

# Celiac Disease Patients Attempting Adherence To A Gluten-Free Diet Who Continue To Have Moderate Or Severe Symptoms

## Have Clinically Significant Mucosal Injury (ClinicalTrials.gov NCT01917630)

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### ABSTRACT

**Introduction:** Ingestion of gluten in patients (pts) with celiac disease (CD) can cause intestinal mucosal injury, gastrointestinal (GI) symptoms as well as extraintestinal manifestations. Lifelong adherence to a gluten-free diet (GFD) is the only option currently available. Despite attempting adherence to a GFD, many patients continue to experience symptoms and intestinal mucosal inflammation. Because a CD-specific patient-reported outcome (PRO) instrument has only recently become available, the association of CD-specific symptoms and mucosal injury has not yet been rigorously studied.

**Aims and Methods:** We sought to understand the association of symptoms and mucosal inflammation in pts with CD attempting adherence to a GFD. The Celiac Disease Symptom Diary (CDS<sup>®</sup>), a CD-specific (PRO) diary, was developed in line with the US Food and Drug Administration PRO Guidance (2009), and is being used to assess symptoms in pts with CD while on a GFD. Physician-diagnosed pts with CD recruited into the CeliAction Study™ recorded symptoms for 28 days using the CDS<sup>®</sup>. Pts having ≥1 day of moderate or severe symptoms during the data collection period underwent upper GI endoscopy and 4 mucosal biopsies from the distal duodenum. All biopsies were centrally read with quantitative assessment of the average ratio of villus height to crypt depth (Vh:Cd) from 5-12 properly oriented biopsy villus-crypt units.

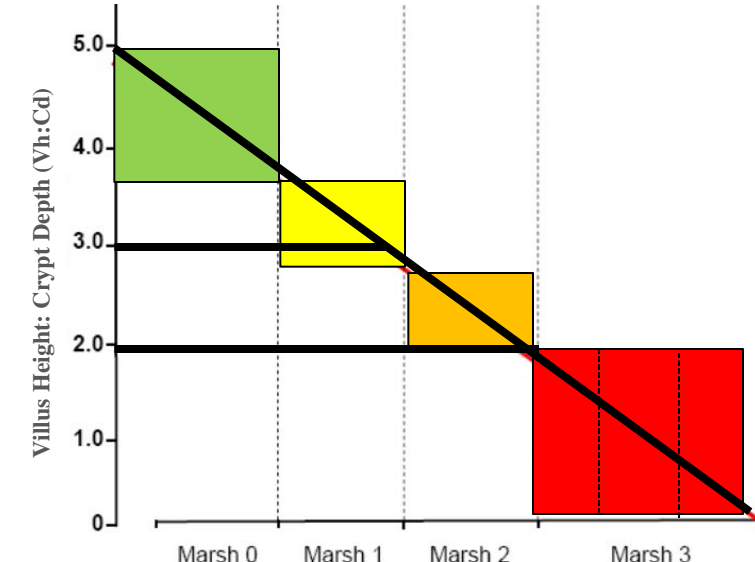
**Results:** 117 pts in the US (97 women [ave=45.1 yrs, range 20-76], 20 men [ave=50.9 yrs, range 22-72]), on a GFD ≥1 yr reported symptoms daily using the CDS<sup>®</sup> for 28 days. 14% of these pts were TG2-IgA antibody positive; All pts reported ≥1 day of CD-associated GI symptoms (e.g., abdominal pain, bloating, diarrhea, constipation, or nausea) and underwent duodenal mucosal biopsies. The average Vh:Cd for pts with ≥1 day of symptoms was 1.7 (SD=0.7, range 0-3.4). The percent of patients with Vh:Cd <3.0 and ≤ 2.0 was 95% and 65%, respectively.

**Conclusions:** Many pts with CD have significant disease-associated symptoms and intestinal mucosal injury despite attempted adherence to a GFD. In this study, 95% of pts with ongoing CD-associated symptoms have abnormal mucosal morphometry (Vh:Cd < 3.0). These data suggest that the GFD is inadequate as solo therapy for many CD pts; a pharmacologic treatment option is needed.

### BACKGROUND

- Celiac disease (CD) is an autoimmune disorder triggered in susceptible individuals by dietary exposure to gluten proteins found in wheat, barley and rye
- Strict lifelong exclusion of dietary gluten is the only option available to treat CD, but gluten is ubiquitous in most Western diets; strict adherence to the gluten-free diet (GFD) is extremely difficult to maintain due to inadvertent exposure, and thus many patients remain symptomatic and have ongoing intestinal inflammation
- The CeliAction Study™ is an on-going phase 2b, double-blind, randomized, placebo-controlled clinical study of the safety and efficacy of ALV003 in symptomatic patients with CD maintained on a GFD
- All qualified patients underwent baseline small intestinal mucosal biopsy prior to randomization
- The extent of mucosal injury in symptomatic patients with celiac disease was systematically evaluated by determining the ratio of the villus height to crypt depth (Vh:Cd) from endoscopically-obtained, properly-oriented duodenal mucosal biopsies
- The Vh:Cd is a continuous measure of mucosal inflammation and therefore a more sensitive measure of change than the categorical measures of the Marsh-Oberhuber classification (Figure 1)

**Figure 1:** Vh:Cd as a continuous measure compared to the categorical Marsh-Oberhuber classification of celiac disease. Marsh criteria are typically used to confirm the clinical diagnosis of celiac disease. The continuous Vh:Cd measure provides greater sensitivity to change when measuring the effects of a potential therapeutic intervention or in response to change in gluten intake over time (figure modified with permission from M. Maki).



- Vh:Cd ≥ 3.0 is considered to be “normal”
- ≤ 2.0 (equivalent to Marsh 3a) is consistent with a diagnosis of celiac disease

### PROTOCOL DESIGN

#### Hypothesis

- Patients with celiac disease who are attempting to adhere to a GFD continue to experience gluten-associated symptoms and significant mucosal inflammation

#### Major Entry Criteria

- Patients with physician-diagnosed CD, documented by small-bowel biopsy
- Attempted adherence to a GFD ≥ 1 year prior to randomization
- At least one self-reported moderate or severe symptom attributable to CD in the previous month
- Meet all the enrollment criteria specified by the CeliAction Study™ protocol
- Signed informed consent

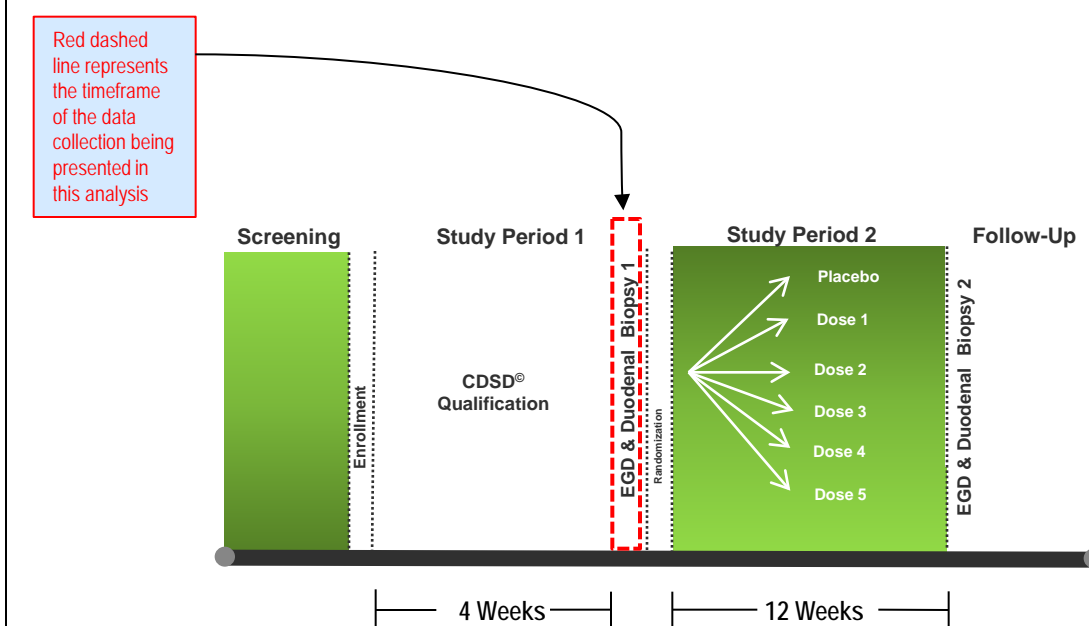
#### Institutional Review Board Approval

- The protocol had Institutional Review Board approval
- Informed consent was obtained from all patients prior to enrollment in the study

#### Study Design

- Randomized, double-blind, placebo-controlled dose-ranging study in symptomatic, established patients with CD attempting a GFD for ≥ 1 year prior to randomization
- Screening
  - Informed consent
  - Self-reported moderate to severe symptoms in previous month
- Enrollment
  - 28 day “run-in” period
  - Collect daily symptoms using the Celiac Disease Symptom Diary (CDS<sup>®</sup>)
  - If meeting pre-specified criteria, undergo baseline UGI endoscopy and biopsy
- Randomization
  - Requires all randomization criteria met, including a Vh:Cd of ≤ 2.0
  - Randomized assignment to either placebo or one of five active drug treatment arms

#### Study Schema



#### Pre-Randomization Measures

- Demographics
- Serostatus
  - Seropositivity defined as any of the following being positive
    - TG2-IgA
    - DGP-IgA
    - DGP-IgG
- Duration of dietary gluten restrictions
- Ratio of villus height to crypt depth (Vh:Cd) in duodenal mucosal biopsies

### RESULTS

#### Demographics and Baseline Characteristics

	Age (years)	Women (n=97)	Men (n=20)	Overall (n=117)
Mean	46.1	46.1	50.9	46.9
S.D.	13.2	13.2	13.7	13.4
Median	47.0	47.0	53.5	48.0
Min, Max	20, 76	20, 76	22, 72	20, 76
Years Since Diagnosis				
Mean	6.6	6.6	6.8	6.6
S.D.	6.6	6.6	3.9	6.2
Median	5.0	5.0	5.1	5.0
Min, Max	1.0, 43.7	1.0, 43.7	1.4, 14.9	1.0, 43.7
Duration of GFD (years)				
Mean	6.3	6.3	6.2	6.2
S.D.	5.6	5.6	4.1	5.3
Median	4.8	4.8	5.1	4.9
Min, Max	1.1, 36.8	1.1, 36.8	1.0, 15.0	1.0, 36.8

#### Villus Height:Crypt Depth Ratio of Patients on a GFD

Vh:Cd	Women (n=97)	Men (n=20)	Overall (n=117)
Mean	1.8	1.6	1.7
S.D.	0.68	0.68	0.68
Median	1.8	1.7	1.8
Min, Max	0.0, 3.4	0.3, 2.8	0.0, 3.4

#### Impact of Mucosal Injury

Vh:Cd Value	Percent of Patient Population
< 3.0	95%
≤ 2.0	65%

#### Villus Height:Crypt Depth – By Decade

	20-29	30-39	40-49	50-59	60-69	70-79
Average Vh:Cd	1.8	2.1	1.8	1.6	1.8	1.3
Total n	20	12	31	32	19	3
n < 3.0	18.0	12.0	29.0	31.0	18.0	3.0
n ≤ 2.0	14.0	7.0	20.0	21.0	14.0	2.0
% < 3.0	90.0	100.0	93.5	96.9	94.7	100.0
% ≤ 2.0	70.0	58.3	64.5	65.6	73.7	66.7
Ave Yrs on GFD	3.4	5.6	5.2	7.6	9.1	2.9

#### Villus Height:Crypt Depth – By Serostatus

	Serostatus	
	Negative	Positive
n	90	27
%	77	23
Average Age (yrs)	46.0	50.0
Range	20-71	23-76
Ave Yrs on GFD (range)	6.3(1.2-36.8)	5.6 (1.8-28.8)
<b>Average Vh:Cd</b>	<b>1.9</b>	<b>1.3</b>

### SUMMARY & CONCLUSIONS

#### Summary

- Many patients with celiac disease have significant disease-associated symptoms and intestinal mucosal injury despite attempted adherence to a GFD
  - 95% of patients with moderate or severe celiac disease-associated symptoms have abnormal mucosal morphometry
  - 65% of patients in this study, despite attempting to adhere to a GFD, have mucosal injury consistent with untreated celiac disease
- In this study, despite adherence to the GFD and negative celiac antibodies, patients showed significant mucosal inflammation, with Vh:Cd values that were diagnostic of celiac disease

#### Conclusions:

- These data suggest that the GFD is inadequate as solo therapy for many patients with celiac disease, irrespective of serologic status
- A pharmacologic treatment option as an adjunct to the GFD is needed