

UC San Diego

UC San Diego Previously Published Works

Title

Heterogeneity in Clinical, Endoscopic, and Histologic Outcome Measures and Placebo Response Rates in Clinical Trials of Eosinophilic Esophagitis: A Systematic Review

Permalink

<https://escholarship.org/uc/item/1nj2s75w>

Journal

Clinical Gastroenterology and Hepatology, 16(11)

ISSN

1542-3565

Authors

Ma, Christopher
van Rhijn, Bram D
Jairath, Vipul
et al.

Publication Date

2018-11-01

DOI

10.1016/j.cgh.2018.06.005

Peer reviewed

Accepted Manuscript

Heterogeneity in Clinical, Endoscopic, and Histologic Outcome Measures and Placebo Response Rates in Clinical Trials of Eosinophilic Esophagitis: A Systematic Review

Christopher Ma, Bram D. van Rhijn, Vipul Jairath, Tran M. Nguyen, Claire E. Parker, Seema S. Aceves, Glenn T. Furuta, Sandeep K. Gupta, David A. Katzka, Ekaterina Safroneeva, Alain M. Schoepfer, Alex Straumann, Jonathan M. Spergel, Rish K. Pai, Brian G. Feagan, Ikuo Hirano, Evan S. Dellon, Albert J. Bredenoord

PII: S1542-3565(18)30610-4
DOI: [10.1016/j.cgh.2018.06.005](https://doi.org/10.1016/j.cgh.2018.06.005)
Reference: YJCGH 55903

To appear in: *Clinical Gastroenterology and Hepatology*
Accepted Date: 7 June 2018

Please cite this article as: Ma C, van Rhijn BD, Jairath V, Nguyen TM, Parker CE, Aceves SS, Furuta GT, Gupta SK, Katzka DA, Safroneeva E, Schoepfer AM, Straumann A, Spergel JM, Pai RK, Feagan BG, Hirano I, Dellon ES, Bredenoord AJ, Heterogeneity in Clinical, Endoscopic, and Histologic Outcome Measures and Placebo Response Rates in Clinical Trials of Eosinophilic Esophagitis: A Systematic Review, *Clinical Gastroenterology and Hepatology* (2018), doi: [10.1016/j.cgh.2018.06.005](https://doi.org/10.1016/j.cgh.2018.06.005).

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.



1 **Heterogeneity in Clinical, Endoscopic, and Histologic Outcome**
2 **Measures and Placebo Response Rates in Clinical Trials of**
3 **Eosinophilic Esophagitis: A Systematic Review**

4
5 **Short Title:** Outcomes in EoE RCTs
6

7 **Authors:**

8 Christopher Ma^{1,2}, Bram D. van Rhijn³, Vipul Jairath^{2,4,5}, Tran M. Nguyen², Claire E. Parker²,
9 Seema S. Aceves^{6,7,8}, Glenn T. Furuta⁹, Sandeep K. Gupta¹⁰, David A. Katzka¹¹, Ekaterina
10 Safroneeva¹², Alain M. Schoepfer¹³, Alex Straumann¹⁴, Jonathan M. Spergel^{15,16}, Rish K. Pai¹⁷,
11 Brian G. Feagan^{2,4,5}, Ikuo Hirano¹⁸, Evan S. Dellon¹⁹, and Albert J. Bredenoord²⁰
12

13 **Affiliations:**

14 ¹ Division of Gastroenterology and Hepatology, University of Calgary, Calgary, Alberta, Canada

15 ³ Robarts Clinical Trials Inc., London, Ontario, Canada

16 ³ Department of Dermatology and Allergology, University Medical Center Utrecht, Utrecht, The
17 Netherlands

18 ⁴ Department of Medicine, Western University, London, Ontario, Canada

19 ⁵ Department of Epidemiology and Biostatistics, Western University, London, Ontario, Canada

20 ⁶ Division of Allergy and Immunology, Department of Pediatrics, University of California San
21 Diego, La Jolla, California, United States

22 ⁷ Division of Allergy and Immunology, Department of Medicine, University of California San
23 Diego, La Jolla, California, United States

24 ⁸ Rady Children's Hospital San Diego, San Diego, California, United States

*Ma et al.***Outcomes in EoE RCTs**

25 ⁹ Division of Gastroenterology, Children's Hospital of Colorado, University of Colorado School of
26 Medicine, Aurora, Colorado, United States

27 ¹⁰ Division of Pediatric Gastroenterology, Hepatology and Nutrition, University of Illinois College
28 of Medicine, Peoria, Illinois, United States

29 ¹¹ Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, Minnesota, United
30 States

31 ¹² Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland

32 ¹³ Division of Gastroenterology and Hepatology, Centre Hospitalier Universitaire Vaudois
33 (CHUV) and University of Lausanne, Lausanne, Switzerland

34 ¹⁴ Division of Gastroenterology and Hepatology, Department of Internal Medicine, University
35 Hospital Zurich, Ramistrasse 100, 8091 Zurich, Switzerland

36 ¹⁵ Department of Pediatrics, Division of Allergy and Immunology, The Children's Hospital of
37 Philadelphia, Philadelphia, Pennsylvania, United States

38 ¹⁶ Institute for Immunology, Perelman School of Medicine at the University of Pennsylvania,
39 Philadelphia, Pennsylvania, United States

40 ¹⁷ Department of Pathology and Laboratory Medicine, Mayo Clinic Arizona, Scottsdale, Arizona,
41 United States

42 ¹⁸ Division of Gastroenterology and Hepatology, Northwestern University Feinberg School of
43 Medicine, Chicago, Illinois, United States

44 ¹⁹ Center for Esophageal Disease and Swallowing, Division of Gastroenterology and
45 Hepatology, University of North Carolina School of Medicine, Chapel Hill, North Carolina, United
46 States

47 ²⁰ Department of Gastroenterology and Hepatology, Academic Medical Centre, Amsterdam, The
48 Netherlands

49

50 **Grant Support:** Christopher Ma is supported by a Clinician Fellowship from
51 the Canadian Association of Gastroenterology and the
52 Canadian Institutes of Health Research
53

54 **Abbreviations:** COS (core outcome set), COMET (Core Outcome
55 Measures in Effectiveness Trials), DP (distensibility
56 plateau), EEsAI (Eosinophilic Esophagitis Activity Index),
57 EMA (European Medicines Agency), EoE (eosinophilic
58 esophagitis), eos (eosinophils), EoE-HSS (EoE Histology
59 Scoring System), EREFS (EoE Endoscopic Reference
60 Score), FDA (Food and Drug Administration), FLIP
61 (functional lumen imaging probe), HPF (high power field),
62 IBD (inflammatory bowel disease), IL (interleukin), PPI
63 (proton pump inhibitor), PRO (patient-reported outcome),
64 RCT (randomised controlled trial), TGF (transforming
65 growth factor)
66

67 **Additional Keywords:** endoscopy; histology; patient-reported outcomes; placebo
68

69 **Correspondence:**
70 Dr. Albert J. Bredenoord, MD, PhD
71 Department of Gastroenterology and Hepatology
72 Academic Medical Centre
73 Room C2-325, PO Box 22700
74 1100 DE Amsterdam, the Netherlands
75 Email: a.j.bredenoord@amc.uva.nl
76 Fax: +31-20-6917033
77

78 **Disclosures:**
79
80 Christopher Ma has no conflicts of interest to declare.
81
82 Bram van Rhijn has no conflicts of interest to declare.
83
84 Vipul Jairath has received consulting fees from AbbVie, Sandoz, Takeda, Janssen, Robarts
85 Clinical Trials; speaker's fees from Takeda, Janssen, Shire, Ferring. Vipul Jairath is the Director
86 for Medical Research & Development at Robarts Clinical Trials.
87
88 Tran Nguyen is an employee of Robarts Clinical Trials
89
90 Claire Parker is an employee of Robarts Clinical Trials
91
92 Seema Aceves is a co-inventor of oral viscous budesonide (UCSD patented, licensed to Shire
93 Pharma), and has received consulting fees from Regeneron.
94
95 Glenn Furuta is the founder of EnteroTrack, has received royalties from UpToDate, and
96 consulting fees from Shire.
97
98 Sandeep Gupta has received consulting fees from Abbott, Allakos, Receptos, and QOL; and
99 research support from Shire.
100

101 David Katzka has received research support from Shire.

102
103 Ekaterina Safroneeva has received consulting fees from Celgene Corp., Regeneron
104 Pharmaceuticals Inc., and Novartis AG.

105
106 Alain Schoepfer has received consulting fees and/or speaker fees and/or research grants from
107 Adare Pharmaceuticals, Inc., AstraZeneca, AG, Switzerland, Aptalis Pharma, Inc., Dr. Falk
108 Pharma, GmbH, Germany, Glaxo Smith Kline, AG, Nestlé S. A., Switzerland, Receptos, Inc.
109 and Regeneron Pharmaceuticals, Inc.

110
111 Alex Straumann has no conflicts of interest to declare.

112
113 Jonathan Spergel has no conflicts of interest to declare.

114
115 Rish Pai has received consulting fees from Genentech.

116
117 Brian Feagan has received grant/research support from Millennium Pharmaceuticals, Merck,
118 Tillotts Pharma AG, AbbVie, Novartis Pharmaceuticals, Centocor Inc., Elan/Biogen, UCB
119 Pharma, Bristol-Myers Squibb, Genentech, ActoGenix, and Wyeth Pharmaceuticals Inc.;
120 consulting fees from Millennium Pharmaceuticals, Merck, Centocor Inc., Elan/Biogen, Janssen-
121 Ortho, Teva Pharmaceuticals, Bristol-Myers Squibb, Celgene, UCB Pharma, AbbVie, Astra
122 Zeneca, Serono, Genentech, Tillotts Pharma AG, Unity Pharmaceuticals, Albireo Pharma,
123 Given Imaging Inc., Salix Pharmaceuticals, Novonordisk, GSK, Actogenix, Prometheus
124 Therapeutics and Diagnostics, Athersys, Axcan, Gilead, Pfizer, Shire, Wyeth, Zealand Pharma,
125 Zyngeia, GiCare Pharma Inc., and Sigmoid Pharma; and speakers bureaux fees from UCB,
126 AbbVie, and J&J/Janssen. Brian Feagan is the Senior Scientific Director for Robarts Clinical
127 Trials.

128
129 Ikuo Hirano has received consulting fees from Receptos, Regeneron, Shire and Roche.

130
131 Evan Dellon has received research funding from Adare, Meritage, Miraca, Nutricia,
132 Celgene/Receptos, and Shire; has consulted for Adare, Alivio, Allakos, AstraZeneca, Banner,
133 Enumeral, Celgene/Receptos, GSK, Regeneron, and Shire, and has received educational
134 grants from Banner and Holoclara.

135
136 Albert Bredenoord has received research funding from Nutricia and Bayer and received speaker
137 and/or consulting fees from MMS, Dr Falk Pharma, Regeneron, Astellas, AstraZeneca, Bayer,
138 Norgine, Almirall and Allergan

139
140 Robarts Clinical Trials began in 1986 as an academic research unit within the Robarts Research
141 Institute which is affiliated with University Hospital and the University of Western Ontario. A
142 subsequent international (United States of America and Netherlands) expansion in 2012
143 necessitated establishment of a corporate entity to meet international federal/taxation
144 regulations. All profits from Robarts Clinical Trials, Inc. are directed towards academic research.
145 None of the authors with affiliation to Robarts Clinical Trials, Inc. have an equity position or any
146 shares in the corporation. Robarts Clinical Trials provides central endoscopy and histology
147 reading as a commercial service. Affiliated authors have not received specific individual
148 research support from Robarts Clinical Trials.

149
150 **Author Contributions:**

151

Ma *et al.***Outcomes in EoE RCTs**

152 CM, BDvR, VJ: study conception and design, data collection, data analysis, manuscript drafting,
153 manuscript editing

154 TMN, CEP: study conception and design, data collection, manuscript editing

155 SSA, GTF, SKG, DAK, ES, AMS, AS, JMS, RKP, BGF, IH, ESD: manuscript editing

156 AJB: study conception and design, manuscript editing

157 AJB is acting as the guarantor of the article.

158

Word Counts:

160 Abstract: 299

161 Manuscript: 3992

162 Manuscript with references: 5739

163 Tables: 4

164 Figures: 2

165 Supplemental Files: 3

166

167 **Version:** May 16, 2018

168

169 **Abstract**

170 *Background & Aims:* Agents are being developed for treatment of eosinophilic esophagitis
171 (EoE). However, it is not clear what outcome measures would best determine the efficacy and
172 safety of these agents in clinical trials. We performed a systematic review of outcomes used in
173 randomized placebo-controlled trials of EoE and we estimate the placebo response and rates of
174 remission.

175

176 *Methods:* We searched MEDLINE, Embase, CENTRAL, ClinicalTrials.gov, and the EU Clinical
177 Trials Register from inception through February 20, 2018 for randomized controlled trials of
178 pharmacologic therapies for EoE. Efficacy outcome definitions, measurement tools, and the
179 proportion of patients responding to placebo were collected and stratified by based on
180 histologic, endoscopic, and patient-reported outcomes.

181

182 *Results:* We analyzed data from 22 placebo-controlled trials, comprising 1112 patients with
183 EoE. Ten additional active registered trials were identified. Most published trials evaluated
184 topical corticosteroid therapy (13/22, 59.1%). Histologic outcomes measuring eosinophil density
185 and patient-reported outcomes were reported in 21/22 published trials (95.5%). No consistently
186 applied definitions of histologic or patient-reported response or remission were identified.
187 Endoscopic outcomes were described in 60% (12/20) of published trials. The EoE Endoscopic
188 Reference Score is the most commonly applied tool for describing changes in endoscopic
189 appearance. The median histologic response to placebo was 3.7% (range 0%-31.6%) and the
190 median rate of remission in patients given placebo was 0.0% (range 0%-11.0%). The median
191 patient-reported response to placebo was 14.4% (range 8.6%-77.8%) and rate of remission in
192 patients given placebo was 26.2% (range 13.2%-35.7%).

193

Ma *et al.***Outcomes in EoE RCTs**

194 *Conclusions:* In a systematic review of the literature, we found that no standardized definitions
195 of histologic, endoscopic, or patient-reported outcomes are used to determine whether
196 pharmacologic agents produce a response or remission in patients with EoE. A core outcome
197 set is needed to reduce heterogeneity in outcome reporting and facilitate trial interpretation and
198 comparison of results from trials.

199

200 *Keywords:*

201 esophagus, inflammation, drug, endoscopy, histology

202

203 **Background & Aims**

204 Eosinophilic esophagitis (EoE) is a chronic inflammatory condition characterized histologically
205 by eosinophilic infiltration and clinically by symptoms of esophageal dysfunction in the context of
206 an antigen-mediated immune response.¹ Consensus guidelines have established first-line
207 pharmacologic, dietary, and endoscopic treatment for EoE, emphasizing the role of topical
208 corticosteroids, dietary restriction, and endoscopic dilation targeted at improving patient
209 symptoms and reducing histologic eosinophil burden.^{2,3} Topical corticosteroids are the mainstay
210 of drug-based therapy, but there are no US Food and Drug Administration (FDA)-approved
211 treatments and only one orodispersible budesonide formulation has been approved by the
212 European Medicines Agency (EMA) for treatment of EoE.^{4,5} Accordingly, there is great interest
213 in therapeutic development in this field with multiple classes of agents under evaluation.

214
215 Several barriers to efficient drug development in EoE exist.⁶ Importantly, there is a lack of
216 standardized outcome measures for use in registration trials that can support labelling claims.
217 The FDA mandates that “clinically meaningful” endpoints that measure the way patients feel,
218 function, and survive be used.⁷ Therefore, analogous to randomised controlled trials (RCTs) in
219 inflammatory bowel disease (IBD), future EoE clinical trials are likely to incorporate coprimary
220 endpoints featuring both patient-reported outcomes (PROs) and objective inflammatory
221 measures. Nevertheless, there is uncertainty regarding the appropriateness of endpoint
222 definitions and the responsiveness of current disease activity indices in EoE⁸ and unsurprisingly,
223 there is lack of consensus on the type of outcomes to measure, the way these outcomes should
224 be defined, and the circumstances in which these outcomes should be assessed.⁹

225
226 Developing a core outcome set (COS) is thus a priority in EoE research. A COS is a consensus-
227 derived minimum set of outcomes that should be measured and reported in all clinical trials in a
228 given field.¹⁰ Adoption of a COS minimizes heterogeneity in reporting and potential publication

229 bias, improves the quality of evidence synthesis, and facilitates comparisons of interventions in
230 meta-analyses. COS development is a multi-step process that involves systematically reviewing
231 the literature to identify current trial endpoints, surveying affected stakeholders, and achieving
232 consensus.¹⁰ A similar COS development initiative is underway in IBD.^{11, 12} In addition to
233 selecting appropriate endpoints, understanding the placebo response in clinical trials is critical
234 for efficient drug development. Furthermore, this process facilitates accurate sample size
235 calculations and maximizes assay sensitivity for detecting true differences between active
236 comparator and placebo. Whilst placebo rates in other gastrointestinal disorders have been well
237 characterized,¹³⁻¹⁵ placebo rates and the determinants of the placebo response in EoE RCTs
238 require further evaluation. Hirano *et al.* have previously demonstrated in a phase 2 trial of
239 budesonide oral suspension that despite a placebo run-in period, symptom improvement
240 occurred in approximately one quarter of patients randomised to placebo with no baseline
241 demographic features predictive of this response.¹⁶

242
243 To address these limitations, we systematically reviewed all randomised, placebo-controlled
244 RCTs of pharmacologic interventions in EoE. We aim to describe placebo rates in EoE trials,
245 identify relevant endpoints and outcome definitions used in current EoE trials, and establish a
246 conceptual framework by which a COS for future EoE trials can be developed.

247

248 **Methods**249 **Search Strategy**

250 MEDLINE (Ovid, 1948-2017), Embase (Ovid, 1947-2017), and CENTRAL (1994-2017) were
251 searched without language restriction from inception to February 20, 2018 for RCTs of
252 pharmacologic interventions in EoE. Using the PICO framework, we aimed to capture all studies
253 enrolling patients with EoE regardless of age (patient population), undergoing pharmacologic
254 therapy (intervention), compared against placebo (comparator), and describing any symptom-
255 based, endoscopic, histologic, or exploratory outcomes (outcome). The search strategy is
256 outlined in **Supplemental File 1**. Conference proceedings from Digestive Disease Week and
257 United European Gastroenterology Week (2012-2017) and references of relevant studies and
258 review articles were hand-searched to identify additional studies. Finally, ClinicalTrials.gov and
259 the European Union (EU) Clinical Trials Register were searched for registered, actively
260 recruiting RCTs. Citations and abstracts were screened and complete manuscripts were
261 retrieved for potentially eligible studies. Articles were independently assessed by two
262 investigators (TMN, BvR) and disagreement was resolved by consensus and discussion with a
263 third reviewer (CM). All data were extracted independently and accuracy was verified in a
264 quality control process by a third investigator (CEP).

265

266 **Study Eligibility Criteria**

267 Studies were eligible for inclusion if they reported a randomised, placebo-controlled trial in
268 patients with EoE that evaluated a pharmacologic intervention. Similar criteria were applied to
269 registered trials on ClinicalTrials.gov and the EU Clinical Trials Register. Studies of children,
270 adolescents, or adults were eligible. However, trials of endoscopic dilation or dietary exclusion
271 therapies, and trials without a placebo comparator arm were excluded. These restrictions were
272 applied to focus this review on pharmacologic interventions, although we recognize that similar
273 challenges with respect to minimizing placebo response and outcome heterogeneity apply to

274 trials of dietary or endoscopic therapy and non-placebo controlled studies. Separately published
275 *post-hoc* or retrospective analyses of RCTs were not included to avoid duplicate inclusion.

276

277 **Data Extraction**

278 The primary data extraction included: (1) descriptions of primary and secondary efficacy
279 outcomes, definitions, and measurement tools; (2) descriptions of exploratory outcomes; and (3)
280 the proportion of patients randomised to placebo achieving patient-reported, endoscopic, or
281 histologic response and remission (as defined by the original study authors). Additionally,
282 information regarding trial design (publication year, trial phase, number of treatment arms, trial
283 location and number of trial centres, total participants and participants randomised to placebo,
284 follow-up duration), trial-level patient data (age and gender distribution, proportion on proton
285 pump inhibitor (PPI) therapy at baseline, disease duration), and the active comparator (drug
286 class and route of administration) were collected.

287

288 The risk of bias in the published studies was assessed using the Cochrane risk of bias tool,
289 which assesses the following domains: 1) selection bias (random sequence generation,
290 allocation concealment); 2) performance bias (blinding of participants and personnel); 3)
291 detection bias (blinding of outcome assessment); 4) attrition bias (incomplete outcome data); 5)
292 reporting bias (selective reporting); and 6) other sources of bias.¹⁷

293

294 **Data Synthesis and Analysis**

295 Standard descriptive statistics were used to describe trial characteristics. A comprehensive
296 inventory of outcomes and definitions was generated through qualitative review and
297 subsequently organized into subdomains (histology, endoscopy, patient-reported outcomes).

298 The proportion of studies reporting each outcome was calculated and stratified by year of
299 publication.

300

301 In the initial study protocol, we planned to pool histologic, endoscopic, and patient-reported
302 placebo response and remission rates in meta-analysis using a random-effects model; however,
303 due to the small number of trials and significant heterogeneity in outcome definitions, it was
304 methodologically inappropriate to formally pool reported placebo rates. Additionally, a
305 substantial proportion of trials reported placebo rates of 0% (see **Results**); pooling these
306 studies in meta-analysis, even with a continuity factor, would likely result in biased estimates.
307 Therefore, we generated a descriptive summary of the proportion of placebo responders or
308 remitters where available but without pooled point estimates. For studies reporting quantitative
309 before and after treatment changes in the mean or median scoring index, the percentage
310 change in the placebo group was calculated by dividing the difference in quantitative score after
311 treatment by the scale of the scoring instrument. The median and interquartile range of placebo
312 response and remission rates was calculated and then graphically depicted in box-and-whisker,
313 stratified by outcome domain. All statistical analyses were conducted using STATA 14.2
314 (StataCorp, College Station, TX: StataCorp LP).

315

316 This meta-analysis conforms to the Preferred Reporting Items for Systematic Reviews and
317 Meta-Analyses (PRISMA) recommendations.¹⁸

318

319 **Results**320 **Search Results and Study Characteristics**

321 The flow diagram for inclusion of trials identified by the literature search is illustrated in
322 **Supplemental Figure 1**. Twenty-two placebo-controlled RCTs¹⁹⁻⁴⁰ were identified; another ten
323 registered and enrolling trials were identified through ClinicalTrials.gov and the EU Clinical
324 Trials Register. Baseline study characteristics are summarized in **Table 1**. Most of the published
325 trials were phase II studies (81.8%, 18/22), enrolling adult patients (54.5%, 12/22). Thirteen
326 studies (59.1%, 13/22) compared a corticosteroid preparation against placebo. Ten trials
327 reported concomitant PPI use; the mean proportion of EoE patients receiving concomitant PPI
328 therapy was 57.0% (standard deviation \pm 26.5%, range 13.2%-100%). The mean follow-up
329 duration was 12.1 weeks (SD \pm 10.7 weeks, range 2-50 weeks). Risk of bias assessment is
330 summarized in **Supplemental Table 1**; most studies were judged to be at low risk of bias for
331 most domains.

332

333 **Outcome Reporting**

334 The proportion of trials reporting histologic, endoscopic, and patient-reported outcomes is
335 summarized in **Figure 1**, stratified by year of publication. Both histologic and patient-reported
336 outcomes were described in nearly all reported trials (95.5%, 21/22) and registered studies
337 (90%, 9/10). In contrast, only 13 reported RCTs (59.1%) and four (40%) registered trials defined
338 *a priori* endoscopic endpoints. Exploratory outcomes were evaluated in 68.2% (15/22) of
339 reported RCTs and included: (1) serum or tissue biomarkers (including MIB-1/Ki-67¹⁹,
340 interleukin (IL)-5^{22, 25}, IL13^{25, 27, 35}, eotaxin^{22, 30}, tryptase for mast cells^{19, 21, 23, 25, 27, 29}, tumor
341 necrosis factor^{21, 22}, tenascin C^{21, 27}, cytokeratin^{21, 23}, terminal deoxynucleotidyl transferase-
342 mediated deoxyuridine triphosphate nick-end labeling positive inflammatory and epithelial
343 cells^{21, 23}, transforming growth factor beta (TGF- β)^{20-23, 25, 27}, CD3/8^{19, 21-23}, eosinophil cationic
344 protein²¹⁻²³, eosinophil derived neurotoxin^{22, 24}, eosinophil peroxidase²⁷, serum

345 immunoglobulins²⁹, and thymic stromal lymphopoietin³⁵); (2) esophageal thickness²³ (as
346 measured on endoscopic ultrasound); (3) genetic factors associated with EoE (including single
347 nucleotide polymorphisms of TGF- β ²⁰ and measures of the EoE transcriptome^{28, 30}), and (4)
348 esophageal distensibility measures as assessed by functional lumen imaging probe (FLIP).³⁸

349

350 Histology Outcome Definitions

351 Definitions of histology outcomes for reported RCTs are summarized in **Table 2** and for
352 registered RCTs in **Table 3**. Most trials defined histology outcomes using eosinophil density as
353 defined most commonly by peak eosinophil counts although no consistent thresholds for
354 defining histologic response or remission were used. Furthermore, the definition of peak
355 eosinophil count varied depending on field size, number of HPFs evaluated, and from which
356 level of the esophagus samples were obtained. For histologic remission, peak eosinophil
357 thresholds ranged from 0 to 6 eosinophils/high power field (HPF); for histologic response, peak
358 eosinophil count thresholds ranged from 5 to 24 eosinophils/HPF. Fourteen studies reported
359 change in absolute eosinophil counts before and after therapy or by percentage changes from
360 baseline in eosinophil density.^{23, 24, 26-30, 32, 33, 35, 37-40} One study used the EoE Histology Scoring
361 System (EoE-HSS) to evaluate both severity and extent of eight features (eosinophil density,
362 basal zone hyperplasia, eosinophil abscesses, eosinophil surface layering, dilated intercellular
363 spaces, surface epithelial alteration, dyskeratotic epithelial cells, and lamina propria fibrosis).³⁸
364 Four studies specified that histologic outcomes required changes at multiple esophageal levels
365 (e.g. proximal and distal esophagus).^{19, 28, 30, 31}

366

367 Endoscopy Outcome Definitions

368 Definitions of endoscopy outcomes for reported RCTs are summarized in **Table 2** and for
369 registered RCTs in **Table 3**. Several authors used non-validated changes in overall or global

370 endoscopic appearance with descriptions of classic EoE endoscopy findings (such as linear
371 furrows, white exudates, and esophageal rings). Two studies used a visual analogue scale^{27, 33}
372 and four studies used the EoE Endoscopic Reference Score (EREFS).^{32, 36-38} The EREFS is the
373 only endoscopic outcome instrument that has undergone inter- and intra-observer validation in
374 both North American and European studies. The EREFS is also the most commonly used
375 measurement tool for endoscopy outcomes in registered trials (4 studies, 40%). No consistently
376 used thresholds for endoscopy scores were identified to determine endoscopic
377 response/remission; rather, changes compared to baseline were commonly reported.

378

379 Patient-Reported Outcome Definitions

380 Definitions of patient-reported outcomes for reported RCTs are summarized in **Table 2** and for
381 registered RCTs in **Table 3**. Multiple different scoring systems, mostly non- or only partially
382 validated, have been used to assess patient-reported response or remission. These include the
383 Mayo Dysphagia Questionnaire^{24, 30, 34}, the Dysphagia Symptom Questionnaire³⁶, the EoE
384 Activity Index (EEsAI)⁴⁰, patient or physician global assessments of disease severity^{26, 32, 37, 40},
385 the Dysphagia Score (also termed the Straumann Dysphagia Index)²¹⁻²³, the EoE Clinical
386 Symptom Score^{28, 31}, the Pediatric Eosinophilic Esophagitis Symptom Score (PEESS)²⁰, and the
387 Visual Dysphagia Questionnaire.²⁷ As with endoscopy and histology endpoints, no uniformly
388 applied thresholds for patient-reported remission or response have been identified although the
389 complete absence of symptoms has been used by some authors to define remission. Health-
390 related quality of life was not specifically defined as a treatment endpoint in any of the currently
391 published RCTs.

392

393 Histology, Endoscopy, and Patient-Reported Placebo Rates

394 Placebo rates in EoE RCTs are summarized in **Figure 2** and **Table 4**, presented as either: (1)
395 proportion of patients achieving response/remission defined by the original study authors; or (2)

396 percentage change in before and after treatment disease activity scores relative to the scale of
397 scoring index when placebo response was reported as a continuous variable. The median
398 histologic placebo response rate was 3.7% (range 0% to 31.6%). Two studies reported
399 histologic placebo response or partial remission rates of >20%. Both studies used an eosinophil
400 density cutoff of <20 eos/HPF (<65 eos/mm² HPF).^{23, 33} The median histologic placebo
401 remission rate was 0.0% (range 0% to 11.0%). Eight studies reported histologic placebo
402 remission rates of 0%.^{20, 21, 23, 24, 28, 33, 39, 40} When assessed as a continuous measure relative to
403 the scale of the measurement tool, endoscopy scores before and after placebo administration
404 changed between -0.6% to -16%. Larger variances were evident when assessing patient-
405 reported placebo response (**Figure 2**): patient-reported scores before and after placebo
406 administration varied between -28.6% to +36.6. The median symptomatic response rate was
407 14.4% (range 8.6% to 77.8%); the median symptomatic remission rate was 26.2% (range 13.2%
408 to 35.7%).

409

410 **Discussion**

411 Over the past two decades, clinical trials of therapeutic agents in EoE have evolved from
412 retrospective case series with symptom-based outcomes to prospective, randomised, placebo-
413 controlled trials that include both valid patient-reported outcomes and objective measures such
414 as histopathology and endoscopy. In this systematic review of all reported and registered
415 placebo-controlled trials of pharmacologic therapies for EoE, we describe the placebo response
416 and summarise the outcome measures used in existing and planned RCTs. We found that
417 histologic placebo response and remission rates in EoE trials are relatively low compared to
418 RCTs in other gastrointestinal disorders, although there is greater variance in patient-reported
419 placebo responses. We also highlight the significant heterogeneity in outcome measurement
420 and outcome definitions used in current studies for histology, endoscopy, and patient-reported
421 endpoints and there is no consensus on thresholds for defining response or remission.⁹
422 Development of a COS that standardises outcome measurement and reporting in EoE RCTs is
423 thus a priority.

424 Potential determinants of the histologic placebo response in EoE RCTs include: 1) inclusion of
425 patients with PPI-responsive EoE who derive both clinical and histologic benefits from
426 concomitant PPI therapy⁴¹; 2) sampling of histologically normal mucosa in the context of patchy
427 eosinophilic infiltration in EoE; 3) regression to the mean; and 4) spontaneous changes in
428 disease activity in the natural history of EoE, possibly as a response to fluctuations in allergen
429 or dietary exposures. Although symptomatic placebo rates in EoE tend to be lower than in other
430 allergic and gastrointestinal disorders,^{42, 43} they still remain higher and more variable compared
431 to histologic placebo response. Some EoE studies report greater than one third to one half of
432 placebo patients achieving response or remission using patient-reported endpoints.^{23, 31, 36}
433 Symptomatic placebo rates may be influenced by dietary avoidance or modifications that reduce
434 dysphagia or by endoscopic dilation at baseline if not precluded by the study entry criteria.
435 However, this discrepancy between histologic and symptomatic placebo response also

436 underscores the discordance between patient-reported symptoms and objective measures of
437 disease activity: in an international cohort study of 269 EoE patients, an Eosinophilic
438 Esophagitis Activity Index (EEsAI) patient-reported outcome score of ≤ 15 points identified only
439 67.2% of patients with endoscopic and histologic remission.⁴⁴

440
441 Additionally, histologic endpoints defined by eosinophil density may not closely correlate with
442 patient-reported outcomes because dysphagia symptoms and risk of food impaction in EoE are
443 driven primarily by complications of esophageal remodeling, rather than mucosal
444 inflammation.^{45, 46} Histologic outcomes are assessed in nearly all EoE RCTs defined by either
445 peak or mean eosinophil count per HPF. Although this paradigm is attractive because it
446 provides a quantitative measure of inflammatory burden, several potential pitfalls exist. First,
447 variability in results may be influenced by technical factors such as the cross-sectional area of
448 the microscope manufacturer (correctable by using normalised density to eosinophils per mm^2)
449 and by sampling differences in the number and location of acquired biopsies.⁴⁷⁻⁴⁹ Second,
450 mucosal biopsies may underestimate the full extent of histologic involvement in EoE given that
451 eosinophilic infiltration is not confined to the superficial mucosa, eosinophil density does not
452 necessarily correlate with eosinophil degranulation or function, and other histologic features
453 such as basal cell hyperplasia, mast cell infiltration, and subepithelial fibrosis are not
454 captured.^{50, 51}

455
456 To address some of these potential limitations of peak eosinophil density as a measure of
457 disease activity in EoE, Collins *et al.* have developed and validated an EoE Histology Scoring
458 System (EoE-HSS), based on eight features (eosinophil density, basal zone hyperplasia,
459 eosinophil abscesses, eosinophil surface layering, dilated intercellular spaces, surface epithelial
460 alteration, dyskeratotic epithelial cells, and lamina propria fibrosis), graded and staged using a
461 four point scale.⁵² Future studies should assess the responsiveness to change of this instrument

462 after a therapeutic intervention. Furthermore, adoption of blinded central reading to minimize
463 observation bias at both enrolment and outcome ascertainment has gained traction in IBD.
464 Although a single pathologist frequently evaluates histologic endpoints in current EoE RCTs,
465 proper assessment inter- and intra-rater reliability using multiple blinded central readers for EoE
466 histopathology endpoints is needed before this is routinely incorporated in clinical trials.

467
468 Patient-reported outcomes will likely be an essential component of future registration trials in
469 EoE based upon existing precedents in both ulcerative colitis and Crohn's disease, whereby co-
470 primary endpoints of PROs and objective assessment of inflammation (endoscopy) have been
471 mandated. Although multiple scoring systems have been used to assess dysphagia symptoms
472 in EoE RCTs most have not been validated in this disease. Two disease-specific, validated
473 symptom scoring systems have recently been developed. The Dysphagia Symptom
474 Questionnaire was developed from patient focus groups and primarily assesses frequency and
475 intensity of dysphagia symptoms, with demonstrated responsiveness in an RCT of budesonide
476 oral suspension.³⁶ The EEsAI was prospectively developed and validated for use in adults with
477 EoE and additionally captures food avoidance and behavioral modifications,⁵³ a common source
478 of reduced quality of life in EoE patients, particularly among those with previous food bolus
479 impactions. Notwithstanding that eating behaviors such as careful mastication, prolonged meal
480 times, and dietary restriction may not be adequately captured by assessment of dysphagia
481 symptoms alone, both indices are candidate measurement tools for evaluating patient-reported
482 outcomes in future RCTs.

483
484 Endoscopic outcomes offer another potential objective treatment target in EoE RCTs. Earlier
485 studies used non-validated global assessments of endoscopic appearance based on common
486 EoE features. Development of the EoE Endoscopic Reference Score (EREFS), which
487 incorporates both major (fixed rings, exudates, furrows, edema, stricture) and minor features

488 (crepe paper esophagus) has been an important advance.⁵⁴ The items for the EREFS were
489 identified through a literature review and a grading scheme was developed through consensus
490 expert opinion. Internal validation, based on evaluation of a sampling of videos by 21
491 endoscopists with diverse experience and practice patterns, demonstrated moderate to good
492 interobserver reliability. The EREFS is the proposed endoscopic endpoint in four registered
493 RCTs, but it still requires further external validation, particularly evaluating the role of central
494 blinded endoscopy reading and comparison of video versus still-image endoscopic assessment
495 on reliability performance characteristics.⁵⁵

496
497 Although histologic, endoscopic, and symptom-based outcomes have traditionally been used to
498 assess EoE activity, there has been growing interest in quantifying and targeting esophageal
499 distensibility as a measure of end organ remodeling. Functional lumen imaging probe (FLIP)
500 uses impedance planimetry to quantify esophageal distention.⁶ Lower distensibility plateaus
501 (DP) are associated with food bolus impaction and the need for esophageal dilation.⁴⁵ In
502 contrast, dietary and medical therapies have been demonstrated to improve DPs and this
503 reduction correlates with better symptomatic outcomes.⁵⁶ In a recent phase 2 placebo-controlled
504 RCT, treatment with dupilumab, a humanised anti-IL-4R α monoclonal antibody, improved
505 esophageal distensibility and highlighted the potential of FLIP as a responsive biomarker to
506 medical therapy.³⁸

507
508 Understanding outcome definitions in clinical trials is crucial for translating evidence-based
509 research to clinical practice. Indeed, many of the newer EoE disease activity indices such as the
510 EoEHSS, EEsAI, and EREFS have not yet been routinely incorporated in daily care. It is
511 important for physicians to recognize that heterogeneity in outcome definitions used in clinical
512 trials may influence interpretations of response to therapy. As the patient's treatment goals are
513 typically resolution of dysphagia symptoms, avoidance of food bolus impactions, prevention of

514 long-term disease complications, and ultimately, optimization of quality of life, these are
515 parameters should be captured in outcome definitions for use in RCTs. Additionally, choosing
516 appropriate histologic and endoscopic targets will help dictate therapeutic decisions in clinical
517 practice: for example, targeting more stringent histologic endpoints (<5 eos/hpf vs. <15
518 eos/hpf)⁵⁷ or endoscopic resolution⁵⁸ is associated with improved treatment response and
519 symptom alleviation.

520

521 Our study has some limitations. First, we included only placebo-controlled RCTs and a
522 substantial proportion of the EoE literature is rooted in observational studies and non-controlled
523 trials. Thus, there may be outcomes of interest that are not captured in this review. Second, we
524 excluded trials of endoscopic therapies or dietary interventions. We restricted the inclusion
525 specifically to RCTs investigating pharmacologic therapies because the focus of COS
526 development will be primarily applicable to RCTs of novel therapeutic compounds. However,
527 similar symptom-based and histologic outcomes are measured in both prospective and
528 retrospective observational studies of dietary interventions in EoE, with heterogeneity in the
529 defined thresholds for response and remission remaining an important challenge.⁵⁹⁻⁶³ A previous
530 systematic review has also evaluated outcomes after endoscopic dilation for EoE⁶⁴: efficacy was
531 typically assessed using dysphagia scoring systems although there is an increased focus on
532 safety outcomes, particularly with respect to esophageal perforation. Finally, we could not pool
533 placebo rates to generate single point estimates. However, it is considered methodologically
534 inappropriate to pool studies with such heterogeneity in outcome definitions, leading to a
535 potentially biased point estimate that is not representative of the literature. Thus, we have
536 presented the median as a measure of central tendency with ranges rather than a pooled point
537 estimate.

538

539 The next steps in COS development have been outlined in the Core Outcome Measures in
540 Effectiveness Trials (COMET) handbook.⁶⁵ First, input from relevant stakeholders, including
541 patients, health care providers, trialists, regulators, industry representatives, health policy-
542 makers, and researchers, will be sought. Next, relevant outcome domains will be defined. We
543 propose that a similar framework to that presented in this review be considered, wherein a
544 coprimary endpoint incorporating a patient-reported outcome measure and an objective
545 histologic or endoscopic outcome in accordance with regulatory requirements be adopted. A
546 consensus on specific outcome definitions and thresholds will be achieved through a multi-
547 round Delphi process that permits anonymized feedback to participants. Finally, the COS will be
548 ratified and disseminated for implementation in future RCTs.

549

550 CONCLUSION

551 In conclusion, choosing appropriate treatment endpoints is crucial for clinical trial design.
552 Outcomes should be relevant, valid, support regulatory and labelling claims, and correlate with
553 meaningful changes in quality of life and disease course. In EoE, this translates to
554 improvements in patient-reported symptoms, histologic burden of inflammation, and possibly
555 reversal or prevention of fibrostenotic EoE complications. Although there has been significant
556 progress in clinical trial research in EoE over the past two decades, we identify the substantial
557 heterogeneity in outcome definitions in this field. Many instruments for EoE outcome
558 assessment have only recently been developed and additional RCT data applying these
559 instruments is required to adequately define response and remission cutoffs using anchor-
560 based methods. This systematic review serves as a conceptual framework for COS
561 development in EoE.

562

563 **Tables and Figures Legend**564 **Table 1.** Baseline study characteristics565 **Table 2.** Histology, endoscopy, and symptom-based endpoints in published eosinophilic
566 esophagitis placebo-controlled clinical trials567 **Table 3.** Histology, endoscopy, and symptom-based endpoints in registered eosinophilic
568 esophagitis placebo-controlled clinical trials569 **Table 4.** Histology, endoscopy, and symptom-based placebo rates in published eosinophilic
570 esophagitis placebo-controlled clinical trials

571

572 **Figure 1.** Endpoint reporting in eosinophilic esophagitis placebo-controlled clinical trials,
573 stratified by year of publication574 **Figure 2.** Box-and-whisker plots for histologic, endoscopic, and symptom-based placebo
575 response and remission in eosinophilic esophagitis clinical trials.

576

577 **Supplemental File 1.** Search strategy578 **Supplemental Figure 1.** PRISMA diagram579 **Supplemental Table 1.** Risk of bias assessment

580 **References**

- 581 1. Furuta GT, Katzka DA. Eosinophilic Esophagitis. *N Engl J Med* 2015;373:1640-8.
- 582 2. Dellon ES, Gonsalves N, Hirano I, et al. ACG clinical guideline: evidenced based
583 approach to the diagnosis and management of esophageal eosinophilia and eosinophilic
584 esophagitis (EoE). *Am J Gastroenterol* 2013;108:679-692.
- 585 3. Lucendo AJ, Molina-Infante J, Arias A, et al. Guidelines on eosinophilic esophagitis:
586 evidence-based statements and recommendations for diagnosis and management in
587 children and adults. *United European Gastroenterol J* 2017;5:335-358.
- 588 4. Fiorentino R, Liu G, Pariser AR, et al. Cross-sector sponsorship of research in
589 eosinophilic esophagitis: a collaborative model for rational drug development in rare
590 diseases. *J Allergy Clin Immunol* 2012;130:613-6.
- 591 5. Rothenberg ME, Aceves S, Bonis PA, et al. Working with the US Food and Drug
592 Administration: progress and timelines in understanding and treating patients with
593 eosinophilic esophagitis. *J Allergy Clin Immunol* 2012;130:617-619.
- 594 6. Hirano I, Spechler S, Furuta G, et al. White Paper AGA: Drug Development for
595 Eosinophilic Esophagitis. *Clin Gastroenterol Hepatol* 2017;15:1173-1183.
- 596 7. US Food and Drug Administration. Guidance for industry; patient-reported outcome
597 measures: use in medical product development to support labeling claims. Volume 2018,
598 2009.
- 599 8. Warners MJ, Hindryckx P, Levesque BG, et al. Systematic Review: Disease Activity
600 Indices in Eosinophilic Esophagitis. *Am J Gastroenterol* 2017;112:1658-1669.
- 601 9. Rubin T, Clayton J, Adams D, et al. Systematic review of outcome measures in pediatric
602 eosinophilic esophagitis treatment trials. *Allergy Asthma Clin Immunol* 2016;12:45.
- 603 10. Williamson PR, Altman DG, Blazeby JM, et al. Developing core outcome sets for clinical
604 trials: issues to consider. *Trials* 2012;13:132.

- 605 11. Ma C, Hussein IM, Al-Abbar YJ, et al. Heterogeneity in Definitions of Efficacy and Safety
606 Endpoints for Clinical Trials of Crohn's Disease: A Systematic Review for Development
607 of a Core Outcome Set. *Clin Gastroenterol Hepatol* 2018.
- 608 12. Ma C, Panaccione R, Fedorak RN, et al. Heterogeneity in Definitions of Endpoints for
609 Clinical Trials of Ulcerative Colitis: A Systematic Review for Development of a Core
610 Outcome Set. *Clin Gastroenterol Hepatol* 2018;16:637-647 e13.
- 611 13. Jairath V, Zou G, Parker CE, et al. Systematic review with meta-analysis: placebo rates
612 in induction and maintenance trials of Crohn's disease. *Aliment Pharmacol Ther*
613 2017;45:1021-1042.
- 614 14. Jairath V, Zou G, Parker CE, et al. Systematic Review and Meta-analysis: Placebo
615 Rates in Induction and Maintenance Trials of Ulcerative Colitis. *J Crohns Colitis*
616 2016;10:607-18.
- 617 15. Elsenbruch S, Enck P. Placebo effects and their determinants in gastrointestinal
618 disorders. *Nat Rev Gastroenterol Hepatol* 2015;12:472-85.
- 619 16. Hirano I, Williams J, Collins MH, et al. Clinical Features at Baseline are Not Clearly
620 Associated with Symptomatic Placebo Response in Adolescents and Adults with
621 Eosinophilic Esophagitis During a Placebo Run-in Period of a Double-Blind,
622 Randomized, Controlled Trial of Budesonide Oral Suspension. *Gastroenterology*
623 2017;152:S854.
- 624 17. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for
625 assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928.
- 626 18. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic
627 reviews and meta-analyses of studies that evaluate healthcare interventions: explanation
628 and elaboration. *BMJ* 2009;339:b2700.

- 629 19. Konikoff MR, Noel RJ, Blanchard C, et al. A randomized, double-blind, placebo-
630 controlled trial of fluticasone propionate for pediatric eosinophilic esophagitis.
631 *Gastroenterology* 2006;131:1381-91.
- 632 20. Dohil R, Newbury R, Fox L, et al. Oral viscous budesonide is effective in children with
633 eosinophilic esophagitis in a randomized, placebo-controlled trial. *Gastroenterology*
634 2010;139:418-29.
- 635 21. Straumann A, Conus S, Degen L, et al. Budesonide is effective in adolescent and adult
636 patients with active eosinophilic esophagitis. *Gastroenterology* 2010;139:1526-37, 1537
637 e1.
- 638 22. Straumann A, Conus S, Grzonka P, et al. Anti-interleukin-5 antibody treatment
639 (mepolizumab) in active eosinophilic oesophagitis: a randomised, placebo-controlled,
640 double-blind trial. *Gut* 2010;59:21-30.
- 641 23. Straumann A, Conus S, Degen L, et al. Long-term budesonide maintenance treatment is
642 partially effective for patients with eosinophilic esophagitis. *Clin Gastroenterol Hepatol*
643 2011;9:400-9 e1.
- 644 24. Alexander JA, Jung KW, Arora AS, et al. Swallowed fluticasone improves histologic but
645 not symptomatic response of adults with eosinophilic esophagitis. *Clin Gastroenterol*
646 *Hepatol* 2012;10:742-749 e1.
- 647 25. Ghaffari G. A Randomized Double Blind Placebo Controlled Crossover Study of the
648 Effect of Swallowed Beclomethasone Dipropionate on Inflammatory Markers in Adult
649 Patients with Eosinophilic Esophagitis: A Pilot Study. *Ann Allergy Asthma Immunol.*
650 2012;109:A19.
- 651 26. Spergel JM, Rothenberg ME, Collins MH, et al. Reslizumab in children and adolescents
652 with eosinophilic esophagitis: results of a double-blind, randomized, placebo-controlled
653 trial. *J Allergy Clin Immunol* 2012;129:456-63, 463 e1-3.

- 654 27. Straumann A, Hoesli S, Bussmann C, et al. Anti-eosinophil activity and clinical efficacy
655 of the CRTH2 antagonist OC000459 in eosinophilic esophagitis. *Allergy* 2013;68:375-85.
- 656 28. Butz BK, Wen T, Gleich GJ, et al. Efficacy, dose reduction, and resistance to high-dose
657 fluticasone in patients with eosinophilic esophagitis. *Gastroenterology* 2014;147:324-33
658 e5.
- 659 29. Clayton F, Fang JC, Gleich GJ, et al. Eosinophilic esophagitis in adults is associated
660 with IgG4 and not mediated by IgE. *Gastroenterology* 2014;147:602-9.
- 661 30. Rothenberg ME, Wen T, Greenberg A, et al. Intravenous anti-IL-13 mAb QAX576 for the
662 treatment of eosinophilic esophagitis. *J Allergy Clin Immunol* 2015;135:500-7.
- 663 31. Gupta SK, Vitanza JM, Collins MH. Efficacy and safety of oral budesonide suspension in
664 pediatric patients with eosinophilic esophagitis. *Clin Gastroenterol Hepatol* 2015;13:66-
665 76 e3.
- 666 32. Hirano I, Collins M, Assouline-Dayyan Y, et al. A Randomised, Double-Blind, Placebo-
667 Controlled Trial of A Novel Recombinant, Humanised, Anti-Interleukin-13 Monoclonal
668 Antibody (RPC4046) In Patients With Active Eosinophilic Oesophagitis: Results Of The
669 HEROES Study. *United European Gastroenterol J* 2016;2.
- 670 33. Miehlik S, Hruz P, Vieth M, et al. A randomised, double-blind trial comparing
671 budesonide formulations and dosages for short-term treatment of eosinophilic
672 oesophagitis. *Gut* 2016;65:390-9.
- 673 34. Alexander JA, Ravi K, Enders FT, et al. Montelukast Does not Maintain Symptom
674 Remission After Topical Steroid Therapy for Eosinophilic Esophagitis. *Clin Gastroenterol*
675 *Hepatol* 2017;15:214-221 e2.
- 676 35. Bhardwaj N, Ishmael F, Lehman E, et al. Effect of topical beclomethasone on
677 inflammatory markers in adults with eosinophilic esophagitis: A pilot study. *Allergy Rhinol*
678 (Providence) 2017;8:85-94.

- 679 36. Dellon ES, Katzka DA, Collins MH, et al. Budesonide Oral Suspension Improves
680 Symptomatic, Endoscopic, and Histologic Parameters Compared With Placebo in
681 Patients With Eosinophilic Esophagitis. *Gastroenterology* 2017;152:776-786 e5.
- 682 37. Hirano I, Schoepfer AM, Comer GM, et al. A Randomized, Double-Blind, Placebo-
683 Controlled Trial of a Fluticasone Propionate Orally Disintegrating Tablet in Adult and
684 Adolescent Patients with Eosinophilic Esophagitis: A Phase 1/2A Safety and Tolerability
685 Study. *Gastroenterology* 2017;152:S195.
- 686 38. Hirano I, Dellon ES, Hamilton JD, et al. Dupilumab Efficacy and Safety in Adult Patients
687 with Active Eosinophilic Oesophagitis: A Randomised Double-Blind Placebo-Controlled
688 Phase 2 Trial. *United European Gastroenterol J* 2017;5:1146-7.
- 689 39. Lieberman J, Zhang J, Cavender C. Viscous oral cromolyn for the treatment of
690 eosinophilic esophagitis: A double-blind, placebo-controlled trial. *Annals of Allergy,*
691 *Asthma and Immunology* 2017;119 (5 Supplement 1):S9.
- 692 40. Lucendo A, Miehlke S, Vieth M, et al. Budesonide Orodispersible Tablets are Highly
693 Effective for Treatment of Active Eosinophilic Esophagitis: Results from a Randomized,
694 Double-Blind, Placebo-Controlled, Pivotal Multicenter Trial (EOS-1). *Gastroenterology*
695 2017;152:S207.
- 696 41. Eluri S, Dellon ES. Proton pump inhibitor-responsive oesophageal eosinophilia and
697 eosinophilic oesophagitis: more similarities than differences. *Curr Opin Gastroenterol*
698 2015;31:309-15.
- 699 42. Dutile S, Kaptchuk TJ, Wechsler ME. The placebo effect in asthma. *Curr Allergy Asthma*
700 *Rep* 2014;14:456.
- 701 43. Patel SM, Stason WB, Legedza A, et al. The placebo effect in irritable bowel syndrome
702 trials: a meta-analysis. *Neurogastroenterol Motil* 2005;17:332-40.

- 703 44. Safroneeva E, Straumann A, Coslovsky M, et al. Symptoms Have Modest Accuracy in
704 Detecting Endoscopic and Histologic Remission in Adults With Eosinophilic Esophagitis.
705 *Gastroenterology* 2016;150:581-590 e4.
- 706 45. Nicodeme F, Hirano I, Chen J, et al. Esophageal distensibility as a measure of disease
707 severity in patients with eosinophilic esophagitis. *Clin Gastroenterol Hepatol*
708 2013;11:1101-1107 e1.
- 709 46. Hirano I, Aceves SS. Clinical implications and pathogenesis of esophageal remodeling in
710 eosinophilic esophagitis. *Gastroenterol Clin North Am* 2014;43:297-316.
- 711 47. Nielsen JA, Lager DJ, Lewin M, et al. The optimal number of biopsy fragments to
712 establish a morphologic diagnosis of eosinophilic esophagitis. *Am J Gastroenterol*
713 2014;109:515-20.
- 714 48. Gonsalves N, Policarpio-Nicolas M, Zhang Q, et al. Histopathologic variability and
715 endoscopic correlates in adults with eosinophilic esophagitis. *Gastrointest Endosc*
716 2006;64:313-9.
- 717 49. Dellon ES, Aderoju A, Woosley JT, et al. Variability in diagnostic criteria for eosinophilic
718 esophagitis: a systematic review. *Am J Gastroenterol* 2007;102:2300-13.
- 719 50. Collins MH. Histopathologic features of eosinophilic esophagitis and eosinophilic
720 gastrointestinal diseases. *Gastroenterol Clin North Am* 2014;43:257-68.
- 721 51. Schoepfer AM, Simko A, Bussmann C, et al. Eosinophilic Esophagitis: Relationship of
722 Subepithelial Eosinophilic Inflammation With Epithelial Histology, Endoscopy, Blood
723 Eosinophils, and Symptoms. *Am J Gastroenterol* 2018;113:348-357.
- 724 52. Collins MH, Martin LJ, Alexander ES, et al. Newly developed and validated eosinophilic
725 esophagitis histology scoring system and evidence that it outperforms peak eosinophil
726 count for disease diagnosis and monitoring. *Dis Esophagus* 2017;30:1-8.

- 727 53. Schoepfer AM, Straumann A, Panczak R, et al. Development and validation of a
728 symptom-based activity index for adults with eosinophilic esophagitis. *Gastroenterology*
729 2014;147:1255-66 e21.
- 730 54. Hirano I, Moy N, Heckman MG, et al. Endoscopic assessment of the oesophageal
731 features of eosinophilic oesophagitis: validation of a novel classification and grading
732 system. *Gut* 2013;62:489-95.
- 733 55. van Rhijn BD, Warners MJ, Curvers WL, et al. Evaluating the endoscopic reference
734 score for eosinophilic esophagitis: moderate to substantial intra- and interobserver
735 reliability. *Endoscopy* 2014;46:1049-55.
- 736 56. Carlson DA, Hirano I, Zalewski A, et al. Improvement in Esophageal Distensibility in
737 Response to Medical and Diet Therapy in Eosinophilic Esophagitis. *Clin Transl*
738 *Gastroenterol* 2017;8:e119.
- 739 57. Reed CC, Wolf WA, Cotton CC, et al. Optimal Histologic Cutpoints for Treatment
740 Response in Patients With Eosinophilic Esophagitis: Analysis of Data From a
741 Prospective Cohort Study. *Clin Gastroenterol Hepatol* 2018;16:226-233 e2.
- 742 58. Wechsler JB, Bolton S, Amsden K, et al. Eosinophilic Esophagitis Reference Score
743 Accurately Identifies Disease Activity and Treatment Effects in Children. *Clin*
744 *Gastroenterol Hepatol* 2017.
- 745 59. Peterson KA, Byrne KR, Vinson LA, et al. Elemental diet induces histologic response in
746 adult eosinophilic esophagitis. *Am J Gastroenterol* 2013;108:759-66.
- 747 60. Spergel JM, Beausoleil JL, Mascarenhas M, et al. The use of skin prick tests and patch
748 tests to identify causative foods in eosinophilic esophagitis. *J Allergy Clin Immunol*
749 2002;109:363-8.
- 750 61. Henderson CJ, Abonia JP, King EC, et al. Comparative dietary therapy effectiveness in
751 remission of pediatric eosinophilic esophagitis. *J Allergy Clin Immunol* 2012;129:1570-8.

Ma *et al.***Outcomes in EoE RCTs**

- 752 62. Gonsalves N, Yang GY, Doerfler B, et al. Elimination diet effectively treats eosinophilic
753 esophagitis in adults; food reintroduction identifies causative factors. *Gastroenterology*
754 2012;142:1451-9 e1; quiz e14-5.
- 755 63. Lucendo AJ, Arias A, Gonzalez-Cervera J, et al. Empiric 6-food elimination diet induced
756 and maintained prolonged remission in patients with adult eosinophilic esophagitis: a
757 prospective study on the food cause of the disease. *J Allergy Clin Immunol*
758 2013;131:797-804.
- 759 64. Moole H, Jacob K, Duvvuri A, et al. Role of endoscopic esophageal dilation in managing
760 eosinophilic esophagitis: A systematic review and meta-analysis. *Medicine (Baltimore)*
761 2017;96:e5877.
- 762 65. Williamson PR, Altman DG, Bagley H, et al. The COMET Handbook: version 1.0. *Trials*
763 2017;18:280.
764

765 **Table 1.** Baseline study characteristics

766

		n = 22
Trial Participants (n)	Total randomised participants	1112
	Participants randomised to placebo	410
Trial Phase (n, %)	Phase I	2 (9.1)
	Phase II	18 (81.8)
	Phase III	2 (9.1)
Trial Publication Year (n, %)	2006-2010	4 (18.2)
	2011-2015	9 (40.9)
	2016-2017	9 (40.9)
Active Comparator (n, %)	Corticosteroid	13 (59.1)
	Biologic Agent	6 (27.3)
	Other	3 (13.6) [†]
Trial Population (n, %)	Pediatric/adolescent	5 (22.7)
	Adult	12 (54.5)
	Mixed	5 (22.7)
Patient Characteristics	Mean participant age (years, SD)	25.8 (13.6)
	Mean disease duration (years, SD)	4.1 (1.9)
	Mean percentage of enrolled males (% , SD)	69.0 (14.1)
	Mean percentage of concurrent PPI (% SD)	57.0 (26.5)
Follow-up (weeks, SD)	Mean follow-up duration	12.1 (10.7)

767

768 [†] One trial of montelukast, one trial of prostaglandin D2 receptor CRTH2 antagonist, one trial of
769 cromolyn sodium

770 **Table 2.** Histology, endoscopy, and symptom-based endpoints in published eosinophilic esophagitis placebo-controlled clinical trials

771

Study	Comparator and Time to Outcome Assessment	Histology Endpoints	Endoscopy Endpoints	Symptom-Based Endpoints
Konikoff 2006 ¹⁹	Fluticasone 12 weeks	Response: peak eosinophil count >1 and <24 eos per 400x HPF, in both proximal and distal esophagus Remission: peak eosinophil count <1 eosinophil in all 400x HPFs in both proximal and distal esophagus	Presence of endoscopic furrowing, epithelial hyperplasia	Presence of clinical symptoms (abdominal pain, vomiting, dysphagia)
Dohil 2010 ²⁰	Budesonide 12 weeks	Response: peak eosinophil count 7-9 eos/HPF Remission: peak eosinophil count 0-6 eos/HPF Change in epithelial histology, lamina propria histology, and lamina propria fibrosis	Change in endoscopy scoring tool (mucosal pallor/reduced vasculature, linear furrows/mucosal thickening, white plaques, concentric rings/stricture, friability/"tissue-paper" mucosa	Change in symptom scoring tool (heartburn/regurgitation, abdominal pain, nausea/vomiting, anorexia/early satiety, dysphagia, symptom-induced nocturnal waking, gastro-intestinal bleeding)
Straumann 2010a ²¹	Budesonide 2 weeks	Response: 5-20 eos/HPF Remission: <5 eos/HPF	Change in endoscopic appearance (white exudates, red furrows, corrugated rings, solitary ring, crepe-paper sign, severe stenosis)	Response: reduction in clinical symptom score ≥ 3 points compared to baseline using patient-reported outcome (frequency of dysphagia, intensity of dysphagia)
Straumann 2010b ²²	Mepolizumab 34 weeks	Response: peak eosinophil count <5 eos/HPF	Change in endoscopic appearance (minor: fine nodules, fine whitish reticular structures, furrows; moderate: bright white scale- or plaque-like structures, corrugated rings; or severe: mucosal lesions, fixed stenosis)	Patient-reported Dysphagia Score (frequency of dysphagia, intensity of dysphagia, score 0-9)

Study	Comparator and Time to Outcome Assessment	Histology Endpoints	Endoscopy Endpoints	Symptom-Based Endpoints
Straumann 2011 ²³	Budesonide 50 weeks	Remission: mean eosinophil count <5 eos/HPF (measured in 40 HPF) Partial remission: mean eosinophil count 5-20 eos/HPF	Endoscopic ultrasound (thickness of mucosa, submucosa, muscularis propria)	Patient-reported Dysphagia Score (frequency of dysphagia, intensity of dysphagia, score 0-9)
Alexander 2012 ²⁴	Fluticasone 6 weeks	Complete response: >90% reduction in mean eosinophil count (from 5 HPF) Partial response: >50% reduction in mean eosinophil count	Resolution of all endoscopic findings	Complete response: answer of "no" to all questions by Mayo Dysphagia Questionnaire (MDQ-30) Partial response: decrease in severity of at least 2 levels
Ghaffari 2012 ^{†25}	Beclomethasone 8 weeks	Tissue cytokine staining	Not reported	Not reported
Spergel 2012 ²⁶	Reslizumab 15 weeks	Percentage change in peak eosinophil count	Not reported	Change in Physician's Eosinophilic Esophagitis Global Assessment (physical findings, vital signs, predominant eosinophilic esophagitis symptom assessment, patient's symptom diary, dietary questions)
Straumann 2013 ²⁷	Prostaglandin D2 receptor CRTH2 antagonist 8 weeks	Reduction in esophageal eosinophil load (mean eosinophil count in 40 HPF)	Global appearance of endoscopic appearance using 10cm visual analogue scale	Combination visual dysphagia questionnaire (VDQ 0-36), chest pain questionnaire (0-9) PRO
Butz 2014 ²⁸	Fluticasone 6 months	Complete remission: ≤1 eos/HPF in proximal and distal esophagus Response: peak eosinophil count ≤6 eos/HPF, peak ≤14 eos/HPF, mean eosinophil count ≤1 eos/HPF, mean eosinophil count ≤2 eos/HPF, decrease in eosinophil count ≥90-95%	Not reported	EoE Symptom Score (vomiting, nausea, abdominal pain, dysphagia, heartburn, chest pain, regurgitation, food impactions, early satiety, poor appetite)

Outcomes in EoE RCTs

Study	Comparator and Time to Outcome Assessment	Histology Endpoints	Endoscopy Endpoints	Symptom-Based Endpoints
Clayton 2014 ²⁹	Omalizumab 16 weeks	Reduction in esophageal eosinophil content (maximum eos/HPF)	Not reported	Change in dysphagia score (0-6 Likert scale)
Rothenberg 2014 ³⁰	Anti-IL13 (QAX576) 6 months	75% reduction in peak eosinophil count in proximal and distal esophagus	Not reported	Change in Mayo Dysphagia Questionnaire (eosinophilic esophagitis relevant questions, MDQ-30)
Gupta 2015 ³¹	Budesonide 12 weeks	Response: peak eosinophil count ≤ 6 eos/HPF in all esophageal levels (composite outcome with clinical outcomes) Remission: peak eosinophil count ≤ 1 eos/HPF in all esophageal levels	Not reported	Symptom response: >50% reduction in Eosinophilic Esophagitis Clinical Symptom Score (EoE CSS) Symptom resolution: EoE CSS of 0
Hirano 2016 ³²	Anti-IL13 (RPC4046) 16 weeks	Response: change in mean eosinophil count	Change in EoE Endoscopic Reference Score (EREFS)	Change in Daily Symptom Diary (DSD), EEsAI PRO, and Subject's Global Assessment of Disease Severity
Miehlke 2016 ³³	Budesonide 2 weeks	Response: mean eosinophil count < 65 eos/mm ² HPF Remission: mean eosinophil count < 16 eos/mm ² HPF	Change in endoscopic intensity score (white exudates, furrows, oedema, fixed rings, crepe paper sign, short segment stenosis, long-distance stenosis, 0-21) Global assessment of endoscopy appearance using 100mm visual analogue scale	Response: decrease in Dysphagia Score ≥ 3 (frequency of dysphagia, intensity of dysphagia, score 0-9)
Alexander 2017 ³⁴	Montelukast 26 weeks	Not reported	Not reported	Symptom remission: absence of dysphagia as measured by dysphagia frequency, severity, and food impaction questions from the Mayo Dysphagia Questionnaire, 2-week version

Study	Comparator and Time to Outcome Assessment	Histology Endpoints	Endoscopy Endpoints	Symptom-Based Endpoints
Bhardwaj 2017 ³⁵	Beclomethasone 8 weeks	Response: change in peak eosinophil count	Not reported	Symptom response: reduction in dysphagia, heartburn, abdominal pain, and other symptoms
Dellon 2017 ³⁶	Budesonide 12 weeks	Response: ≤ 6 eos/HPF	Change in EoE Endoscopic Reference Score (EREFS)	Change in Dysphagia Symptom Questionnaire (DSQ, 0-84), $\geq 30\%$ reduction in DSQ, $\geq 50\%$ reduction in DSQ
Hirano 2017a ^{†37}	Fluticasone (oral disintegrating tablet) 8 weeks	Change in median eosinophil count	Improvement in endoscopic features as measured by the EoE Endoscopic Reference Score (EREFS)	Improvement in Patient Global Assessment of Disease Severity (PatGA), EEsAI PRO
Hirano 2017b ^{†38}	Dupilumab 12 weeks	Change in overall peak eosinophil count, response (peak eosinophil < 6 eos/hpf, < 15 eos/hpf) Change in EoE Histological Scoring System	Change in EoE Endoscopic Reference Score (EREFS)	Response: reduction in Straumann Dysphagia Index ≥ 3 points Response: reduction in EEsAI PRO by $\geq 40\%$
Liebermann 2017 ^{†39}	Cromolyn sodium Follow-up not reported	Change in peak eosinophil count Remission: complete resolution of eosinophilia	Not reported	Symptom reduction by symptom score (not further specified)
Lucendo 2017 ^{†40}	Budesonide 6 weeks	Remission: clinicopathological remission (not further specified) Change in peak eosinophil count	Rate of endoscopic normalization Change in total modified EEsAI endoscopic instrument score	Remission: EEsAI-PRO ≤ 20 Remission: resolution of dysphagia and pain during swallowing Time to first symptom resolution, change in Patient's and Physician's Global Assessment of EoE Activity Score

772

773

774

†Results reported in abstract form

EEsAI (Eosinophilic Esophagitis Activity Index), Eos (eosinophils), HPF (high power field), PRO (patient-reported outcome)

Ma *et al.***Outcomes in EoE RCTs**775 **Table 3.** Histology, endoscopy, and symptom-based endpoints in registered eosinophilic esophagitis placebo-controlled clinical trials

776

Study (Clinicaltrials.gov)	Comparator and Time to Outcome Assessment	Histology Endpoints	Endoscopy Endpoints	Symptom-Based Endpoints
NCT02113267 EudraCT 2012-005842-39	Mometasone 8 weeks	Not reported	Not reported	Change in Watson Dysphagia Scale Score (WDS) Change in EORTC QLQ-OES18 Dysphagia Scale (eating scale and choking item) Global health/social functioning dimensions of SF-36
NCT02605837	Oral budesonide suspension 16 weeks	Response: peak eosinophil count ≤ 6 eos/HPF Change in peak eosinophil count, change in histopathologic epithelial features (by central reviewer)	Change in EoE Endoscopic Reference Score (EREFS)	Symptom response: $\geq 30\%$ reduction in Dysphagia Symptom Questionnaire combined score Change in pain with swallowing
NCT01702701	Montelukast 12 weeks	Change in esophageal eosinophilia	Not reported	Improvement in Dysphagia Symptom Score
NCT03191864 EudraCT 2016-004749-10	APT-1011 12 weeks	Response: peak eosinophil count ≤ 6 eos/HPF (from 5-6 biopsies from proximal and distal esophagus) Response: percentage of patients with peak eosinophil count < 1 eos/HPF, < 15 eos/HPF Sustained response (histology response maintained at week 12, 26, and 52)	Change in EoE Endoscopic Reference Score (EREFS)	Change in baseline Global EoE Symptom Score Change in number of dysphagia episodes at baseline
NCT02873468	Fluticasone 8 weeks	Change in eosinophilic infiltration (not further specified)	Not reported	Not reported
NCT02371941	Cromolyn sodium 2 months	Change in peak esophageal eosinophil count	Not reported	Change in symptom score by Pediatric Esophagitis Symptom

Ma *et al.*

Outcomes in EoE RCTs

Study (Clinicaltrials.gov)	Comparator and Time to Outcome Assessment	Histology Endpoints	Endoscopy Endpoints	Symptom-Based Endpoints
				Score
NCT02019758	Budesonide Fluticasone 8 weeks	Change in maximum eosinophil count	Change in EoE Endoscopic Reference Score (EREFS)	Change in Dysphagia Symptom Questionnaire
NCT02493335	Budesonide orodispersible tablet 48 weeks	Rate of patients with histological relapse	Not reported	Rate of patients free of treatment failure Rate of patients with clinical relapse
NCT02736409	Oral budesonide suspension 36 weeks	Change in peak eosinophil count	Change in EoE Endoscopic Reference Score (EREFS)	Change in Dysphagia Symptom Questionnaire
EudraCT 2005-006074-10	Mepolizumab 12 weeks	Reduction in peak eosinophil count to <5 eos/HPF	Not reported	Frequency and severity of eosinophilic esophagitis- related pain, regurgitation, vomiting, swallowing disorders, feeding difficulties

777
778

779 **Table 4.** Histology, endoscopy, and symptom-based placebo and active comparator rates in published eosinophilic esophagitis
 780 placebo-controlled clinical trials

Study	Placebo Histology Rate	Active Comparator Histology Rate	Placebo Endoscopy Rate	Active Comparator Endoscopy Rate	Placebo Symptom-Based Rate	Active Comparator Symptom-Based Rate
Konikoff 2006 ¹⁹	Response: 20.0% (3/15) Remission: 6.7% (1/15)	Response: 55.0% (11/20) Remission: 50.0% (10/20)	NR	NR	NR	NR
Dohil 2010 ²⁰	Response: 0.0% (0/9) Remission: 0.0% (0/9) Δ mean peak eosinophil count: -18.3 eos/HPF	Response: 6.7% (1/15) Remission: 86.7% (13/15) Δ mean peak eosinophil count: -61.9 eos/HPF	Δ mean endoscopy score: -16.0% (-2.4/15)	Δ mean endoscopy score: -20.7% (-3.1/15)	Δ mean symptom scoring tool: -6.4% (-0.9/14)	Δ mean symptom scoring tool: -16.4% (-2.3/14)
Straumann 2010a ²¹	Response: 0.0% (0/18) Remission: 11.1% (2/18) Δ mean eosinophil count: -5.8 eos/HPF	Response: 16.7% (3/18) Remission: 72.2% (13/18) Δ mean eosinophil count: -62.7 eos/HPF	NR	NR	Δ mean symptom score: -6.8% (-0.61/9)	Δ mean symptom score: -37.7% (-3.39/9)
Straumann 2010b ²²	Δ mean peak eosinophil count: -2.7 eos/HPF	Δ mean peak eosinophil count: -39.4 eos/HPF	NR	NR	NR	NR
Straumann 2011 ²³	Partial remission: 28.6% (4/14) Remission: 0.0% (0/14) Δ mean eosinophil count: +64.3 eos/HPF	Partial remission: 14.3% (2/14) Remission: 35.7% (5/14) Δ mean eosinophil count: +31.4 eos/HPF	NR	NR	Remission: 35.7% (5/14) Δ mean symptom score: +36.6% (+3.29/9)	Remission: 64.3% (9/14) Δ mean symptom score: +16.7% (+1.5/9)
Alexander 2012 ²⁴	Response: 0.0% (0/21)	Response: 61.9% (13/21)	Remission: 4.8% (1/21)	Remission: 26.7% (4/15)	Response: 33.3% (7/21)	Response: 57.1% (12/21)

Study	Placebo Histology Rate	Active Comparator Histology Rate	Placebo Endoscopy Rate	Active Comparator Endoscopy Rate	Placebo Symptom-Based Rate	Active Comparator Symptom-Based Rate
					Remission: 28.6% (6/21)	Remission: 42.9% (9/21)
Ghaffari 2012 ^{†25}	NR	NR	NR	NR	NR	NR
Spergel 2012 ²⁶	NR	NR	NR	NR	Δ mean physician's EoE global assessment score: -11.4% (-1.14/10) Δ mean EoE predominant symptom assessment score: -14.4% (-1.44/10)	Δ mean physician's EoE global assessment score: -11.2% (-1.12/10) Δ mean EoE predominant symptom assessment score: -12.8% (-1.28/10)
Straumann 2013 ²⁷	Δ mean eosinophil count: -3.3 eos/HPF	Δ mean eosinophil count: -41.6 eos/HPF	Δ mean global endoscopy assessment score: -0.6% (-0.06/10)	Δ mean global endoscopy assessment score: -3.6% (-0.36/10)	Δ mean Visual Dysphagia Questionnaire: -18.9% (-6.82/36)	Δ mean Visual Dysphagia Questionnaire: -15.8% (-5.71/36)
Butz 2014 ²⁸	Remission: 0.0% (0/13)	Remission: 65.2% (15/23)	NR	NR	NR	NR
Clayton 2014 ²⁹	Δ mean eosinophil count: -4 eos/HPF	Δ mean eosinophil count: -2 eos/HPF	NR	NR	Δ dysphagia score: -25.2% (-1.7/6)	Δ dysphagia score: -20.0% (-1.2/6)
Rothenberg 2014 ³⁰	Response: 12.5% (1/8)	Response: 40.0% (6/15)	NR	NR	NR	Response: 66.7% (10/15)
Gupta 2015 ³¹	Response: 5.6% (1/18)	Response: 94.1% (16/17)	NR	NR	Response: 77.8% (14/18) Remission: 33.3% (6/18)	Response: 52.9% (9/17) Remission: 17.6% (3/17)
Hirano 2016 ^{*32}	Δ mean eosinophil count: -4.4 eos/HPF	Δ mean eosinophil count: -99.9 eos/HPF	Δ mean EREFS score: -4.5% (-0.9/20)	Δ mean EREFS score: -24.0% (-4.8/20)	Δ Daily Symptom Diary score: -7.6% (-6.4/84)	Δ Daily Symptom Diary score: -15.8% (-13.3/84)
Miehlke 2016 ³³	Response: 31.6% (6/19) Remission: 0.0% (0/19) Δ mean eosinophil count: -30 eos/HPF	Response: 94.7% (18/19) Remission: 89.5% (17/19) Δ mean eosinophil count: -287 eos/HPF	Response: 26.3% (5/19) Δ mean total endoscopic abnormality score: -3.3% (-0.7/21)	Response: 57.9% (11/19) Δ mean total endoscopic abnormality score: -16.8% (-3.4/21)	Δ mean dysphagia score: -28.6% (-2.0/9)	Δ mean dysphagia score: -20.0% (-1.8/9)

Study	Placebo Histology Rate	Active Comparator Histology Rate	Placebo Endoscopy Rate	Active Comparator Endoscopy Rate	Placebo Symptom-Based Rate	Active Comparator Symptom-Based Rate
Alexander 2017 ³⁴	NR	NR	NR	NR	Remission: 23.8% (5/21)	Remission: 40.0% (8/20)
Bhardwaj 2017 ³⁵	Δ eosinophil count: -25.3 eos/HPF	Δ eosinophil count: -50.7 eos/HPF	NR	NR	NR	NR
Dellon 2017 ³⁶	Response: 2.6% (1/38) Δ peak eosinophil count: -17.3 eos/HPF	Response: 38.8% (19/49) Δ peak eosinophil count: -117.0 eos/HPF	Δ mean EREFS score: 2.0% (0.4/20)	Δ mean EREFS score: -19.0% (-3.8/20)	Response: 44.7% (17/38) Remission: 13.2% (5/38) Δ mean Dysphagia Symptom Questionnaire: -8.9% (-7.5/84)	Response: 69.4% (34/49) Remission: 20.4% (10/49) Δ mean Dysphagia Symptom Questionnaire: -17.0% (-14.3/84)
Hirano 2017a ³⁷	Δ median eosinophil count: -136 cells/mm ² HPF	Δ median eosinophil count: -355 cells/mm ² HPF	Δ median EREFS score: -7.5% (-1.5/20)	Δ median EREFS score: -17.5% (-3.5/20)	Δ mean global assessment: -5.0% (-0.5/10)	Δ mean global assessment: -25.0% (-2.5/10)
Hirano 2017b ³⁸	Response: 0.0% (0/24) for both <6 and <15 eos/HPF Δ peak eosinophil count: -7.4 eos/HPF Δ Histology Scoring System (HSS) grade: +3.9% Δ Histology Scoring System (HSS) stage: -3.5%	Response: 60.9% (14/23) for <6 eos/HPF and 78.3% (18/23) for <15 eos/HPF Δ peak eosinophil count: -94.1 eos/HPF Δ Histology Scoring System (HSS) grade: -64.2% Δ Histology Scoring System (HSS) stage: -58.1%	Δ median EREFS score: -1.5% (-0.3/20)	Δ median EREFS score: -9.5% (-1.9/20)	Response: 12.5% (3/24) by Straumann Dysphagia Index, 8.3% (2/24) by EEsAI PRO Δ Straumann Dysphagia Index: -14.4% (-1.3/9) Δ EEsAI: -11.3% (-11.3/100)	Response: 39.1% (9/23) by Straumann Dysphagia Index, 26.1% (6/23) by EEsAI PRO Δ Straumann Dysphagia Index: -33.3% (-3.0/9) Δ EEsAI: -34.6% (-34.6/100)
Lieberman 2017 ³⁹	Remission: 0.0% (0/7)	Remission: 11.1% (1/9) Δ mean peak eosinophil count: -11.6 eos/HPF	NR	NR	Δ Symptom Score: -30.7% (-9.9/32.2)	Δ Symptom Score: -58.8% (-22.3/37.9)

Ma *et al.*

Outcomes in EoE RCTs

Study	Placebo Histology Rate	Active Comparator Histology Rate	Placebo Endoscopy Rate	Active Comparator Endoscopy Rate	Placebo Symptom-Based Rate	Active Comparator Symptom-Based Rate
Lucendo 2017 ^{†40}	Remission: 0.0% (0/29) Δ mean peak eosinophil count: -4 eos/mm ² HPF	Remission: 93.2% (55/59) Δ mean peak eosinophil count: -226 eos/mm ² HPF	Remission: 0.0% (0/29)	Remission: 61.0% (36/59)	Remission: 13.8% (4/29) Δ mean patient global assessment: -19.0% (-1.9/10)	Remission: 59.3% (35/59) Δ mean patient global assessment: -38.0% (-3.8/10)

781

782 For trials with multiple active comparators, results reported for highest administered dose

783 [†] Results reported in abstract form

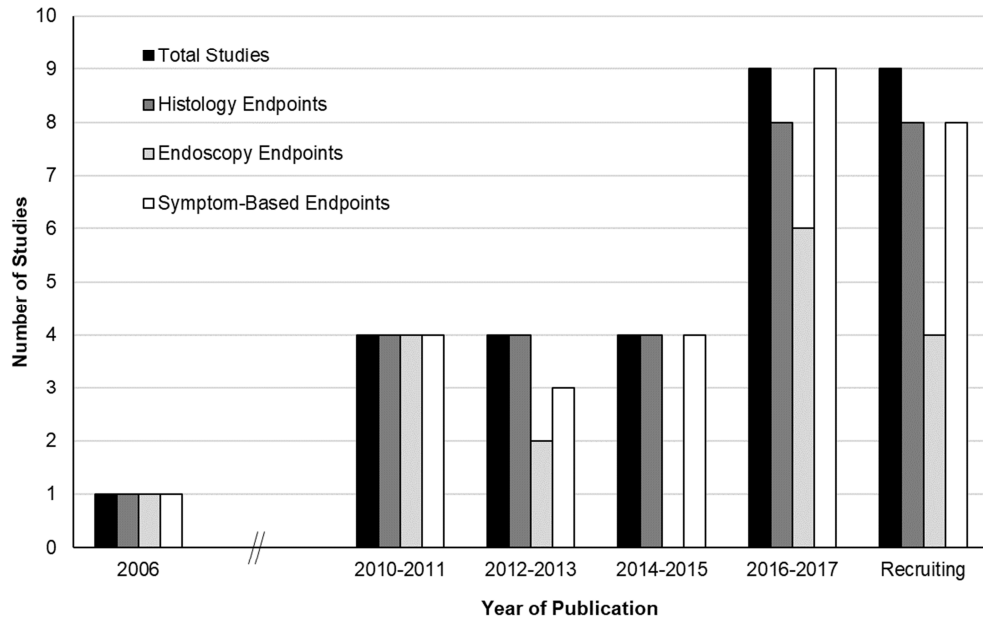
784 EEsAI EoE Activity Index, HPF high power field, HSS Histology Scoring System, NR not reported, eos eosinophils, EREFS EoE

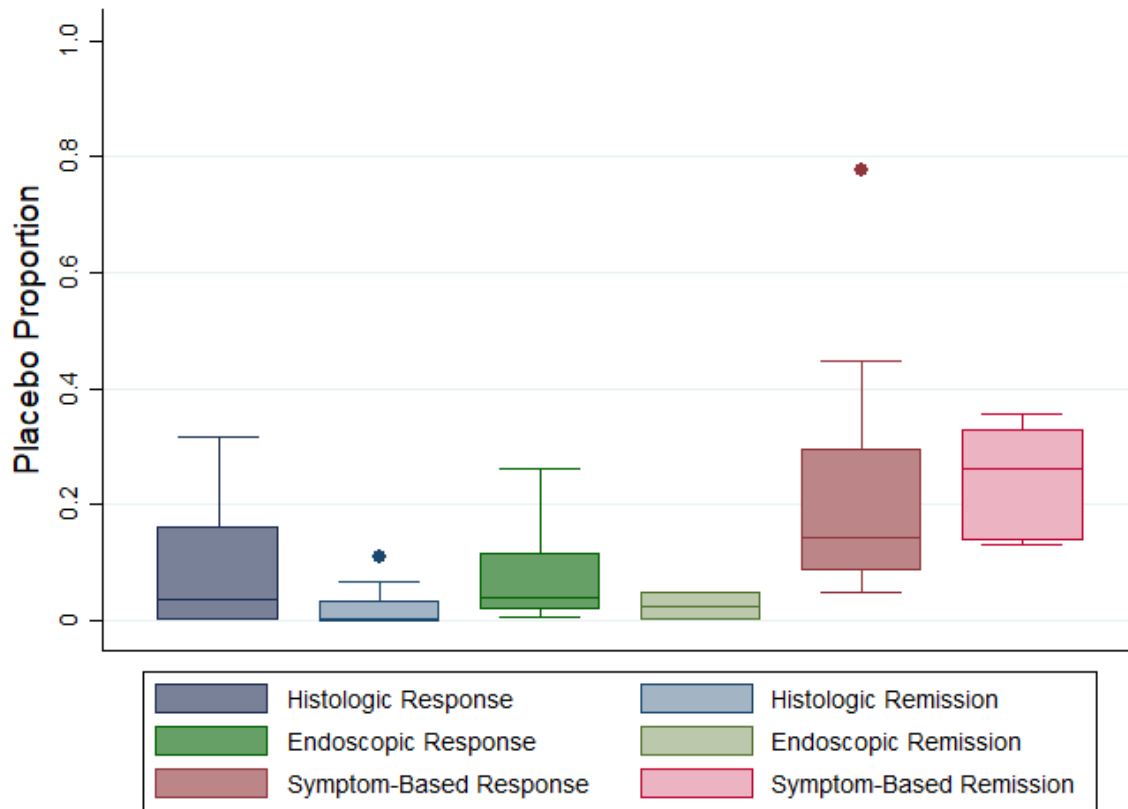
785 Endoscopic Reference Scoring System

786 Δ Change in pre- and post-treatment mean score in the placebo group, percentage change calibrated to scale of measurement

787 instrument

788





Supplemental File 1. Search strategy*MEDLINE*

1. random\$.tw.
2. factorial\$.tw.
3. (crossover\$ or cross over\$ or cross-over\$).tw.
4. placebo\$.tw.
5. single blind.mp.
6. double blind.mp.
7. triple blind.mp.
8. (singl\$ adj blind\$).tw.
9. (double\$ adj blind\$).tw.
10. (tripl\$ adj blind\$).tw.
11. assign\$.tw.
12. allocat\$.tw.
13. randomized controlled trial/
14. or/1-13
15. (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.)
16. 14 not 15
17. eosinophilic esophagitis.mp. or exp eosinophilic esophagitis/
18. (eosinophil* and esophag*).mp.
19. (eosinophil* and oesophag*).mp.
20. or/17-19
21. 16 and 20

EMBASE

1. random\$.tw.
2. factorial\$.tw.
3. (crossover\$ or cross over\$ or cross-over\$).tw.
4. placebo\$.tw.
5. single blind.mp.
6. double blind.mp.
7. triple blind.mp.
8. (singl\$ adj blind\$).tw.
9. (double\$ adj blind\$).tw.
10. (tripl\$ adj blind\$).tw.
11. assign\$.tw.
12. allocat\$.tw.
13. crossover procedure/
14. double blind procedure/
15. single blind procedure/
16. triple blind procedure/
17. randomized controlled trial/
18. or/1-17
19. (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.)
20. 18 not 19
21. eosinophilic esophagitis.mp. or exp eosinophilic esophagitis/
22. (eosinophil* and esophag*).mp.
23. (eosinophil* and oesophag*).mp.

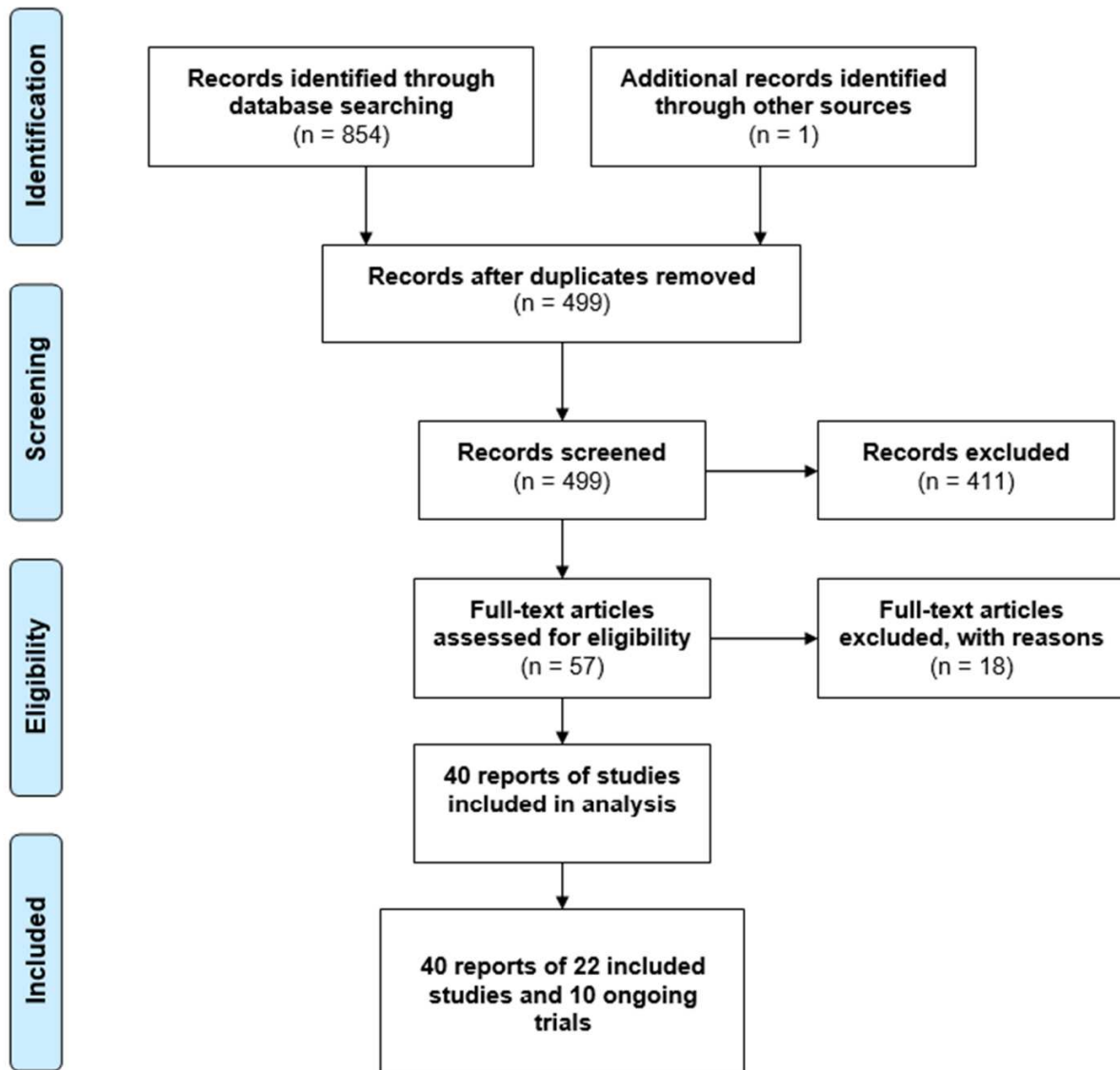
Ma *et al.*

Outcomes in EoE RCTs

- 24. or/21-23
- 25. 20 and 24

Cochrane Central Register of Controlled Trials

1. eosinophilic esophagitis
2. eosinophilic oesophagitis
3. or/1-2



Supplemental Figure 1. PRISMA diagram

