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Variability in Placebo Response Across Biologic and Small Molecule Classes in Induction Randomized Controlled Trials for Ulcerative Colitis: A Systematic Review and Meta-Analysis

Mohammad Adam

Moh.nooraldaim@gmail.com

University of Missouri-Kansas City

Fatima Elmustafa

Henry Ford Health

Harpreet Kaur

Allegheny Health Network

Yasmin Ali

Hennepin Healthcare System Inc

Miqdad Dafaallah

Mercy One Des Moines Medical Center

Abdellatif Ismail

University of Maryland Medical Center

Amro Abdelatif

Howard University

Ali Osman

Washington University

Mohamed Refaat

University of Missouri-Kansas City

Rahul Karna

University of Minnesota

Mouhanad Mohamed

Mayo Clinic-Rochester

Mohammad Bilal

University of Colorado

Mohamed Abdallah

Corewell Health Beaumont Hospital

Suha Abushamma

Cleveland Clinic, Gastroenterology-IBD Division

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Abstract

Background: Placebo response is crucial in interpreting treatment efficacy in ulcerative colitis (UC) trials. While it has been broadly studied, it remains underexplored in trials involving the growing number of biologics and small molecules for ulcerative colitis.

Methods: We systematically searched PubMed, Embase, Scopus, Web of Science, and Cochrane CENTRAL from inception to November 13, 2024. Eligible studies were induction-phase RCTs, including adult patients with moderate-to-severe UC who received a biologic and a small-molecule against a placebo. Primary outcomes were pooled clinical and endoscopic response and remission rates. Safety outcomes included adverse events (AEs), serious adverse events (SAEs), and withdrawal rates. Random-effect models were used for meta-analysis. Meta-regression identified predictors of placebo outcomes.

Results: 26 induction RCTs with 3,937 placebo-treated patients were included. IL inhibitor trials had the highest placebo clinical response (36%) and endoscopic remission (21%), while JAK inhibitors had the lowest (21% and 2%). Overall placebo rates were 34% for clinical response, 8% for clinical remission, 19% for endoscopic response, and 11% for endoscopic remission. Adverse events occurred in 54%, SAEs in 8%, and withdrawals in 18%. Younger age and longer follow-up were linked to higher placebo responses; recent trials showed reduced endoscopic effects.

Conclusion: These findings highlight the need to account for placebo variability in trial design and interpretation, particularly as biologic and small-molecule therapies continue to expand in UC treatment.

Study Highlights

WHAT IS KNOWN

Placebo response rates in UC trials vary widely by endpoint and trial design.

Previous meta-analyses included both non-biologic and biologic therapies.

WHAT IS NEW HERE

Focused analysis on biologics and small molecules in UC induction trials.

IL inhibitor trials had the highest placebo response; JAK inhibitors had the lowest.

Longer follow-ups and younger ages increase placebo clinical and endoscopic responses.

I. Introduction

The treatment landscape of ulcerative colitis (UC) has been transformed by the introduction of biologics and small molecules, offering improved efficacy and reshaping therapeutic strategies over the past two decades(1, 2). A critical aspect of assessing the efficacy and safety of these treatments in randomized controlled trials (RCTs) is the choice of an appropriate comparison group. When ethically and practically

feasible, the placebo control groups remain the gold standard for establishing a benchmark for treatment efficacy(3, 4). A thorough understanding of placebo response rates is not only crucial for accurately interpreting trial outcomes but also for optimizing study design, improving patient selection, and mitigating biases in future RCTs (5–7).

Placebo response rates are influenced by multiple factors that either amplify or diminish the response; these factors include study design, population characteristics, and baseline disease severity [5,7]. These responses can also vary based on the type of therapeutic mechanism being evaluated and the criteria used to define outcomes such as clinical remission or endoscopic improvement (8). The introduction of biologics and small molecules has further highlighted the importance of carefully analyzing placebo outcomes, as these studies differ in design & methodology from traditional non-biologic therapies, potentially influencing placebo response rates in trials (9–11).

While earlier meta-analyses primarily focused on placebo responses in the pre-biologics era, reporting a placebo clinical response rate of 28%(12), more recent analyses, including trials of biologics, small molecules, and non-biologic therapies, have shown a higher placebo response rate of 32%. These studies have identified key determinants of placebo response, such as centralized endoscopy readings, baseline disease severity, prior biologic exposure, and follow-up duration(7). Given these evolving placebo response patterns and the increasing use of biologics and small molecules, a contemporary analysis is warranted. Unlike prior meta-analyses, which included non-biologic therapies and did not include newly approved therapies, our meta-analysis focuses exclusively on biologics and small molecules, incorporating recent RCTs evaluating newer agents such as Filgotinib, Ozanimod, Etrolizumab, Etrasimod, Mirikizumab, Upadacitinib, and Risankizumab. This updated analysis provides a more contemporary and targeted assessment of placebo responses in trials of advanced therapies.

II. Methods

Search Strategy

This systematic review and meta-analysis adhered to the PRISMA guidelines. A comprehensive literature search was conducted across five databases: PubMed, Embase, Scopus, Web of Science, and Cochrane CENTRAL. The search covered studies published from database inception to November 13, 2024, using a combination of keywords and MeSH terms related to "Ulcerative Colitis", "placebo effect," and "Adverse effect." Detailed search strategies are available in the supplementary material **(Supplementary Table 1).**

Study Selection and Eligibility Criteria

Studies were eligible for inclusion, provided they fulfilled the following criteria: 1) Induction Randomized controlled Trials; 2) Population includes adults aged 18 years or older with moderate-to-severe ulcerative colitis; 3) Intervention focused on placebo arms of randomized controlled trials, while 4) Comparator included biologic agents or small molecules. Exclusion criteria encompassed phase 1 or 2 RCTs, nonrandomized trials, studies involving pediatric populations, observational studies, case series, qualitative data, and conference abstracts lacking complete datasets. Four reviewers screened Titles and abstracts

independently (Y.A., M.D., A.A. & A.I.) using predefined eligibility criteria. Full-text articles were reviewed to confirm inclusion, with any disagreements resolved by the principal Author (M.A.) through discussion. The entire selection process was documented using a PRISMA flow diagram.

Data Extraction and Study Outcomes

Two reviewers independently (H.K. & F.A.) extracted data, which was then cross-verified for accuracy. The extracted variables included study characteristics (publication year, phase, follow-up duration, and sample size), patient characteristics (age, sex ratio, disease severity, and prior biologic exposure), and outcomes (clinical and endoscopic placebo response/remission rates, adverse events [AEs], serious adverse events [SAEs], and withdrawal rates). Information on the intervention drug and its pharmacologic therapeutic class in the comparison arm was also recorded. All data were extracted into Microsoft Excel® [Version 2412 Build 16.0.18324.20092]. Outcome proportions were analyzed using an intention-to-treat approach, and the definitions used by each trial for clinical response, clinical remission, and endoscopic response outcomes included in our meta-analysis are detailed in (**Supplementary Table 8)**.

Statistical Analysis

The statistical analysis evaluated pooled placebo response, remission, and safety outcomes in clinical trials for moderate-to-severe ulcerative colitis. Pooled proportions for clinical remission, clinical response, endoscopic remission, endoscopic response, adverse events (AEs), serious adverse events (SAEs), and withdrawal rates were calculated using random-effects models, with effect sizes (ES) and 95% confidence intervals (CIs) reported. Heterogeneity was assessed using the I^2 statistics. Subgroup pooled proportion based on drug intervention & pharmacologic therapeutic class was also calculated. Meta-regression analyses explored study-level predictors of placebo response, remission, and safety outcomes, including mean age, follow-up duration, year of publication, sample size, gender ratio, disease duration, and prior TNF inhibitor exposure. Statistical analyses and visualizations, including forest plots, were conducted using Stata 18, providing valuable insights into the efficacy and safety of placebos in ulcerative colitis trials.

III. Results

Search Result & Study Selection

A total of 3,460 records were identified through database searches across PubMed, Cochrane, WOS, SCOPUS, and EMBASE. After removing 1,520 duplicates and 89 records deemed ineligible by automation tools, 2,439 reports were assessed for retrieval. Among these, 1,423 reports were excluded, and 246 were excluded due to phase 1 or 2 status, secondary analysis, or post hoc studies. A total of 26 trials were included in this analysis following a systematic review process **(Supplementary Fig. 1).** Across all trials, 3,937 participants were randomized to placebo.

Studies Characteristics

The mean follow-up duration was 16.58 weeks (6–54 weeks), with placebo group populations ranging from 41 to 331 patients per trial. The mean participant age was 40.28 years (34.5–44.5), and disease duration

averaged 6.28 years (range: 1.0–10.2). The total number of males was 2,441 and females 1,496, resulting in a male-to-female ratio of 1.63:1. Interventions comparison included TNF inhibitors (Infliximab, Adalimumab, Golimumab), integrin inhibitors (Vedolizumab, Etrolizumab), IL inhibitors (Ustekinumab, Risankizumab, Mirikizumab), JAK inhibitors (Tofacitinib, Upadacitinib, Filgotinib) and S1P receptor modulators (Ozanimod, Etrasimod) (Table 1).

Table 1
Summary characteristics of the included RCTs.

Trial Name (Identifier)	Study ID	Intervention	Follow-up Duration (Weeks)	Total population of the Placebo Group	Mean Age (Yrs)	M/F (No.)	Disease Duration (Yrs, Mean)
ACT1	Rutgeerts, 2005	Infliximab	54	121	41.5	72/49	6.2
ACT2	Rutgeerts, 2005	Infliximab	30	123	40.5	71/52	6.5
No Name	Reinisch, 2011	Adalimumab	8	130	37	246	5.4
ULTRA 2	Sandborn, 2012	Adalimumab	8	246	41.3	152/94	8.5
GEMINI 1	Feagan, 2013	Vedolizumab	6	149	41.2	92/57	7.1
No Name	Suzuki, 2013	Adalimumab	52	96	42.7	70/26	8
The PURSUIT-SC	Sandborn, 2014	Golimumab	6	331	40	175/156	6.3
No Name	Jiang, 2015	Infliximab	30	41	34.5	25/16	4.4
No Name	Kobayashi, 2015	Infliximab	38	104	38.9	133/75	7.6
OCTAVE 1	Sandborn, 2017	Tofacitinib	8	122	41.8	77/45	6
OCTAVE 2	Sandborn, 2017	Tofacitinib	8	112	40.4	55/57	6.2
UNIFI	Sands, 2019	Ustekinumab	8	319	41.2	197/122	8
SELECTION (A)	Feagan, 2021	Filgotinib	10	137	41	87/50	6.4
SELECTION (B)	Feagan, 2021	Filgotinib	10	142	44	86/56	10.2
TRUE NORTH	Sandborn, 2021	Ozanimod	10	216	41.9	143/73	6.8
U-ACHIEVE	Danese 2022	Upadacitinib	8	154	44.5	97/57	6
U-ACCOMPLISH	Danese 2022	Upadacitinib	8	174	42	107/67	4.9

Trial Name (Identifier)	Study ID	Intervention	Follow-up Duration (Weeks)	Total population of the Placebo Group	Mean Age (Yrs)	M/F (No.)	Disease Duration (Yrs, Mean)
HIBISCUS I	Rubin 2022	Etrolizumab	10	72	36	39/33	4.7
HIBISCUS II	Rubin 2022	Etrolizumab	10	72	36.5	38/34	4
HICKORY	Peyrin-Biroulet, 2022	Etrolizumab	14	95	36	54/41	7.4
LUCENT	D'Haens, 2023	Mirikizumab	12	294	41.3	165/129	6.9
EARNEST	Travis, 2023	Vedolizumab	34	51	43.5	32/19	1
TACOS	Singh,2023	Tofacitinib	13	51	37.5	30/21	2.5
ELEVATE UC 52	Sandborn, 2023	Etrasimod	12	144	38.9	88/56	7.7
ELEVATE UC 12	Sandborn, 2023	Etrasimod	12	116	40.4	73/43	5.9
INSPIRE & COMMAND	Louis, 2024	Risankizumab	12	325	42.8	201/124	8.4

Placebo Response Rates

Clinical Response

The pooled rate across 24 studies evaluating clinical response was 34% (95% CI: 31–38%, I^2 = 76.04) **(**Fig. 1**).** Response rates have fluctuated between 30% and 50% over time, with notable variations among drug classes. IL inhibitors studies exhibited the highest placebo response rate at 36% (95% CI: 33–39%), followed by Anti-TNF agents & integrin inhibitors studies at 33% (95% CI: 31–36%, 29%-38% respectively). S1P receptor modulators demonstrated response rates of 31% (95% CI: 27–35%). Meanwhile, JAK inhibitors recorded the lowest response at 21% (95% CI: 18–24%), **(**Fig. 2**).** Individual drug-level analysis revealed Mirikizumab (42%) and Etrolizumab (39%) as having the highest placebo response rates, whereas Golimumab (23%) had the lowest rate **(**Fig. 3**).**

Clinical Remission

In 25 studies assessing clinical remission, the pooled rate was 8% (95% CI: 7–10%, I^2 = 70.31%) **(**Fig. 4**).** Across therapeutic categories, remission rates were relatively consistent (6–9%), with JAK inhibitors studies showing the lowest rate at 6% (95% CI: 5–8%), while Anti-TNF agents, IL inhibitors, and S1P receptor modulators exhibited remission rates between 8% and 9% (Fig. 5**).** Drug-specific analysis showed remission rates ranging from 4% (Upadacitinib) to 13% (Mirikizumab and Infliximab) **(**Fig. 6**)**.

Endoscopic Response

Eighteen studies investigated endoscopic response, revealing a pooled rate of 19% (95% CI: 15–23%, I^2 = 90.18%) **(**Fig. 7**).** Response rates varied widely (12–42%). Anti TNF trials demonstrated the highest response at 16% (95% CI: 14–19%), followed by integrin inhibitor and S1P receptor modulator trials (14% each, 95% CI: 11–17%). JAK inhibitors recorded the lowest response at 6% (95% CI: 5–8%) **(**Fig. 8**).** Among individual drugs, Etrolizumab (26%) and Golimumab (22%) studies had the highest response rates, whereas Upadacitinib (8%) and Infliximab (10%) trials exhibited the lowest **(**Fig. 9**).**

Endoscopic Remission

Placebo-induced endoscopic remission was assessed in 19 studies, with a pooled rate of 11% (95% CI: 6–15%, I^2 = 97.87%) **(**Fig. 10**).** Anti TNF and Integrin inhibitors RCTs showed the highest placebo remission rate at 13%, followed by IL inhibitors at 11% (95% CI: 9–13%). JAK inhibitors, in contrast, had the lowest remission rate at just 2% (95% CI: 1–3%) **(**Fig. 11**).** Among the individual therapies, Mirikizumab and Infliximab studies demonstrated the highest response rate at 21% and 20%, respectively, whereas Upadacitinib and tofacitinib had the lowest response rate at 2% and 1%, respectively **(**Fig. 12**).**

Placebo Safety

Adverse Effect

The pooled rate in 25 studies assessing adverse events in placebo arms was 54% (95% CI: 45–63%, I^2 = 97.95%) **(Supplementary Fig. 2).** Among therapeutic classes, Anti-TNF agents had the highest placebo adverse event rate (64%, 95% CI: 61–66%), followed by integrin inhibitors (54%, 95% CI: 49–58%) and JAK inhibitors (52%, 95% CI: 49–55%) studies. S1P receptor modulators reported the lowest rates at 29% (95% CI: 25–33%) **(Supplementary Fig. 3).** The highest rates were observed in trials involving Infliximab (78%) and Adalimumab (69%), while the lowest was seen with Etrasimod (21%) **(Supplementary Fig. 4).**

Placebo Severe Adverse Event Rates

Twenty-three studies reported severe adverse events, with a pooled SAE rate of 8% (95% CI: 6–10%, I^2 = 92.03%) **(Supplementary Fig. 5).** Across therapeutic classes, Anti-TNF agents exhibited the highest SAE rate at 12% (95% CI: 10–14%), whereas S1P receptor modulators had the lowest at 2% (95% CI: 1–3%) **(Supplementary Fig. 6).** The highest SAE rate was observed in placebo-treated participants from Infliximab trials (20%), while the lowest was in Etrasimod trials (1%) **(Supplementary Fig. 7).**

Withdrawal Rates

Withdrawal due to placebo treatment was analyzed in 19 studies, yielding a pooled rate of 18% (95% CI: 9–27%, I^2 = 99.07%) **(Supplementary Fig. 8).** Among therapeutic classes, Anti-Integrin agents had the highest withdrawal rates (19%, 95% CI: 15–23%), whereas S1P receptor modulators and JAK inhibitors had the lowest at 5% and 6%, respectively **(Supplementary Fig. 9)**. Infliximab studies reported the highest withdrawal rate at 38%, while Adalimumab trials had the lowest at 2% **(Supplementary Fig. 10).**

Factors Affecting Placebo Response

Clinical Response and Remission Predictors

The meta-regression analysis identified several factors influencing placebo-induced clinical response and remission rates. For clinical response, a higher mean age was associated with lower odds of response (OR = 0.984, p = 0.010), while a longer follow-up duration was associated with higher odds of placebo response (OR = 1.063, p = 0.040). Other variables, including year of publication, sample size, sex ratio, disease duration, and prior TNF exposure, were not statistically significant **(**Table 2**).** For clinical remission, longer follow-up duration was associated with higher odds of achieving placebo-induced remission (OR = 1.002, p = 0.001). However, year of publication, sample size, sex ratio, mean age, disease duration, and prior TNF exposure did not significantly influence clinical remission rates **(Supplementary Table 2).**

Table 2
Multivariate Meta-Regression Analysis of Study Characteristics for Predicting Clinical Response

Clinical Response Predictors				
Study Characteristics	Odd Ratio	P Value	[95% conf.	interval]
Year of Publication	1.001	0.626	0.996	1.007
Sample Size	0.999	0.147	< 0.999	> 1.000
Gender Ratio (M/F)	0.993	0.895	0.901	1.095
Mean Age (Y)	0.984	0.010	0.972	0.996
Follow-up Duration (Weeks)	1.063	0.040	1.003	1.127
Duration Disease (Weeks)	0.990	0.286	0.971	1.009
Previous TNF Exposure	0.958	0.244	0.892	1.029

Endoscopic Response and Remission Predictors

For endoscopic response, a longer follow-up duration (OR = 1.004, p = 0.042) and younger age (OR = 0.978, p < 0.001) were associated with higher odds of placebo-induced endoscopic improvement. Later years of publication (OR = 0.986, p = 0.001) and prior TNF exposure (OR = 0.873, p < 0.001) were associated with lower odds of endoscopic response **(Supplementary Table 3).** For endoscopic remission, a longer follow-up duration was associated with increased odds of remission (OR = 1.006, p = 0.002), whereas more recent trial publication years were associated with lower odds of placebo-induced remission (OR = 0.985, p < 0.001) **(Supplementary Table 4).**

Adverse Effects & Withdrawal Effects Predictors

The occurrence of any adverse events showed lower odds in more recently published trials (OR = 0.986, p = 0.089), although this did not reach statistical significance **(Supplementary Table 5).** Severe adverse events were associated with higher odds with longer follow-up duration (OR = 1.003, p < 0.001) but lower odds in more recent trials (OR = 0.993, p < 0.001) and among patients with prior TNF inhibitor exposure (OR = 0.951,

p = 0.014). Withdrawal due to adverse effects followed a similar pattern, with younger age (OR = 0.962, p = 0.045) and longer follow-up duration (OR = 1.013, p < 0.001) associated with higher odds of withdrawal, whereas more recent trial publication years were associated with lower odds (OR = 0.983, p = 0.026) **(Supplementary Tables 6 & 7).**

IV. Discussion

We found substantial placebo effects across clinical and endoscopic endpoints in this systematic review and meta-analysis of 26 induction RCTs involving biologics and small molecules for ulcerative colitis (UC). Among 3,937 placebo-treated patients, the pooled clinical response rate was 34%, with a markedly lower clinical remission rate of 8%. Endoscopic response and remission rates were also modest, at 19% and 11%, respectively. These results emphysize the ongoing influence of placebo effects in UC trials, even in the setting of advanced, targeted therapies(7, 13).

Also there were meaningful variability in placebo outcomes across therapeutic classes. Trials involving IL inhibitors exhibited the highest placebo clinical response (36%) and endoscopic remission (21%), while JAK inhibitor trials had the lowest placebo effects (21% clinical response, 2% endoscopic remission). These differences may be driven by trial design, route of administration, patient expectations, or disease phenotype. For instance, drugs administered intravenously or perceived as more potent may elicit stronger placebo responses(7). At the drug level, Mirikizumab and Infliximab were associated with higher placebo effects, while Upadacitinib and Tofacitinib consistently showed the lowest.

Meta-regression further identified younger patient age and longer trial duration as independent predictors of higher placebo response and remission rates(14). Conversely, more recent trials and prior TNF exposure were associated with lower endoscopic placebo effects. These findings suggest that advancements in trial methodology, such as central reading of endoscopy and objective endpoint definitions, may help attenuate placebo signals over time (16). Our study aligns with prior meta-analyses but offers a narrower, class-specific lens focused exclusively on biologics and small molecules, making it particularly relevant to modern UC trial design.

Despite its strengths, this analysis has limitations. Heterogeneity across studies in population characteristics, outcome definitions, and follow-up periods may have influenced pooled estimates. While meta-regression helped adjust for key variables, residual confounding remains possible. Our focus on phase 3 RCTs enhances internal validity but may limit applicability to real-world settings. Safety outcome reporting also varied, particularly about how adverse events and withdrawals were defined

Nevertheless, our findings are clinically and methodologically important, highlighting factors of placebo arms, which must be considered when interpreting both efficacy and safety outcomes in UC trials. In summary, placebo effects in UC trials remain variable and clinically meaningful, particularly across biologic and small-molecule classes. Future trials should account for placebo susceptibility as these therapies expand by incorporating standardized designs, objective endpoints, and robust blinding methods. Understanding the drivers of placebo response is essential to assess treatment efficacy and accurately improve trial design in UC.

Abbreviations

UC: Ulcerative colitis; AE: Adverse event; SAE: Serious adverse event; TNF: Tumor necrosis factor; RCT: Randomized controlled trial; S1P: Sphingosine-1-phosphate.

Declarations

Ethics approval and consent to participate

Not applicable. This study used data from previously published randomized controlled trials.

Consent for publication

Not applicable.

Availability of data and materials

This published article and its supplementary information files include all data generated or analyzed during this study.

Competing Interests

The authors declare that they have no competing interests.

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Authors' contributions

Mohammad Adam conceptualized the study, conducted the literature review, and drafted the original manuscript.

Fatima Elmustafa, Harpreet Kaur, Yasmin Ali, Miqdad Dafaallah and Mohamed Refaat contributed to study screening, data extraction, and quality assessment.

Abdellatif Ismail, Amro Abdelatif, Ali Osman, Rahul Karna, and Mouhanad Mohamed contributed to data interpretation, manuscript editing, and critical manuscript revision.

Mohammad Bilal, Mohamed Abdallah, and Suha Abushamma supervised the study, contributed to critical intellectual input, and approved the final manuscript.

All authors reviewed and approved the final version of the manuscript.

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Figures

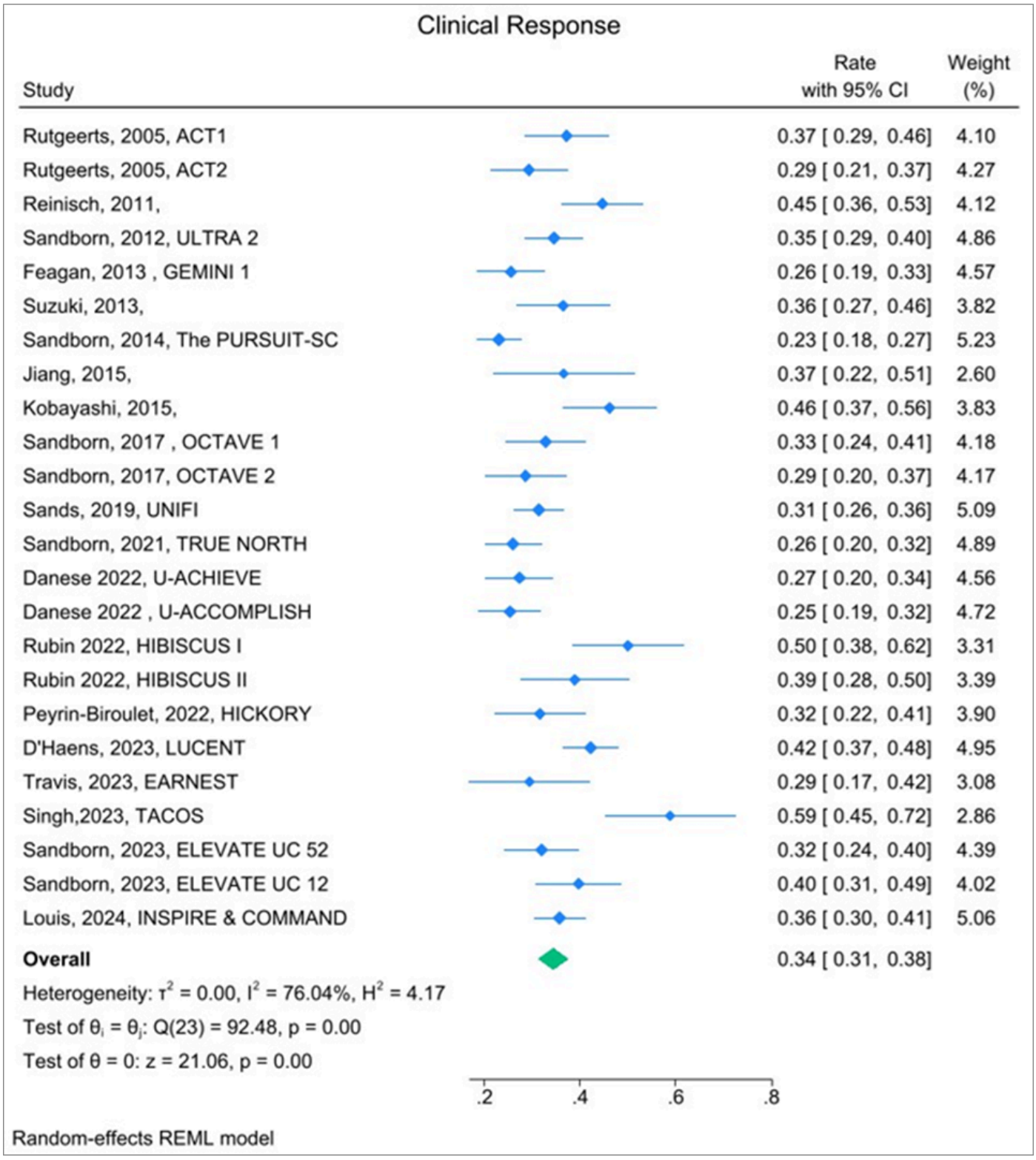


Figure 1

Pooled placebo Clinical Response among RCTs, CI: confidence interval

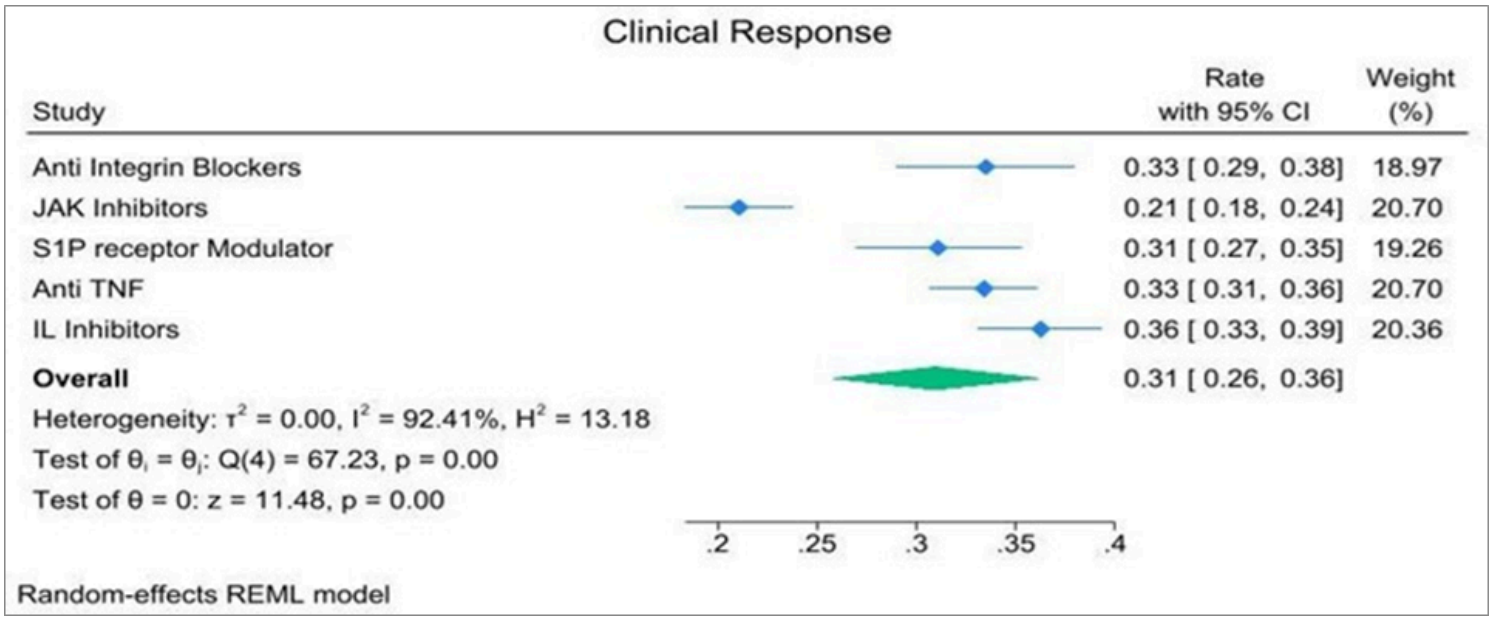


Figure 2

Pooled placebo Clinical Response among therapeutic class subgroup analysis,, CI: confidence interval

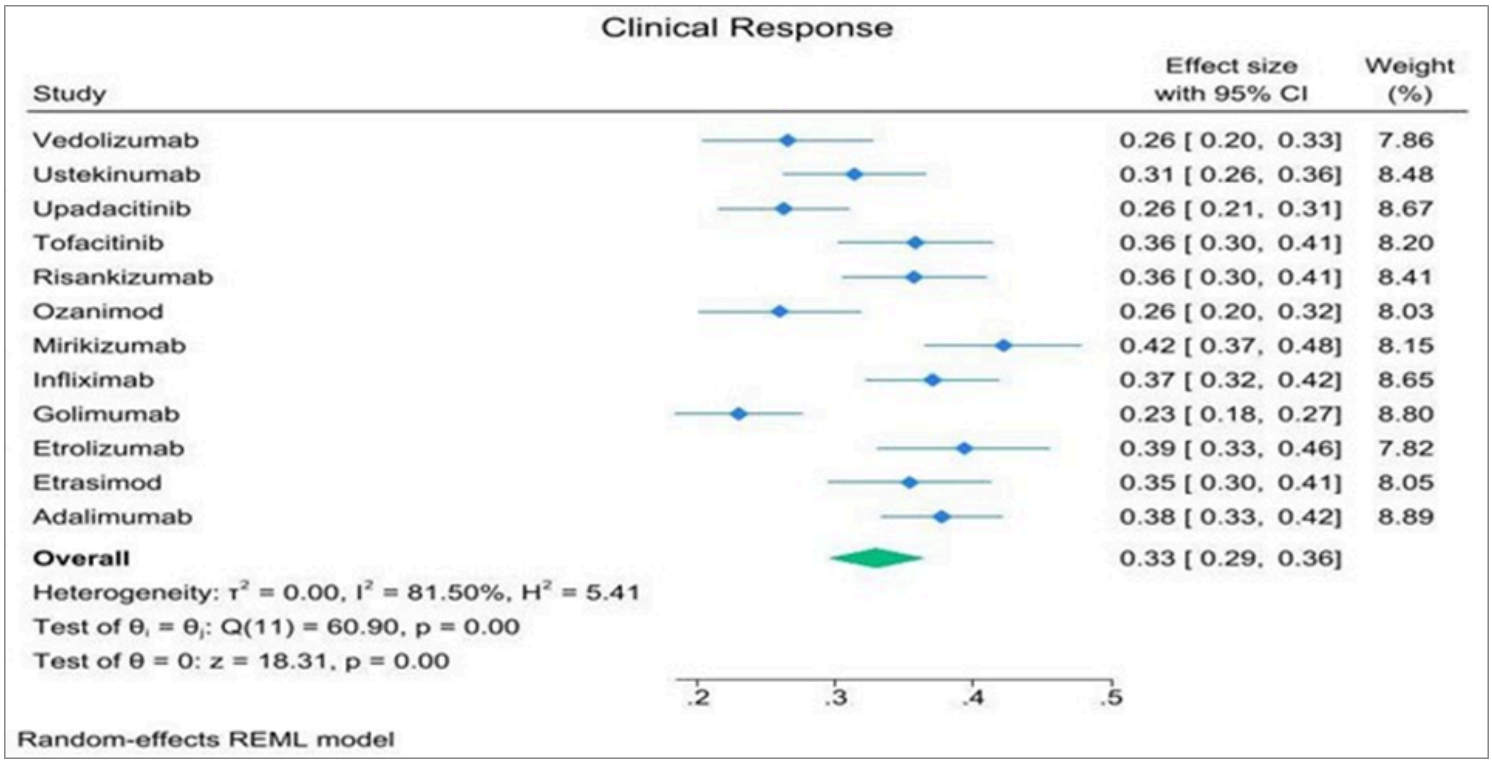


Figure 3

Pooled placebo Clinical Response based on drug class subgroup analysis, CI: confidence interval

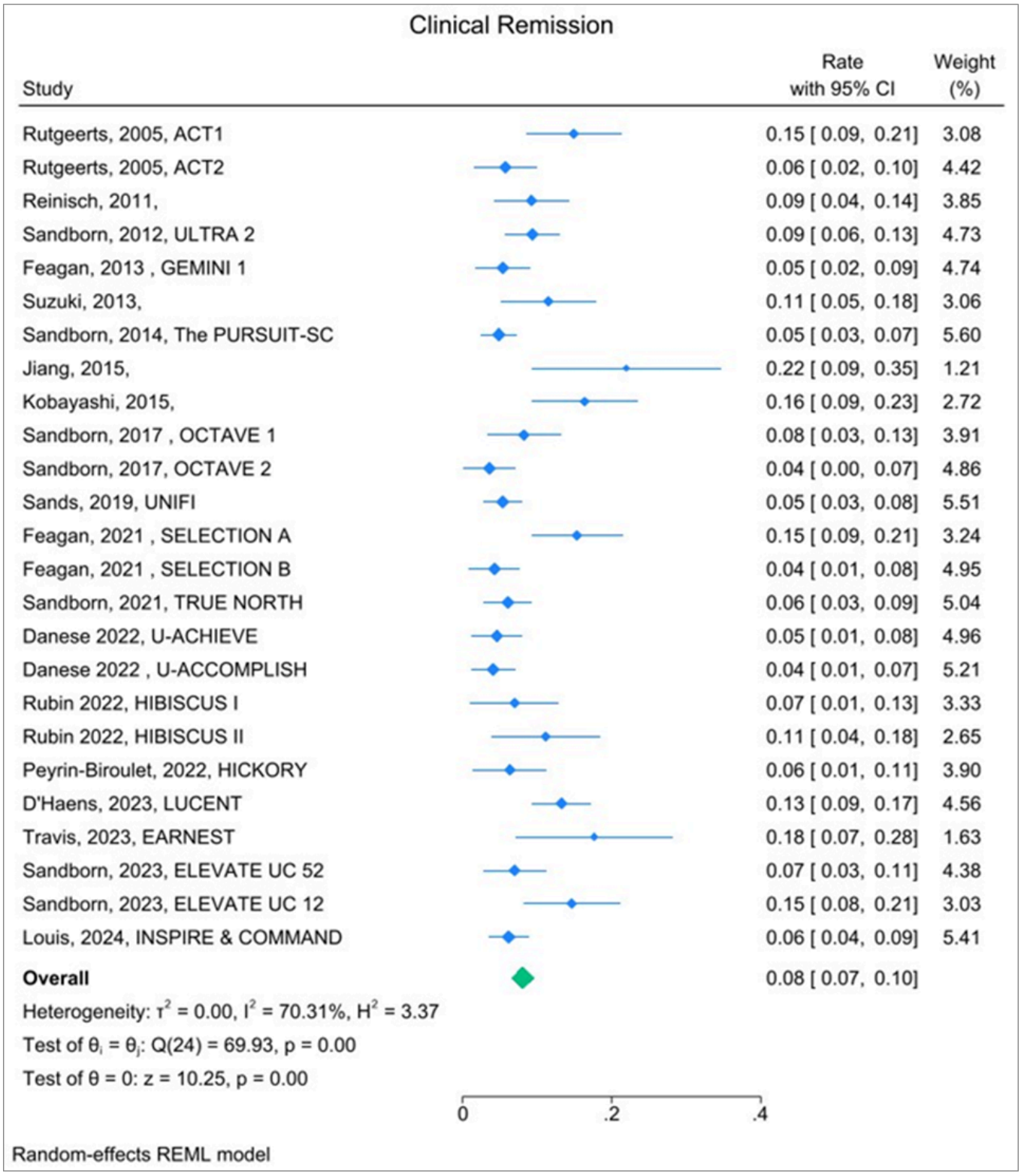


Figure 4

Pooled placebo Clinical Remission among RCTs, CI: confidence interval

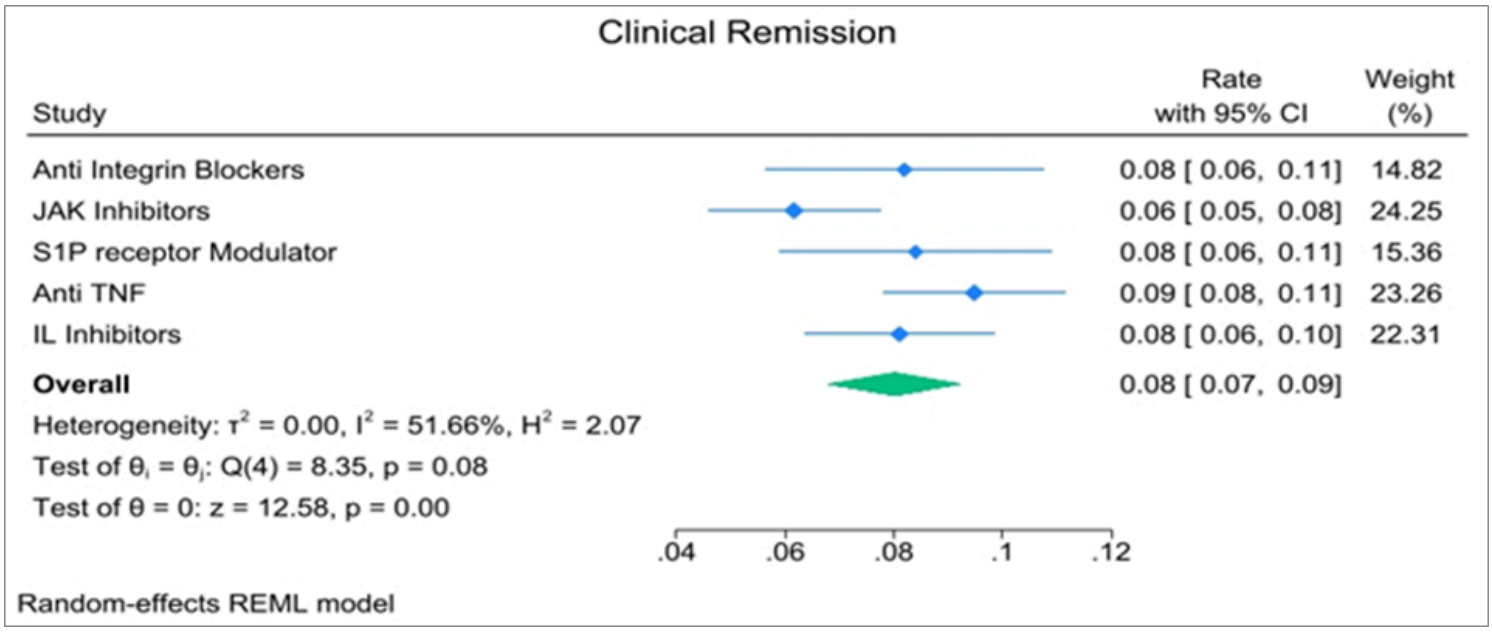


Figure 5

Pooled placebo Clinical Remission among therapeutic class subgroup analysis,, CI: confidence interval

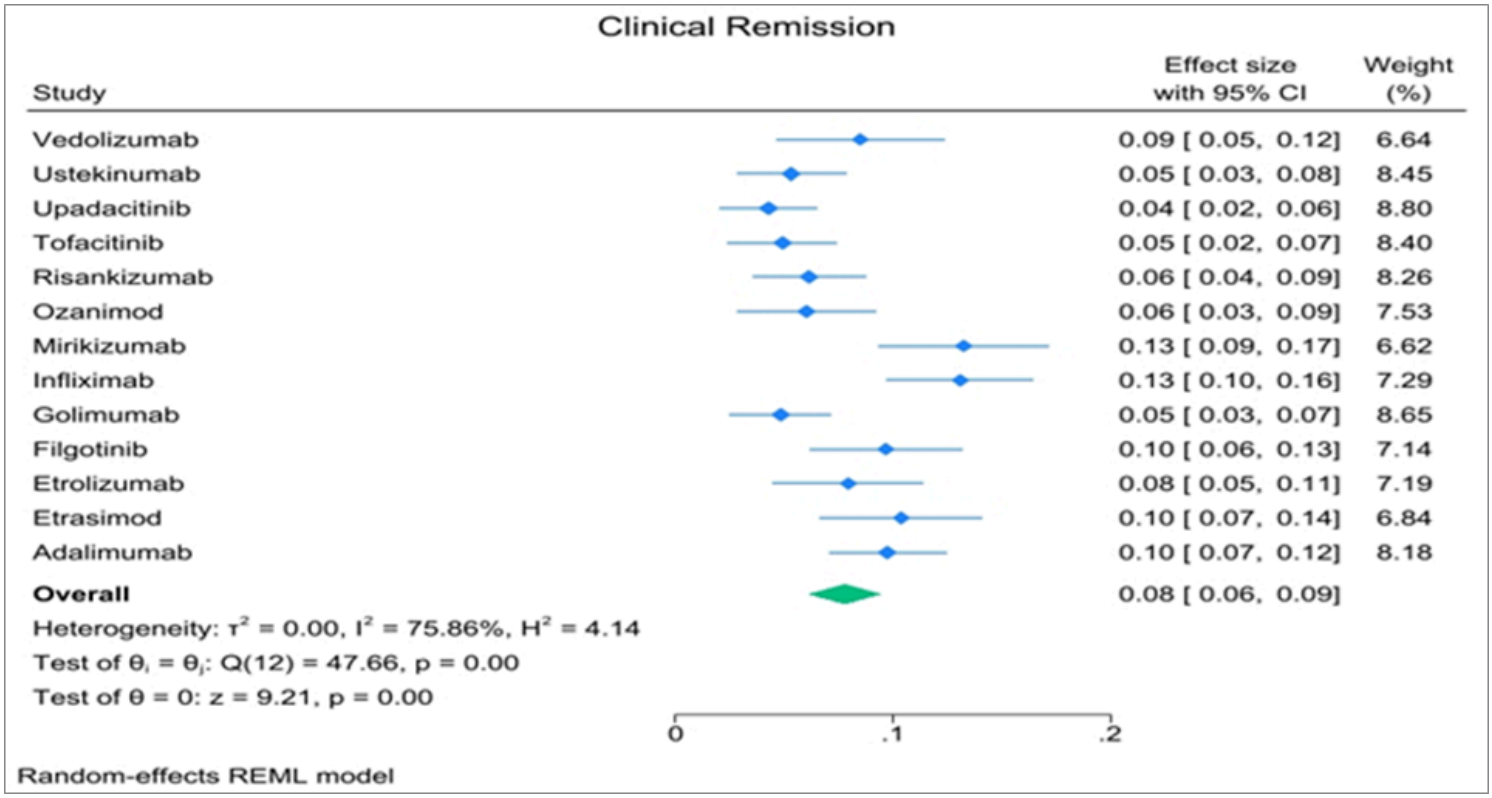


Figure 6

Pooled placebo Clinical Remission based on drug class subgroup analysis, CI: confidence interval

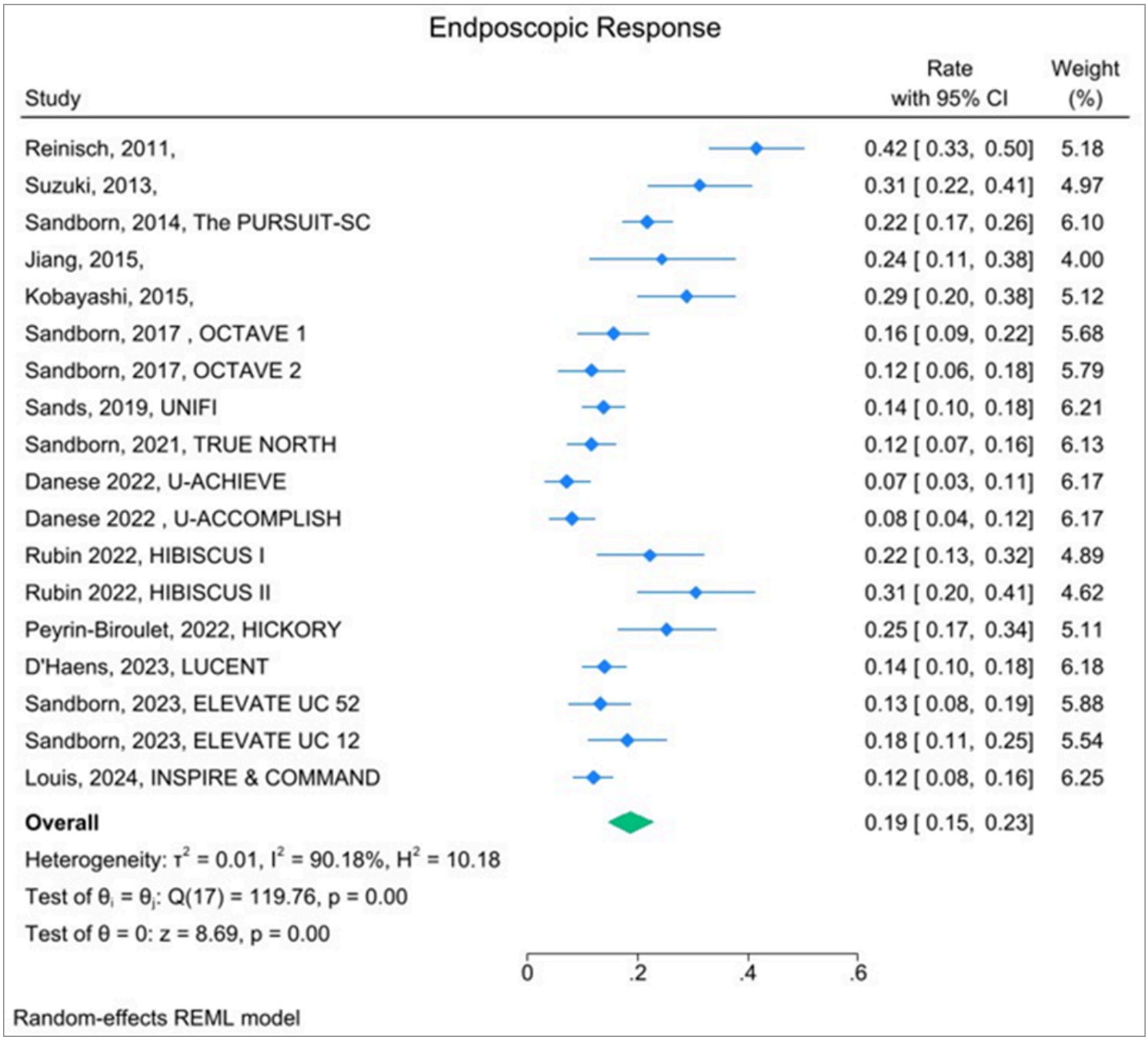


Figure 7

Pooled placebo Endoscopic Response among Published RCTs, CI: confidence interval

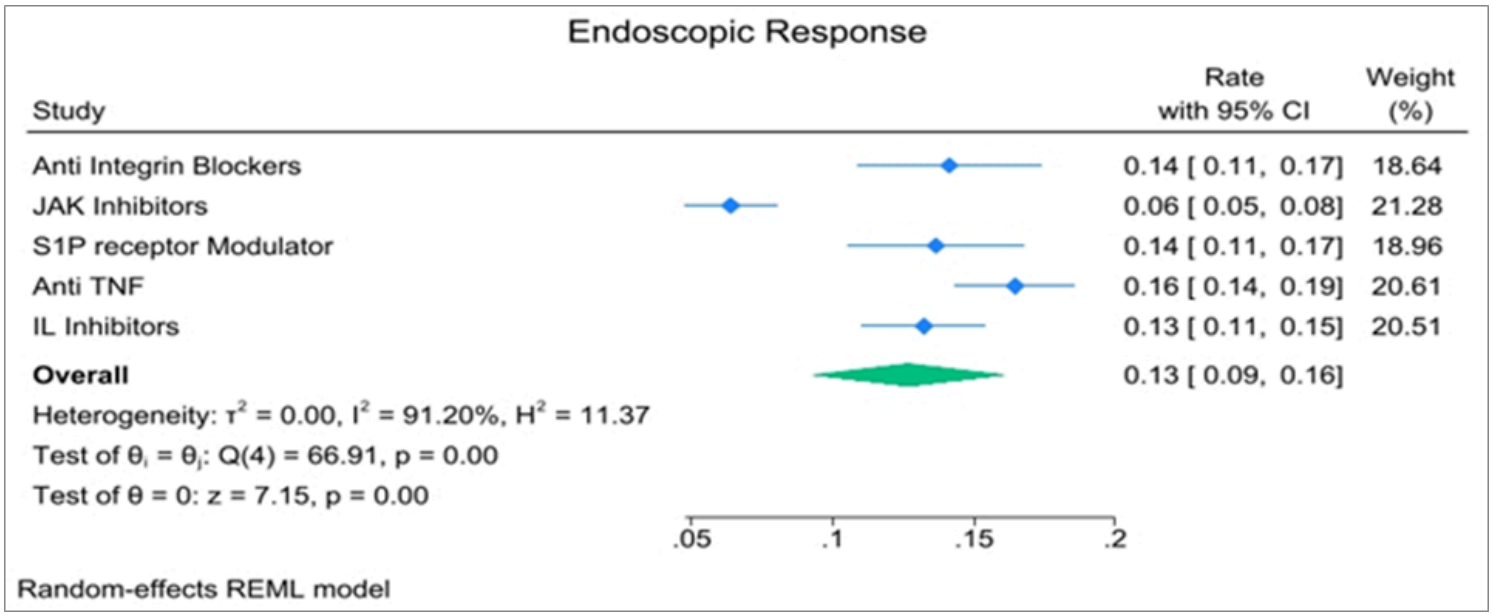


Figure 8

Pooled placebo Endoscopic Response among therapeutic class subgroup analysis,, CI: confidence interval

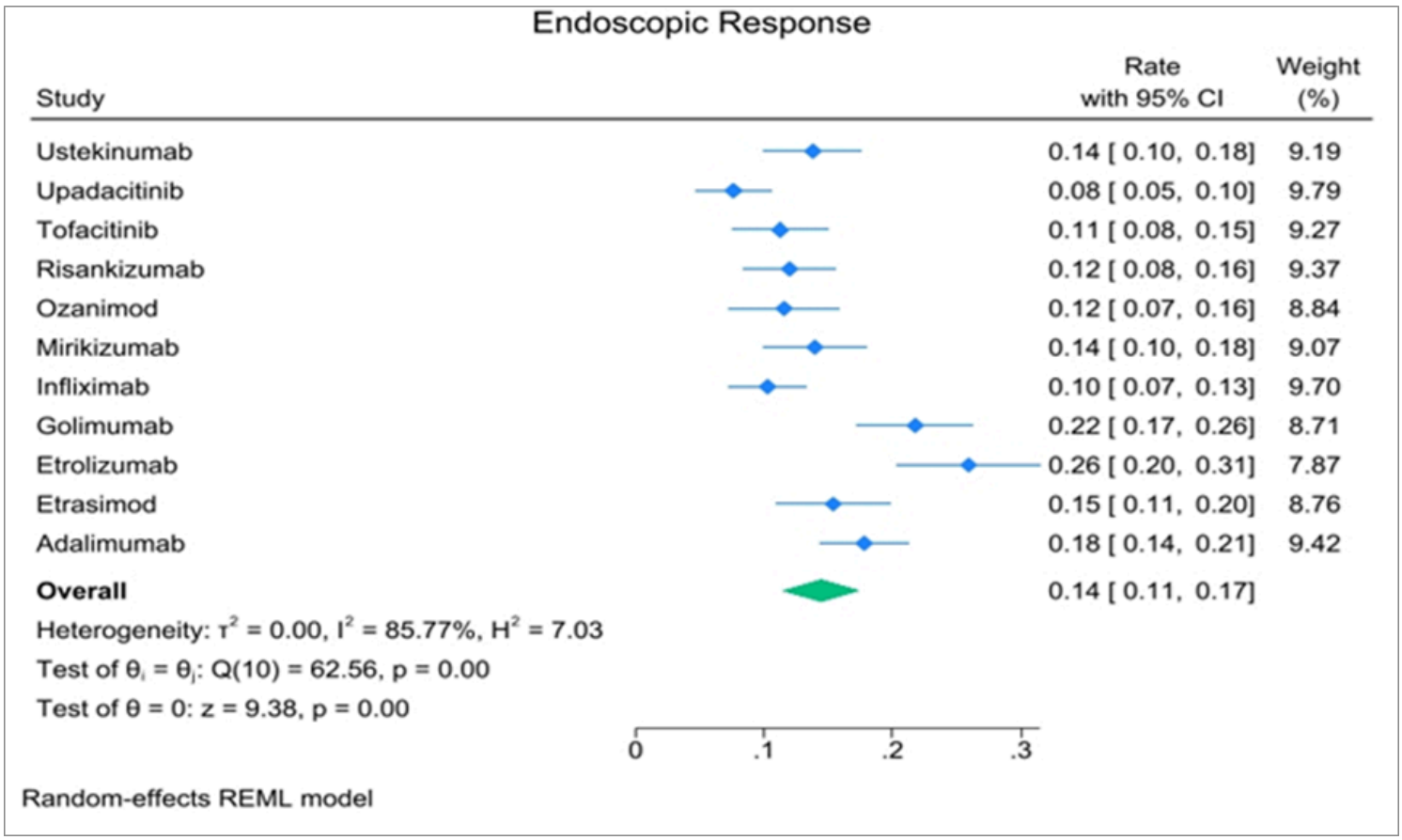


Figure 9

Pooled placebo Endoscopic Response based on drug class subgroup analysis, CI: confidence interval

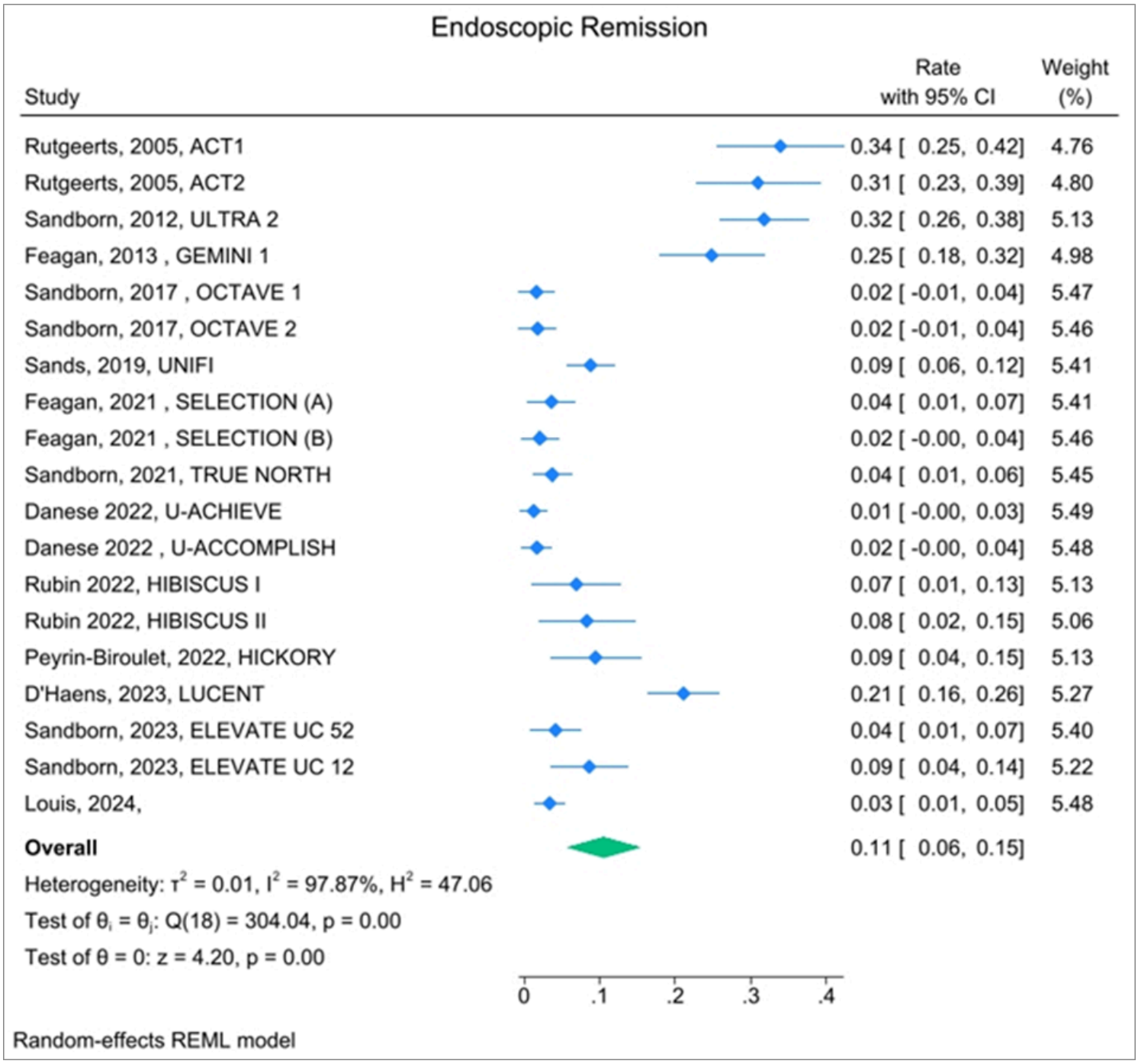


Figure 10

Pooled placebo Endoscopic Remission among Published RCTs, CI: confidence interval

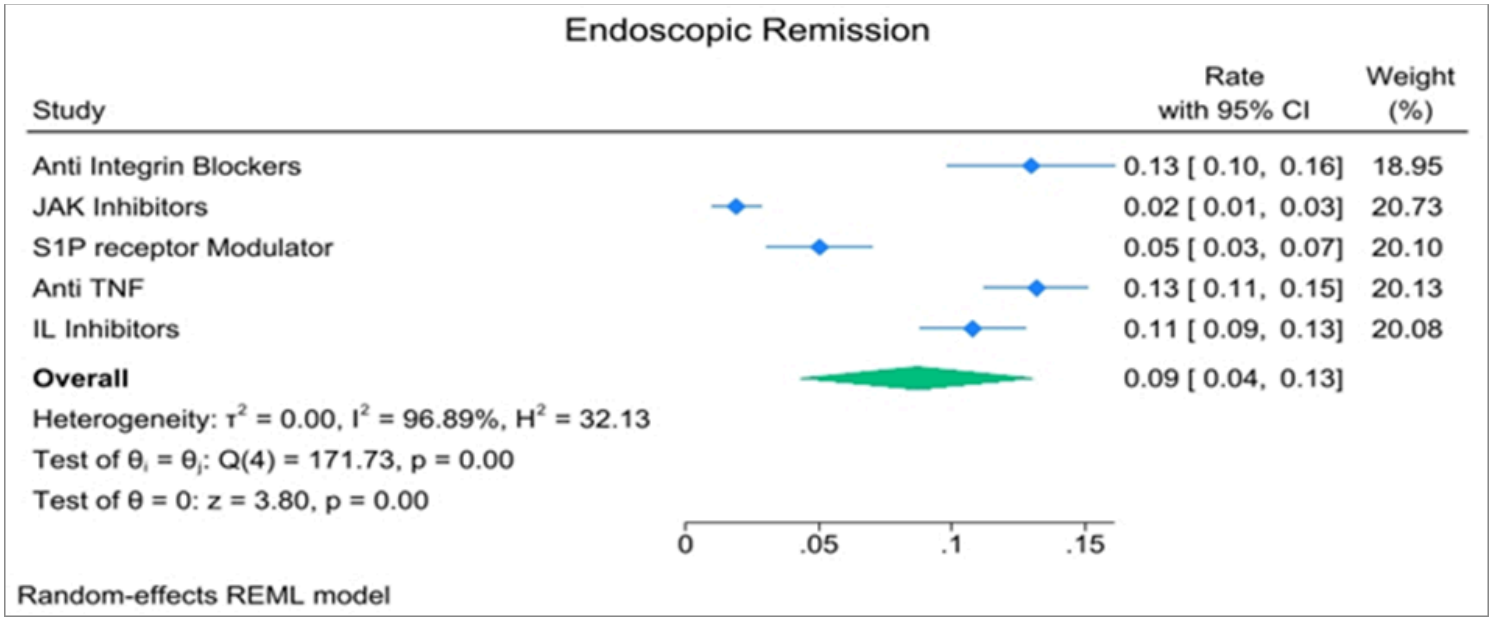


Figure 11

Pooled placebo Endoscopic Remission among therapeutic class subgroup analysis,, CI: confidence interval

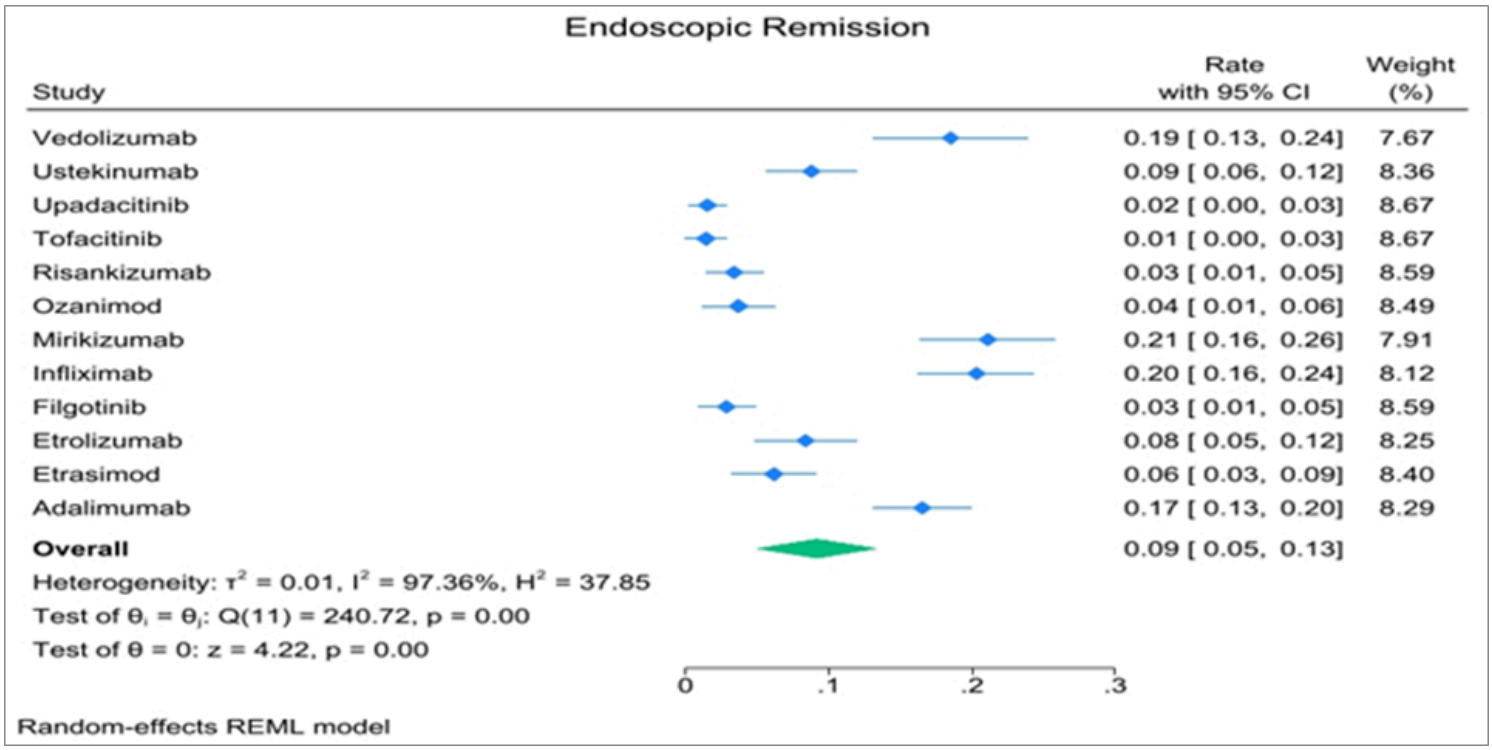


Figure 12

Pooled placebo Endoscopic Remission based on drug class subgroup analysis, CI: confidence interval

Supplementary Files

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- Supplementary.docx