Efficacy and Safety of Dupilumab in Adult and Adolescent Patients With Eosinophilic Esophagitis: Results From Part A of a Randomized, Placebo-Controlled, Three-Part, Phase 3 Study

Evan S. Dellon[1], Marc E. Rothenberg[2], Margaret H. Collins[2], Ikuo Hirano[3], Mirna Chehade[4], Albert J. Bredenoord[5], Alfredo J. Lucendo[6], Jonathan M. Spergel[7], Qiong Zhao[8], Jennifer D. Hamilton[8], Bethany Beazley[8], Isabelle Guillemin[9], Siddhesh Kamat[8], Marcella Ruddy[8], Elizabeth Laws[10], Bolanle Akinlade[8], Nikhil Amin[8], Allen Radin[8], Brad Shumel[8]*, Jennifer Maloney[8]*

[1]University of North Carolina School of Medicine, Chapel Hill, NC, USA; [2]Cincinnati Children's Hospital Medical Center and University of Cincinnati College of Medicine, Cincinnati, OH, USA; [3]Northwestern University Feinberg School of Medicine, Chicago, IL, USA; [4]Mount Sinai Center for Eosinophilic Disorders, Icahn School of Medicine at Mount Sinai, New York, NY, USA; [5]Amsterdam University Medical Center, Amsterdam, Netherlands; [6]Hospital General de Tomelloso, Tomelloso, Spain; [7]Children's Hospital of Philadelphia, Philadelphia, PA, USA; [8]Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA; [9]Sanofi, Chilly-Mazarin, France; [10]Sanofi, Bridgewater, NJ, USA; *co-last authors

BACKGROUND

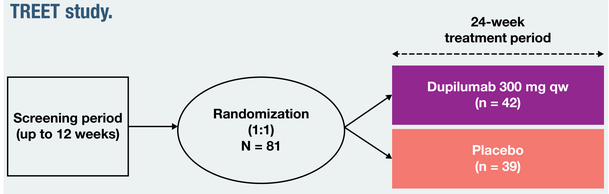
- Eosinophilic esophagitis (EoE) is a chronic, type 2 inflammatory disease of the esophagus, characterized by eosinophilic inflammation leading to symptoms of esophageal dysfunction[1–4]
- Current therapeutic approaches include chronic dietary elimination, swallowed topical corticosteroids, and esophageal dilation
- Dupilumab is a fully human VelocImmune®-derived[5,6] monoclonal antibody that blocks the shared receptor component for interleukin (IL)-4 and IL-13, thus inhibiting signaling of both IL-4 and IL-13, key and central drivers of type 2 inflammation in multiple diseases, including EoE[7,8]
- In a previous phase 2, proof-of-concept trial in adults with EoE, dupilumab demonstrated substantial improvements compared with placebo in clinical, histologic, and endoscopic aspects of the disease and was generally well tolerated[9]

OBJECTIVE

Part A of the 3-part, randomized, double-blind, placebo-controlled phase 3 LIBERTY EoE TREET study (NCT03633617) evaluated the efficacy and safety of weekly (qw) dupilumab 300 mg vs placebo in adult and adolescent EoE patients for 24 weeks

METHODS

Figure 1. Study design showing Part A of the dupilumab EoE phase 3 TREET study.



Part A of the TREET study enrolled 81 patients aged ≥ 12 years fulfilling the following criteria

- A documented diagnosis of EoE by endoscopic biopsy and unresponsive to 8-week treatment with high-dose proton-pump inhibitors; a peak eosinophil count of ≥ 15 eosinophils (eos)/high-power field (hpf) in at least 2 of the 3 esophageal regions sampled; no other causes of eosinophilic gastrointestinal disease; stable diet; a history of ≥ 2 episodes of dysphagia per week over 4 weeks; ≥ 4 episodes of dysphagia in the 2 weeks prior to baseline visit, ≥ 2 of which required medical attention; and a Dysphagia Symptom Questionnaire (DSQ) score ≥ 10

Study assessments

- **Co-primary endpoints**
  - Proportion of patients achieving peak esophageal intraepithelial eosinophil count of ≤ 6 eos/hpf at Week 24
  - Absolute change in DSQ score from baseline to Week 24

METHODS (CONT.)

- **Key secondary endpoints**
  - Percent change in peak esophageal intraepithelial eosinophil count from baseline to Week 24
  - Absolute change in EoE-Histological Scoring System (HSS) grade score from baseline to Week 24
  - Absolute change in EoE-HSS stage score from baseline to Week 24
  - Absolute change in EoE- Endoscopic Reference Score (EREFS) from baseline to Week 24
- **Other secondary endpoints**
  - Proportion of patients achieving peak esophageal intraepithelial eosinophil count of < 15 eos/hpf at Week 24
  - Normalized enrichment score (NES) for the relative change from baseline to Week 24 in the EoE diagnostic panel (EDP) transcriptome signature
  - NES for the relative change from baseline to Week 24 in the type 2 inflammation transcriptome signature
  - Proportion of patients achieving peak esophageal intraepithelial eosinophil count of ≤ 1 eos/hpf at Week 24

RESULTS

Table 1. Baseline demographics and clinical characteristics.

	Placebo (n = 39)	Dupilumab 300 mg qw (n = 42)	Total (N = 81)
Age, mean (SD), years	28.8 (12.5)	33.9 (15.5)	31.5 (14.3)
Female sex, n (%)	18 (46.2)	14 (33.3)	32 (39.5)
Duration of EoE, mean (SD), years	4.77 (4.6)	5.23 (4.2)	5.01 (4.3)
History of prior use of swallowed topical corticosteroids for EoE, n (%)	31 (79.5)	29 (69.0)	60 (74.1)
Topical corticosteroid for EoE effective, n (%)			
Yes	10 (25.6)	6 (14.3)	16 (19.8)
No	21 (53.8)	23 (54.8)	44 (54.3)
History of esophageal dilations, n (%)	17 (43.6)	18 (42.9)	35 (43.2)
Number of prior esophageal dilations, mean (SD)	2.0 (1.4)	1.9 (1.2)	2.0 (1.3)
Food elimination at screening, n (%)	16 (41.0)	17 (40.5)	33 (40.7)
Baseline DSQ score, mean (SD)	35.1 (12.11)	32.2 (12.7)	33.6 (12.4)
Baseline HSS grade score, mean (SD)	1.32 (0.5)	1.26 (0.4)	1.29 (0.4)
Baseline HSS stage score, mean (SD)	1.38 (0.4)	1.30 (0.3)	1.34 (0.4)
Baseline EREFS total score including stricture (proximal and distal regions), mean (SD)	6.0 (2.4)	6.5 (3.2)	6.3 (2.8)
Baseline peak eosinophils count in 3 regions, mean (SD), eos/hpf	96.5 (54.7)	82.6 (41.0)	89.3 (48.3)
Baseline blood peripheral eosinophils, mean (SD), Giga/L	0.50 (0.3)	0.43 (0.2)	0.46 (0.2)

All percentages are based on the number of full analysis set patients in each treatment group as the denominator. DSQ: score ranges from 0 to 84, with higher scores indicating more severe/more frequent dysphagia. HSS: scale ranges from 0 to 3, with higher scores indicating more severe histologic findings. EREFS: score ranges from 0 to 18, with higher scores indicating higher severity/presence. SD, standard deviation.

RESULTS (CONT.)

Figure 2. Coprimary endpoints. (A) Absolute change in DSQ total score from baseline. (B) Proportion of patients achieving peak esophageal intraepithelial eosinophil counts of ≤ 6 eos/hpf at Week 24.

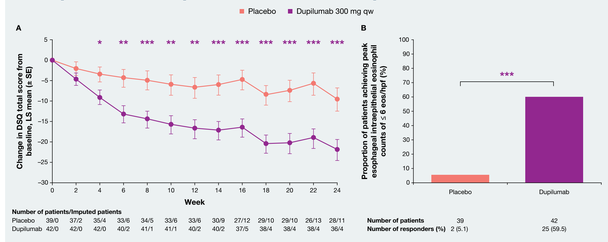
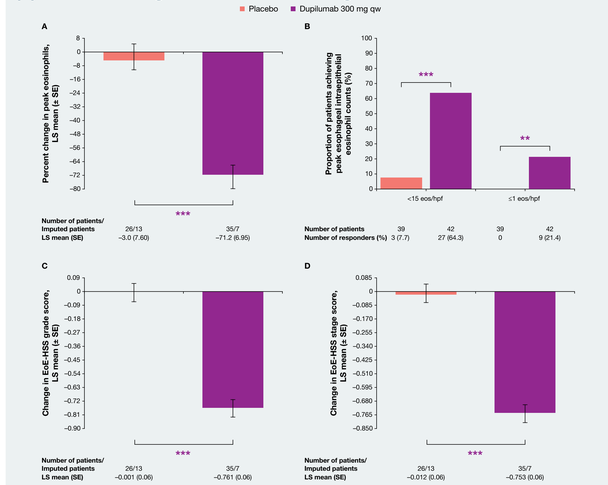


Figure 3. Effect of dupilumab on histologic endpoints. (A) Percent change in peak eosinophils from baseline. (B) Proportion of patients achieving peak esophageal intraepithelial eosinophil counts of < 15 eos/hpf or ≤ 1 eos/hpf. (C) Absolute change in EoE-HSS mean grade score from baseline. (D) Absolute change in EoE-HSS mean stage score from baseline.



** $P < 0.01$; *** $P < 0.001$. SE, standard error.

Figure 4. Effect of dupilumab on endoscopic endpoints. Absolute change in EREFS total score from baseline.

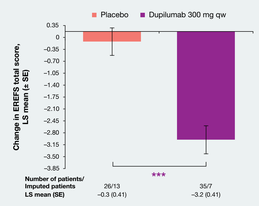
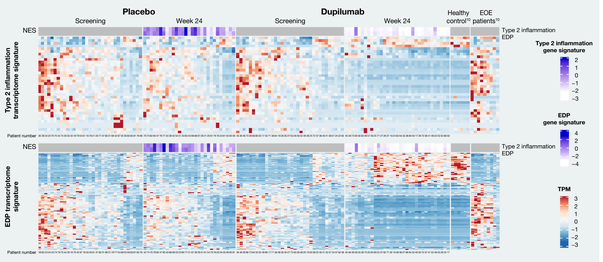


Table 2. Overall safety.

Event, n (%)	Placebo (n = 39)	Dupilumab 300 mg qw (n = 42)
Deaths	0	0
TEAEs	32 (82.1)	36 (85.7)
TE SAEs	0	2 (4.8)[a]
AEs leading to treatment discontinuation	0	1 (2.4)
AEs in ≥ 10% patients		
Injection-site reaction (PT)	4 (10.3)	7 (16.7)
Nasopharyngitis	4 (10.3)	5 (11.9)
Injection-site erythema	5 (12.8)	3 (7.1)
Headache	4 (10.3)	2 (4.8)
Rash	4 (10.3)	0
Conjunctivitis (broad CMQ)[b]	1 (2.6)	2 (4.8)

[a]Abdominal pain and uterine polyp – assessed as not related to study medication. [b]16 terms: Conjunctivitis, conjunctivitis allergic, conjunctivitis bacterial, conjunctivitis viral, atopic keratoconjunctivitis, blepharitis, dry eye, eye irritation, eye pruritus, lacrimation increased, eye discharge, foreign body sensation in eyes, photophobia, xerophthalmia, ocular hyperemia, conjunctival hyperemia. AE, adverse event; CMQ, Customized MedDRA Queries; MedDRA, Medical Dictionary for Regulatory Activities; PT, MedDRA Preferred Term; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Figure 5. Effect of dupilumab on transcriptomic endpoints. (A) The type 2 inflammation transcriptome signature. (B) EDP transcriptome signature.



Change from baseline in mean gene expression of the 3 esophageal regions for each patient per time point was examined, and NES averaged for each patient using an in-house curated set of type 2 inflammatory genes or the EDP. TPM, transcripts per million.

CONCLUSIONS

- **Dupilumab vs placebo significantly improved clinical, endoscopic, and histologic measures of EoE, meeting both co-primary endpoints and all key secondary endpoints**
  - **This is the first time a phase 3 trial with a biologic has reported improvement in patients' ability to swallow food, as assessed by the DSQ**
  - **Esophageal eosinophil counts were reduced to ≤ 6 eos/hpf in 60% of dupilumab-treated patients vs 5% of placebo-treated patients**
  - **Dupilumab suppressed expression of genes associated with EoE and with type 2 inflammation, indicating molecular reversal of disease**
- **Dupilumab was generally well tolerated with no new safety signals observed**
- **The ongoing part B portion of the trial is evaluating another dupilumab dosing regimen; part C will provide 52-week data for both dose regimens**

References: 1. Furuta GT, Aceves SS. J Allergy Clin Immunol. 2017;139:1131-4. 2. Liacouras CA, et al. J Allergy Clin Immunol. 2011;128:3-20. 3. DeBrosse CW, et al. J Allergy Clin Immunol. 2011;128;132-8. 4. Falk GW. Gastroenterol Clin North Am. 2014;43;231-42. 5. Macdonald LE, et al. Proc Natl Acad Sci U S A. 2014;111:5147-52. 6. Murphy AJ, et al. Proc Natl Acad Sci U S A. 2014;111:5153-8. 7. Gandhi NA, et al. Nat Rev Drug Discov. 2016;15:35-50. 8. Le Floc'h A, et al. Allergy. 2020;75:1188-204. 9. Hirano I, et al. Gastroenterology. 2020;158:111-22. 10. Sherrill JD, et al. Genes Immun. 2014;15;361-9.

Acknowledgments and funding sources: Data first presented at the United European Gastroenterology (UEG) Week Virtual Congress 2020; October 11–13, 2020. Critical feedback on the abstract provided by Leda P. Mannent of Sanofi, Chilly-Mazarin, France. Research sponsored by Sanofi and Regeneron Pharmaceuticals, Inc. ClinicalTrials.gov Identifier: NCT02379052. Medical writing/editorial assistance was provided by Anthony Gaba, PhD, of Excerpta Medica, and was funded by Sanofi Genzyme and Regeneron Pharmaceuticals, Inc., according to the Good Publication Practice guideline.

Disclosures: Dellon ES: Abbott, Adare Pharma Solutions, Aimmune Therapeutics, Allakos, Amgen, Arena Pharmaceuticals, AstraZeneca, Biorasi, BMS, Calypso Biotech, Eli Lilly, EsoCap, GSK, Gossamer Bio, Parexel, Receptos/BMS, Regeneron Pharmaceuticals, Inc., Robarts Clinical Trials, Salix Pharmaceuticals, Shire/Takeda – consultant; Adare Pharma Solutions, Allakos, BMS, GSK, Meritage Pharma, Miraca Life Sciences, Nutricia, Receptos/BMS, Regeneron Pharmaceuticals, Inc., Shire/Takeda – research funding; Allakos, Banner Pharmaceuticals, Holoclara – educational grant. **Rothenberg ME:** Allakos, AstraZeneca, BMS, ClostraBio, PulmOne, Spoon Guru – consultant; ClostraBio, PulmOne, Spoon Guru – equity interest; Teva Pharmaceuticals – royalties from reslizumab; Mapi Research Trust – royalties from PEESSv2; UpToDate – royalties; inventor of patents owned by Cincinnati Children's Hospital. **Collins MH:** Allakos, Arena Pharmaceuticals, AstraZeneca, BMS, Calypso Biotech, EsoCap, GSK, Regeneron Pharmaceuticals, Inc., Shire – consultant; Receptos/BMS, Regeneron Pharmaceuticals, Inc., Shire – research funding. **Hirano I:** Adare Pharma Solutions, Receptos/BMS, Regeneron Pharmaceuticals, Inc., Shire – consultant; Meritage, Receptos/BMS, Regeneron Pharmaceuticals, Inc., Shire – research funding. **Chehade M:** Adare Pharma Solutions, Allakos, AstraZeneca, Nutricia, Regeneron Pharmaceuticals, Inc., Shire – consultant; Allakos, Regeneron Pharmaceuticals Inc., Shire – research funding; Medscape, Nutricia – honoraria for lectures. **Bredenoord AJ:** Arena Pharmaceuticals, AstraZeneca, Calypso Biotech, Dr. Falk Pharma, EsoCap, Gossamer Bio, Laborie, Medtronic, RB Pharma, Regeneron Pharmaceuticals, Inc., Robarts Clinical Trials – consultant; Bayer, Nutricia, SST – research funding; SST – equity interest. **Lucendo AJ:** EsoCap, Dr. Falk Pharma – consultant; Dr. Falk Pharma, Regeneron Pharmaceuticals, Inc. – research funding. **Spergel JM:** Allakos, DBV Technologies, Novartis, Regeneron Pharmaceuticals, Inc., Shire, Takeda –consultant; DBV Technologies, Regeneron Pharmaceuticals, Inc. – grant support. **Zhao Q, Hamilton JD, Beazley B, Kamat S, Ruddy M, Akinlade B, Amin N, Radin A, Shumel B, Maloney J:** Regeneron Pharmaceuticals, Inc. – employees and shareholders. **Guillemin I:** Sanofi – prior employee, may hold stock and/or stock options in the company. **Mannent LP, Laws E:** Sanofi – employees, may hold stock and/or stock options in the company.

Presented at the 4th Annual Gastroenterology & Hepatology Advanced Practice Providers Conference; Las Vegas, NV, USA; September 9-11, 2021.