential part of the scale.[30]

Gluten Challenge Compliance

The measured GIP concentrations in urine for placebo showed a wide variability despite the constant GC consumption prescribed for all patients (Figures 3*B* and 3*C*), suggesting that perhaps there was some noncompliance in consuming the prescribed gluten by some patients. However, other explanations for individual variability need to be considered, such as differences in biological factors, size, environmental factors, fluid intake, etc.[31] For example, it has been reported that hydration and the timing of liquid consumption, not surprisingly, have a large effect on the measured GIP concentration in urine.[32] Another explanation comes from a recent report where it was observed that GIP in urine values (measured by mass spectrometry) were lower in healthy non-CeD patients than in CeD patients.[33] This suggests that permeability might be greater in CeD patients (eg, because of a leaky gut), suggesting the possibility that permeability could vary for individual CeD patients based on their general histologic health.

As to the possibility that the large GIP variation for placebo might be due in part to noncompliance in taking the daily gluten, we correlated GIP to change in Vh:Cd and found a statistically significant trend ($P = .012$) toward decreased GIP with decreased change in Vh:Cd for the placebo group (Supplementary Figure 6). We observed a nonstatistically significant trend for the IMGX003 group, likely because the breakdown of gluten by IMGX003 in those patients made the GIP variability very small and giving less reason for noncompliance. To further test this hypothesis, we did a retrospective subgroup analysis on histology. The removal

Table 3. TEAEs—Overall Summary in Safety Population, n (%)

Patients who experienced at least 1	Placebo (n = 24)	IMGX003 (n = 26)	Total (N = 50)
TEAE	17 (70.8)	20 (76.9)	37 (74.0)
Related to study medication	0 (0)	0 (0)	0 (0)
Related to gluten	14 (58.3)	19 (73.1)	33 (66.0)
Related to procedure	0 (0)	0 (0)	0 (0)
Patients with at least 1 TEAE			
Mild	10 (41.7)	16 (61.5)	26 (52.0)
Moderate	6 (25.0)	4 (15.4)	10 (20.0)
Severe	1 (4.2)	0 (0)	1 (2.0)
Serious TEAE	0 (0)	0 (0)	0 (0)
Related to study medication	0 (0)	0 (0)	0 (0)
Related to gluten	0 (0)	0 (0)	0 (0)
Related to procedure	0 (0)	0 (0)	0 (0)
GI disorders	12 (50.0)	16 (61.5)	28 (56.0)
Nausea	5 (20.8)	4 (15.4)	9 (18.0)
Abdominal distension	3 (12.5)	5 (19.2)	8 (16.0)
Diarrhea	4 (16.7)	4 (15.4)	8 (16.0)
Flatulence	4 (16.7)	2 (7.7)	6 (12.0)
Vomiting	2 (8.3)	3 (11.5)	5 (10.0)
General disorders and administration site conditions	3 (12.5)	4 (15.4)	7 (14.0)
Fatigue	3 (12.5)	4 (15.4)	7 (14.0)
Musculoskeletal and connective tissue disorders	3 (12.5)	0 (0)	3 (6.0)
Arthralgia	2 (8.3)	0 (0)	2 (4.0)
Myalgia	1 (4.2)	0 (0)	1 (2.0)
Nervous system disorders	0 (0)	3 (11.5)	3 (6.0)
Headache	0 (0)	2 (7.7)	2 (4.0)
Migraine	0 (0)	1 (3.8)	1 (2.0)

Table 4. Summary of Histology for Various Treatment Populations and Subgroup Analysis

Outcome measure	Population, n		*P* Value	Reduction (%)
	IMGX003	Placebo		
Prospective				
Vh:Cd (mITT)[a]	21	22	.057	88
IEL (mITT)	21	22	.018	60
Retrospective				
VCIEL	21	22	.010	90
M-O	21	22	.035	75
Vh:Cd (subgroup)[b]	17	18	.050	98
Vh:Cd (subgroup)[c]	19	20	.027	90
Vh:Cd (subgroup)[d]	18	18	<.001	100

[a]The Finnish method for average Vh:Cd is the average of individual Sum(Vh)/Sum(Cd) and is the method used in the predecessor study ALV003-1021. The Mayo Clinic method for average Vh:Cd is the average of individual Vh:Cd ratios and gives $P = .076$ and a reduction of 86%.
[b]Subgroup analysis: drop 4 patients (approximately 20%) in each group with the lowest GIP concentrations in urine.
[c]Drop the highest and lowest change in Vh:Cd values in each group.
[d]Subgroup analysis: exclude patients with VCIEL of <2.0 at baseline.

of the 20% of patients (4 each from IMGX003 and placebo) with the lowest measured GIP concentrations during the GC period led to a calculated reduction in Vh:Cd damage of 98% for IMGX003 vs placebo and an improved $P = .050$, despite the subgroup populations decreasing to n = 17 (IMGX003) and n = 18 (placebo) (Table 4).

Symptoms

The current study evaluated the capability to measure clinically and statistically meaningful changes in symptom response due to the GC period and to detect meaningful reduction of the IMGX003 group relative to placebo. We did not expect the symptom endpoints to be well powered because of the low—and therefore noisy—baseline symptom scores for these relatively healthy patients. This may have accounted for the ANCOVA analysis not meeting statistical significance, because the baseline scores are a weak covariate (Supplementary Table 1), whereas the analysis of variance *P* values were more significant in most cases. We did expect to see clinically significant trends, which was observed in Figure 2, with statistical significance observed for the 3 × 2-week trend analysis for abdominal pain, bloating, and tiredness as well as the nonstool gastrointestinal composite (Figure 2*B*).

In summary, a gluten-targeting dual-enzyme therapeutic candidate reduced the histologic, symptomatic, and serologic worsening resulting from a 6-week daily GC by breaking down the gluten in the stomach after consumption with a meal. Measurement of GIP in urine demonstrated the purported mechanism of action of IMGX003, namely, degradation of gluten in the stomach, thereby preventing the triggering of the immunogenic autoimmune response. Targeting gluten by degrading the immunogenic peptides before absorption minimizes or abrogates the cascading innate and adaptive immune responses that characterize the inflammatory responses to gluten in CeD.

Supplementary Material

Note: To access the Supplementary Material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2022.07.071.

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Conflicts of interest

Joseph A. Murray has received study grants from ImmusanT, National Institutes of Health (NIH), ImmunogenX, Johnson & Johnson, Kanyos/Anakion, Takeda Pharmaceutical, Allakos, Oberkotter, and Cour; has received consultancy fees from Bioniz, UKKO, Dren Bio, Dr. Schar USA, Chugai Pharma, and GSK; holds patents licensed to Evelo Biosciences; and has received royalties from Torax Medical. Jack A. Syage has received a grant from National Center for Complementary and Integrative Health of the NIH (grant no. R33AT009637) for work reported here; has received 2 other active NIH grants; and is a cofounder and stockholder in ImmunogenX, Inc. Tseng-Teh Wu has received grants from Cour Therapeutics and Johnson & Johnson. Matthew A. Dickason is a stockholder in ImmunogenX, Inc. Ana G. Ramos is a stockholder in ImmunogenX, Inc. Philip T. Lavin is a consultant to ImmunogenX. Markku Mäki is owner and chair of the board at Maki HealthTech Ltd (MHT), which has received management/advisory affiliation fees from Dr. Falk Pharma, Actobio Therapeutics, Jilab, CO Consult, Ukko, Johnson & Johnson, Takeda Pharmaceutical Company Ltd, and Teva Pharmaceuticals; holds a patent licensed to Labsystems Diagnostics from which MHT receives royalties via Tampere University Hospital; and is on the scientific advisory board of ImmunogenX. Konstantinos A. Papadakis is a stockholder in Abbott Laboratories, Amgen Inc, Johnson & Johnson, and Medtronic PLC. Chaitan Khosla has received grants from the NIH; is a stockholder and member of the board of directors of ImmunogenX, Inc; and has received consulting fees from GlaxoSmithKline plc. Jennifer A. Sealey-Voyksner is a cofounder of and stockholder in ImmunogenX, Inc. The remaining authors disclose no conflicts.

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Supplementary Materials and Methods

Additional Methods

Enrollment. At V3, patients were dispensed their MSM and given their gluten supplies, and a urine sample was collected. During the treatment phase, patients self-administered treatment (placebo or 1200 mg IMGX003) and 2 g gluten daily with their evening meal (eg, dinner) for 6 consecutive weeks and continued daily CDSD reporting. Study patients were given urine specimen cups and instructed to collect a single 50-mL urine sample weekly (same day of the week) during the 6-week treatment period from the first urination event occurring 6–12 hours after administration of MSM and gluten at the evening meal. Patients were instructed to store the urine samples in their freezer until their return to the clinic for V4.

Study Medication. IMGX001 is a modified recombinant version of cysteine endoprotease B, isoform 2 (EP-B2), which occurs naturally in germinating barley (*Hordeum vulgare*) and is expressed in and purified from *Escherichia coli*. IMGX002 is a modified recombinant version of a prolyl endopeptidase from the bacterium *Sphingomonas capsulata* and is also expressed in and purified from *E coli*. The third component is an excipient pack containing flavor and buffers. All 3 components are mixed with room temperature water and ingested with a meal.

Gluten (2 g) used in this study was wheat based and consisted of commercially available whole wheat breadcrumbs, made from scratch using whole wheat bread (365 Brand, Whole Foods Market). The breadcrumb food article was analyzed for gluten content using the R5 ELISA Ridascreen Gliadin (R7001) sandwich enzyme immunoassay kit (R-Biopharm AG). Testing was performed by Bia Diagnostics.

Celiac Disease Symptom Diary Scoring Procedure

The CDSD is a daily diary scored across a 7-day period that assesses 6 common celiac symptoms: abdominal pain, bloating, tiredness, diarrhea, nausea, and constipation (complete spontaneous bowel movement [CSBM]). The presence or absence of each of the symptoms over the previous 24 hours was reported. If the respondent indicated the presence of a particular symptom, contingent follow-up questions were asked to assess severity for that symptom. If a patient reported no symptoms, the severity was registered as 0.

For abdominal pain, bloating, and tiredness, a daily severity score was computed by transforming the response to each daily follow-up question onto a scale from 0 to 10 so that severity dimensions were the same for all symptoms. A summary of these transformations is outlined as follows:

abdominal pain daily severity = response range for question (Q) 3a is 0–10, so no conversion needed

bloating daily severity = response range for Q4a is 1–5, so conversion = [(2.25) × (response to Q4a)] – 1.25

tiredness daily severity = response range for Q6a is 1–5, so conversion = [(2.25) × (response to Q6a)] – 1.25

Constipation was evaluated by assessing responses to the CSBM question over time. The clinical definition of constipation generally requires a week of follow-up (ie, fewer than 3 CSBMs within a 1-week timeframe). Hence, constipation was evaluated only on a weekly basis, whereas all other symptoms were evaluated daily.

The number of CSBMs were counted across the study week. If a patient indicated 3 or more CSBMs, then the weekly severity score was set to 0 (ie, no constipation). If a patient reported fewer than 3 CSBMs, the weekly severity score was converted to a scale of 0–70 as follows:

$$\text{CSBM weekly severity} = [(-31.5) \times (\text{weekly number of CSBMs})] + 70;\ \text{contingent upon weekly number of CSBMs} < 3$$

For each symptom with daily severity, a weekly severity score was calculated by summing the daily severity scores (range, 0–10) over the week, which yielded a range of 0–70 for each weekly symptom severity score.

Weekly severity scores for abdominal pain, bloating, tiredness, and constipation were calculated for each week between V2 (day –14) and visit 4 (day 42), resulting in 8 weekly scores. The 2 weekly scores leading up to V3 (day 0, baseline) were averaged together to form the baseline score for each participant. Each of the 6 individual postbaseline weekly scores was combined into 3 2-week average severity scores (ie, the average of consecutive weekly scores [1 and 2, 3 and 4, 5 and 6] and were averaged to form "2-week" average scores). A 6-week average severity score was calculated similarly. Finally, both change and percent change from baseline were calculated for each participant and then averaged within treatment group.

Simvastatin Blood Measurements for Histologic Change

Method. We describe the procedure for monitoring mucosal villous health using our disease management tool (named CypCel). Fasting patients (also instructed not to ingest any citrus 24 hours prior) were administered simvastatin (SV) (Zocor) orally (40 mg) in clinic at V3 and V4, and blood draws were collected at 0, 30, 60, 90, 120, and 180 minutes after SV administration. Blood samples were processed into both serum and plasma and frozen at –80°C. Samples were analyzed for SV and metabolites using liquid chromatography/mass spectrometry.

Results. The maximum value of SV concentration in the blood samples collected between 0 and 180 minutes after the dose of SV showed an expected increase over the GC period for patients in the placebo cohort. In contrast, the average SV_{max} showed a modest decrease over the same period in the IMGX003 cohort. In the cohort of placebo patients, 15 individuals showed an increase in SV_{max}, whereas only 6 showed a decrease. In contrast, the corresponding values for the IMGX003 cohort were 7 and 14,

respectively ($P = .029$ by Fisher exact test). However, quantitative analysis of ΔSV values yields a nonstatistically significant difference between the 2 cohorts ($P = .458$ by a 2-tailed, unpaired t test).

Discussion. Although ΔSV values moved in expected directions for the IMGX003 and placebo groups, the magnitude of change did not correlate with similar changes for other endpoints. For example, we observed a small subset of placebo patients who recorded very high SV values before treatment (V3) and very low SV values after treatment despite these patients exhibiting some of the greatest histologic worsening. SV concentrations in blood are dependent on CYP3A4 metabolism on the villi of the small intestine, and this is the basis for using SV as a drug biomarker of villous health. However, other pharmacokinetic properties can also influence SV concentrations, including absorption uptake in the bloodstream, which is also dependent on villous health and may give a countering effect. Furthermore, gluten challenge ingestions over short periods of time generally cause proximal damage of the small intestine, whereas the SV levels are sensitive to a much greater length of the small intestine.[1] We intend to study these still uncertain processes further in an effort to improve the utility of SV monitoring of villous health.

Verification of Compliance

Patients were instructed to answer study medication and gluten compliance questions daily concurrent with CDSD diary completion. In addition, patients were instructed to retain all used and unused study medication and gluten and return them at V3 (MSM only) and V4 (MSM and gluten). All returned study medication and gluten was recorded in accountability logs.

Supplementary Histology Results

The participant-specific results for Vh:Cd and IEL are presented in Supplementary Figures 1 and 2, respectively. Careful inspection of the color-coded patient responses for Vh:Cd and IEL in these figures show that Vh:Cd and IEL do not correlate very strongly, yet each is a good measure of histology as judged by statistical P values for differentiation of the IMGX003 and placebo groups. We developed a blended score, VCIEL, that retains the general range of the Vh:Cd score but includes IEL changes with equal weighing. The equation used is as follows:.

$$\mathrm{VCIEL} = \mathrm{S} \times (\mathrm{Vh{:}Cd} + \mathrm{IEL/F}) \quad (1)$$

where F accounts for the different ranges of change for Vh:Cd and IEL and is given by

$$\mathrm{F} = (\Delta\mathrm{Vh{:}Cd[A]} - \Delta\mathrm{Vh{:}Cd[P]})/(\Delta\mathrm{IEL[A]} - \Delta\mathrm{IEL[P]}) \quad (2)$$

where [A] and [P] denote the IMGX003 and placebo groups, respectively, and S is a scaling factor to make the average VCIEL = average Vh:Cd. This scale helps minimize the discordance between ΔVh:Cd and ΔIEL for some patients and apparently leads to a narrower overall variance in results. The individual participant results are presented in Supplementary Figure 3, and this modified histology scale led to a calculated attenuation of 90% and $P = .010$ for latiglutenase (IMGX003) vs placebo. We believe that this scale is worthy of further consideration, and it would be interesting to apply it to the patient data from other GC trials.

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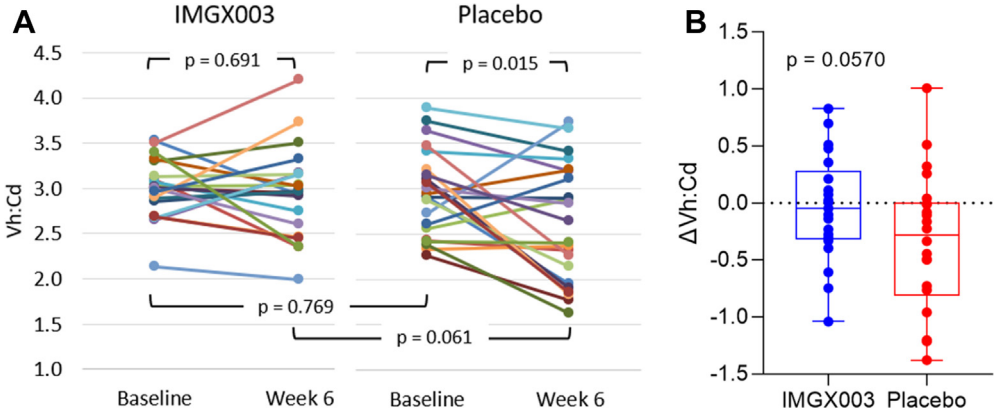
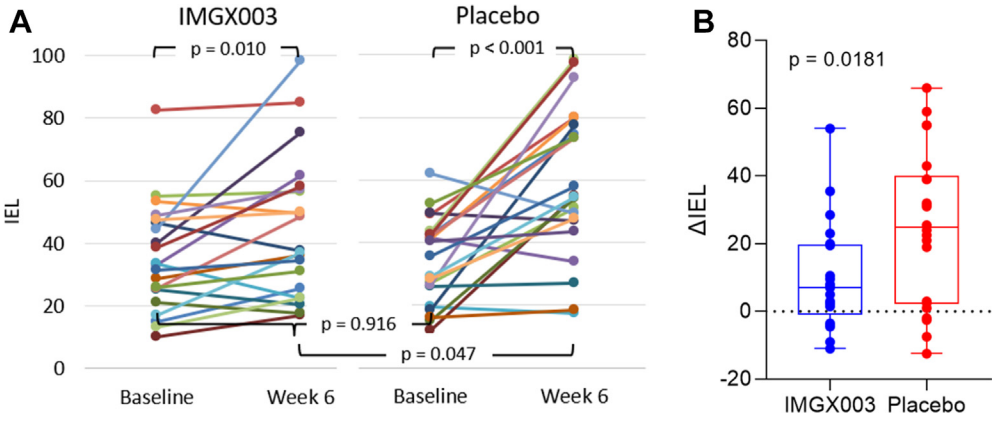
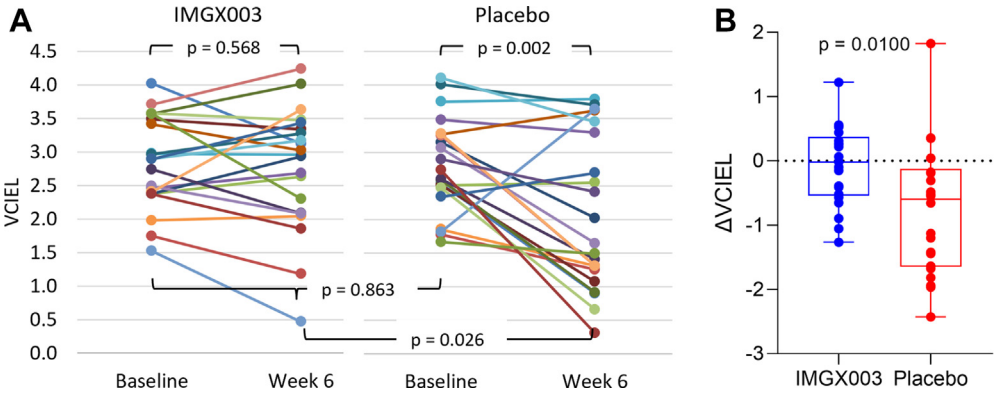


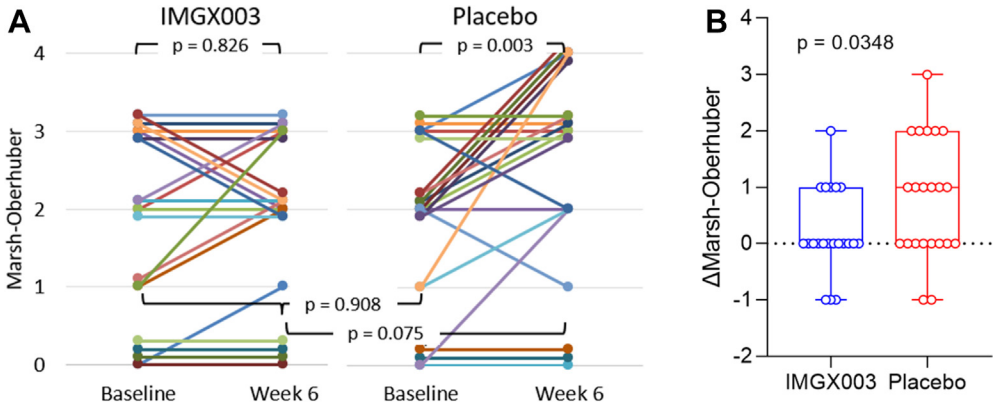
Supplementary Figure 1. Participant responses for Vh:Cd. (*A*) Individual participant changes. (*B*) Box-and-whisker plot showing minimum and maximum, first and third quartiles, median, and ANCOVA *P* value.



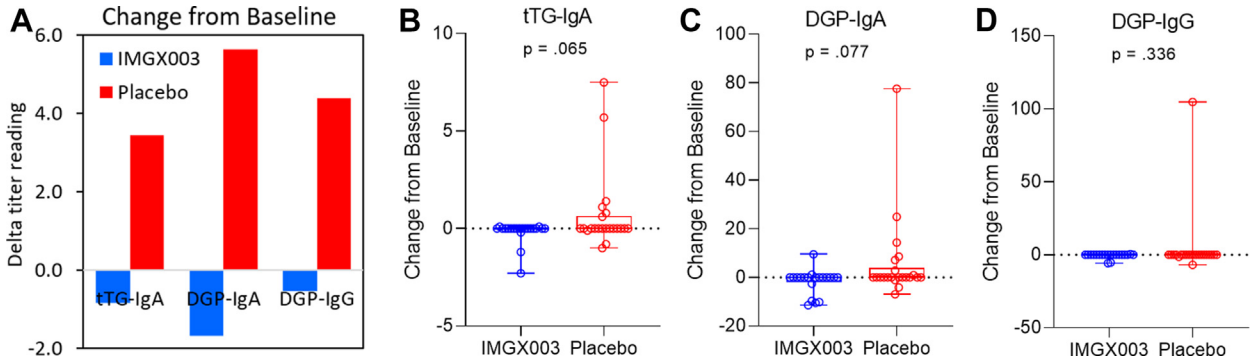
Supplementary Figure 2. Participant responses for IEL. (*A*) Individual participant changes. (*B*) Box-and-whisker plot showing minimum and maximum, first and third quartiles, median, and ANCOVA *P* value.



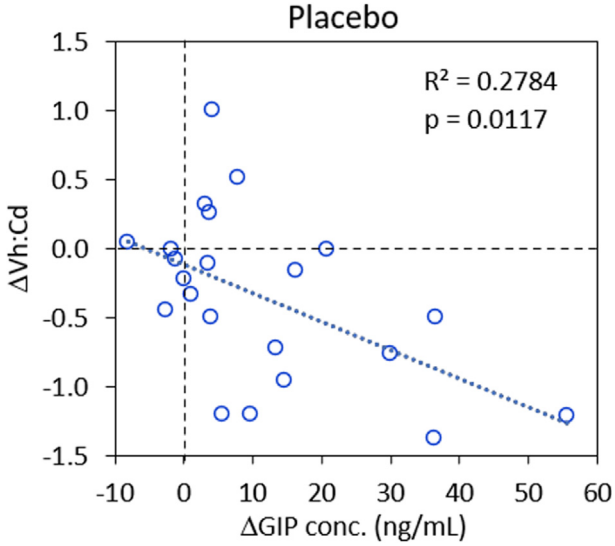
Supplementary Figure 3. Participant responses for VCIEL. (*A*) Individual participant changes. (*B*) Box-and-whisker plot showing minimum and maximum, first and third quartiles, median, and ANCOVA *P* value.



Supplementary Figure 4. Participant responses for conversion of Vh:Cd and IEL values to a Marsh-Oberhuber score. (*A*) Individual participant changes. (*B*) Box-and-whisker plot showing minimum and maximum, first and third quartiles, median, and ANCOVA *P* value. Scores of 3 and 4 represent Q3a and Q3b, respectively.



Supplementary Figure 5. Serology results. (*A*) Mean change from baseline for all 3 titers. (*B–D*) Box-and-whisker plots showing minimum and maximum, first and third quartiles, median, and ANCOVA *P* value for (*B*) tTG-IgA, (*C*) DGP-IgA, and (*D*) DGP-IgG.



Supplementary Figure 6. Correlation of ΔVh:Cd vs ΔGIP concentration (conc.) for placebo patients. *P* value is by linear regression.

Supplementary Table 1. Summary of Symptom Results (6-Week Average): mITT Population

Symptoms	Placebo (n = 22)	IMGX003 (n = 21)
Abdominal pain		
Baseline: days −14 to −1		
n	22	21
Mean (SD)	0.75 (2.181)	1.30 (2.215)
Median	0.00	1.00
Minimum, maximum	0.00, 9.70	0.00, 10.00
Postbaseline 6-week average		
n	22	21
Mean (SD)	2.38 (3.552)	1.51 (1.679)
Median	0.58	0.50
Minimum, maximum	0.00, 13.33	0.00, 4.87
Change from baseline to postbaseline 6-week average		
n	22	21
Mean (SD)	1.63 (3.457)	0.22 (2.752)
Median	0.33	0.33
Minimum, maximum	−2.07, 12.33	−9.50, 4.23
Within-group *P* value[a]	.0380	.7236
Between-group *P* value[b]	—	.2308
Bloating		
Baseline: days −14 to −1		
n	22	21
Mean (SD)	3.38 (7.053)	2.10 (5.425)
Median	0.00	0.00
Minimum, maximum	0.00, 23.00	0.00, 20.50
Postbaseline 6-week average		
n	22	21
Mean (SD)	6.67 (11.922)	3.06 (6.691)
Median	0.71	1.25
Minimum, maximum	0.00, 42.29	0.00, 30.51
Change from baseline to postbaseline 6-week average		
n	22	21
Mean (SD)	3.29 (5.737)	0.96 (4.504)
Median	0.43	0.33
Minimum, maximum	0.00, 19.29	−13.48, 10.01
Within-group *P* value[a]	.0138	.3402
Between-group *P* value[b]	—	.2035
Tiredness		
Baseline: days −14 to −1		
n	22	21
Mean (SD)	6.13 (11.048)	6.80 (12.099)
Median	1.76	0.00
Minimum, maximum	0.00, 38.50	0.00, 44.13
Postbaseline 6-week average		
n	22	21
Mean (SD)	9.33 (12.971)	6.82 (11.087)
Median	4.80	1.46
Minimum, maximum	0.00, 41.13	0.00, 42.63
Change from baseline to postbaseline 6-week average		
n	22	21
Mean (SD)	3.20 (8.228)	0.02 (3.327)
Median	0.32	0.00
Minimum, maximum	−7.17, 31.25	−5.40, 8.95
Within-group *P* value[a]	.0824	.9805
Between-group *P* value[b]		.1130
Nonstool composite		
Baseline: days −14 to −1		
n	22	21
Mean (SD)	2.74 (3.322)	2.60 (4.041)

Supplementary Table 1. Continued

Symptoms	Placebo (n = 22)	IMGX003 (n = 21)
Median	1.35	0.91
Minimum, maximum	0.00, 9.63	0.00, 15.15
Postbaseline 6-week average		
n	22	21
Mean (SD)	5.01 (6.647)	3.24 (3.838)
Median	2.20	1.56
Minimum, maximum	0.00, 27.28	0.08, 14.00
Change from baseline to postbaseline 6-week average		
n	22	21
Mean (SD)	2.27 (4.696)	0.64 (2.210)
Median	0.50	0.98
Minimum, maximum	–2.09, 18.69	–6.85, 4.48
Within-group *P* value[a]	.0341	.1989
Between-group *P* value[b]	—	.1633

SD, standard deviation.
[a]*P* value was calculated using a paired *t* test of the postbaseline visit compared to baseline values within each treatment arm and indicates if the change at the postbaseline visit is statistically significantly different than 0.
[b]*P* value was calculated using an ANCOVA model including baseline symptoms and treatment as covariates.