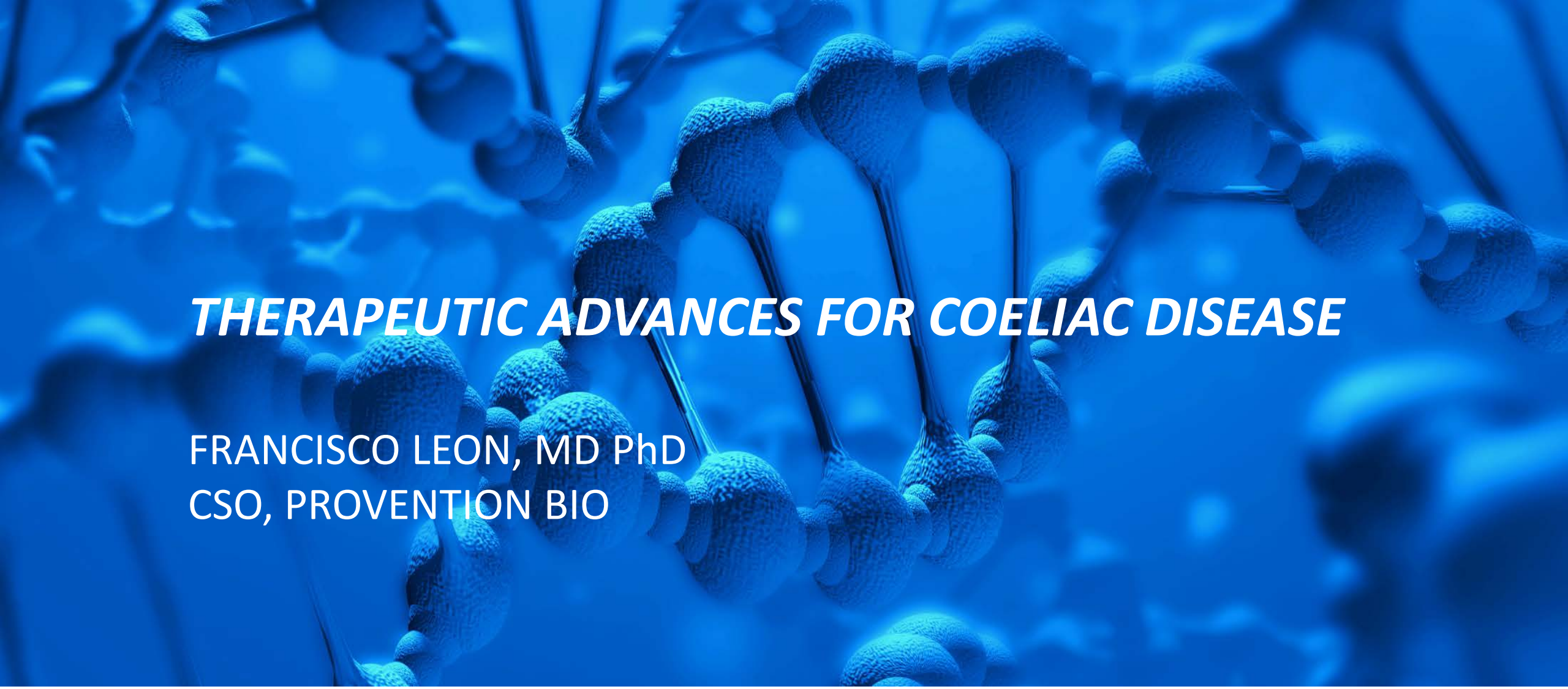

THERAPEUTIC ADVANCES FOR COELIAC DISEASE

FRANCISCO LEON, MD PhD
CSO, PROVENTION BIO

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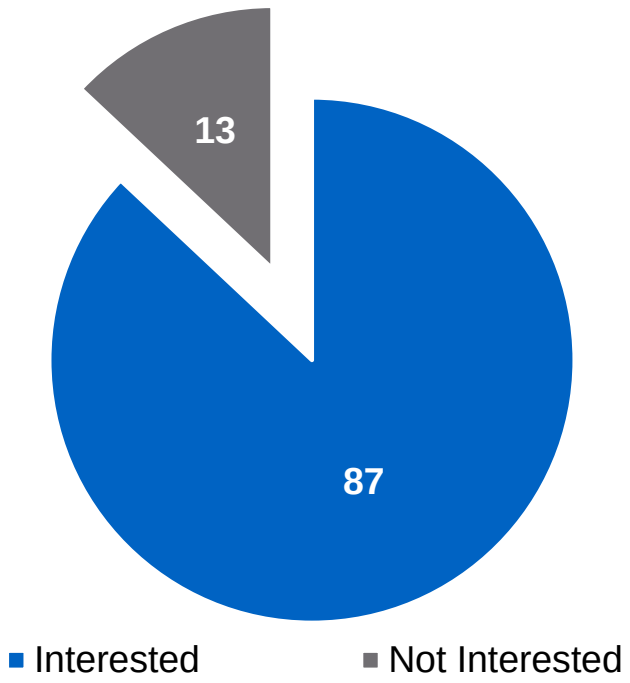
DISCLOSURES

- Co-founder, Chief Scientific Officer, **Provention Bio**
  - Provention Bio and Amgen entered into a License and Collaboration Agreement for AMG 714 (PRV-015) in November 2018
- Former co-founder, CEO, Chief Medical Officer, **Celimmune**
  - Amgen licensed AMG 714 to Celimmune in 2015
  - Celimmune conducted celiac and RCD-II studies with AMG 714
  - Amgen acquired Celimmune in 2017
- Former Chief Medical Officer, **Alba Therapeutics**
- Partner, **Biomedal**
- Co-founder, **Glutenostics** (GlutenDetective.com)

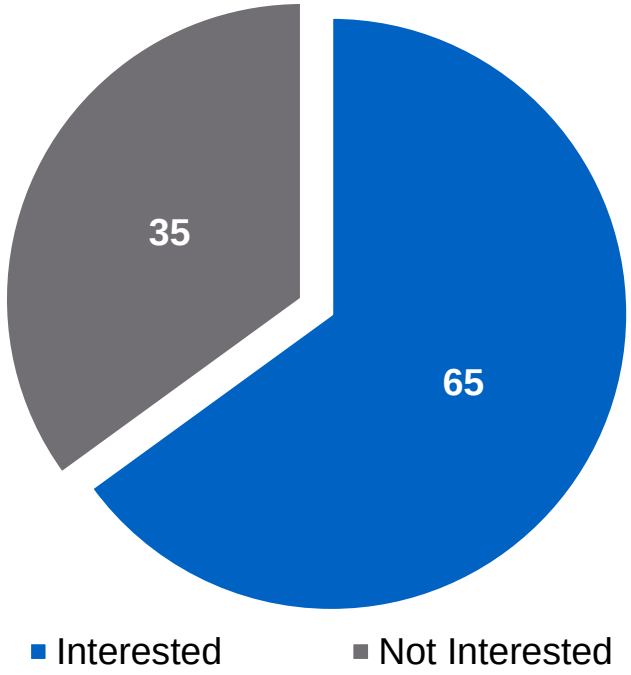
CELIAC DISEASE PATIENTS ARE INTERESTED IN A DRUG TO PREVENT THE SYMPTOMS AND EFFECTS OF GLUTEN CONTAMINATION

Tomal J, McKiernan D, Guandalini S, Semrad CE, Kupfer SS. Celiac patients' attitudes regarding novel therapies. *Minerva Gastroenterol Dietol* 2016;62:275-80

Cross-contamination (Adjunct to Gluten-Free Diet)



Gluten consumption (Replacement of Gluten Free Diet)



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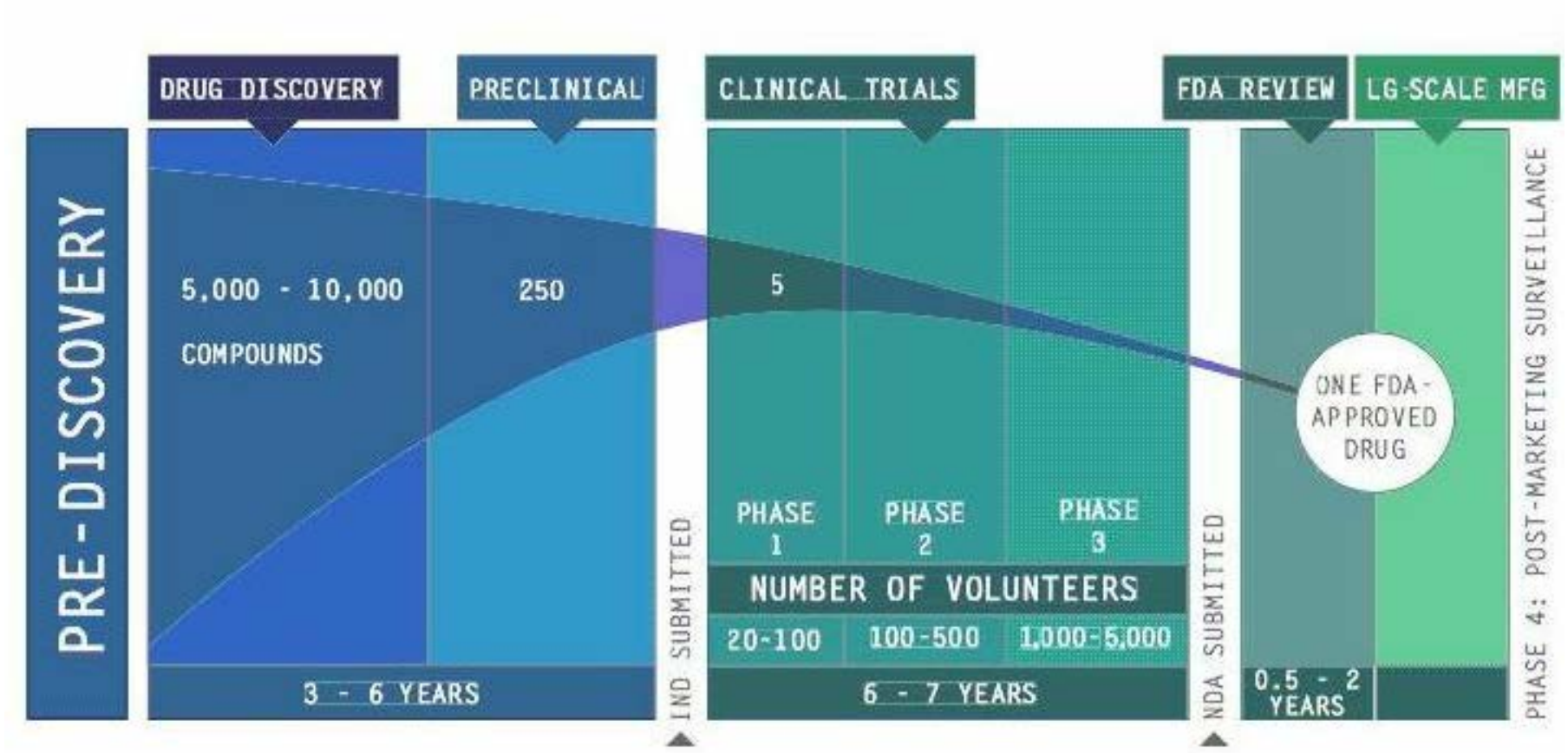
WE NEED MULTIPLE SHOTS ON GOAL

SINCE: 1) MOST MEDICINES FAIL TO BE APPROVED

2) IT'S LIKELY THAT COMBINATIONS WILL BE NEEDED



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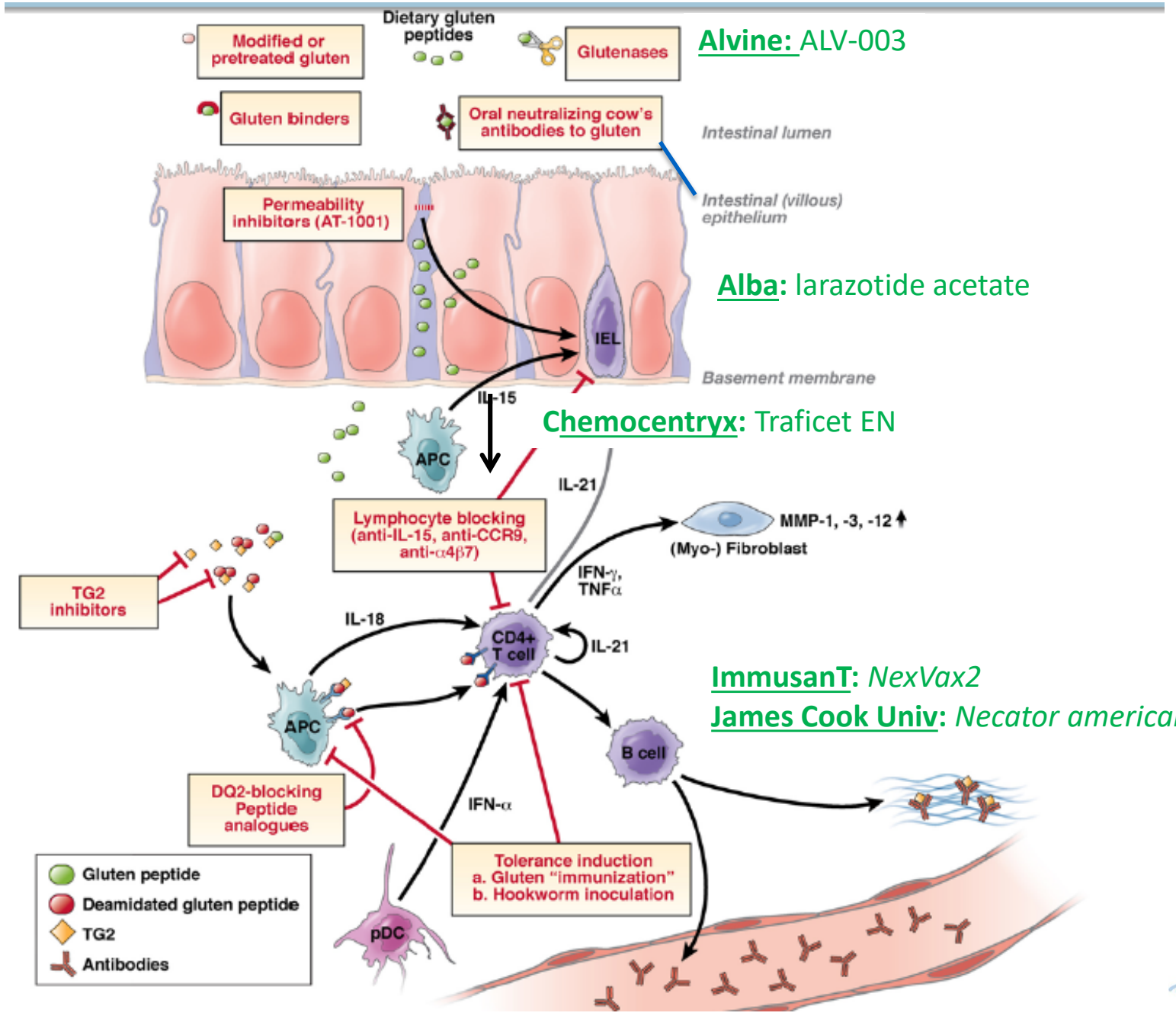
Experimental non-dietary therapies for celiac disease (2010)



Alvine: ALV-003

Alba: larazotide acetate

Chemocentryx: Traficet EN

ImmusanT: *NexVax2*

James Cook Univ: *Necator americanus*

Schuppan Gastroenterology 2009, modified

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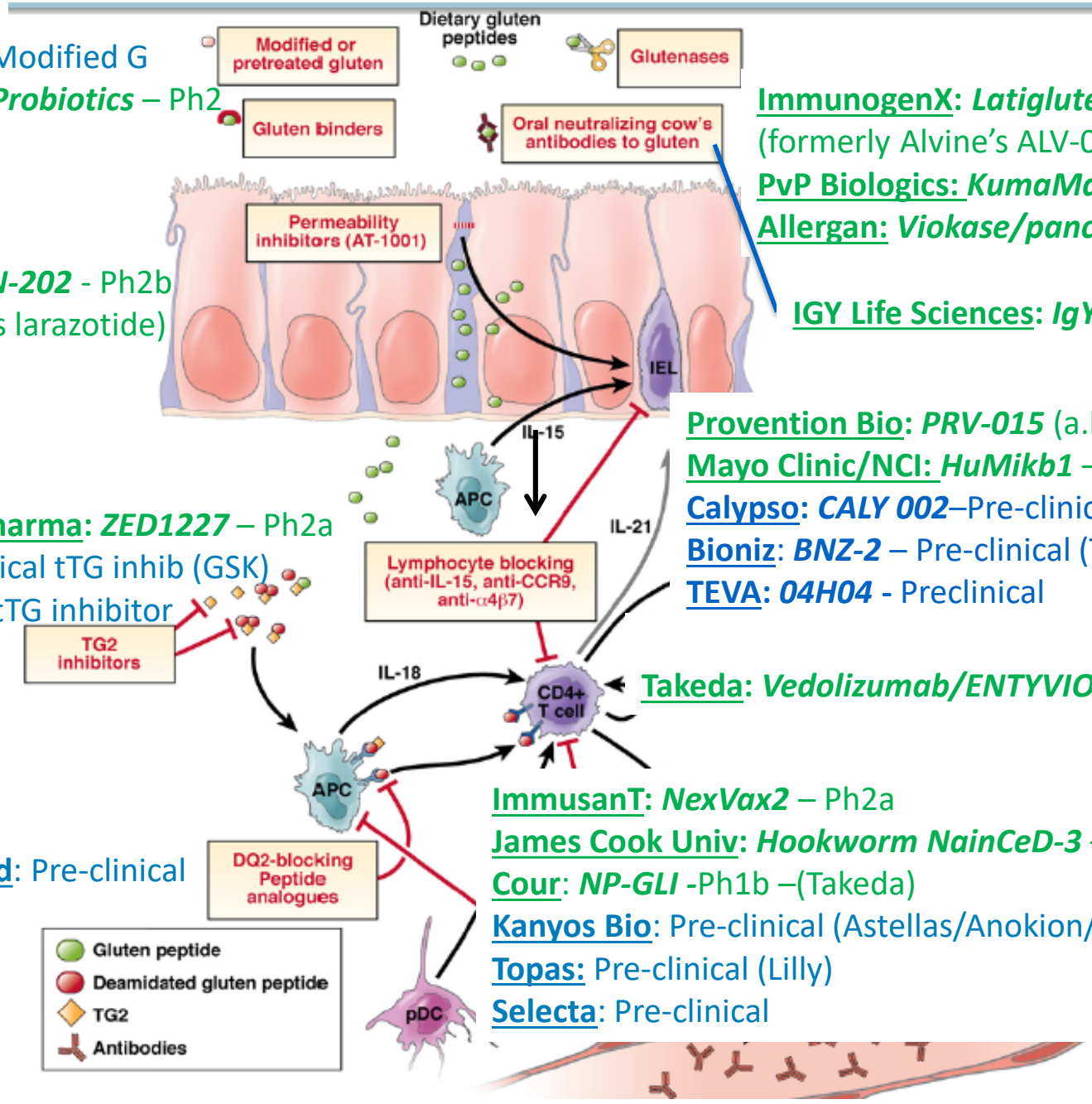
Experimental non-dietary therapies for celiac disease (2/2019)

Universities: Modified G
Probiotics – Ph2

Innovate: – ***INN-202*** - Ph2b
(formerly Alba's larazotide)

Zedira/Falk Pharma: ***ZED1227*** – Ph2a
Sitari: Pre-clinical tTG inhib (GSK)
UCB: Pre-clin tTG inhibitor

Provid: Pre-clinical



Schuppan Gastroenterology 2009, modified

ImmunogenX: ***Latiglutenase/IMGX-003***
(formerly Alvine's ALV-003)- Ph2b
PvP Biologics: ***KumaMax*** **–** Ph1 (Takeda)
Allergan: ***Viokase/pancrelipase*** – Ph2a

IGY Life Sciences: ***IgY*** – Ph1/2

Provention Bio: ***PRV-015*** (a.k.a. AMG 714) –Ph2b (Amgen)
Mayo Clinic/NCI: ***HuMikb1*** – Ph2a
Calypso: ***CALY 002***–Pre-clinical (Merck KGa)
Bioniz: ***BNZ-2*** – Pre-clinical (Takeda)
TEVA: ***04H04*** **-** Preclinical

Takeda: ***Vedolizumab/ENTYVIO*** – Ph1b

ImmusanT: ***NexVax2*** – Ph2a
James Cook Univ: ***Hookworm NainCeD-3*** – P1b
Cour: ***NP-GLI*** **-**Ph1b –(Takeda)
Kanyos Bio: Pre-clinical (Astellas/Anokion/Celgene)
Topas: Pre-clinical (Lilly)
Selecta: Pre-clinical

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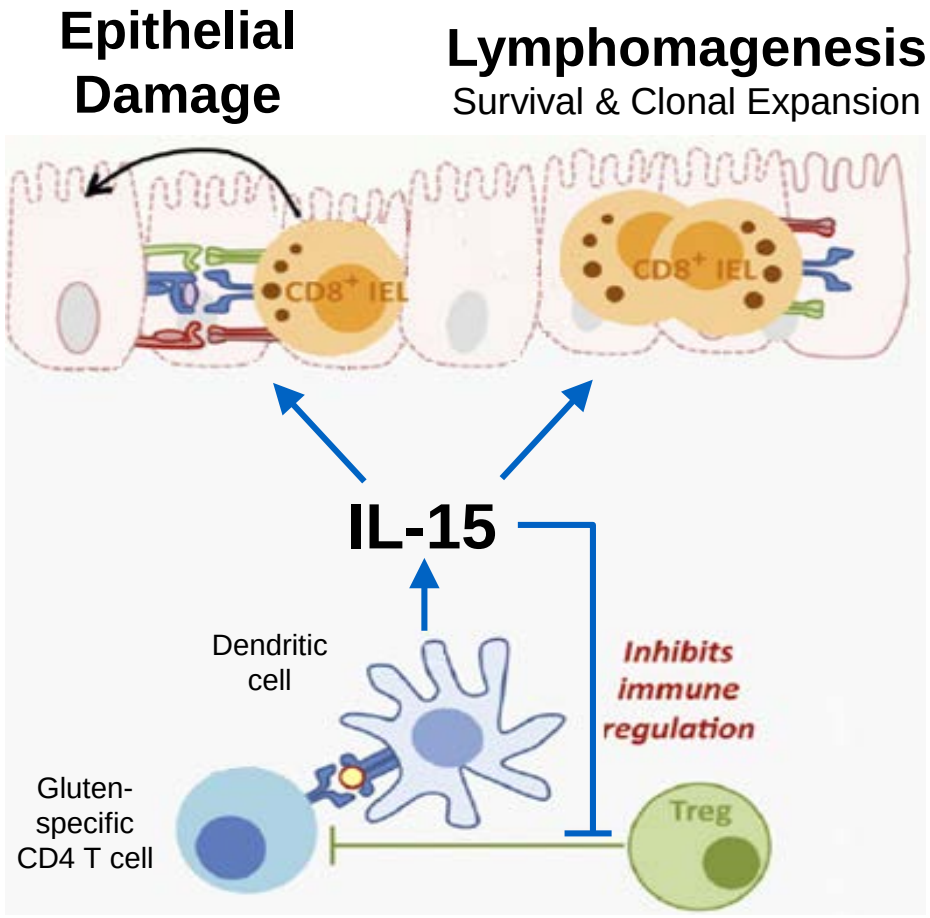
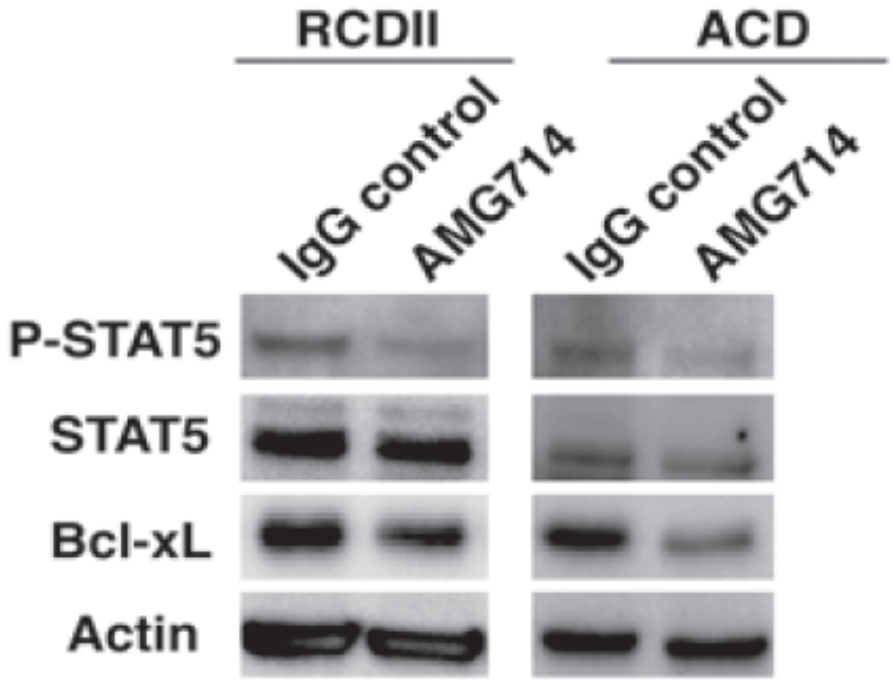
RATIONALE FOR IL-15 INHIBITION IN CELIAC

IL-15 IS A DRIVER OF INTRA-EPITHELIAL LYMPHOCYTES (IELS) IN CELIAC AND REFRACTORY CELIAC DISEASE TYPE-II (RCD-II), A.K.A. PRE-ENTEROPATHY-ASSOCIATED T CELL LYMPHOMA (PRE-EATL)





Malamut et al. “IL-15 triggers an antiapoptotic pathway in human intraepithelial lymphocytes that is a potential new target in celiac disease–associated inflammation and lymphomagenesis.” J Clin Invest 2010

AMG 714 (ANTI-IL-15 MAB) AMELIORATES THE EFFECTS OF GLUTEN CONSUMPTION IN CELIAC DISEASE: A PHASE 2A, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY EVALUATING AMG 714 IN ADULT PATIENTS WITH CELIAC DISEASE EXPOSED TO A HIGH-DOSE GLUTEN CHALLENGE.

MARJA-LEENA LÄHDEAHO, MIKA SCHEININ, MARKO PESU, LAURA KIVELÄ, ZSÓFIA LOVRÓ, JONI KEISALA, FRANCISCO LEON, MARKKU MAKI

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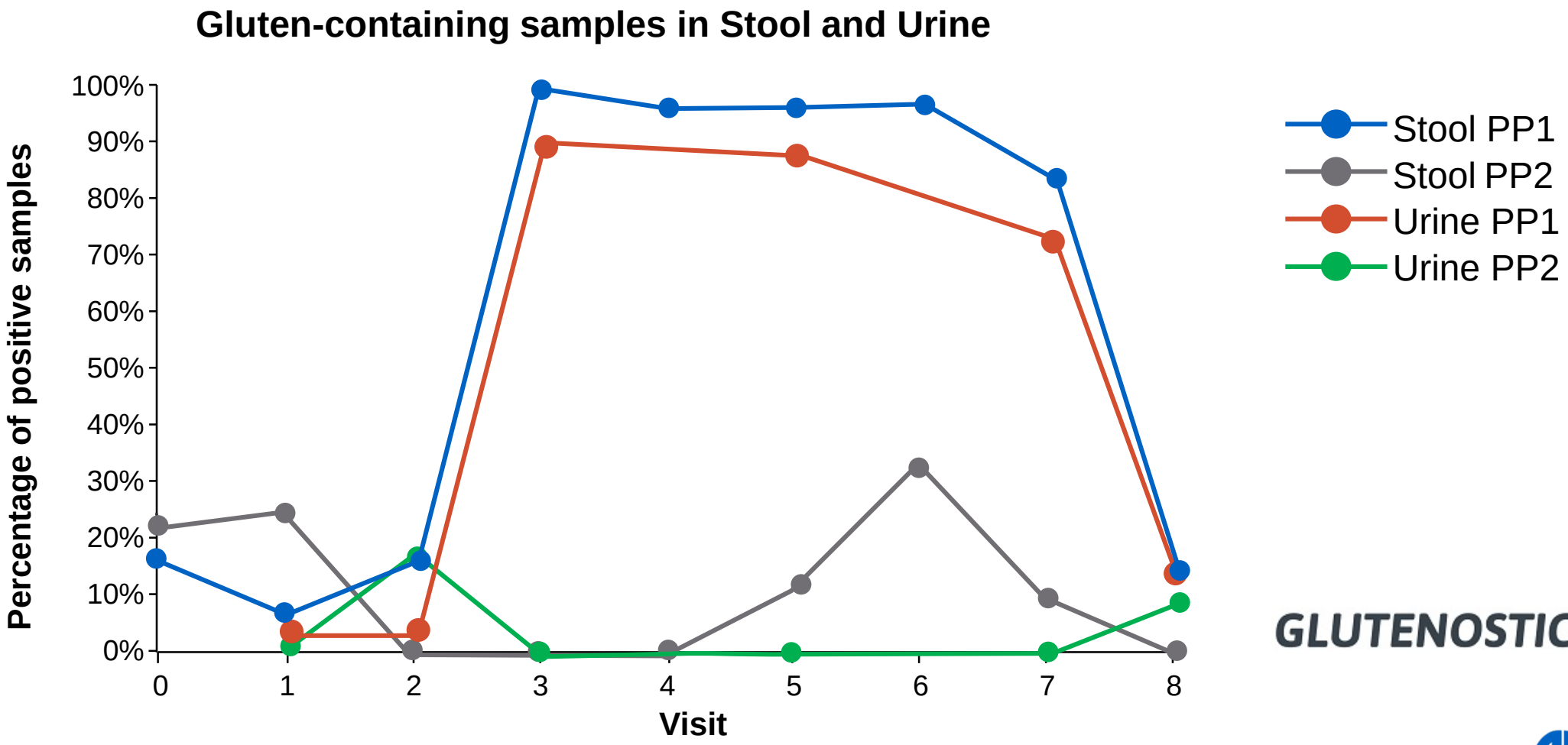
GENERAL COMPLIANCE AND BALANCE IN THE GLUTEN CHALLENGE

STOOL AND URINE GLUTEN TEST CONFIRM GLUTEN CHALLENGE IN PP1 AND REVEAL TRANSGRESSIONS IN PP2



GLUTENOSTICS

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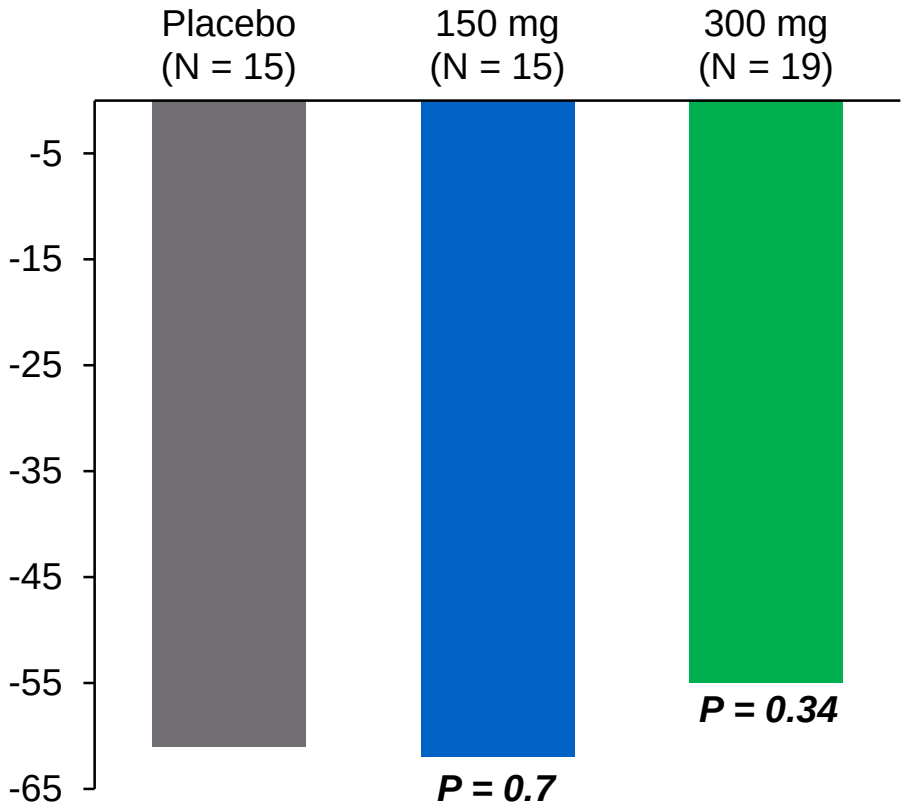
EFFECT OF AMG 714 ON GLUTEN-TRIGGERED DAMAGE ON INTESTINAL HISTOLOGY

Change from baseline to Week 12 in VH:CD. Primary efficacy endpoint in PP1 (not met).

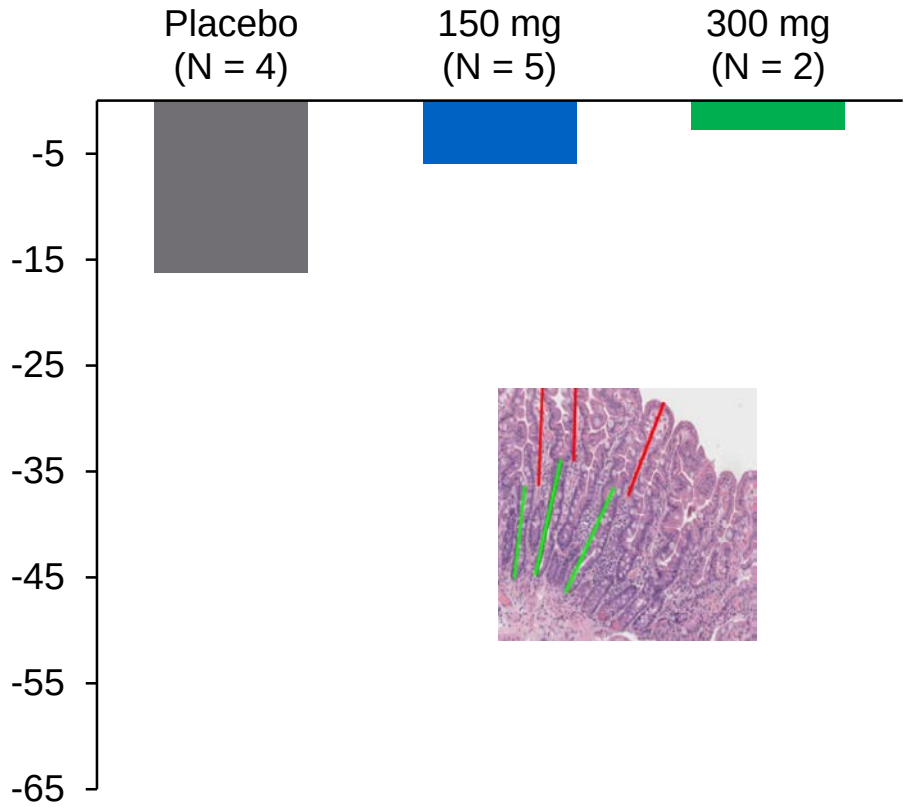
PP1: High-dose gluten challenge (2-4 g/d, 10 w). N = 49

% Change from Baseline in VH:CD



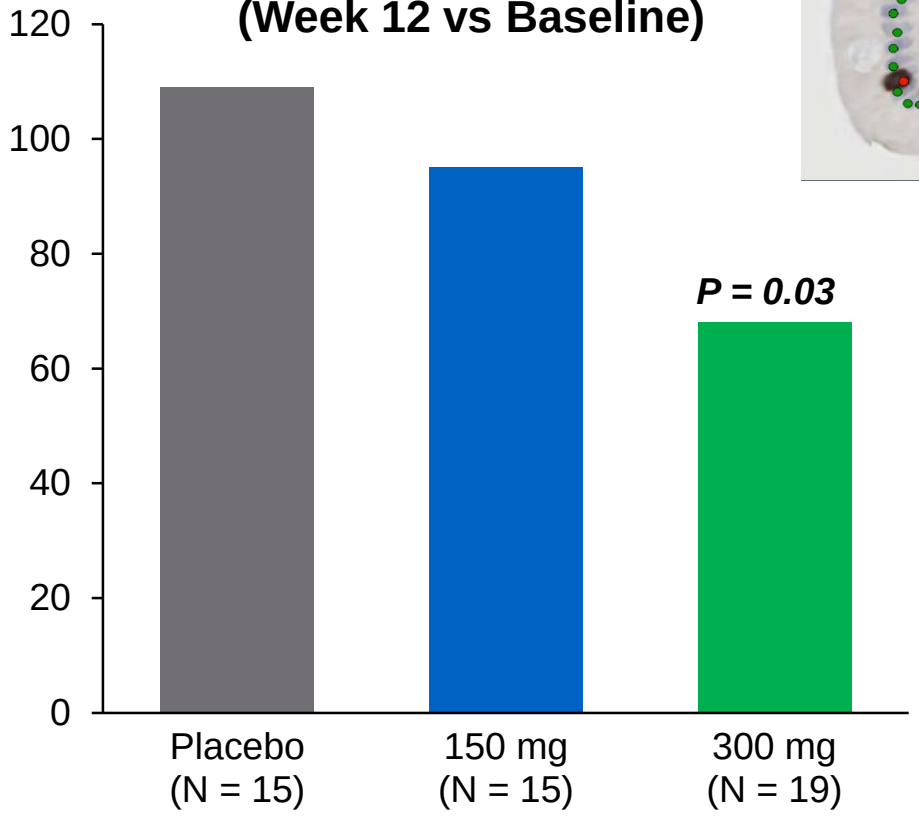
PP2: No or low gluten exposure. N = 11

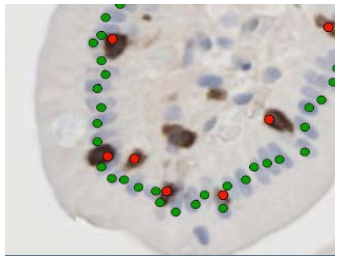
% Change from Baseline in VH:CD

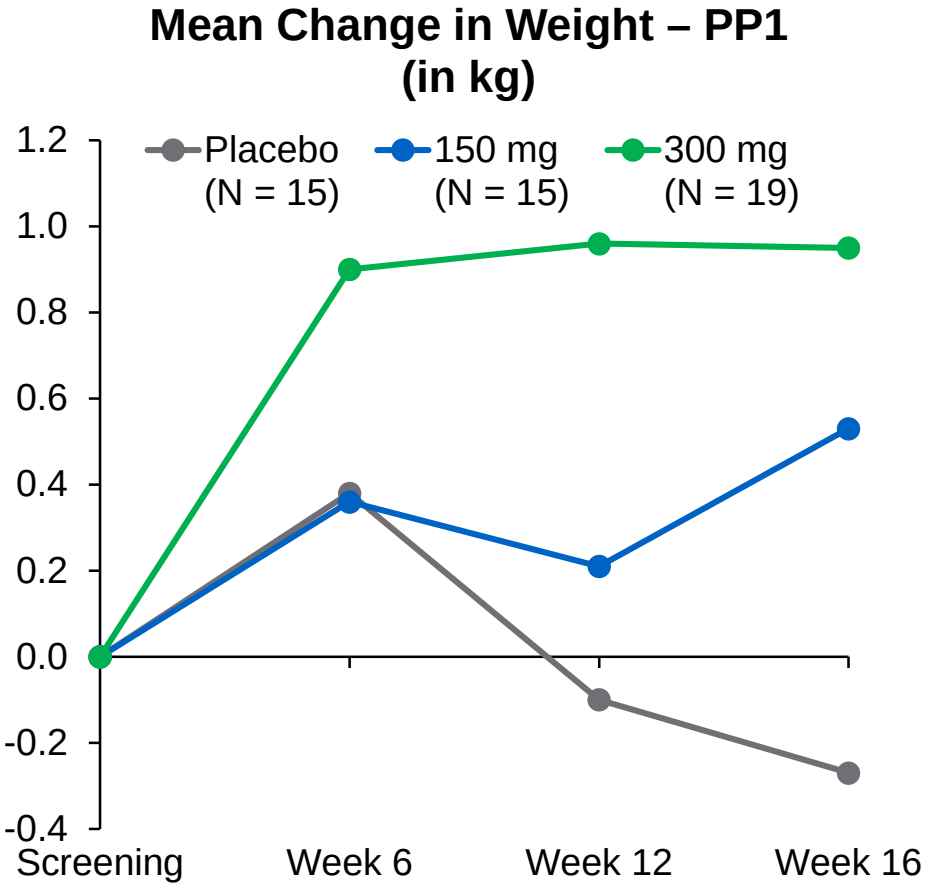


EFFECT OF AMG 714 ON GLUTEN-TRIGGERED INCREASE IN INTRAEPITHELIAL LYMPHOCYTES (IEL), AND ON WEIGHT LOSS

PP1: High-dose gluten challenge (2-4 g/day for 10 weeks). N = 49



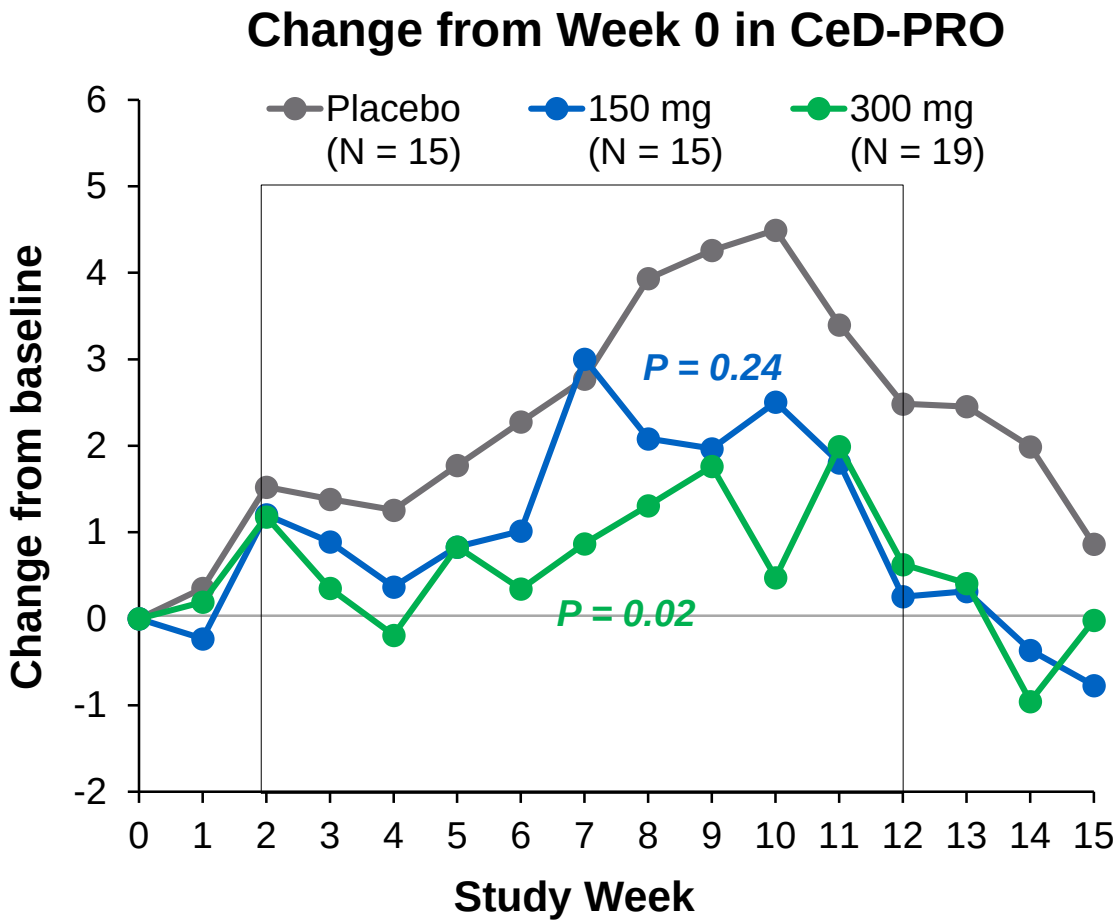


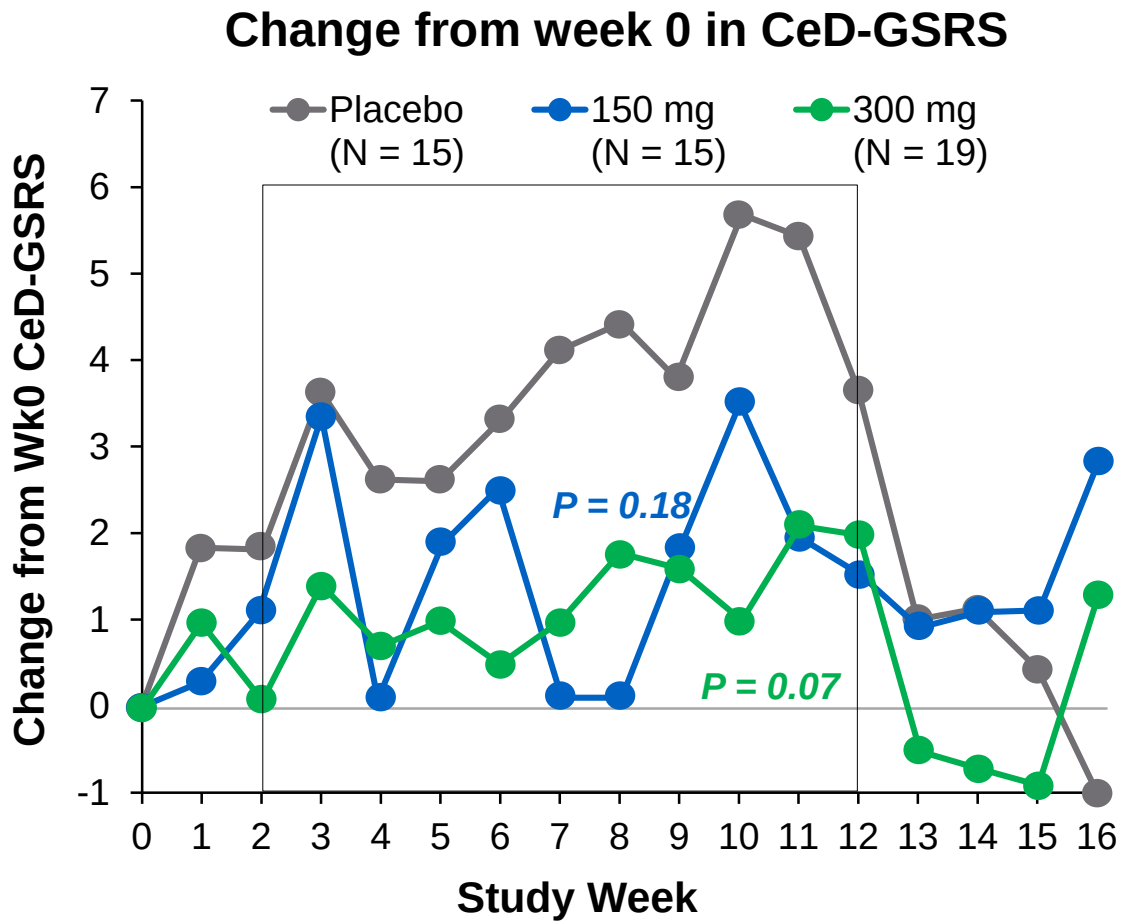


EFFECT OF AMG 714 ON GLUTEN-TRIGGERED SYMPTOMS:

CED-PRO (CELIAC DISEASE PATIENT REPORTED OUTCOME) AND CED-GSRS (CELIAC DISEASE GASTROINTESTINAL SYMPTOM RATING SCALE)

PP1: High-dose gluten challenge (2-4 g/day for 10 weeks). N = 49



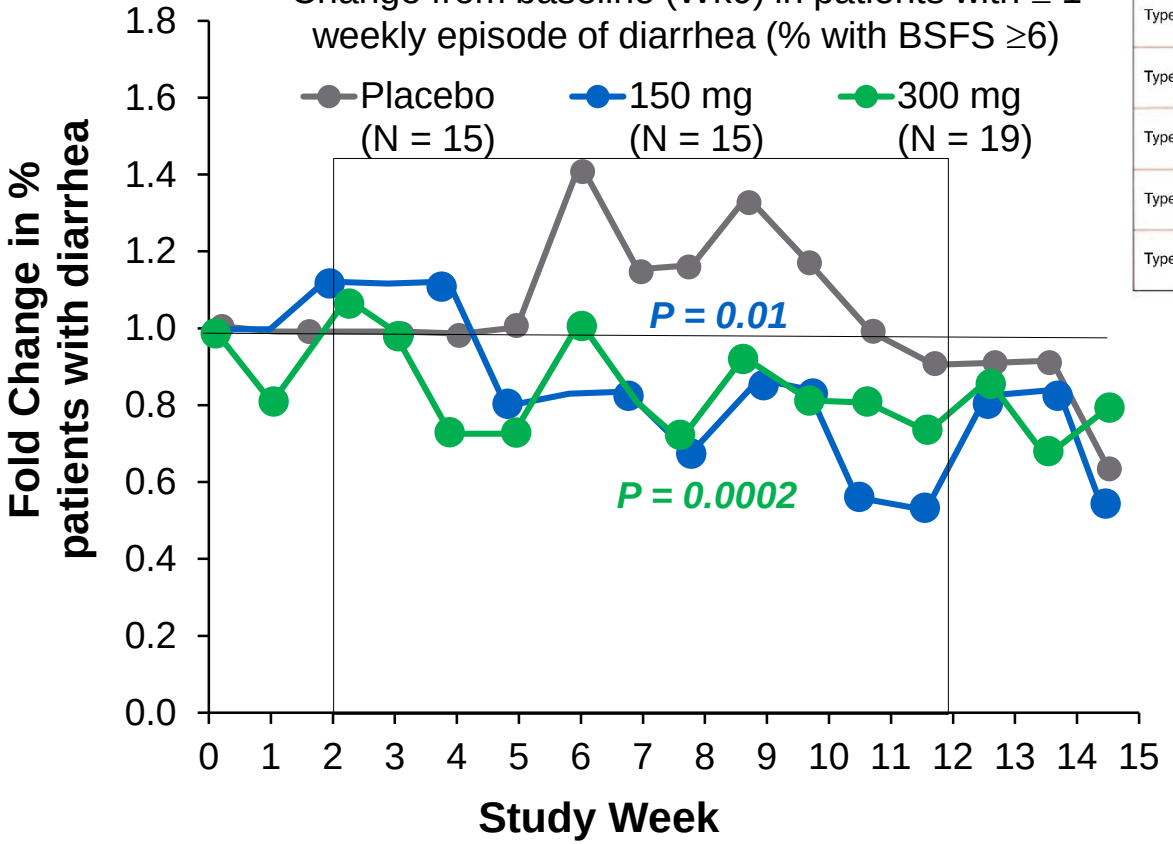


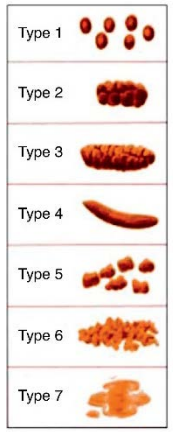
Notes: baseline is on-study Day 0-6.
P value for LS Means of individual active arms vs placebo, change from baseline over 12 weeks

EFFECT OF AMG 714 ON GLUTEN-TRIGGERED DIARRHEA AND PHYSICIAN GLOBAL ASSESSMENT

Weeks with Diarrhea according to the Bristol Stool Form Scale (BSFS)

Change from baseline (Wk0) in patients with ≥ 1 weekly episode of diarrhea (% with BSFS ≥6)





PGA – Physician's Global Assessment: PGA >2 (Disease Activity)

Proportion of subjects with PGA >2 on Wk 12: 33% in the placebo group, compared with:

- 13.3% in the AMG 714 150 mg group (***p = 0.39***)
- 0% in the AMG 714 300 mg group (***p = 0.01***)

No patient in the 300 mg group was found by the PI to have disease activity clinically at week 12 despite the high-dose gluten challenge.

PP1: **High-dose gluten challenge (2-4 g/day for 10 weeks).** N = 49

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CONCLUSIONS:

AMG 714 IS A PROMISING EXPERIMENTAL THERAPY FOR GLUTEN-FREE DIET NON-RESPONSIVE CELIAC DISEASE

- **Proof-of-mechanism: IL-15 plays a role in the pathophysiology of celiac disease**
- **Proof-of-concept: consistent efficacy signals for AMG 714 300 mg SC across multiple endpoints (e.g., symptoms, gut inflammatory cells, physician global assessment)**
- **Acceptable safety profile (no SAEs) and immunogenicity**
- **Favorable PK**

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AMG 714 (ANTI-IL 15 MAB) HALTS THE PROGRESSION OF ABERRANT INTRAEPITHELIAL LYMPHOCYTES IN REFRACTORY CELIAC DISEASE TYPE II (RCD –II): A PHASE 2A, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY EVALUATING AMG 714 IN ADULT PATIENTS WITH RCD-II/PRE-EATL

CHRISTOPHE CELLIER, GERD BOUMA, TOM VAN GILS, SHERINE KHATER, GEORGIA MALAMUT, LAURA CRESPO, PEKKA COLLIN, PETER GREEN, SHEILA CROWE, WAYNE TSUJI, FRANCISCO LEON, CHRIS MULDER DAVID SANDERS, VALERIE BYRNE, KNUT LUNDIN, MICHAEL SCHUMAN

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DIAGNOSIS OF REFRACTORY CELIAC DISEASE TYPE 2 (PRE-EATL, *IN SITU* LYMPHOMA)

CLASSIFICATION OF RCD

Based on characterization of the intraepithelial lymphocytes (IELs)

- **TYPE I**

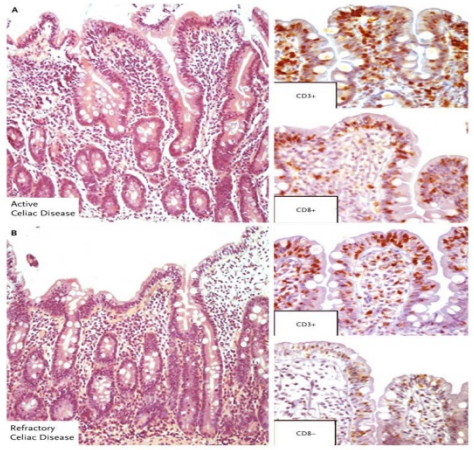
normal IEL surface CD3+, CD8+

- **TYPE II:**

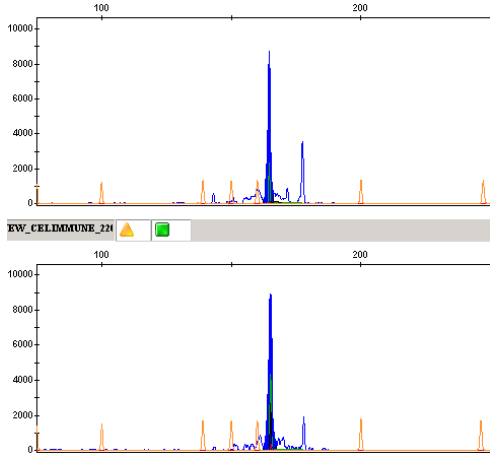
aberrant IEL (IHC, Flow and PCR)

- cytoplasmic CD3+,
- surface markers CD3-, CD8-
- clonal TCRγ gene rearrangement

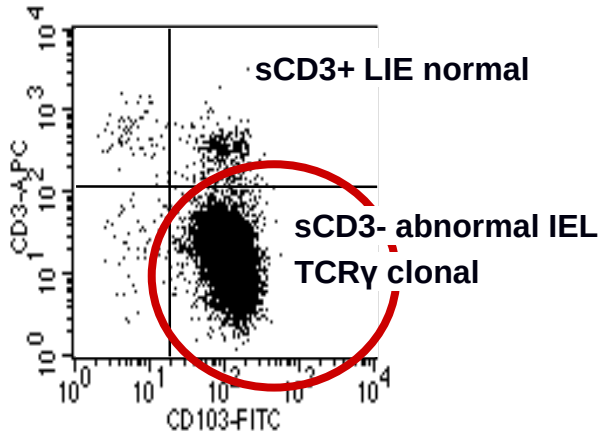
Cryptic T cell lymphoma (Pre-EATL : death ~50% at 5 years)



CD3+/CD8- (IHC)



Clonal peak PCR



Flow cytometry (Gold standard Diagnostic test)

Cellier, *Lancet*. 2000.

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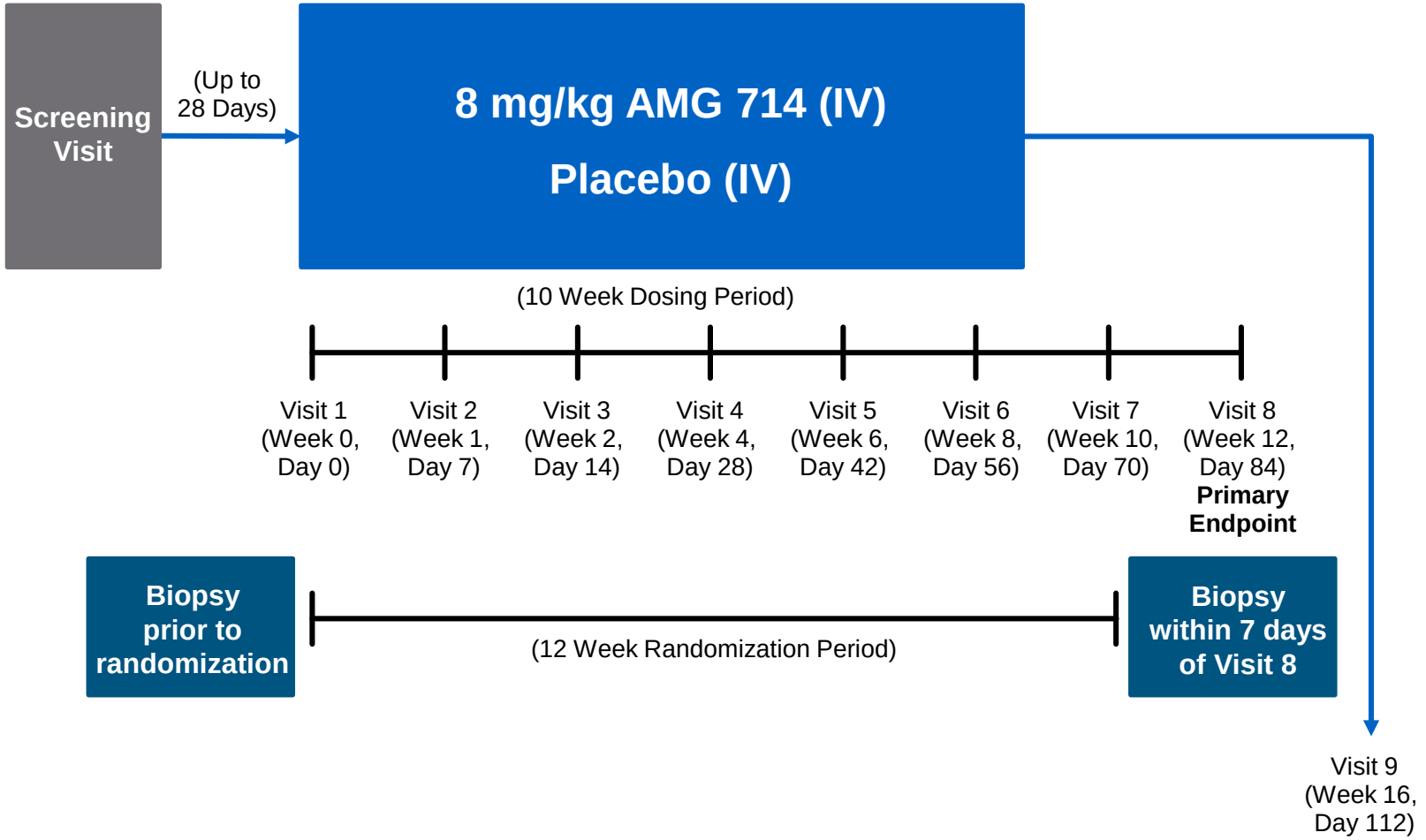
IL-15 INHIBITION IN RCD-II: PROOF OF CONCEPT STUDY CELIM-RCD-002 (MULTICENTER PROSPECTIVE TRIAL)

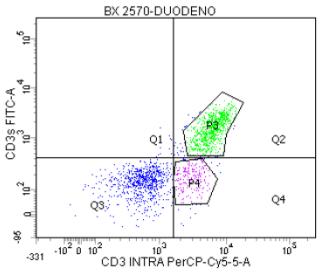


Populations:

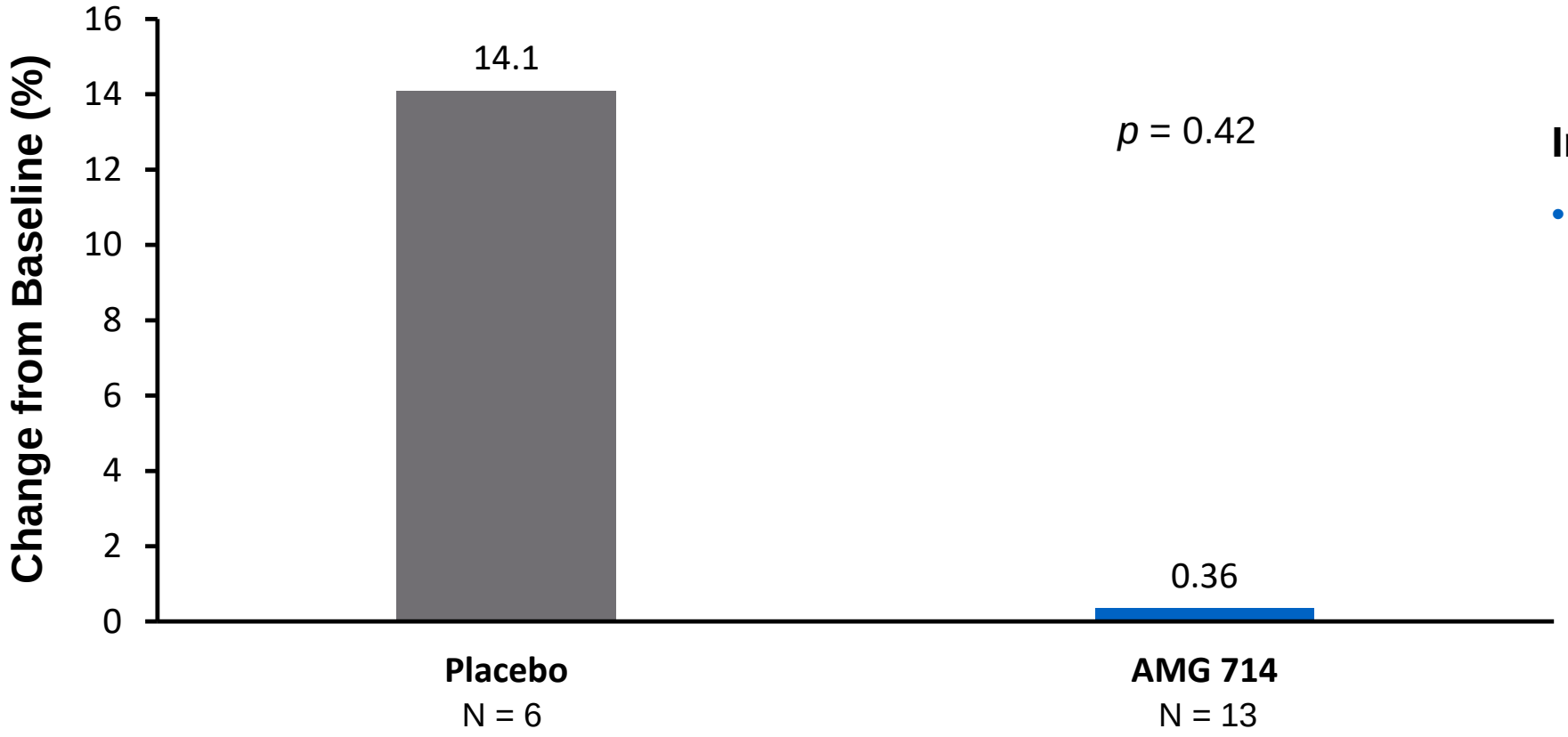
- *Intent to Treat (ITT): all randomized subjects (N = 28). All received study drug*
- *Per Protocol (PP): evaluable biopsy at baseline and week 12 (N = 26)*
- **Pure RCD-II: ad hoc population, strict definition of RCD-II (monoclonal, classic IEL phenotype; N = 19)**

Power: Empirical sample size, not based on statistical power considerations (no prior RCD-II 12-week data).

AMG 714 LIMITS DEVELOPMENT OF ABERRANT INTRAEPITHELIAL LYMPHOCYTES (AIEL)



Pure RCD-II: Relative (%) Change from Baseline in aIELs vs Total IELs

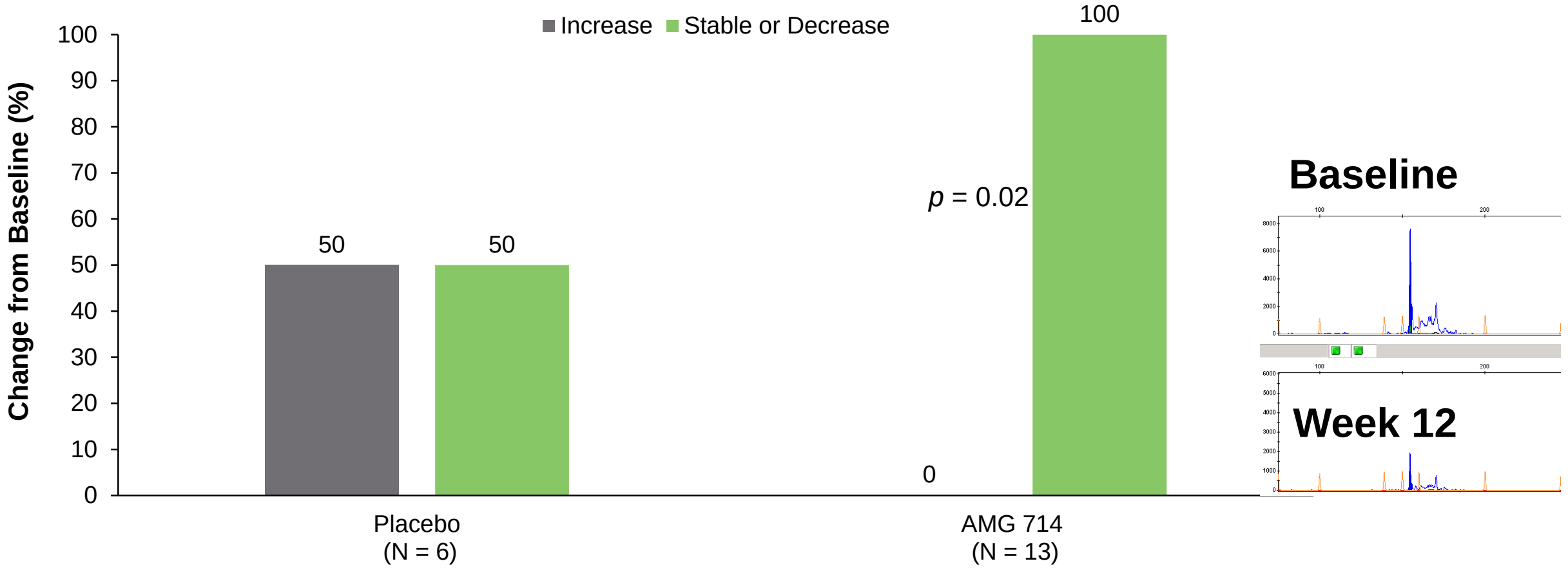


Immunological Response 1

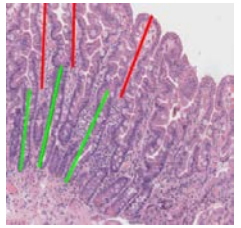
- **% of aberrant IEL vs total IEL by Flow Cytometry, Baseline to Week 12- Primary efficacy endpoint (not met)**

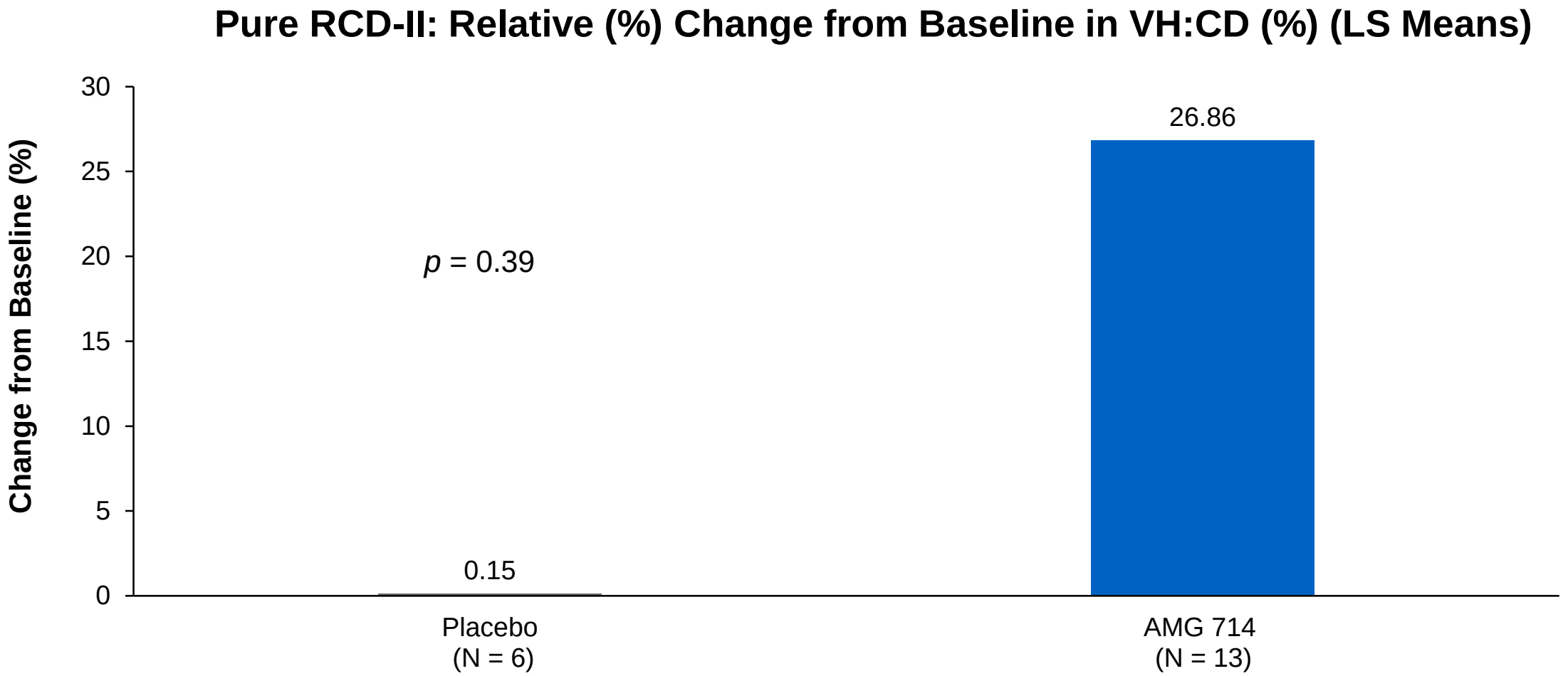
AMG 714 PREVENTS INCREASE IN IEL TCR CLONALITY IN RCD-II/PRE-EATL

Pure RCD-II: TcR Clonality, Change from Baseline to Week 12 (% Patients and Change in TcR Clonality)

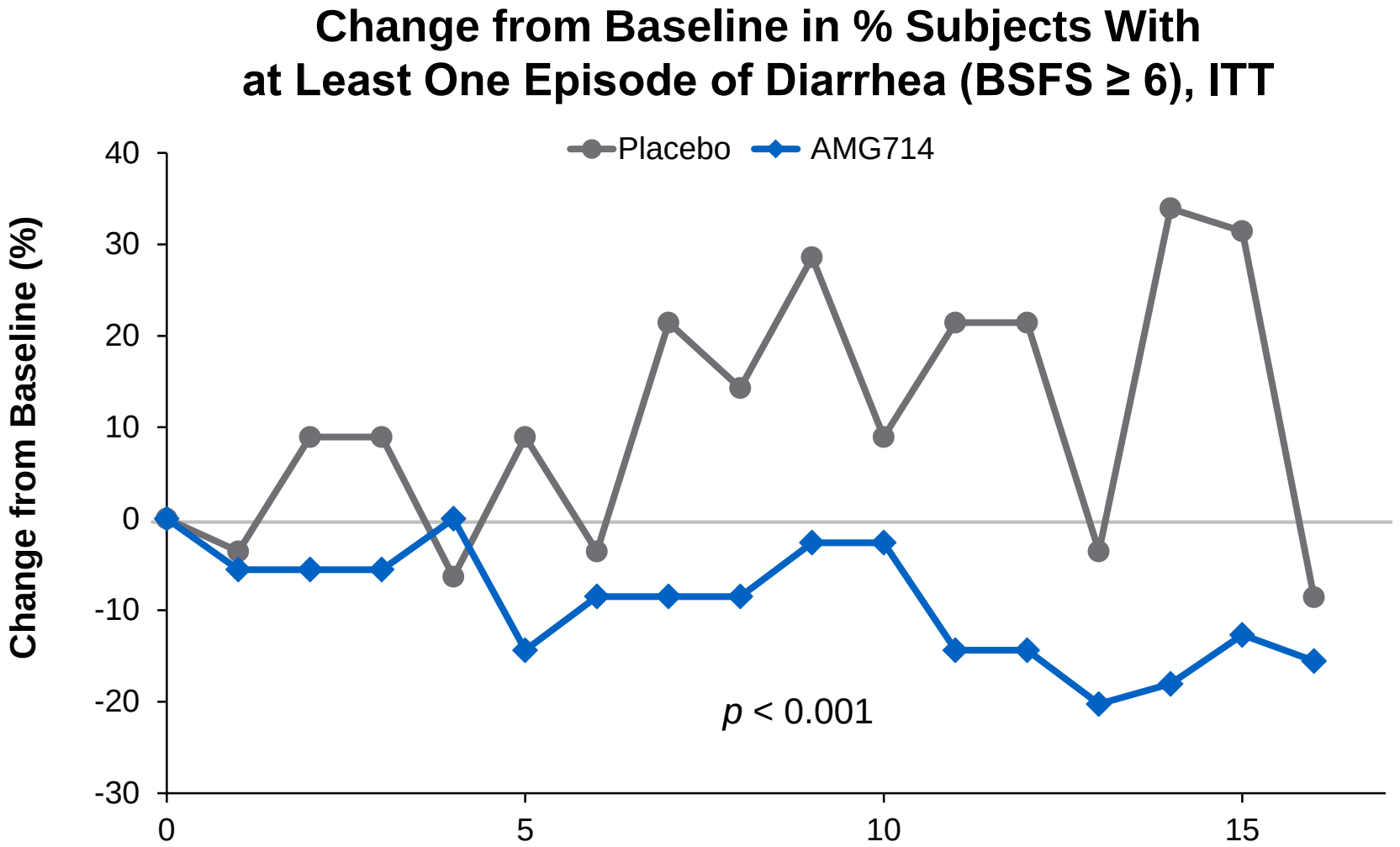


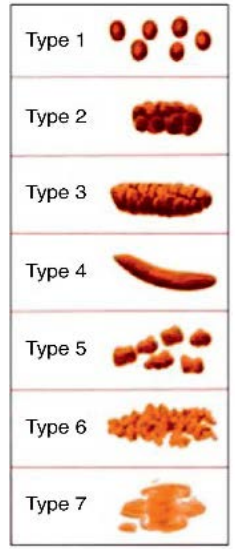
AMG 714 IMPROVES INTESTINAL HISTOLOGY IN RCD-II





AMG 714 REDUCES DIARRHEA, AS MEASURED BY BRISTOL STOOL FORM SCALE (BSFS)





CONCLUSIONS: AMG 714 (ANTI-IL15 MAB) IS A PROMISING EXPERIMENTAL THERAPY FOR RCD-II/PRE-EATL

- **Proof-of-Mechanism: IL-15 plays a role in the pathophysiology of RCD-II**
- **Proof-of-Concept: clinically meaningful differences**
- **Consistent favorable clinically-meaningful results across endpoints. Statistically significant results for AMG 714 8 mg/kg on symptoms (BSFS/diarrhea) and progression of TcR Clonality.**
- **Acceptable safety profile in this very sick population.**
- **No immunogenicity.**
- **Weaknesses: short time follow-up and steroids interference for IEL count**
- **Need for longer duration and larger studies**
- **Hope for preventing lymphoma in celiac disease**

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CONCLUSION: EXPERIMENTAL THERAPIES IN CD AND RCD-II

- Multiple projects on-going to develop medications for celiac and refractory celiac disease
  - Medication(s) could be available in the next 3-5 years (Adjunct to GFD)
- Clinical trials are feasible (with and without gluten challenge)
  - Essential to measure gluten consumption, also in basic research
- > 2,500 patients (heroes) have participated in investigational medication trials world-wide
  - We need volunteers to test these experimental medications
  - Thank you to all the patient support groups

THANK YOU TO ALL CELIAC PATIENTS

WHO MAKE RESEARCH POSSIBLE!

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