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Impact of Pharmacological Treatments for Chronic Spontaneous Urticaria with an Inadequate Response to H1-antihistamines on Health-Related Quality of Life: A Systematic Review and Network Meta-Analysis

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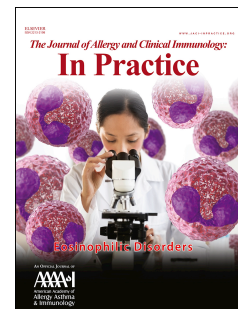
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Title: Impact of Pharmacological Treatments for Chronic Spontaneous Urticaria with an Inadequate Response to H1-antihistamines on Health-Related Quality of Life: A Systematic Review and Network Meta-Analysis

Short title: Treatments to Improve HRQOL for Refractory CSU

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Competing interests

The authors declare that they have no competing interests.

ABSTRACT

BACKGROUND: Recently, pharmacological treatment options for H1-antihistamine-refractory chronic spontaneous urticaria (CSU) have increased dramatically; however, their effects on patient-reported outcomes (PROs), including health-related quality of life (HRQOL), remain unclear.

OBJECTIVE: This study was designed to compare the impact of these treatments on HRQOL among H1-antihistamine-refractory CSU patients.

METHODS: We completed a comprehensive search of the available literature in the electronic databases, grey literature, and preprint reports up to April 19, 2021, with no language restrictions. The primary outcome for evaluation was a change in HRQOL from the baseline and secondary outcomes included patient unacceptability and other PROs. We used a random-effects network meta-analysis and estimated differences in standardized mean differences (SMDs) and odds ratios with 95% confidence intervals. Evidence-based synthesis was based on magnitudes of effect size, evidence certainty, ranking of treatment effects, and clinically meaningful improvement.

RESULTS: Twelve randomized controlled trials encompassed 1,866 adolescent and adult patients were included. Our evidence synthesis analyses revealed that hydroxychloroquine (SMD, -1.00 [-1.61 to -0.39]), 72 mg ligelizumab (SMD, -0.66 [-0.96 to -0.35]), 240 mg ligelizumab (SMD, -0.67 [-0.98 to -0.37]), and 300 mg omalizumab (SMD, -0.53 [-0.67 to -0.39]) significantly improved HRQOL with a moderate beneficial effect. However, the use of hydroxychloroquine seems to be limited by a higher risk of patient unacceptability of treatment. Other secondary outcomes remain inconclusive based on the available evidence.

CONCLUSION: Both ligelizumab (72 or 240 mg) and 300 mg omalizumab appeared to be effective treatments for H1-antihistamine-refractory CSU, as they were closely associated with improved HRQOL.

HIGHLIGHTS BOX

What is already known about this topic?

- Several pharmacological treatments for H1-antihistamines-refractory chronic spontaneous urticaria (CSU) have been available, but their impact on patient-reported outcomes, including health-related quality of life (HRQOL) is unclear.

What does this article add to our knowledge?

- Based on the best available evidence synthesis, ligelizumab (72 or 240 mg) and 300 mg omalizumab significantly improved HRQOL with a moderate beneficial effect.

How does this study impact current management guidelines?

- To facilitate clinical meaningful improvements in HRQOL, biologics ligelizumab (72 or 240 mg) and 300 mg omalizumab appeared to be effective treatments for H1-antihistamine-refractory CSU.

Key words: chronic spontaneous urticaria; health-related quality of life; network meta-analysis; patient-reported outcomes; resistant H1-antihistamines

Abbreviations used

ASST	Autologous serum skin test
AE-QoL	Angioedema QoL Questionnaire
CIs	Confidence intervals
CSU	Chronic spontaneous urticarial
CU-Q2oL	Chronic Urticaria Quality of Life questionnaire
DLQI	Dermatology Life Quality Index
HRQOL	Health-related quality of life
MCID	Minimal clinically important difference
MD	Mean difference
NMA	network meta-analysis

101	ORs	Odds ratios
102	PROs	Patient-reported outcomes
103	RCTs	Randomized controlled trials
104	SD	Standard deviation
105	sgAHs	Second-generation H1-antihistamines
106	SMDs	Standardized mean differences
107	SUCRA	Surface under the cumulative ranking curve
108	UAS7	Urticaria activity score over 7 days

INTRODUCTION

Chronic spontaneous urticaria (CSU) is characterized as the presence of recurrent wheals, angioedema, or both for more than six weeks, without any explicit trigger.(1) At a global level, the lifetime prevalence rate of chronic urticaria in children and adults has been estimated as high as 4.4%, but it has been shown to be increasing over time.(2) Unfortunately, even with the widespread use of licensed doses and up-dosed of non-sedating second-generation H1-antihistamines (sgAHs)(3), less than 50% of patients with CSU have an adequate response to this treatment approach.(4, 5) CSU places significant social and economic burdens on patients, with many experiencing reduced sleep quality, reduced work or school productivity, fatigue due to treatment, fear of attacks, sex life, as well as worsened physical and social interactions leading to psychosocial, mental health, and well-being issues.(6)

CSU not only places immense strains on the healthcare system, but also significantly impairs patient-reported outcomes (PROs), such as health-related quality of life (HRQOL), activity limitations or impairment, and psychosocial aspects when compared to other chronic skin diseases.(7, 8) Theoretically, PROs reflect the patients' viewpoint on the clinical benefit and acceptability of treatments.(9, 10) CSU is unpredictable and debilitating; treatment goals are therefore not curative, but interventions are designed to control the symptoms, enhance HRQOL, and reduce its economic impact. This means that establishing effective disease management treatments, with respect to PROs and producing improvements in HRQOL and other relevant criteria, is particularly challenging. These outcomes have been used as endpoint in clinical practice.(1, 10, 11)

Recently, several pharmacological treatment options for H1-antihistamines-refractory CSU have become available.(12) However, the effectiveness of these treatments with respect to PROs has never been systematically compared; therefore, it remains unknown which

treatments should be recommended for patients with sgAH-refractory CSU. A previous study performed a pairwise meta-analysis and focused only on the effect of biological omalizumab on HRQOL.(13) For this reason, we conducted a systematic review and network meta-analysis (NMA) of randomized controlled trials (RCTs) to compare the efficacy of all of the available pharmacological treatments for H1-antihistamine-refractory CSU. We used the contextualized clinical and methodological approach to identify pharmacological treatments that can improve the HRQOL of CSU patients with an inadequate response to sgAHs.

METHODS

Data sources and search methods

We followed the guidelines described in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension statement for reporting of NMAs (see Appendix I) to complete our data collection and establish our search framework for this study.⁽¹⁴⁾ Owing to systematic review and meta-analysis study is based on the existing published data, ethical approval is not required. Detailed information regarding the methodology used is available in the Supplementary File in Appendix II (PROSPERO registration: CRD42020196592). Briefly, we identified eligible RCTs using a systematic search of the following electronic databases: Medline, Embase, PubMed, Cochrane Library, Web of Science, Scopus, CINAHL, Google Scholar, clinical trial register, and preprints reports (medRxiv, bioRxiv, and Research Square). This literature search was repeated several times up to and including April 19, 2021, with no language restrictions (the search terms are available in Table E1). We supplemented our search for RCTs by searching within the reference lists of the included studies and identified previous systematic reviews and NMAs, as well as conference meetings from major international dermatology, allergy, and immunology congresses.

Study eligibility criteria

SN and MC independently screened, reviewed, and selected studies based on the study inclusion and exclusion criteria. Any disagreement was resolved through a team discussion. We included all RCTs (parallel and crossover trials) that: (i) compared pharmacological interventions with placebo- or active interventions for the treatment of adolescent or adult (12 years or older) CSU patients with an inadequate response to H1-antihistamines; and (ii) focused on the change in HRQOL among treatment comparisons

using validated measurement tools and a study treatment follow-up of more than 2 weeks (details of the study eligibility criteria are described in Table E2). We assembled the relevant information from companion trials and post-hoc analyses for studies that contained overlapping participants and study periods.

Outcomes

The primary outcome of interest was a change in patient-reported HRQOL measured using multidimensional validated general- or dermatology-specific instruments. It is well-established that changes in HRQOL are associated with changes in disease activity.(15, 16) When applicable, we preferred to use the Dermatology Life Quality Index (DLQI), a well-established instrument that has been validated and used in various populations including CSU trials.(17, 18) We stratified our data analyses according to the duration of treatment with respect to the change in HRQOL from baseline producing two groups, (i) 12 weeks or less and (ii) greater than 12 weeks, to evaluate the intermediate- and long-term effects of specific treatments.

The secondary outcomes of interest included (i) patient unacceptability, defined as all-cause study withdrawals (all-cause dropouts); (ii) patient-reported chronic urticaria-specific or angioedema-specific measures (e.g., Chronic Urticaria Quality of Life questionnaire [CU-Q2oL](19) or Angioedema QoL Questionnaire [AE-QoL](20)); (iii) impact on sleep (e.g., sleep quality, insomnia, and sleep problems); (iv) symptom burden (e.g., fatigue, dyspnea, pain, difficulty in eating or swallowing); (v) psychosocial aspects (e.g., symptoms of depression, anxiety, distress, and general well-being); (vi) work impairment (e.g., absenteeism, presenteeism, work productivity and/or school performance); and (vii) healthcare utilization (e.g., emergency/unplanned visit during follow-up and costs of care).

Data extraction and risk-of-bias assessment

SN and MC independently reviewed the main studies, supplementary materials, and relevant post-hoc studies, extracted the pre-specified data using a standardized approach, and entered the information into the electronic extraction forms. Quantitative data reported in figures only were digitized in order to compile the specific numerical values for these data sets. As not all studies used the same instruments for endpoint measurement, we estimated treatment effects using standardized mean difference (SMD) for any continuous outcome parameters between baseline and endpoint. However, if unavailable, we calculated the standard deviation (SD) of the SMD using a value of 0.5 for the correlation coefficient (ρ) between the baseline and endpoint, with equal variances among the intervention and comparison groups.(21) In cases where the published information was incomplete/unclear, we contacted the corresponding author for further clarification. If the authors did not reply after three attempts, we used the most relevant published data or excluded the study from our analyses. CR and RA independently cross-checked the final set of data extraction and any discrepancies were resolved through a team discussion.

Two investigators (SN and MC) independently evaluated the methodological quality of the included studies using the Cochrane revised tool for risk of bias assessment (RoB 2) (22) and categorized the overall risk of bias rating for each study into either low, some concerns, or high risk.

Statistical analysis

All analyses were performed using Stata, version 16.0 (StataCorp, College Station, TX, USA). A two-tailed test based on an alpha level of 0.05, was used to identify statistically significant differences between interventions. First, we performed traditional pairwise meta-analysis using a random-effects model to explore potential heterogeneity between

studies.(23) The effect estimates of the direct treatment comparisons were pooled and expressed as SMDs and odds ratios (ORs) along with their 95% confidence intervals (CIs).

We then performed a random-effects model NMA to incorporate direct and indirect estimates for each comparison into a single-framework allow for evidence synthesis. Each possible treatment comparison was placed in a league table with summary effect estimates for each outcome expressed as SMDs or ORs with 95% CIs. The surface under the cumulative ranking curve (SUCRA) was then estimated to create a hierarchy of pharmacological treatments for each outcome of interest.(24) A higher SUCRA score indicates a higher probability ranking for the outcome of interest.

We attempted to assess the transitivity assumption by exploring the distribution of the participants' demographics and study characteristics across all included studies. A common heterogeneity estimate was reported as the between-study variance (τ^2) for each outcome in the entire network. We categorized the degree of heterogeneity as low ($\tau^2=0.04$), moderate ($\tau^2=0.16$), or high ($\tau^2=0.36$)(25) and evaluated statistical disagreements between direct and indirect evidence (incoherence assumption) using (i) a loop-specific approach in which we assessed for inconsistency in every closed loop of evidence; and (ii) the design-by-treatment interaction model, which assesses for inconsistency through all possible sources in the network conjointly.(26) We assessed potential small-study effects from small trials using comparison-adjusted funnel plot symmetry(24) and accounted for a predicted range of the true treatment effect in individual studies by estimating the 95% prediction intervals, which also provided the expected uncertainty of each estimate in a future study.(27)

Preplanned subgroup analysis was performed to assess the potential effect modifiers based on age (adolescents or adults), sex, baseline CSU severity (urticaria activity score over 7 days [UAS7]), presence of angioedema, positive autologous serum skin test (ASST), and sample size. Network meta-regression analysis was also planned to evaluate the reasons for

this heterogeneity and were performed by adjusting the covariates mentioned above in the NMA model. A set of sensitivity analyses were also conducted to assess the robustness of the primary findings by (i) assuming a p value of 0.7, in cases with missing SD values for continuous outcomes (ii) restricting the analysis to studies that used the DLQI for HRQOL measure; (iii) excluding trials with crossover design; (iv) excluding single-center trials; and (v) limiting the analysis to trials with a low risk of bias.

Certainty assessment and interpretation of evidence findings

Two investigators (SN and MC) assessed the evidence limitations for each outcome using confidence in network meta-analysis (CINeMA), with five domains, including within-study bias, reporting bias, indirectness, imprecision, heterogeneity, and incoherence (the assessment criteria are described in Appendix III).(28) Next, we graded the quality of the evidence findings and categorized them as very low, low, moderate, and high quality of evidence using the Grading of Recommended Assessment, Development, and Evaluation (GRADE) approach.(29)

Finally, we drew an evidence-based conclusion on whether specific treatments can improve HRQOL based on a contextualized clinical and methodological approach, considering magnitudes of effect size, evidence certainty, SUCRA value, and minimal clinically important difference (MCID). The magnitude of effect was determined using Cohen's criteria as a guide and we classified these effect estimates as small (SMD, -0.2), medium (SMD, -0.5), and large (SMD, -0.8).(30) We established an MCID for change in HRQOL using the pooled SMDs which were re-expressed(31) (value on an original instrument: $SMD \times \text{standard deviation } [SD]_{\text{reference}}$ and 7.0 was chosen as the reference pooled SD based on the landmark clinical trials(32-35)). We chose an MCID of 2.24 to 3.10 for the DLQI instrument in CSU patients(36) and incorporated a tradeoff for patient unacceptability

268 of treatment using methodological approach as mentioned into the contextualized framework.
269 As a result, we classified pharmacological interventions as having trivial (not different from
270 placebo), small, moderate, and large effect on the HRQOL of CSU patients with an
271 inadequate response to H1-antihistamines.

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RESULTS

Study characteristics

After title and abstract screening, we identified 492 relevant articles for further review (Figure E1). Of these, 17 publications reporting 12 unique RCTs(32-35, 37-49) were included in this review. The characteristics of all of these studies are summarized in Table I and Supplementary Tables E3 and E4. In total, 1,866 CSU patients were involved with a mean age ranging from 33.5 to 45.7 years, and mean UAS7 or weighted score from 23.2 to 31.1. A total of six RCTs(32, 38, 40, 41, 44, 48) followed CSU patients with an inadequate response to up-dosed (two- to four-fold) of H1-antihistamines, four RCTs(33, 34, 37, 43) focused on licensed dose H1-antihistamine-refractory CSU patients, one trial(35) on mixed cases (57.1% refractory to up-dosed H1-antihistamines), and one trial(49) with an unclear definition of CSU that was refractory to licensed or up-dosed H1-antihistamine.

These trials allowed us to compare 11 pharmacological treatments, dosages, and one placebo. The geometry of the networks for all treatment comparisons for changes in HRQOL from baseline and for the other secondary outcomes are illustrated in Figure 1 and Supplementary Figure E2, respectively. A total of 10 RCTs (83.3%) measured HRQOL using the DLQI system (Table E5). The detailed risk of bias assessment is provided in Table E6. Briefly, eight RCTs (66.7%)(32-35, 37, 40, 43, 48) were assessed to have a low risk of bias, four RCTs (33.3%)(38, 41, 44, 49) had some concerns, and no studies had a high risk of bias (Table I).

Change in HRQOL from baseline

Overall, the network estimates showed that hydroxychloroquine, ligelizumab (72 or 240 mg), and omalizumab (150 or 300 mg) were significantly more effective than placebo

when evaluating improvements in HRQOL (12 studies, n=1,779 patients; Table E7). With respect to the intermediate- (≤ 12 weeks; Table II, lower left portion) and long-term impact (> 12 weeks; Table II, upper right portion) on HRQOL, 72 mg ligelizumab (SMD, -0.71 [-1.00 to -0.42] for intermediate response; SMD, -0.61 [-1.09 to -0.13] for long-term response); 240 mg ligelizumab (SMD, -0.73 [-1.02 to -0.43] for intermediate response; SMD, -0.63 [-1.11 to -0.15] for long-term response); 300 mg omalizumab (SMD, -0.61 [-0.75 to -0.48] for intermediate response; SMD, -0.49 [-0.76 to -0.23] for long-term response) were significantly more effective than placebo. Based on the SUCRA values (Table III) and rankograms (Figure E3), the two top-ranked treatments were hydroxychloroquine (93.5%) and 240 mg ligelizumab (81.2%), respectively. Findings from the pairwise meta-analyses were consistent with our NMA findings (Table E8).

Secondary outcomes

Although, we did not observe a significant difference in patient unacceptability across the treatment comparisons (Table E9). However, with respect to the SUCRA values, dapsone, miltefosine, hydroxychloroquine, and cyclosporine had a higher risk of patient unacceptability in terms of all-cause dropouts (Table IV). We were unable to compare other secondary outcomes due to the limited number of secondary outcomes included in these studies (Table E9). Network estimates based on five RCTs (n=1,188 patients) showed that ligelizumab (72 or 240 mg) and 300 mg omalizumab were more effective in improving the quality of sleep compared to the placebo. While the NMA results of four RCTs (n=820 patients) indicated that 300 mg omalizumab improved HRQOL as measured by CU-Q2oL compared to the placebo. Only one trial reported significant benefits of 300 mg omalizumab on AE-QoL and well-being compared to the placebo (Table E10) and the rankograms for secondary outcomes are illustrated in Figure E3, and suggest that ligelizumab and

omalizumab seem to have the higher probability of desirable outcome effects compared to other treatments. The results from the pairwise meta-analyses were in line with our NMA findings for all secondary outcomes, except for the impact on sleep quality (240 mg ligelizumab and 150 mg omalizumab, Table E10).

Subgroup analysis, network meta-regression, sensitivity analyses, and network assumptions

Because of the limited number of trials and the small sample size, preplanned subgroup analysis and network meta-regression could not be performed. Based on the preplanned sensitivity analyses, our findings were almost identical to those the primary analysis (Table E11). However, the use of cyclosporine became significant after using a correlation coefficient of 0.7 for change in HRQOL at treatment follow-up for 12 weeks or less (SMD, -0.68 [-1.35 to -0.00]).

Although the between-study variance indicated a low degree of heterogeneity in all outcome analyses (except for patient unacceptability [$\tau^2=0.20$, moderate heterogeneity]), limitations pertaining to the transitivity assumption cannot be ruled out because of imbalanced treatment comparisons and lack of data across the included studies (Table I and Supplementary Tables E3 and E4). However, statistical disagreements between direct and indirect evidence (incoherence assumption) were not identified in any outcome (Tables E12 and E13). Moreover, potential small-study effects were not recognized for any outcome, except for patient-reported CU-Q2oL (Figure E4).

Evidence synthesis and interpretation of findings

According to the CINeMA and GRADE assessment, most treatments were graded as very low or low evidence certainty, while ligelizumab and omalizumab were graded as

moderate or high (Table E14). Given this we determined that hydroxychloroquine, ligelizumab (72 or 240 mg), 300 mg omalizumab had a moderate beneficial effect with an MCID when using the DLQI instrument for evaluating HRQOL above 2.24 to 3.10, which is considered to be clinically important for evaluating treatment effect (Table III). Based on the tradeoff between efficacy and patient unacceptability, 72 mg ligelizumab was ranked as the most effective and desirable treatment (Figure 2).

DISCUSSION

Summary of the findings

This systematic review and NMA focused on the impact of all available pharmacological treatments for CSU with an inadequate response to H1-antihistamines on HRQOL. This review incorporated direct and indirect evidence from 12 unique trials encompassing 1,866 participants, comparing 11 different treatments, dosages, and a placebo. Based on the best available evidence, the use of hydroxychloroquine, ligelizumab (72 or 240 mg), and 300 mg omalizumab provides moderate beneficial effects and can be recommended as an effective treatment for patients with this kind of pathology as they have been shown to improve HRQOL among H1-antihistamines-refractory CSU patients. However, besides limited evidence on the long-term response (>12 weeks), it seems that the treatment effects in improving HRQOL may decrease over time. Given the limits in the magnitudes of effect size, evidence certainty, and MCID, the use of other treatments is not recommended because of the lack of efficacy or less meaningful impact from the patients' point of view.

Comparison with other studies

Our findings contribute to the existing literature by expanding on the findings of previous systematic reviews(50) and pairwise meta-analyses(13, 51) that focused on the effects of omalizumab use on HRQOL. Here we simultaneously combined direct and indirect evidence with a larger sample size into a single-framework analysis. Our findings are in line with those reviews on the effects of omalizumab, particularly with doses of 150 and 300 mg. The Rubini et al. (2019) pairwise meta-analysis demonstrated that omalizumab (150 or 300 mg) was closely associated with improved HRQOL (measured using the DLQI) at 12 weeks with the mean difference (MD) in this study reported as -1.56 (-2.58 to -0.53) for 150 mg omalizumab and -3.50 (-4.40 to -2.61) for 300 mg omalizumab, which was consistent with

our re-expressed MD effect estimates (Table III). However, our NMA highlighted that only 300 mg omalizumab had a clinically meaningful benefit with an MCID for DLQI above the established threshold level.

Strengths and weaknesses of the study

To the best of our knowledge, this study is the first NMA to compare and rank different treatment options and dosages of different pharmacological treatments for CSU patients with an inadequate response to H1-antihistamines. Apart from a rigorous and comprehensive methodological approach, we also addressed clinimetric considerations using an MCID during evidence synthesis to facilitate the drawing of evidence-based conclusions. We postulate that this approach is more informative for decision-making in clinical practice, which accounts for the patients' perspective.

However, this study has some limitations. First, most of the included studies had small sample sizes and reported incomplete data. This means that we were unable to consider the key patient characteristics, such as age, presence of angioedema, positive ASST, or severity of urticaria symptoms based on UAS7 in our subgroup analysis, as well as network meta-regression, owing to lack of information and multicollinearity. Moreover, some treatment nodes were not well connected and were based on a single trial; inferences and irrelative effect estimates shown in this study should be cautiously interpreted. However, we did not find evidence of an inconsistency between the direct and indirect effects. Second, apart from the single-trial or trials with small sample size, zero events or poorly reported in the patient unacceptability and safety profiles should be addressed, resulting in a less-precise network estimation of undesirable treatment. Third, few trials reported PRO-specific instruments for urticaria symptoms, or other PROs, such as sleep problems, symptom burden, psychosocial and mental health problems, work or school impairment, and healthcare

utilization. As a result, these outcomes were insufficiently connected in our network estimates, and the findings remain inconclusive. Fourth, because of the limited participant-level data, our analyses were based on study-level data, which may preclude any differences observed in clinical settings. Fifth, a transitivity assumption is warranted in this case owing to the variation in the study population and the limited information describing these populations in these studies. Nevertheless, between-study variance suggests that most outcome analyses demonstrated a low degree of heterogeneity (except for patient unacceptability). Sixth, although the comparison-adjusted funnel plot symmetry did not find any significant concerns, potential small-study effects may exist and might contribute to some of our effect estimates, particularly for patient-reported CU-Q2oL. Finally, we excluded non-randomized studies to preserve the similarity across the network estimates, which may limit the generalization of our findings in real-world settings.

Practice implications, future research, and conclusions

This study has important clinical practice, research, and policy implications. Based on the best available evidence supporting clinically meaningful improvements in patient HRQOL, hydroxychloroquine, ligelizumab (72 or 240 mg), and 300 mg omalizumab can be recommended as treatments for H1-antihistamine-refractory CSU. Interestingly, ligelizumab (72 or 240 mg) and 300 mg omalizumab showed treatment effects in both intermediate response (≤ 12 weeks) and long-term response (> 12 weeks) groups. However, because of reduced patient unacceptability (all-cause dropouts) and low-quality evidence, the risk-benefit for hydroxychloroquine use should be carefully considered before using it in a clinical setting (Figure 2).

In addition to the clinical outcomes, international guideline development and clinicians should consider PROs, including HRQOL, as a part of their treatment decision-

making. From the patient's perspective, HRQOL can be a paramount outcome for the management of people living with CSU, due to their chronic disease nature and lack of curable treatments. We encourage the incorporation of rigorous PRO measurement into future trials and daily clinical practice, particularly the adoption of specific instruments that directly capture urticaria symptoms (e.g., CU-Q2oL or AE-QoL) as per EAACI/GA²LEN/EDF/WAO.(1) Future research should focus on more PROs, including HRQOL, as part of their study outcomes, in order to facilitate a better understanding of the perspectives of patients living with CSU.

In conclusion, our findings suggest that biological agents ligelizumab (72 or 240 mg) and 300 mg omalizumab appeared to be effective treatments for H1-antihistamine-refractory CSU patients to facilitate clinically meaningful improvements in HRQOL. Future head-to-head trials are needed to confirm our findings.

Author contributions

SN and MC conceived the study, developed the protocol, did the literature search, selected the studies, extracted the relevant information, synthesized the data, and wrote the first draft of the paper. CR and RA cross-checked the data. NT, SC, BH, and KT critically revised successive drafts of the paper. All authors approved the final draft of the manuscript. SN and CM are the guarantors of the study.

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Data sharing statement

All data generated or analyzed during this study are included in this article and its supplementary information files.

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TABLE I. Characteristics of included studies

Author, year	Study design	Sample size	Pharmacological treatment		Mean age (SD)		Female, N (%)		Definition of H1-antihistamine-refractory CSU	Mean baseline urticaria symptoms (SD)		Mean duration of CSU (SD), year		Study duration	Outcomes reported	Overall RoB
			Intervention	Control	Intervention	Control	Intervention	Control		Intervention	Control	Intervention	Control			
Kaplan et al(32, 39, 42), 2013	RCT: Double-blind, parallel-group, multicenter	335	Omalizumab: 300 mg SQ at interval of 4 weeks	Placebo: SQ	42.7 (13.9)	44.3 (14.7)	186 (73.8)	55 (66.3)	Had itch and hives >6 consecutive weeks before enrollment, despite H1-antihistamines (up to 4 times the approved dosage) plus H2-antihistamines, LTRAs, or both	UAS7: 31.2 (6.6)	UAS7: 30.2 (6.7)	7.0 (8.8); median 3.4 (range, 0.5-50.3)	8.8 (11.2); median 4.1 (range, 0.6-54.1)	24-week treatment period	HRQOL (DLQI, CU-Q2oL), patient unacceptability, impact on sleep	Low risk
Margerl et al(37), 2013	RCT: Double-blind, parallel-group, multicenter	76	Miltefosine: 150 mg daily (100 mg if evidence of intolerance occurred)	Placebo: orally	45.0 (12.4)	42.6 (12.5)	28 (56.0)	14 (53.8)	Resistant to standard treatment with antihistamines (maximum labelled dose of a non-sedating antihistamine)	UAS7: 25.7 (7.4)	UAS7: 25.1 (6.9)	NR	NR	4-week treatment period	HRQOL (DLQI, CU-Q2oL), patient unacceptability	Low risk
Maurer et al(33, 39, 42), 2013	RCT: Double-blind, parallel-group, multicenter	323	Omalizumab: 75 mg, 150 mg, or 300 mg SQ at interval of 4 weeks	Placebo: SQ	42.3 (14.0)	43.1 (12.5)	189 (77.8)	55 (69.6)	Remained symptomatic despite the use of approved doses of H1-antihistamines	UAS7: 30.5 (6.9)	UAS7: 31.0 (6.6)	6.2 (7.8)	7.2 (10.7)	12-week treatment period	HRQOL (DLQI), patient unacceptability, impact on sleep	Low risk
Morgan et al(38), 2014	RCT: Double-blind, crossover trial, single center	22	Dapsone: 100 mg orally once daily	Placebo: orally once daily	41.9 (11.0)	44.8 (13.9)	2 (20.0)	3 (25.0)	Had itch and hives present ≥ 4 days in a week despite therapy in excess of standard H1-antihistamines dosage (usually 2 to 4 times the standard dose, or simultaneous use of multiple H1-antihistamines)	WHS-WIS: 12.9 (3.5); weighted-UAS7: 25.8 (7.1)	WHS-WIS: 13.1 (3.0); weighted-UAS7: 26.2 (6.0)	Median 1.0 (range, 0.5-5.0)	Median 1.3 (range, 0.3-10.0)	6-week treatment period	HRQOL (MOSS-SF 12), patient unacceptability	Some concerns
Saini et al(34, 39, 42), 2015	RCT: Double-blind, parallel-group, multicenter	319	Omalizumab: 75 mg, 150 mg, or 300 mg SQ at interval of 4 weeks	Placebo: SQ	41.4 (14.1)	40.4 (15.6)	179 (75.2)	52 (65.0)	Remained symptomatic despite the use of approved doses of H1-antihistamines	UAS7: 31.1 (6.6)	UAS7: 31.1 (6.7)	6.9 (9.0)	7.0 (9.7)	24-week treatment period	HRQOL (DLQI, CU-Q2oL), patient unacceptability, impact on sleep	Low risk
Staubach et al(40, 45), 2016	RCT: Double-blind, parallel-group, multicenter	91	Omalizumab: 300 mg SQ at interval of 4 weeks	Placebo: SQ	44.9 (range, 20-73)	41.4 (range, 20-61)	30 (68.2)	33 (70.2)	Defined as those who were symptomatic despite high-dose second generation H1-antihistamines (2 to 4 times the approved dose)	UAS7: 26.5 (8.2)	UAS7: 27.9 (8.7)	8.4 (9.3); median 5.0 (range, 0.0-40.0)	7.4 (8.8); median 5.0 (range, 0.0-41.0)	24-week treatment period	HRQOL (CU-Q2oL), patient unacceptability, patient well-being	Low risk
Boonpiyathad et al(41), 2017	RCT: Single-blind, parallel-group, single center	55	Hydroxy-chloroquine: 400 mg/day orally	Placebo: orally	33.0 (12.1)	34.0 (11.9)	21 (87.5)	20 (83.3)	Failure to respond to 4 tablets of H1-antihistamines for 4 weeks	USS: 45.5 (11.2); weighted-UAS7: 20.6 (5.1)	USS: 43.4 (12.3); weighted-UAS7: 19.6 (5.5)	0.4 (0.4)	0.5 (0.5)	12-week treatment period	HRQOL (DLQI), patient unacceptability	Some concerns
Hide et al(43), 2017	RCT: Double-blind, parallel-group, multicenter	218	Omalizumab: 150 mg or 300 mg SQ at interval of 4 weeks	Placebo: SQ	43.6 (12.2)	42.5 (14.3)	83 (57.6)	48 (64.9)	Symptomatic despite approved-dose non-sedating H1-antihistamine treatment	UAS7: 30.7 (7.2)	UAS7: 30.1 (6.5)	4.0 (4.7)	4.7 (6.2)	12-week treatment period	HRQOL (DLQI), patient unacceptability	Low risk
Sánchez et al(44), 2018	RCT: Open-label, parallel-group, multicenter	35	Omalizumab: 300 mg SC at interval of 4 weeks	Cyclosporine: 3 mg/kg/day (100-250 mg)	NR	NR	NR	NR	Inadequately controlled with high dose H1-antihistamines (at up to 4 times of the conventional dose)	NR	NR	NR	NR	16-week treatment period	HRQOL (DLQI), patient unacceptability	Some concerns

Maurer et al(35, 46, 47), 2019	RCT: Double-blind, parallel-group, multicenter	297	Ligelizumab (72 mg, or 240 mg), Omalizumab 300 mg; SQ at interval of 4 weeks	Placebo: SQ	Ligelizumab: 43.5 (11.2); Omalizumab: 41.8 (13.1)	45.4 (11.2)	Ligelizumab: 128 (75.7); Omalizumab 66 (77.6)	31 (72.1)	Inadequately controlled with H1-antihistamines at approved or increased doses alone or in combination with H2-antihistamines or LTRAs (57.1% escalated dose of approved H1-antihistamines)	UAS7: Ligelizumab: 31.0 (7.4); UAS7, Omalizuma: 29.3 (7.9)	UAS7: 31.1 (6.8)	Ligelizumab: 4.0 (5.5); Omalizumab: 5.1 (7.5)	3.6 (3.5)	20-week treatment period	HRQOL (DLQI), patient unacceptability, impact on sleep	Low risk
Leducq et al(48), 2020	RCT: Double-blind, parallel-group, multicenter	75	Methotrexate : 0.2 mg/kg/week as a single dose, orally for 8 weeks (increased to 2.5 mg/kg/week in case of inadequate control	Placebo: Orally	46.4 (12.6)	45.0 (13.2)	28 (71.8)	29 (80.6)	Previous received ≥ 3 different molecules of H1-antihistamines or 1 molecules of H1-antihistamines with at least a double dose, for a total treatment duration of at least 12 weeks before inclusion; Persistent urticarial lesions in the months before enrollment (at least 7 days)	NR	NR	3.8 (2.6)	3.7 (4.6)	18-week treatment period	HRQOL (DLQI), patient unacceptability, impact on sleep	Low risk
Maul et al(49), 2021	RCT: Double-blind, parallel-group, single center	20	Canakinumab : 150 mg SQ once at baseline	Placebo: SQ	42.2 (17.9)	38.7 (9.6)	6 (60.0)	6 (60.0)	Symptomatic despite use of non-sedating antihistamine with or without concomitant LTRAs/corticosteroids (not specified)	UAS7: 26.3 (9.4)	UAS7: 22.2 (5.3)	2.7 (2.6)	9.4 (6.4)	4-week treatment period	HRQOL (DLQI), patient unacceptability	Some concerns

Abbreviations: AE-QoL, Angioedema Quality of Life questionnaire; CSU, chronic spontaneous urticaria; CU-Q2oL, Chronic Urticaria Quality of Life Questionnaire; DLQI, Dermatology Life Quality Index; HRQOL, health-related quality of life; LTRAs, leukotriene receptor antagonists; MOSS-SF12, Medical Outcomes Study Survey-Short Form 12 Item; NR, not reported; NS, not specified; RCT, randomized controlled trial; RoB, risk of bias; SD, standard deviation; SQ, subcutaneous.

TABLE II. Change in HRQOL from baseline according to study treatment follow-up[†]

		Treatment follow-up of greater than 12 weeks										
Treatment follow-up of 12 weeks or less	Placebo	NA	-0.49 (-1.32, 0.33)	NA	NA	-0.61 (-1.09, -0.13)[†]	-0.63 (-1.11, -0.15)[†]	NA	-0.15 (-0.77, 0.46)	NA	-0.13 (-0.60, 0.33)	-0.49 (-0.76, -0.23)[†]
	-0.27 (-1.15, 0.61)	Canakinumab	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	-0.66 (-1.34, 0.01)	-0.39 (-1.50, 0.72)	Cyclosporine	NA	NA	-0.12 (-1.03, 0.79)	-0.13 (-1.04, 0.78)	NA	0.34 (-0.69, 1.37)	NA	0.36 (-0.55, 1.27)	-0.00 (-0.78, 0.78)
	0.34 (-0.50, 1.19)	0.62 (-0.61, 1.84)	1.01 (-0.08, 2.09)	Dapsone	NA	NA	NA	NA	NA	NA	NA	NA
	-1.00 (-1.60, -0.40)[†]	-0.73 (-1.80, 0.34)	-0.34 (-1.24, 0.57)	-1.35 (-2.38, -0.31)[†]	Hydroxy-chloroquine	NA	NA	NA	NA	NA	NA	NA
	-0.71 (-1.00, -0.42)[†]	-0.44 (-1.36, 0.49)	-0.04 (-0.76, 0.67)	-1.05 (-1.95, -0.16)[†]	0.29 (-0.37, 0.96)	Ligelizumab (72 mg)	-0.02 (-0.53, 0.49)	NA	0.46 (-0.32, 1.23)	NA	0.48 (-0.16, 1.11)	0.12 (-0.35, 0.59)
	-0.73 (-1.02, -0.43)[†]	-0.45 (-1.38, 0.47)	-0.06 (-0.78, 0.66)	-1.07 (-1.96, -0.18)[†]	0.28 (-0.39, 0.94)	Ligelizumab (240 mg)	-0.02 (-0.32, 0.28)	NA	0.47 (-0.30, 1.25)	NA	0.49 (-0.14, 1.13)	0.13 (-0.34, 0.60)
	-0.02 (-0.49, 0.46)	0.26 (-0.75, 1.26)	0.65 (-0.18, 1.47)	-0.36 (-1.33, 0.61)	0.98 (0.22, 1.75)[†]	0.69 (0.13, 1.25)[†]	0.71 (0.15, 1.26)[†]	Miltefosine	NA	NA	NA	NA
	-0.27 (-0.72, 0.19)	0.01 (-0.99, 1.00)	0.40 (-0.42, 1.21)	-0.61 (-1.57, 0.35)	0.73 (-0.02, 1.49)	0.44 (-0.10, 0.98)	0.46 (-0.08, 1.00)	-0.25 (-0.91, 0.41)	Methotrexate	NA	0.02 (-0.75, 0.79)	-0.34 (-1.01, 0.33)
	-0.13 (-0.33, 0.07)	0.14 (-0.76, 1.04)	0.53 (-0.16, 1.22)	-0.48 (-1.34, 0.39)	0.87 (0.24, 1.50)[†]	0.58 (0.24, 0.91)[†]	0.59 (0.26, 0.93)[†]	-0.11 (-0.63, 0.40)	0.14 (-0.36, 0.63)	Omalizumab (75 mg)	NA	NA
	-0.33 (-0.50, -0.16)[†]	-0.06 (-0.96, 0.84)	0.33 (-0.35, 1.02)	-0.68 (-1.54, 0.19)	0.67 (0.04, 1.30)[†]	0.38 (0.06, 0.70)[†]	0.39 (0.08, 0.71)[†]	-0.31 (-0.82, 0.19)	-0.06 (-0.55, 0.42)	-0.20 (-0.41, 0.01)	Omalizumab (150 mg)	-0.36 (-0.82, 0.10)
	-0.61 (-0.75, -0.48)[†]	-0.34 (-1.23, 0.55)	0.05 (-0.61, 0.71)	-0.96 (-1.81, -0.10)[†]	0.39 (-0.23, 1.00)	0.09 (-0.19, 0.37)	0.11 (-0.17, 0.39)	-0.60 (-1.09, -0.10)[†]	-0.35 (-0.82, 0.13)	-0.48 (-0.68, -0.28)[†]	-0.28 (-0.45, -0.11)[†]	Omalizumab (300 mg)

[†]Network meta-analysis results are expressed as SMDs (95% CIs). For study duration ≤12 weeks (lower left portion [blue]), SMDs less than 0 indicate that the treatment specified in the row is more effective than that specified in the column. For study duration >12 weeks (upper right portion [green]), SMDs less than 0 indicate that the treatment specified in the column is more effective than that specified in the row. To obtain SMDs for comparisons in the opposite direction, negative values should be converted into positive values and vice versa.

*Statistically significant.

Abbreviations: CIs, confidence intervals; CSU, chronic spontaneous urticaria; HRQOL, health-related quality of life; NA, not applicable; SMDs, standardized mean differences.

TABLE III. Interpretation of pharmacological treatments effect on HRQOL based on network meta-analysis for H1-antihistamine-refractory CSU

Treatment comparison (reference: placebo)	SMD (95% CI)	Corresponding 95% prediction interval	SUCRA score [†]	Magnitudes of effect size [‡]	Evidence certainty [§]	Re-expressed on HRQOL: MD (95% CI)	Clinically important? (≥MCID of 2.24 to 3.10 for DLQI)	Interpretation of treatment effect
Hydroxychloroquine	-1.00 (-1.61 to -0.39)	-1.70 to -0.30	93.5	Large	Low	-7.00 (-11.27 to -2.73)	Yes (benefit)	Moderate beneficial effect
Ligelizumab (240 mg)	-0.67 (-0.98 to -0.37)	-1.04 to -0.31	81.2	Medium	Moderate	-4.69 (-7.28 to -2.59)	Yes (benefit)	
Ligelizumab (72 mg)	-0.66 (-0.96 to -0.35)	-1.02 to -0.29	79.9	Medium	Moderate	-4.62 (-6.72 to -2.45)	Yes (benefit)	
Omalizumab (300 mg)	-0.53 (-0.67 to -0.39)	-0.71 to -0.34	68.6	Medium	High	-3.71 (-4.69 to -2.73)	Yes (benefit)	
Omalizumab (150 mg)	-0.26 (-0.44 to -0.08)	-0.49 to -0.03	44.7	Small	High	-1.82 (-3.08 to -0.56)	No	Trivial to no effect (not different than placebo)
Cyclosporine	-0.53 (-1.21 to 0.15)	-1.31 to 0.26	65.3	Not estimated (non-statistically significant)	Very low	-3.71 (-8.47 to 1.05)	Not estimated (non-statistically significant)	
Canakinumab	-0.27 (-1.16 to 0.61)	-1.29 to 0.74	45.7	Not estimated (non-statistically significant)	Low	-1.89 (-8.12 to 4.27)	Not estimated (non-statistically significant)	
Omalizumab (75 mg)	-0.16 (-0.43 to 0.12)	-0.49 to 0.18	34.1	Not estimated (non-statistically significant)	Moderate	-1.12 (-3.01 to 0.84)	Not estimated (non-statistically significant)	
Methotrexate	-0.15 (-0.62 to 0.31)	-0.69 to 0.39	34.8	Not estimated (non-statistically significant)	Moderate	-1.05 (-4.34 to 2.17)	Not estimated (non-statistically significant)	
Miltefosine	-0.02 (-0.50 to 0.47)	-0.58 to 0.54	23.8	Not estimated (non-statistically significant)	Low	-0.14 (-3.5 to 3.29)	Not estimated (non-statistically significant)	
Dapsone	0.34 (-0.51 to 1.20)	-0.63 to 1.32	10.4	Not estimated (non-statistically significant)	Low	2.38 (-3.57 to 9.24)	Not estimated (non-statistically significant)	Small harmful effect

[†]Large SUCRA values indicate better treatments: SUCRA values for placebo=18.1.

[‡]To estimate treatment effects, SMD of <0.2, 0.2-0.4, 0.5-0.7, and ≥0.8 are considered to be very small, small, medium, and large, respectively.

[§]Note: See Appendix-III for full details of criteria for downgrading evidence certainty.

Abbreviations: CI, confidence interval; CSU, chronic spontaneous urticaria; DLQI, Dermatology Life Quality Index; MCID, minimal clinically important difference; MD mean difference; SMD, standardized mean difference.

TABLE IV. Patient unacceptability of treatment based on network meta-analysis for H1-antihistamine-refractory CSU

Treatment comparison (reference: placebo)	OR (95% CI)	Corresponding 95% prediction interval	SUCRA score[†]	Magnitudes of effect size[‡]	Evidence certainty[§]	Interpretation of treatment effect
Dapsone	2.56 (0.07 to 94.90)	0.04 to 175.61	69.4	Not estimated (non-statistically significant)	Low	Small harmful effect
Miltefosine	1.38 (0.29 to 6.46)	0.18 to 10.42	65.3	Not estimated (non-statistically significant)	Moderate	
Hydroxychloroquine	1.33 (0.21 to 8.29)	0.13 to 13.40	62.7	Not estimated (non-statistically significant)	Low	
Cyclosporine	1.33 (0.04 to 49.38)	0.02 to 91.38	58.4	Not estimated (non-statistically significant)	Very low	Trivial to no effect (not different than placebo)
Canakinumab	1.00 (0.02 to 61.41)	0.01 to 119.99	52.1	Not estimated (non-statistically significant)	Low	
Omalizumab (150 mg)	0.87 (0.41 to 1.84)	0.23 to 3.25	51.5	Not estimated (non-statistically significant)	High	
Ligelizumab (240 mg)	0.86 (0.26 to 2.82)	0.16 to 4.62	50.2	Not estimated (non-statistically significant)	Moderate	
Omalizumab (300 mg)	0.68 (0.39 to 1.20)	0.21 to 2.24	36.7	Not estimated (non-statistically significant)	High	
Omalizumab (75 mg)	0.64 (0.27 to 1.50)	0.16 to 2.57	34.6	Not estimated (non-statistically significant)	High	
Methotrexate	0.57 (0.11 to 2.88)	0.07 to 4.65	34.5	Not estimated (non-statistically significant)	Moderate	
Ligelizumab (72 mg)	0.47 (0.13 to 1.71)	0.08 to 2.78	24.8	Not estimated (non-statistically significant)	Moderate	

[†]Large SUCRA values indicate undesirable treatment with a higher risk of all-cause dropouts: SUCRA values for placebo=59.8.

[‡]To estimate treatment effects, OR of <1.68, 1.68-3.46, 3.47-6.71, and >6.71 are considered to be very small, small, medium, and large, respectively.

[§]Note: See Appendix-III for full details of criteria for downgrading evidence certainty.

Abbreviations: CI, confidence interval; CSU, chronic spontaneous urticaria; OR, odds ratio.

FIGURE LEGENDS

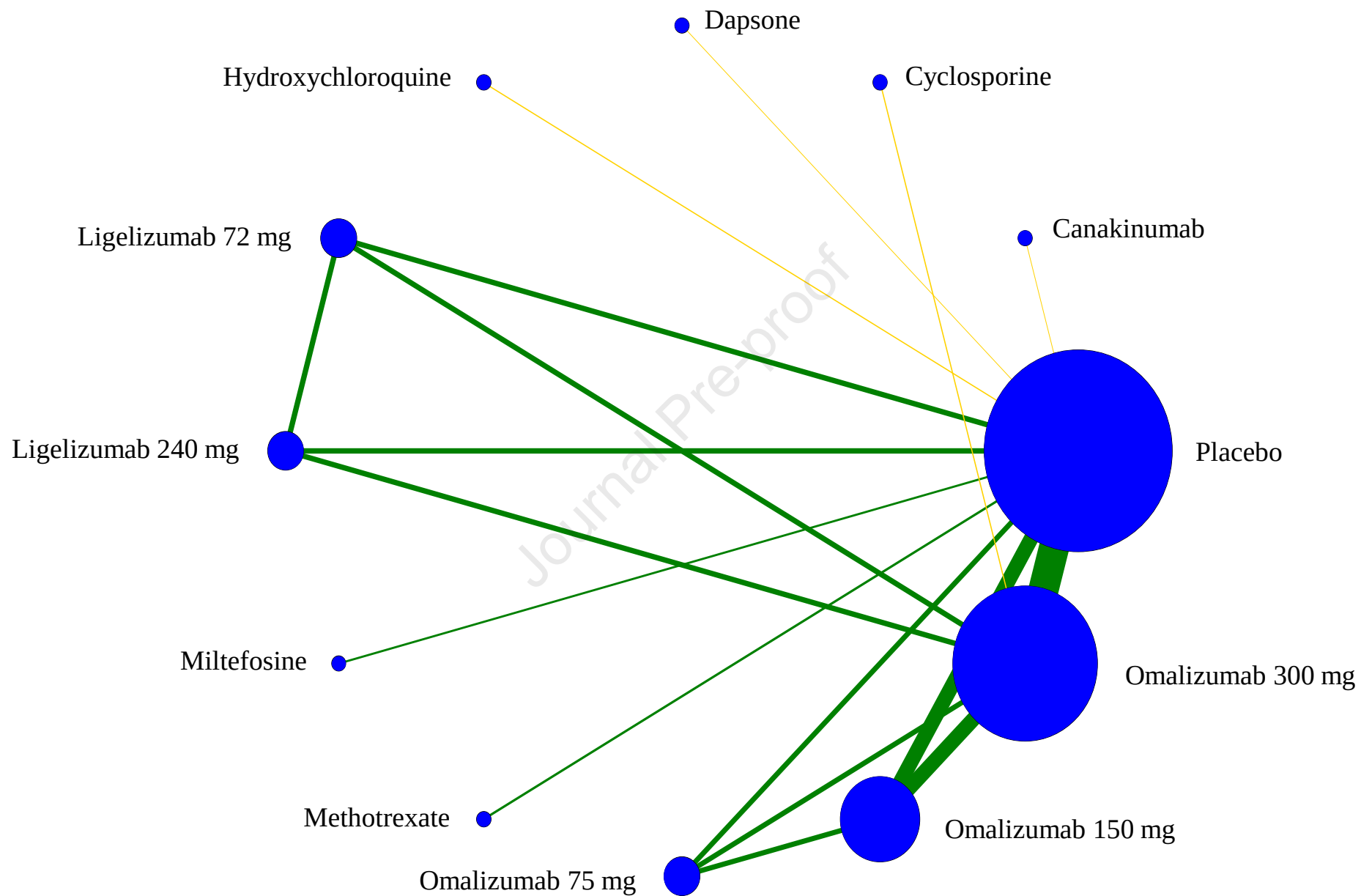
FIGURES 1. Network plot of included trials with available direct comparisons for change in HRQOL from baseline of pharmacological treatments for H1-antihistamine-refractory CSU

Note: nodes indicate pharmacological treatments, and lines indicate trials performing the corresponding treatment comparison. The size of a node is proportional to the number of trials that included the corresponding treatment. The thickness of the lines corresponds to the number of trials performing each comparison (also green and yellow lines represent trials with a low risk of bias and some concerns according to the overall risk of bias assessment). Abbreviations: CSU, chronic spontaneous urticaria; HRQOL, health-related quality of life.

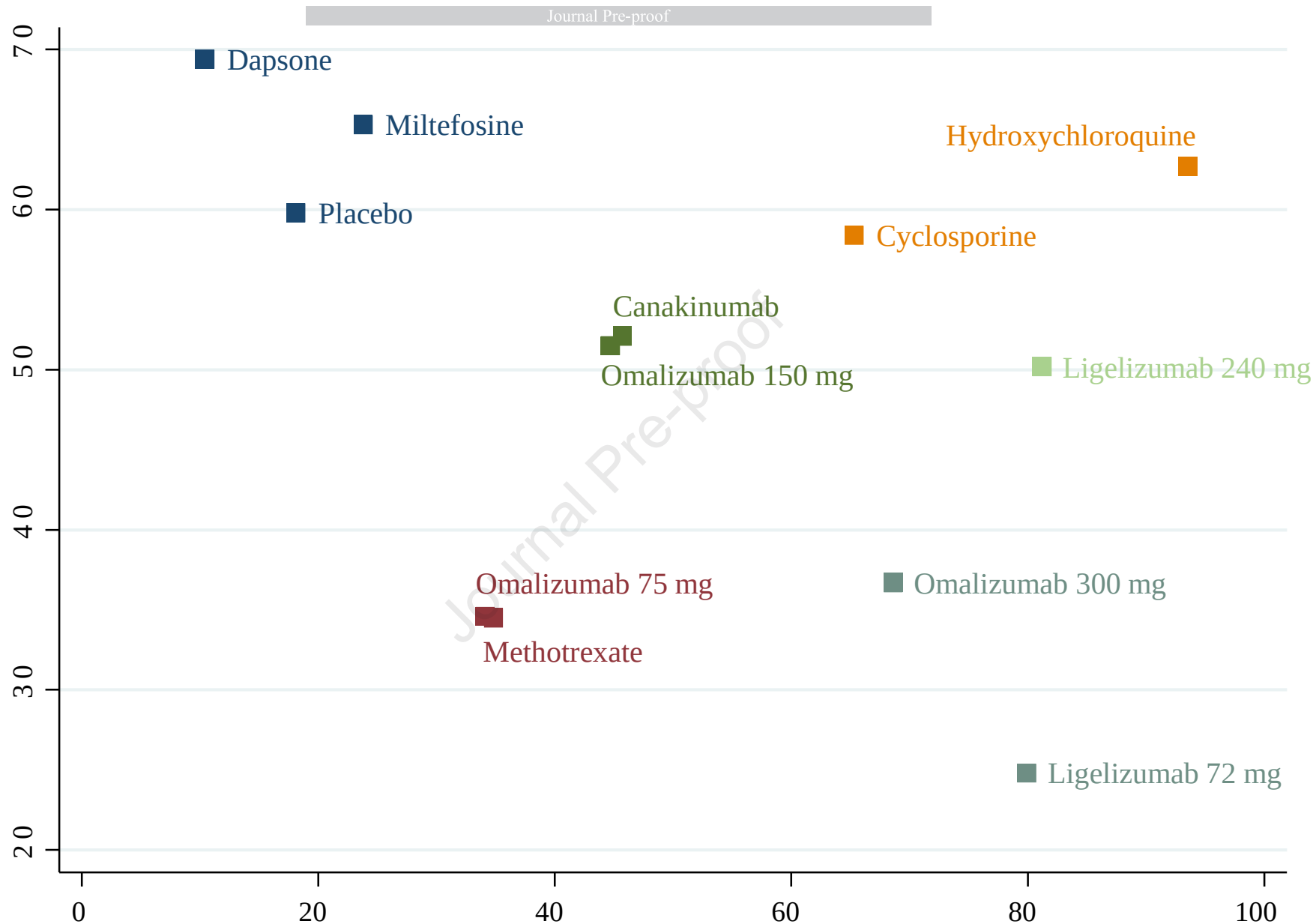
FIGURE 2. Cluster ranking plot for HRQOL and patient unacceptability (all-cause dropouts) of pharmacological treatment for H1-antihistamine-refractory CSU

Note: For effectiveness, a higher SUCRA score denotes better treatment for change in HRQOL from baseline with a higher improvement in HRQOL. For unacceptability of treatment, a higher SUCRA score denotes undesirable treatment with a higher risk of all-cause dropouts.

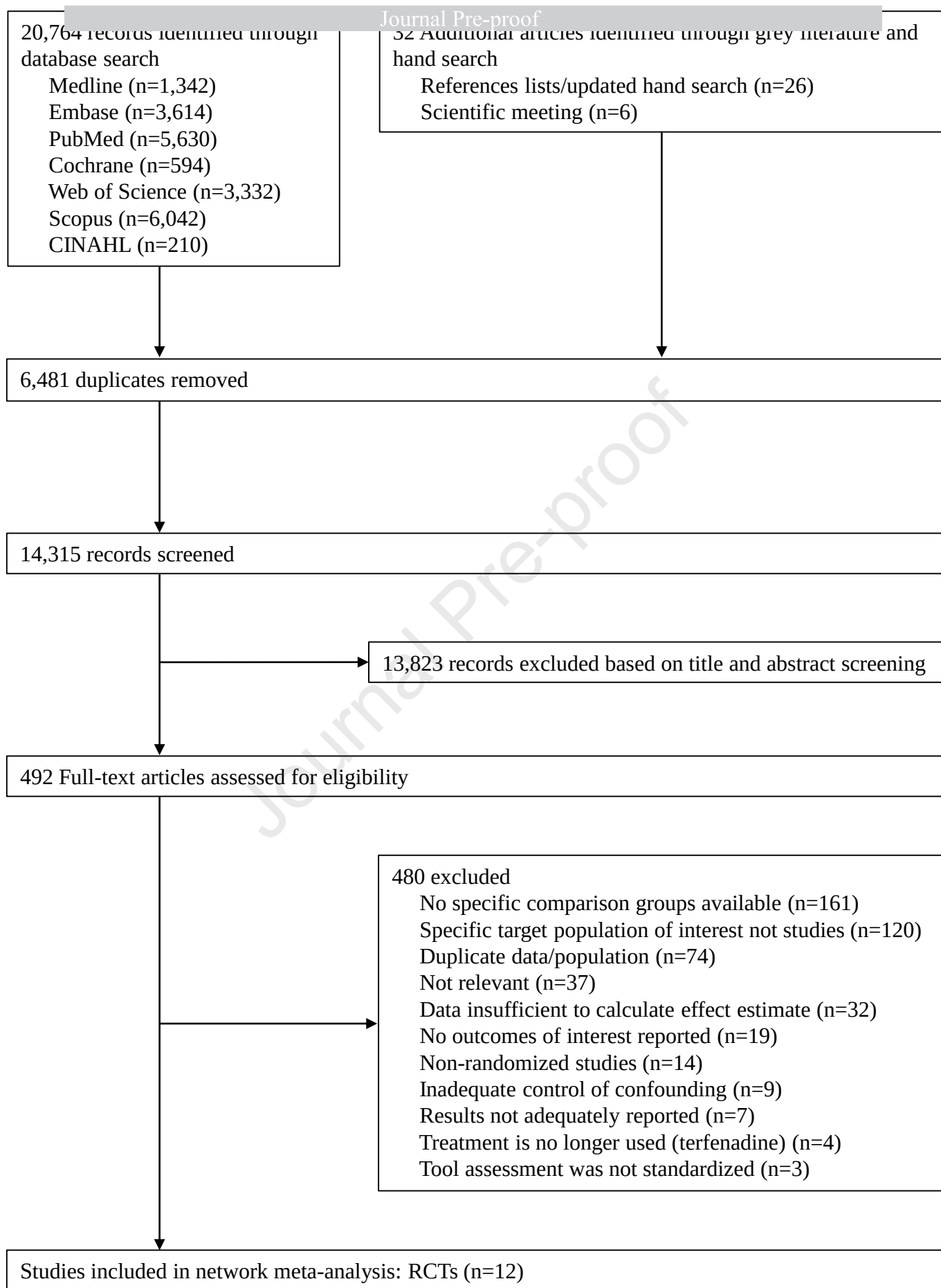
Abbreviations: CSU, chronic spontaneous urticaria; HRQOL, health-related quality of life; SUCRA, the surface under the cumulative ranking curve.



Patient unacceptability, (all-cause dropouts), SUCRA score

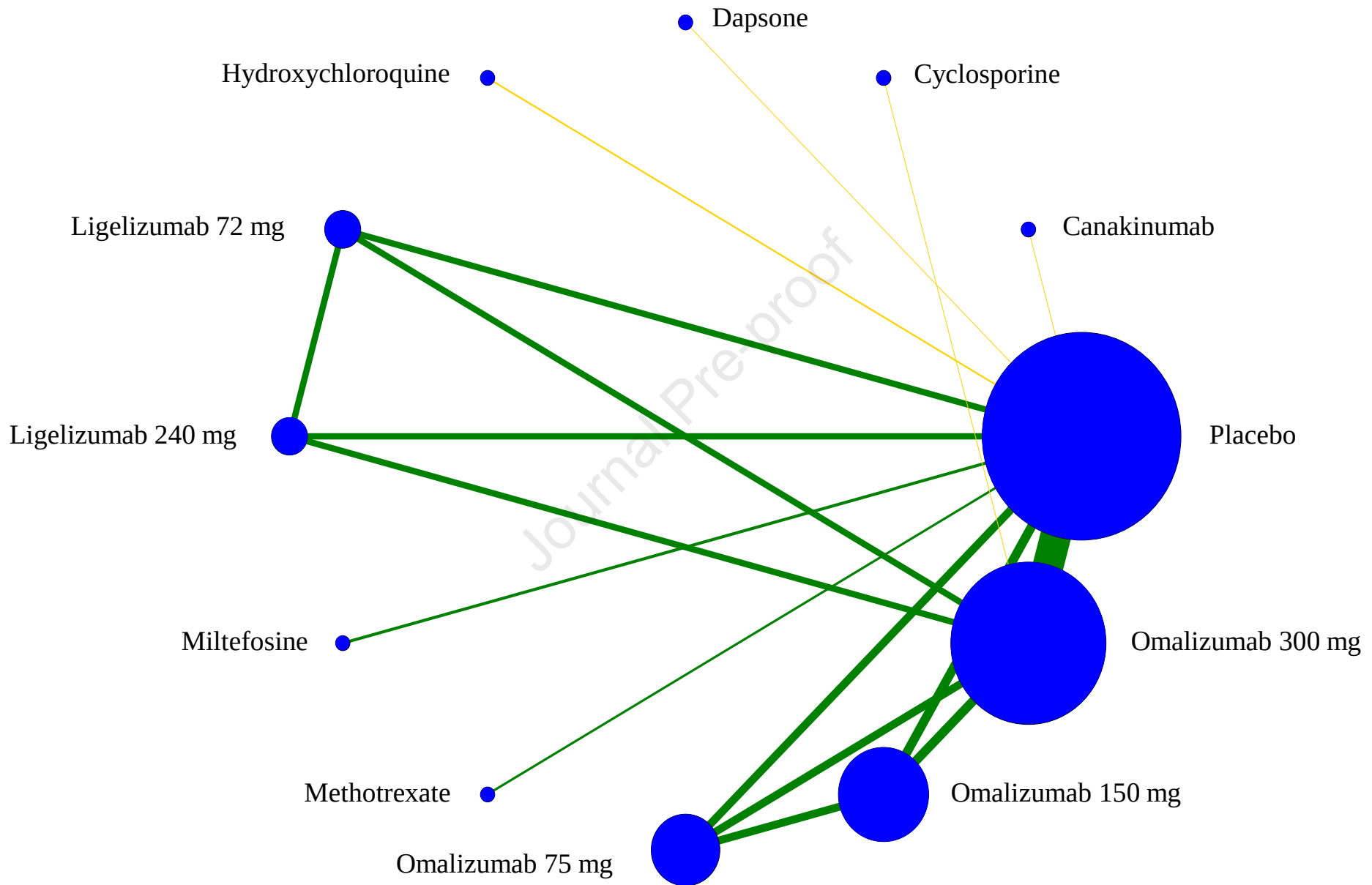


Change in HRQOL from baseline, SUCRA score

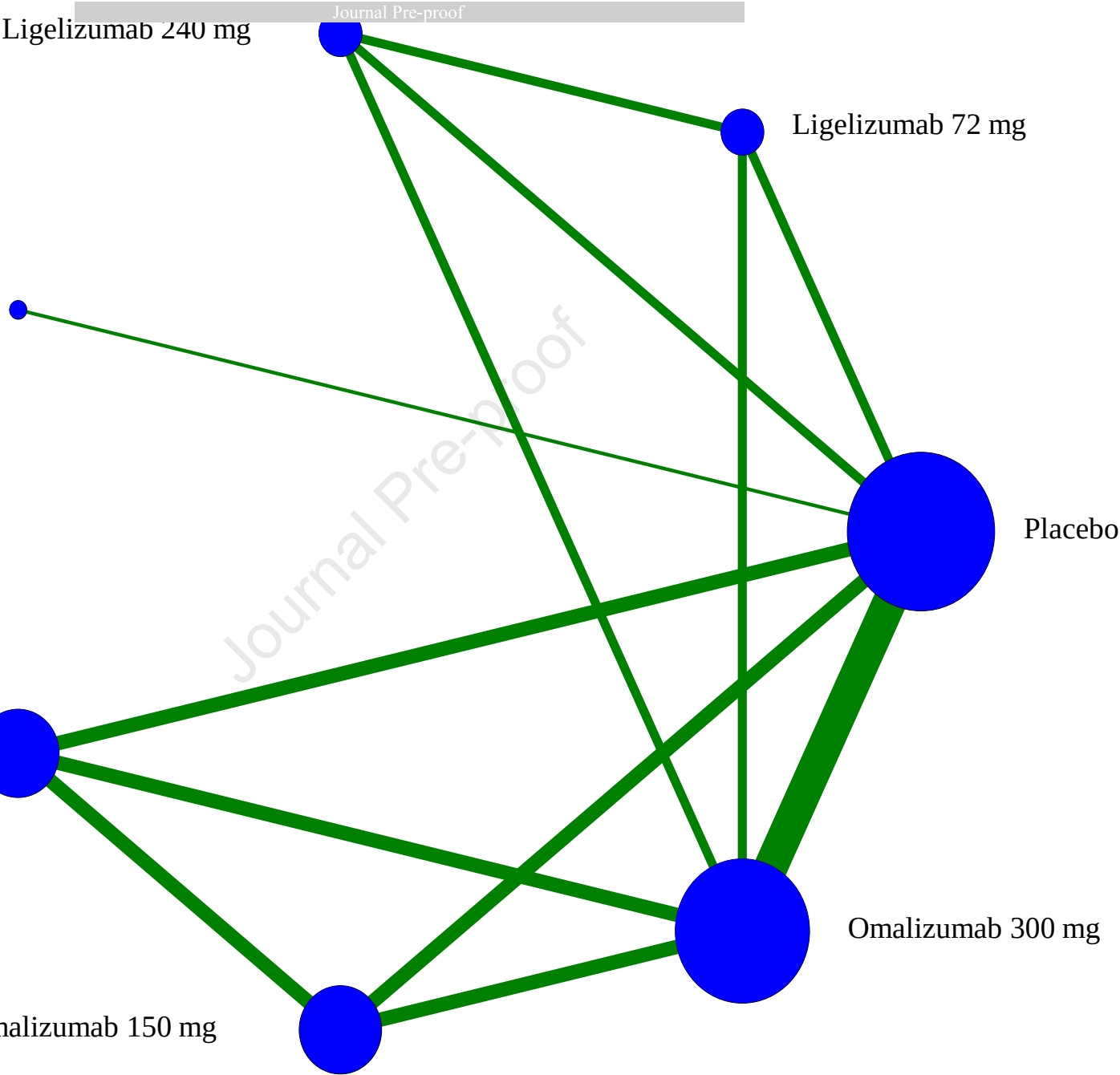


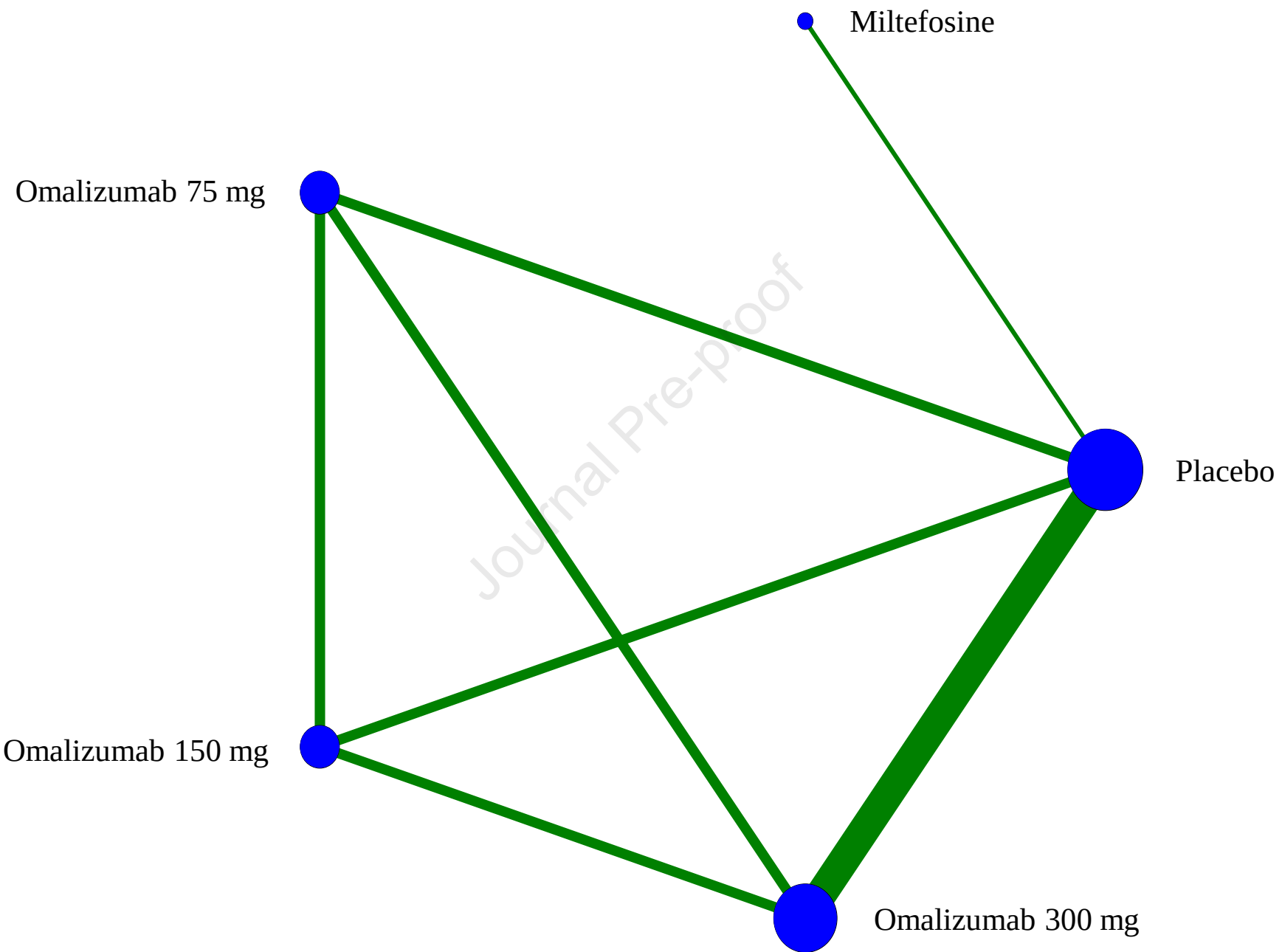
(A) Patient unacceptability

Journal Pre-proof



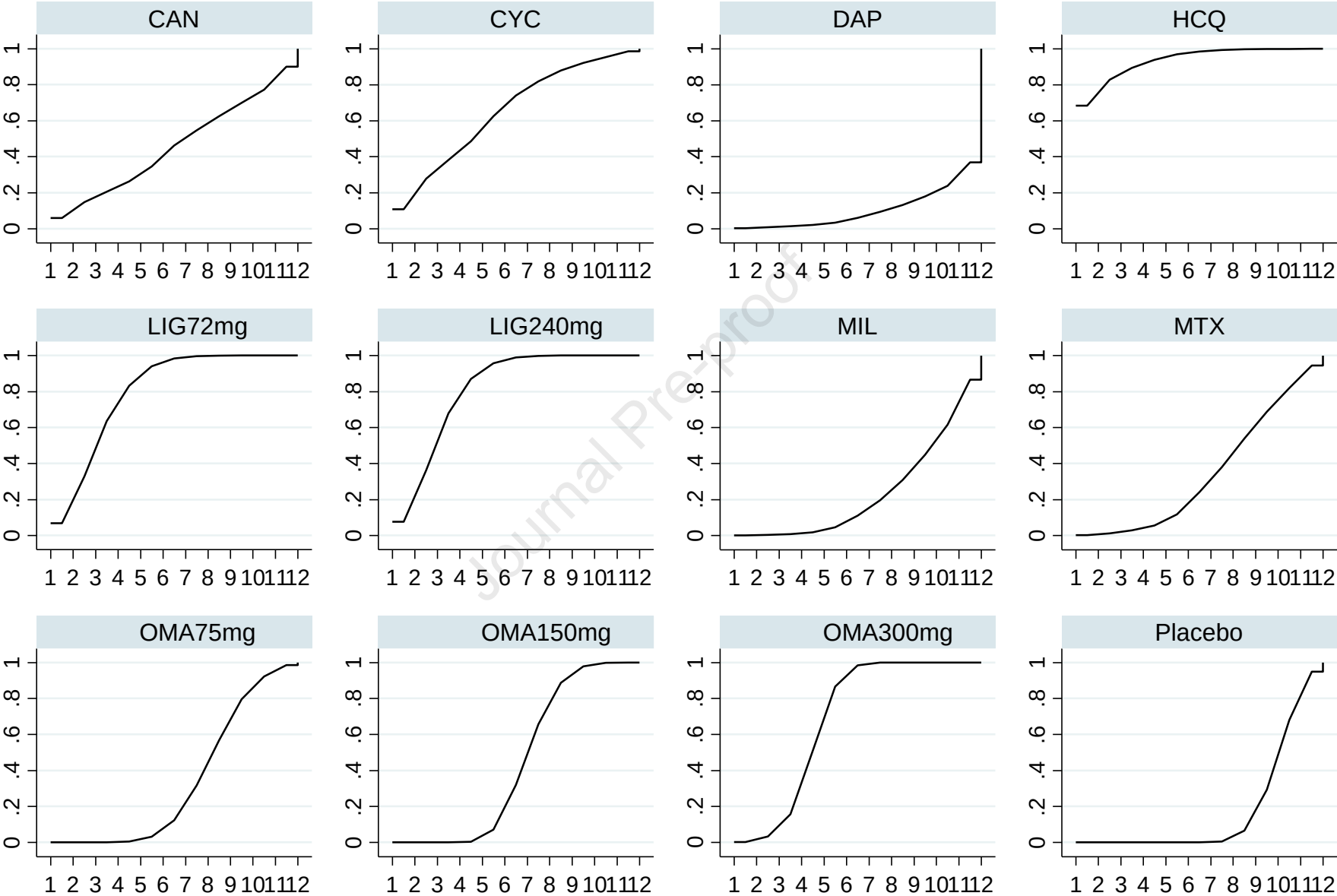
(B) Impact on sleep





(A) Health-related quality of life

Cumulative Probabilities

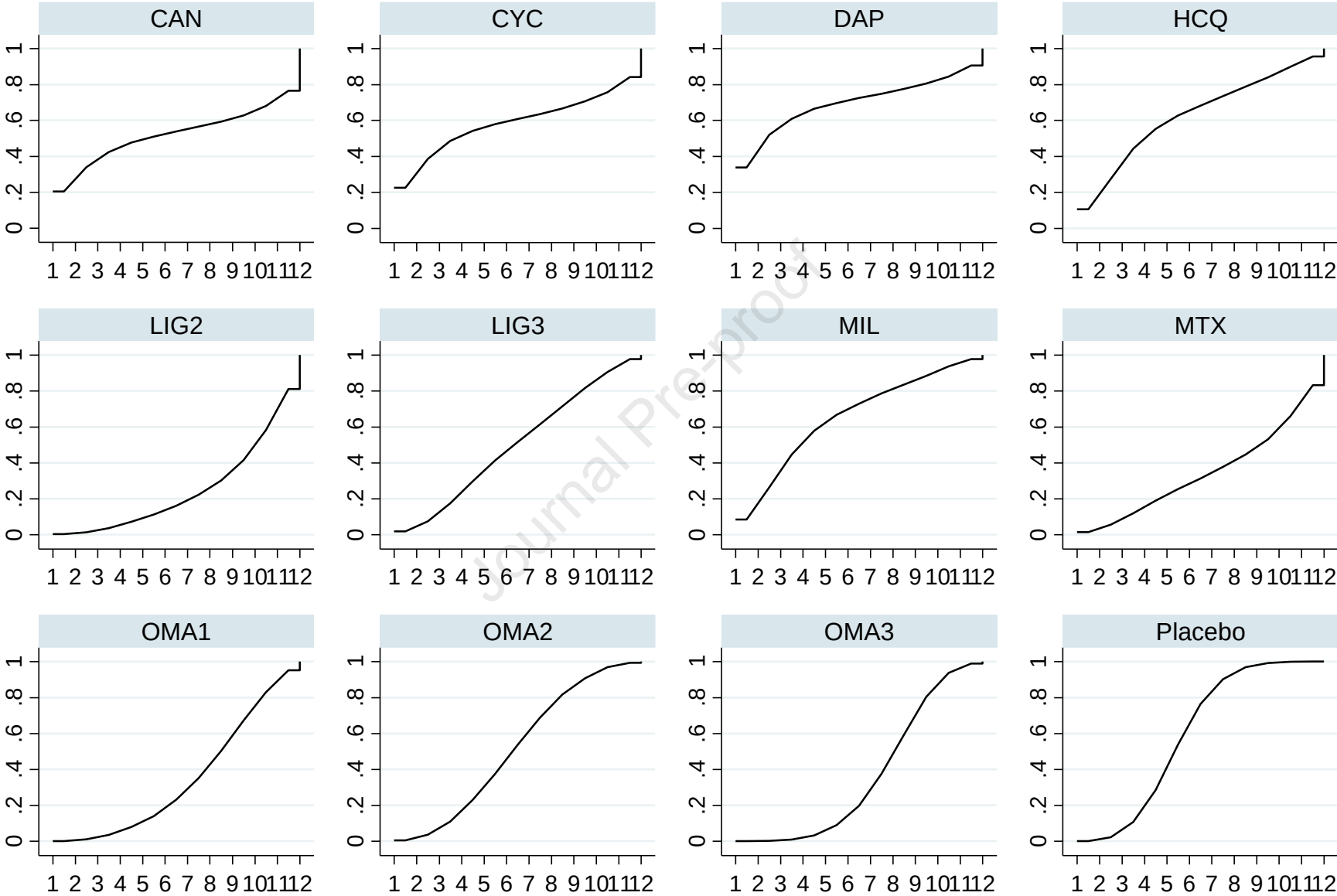


Rank

Graphs by Treatment

(B) Patient Unacceptability

Cumulative Probabilities

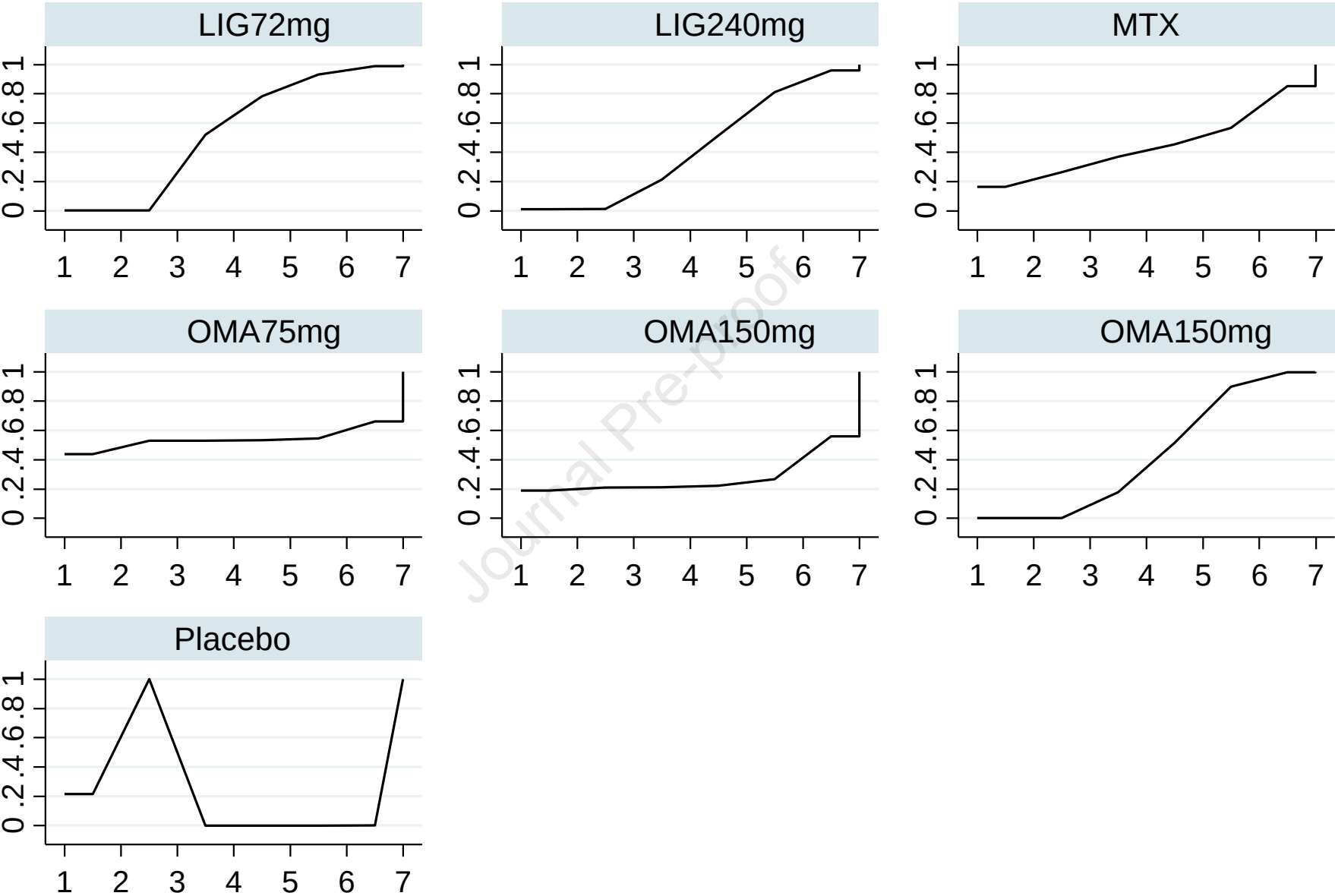


Rank

Graphs by Treatment

(C) Impact on sleep

Cumulative Probabilities

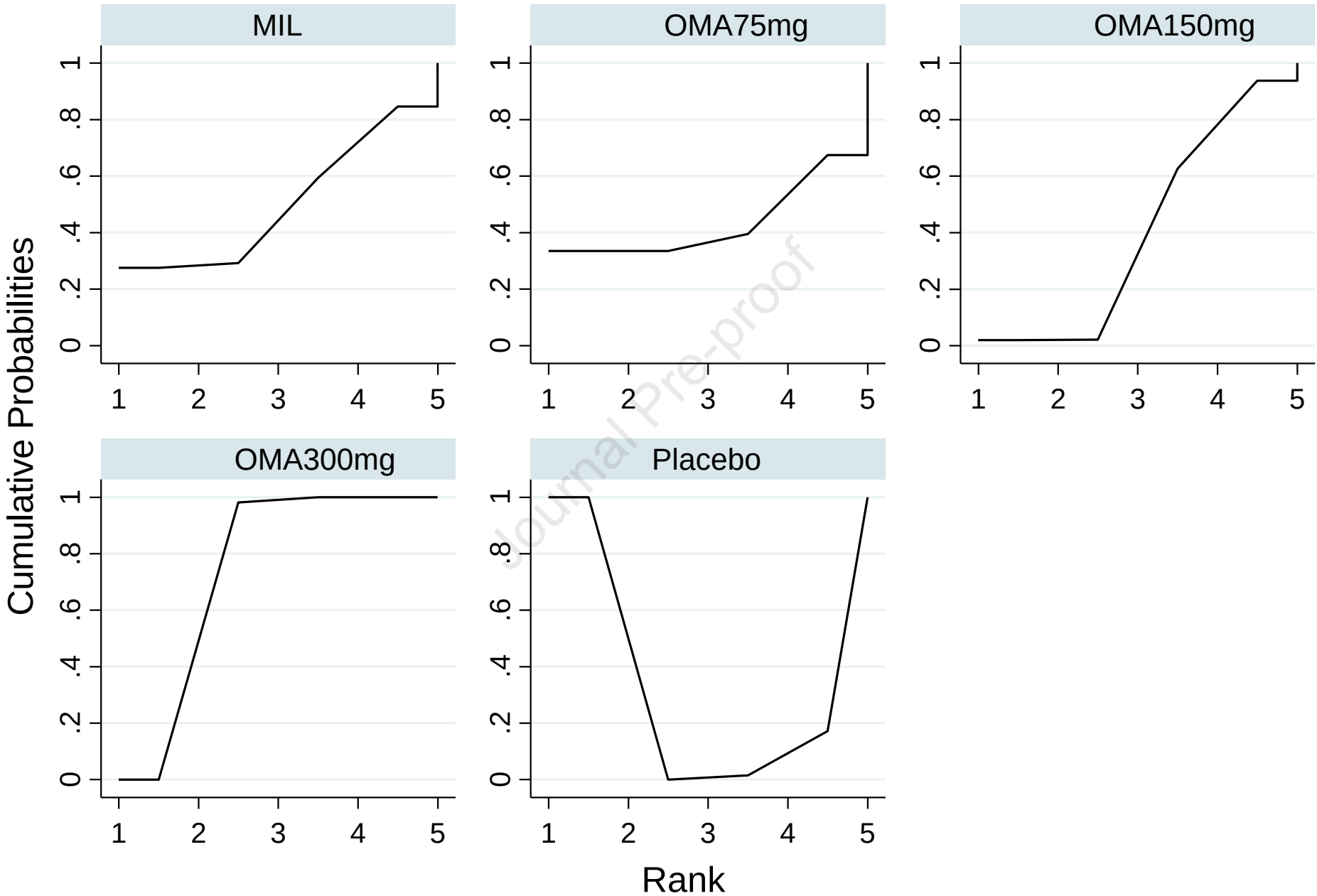


Rank

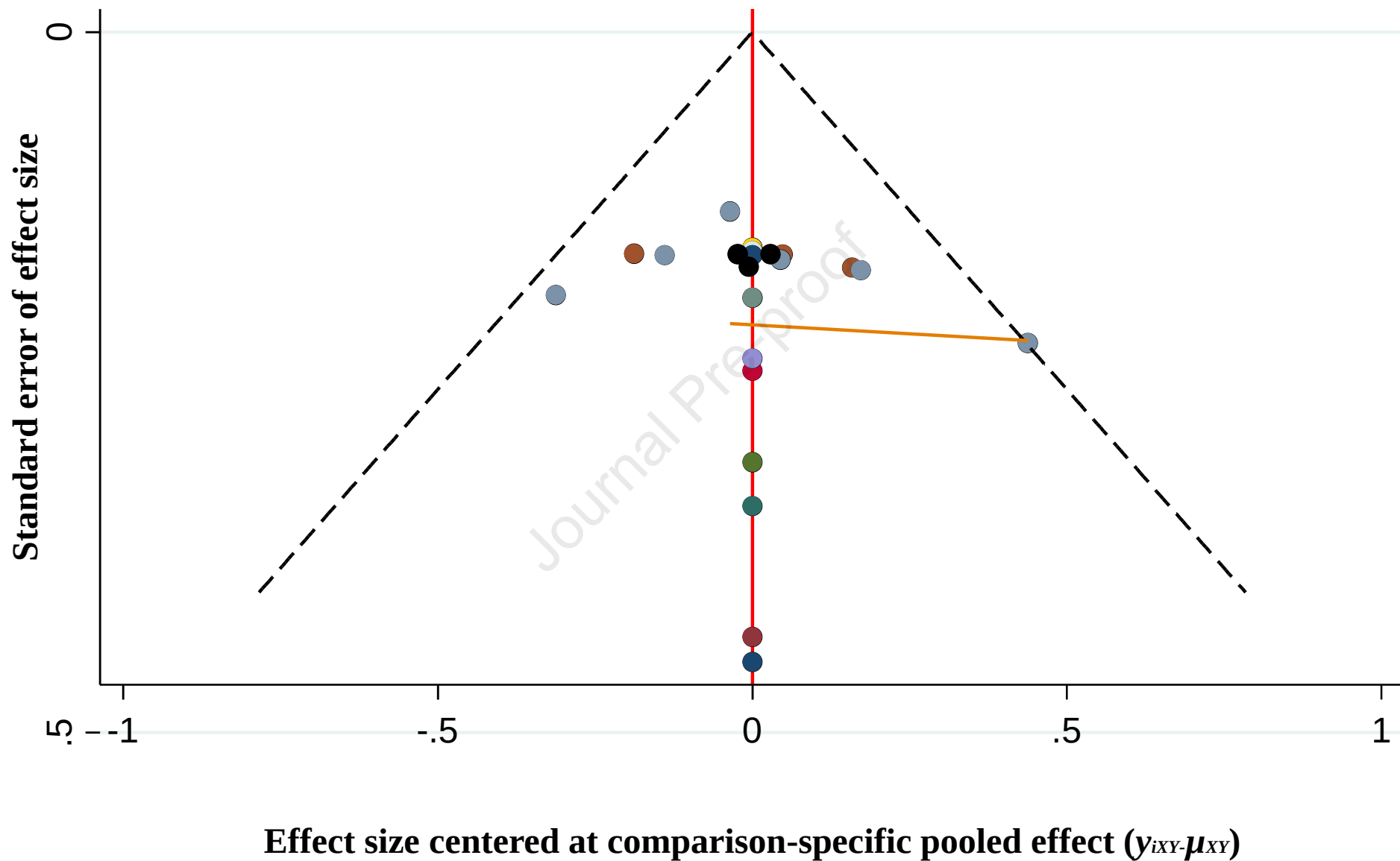
Graphs by Treatment

(D) Patient-reported chronic urticaria-specific measure: CU-O2oL

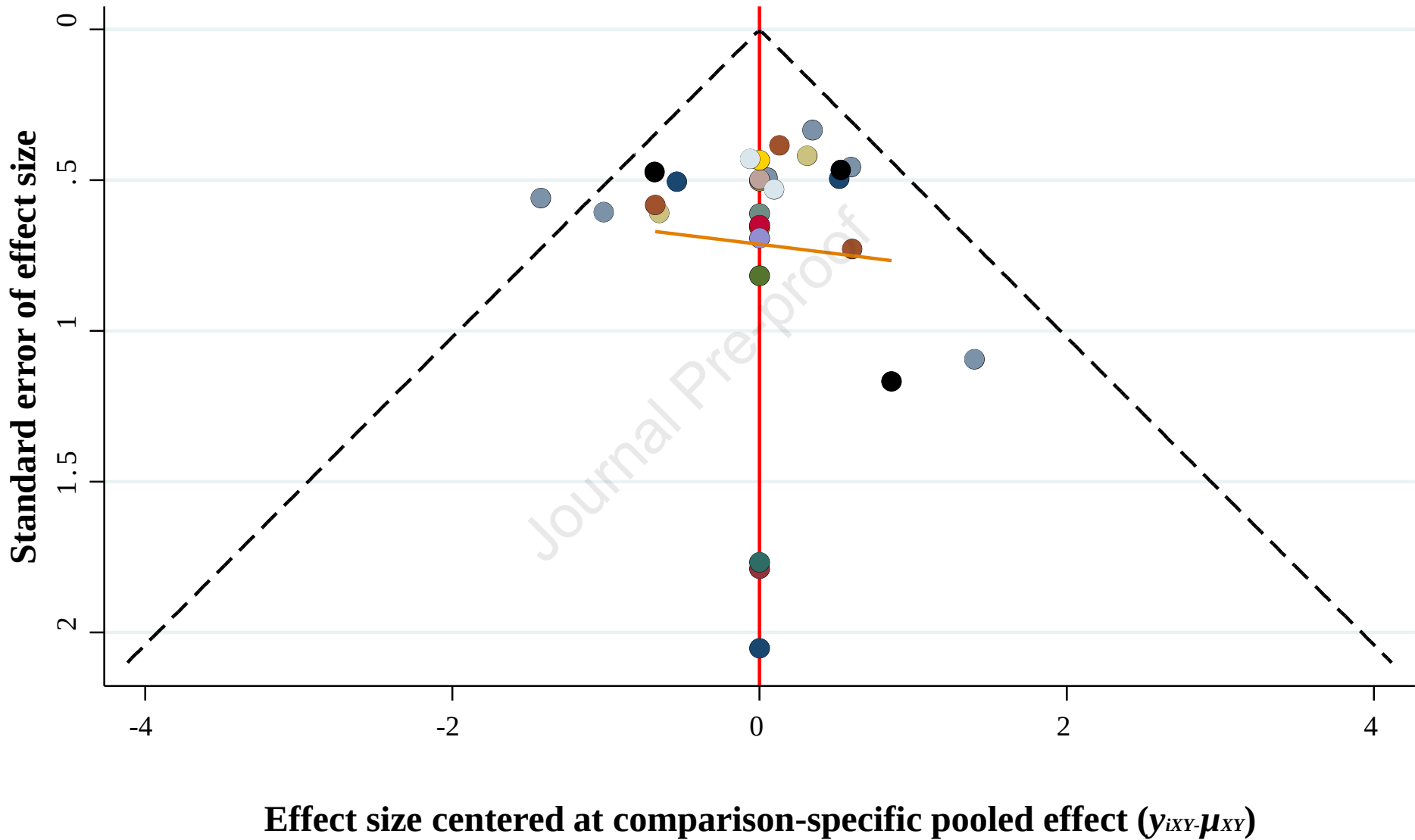
Journal Pre-proof

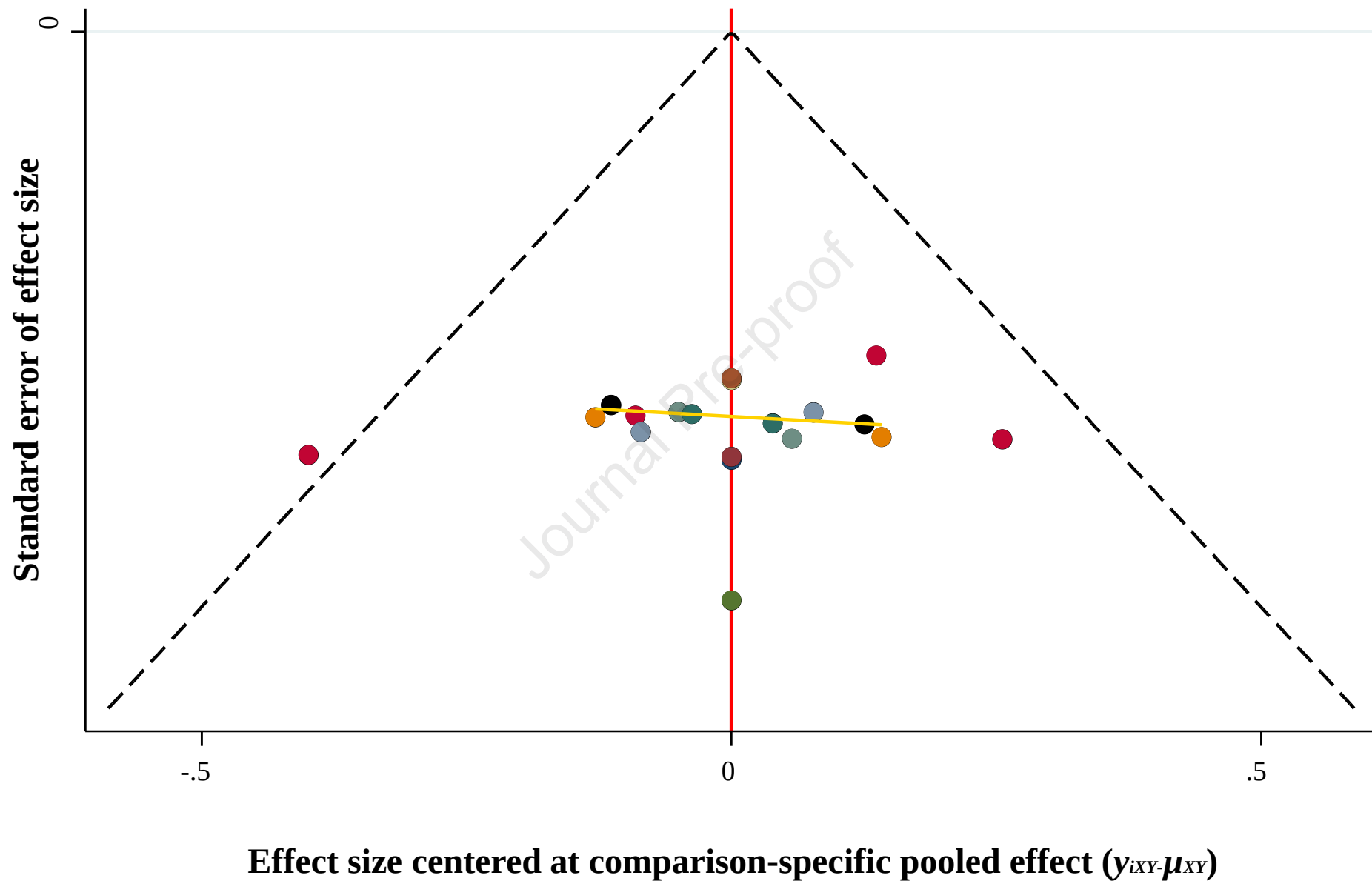


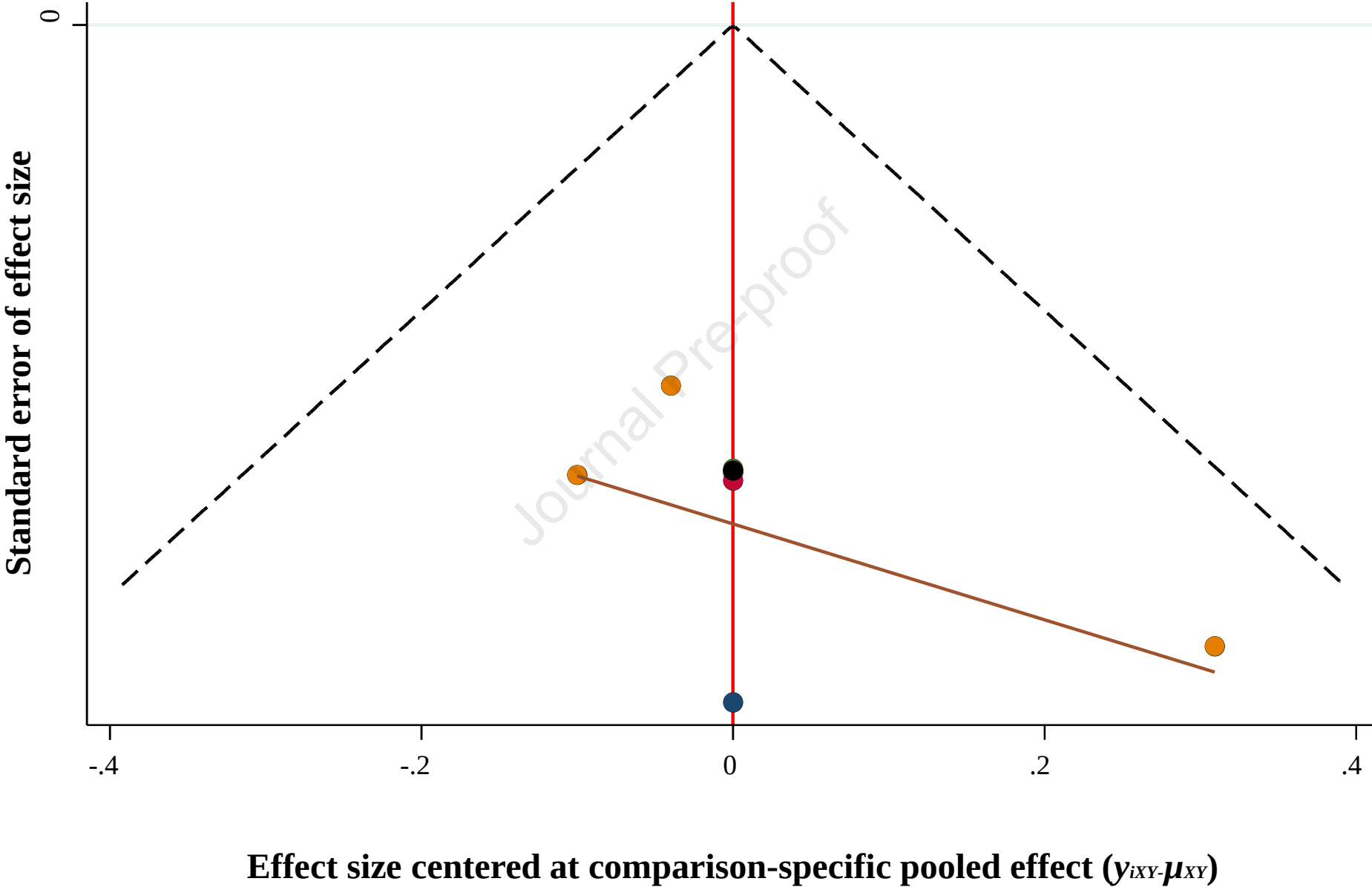
Graphs by Treatment



(B) Patient unacceptability







Supplementary Online

Pharmacological Treatments to Improve Health-Related Quality of Life Among Chronic Spontaneous Urticaria Patients with an Inadequate Response to H1-antihistamines: A Systematic Review and Network Meta-Analysis

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Table E1 Systematic review search strategy: Medline (via OVID), from inception to 19 April, 2021

Search	Query	Items found
#1	exp Urticaria/	16700
#2	Urticaria.mp.	19175
#3	exp Chronic urticaria/	195
#4	Chronic urticaria.mp.	2982
#5	exp Hives/	16700
#6	exp Angioneurotic \$edema/	6114
#7	exp Chronic spontaneous urticaria/	195
#8	Chronic spontaneous urticaria.mp.	1042
#9	exp Chronic idiopathic urticaria/	195
#10	Chronic idiopathic urticaria.mp.	762
#11	refractory urticaria.mp.	31
#12	(chronic or persis*) adj (urticaria* or itch* or prurit* or hive* or w\$eal* or CU or CSU or CIU).ti,ab,kf.	4271
#13	((refractory or antihistamin* or resistant or inadequate* or unrespons*) adj3 (urticaria* or CU or CSU or CIU)).ti,ab,kf.	632
#14	or/1-13	25282
#15	(anti-immunoglobulin E or anti-IgE* or monoclonal antibody* or spleen tyrosine kinase inhibitor* or syk inhibitor* or anti-sialic acid binding immunoglobulin-like lectin-8 or anti-Siglec8 or Bruton tyrosine kinase inhibitor* or anti-CRTH2 or CRTH2 antagonist or anti-IL-1 or IL-1 inhibitor* or anti IL-5 or BTK inhibitor* or anti-tumor necrosis factor alpha or anti-TNF* or immunosupp* or calcineurin inhibitor*).ti,ab.	273536
#16	(immunomodulatory or immunotherapy or anti-inflammatory agent* or leukotriene receptor antagonist* or antileukotriene* or LTRA* or antifibrinolytic or anticoagula* or antihistamin* or histamine* antagonist* or up-dosing or up dosing or high dosage or increase dose or methylxanthin* or (serotonin inhibitor*) or SSRI* or SNRI* or androgen* or allergen immunotherapy or pseudoallergen-free diet or diet or low histamine diet or probiotic* or herbal therap* or vitamin or nonbiologi* or nonpharmaco* or (autologous adj (blood or serum)) or phototherapy or UV or ultraviolet light or UVA or UVB or PUVA or narrow band UV or NBUVB or plasmapheresis or plasma exchange or acupuncture or alternative treatment* or holistic medicine).ti,ab.	1133592
#17	(omalizumab or ligelizumab or QGE031 or quilizumab or UB-221 or dupilumab or AZD1981 or mepolizumab or reslizumab or ibrutinib or fenebrutinib or GDC-0853 or LOU064 or GSK2646264 or AK002 or adalimumab or abatacept or etanercept or infliximab or benralizumab or rituximab or anakinra or canakinumab or rilonacept).ti,ab.	50210
#18	(cyclosporine or CsA or tacrolimus or sirolimus or methotrexate or cyclophosphamide or azathioprine or mycophenolic acid or mycophenolate mofetil or MMF or MPA or miltefosine or interferon alpha or protease inhibitor* or cromolyn or camostat mesylate or nafamostat mesylate or montelukast or zafirlukast).ti,ab.	251883
#19	(cimetidine or ranitidine or famotidine or vitamin D or vitamin D3 or cholecalciferol or hydroxychloroquine or chloroquine or HCQ or dapsone or sulfasalazine or colchicine or steroid* or immunoglobulin or IVIG or histaglobulin or heparin or warfarin or coumadin or ketotifen or danazol or stanozol or stanozolol or tranexamic acid or dipyridamole or levamisole or doxepin or mirtazapine or theophylline or gold or nifedipine or mizoribine).ti,ab.	820805
#20	or/15-19	2231585
#21	14 and 20	6275
#22	(news or newspaper article or comment or editorial or interview or letter or review or systematic review or case report or case series or cross-sectional).pt.	4991200
#23	21 not 22	4454
#24	exp Clinical Trials as Topic/	355330
#25	randomi\$ed controlled trial* or controlled clinical trial*	126823
#26	random allocation or double-blind method or single-blind method or clinical trial/	716445
#27	(controlled clinical trial) or (randomi\$ed controlled trial) or (clinical trial).pt	563319
#28	(control* adj2 trial*).tw,kw.	296808
#29	((clinical adj trial*) or (randomly allocated) or (allocated adj2 random*) or randomi\$ed or RCT\$1 placebo*).tw,kw.	424945
#30	((singl* or doubl* or trebl* or tribl*) adj (blind* or mask* or dumm*)).tw,kw.	178488

#31	(nRCT or nRCTs or non-RCT?).tw,kw.	1046
#32	(control* adj3 ("before and after" or "before after")).tw,kw.	4564
#33	(time series adj3 interrupt*).tw,kw.	3675
#34	(pre- adj3 post-).tw,kw.	90759
#35	(pretest adj3 posttest).tw,kw.	6056
#36	(control* adj2 stud\$3).tw,kw.	244925
#37	control group/	1728
#38	(control* adj2 group\$1).tw,kw.	533087
#39	or/24-38	2081972
#40	exp comparative study/	1887474
#41	((comparative or comparison) adj stud\$3).tw,kw.	114833
#42	exp cohort study/	2115009
#43	(cohort* adj2 stud\$3).tw,kw.	256891
#44	exp case control study/	1159190
#45	((case-control* or case-based or case-comparison) adj stud\$3).tw,kw.	113193
#46	or/40-45	4035941
#47	23 and 39	844
#48	23 and 46	925
#49	47 or 48	1468
#50	limit 49 to human	1342

Table E1 Systematic review search strategy: Embase (via OVID), from inception to 19 April, 2021 (continued)

Search	Query	Items found
#1	exp Urticaria/	43416
#2	Urticaria.mp.	46085
#3	exp Chronic urticaria/	5638
#4	Chronic urticaria.mp.	6756
#5	exp Hives/	43416
#6	exp Angioneurotic \$edema/	20961
#7	exp Chronic spontaneous urticaria/	5638
#8	Chronic spontaneous urticaria.mp.	1775
#9	exp Chronic idiopathic urticaria/	5638
#10	Chronic idiopathic urticaria.mp.	1256
#11	refractory urticaria.mp.	64
#12	(chronic or persis*) adj (urticaria* or itch* or prurit* or hive* or w\$eal* or CU or CSU or CIU).ti,ab,kw.	6914
#13	((refractory or antihistamin* or resistant or inadequate* or unrespons*) adj3 (urticaria* or CU or CSU or CIU)).ti,ab,kw.	1156
#14	or/1-13	61991
#15	(anti-immunoglobulin E or anti-IgE* or monoclonal antibody* or spleen tyrosine kinase inhibitor* or syk inhibitor* or anti-sialic acid binding immunoglobulin-like lectin-8 or anti-Siglec8 or Bruton tyrosine kinase inhibitor* or anti-CRTH2 or CRTH2 antagonist or anti-IL-1 or IL-1 inhibitor* or anti IL-5 or BTK inhibitor* or anti-tumor necrosis factor alpha or anti-TNF* or immunosupp* or calcineurin inhibitor*).ti,ab.	388925
#16	(immunomodulatory or immunotherapy or anti-inflammatory agent* or leukotriene receptor antagonist* or antileukotriene* or LTRA* or antifibrinolytic or anticoagula* or antihistamin* or histamine* antagonist* or up-dosing or up dosing or high dosage or increase dose or methylxanthin* or (serotonin inhibitor*) or SSRI* or SNRI* or androgen* or allergen immunotherapy or pseudoallergen-free diet or diet or low histamine diet or probiotic* or herbal therap* or vitamin or nonbiologi* or nonpharmaco* or (autologous adj (blood or serum)) or phototherapy or UV or ultraviolet light or UVA or UVB or PUVA or narrow band UV or NBUVB or plasmapheresis or plasma exchange or acupuncture or alternative treatment* or holistic medicine).ti,ab.	1477108
#17	(omalizumab or ligelizumab or QGE031 or quilizumab or UB-221 or dupilumab or AZD1981 or mepolizumab or reslizumab or ibrutinib or fenebrutinib or GDC-0853 or LOU064 or GSK2646264 or AK002 or adalimumab or abatacept or etanercept or infliximab or benralizumab or rituximab or anakinra or canakinumab or rilonacept).ti,ab.	109824
#18	(cyclosporine or CsA or tacrolimus or sirolimus or methotrexate or cyclophosphamide or azathioprine or mycophenolic acid or mycophenolate mofetil or MMF or MPA or miltefosine or interferon alpha or protease inhibitor* or cromolyn or camostat mesylate or nafamostat mesylate or montelukast or zafirlukast).ti,ab.	361710
#19	(cimetidine or ranitidine or famotidine or vitamin D or vitamin D3 or cholecalciferol or hydroxychloroquine or chloroquine or HCQ or dapsone or sulfasalazine or colchicine or steroid* or immunoglobulin or IVIG or histaglobulin or heparin or warfarin or coumadin or ketotifen or danazol or stanozol or stanozolol or tranexamic acid or dipyridamole or levamisole or doxepin or mirtazapine or theophylline or gold or nifedipine or mizoribine).ti,ab.	1064755
#20	or/15-19	2907075
#21	14 and 20	18460
#22	(news or newspaper article or comment or editorial or interview or letter or review or systematic review or case report or case series or cross-sectional).pt.	4564090
#23	21 not 22	14580
#24	exp Clinical Trials as Topic/	350405
#25	randomi\$ed controlled trial* or controlled clinical trial*	506345
#26	random allocation or double-blind method or single-blind method or clinical trial/	1022623
#27	(controlled clinical trial) or (randomi\$ed controlled trial) or (clinical trial).pt	493863
#28	(control* adj2 trial*).tw,kw.	402912
#29	((clinical adj trial*) or (randomly allocated) or (allocated adj2 random*) or randomi\$ed or RCT\$1 placebo*).tw,kw.	623493

#30	((singl* or doubl* or trebl* or tribl*) adj (blind* or mask* or dumm*)).tw,kw.	244888
#31	(nRCT or nRCTs or non-RCT?).tw,kw.	1464
#32	(control* adj3 ("before and after" or "before after")).tw,kw.	5935
#33	(time series adj3 interrupt*).tw,kw.	4720
#34	(pre- adj3 post-).tw,kw.	163587
#35	(pretest adj3 posttest).tw,kw.	7322
#36	(control* adj2 stud\$3).tw,kw.	330935
#37	control group/	110007
#38	(control* adj2 group\$1).tw,kw.	767571
#39	or/24-38	2973357
#40	exp comparative study/	1364497
#41	((comparative or comparison) adj stud\$3).tw,kw.	131808
#42	exp cohort study/	685417
#43	(cohort* adj2 stud\$3).tw,kw.	390674
#44	exp case control study/	187146
#45	((case-control* or case-based or case-comparison) adj stud\$3).tw,kw.	149853
#46	or/40-45	2338613
#47	23 and 39	3199
#48	23 and 46	1062
#49	47 or 48	3802
#50	limit 49 to human	3614

Table E1 Systematic review search strategy: PubMed, from inception to 19 April, 2021 (continued)

Search	Query	Items found
#1	((((((((((urticaria[MeSH Terms]) OR (urticaria[Title/Abstract])) OR (chronic urticaria)) OR (hives)) OR (angioneurotic \$edema)) OR (chronic spontaneous urticaria)) OR (chronic idiopathic urticaria)) OR (refractory urticaria)) OR (antihistamin* resistant chronic urticaria)) OR (CU)) OR (CSU)) OR (CIU))	165414
#2	((((((((((((((((anti-immunoglobulin E[Title/Abstract]) OR (anti-IgE*[Title/Abstract])) OR (monoclonal antibody*[Title/Abstract])) OR (spleen tyrosine kinase inhibitor*[Title/Abstract])) OR (syk inhibitor*[Title/Abstract])) OR (anti-sialic acid binding immunoglobulin-like lectin-8[Title/Abstract])) OR (anti-Siglec-8[Title/Abstract])) OR (Bruton tyrosine kinase inhibitor*[Title/Abstract])) OR (anti-CRTH2[Title/Abstract])) OR (CRTH2 antagonist[Title/Abstract])) OR (anti-IL-1[Title/Abstract])) OR (IL-1 inhibitor*[Title/Abstract])) OR (anti IL-5[Title/Abstract])) OR (BTK inhibitor*[Title/Abstract])) OR (anti-tumor necrosis factor alpha[Title/Abstract])) OR (anti-TNF*[Title/Abstract])) OR (immunosupp*[Title/Abstract])) OR (calcineurin inhibitor*[Title/Abstract]))	279297
#3	((((((((((((((((((((((((((((((immunomodulatory[Title/Abstract]) OR (immunotherapy[Title/Abstract])) OR (anti-inflammatory agent*[Title/Abstract])) OR (leukotriene receptor antagonist*[Title/Abstract])) OR (anti-leukotriene*[Title/Abstract])) OR (LTRA*[Title/Abstract])) OR (anti-fibrinolytic[Title/Abstract])) OR (anticoagula*[Title/Abstract])) OR (antihistamin*[Title/Abstract])) OR (histamine* antagonist*[Title/Abstract])) OR (up-dosing[Title/Abstract])) OR (high dosage[Title/Abstract])) OR (increase dose[Title/Abstract])) OR (methylxanthin*[Title/Abstract])) OR (serotonin inhibitor*[Title/Abstract])) OR (SSRI*[Title/Abstract])) OR (SNRI*[Title/Abstract])) OR (androgen*[Title/Abstract])) OR (allergen immunotherapy[Title/Abstract])) OR (pseudoallergen-free diet[Title/Abstract])) OR (diet[Title/Abstract])) OR (low histamine diet[Title/Abstract])) OR (probiotic*[Title/Abstract])) OR (herbal therap*[Title/Abstract])) OR (vitamin[Title/Abstract])) OR (nonbiologi*[Title/Abstract])) OR (nonpharmaco*[Title/Abstract])) OR (autologous adj (blood[Title/Abstract] OR serum)[Title/Abstract])) OR (phototherapy[Title/Abstract])) OR (UV[Title/Abstract])) OR (ultraviolet light[Title/Abstract])) OR (UVA[Title/Abstract])) OR (UVB[Title/Abstract])) OR (PUVA[Title/Abstract])) OR (narrow band UV[Title/Abstract])) OR (NBUBV[Title/Abstract])) OR (plasmapheresis[Title/Abstract])) OR (plasma exchange[Title/Abstract])) OR (acupuncture[Title/Abstract])) OR (alternative treatment*[Title/Abstract])) OR (holistic medicine[Title/Abstract]))	1181118
#4	((((((((((((((((((((((((((((((omalizumab[Title/Abstract]) OR (ligelizumab[Title/Abstract])) OR (QGE031[Title/Abstract])) OR (quilizumab[Title/Abstract])) OR (UB-221[Title/Abstract])) OR (dupilumab[Title/Abstract])) OR (AZD1981[Title/Abstract])) OR (mepolizumab[Title/Abstract])) OR (reslizumab[Title/Abstract])) OR (ibrutinib[Title/Abstract])) OR (fenebrutinib[Title/Abstract])) OR (GDC-0853[Title/Abstract])) OR (LOU064[Title/Abstract])) OR (GSK2646264[Title/Abstract])) OR (AK002[Title/Abstract])) OR (adalimumab[Title/Abstract])) OR (abatacept[Title/Abstract])) OR (etanercept[Title/Abstract])) OR (infliximab[Title/Abstract])) OR (benralizumab[Title/Abstract])) OR (rituximab[Title/Abstract])) OR (anakinra[Title/Abstract])) OR (canakinumab[Title/Abstract])) OR (rilonacept[Title/Abstract]))	51386
#5	((((((((((((((((((((((((((((((cyclosporine[Title/Abstract]) OR (CsA[Title/Abstract])) OR (tacrolimus[Title/Abstract])) OR (sirolimus[Title/Abstract])) OR (methotrexate[Title/Abstract])) OR (cyclophosphamide[Title/Abstract])) OR (azathioprine[Title/Abstract])) OR (mycophenolic acid[Title/Abstract])) OR (mycophenolate mofetil[Title/Abstract])) OR (MMF[Title/Abstract])) OR (MPA[Title/Abstract])) OR (miltefosine[Title/Abstract])) OR (interferon alpha[Title/Abstract])) OR (protease inhibitor*[Title/Abstract])) OR (cromolyn[Title/Abstract])) OR (camostat mesylate[Title/Abstract])) OR (nafamostat mesylate[Title/Abstract])) OR (montelukast[Title/Abstract])) OR (zafirlukast[Title/Abstract]))	256411
#6	((((((((((((((((((((((((((((((cimetidine[Title/Abstract]) OR (ranitidine[Title/Abstract])) OR (famotidine[Title/Abstract])) OR (vitamin D[Title/Abstract])) OR (vitamin D3[Title/Abstract])) OR (cholecalciferol[Title/Abstract])) OR (hydroxychloroquine[Title/Abstract])) OR (chloroquine[Title/Abstract])) OR (HCQ[Title/Abstract])) OR (dapson[Title/Abstract])) OR (sulfasalazine[Title/Abstract])) OR (colchicine[Title/Abstract])) OR (steroid*[Title/Abstract])) OR (immunoglobulin[Title/Abstract])) OR (IVIG[Title/Abstract])) OR (histaglobulin[Title/Abstract])) OR (heparin[Title/Abstract])) OR (warfarin[Title/Abstract]))	837578

	OR (coumadin[Title/Abstract])) OR (ketotifen[Title/Abstract])) OR (danazol[Title/Abstract])) OR (stanozol[Title/Abstract])) OR (stanozolol[Title/Abstract])) OR (tranexamic acid[Title/Abstract])) OR (dipyridamole[Title/Abstract])) OR (levamisole[Title/Abstract])) OR (doxepin[Title/Abstract])) OR (mirtazapine[Title/Abstract])) OR (theophylline[Title/Abstract])) OR (gold[Title/Abstract])) OR (nifedipine[Title/Abstract])) OR (mizoribine[Title/Abstract]))	
#7	#2 OR #3 OR #4 OR #5 OR #6	2295876
#8	#1 AND #7	20161
#9	(((((Case Reports[Publication Type]) OR Comment[Publication Type]) OR Editorial[Publication Type]) OR Guideline[Publication Type]) OR Letter[Publication Type]) OR News[Publication Type]) OR Newspaper Article[Publication Type]) OR Review[Publication Type]	6760906
#10	#8 NOT #9	16190
#11	Filters: Humans	5630

Table E1 Systematic review search strategy: Cochrane Library, from inception to 19 April, 2021 (continued)

Search	Query	Items found
#1	MeSH descriptor: [Chronic Urticaria] explode all trees	7
#2	(Urticarial OR “chronic urticarial” OR hives OR “angioneurotic \$edema” OR “chronic spontaneous urticarial” OR “chronic idiopathic urticarial” OR “refractory urticarial” OR “antihistamin* resistant chronic urticarial” OR CSU OR CIU):ti,ab,kw	1281
#3	#1 OR #2	1286
#4	(“anti-immunoglobulin” OR anti-IgE* OR “monoclonal antibody*” OR “spleen tyrosine kinase inhibitor*” OR “syk inhibitor*” OR “anti-sialic acid binding immunoglobulin-like lectin-8” OR “anti-Siglec-8” OR “Bruton tyrosine kinase inhibitor*” OR “anti-CRTH2” OR “CRTH2 antagonist” OR anti-IL-1 OR “IL-1 inhibitor*” OR anti IL-5 OR “BTK inhibitor*” OR “anti-tumor necrosis factor alpha” OR anti-TNF* OR immunosupp* OR “calcineurin inhibitor*”):ti,ab,kw	17775
#5	(immunomodulatory OR immunotherapy OR “anti-inflammatory agent*” OR “leukotriene receptor antagonist*” OR anti-leukotriene* OR LTRA* OR anti-fibrinolytic OR anticoagula* OR antihistamin* OR “histamine* antagonist*” OR up-dosing OR “high dosage” OR “increase dose” OR methylxanthin* OR “serotonin inhibitor*” OR SSRI* OR SNRI* OR androgen* OR “allergen immunotherapy” OR “pseudoallergen-free diet” OR diet OR “low histamine diet” OR probiotic* OR “herbal therap*” OR vitamin OR nonbiologi* OR nonpharmaco* OR autologous blood OR autologous serum OR phototherapy OR UV OR “ultraviolet light” OR UVA OR UVB OR PUVA OR “narrow band UV” OR NBUVB OR plasmapheresis OR “plasma exchange” OR acupuncture OR “alternative treatment*” OR “holistic medicine”):ti,ab,kw	169394
#6	(omalizumab OR ligelizumab OR QGE031 OR quilizumab OR UB-221 OR dupilumab OR AZD1981 OR mepolizumab OR reslizumab OR ibrutinib OR fenebrutinib OR GDC-0853 OR LOU064 OR GSK2646264 OR AK002 OR adalimumab OR abatacept OR etanercept OR infliximab OR benralizumab OR rituximab OR anakinra OR canakinumab OR rilonacept):ti,ab,kw	15168
#7	(cyclosporine OR CsA OR tacrolimus OR sirolimus OR methotrexate OR cyclophosphamide OR azathioprine OR mycophenolic acid OR mycophenolate mofetil OR MMF OR MPA OR miltefosine OR interferon alpha OR protease inhibitor* OR cromolyn OR camostat mesylate OR nafamostat mesylate OR montelukast OR zafirlukast):ti,ab,kw	51373
#8	(cimetidine OR ranitidine OR famotidine OR vitamin D OR vitamin D3 OR cholecalciferol OR hydroxychloroquine OR chloroquine OR HCQ OR dapsone OR sulfasalazine OR colchicine OR steroid* OR immunoglobulin OR IVIG OR histaglobulin OR heparin OR warfarin OR coumadin OR ketotifen OR danazol OR stanozol OR stanozolol OR “tranexamic acid” OR dipyridamole OR levamisole OR doxepin OR mirtazapine OR theophylline OR gold OR nifedipine OR mizoribine):ti,ab,kw	107716
#9	#4 OR #5 OR #6 OR #7 OR #8	300602
#10	#3 AND #9	619
#11	limit in trials	594

Table E1 Systematic review search strategy: Web of Science, from inception to 19 April, 2021 (continued)

Search	Query	Items found
#1	TS=(urticarial OR “chronic urticarial” OR hives OR “angioneurotic \$edema” OR “chronic spontaneous urticarial” OR “chronic idiopathic urticarial” OR “refractory urticarial” OR “antihistamin* resistant chronic urticarial” OR CSU OR CIU)	14451
#2	TS=(“anti-immunoglobulin” OR anti-IgE* OR “monoclonal antibody*” OR “spleen tyrosine kinase inhibitor*” OR “syk inhibitor*” OR “anti-sialic acid binding immunoglobulin-like lectin-8” OR “anti-Siglec-8” OR “Bruton tyrosine kinase inhibitor*” OR “anti-CRTH2” OR “CRTH2 antagonist” OR anti-IL-1 OR “IL-1 inhibitor*” OR anti IL-5 OR “BTK inhibitor*” OR “anti-tumor necrosis factor alpha” OR anti-TNF* OR immunosupp* OR “calcineurin inhibitor”)	362714
#3	TS=(immunomodulatory OR immunotherapy OR “anti-inflammatory agent*” OR “leukotriene receptor antagonist*” OR anti-leukotriene* OR LTRA* OR anti-fibrinolytic OR anticoagula* OR antihistamin* OR “histamine* antagonist*” OR up-dosing OR “high dosage” OR “increase dose” OR methylxanthin* OR “serotonin inhibitor*” OR SSRI* OR SNRI* OR androgen* OR “allergen immunotherapy” OR “pseudoallergen-free diet” OR diet OR “low histamine diet” OR probiotic* OR “herbal therap*” OR vitamin OR nonbiologi* OR nonpharmaco* OR autologous blood OR autologous serum OR phototherapy OR UV OR “ultraviolet light” OR UVA OR UVB OR PUVA OR “narrow band UV” OR NBUVB OR plasmapheresis OR “plasma exchange” OR acupuncture OR “alternative treatment*” OR “holistic medicine”)	2046063
#4	TS=(omalizumab OR ligelizumab OR QGE031 OR quilizumab OR UB-221 OR dupilumab OR AZD1981 OR mepolizumab OR reslizumab OR ibrutinib OR fenebrutinib OR GDC-0853 OR LOU064 OR GSK2646264 OR AK002 OR adalimumab OR abatacept OR etanercept OR infliximab OR benralizumab OR rituximab OR anakinra OR canakinumab OR rilonacept)	114884
#5	TS=(cyclosporine OR CsA OR tacrolimus OR sirolimus OR methotrexate OR cyclophosphamide OR azathioprine OR mycophenolic acid OR mycophenolate mofetil OR MMF OR MPA OR miltefosine OR interferon alpha OR protease inhibitor* OR cromolyn OR camostat mesylate OR nafamostat mesylate OR montelukast OR zafirlukast)	582718
#6	TS=(cimetidine OR ranitidine OR famotidine OR vitamin D OR vitamin D3 OR cholecalciferol OR hydroxychloroquine OR chloroquine OR HCQ OR dapsone OR sulfasalazine OR colchicine OR steroid* OR immunoglobulin OR IVIG OR histaglobulin OR heparin OR warfarin OR coumadin OR ketotifen OR danazol OR stanozol OR stanozolol OR “tranexamic acid” OR dipyridamole OR levamisole OR doxepin OR mirtazapine OR theophylline OR gold OR nifedipine OR mizoribine)	1416098
#7	#2 OR #3 OR #4 OR #5 OR #6	3744523
#8	#1 AND #7	4728
#9	Refined by: [excluding] DOCUMENT TYPES: (CASE REPORT OR BOOK OR LETTER OR EDITORIAL MATERIAL OR NEWS OR REVIEW)	3332

Table E1 Systematic review search strategy: Scopus, from inception to 19 April, 2021 (continued)

Search	Query	Items found
#1	TITLE-ABS-KEY (urticarial OR "chronic urticarial" OR hives OR "angioneurotic \$edema" OR "chronic spontaneous urticarial" OR "chronic idiopathic urticarial" OR "refractory urticarial" OR "antihistamin* resistant chronic urticarial" OR csu OR ciu)	29533
#2	TITLE-ABS-KEY ("anti-immunoglobulin" OR anti-ige* OR "monoclonal antibody*" OR "spleen tyrosine kinase inhibitor*" OR "syk inhibitor*" OR "anti-sialic acid binding immunoglobulin-like lectin-8" OR "anti-Siglec-8" OR "Bruton tyrosine kinase inhibitor*" OR "anti-CRTH2" OR "CRTH2 antagonist" OR anti-il-1 OR "IL-1 inhibitor*" OR anti AND il-5 OR "BTK inhibitor*" OR "anti-tumor necrosis factor alpha" OR anti-tnf* OR immunosupp* OR "calcineurin inhibitor*")	72306
#3	TITLE-ABS-KEY (immunomodulatory OR immunotherapy OR "anti-inflammatory agent*" OR "leukotriene receptor antagonist*" OR anti-leukotriene* OR ltra* OR anti-fibrinolytic OR anticoagula* OR antihistamin* OR "histamine* antagonist*" OR up-dosing OR "high dosage" OR "increase dose" OR methylxanthin* OR "serotonin inhibitor*" OR ssri* OR snri* OR androgen* OR "allergen immunotherapy" OR "pseudoallergen-free diet" OR diet OR "low histamine diet" OR probiotic* OR "herbal therap*" OR vitamin OR nonbiologi* OR nonpharmaco* OR autologous AND blood OR autologous AND serum OR phototherapy OR uv OR "ultraviolet light" OR uva OR uvb OR puva OR "narrow band UV" OR nbuvb OR plasmapheresis OR "plasma exchange" OR acupuncture OR "alternative treatment*" OR "holistic medicine")	143838
#4	TITLE-ABS-KEY (omalizumab OR ligelizumab OR qge031 OR quilizumab OR ub-221 OR dupilumab OR azd1981 OR mepolizumab OR reslizumab OR ibrutinib OR fenebrutinib OR gdc-0853 OR lou064 OR gsk2646264 OR ak002 OR adalimumab OR abatacept OR etanercept OR infliximab OR benralizumab OR rituximab OR anakinra OR canakinumab OR rilonacept)	129890
#5	TITLE-ABS-KEY (cyclosporine OR csa OR tacrolimus OR sirolimus OR methotrexate OR cyclophosphamide OR azathioprine OR "mycophenolic acid" OR "mycophenolate mofetil" OR mmf OR mpa OR miltefosine OR "interferon alpha" OR "protease inhibitor*" OR cromolyn OR "camostat mesylate" OR "nafamostat mesylate" OR montelukast OR zafirlukast)	860087
#6	TITLE-ABS-KEY (cimetidine OR ranitidine OR famotidine OR "vitamin D" OR "vitamin D3" OR cholecalciferol OR hydroxychloroquine OR chloroquine OR hcq OR dapsone OR sulfasalazine OR colchicine OR steroid* OR immunoglobulin OR ivig OR histaglobulin OR heparin OR warfarin OR coumadin OR ketotifen OR danazol OR stanozol OR stanozolol OR "tranexamic acid" OR dipyrindamole OR levamisole OR doxepin OR mirtazapine OR theophylline OR gold OR nifedipine OR mizoribine)	2277803
#7	#2 OR #3 OR #4 OR #5 OR #6	3159228
#8	#1 AND #7	9400
#9	Filters: (EXCLUDE (DOCTYPE , "re") OR EXCLUDE (DOCTYPE , "le") OR EXCLUDE (DOCTYPE , "no") OR EXCLUDE (DOCTYPE , "sh") OR EXCLUDE (DOCTYPE , "ed") OR EXCLUDE (DOCTYPE , "ch") OR EXCLUDE (DOCTYPE , "cr") OR EXCLUDE (DOCTYPE , "tb")) AND (EXCLUDE (SRCTYPE , "k") OR EXCLUDE (SRCTYPE , "b") OR EXCLUDE (SRCTYPE , "d"))	6042

Table E1 Systematic review search strategy: CINAHL, from inception to 19 April, 2021 (continued)

Search	Query	Items found
#1	AB (urticarial OR "chronic urticarial" OR hives OR "angioneurotic \$edema" OR "chronic spontaneous urticarial" OR "chronic idiopathic urticarial" OR "refractory urticarial" OR "antihistamin* resistant chronic urticarial" OR csu OR ciu)	773
#2	AB ("anti-immunoglobulin" OR anti-ige* OR "monoclonal antibody*" OR "spleen tyrosine kinase inhibitor*" OR "syk inhibitor*" OR "anti-sialic acid binding immunoglobulin-like lectin-8" OR "anti-Siglec-8" OR "Bruton tyrosine kinase inhibitor*" OR "anti-CRTH2" OR "CRTH2 antagonist" OR anti-il-1 OR "IL-1 inhibitor*" OR anti AND il-5 OR "BTK inhibitor*" OR "anti-tumor necrosis factor alpha" OR anti-tnf* OR immunosupp* OR "calcineurin inhibitor*")	20762
#3	AB (immunomodulatory OR immunotherapy OR "anti-inflammatory agent*" OR "leukotriene receptor antagonist*" OR anti-leukotriene* OR ltra* OR anti-fibrinolytic OR anticoagula* OR antihistamin* OR "histamine* antagonist*" OR up-dosing OR "high dosage" OR "increase dose" OR methylxanthin* OR "serotonin inhibitor*" OR ssri* OR snri* OR androgen* OR "allergen immunotherapy" OR "pseudoallergen-free diet" OR diet OR "low histamine diet" OR probiotic* OR "herbal therap*" OR vitamin OR nonbiologi* OR nonpharmaco* OR autologous AND blood OR autologous AND serum OR phototherapy OR uv OR "ultraviolet light" OR uva OR uvb OR puva OR "narrow band UV" OR nbuvb OR plasmapheresis OR "plasma exchange" OR acupuncture OR "alternative treatment*" OR "holistic medicine")	166285
#4	AB (omalizumab OR ligelizumab OR qge031 OR quilizumab OR ub-221 OR dupilumab OR azd1981 OR mepolizumab OR reslizumab OR ibrutinib OR fenebrutinib OR gdc-0853 OR lou064 OR gsk2646264 OR ak002 OR adalimumab OR abatacept OR etanercept OR infliximab OR benralizumab OR rituximab OR anakinra OR canakinumab OR rilonacept)	9508
#5	AB (cyclosporine OR csa OR tacrolimus OR sirolimus OR methotrexate OR cyclophosphamide OR azathioprine OR "mycophenolic acid" OR "mycophenolate mofetil" OR mmf OR mpa OR miltefosine OR "interferon alpha" OR "protease inhibitor*" OR cromolyn OR "camostat mesylate" OR "nafamostat mesylate" OR montelukast OR zafirlukast)	24091
#6	AB (cimetidine OR ranitidine OR famotidine OR "vitamin D" OR "vitamin D3" OR cholecalciferol OR hydroxychloroquine OR chloroquine OR hcq OR dapsone OR sulfasalazine OR colchicine OR steroid* OR immunoglobulin OR ivig OR histaglobulin OR heparin OR warfarin OR coumadin OR ketotifen OR danazol OR stanozol OR stanozolol OR "tranexamic acid" OR dipyridamole OR levamisole OR doxepin OR mirtazapine OR theophylline OR gold OR nifedipine OR mizoribine)	88071
#7	S2 OR S3 OR S4 OR S5 OR S6	266069
#8	S1 AND S7	224
#9	Expanders - Apply equivalent subjects Source Types - Academic Journals	210

Table E2 The PICOTS: study inclusion/exclusion criteria

Category	Criteria for inclusion	Criteria for exclusion
Populations	Adolescents or adults (12 years or older) diagnosed with refractory to H1-antihistamines (standard dose or up-dosing) CSU	- Studies that recruiting participants aged less than 12 years or unclear definition of CSU - In vitro or animal studies
Interventions	Pharmacological treatment with any route of administered treatments for refractory to H1-antihistamine CSU	- Studies that using non-pharmacological treatments - Studies with the disconnected node of treatments
Comparators	Placebo, active comparator, or standard of care	Studies without control groups (single arm studies)
Outcomes	- Primary outcomes - Patient-reported QOL: general dermatology-specific and chronic urticaria-specific measures - Secondary outcomes - Angioedema-related QOL - Impact on sleep - Symptom burden: fatigue, dyspnea, pain, difficulty in eating or swallowing - Work impairment: absenteeism, presenteeism, work productivity and/or school performance - Psychosocial aspects: depressive symptoms, anxiety, distress, and well-being) - Healthcare utilization: emergency/unplanned visit during follow-up and costs of care	- Studies not providing data for calculate the efficacy or safety of primary outcomes - Studies with a follow-up period of less than two weeks
Timing	An extensive search strategy from the inception of bibliographic databases forward to assure all published literature was identified	- No limit timing of start date - Studies were not limited by language
Setting	Experimental study: RCTs (parallel or crossover trials)	Quasi-randomized studies, cluster-randomized trials, cohort, case-control, cross-sectional, N-of-one, case series/case report, reviews, and systematic review and meta-analysis

Abbreviations: CSU, chronic spontaneous urticarial; QOL, quality of life; RCTs, randomized controlled trials

Table E3 Study population of included studies

Author, year	Study participant	Definition of Refractory to H1-antihistamines CSU	Concomitant medication
Kaplan et al ^{E1} , 2013	Patients aged 12-75 years (18-75 years in Germany); CIU/CSU for 6 months or longer	• CIU/CSU patients with itch and hives for more than 6 consecutive weeks before enrollment, despite H1-antihistamines (up to 4 times the approved dosage) plus H2-antihistamines, LTRAs, or both • UAS7 ≥ 16, weekly itch severity score ≥ 8 during 7 days before randomization; in-clinic physician-assessed UAS ≥ 4 on the one of the screening visit days	• Long-acting H1-antihistamine allowed during the study and could be used at up to four times of approved doses • The H2-antihistamines and LTRAs also allowed during the study period • Diphenhydramine as rescue medication for symptom relief (up to maximum of 3 doses per 24-hour period or fewer depending on local regulations)
Margerl et al ^{E2} , 2013	Adults aged ≥ 18 years suffering from moderate or severe CSU with UAS7 ≥ 15	• Resistant to standard treatment with antihistamines (maximum labelled dose of a non-sedating antihistamine [levocetirizine, cetirizine, fexofenadine, desloratadine, loratadine, ebastine, mizolastine])	• Ongoing therapy with a standard-dosed non-sedating antihistamine
Maurer et al ^{E3} , 2013	Adult and adolescent aged 12-75 years with CIU: UAS7 ≥ 16 and itch component of UAS7 ≥ 8 during the 7 days before randomization	• Remained symptomatic despite the use of approved doses of H1-antihistamines	• Stable doses of pre-randomization H1-antihistamine throughout the treatment period • Diphenhydramine (25 mg) was allowed as rescue medication for itch relief (up to a maximum of three doses in 24 hours)
Morgan et al ^{E4} , 2014	Adults aged 18-80 years with a diagnosis with CIU	• Had itching and hives present at least 4 days in a week despite therapy in excess of standard H1-antihistamines dosage (usually 2 to 4 times the standard dose, or simultaneous use of multiple H1-antihistamines)	• Treatment with other second-line agents, including daily corticosteroids and LTRAs was permitted
Saini et al ^{E5} , 2015	Patients aged 12-75 years (18-75 years in Germany) with a diagnosis of CIU/CSU for ≥ 6 months: UAS7 ≥ 16 and itch component of UAS7 ≥ 8 during the 7 days before randomization	• Remained symptomatic despite the use of approved doses of H1-antihistamines	• For the first 12 weeks of the treatment period, participants were required to maintain stable doses of their pre-randomization H1-antihistamine treatment; • During week 13-24 of the treatment period, patients were allowed to add one additional H1-antihistamine; • Diphenhydramine (25 mg) was allowed as rescue medication for itch relief (up to a maximum of three doses in 24 hours)
Staubach et al ^{E6} , 2016	Adult aged 18-75 years, with wheals and at least four occurrences of angioedema in the last 6 months	• Defined as those who were symptomatic despite high-dose second generation H1-antihistamines (2 to 4 times the approved dose); and an UAS7 of ≥ 14 and a CU-Q2oL score ≥ 30 at baseline	• Treatment with daily intake of high doses (2 to 4 times the approved dose) of second generation H1-antihistamines was allowed • Additional rescue medication was permitted (three tablets of clomastine per day [maximum 3 days/week] and 15 mg betamethasone in case of life-threatening angioedema development)
Boonpiyathad et al ^{E7} , 2017	Adult patients with a diagnosis of CSU	• Failure to respond to 4 tablets of H1-antihistamines for 4 weeks	• Treatment with 4 tablets of H1-antihistamines throughout 12 weeks (NS)

Abbreviations: CIU, chronic idiopathic urticaria; CSU, chronic spontaneous urticaria; LTRAs, leukotriene receptor antagonists; NS, not specified; UAS, urticaria activity score.

Table E3 Study population of included studies (continued)

Author, year	Study participant	Definition of Refractory to H1-antihistamines CSU	Concomitant medication
Hide et al ^{E8} , 2017	CSU patients aged 12-75 years with UAS7 ≥ 16 and itch component of UAS7 ≥ 8 during the 7 days prior to randomization	Symptomatic despite approved-dose non-sedating H1-antihistamine treatment	- Stables doses of pre-randomization H1-antihistamine treatment - Diphenhydramine 10 mg or 25 mg (up to 75 mg/day or 80 mg/day in Korea and Japan, respectively) as rescue medication was allowed
Sánchez et al ^{E9} , 2018	Patients aged ≥ 12 years, with a diagnosis of CSU for ≥ 6 weeks	Patients without clinical response with high dose H1-antihistamines (at up to four times of the conventional dose)	Treatment with daily intake of high doses (2 to 4 times the approved dose) of second generation H1-antihistamines was allowed
Maurer et al ^{E10} , 2019	Adults aged 18-75 years, with a diagnosis of refractory CSU	Inadequately controlled with H1-antihistamines at approved or increased doses alone or in combination with H2-antihistamines or LTRAs (57.1% escalated dose of approved H1-antihistamines); UAS7 ≥ 16 during the 7 days prior to randomization) and an in-clinic UAS ≥ 4 on at least one of the screening visit days	Non-sedating H1-antihistamines (at locally approved doses or at increased doses up to four times the locally approved dose) alone or in combination with H2-antihistamines or LTRAs as background medication were used during the screening, treatment, and follow-up periods
Leducq et al ^{E11} , 2020	Adults aged ≥ 18 years with at least 12 weeks of documented history of CSU diagnosed at enrollment.	Previous received ≥ 3 different molecules of H1-antihistamines or a combination of 2 different molecules of H1-antihistamines or 1 molecules of H1-antihistamines with at least a double dose, for a total treatment duration of at least 12 weeks before inclusion; Persistent urticarial lesions in the month before enrollment (at least 7 days)	H1-antihistamines, no modification of H1-antihistamines regimen was allowed during all the trial
Maul et al ^{E12} , 2020	Adults aged 18-70 years with moderate to severe CSU	Symptomatic despite use of non-sedating antihistamine with or without concomitant LTRAs/corticosteroids (NS)	NR

Abbreviations: CIU, chronic idiopathic urticaria; CSU, chronic spontaneous urticaria; LTRAs, leukotriene receptor antagonists; NR, not reported; NS, not specified; UAS, urticaria activity score.

Table E4 Characteristics of included studies

Author, year	Mean age (SD)		Female, N (%)			Mean duration of CSU (SD), year			
	Overall	Treatment	Control	Overall	Treatment	Control	Overall	Treatment	Control
Kaplan et al ^{E1} , 2013	43.1 (14.1)	42.7 (13.9)	44.3 (14.7)	241 (71.9)	186 (73.8)	55 (66.3)	7.4 (9.5); Median 3.6 (range, 0.5-54.1)	7.0 (8.8); Median 3.4 (range, 0.5-50.3)	8.8 (11.2); Median 4.1 (range, 0.6-54.1)
Margerl et al ^{E2} , 2013	43.8 (12.4)	45.0 (12.4)	42.6 (12.5)	42 (55.3)	28 (56.0)	14 (53.8)	NR	NR	NR
Maurer et al ^{E3} , 2013	42.5 (13.7)	OMA 75 mg: 39.7 (15.0); OMA 150 mg: 43.0 (13.2); OMA 300 mg: 44.3 (13.7)	43.1 (12.5)	244 (75.8)	OMA 75 mg: 61 (74.4); OMA 150 mg: 65 (79.3); OMA 300 mg: 63 (79.7)	55 (69.6)	6.5 (8.6)	OMA 75 mg: 5.3 (7.1); OMA 150 mg: 7.2 (8.9); OMA 300 mg: 6.1 (7.3)	7.2 (10.7)
Morgan et al ^{E4} , 2014 ^a	43.5 (12.4)	41.9 (11.0)	44.8 (13.9)	5 (22.7)	2 (20.0)	3 (25.0)	Median 1.0 (range, 0.3-10)	Median 1.0 (range, 0.5-5)	Median 1.3 (range, 0.3-10)
Saini et al ^{E5} , 2015	41.2 (14.5)	OMA 75 mg: 40.7 (15.2); OMA 150 mg: 41.1 (14.0); OMA 300 mg: 42.4 (13.2)	40.4 (15.6)	231 (72.6)	OMA 75 mg: 55 (71.4); OMA 150 mg: 64 (80.0); OMA 300 mg: 60 (74.1)	52 (65.0)	6.9 (9.1)	OMA 75 mg: 7.0 (9.7); OMA 150 mg: 7.6 (9.2); OMA 300 mg: 6.2 (8.0)	7.0 (9.7)
Staubach et al ^{E6} , 2016	42.9 (12.3)	44.9 (range, 20-73)	41.1 (range, 20-61)	63 (69.2)	30 (68.2)	33 (70.2)	7.9 (9.0)	8.4 (9.3); Median 5.0 (range, 0-40)	7.4 (8.8); Median 5.0 (range, 0-41)
Boonpiyathad et al ^{E7} , 2017	33.5 (12.0)	33.0 (12.1)	34.0 (11.9)	41 (85.4)	21 (87.5)	20 (83.3)	0.5 (0.4)	0.4 (0.4)	0.5 (0.5)
Hide et al ^{E8} , 2017	43.6 (13.9)	OMA 150 mg: 43.6 (12.2); OMA 300 mg: 44.6 (14.9)	42.5 (14.3)	131 (60.1)	OMA 150 mg: 43 (60.6); OMA 300 mg: 40 (54.8)	48 (64.9)	4.5 (5.6)	OMA 150 mg: 5.1 (6.2); OMA 300 mg: 3.6 (4.0)	4.7 (6.2)
Sánchez et al ^{E9} , 2018	NR	NR	NR	NR	NR	NR	NR	NR	NR
Maurer et al ^{E10} , 2019	43.4 (11.7)	LIG 72 mg: 44.3 (12.4); LIG 240 mg: 42.9 (10.5); OMA 300 mg: 41.8 (13.1)	45.4 (11.2)	255 (75.8)	LIG 72 mg: 61 (72.6); LIG 240 mg: 67 (78.8); OMA 300 mg: 66 (77.6)	31 (72.1)	4.0 (5.3)	LIG 72 mg: 3.9 (5.4); LIG 240 mg: 4.1 (5.6); OMA 300 mg: 5.1 (7.5)	3.6 (3.5)
Leducq et al ^{E11} , 2020	45.7 (12.9)	46.4 (12.6)	45.0 (13.2)	57 (76.0)	28 (71.8)	29 (80.6)	3.8 (3.7)	3.8 (2.6); Median 4.9 (IQR, 1.5-4.9)	3.7 (4.6); Median 3.2 (IQR, 1.0-7.0)
Maul et al ^{E12} , 2020	40.4 (14.3)	42.2 (17.9)	38.7 (9.6)	12 (60.0)	6 (60.0)	6 (60.0)	6.1 (4.9)	2.7 (2.6)	9.4 (6.4)

^aOn the basis of crossover trial.

Abbreviations: IQR, interquartile range; LIG, ligelizumab; NR, not reported, NS, not specified; OMA, omalizumab; SD, standard deviation.

Table E4 Characteristics of included studies (continued)

Author, year	Race, white, N (%)		Mean weight (SD), Kg			Angioedema, N (%)			
	Overall	Treatment	Control	Overall	Treatment	Control	Overall	Treatment	Control
Kaplan et al ^{E1} , 2013	298 (89.0)	223 (88.5)	75 (90.4)	85.0 (22.5)	82.8 (21.5)	87.2 (25.2)	178 (53.1)	137 (54.4)	41 (49.4)
Margerl et al ^{E2} , 2013	NR	NR	NR	83.6 (20.1)	84.2 (21.7)	83.1 (16.5)	NR	NR	NR
Maurer et al ^{E3} , 2013	272 (84.5)	OMA 75 mg: 64 (78.0); OMA 150 mg: 70 (85.4); OMA 300 mg: 68 (86.1)	70 (88.6)	82.4 (21.9)	OMA 75 mg: 82.8 (21.2); OMA 150 mg: 82.4 (20.7); OMA 300 mg: 80.3 (19.9)	84.3 (25.7)	131 (40.1)	OMA 75 mg: 31 (37.8); OMA 150 mg: 38 (46.3); OMA 300 mg: 32 (40.5)	30 (38.0)
Morgan et al ^{E4} , 2014 ^a	19 (86.4)	9 (90.0)	10 (83.3)	NR	NR	NR	NR	NR	NR
Saini et al ^{E5} , 2015	263 (82.7)	OMA 75 mg: 62 (80.5); OMA 150 mg: 63 (78.8); OMA 300 mg: 74 (91.4)	64 (80.0)	82.2 (21.1)	OMA 75 mg: 81.1 (19.2); OMA 150 mg: 83.2 (24.4); OMA 300 mg: 81.6 (19.7)	83.0 (20.5)	151 (47.5)	OMA 75 mg: 35 (45.5); OMA 150 mg: 38 (47.5); OMA 300 mg: 34 (42.0)	44 (55.0)
Staubach et al ^{E6} , 2016	88 (96.7)	42 (95.5)	46 (97.9)	NR	NR	NR	54 (59.3)	24 (54.5)	30 (63.8)
Boonpiyathad et al ^{E7} , 2017	NR	NR	NR	NR	NR	NR	NR	NR	NR
Hide et al ^{E8} , 2017	NR	NR	NR	64.4 (13.6)	OMA 150 mg: 65.0 (14.1); OMA 300 mg: 65.3 (13.3)	63.0 (13.4)	39 (17.9)	OMA 150 mg: 12 (16.9); OMA 300 mg: 12 (16.4)	15 (20.3)
Sánchez et al ^{E9} , 2018	NR	NR	NR	NR	NR	NR	NR	NR	NR
Maurer et al ^{E10} , 2019	220 (74.1)	LIG 72 mg: 57 (67.8); LIG 240 mg: 65 (76.5); OMA 300 mg: 67 (78.8)	31 (72.1)	NR	NR	NR	147 (49.5)	LIG 72 mg: 39 (46.4); LIG 240 mg: 39 (45.9); OMA 300 mg: 44 (51.8)	25 (58.1)
Leducq et al ^{E11} , 2020	NR	NR	NR	76.2 (16.1)	76.9 (15.0)	75.5 (17.3)	47 (63.5) ^b	27 (69.2)	20 (57.1) ^b
Maul et al ^{E12} , 2020	NR	NR	NR	NR	NR	NR	NR	NR	NR

Abbreviations: LIG, ligelizumab; IQR, interquartile range; NR, not reported, OMA, omalizumab; SD, standard deviation.

^aOn the basis of crossover trial.

^bData missing for one patient.

Table E4 Characteristics of included studies (continued)

Author, year	Mean IgE (SD), IU/mL			Positive ASST, N (%)			Mean baseline UAS7 (SD)		
	Overall	Treatment	Control	Overall	Treatment	Control	Overall	Treatment	Control
Kaplan et al ^{E1} , 2013	158.5 (287.7); Median 78.0 (range, 1-3,050)	162.3 (306.4); Median 79.0 (1-3,050)	147.2 (224.4); Median 71.0 (range, 1-1,230)	NR	NR	NR	30.9 (6.6)	31.2 (6.6)	30.2 (6.7)
Margerl et al ^{E2} , 2013	NR	NR	NR	NR	NR	NR	25.5 (7.3)	25.7 (7.4)	25.1 (6.9)
Maurer et al ^{E3} , 2013	168.2 (231.9)	NR	NR	NR	NR	NR	30.6 (6.9)	OMA 75 mg: 30.7 (6.9); OMA 150 mg: 31.4 (7.0); OMA 300 mg: 29.5 (6.9)	31.0 (6.6)
Morgan et al ^{E4} , 2014 ^a	NR	NR	NR	NR	NR	NR	WHS-WIS: 13.0 (3.2); weight-UAS7: 26.0 (6.4)	WHS-WIS: 12.9 (3.5); weighted-UAS7: 25.8 (7.1)	WHS-WIS: 13.1 (3.0); weighted-UAS7: 26.2 (6.0)
Saini et al ^{E5} , 2015	182.8 (387.8)	OMA 75 mg: 553.3 (421.9); OMA 150 mg: 1,285.8 (1,033.4); OMA 300 mg: 625.5 (480.6)	298.8 (208.6)	NR	NR	NR	31.1 (6.6)	OMA 75 mg: 31.7 (6.7); OMA 150 mg: 30.3 (7.3); OMA 300 mg: 31.3 (5.8)	31.1 (6.7)
Staubach et al ^{E6} , 2016	NR	NR	NR	NR	NR	NR	27.2 (8.4)	26.5 (8.2)	27.9 (8.7)
Boonpiyathad et al ^{E7} , 2017	NR	NR	NR	39 (81.2)	19 (79.2)	20 (83.3)	USS: 44.6 (11.7); weighted-UAS7: 20.1 (5.3)	USS: 45.5 (11.2); weighted-UAS7: 20.6 (5.1)	USS: 43.4 (12.3); weighted-UAS7: 19.6 (5.5)
Hide et al ^{E8} , 2017	NR	NR	NR	NR	NR	NR	30.5 (6.9)	OMA 150 mg: 29.6 (7.4); OMA 300 mg: 31.8 (7.1)	30.1 (6.5)
Sánchez et al ^{E9} , 2018	NR	NR	NR	NR	NR	NR	NR	NR	NR
Maurer et al ^{E10} , 2019	320.6 (289.4)	LIG 72 mg: 286.0 (193.3); LIG 240 mg: 907.1 (712.9); OMA 300 mg: 3,568.1 (2,888.6)	273.8 (198.6)	NR	NR	NR	30.6 (7.4)	LIG 72 mg: 31.7 (7.3); LIG 240 mg: 30.3 (7.3); OMA 300 mg: 29.3 (7.9)	31.1 (6.8)
Leducq et al ^{E11} , 2020	NR	NR	NR	NR	NR	NR	NR	NR	NR
Maul et al ^{E12} , 2020	NR	NR	NR	NR	NR	NR	23.2 (6.5)	26.3 (9.4)	22.2 (5.3)

Abbreviations: ASST, autologous serum skin test; IgE, Immunoglobulin E; LIG, ligelizumab; IQR, interquartile range; NR, not reported, OMA, omalizumab; SD, standard deviation; UAS7, urticaria activity score over 7 days; USS, urticaria severity score; WHS-WIS, weekly hives severity-weekly itch severity score.

^aOn the basis of crossover trial.

Table E5 Outcome measurement of included studies

Author, year	Outcome: Measurement tool
Kaplan et al ^{E1} , 2013	• HRQOL: DLQI, CU-Q2oL • Patient unacceptability: all-cause study withdrawals • Impact on sleep: UPDD-weekly sleep inference score
Margerl et al ^{E2} , 2013	• HRQOL: DLQI, CU-Q2oL • Patient unacceptability: all-cause study withdrawals
Maurer et al ^{E3} , 2013	• HRQOL: DLQI • Patient unacceptability: all-cause study withdrawals • Impact on sleep: UPDD-weekly sleep inference score
Morgan et al ^{E4} , 2014	• HRQOL: MOSS-SF12 • Patient unacceptability: all-cause study withdrawals
Saini et al ^{E5} , 2015	• HRQOL: DLQI, CU-Q2oL • Patient unacceptability: all-cause study withdrawals • Impact on sleep: UPDD-weekly sleep inference score
Staubach et al ^{E6} , 2016	• HRQOL: CU-Q2oL • Patient unacceptability: all-cause study withdrawals • Patient-reported angioedema-specific measure: AE-QoL • Patient well-being: WHO-5 well-being index
Boonpiyathad et al ^{E7} , 2017	• HRQOL: DLQI • Patient unacceptability: all-cause study withdrawals
Hide et al ^{E8} , 2017	• HRQOL: DLQI • Patient unacceptability: all-cause study withdrawals
Sánchez et al ^{E9} , 2018	• HRQOL: DLQI • Patient unacceptability: all-cause study withdrawals
Maurer et al ^{E10} , 2019	• HRQOL: DLQI • Patient unacceptability: all-cause study withdrawals • Impact on sleep: UPDD-weekly sleep inference score
Leducq et al ^{E11} , 2020	• HRQOL: DLQI • Patient unacceptability: all-cause study withdrawals • Impact on sleep: VAS (0-100)
Maul et al ^{E12} , 2020	• HRQOL: DLQI • Patient unacceptability: all-cause study withdrawals

Abbreviations: AE-QoL, Angioedema Quality of Life questionnaire; CU-Q2oL, Chronic Urticaria Quality of Life Questionnaire; DLQI; Dermatology Life Quality Index; HRQOL, health-related quality of life; MOSS-SF12, Medical Outcomes Study Survey-Short Form 12 Item; VAS, visual analog scale; WHO, World Health Organization.

Table E6 Summary results of risk-of-bias assessment

Author, year	Bias domain: Version 2 of the Cochrane risk-of-bias assessment tool for randomized trials					Overall RoB	
	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result		
Kaplan et al ^{E1} , 2013	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	(+)
Margerl et al ^{E2} , 2013	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	(+)
Maurer et al ^{E3} , 2013	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	(+)
Morgan et al ^{E4} , 2014	Some concerns	Low risk	Low risk	Low risk	Low risk	Some concerns	(!)
Saini et al ^{E5} , 2015	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	(+)
Staubach et al ^{E6} , 2016	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	(+)
Boonpiyathad et al ^{E7} , 2017	Some concerns	Some concerns	Low risk	Some concerns	Some concerns	Some concerns	(!)
Hide et al ^{E8} , 2017	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	(+)
Sánchez et al ^{E9} , 2018	Some concerns	Some concerns	Low risk	Some concerns	Some concerns	Some concerns	(!)
Maurer et al ^{E10} , 2019	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	(+)
Leducq et al ^{E11} , 2020	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	(+)
Maul et al ^{E12} , 2020	Some concerns	Low risk	Low risk	Low risk	Low risk	Some concerns	(!)

Table E7 Network estimates results: change in health-related quality of life from baseline[†]

Placebo													
-0.27 (-1.16, 0.61)	Canakinumab												
-0.53 (-1.21, 0.15)	-0.26 (-1.38, 0.86)	Cyclosporine											
0.34 (-0.51, 1.20)	0.62 (-0.61, 1.85)	0.87 (-0.22, 1.97)	Dapsone										
-1.00 (-1.61, -0.39)[†]	-0.73 (-1.80, 0.35)	-0.47 (-1.39, 0.44)	-1.35 (-2.39, -0.30)[†]	Hydroxy- chloroquine									
-0.66 (-0.96, -0.35)[†]	-0.39 (-1.32, 0.55)	-0.13 (-0.86, 0.61)	-1.00 (-1.91, -0.10)[†]	0.34 (-0.34, 1.03)	Ligelizumab (72 mg)								
-0.67 (-0.98, -0.37)[†]	-0.40 (-1.34, 0.53)	-0.15 (-0.88, 0.59)	-1.02 (-1.92, -0.11)[†]	0.33 (-0.36, 1.01)	-0.02 (-0.33, 0.30)	Ligelizumab (240 mg)							
-0.02 (-0.50, 0.47)	0.26 (-0.75, 1.26)	0.51 (-0.32, 1.35)	-0.36 (-1.34, 0.62)	0.98 (0.21, 1.76)[†]	0.64 (0.07, 1.21)[†]	0.66 (0.09, 1.23)[†]	Miltefosine						
-0.15 (-0.62, 0.31)	0.12 (-0.88, 1.12)	0.38 (-0.45, 1.20)	-0.50 (-1.47, 0.47)	0.85 (0.08, 1.61)[†]	0.50 (-0.05, 1.06)	0.52 (-0.04, 1.08)	-0.14 (-0.81, 0.54)	Methotrexate					
-0.16 (-0.43, 0.12)	0.11 (-0.81, 1.04)	0.37 (-0.35, 1.10)	-0.50 (-1.40, 0.39)	0.84 (0.17, 1.51)[†]	0.50 (0.10, 0.90)[†]	0.52 (0.12, 0.92)[†]	-0.14 (-0.70, 0.42)	-0.00 (-0.55, 0.54)	Omalizumab (75 mg)				
-0.26 (-0.44, -0.08)[†]	0.01 (-0.89, 0.91)	0.27 (-0.42, 0.96)	-0.61 (-1.48, 0.26)	0.74 (0.10, 1.37)[†]	0.40 (0.06, 0.73)[†]	0.41 (0.08, 0.75)[†]	-0.24 (-0.76, 0.27)	-0.11 (-0.61, 0.39)	-0.10 (-0.39, 0.18)	Omalizumab (150 mg)			
-0.53 (-0.67, -0.39)[†]	-0.26 (-1.15, 0.64)	-0.00 (-0.67, 0.67)	-0.87 (-1.74, -0.01)[†]	0.47 (-0.15, 1.10)	0.13 (-0.17, 0.43)	0.15 (-0.15, 0.45)	-0.51 (-1.02, -0.01)[†]	-0.38 (-0.86, 0.11)	-0.37 (-0.65, -0.09)[†]	-0.27 (-0.45, -0.09)[†]	Omalizumab (300 mg)		

[†]Network meta-analysis results are expressed as SMDs (95% CIs). For the change in HRQOL from baseline, SMDs less than 0 indicate that the treatment specified in the row is more effective than that specified in the column. To obtain SMDs for comparisons in the opposite direction, negative values should be converted into positive values and vice versa.

[‡]Statistically significant.

Abbreviations: CIs, confidence intervals; SMDs, standardized mean differences.

Table E8 Pairwise meta-analysis results: change in health-related quality of life from baseline

Treatment Comparison	No. of studies	No. of participants	SMD (95% CI)	P Value	Heterogeneity			
					Q statistic	P value	I ² index (95% CI)	τ^2
Canakinumab								
vs placebo	1	20	-0.27 (-1.15 to 0.61)	0.545	NA	NA	NA	NA
Dapsone								
vs placebo	1	22	0.34 (-0.50 to 1.19)	0.425	NA	NA	NA	NA
Hydroxychloroquine								
vs placebo	1	48	-1.00 (-1.60 to -0.40)	0.001	NA	NA	NA	NA
Ligelizumab 72 mg								
vs placebo	1	127	-0.45 (-0.82 to -0.08)	0.018	NA	NA	NA	NA
vs omalizumab 300 mg	1	169	-0.21 (-0.52 to 0.09)	0.166	NA	NA	NA	NA
Ligelizumab 240 mg								
vs placebo	1	128	-0.47 (-0.84 to -0.10)	0.014	NA	NA	NA	NA
vs ligelizumab 72 mg	1	169	-0.04 (-0.34 to 0.26)	0.811	NA	NA	NA	NA
vs omalizumab 300 mg	1	170	-0.24 (-0.55 to 0.06)	0.113	NA	NA	NA	NA
Miltefosine								
vs placebo	1	76	-0.02 (-0.49 to 0.46)	0.945	NA	NA	NA	NA
Methotrexate								
vs placebo	1	74	-0.15 (-0.61 to 0.30)	0.511	NA	NA	NA	NA
Omalizumab 75 mg								
vs placebo	1	161	-0.19 (-0.50 to 0.12)	0.228	NA	NA	NA	NA
Omalizumab 150 mg								
vs placebo	3	466	-0.27 (-0.47 to -0.07)	0.008	2.39	0.302	16.3% (0.0-77.0%)	0.005
vs omalizumab 75 mg	1	164	-0.12 (-0.42 to 0.19)	0.449	NA	NA	NA	NA
Omalizumab 300 mg								
vs placebo	6	1,020	-0.54 (-0.71 to -0.36)	<0.001	8.61	0.125	41.9% (0.0-75.6%)	0.020
vs cyclosporine	1	35	0.00 (-0.66 to 0.66)	1.000	NA	NA	NA	NA
vs omalizumab 75 mg	1	161	-0.38 (-0.70 to -0.07)	0.015	NA	NA	NA	NA
vs omalizumab 150 mg	3	466	-0.29 (-0.47 to -0.10)	0.002	0.01	0.994	0.0% (0.0-72.9%)	<0.001

Abbreviations: CI, confidence interval; NA, not applicable; SMD, standardized mean difference.

Table E9 Network estimates of secondary outcomes: patient unacceptability[†]

Placebo												
1.00 (0.02, 61.41)	Canakinumab											
1.33 (0.04, 49.38)	1.33 (0.01, 318.55)	Cyclosporine										
2.56 (0.07, 94.90)	2.56 (0.01, 612.34)	1.92 (0.01, 319.28)	Dapsone									
1.33 (0.21, 8.29)	1.33 (0.01, 120.63)	1.00 (0.02, 57.64)	0.52 (0.01, 29.96)	Hydroxy-chloroquine								
0.47 (0.13, 1.71)	0.47 (0.01, 35.38)	0.36 (0.01, 15.63)	0.19 (0.00, 8.59)	0.36 (0.04, 3.31)	Ligelizumab (72 mg)							
0.86 (0.26, 2.82)	0.86 (0.01, 62.32)	0.65 (0.02, 27.43)	0.34 (0.01, 15.08)	0.64 (0.07, 5.69)	1.81 (0.48, 6.79)	Ligelizumab (240 mg)						
1.38 (0.29, 6.46)	1.38 (0.02, 111.86)	1.03 (0.02, 52.80)	0.54 (0.01, 27.44)	1.03 (0.09, 11.31)	2.90 (0.39, 21.62)	2.90 (0.39, 21.62)	Miltefosine					
0.57 (0.11, 2.88)	0.57 (0.01, 47.68)	0.43 (0.01, 22.57)	0.22 (0.00, 11.73)	0.43 (0.04, 4.92)	1.20 (0.15, 9.49)	0.67 (0.09, 4.97)	0.42 (0.04, 3.90)	Methotrexate				
0.64 (0.27, 1.50)	0.64 (0.01, 42.78)	0.48 (0.01, 18.90)	0.25 (0.01, 10.24)	0.48 (0.06, 3.60)	1.35 (0.31, 5.79)	0.74 (0.19, 2.96)	0.46 (0.08, 2.72)	1.12 (0.18, 6.95)	Omalizumab (75 mg)			
0.87 (0.41, 1.84)	0.87 (0.01, 57.33)	0.66 (0.02, 25.34)	0.34 (0.01, 13.69)	0.65 (0.09, 4.71)	1.84 (0.45, 7.53)	1.02 (0.27, 3.83)	0.64 (0.11, 3.54)	1.53 (0.26, 9.07)	1.37 (0.57, 3.31)	Omalizumab (150 mg)		
0.68 (0.39, 1.20)	0.68 (0.01, 43.65)	0.52 (0.01, 18.33)	0.27 (0.01, 10.38)	0.51 (0.08, 3.47)	1.44 (0.42, 4.97)	0.80 (0.26, 2.50)	0.50 (0.10, 2.58)	1.20 (0.22, 6.63)	1.07 (0.46, 2.51)	0.78 (0.37, 1.68)	Omalizumab (300 mg)	

[†]Network meta-analysis results are expressed as ORs (95% CIs). For patient unacceptability, ORs greater than 1 indicate that treatment specified in the row is more all-cause dropouts than that specified in the column. To obtain ORs for comparisons in the opposite direction, reciprocals should be taken to obtain ORs for comparisons in the opposite direction. Abbreviations: CIs, confidence intervals; ORs, odds ratios.

Table E9 Network estimates of secondary outcomes: impact on sleep (continued)[†]

Placebo												
NA	Canakinumab											
NA	NA	Cyclosporine										
NA	NA	NA	Dapsone									
NA	NA	NA	NA	Hydroxy-chloroquine								
-0.70 (-1.09, -0.32)[†]	NA	NA	NA	NA	Ligelizumab (72 mg)							
-0.60 (-0.98, -0.21)[†]	NA	NA	NA	NA	0.11 (-0.29, 0.50)	Ligelizumab (240 mg)						
NA	NA	NA	NA	NA	NA	NA	Miltefosine					
-0.35 (-0.91, 0.20)	NA	NA	NA	NA	0.35 (-0.33, 1.03)	0.24 (-0.43, 0.92)	NA	Methotrexate				
-0.18 (-0.46, 0.10)	NA	NA	NA	NA	0.52 (0.07, 0.97)[†]	0.41 (-0.03, 0.86)	NA	0.17 (-0.45, 0.79)	Omalizumab (75 mg)			
-0.27 (-0.55, 0.01)	NA	NA	NA	NA	0.43 (-0.01, 0.88)	0.33 (-0.12, 0.77)	NA	0.08 (-0.54, 0.71)	-0.09 (-0.39, 0.21)	Omalizumab (150 mg)		
-0.60 (-0.81, -0.39)[†]	NA	NA	NA	NA	0.10 (-0.27, 0.47)	-0.01 (-0.37, 0.36)	NA	-0.25 (-0.85, 0.35)	-0.42 (-0.70, -0.14)[†]	-0.33 (-0.61, -0.05)[†]	Omalizumab (300 mg)	

[†]Network meta-analysis results are expressed as SMDs (95% CIs). For the change in impact on sleep from baseline, SMDs less than 0 indicate that the treatment specified in the row is more effective than that specified in the column. To obtain SMDs for comparisons in the opposite direction, negative values should be converted into positive values and vice versa.

[‡]Statistically significant.

Abbreviations: CIs, confidence intervals; NA, not applicable; SMDs, standardized mean differences.

Table E9 Network estimates of secondary outcomes: patient-reported chronic urticaria-specific measure, CU-Q2oL (continued)[†]

Placebo											
NA	Canakinumab										
NA	NA	Cyclosporine									
NA	NA	NA	Dapsone								
NA	NA	NA	NA	Hydroxy-chloroquine							
NA	NA	NA	NA	NA	Ligelizumab (72 mg)						
NA	NA	NA	NA	NA	NA	Ligelizumab (240 mg)					
-0.11 (-0.58, 0.37)	NA	NA	NA	NA	NA	NA	Miltefosine				
NA	NA	NA	NA	NA	NA	NA	NA	Methotrexate			
-0.02 (-0.31, 0.26)	NA	NA	NA	NA	NA	NA	0.09 (-0.47, 0.64)	NA	Omalizumab (75 mg)		
-0.23 (-0.51, 0.06)	NA	NA	NA	NA	NA	NA	-0.12 (-0.67, 0.43)	NA	-0.20 (-0.52, 0.11)	Omalizumab (150 mg)	
-0.66 (-0.84, -0.48)[‡]	NA	NA	NA	NA	NA	NA	-0.55 (-1.05, -0.04)[‡]	NA	-0.63 (-0.92, -0.35)[‡]	-0.43 (-0.71, -0.15)[‡]	Omalizumab (300 mg)

[†]Network meta-analysis results are expressed as SMDs (95% CIs). For the change in impact on sleep from baseline, SMDs less than 0 indicate that the treatment specified in the row is more effective than that specified in the column. To obtain SMDs for comparisons in the opposite direction, negative values should be converted into positive values and vice versa.

[‡]Statistically significant.

Abbreviations: CIs, confidence intervals; CU-Q2oL, Chronic Urticaria Quality of Life Questionnaire; NA, not applicable; SMDs, standardized mean differences.

Table E10 Pairwise meta-analysis results of secondary outcomes

Treatment Comparison	No. of studies	No. of participants	OR (95% CI)	P Value	Heterogeneity			
					Q statistic	P value	I ² index (95% CI)	τ ²
Patient unacceptability								
Canakinumab								
vs placebo	1	20	1.00 (0.02 to 55.80)	1.000	NA	NA	NA	NA
Dapsone								
vs placebo	1	22	2.56 (0.08 to 85.06)	0.600	NA	NA	NA	NA
Hydroxychloroquine								
vs placebo	1	55	1.33 (0.27 to 6.61)	0.725	NA	NA	NA	NA
Ligelizumab 72 mg								
vs placebo	1	127	0.89 (0.24 to 3.21)	0.854	NA	NA	NA	NA
vs omalizumab 300 mg	1	169	0.50 (0.19 to 1.33)	0.167	NA	NA	NA	NA
Ligelizumab 240 mg								
vs placebo	1	128	1.60 (0.48 to 5.30)	0.440	NA	NA	NA	NA
vs ligelizumab 72 mg	1	169	1.81 (0.68 to 4.84)	0.239	NA	NA	NA	NA
vs omalizumab 300 mg	1	170	0.91 (0.39 to 2.13)	0.829	NA	NA	NA	NA
Miltefosine								
vs placebo	1	76	1.38 (0.39 to 4.90)	0.623	NA	NA	NA	NA
Methotrexate								
vs placebo	1	75	0.57 (0.15 to 2.22)	0.419	NA	NA	NA	NA
Omalizumab 75 mg								
vs placebo	2	319	0.77 (0.31 to 1.94)	0.581	1.70	0.192	41.3% (NA)	0.192
Omalizumab 150 mg								
vs placebo	3	467	0.92 (0.50 to 1.68)	0.777	2.16	0.340	7.4% (0.0-74.8%)	0.024
vs omalizumab 75 mg	2	323	1.43 (0.74 to 2.75)	0.282	0.05	0.819	0.0% (NA)	<0.001
Omalizumab 300 mg								
vs placebo	6	1,020	0.69 (0.34 to 1.40)	0.308	13.75	0.017	63.6% (0.0-82.9%)	0.459
vs cyclosporine	1	35	0.52 (0.02 to 16.42)	0.707	NA	NA	NA	NA
vs omalizumab 75 mg	2	320	1.13 (0.40 to 3.17)	0.822	2.23	0.135	55.3% (NA)	0.308
vs omalizumab 150 mg	3	467	0.70 (0.27 to 1.84)	0.471	3.93	0.140	49.1% (0.0-84.3%)	0.346

Abbreviations: CI, confidence interval; NA, not applicable; OR, odds ratio.

Table E10 Pairwise meta-analysis results of secondary outcomes (continued)

Treatment Comparison	No. of studies	No. of participants	SMD (95% CI)	P Value	Heterogeneity			
					Q statistic	P value	I ² index (95% CI)	τ ²
Impact on sleep								
Ligelizumab 72 mg								
vs placebo	1	127	-0.46 (-0.84 to -0.09)	0.015	NA	NA	NA	NA
vs omalizumab 300 mg	1	169	-0.25 (-0.56 to 0.05)	0.103	NA	NA	NA	NA
Ligelizumab 240 mg								
vs placebo	1	128	-0.36 (-0.73 to 0.01)	0.058	NA	NA	NA	NA
vs ligelizumab 72 mg	1	169	0.10 (-0.20 to 0.40)	0.516	NA	NA	NA	NA
vs omalizumab 300 mg	1	170	-0.15 (-0.45 to 0.15)	0.333	NA	NA	NA	NA
Methotrexate								
vs placebo	1	64	-0.35 (-0.85 to 0.14)	0.162	NA	NA	NA	NA
Omalizumab 75 mg								
vs placebo	2	263	-0.23 (-0.49 to 0.04)	0.094	1.19	0.276	15.7% (NA)	0.006
Omalizumab 150 mg								
vs placebo	2	267	-0.31 (-0.56 to -0.07)	0.011	0.19	0.664	0.0% (NA)	<0.001
vs omalizumab 75 mg	2	268	-0.09 (-0.33 to 0.15)	0.470	0.31	0.580	0.0% (NA)	<0.001
Omalizumab 300 mg								
vs placebo	4	687	-0.60 (-0.86 to -0.33)	<0.001	7.72	0.052	61.1% (0.0-84.9%)	0.045
vs omalizumab 75 mg	2	279	-0.43 (-0.67 to -0.19)	<0.001	0.15	0.700	0.0% (NA)	<0.001
vs omalizumab 150 mg	2	283	-0.33 (-0.57 to -0.10)	0.006	0.80	0.372	0.0% (NA)	<0.001

Abbreviations: CI, confidence interval; NA, not applicable; SMD, standardized mean difference.

Table E10 Pairwise meta-analysis results of secondary outcomes (continued)

Treatment Comparison	No. of studies	No. of participants	SMD (95% CI)	P Value	Heterogeneity			
					Q statistic	P value	I ² index (95% CI)	τ ²
Patient-reported chronic urticaria-specific measure, CU-Q2oL								
Miltefosine								
vs placebo	1	76	-0.11 (-0.58 to 0.36)	0.652	NA	NA	NA	NA
Omalizumab 75 mg								
vs placebo	1	157	0.03 (-0.29 to 0.34)	0.871	NA	NA	NA	NA
Omalizumab 150 mg								
vs placebo	1	160	-0.18 (-0.49 to 0.13)	0.263	NA	NA	NA	NA
vs omalizumab 75 mg	1	157	-0.21 (-0.52 to 0.11)	0.195	NA	NA	NA	NA
Omalizumab 300 mg								
vs placebo	3	587	-0.66 (-0.87 to 0.46)	<0.001	2.42	0.298	17.4% (0.0-77.3%)	0.006
vs omalizumab 75 mg	1	158	-0.59 (-0.91 to -0.27)	<0.001	NA	NA	NA	NA
vs omalizumab 150 mg	1	161	-0.39 (-0.70 to -0.08)	0.014	NA	NA	NA	NA
Patient-reported angioedema-specific measure, AE-QoL								
Omalizumab 300 mg								
vs placebo	1	91	-0.91 (-1.34 to -0.48)	<0.001	NA	NA	NA	NA
Well-being, WHO-5 Well-being Index								
Omalizumab 300 mg								
vs placebo	1	91	0.88 (0.45 to 1.31)	<0.001	NA	NA	NA	NA

Abbreviations: AE-QoL, Angioedema Quality of Life questionnaire; CI, confidence interval; CU-Q2oL, Chronic Urticaria Quality of Life Questionnaire; NA, not applicable; SMD, standardized mean difference; WHO, World Health Organization.

Table E11 Sensitivity analysis of network meta-analysis: assuming the correlation coefficient of 0.7 for estimating the SD_{change}: HRQOL[†]

Placebo											
-0.34 (-1.23, 0.55)	Canakinumab										
-0.53 (-1.21, 0.15)	-0.19 (-1.31, 0.93)	Cyclosporine									
0.42 (-0.44, 1.27)	0.75 (-0.48, 1.99)	0.94 (-0.15, 2.04)	Dapsone								
-1.23 (-1.86, -0.60)*	-0.89 (-1.98, 0.20)	-0.70 (-1.63, 0.23)	-1.64 (-2.70, -0.58)*	Hydroxy-chloroquine							
-0.66 (-0.96, -0.35)*	-0.32 (-1.26, 0.62)	-0.13 (-0.86, 0.61)	-1.07 (-1.98, -0.16)*	0.57 (-0.13, 1.27)	Ligelizumab (72 mg)						
-0.67 (-0.98, -0.37)*	-0.33 (-1.27, 0.60)	-0.15 (-0.88, 0.59)	-1.09 (-2.00, -0.18)*	0.55 (-0.14, 1.25)	-0.02 (-0.33, 0.30)	Ligelizumab (240 mg)					
-0.02 (-0.50, 0.46)	0.32 (-0.69, 1.33)	0.51 (-0.33, 1.35)	-0.44 (-1.42, 0.55)	1.21 (0.42, 2.00)*	0.64 (0.06, 1.21)*	0.65 (0.08, 1.23)*	Miltefosine				
-0.19 (-0.66, 0.27)	0.15 (-0.86, 1.15)	0.34 (-0.49, 1.16)	-0.61 (-1.58, 0.36)	1.04 (0.25, 1.82)*	0.46 (-0.10, 1.02)	0.48 (-0.08, 1.04)	-0.17 (-0.84, 0.50)	Methotrexate			
-0.16 (-0.43, 0.12)	0.18 (-0.75, 1.11)	0.37 (-0.35, 1.10)	-0.57 (-1.47, 0.33)	1.07 (0.39, 1.76)*	0.50 (0.10, 0.90)*	0.52 (0.12, 0.92)*	-0.14 (-0.69, 0.42)	0.04 (-0.51, 0.58)	Omalizumab (75 mg)		
-0.26 (-0.44, -0.08)*	0.08 (-0.83, 0.99)	0.27 (-0.42, 0.96)	-0.68 (-1.55, 0.20)	0.97 (0.32, 1.62)*	0.40 (0.06, 0.73)*	0.41 (0.08, 0.75)*	-0.24 (-0.76, 0.28)	-0.07 (-0.57, 0.43)	-0.10 (-0.39, 0.18)	Omalizumab (150 mg)	
-0.53 (-0.67, -0.39)*	-0.19 (-1.09, 0.71)	-0.00 (-0.67, 0.67)	-0.94 (-1.81, -0.08)*	0.70 (0.06, 1.34)*	0.13 (-0.17, 0.43)	0.15 (-0.15, 0.45)	-0.51 (-1.01, -0.01)*	-0.34 (-0.82, 0.15)	-0.37 (-0.65, -0.09)*	-0.27 (-0.45, -0.09)*	Omalizumab (300 mg)

[†]Network meta-analysis results are expressed as SMDs (95% CIs). For the change in impact on sleep from baseline, SMDs less than 0 indicate that the treatment specified in the row is more effective than that specified in the column. To obtain SMDs for comparisons in the opposite direction, negative values should be converted into positive values and vice versa.

*Statistically significant.

Abbreviations: CIs, confidence intervals; HRQOL, health-related quality of life; NA, not applicable; SMDs, standardized mean differences.

Table E11 Sensitivity analysis of network meta-analysis: assuming the correlation coefficient of 0.7 for estimating the SD_{change}: HRQOL by the duration of treatment (continued)[†]

		Treatment follow-up greater than 12 weeks										
Treatment follow-up 12 weeks or less	Placebo	NA	-0.49 (-1.32, 0.33)	NA	NA	-0.61 (-1.09, -0.13)*	-0.63 (-1.11, -0.15)*	NA	-0.19 (-0.81, 0.42)	NA	-0.13 (-0.60, 0.33)	-0.49 (-0.76, -0.23)*
	-0.34 (-1.22, 0.54)	Canakinumab	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	-0.68 (-1.35, -0.00)*	-0.34 (-1.45, 0.78)	Cyclosporine	NA	NA	-0.12 (-1.03, 0.79)	-0.13 (-1.04, 0.78)	NA	0.30 (-0.73, 1.33)	NA	0.36 (-0.55, 1.27)	-0.00 (-0.78, 0.78)
	0.42 (-0.43, 1.26)	0.75 (-0.47, 1.98)	1.09 (0.01, 2.18)*	Dapsone	NA	NA	NA	NA	NA	NA	NA	NA
	-1.23 (-1.85, -0.61)*	-0.89 (-1.97, 0.19)	-0.55 (-1.47, 0.36)	-1.64 (-2.70, -0.59)*	Hydroxy-chloroquine	NA	NA	NA	NA	NA	NA	NA
	-0.71 (-1.00, -0.42)*	-0.37 (-1.30, 0.56)	-0.03 (-0.75, 0.69)	-1.12 (-2.02, -0.22)*	0.52 (-0.16, 1.21)	Ligelizumab (72 mg)	-0.02 (-0.53, 0.49)	NA	0.42 (-0.36, 1.19)	NA	0.48 (-0.16, 1.11)	0.12 (-0.35, 0.59)
	-0.73 (-1.02, -0.43)*	-0.39 (-1.32, 0.54)	-0.05 (-0.77, 0.67)	-1.14 (-2.04, -0.24)*	0.50 (-0.18, 1.19)	-0.02 (-0.32, 0.28)	Ligelizumab (240 mg)	NA	0.43 (-0.34, 1.21)	NA	0.49 (-0.14, 1.13)	0.13 (-0.34, 0.60)
	-0.02 (-0.50, 0.45)	0.32 (-0.68, 1.32)	0.66 (-0.17, 1.48)	-0.44 (-1.41, 0.54)	1.21 (0.43, 1.99)*	0.69 (0.13, 1.24)*	0.70 (0.15, 1.26)*	Miltefosine	NA	NA	NA	NA
	-0.34 (-0.80, 0.12)	-0.00 (-1.00, 0.99)	0.33 (-0.48, 1.15)	-0.76 (-1.72, 0.21)	0.89 (0.11, 1.66)*	0.36 (-0.18, 0.91)	0.38 (-0.16, 0.93)	-0.32 (-0.98, 0.34)	Methotrexate	NA	0.06 (-0.71, 0.83)	-0.30 (-0.97, 0.37)
	-0.13 (-0.33, 0.07)	0.21 (-0.70, 1.11)	0.54 (-0.15, 1.24)	-0.55 (-1.42, 0.33)	1.10 (0.45, 1.75)*	0.58 (0.24, 0.91)*	0.59 (0.26, 0.93)*	-0.11 (-0.62, 0.40)	0.21 (-0.29, 0.71)	Omalizumab (75 mg)	NA	NA
	-0.33 (-0.50, -0.16)*	0.01 (-0.89, 0.91)	0.35 (-0.34, 1.03)	-0.75 (-1.61, 0.12)	0.90 (0.26, 1.54)*	0.38 (0.06, 0.70)*	0.39 (0.08, 0.71)*	-0.31 (-0.81, 0.19)	0.01 (-0.48, 0.50)	-0.20 (-0.41, 0.01)	Omalizumab (150 mg)	-0.36 (-0.82, 0.10)
	-0.61 (-0.75, -0.48)*	-0.27 (-1.17, 0.62)	0.06 (-0.60, 0.73)	-1.03 (-1.89, -0.17)*	0.62 (-0.02, 1.25)	0.09 (-0.19, 0.37)	0.11 (-0.17, 0.39)	-0.59 (-1.08, -0.10)*	-0.27 (-0.75, 0.21)	-0.48 (-0.68, -0.28)*	-0.28 (-0.45, -0.11)*	Omalizumab (300 mg)

[†]Network meta-analysis results are expressed as SMDs (95% CIs). For study duration ≤12 weeks (lower left portion [blue]), SMDs less than 0 indicate that the treatment specified in the row is more effective than that specified in the column. For study duration >12 weeks (upper right portion [green]), SMDs less than 0 indicate that the treatment specified in the column is more effective than that specified in the row. To obtain SMDs for comparisons in the opposite direction, negative values should be converted into positive values and vice versa.

*Statistically significant.

Abbreviations: CIs, confidence intervals; CSU, chronic spontaneous urticaria; HRQOL, health-related quality of life; NA, not applicable; SMDs, standardized mean differences.

Table E11 Sensitivity analysis of network meta-analysis: assuming the correlation coefficient of 0.7 for estimating the SD_{change}: impact on sleep (continued)[†]

Placebo												
NA	Canakinumab											
NA	NA	Cyclosporine										
NA	NA	NA	Dapsone									
NA	NA	NA	NA	Hydroxy-chloroquine								
-0.70 (-1.09, -0.32)[‡]	NA	NA	NA	NA	Ligelizumab (72 mg)							
-0.60 (-0.98, -0.21)[‡]	NA	NA	NA	MA	0.11 (-0.29, 0.50)	Ligelizumab (240 mg)						
NA	NA	NA	NA	NA	NA	NA	Miltefosine					
-0.45 (-1.01, 0.11)	NA	NA	NA	NA	0.25 (-0.43, 0.93)	0.14 (-0.54, 0.82)	NA	Methotrexate				
-0.18 (-0.46, 0.10)	NA	NA	NA	NA	0.52 (0.07, 0.97)[‡]	0.41 (-0.03, 0.86)	NA	0.27 (-0.36, 0.90)	Omalizumab (75 mg)			
-0.27 (-0.55, 0.01)	NA	NA	NA	NA	0.43 (-0.01, 0.88)	0.33 (-0.12, 0.77)	NA	0.18 (-0.44, 0.81)	-0.09 (-0.39, 0.21)	Omalizumab (150 mg)		
-0.60 (-0.81, -0.39)[‡]	NA	NA	NA	NA	0.10 (-0.27, 0.47)	-0.01 (-0.37, 0.36)	NA	-0.15 (-0.75, 0.45)	-0.42 (-0.70, -0.14)[‡]	-0.33 (-0.61, -0.05)[‡]	Omalizumab (300 mg)	

[†]Network meta-analysis results are expressed as SMDs (95% CIs). For the change in impact on sleep from baseline, SMDs less than 0 indicate that the treatment specified in the row is more effective than that specified in the column. To obtain SMDs for comparisons in the opposite direction, negative values should be converted into positive values and vice versa.

[‡]Statistically significant.

Abbreviations: CIs, confidence intervals; NA, not applicable; SMDs, standardized mean differences.

Table E11 Sensitivity analysis of network meta-analysis: assuming the correlation coefficient of 0.7 for estimating the SD_{change}: patient-reported chronic urticaria-specific measure, CU-Q2oL (continued)[†]

Placebo											
NA	Canakinumab										
NA	NA	Cyclosporine									
NA	NA	NA	Dapsone								
NA	NA	NA	NA	Hydroxy-chloroquine							
NA	NA	NA	NA	NA	Ligelizumab (72 mg)						
NA	NA	NA	NA	NA	NA	Ligelizumab (240 mg)					
-0.14 (-0.61, 0.34)	NA	NA	NA	NA	NA	NA	Miltefosine				
NA	NA	NA	NA	NA	NA	NA	NA	Methotrexate			
-0.02 (-0.31, 0.26)	NA	NA	NA	NA	NA	NA	0.11 (-0.44, 0.67)	NA	Omalizumab (75 mg)		
-0.23 (-0.51, 0.06)	NA	NA	NA	NA	NA	NA	-0.09 (-0.64, 0.46)	NA	-0.20 (-0.52, 0.11)	Omalizumab (150 mg)	
-0.66 (-0.84, -0.48)*	NA	NA	NA	NA	NA	NA	-0.52 (-1.03, -0.01)*	NA	-0.63 (-0.92, -0.35)*	-0.43 (-0.71, -0.15)*	Omalizumab (300 mg)

[†]Network meta-analysis results are expressed as SMDs (95% CIs). For the change in impact on sleep from baseline, SMDs less than 0 indicate that the treatment specified in the row is more effective than that specified in the column. To obtain SMDs for comparisons in the opposite direction, negative values should be converted into positive values and vice versa.

*Statistically significant.

Abbreviations: CIs, confidence intervals; CU-Q2oL, Chronic Urticaria Quality of Life Questionnaire; NA, not applicable; SMDs, standardized mean differences.

Table E11 Sensitivity analysis of network meta-analysis: restricting the analysis to studies that using the DLQI for HRQOL measure (continued)[†]

Placebo												
-0.27 (-1.15, 0.61)	Canakinumab											
-0.48 (-1.16, 0.19)	-0.21 (-1.32, 0.90)	Cyclosporine										
NA	NA	NA	Dapsone									
-1.00 (-1.60, -0.40)*	-0.73 (-1.80, 0.34)	-0.52 (-1.42, 0.39)	NA	Hydroxy- chloroquine								
-0.63 (-0.92, -0.34)*	-0.36 (-1.29, 0.57)	-0.15 (-0.87, 0.57)	NA	0.37 (-0.30, 1.04)	Ligelizumab (72 mg)							
-0.65 (-0.94, -0.36)*	-0.38 (-1.30, 0.55)	-0.16 (-0.88, 0.56)	NA	0.35 (-0.32, 1.02)	-0.02 (-0.32, 0.28)	Ligelizumab (240 mg)						
-0.02 (-0.49, 0.46)	0.26 (-0.75, 1.26)	0.47 (-0.36, 1.29)	NA	0.98 (0.22, 1.75)*	0.61 (0.06, 1.17)*	0.63 (0.07, 1.19)*	Miltefosine					
-0.15 (-0.61, 0.30)	0.12 (-0.87, 1.11)	0.33 (-0.49, 1.15)	NA	0.85 (0.09, 1.60)*	0.48 (-0.07, 1.02)	0.49 (-0.05, 1.04)	-0.14 (-0.79, 0.52)	Methotrexate				
-0.13 (-0.40, 0.13)	0.14 (-0.78, 1.06)	0.35 (-0.36, 1.06)	NA	0.87 (0.21, 1.52)*	0.50 (0.12, 0.87)*	0.51 (0.13, 0.89)*	-0.12 (-0.66, 0.43)	0.02 (-0.51, 0.55)	Omalizumab (75 mg)			
-0.24 (-0.41, -0.07)*	0.03 (-0.86, 0.93)	0.25 (-0.44, 0.93)	NA	0.76 (0.14, 1.39)*	0.39 (0.07, 0.71)*	0.41 (0.09, 0.73)*	-0.22 (-0.73, 0.28)	-0.08 (-0.57, 0.40)	-0.10 (-0.37, 0.17)	Omalizumab (150 mg)		
-0.48 (-0.62, -0.35)*	-0.21 (-1.10, 0.68)	-0.00 (-0.66, 0.66)	NA	0.52 (-0.10, 1.13)	0.15 (-0.14, 0.43)	0.16 (-0.12, 0.44)	-0.47 (-0.96, 0.03)	-0.33 (-0.81, 0.15)	-0.35 (-0.62, -0.08)*	-0.25 (-0.42, -0.07)*	Omalizumab (300 mg)	

[†]Network meta-analysis results are expressed as SMDs (95% CIs). For the change in impact on sleep from baseline, SMDs less than 0 indicate that the treatment specified in the row is more effective than that specified in the column. To obtain SMDs for comparisons in the opposite direction, negative values should be converted into positive values and vice versa.

*Statistically significant.

Abbreviations: CIs, confidence intervals; DLQI, Dermatology Life Quality Index; HRQOL, health-related quality of life; NA, not applicable; SMDs, standardized mean differences.

Table E11 Sensitivity analysis of network meta-analysis: excluding trials with crossover design, HRQOL (continued)[†]

Placebo											
-0.27 (-1.16, 0.61)	Canakinumab										
-0.53 (-1.21, 0.15)	-0.26 (-1.38, 0.86)	Cyclosporine									
NA	NA	NA	Dapsone								
-1.00 (-1.61, -0.39) [‡]	-0.73 (-1.80, 0.35)	-0.47 (-1.39, 0.44)	NA	Hydroxy- chloroquine							
-0.66 (-0.96, -0.35) [‡]	-0.39 (-1.32, 0.55)	-0.13 (-0.86, 0.61)	NA	0.34 (-0.34, 1.03)	Ligelizumab (72 mg)						
-0.67 (-0.98, -0.37) [‡]	-0.40 (-1.34, 0.53)	-0.15 (-0.88, 0.59)	NA	0.33 (-0.36, 1.01)	-0.02 (-0.33, 0.30)	Ligelizumab (240 mg)					
-0.02 (-0.50, 0.47)	0.26 (-0.75, 1.26)	0.51 (-0.32, 1.35)	NA	0.98 (0.21, 1.76) [‡]	0.64 (0.07, 1.21) [‡]	0.66 (0.09, 1.23) [‡]	Miltefosine				
-0.15 (-0.62, 0.31)	0.12 (-0.88, 1.12)	0.38 (-0.45, 1.20)	NA	0.85 (0.08, 1.61) [‡]	0.50 (-0.05, 1.06)	0.52 (-0.04, 1.08)	-0.14 (-0.81, 0.54)	Methotrexate			
-0.16 (-0.43, 0.12)	0.11 (-0.81, 1.04)	0.37 (-0.35, 1.10)	NA	0.84 (0.17, 1.51) [‡]	0.50 (0.10, 0.90) [‡]	0.52 (0.12, 0.92) [‡]	-0.14 (-0.70, 0.42)	-0.00 (-0.55, 0.54)	Omalizumab (75 mg)		
-0.26 (-0.44, -0.08) [‡]	0.01 (-0.89, 0.91)	0.27 (-0.42, 0.96)	NA	0.74 (0.10, 1.37) [‡]	0.40 (0.06, 0.73) [‡]	0.41 (0.08, 0.75) [‡]	-0.24 (-0.76, 0.27)	-0.11 (-0.61, 0.39)	-0.10 (-0.39, 0.18)	Omalizumab (150 mg)	
-0.53 (-0.67, -0.39) [‡]	-0.26 (-1.15, 0.64)	-0.00 (-0.67, 0.67)	NA	0.47 (-0.15, 1.10)	0.13 (-0.17, 0.43)	0.15 (-0.15, 0.45)	-0.51 (-1.02, -0.01)	-0.38 (-0.86, 0.11)	-0.37 (-0.65, -0.09) [‡]	-0.27 (-0.45, -0.09) [‡]	Omalizumab (300 mg)

^aNetwork meta-analysis results are expressed as SMDs (95% CIs). For the change in impact on sleep from baseline, SMDs less than 0 indicate that the treatment specified in the row is more effective than that specified in the column. To obtain SMDs for comparisons in the opposite direction, negative values should be converted into positive values and vice versa.

[‡]Statistically significant.

Abbreviations: CIs, confidence intervals; HRQOL, health-related quality of life; NA, not applicable; SMDs, standardized mean differences.

Table E11 Sensitivity analysis of network meta-analysis: excluding single center trials: HRQOL (continued)[†]

Placebo												
NA	Canakinumab											
-0.53 (-1.21, 0.15)	NA	Cyclosporine										
NA	NA	NA	Dapsone									
NA	NA	NA	NA	Hydroxy-chloroquine								
-0.66 (-0.96, -0.35)*	NA	-0.13 (-0.86, 0.61)	NA	NA	Ligelizumab (72 mg)							
-0.67 (-0.98, -0.37)*	NA	-0.15 (-0.88, 0.59)	NA	NA	-0.02 (-0.33, 0.30)	Ligelizumab (240 mg)						
-0.02 (-0.50, 0.47)	NA	0.51 (-0.32, 1.35)	NA	NA	0.64 (0.07, 1.21)*	0.66 (0.09, 1.23)*	Miltefosine					
-0.15 (-0.62, 0.31)	NA	0.38 (-0.45, 1.20)	NA	NA	0.50 (-0.05, 1.06)	0.52 (-0.04, 1.08)	-0.14 (-0.81, 0.54)	Methotrexate				
-0.16 (-0.43, 0.12)	NA	0.37 (-0.35, 1.10)	NA	NA	0.50 (0.10, 0.90)*	0.52 (0.12, 0.92)*	-0.14 (-0.70, 0.42)	-0.00 (-0.55, 0.54)	Omalizumab (75 mg)			
-0.26 (-0.44, -0.08)*	NA	0.27 (-0.42, 0.96)	NA	NA	0.40 (0.06, 0.73)*	0.41 (0.08, 0.75)*	-0.24 (-0.76, 0.27)	-0.11 (-0.61, 0.39)	-0.10 (-0.39, 0.18)	Omalizumab (150 mg)		
-0.53 (-0.67, -0.39)*	NA	-0.00 (-0.67, 0.67)	NA	NA	0.13 (-0.17, 0.43)	0.15 (-0.15, 0.45)	-0.51 (-1.02, -0.01)*	-0.38 (-0.86, 0.11)	-0.37 (-0.65, -0.09)*	-0.27 (-0.45, -0.09)*	Omalizumab (300 mg)	

[†]Network meta-analysis results are expressed as SMDs (95% CIs). For the change in impact on sleep from baseline, SMDs less than 0 indicate that the treatment specified in the row is more effective than that specified in the column. To obtain SMDs for comparisons in the opposite direction, negative values should be converted into positive values and vice versa.

*Statistically significant.

Abbreviations: CIs, confidence intervals; HRQOL, health-related quality of life; NA, not applicable; SMDs, standardized mean differences.

Table E11 Sensitivity analysis of network meta-analysis: limiting the analysis to studies with low risk of bias: HRQOL (continued)[†]

Placebo											
NA	Canakinumab										
NA	NA	Cyclosporine									
NA	NA	NA	Dapsone								
NA	NA	NA	NA	Hydroxy-chloroquine							
-0.66 (-0.96, -0.35) [‡]	NA	NA	NA	NA	Ligelizumab (72 mg)						
-0.67 (-0.98, -0.37) [‡]	NA	NA	NA	NA	-0.02 (-0.33, 0.30)	Ligelizumab (240 mg)					
-0.02 (-0.50, 0.47)	NA	NA	NA	NA	0.64 (0.07, 1.21) [‡]	0.66 (0.09, 1.23) [‡]	Miltefosine				
-0.15 (-0.62, 0.31)	NA	NA	NA	NA	0.50 (-0.05, 1.06)	0.52 (-0.04, 1.08)	-0.14 (-0.81, 0.54)	Methotrexate			
-0.16 (-0.43, 0.12)	NA	NA	NA	NA	0.50 (0.10, 0.90) [‡]	0.52 (0.12, 0.92) [‡]	-0.14 (-0.70, 0.42)	-0.00 (-0.55, 0.54)	Omalizumab (75 mg)		
-0.26 (-0.44, -0.08) [‡]	NA	NA	NA	NA	0.40 (0.06, 0.73) [‡]	0.41 (0.08, 0.75) [‡]	-0.24 (-0.76, 0.27)	-0.11 (-0.61, 0.39)	-0.10 (-0.39, 0.18)	Omalizumab (150 mg)	
-0.53 (-0.67, -0.39) [‡]	NA	NA	NA	NA	0.13 (-0.17, 0.43)	0.15 (-0.15, 0.45)	-0.51 (-1.02, -0.01) [‡]	-0.38 (-0.86, 0.11)	-0.37 (-0.65, -0.09) [‡]	-0.27 (-0.45, -0.09) [‡]	Omalizumab (300 mg)

[†]Network meta-analysis results are expressed as SMDs (95% CIs). For the change in impact on sleep from baseline, SMDs less than 0 indicate that the treatment specified in the row is more effective than that specified in the column. To obtain SMDs for comparisons in the opposite direction, negative values should be converted into positive values and vice versa.

[‡]Statistically significant.

Abbreviations: CIs, confidence intervals; HRQOL, health-related quality of life; NA, not applicable; SMDs, standardized mean differences.

Table E12 Evaluation of inconsistency: loop-specific approach

Loop	Inconsistency Factor (95% CI)	P Value	Loop Heterogeneity (τ^2)
HRQOL (all)			
Placebo-Ligelizumab 240 mg-Omalizumab 300 mg	0.37 (0.00-0.96)	0.222	0.010
Placebo-Ligelizumab 72 mg-Omalizumab 300 mg	0.37 (0.00-0.96)	0.223	0.010
*Placebo-Omalizumab 75 mg-Omalizumab 150 mg	0.05 (0.00-0.57)	0.859	0.005
Placebo-Omalizumab 75 mg-Omalizumab 300mg	0.04 (0.00-0.79)	0.918	0.032
Placebo-Omalizumab 150 mg-Omalizumab 300 mg	0.03 (0.00-0.45)	0.887	0.014
*Omalizumab 75 mg-Omalizumab 150 mg-Omalizumab 300 mg	0.02 (0.00-0.50)	0.923	<0.001
*Ligelizumab 72 mg-Ligelizumab 240 mg-Omalizumab 300 mg	0.00 (0.00-0.52)	1.000	<0.001
*Placebo-Ligelizumab 72 mg-Ligelizumab 240 mg	0.00 (0.00-0.61)	1.000	<0.001
HRQOL: ≤12 weeks of treatment follow-up			
Placebo-Ligelizumab 72 mg-Omalizumab 300 mg	0.43 (0.00-0.93)	0.094	<0.001
Placebo-Ligelizumab 240 mg-Omalizumab 300 mg	0.43 (0.00-0.93)	0.093	<0.001
*Placebo-Omalizumab 75 mg-Omalizumab 150 mg	0.04 (0.00-0.40)	0.823	<0.001
Placebo-Omalizumab 75 mg-Omalizumab 300 mg	0.03 (0.00-0.50)	0.896	0.015
Placebo-Omalizumab 150 mg-Omalizumab 300 mg	0.03 (0.00-0.38)	0.874	0.004
*Omalizumab 75 mg-Omalizumab 150 mg-Omalizumab 300 mg	0.01 (0.00-0.37)	0.970	<0.001
*Placebo-Ligelizumab 72 mg-Ligelizumab 240 mg	0.00 (0.00-0.61)	1.000	<0.001
*Ligelizumab 72 mg-Ligelizumab 240 mg-Omalizumab 300 mg	0.00 (0.00-0.52)	1.000	<0.001
HRQOL: >12 weeks of treatment follow-up			
Placebo-Ligelizumab 72 mg-Omalizumab 300 mg	0.36 (0.00-1.22)	0.410	0.037
Placebo-Ligelizumab 240 mg-Omalizumab 300 mg	0.36 (0.00-1.21)	0.410	0.037
Placebo-Omalizumab 150 mg-Omalizumab 300 mg	0.15 (0.00-1.20)	0.780	0.073
*Ligelizumab 72 mg-Ligelizumab 240 mg-Omalizumab 300 mg	0.00 (0.00-0.52)	1.000	<0.001
*Placebo-Ligelizumab 72 mg-Ligelizumab 240 mg	0.00 (0.00-0.61)	1.000	<0.001
Patient unacceptability			
Placebo-Ligelizumab 72 mg-Omalizumab 300 mg	1.10 (0.00-3.85)	0.432	0.412
Placebo-Ligelizumab 240 mg-Omalizumab 300 mg	1.10 (0.00-3.75)	0.415	0.412
Placebo-Omalizumab 75 mg-Omalizumab 300mg	0.37 (0.00-1.99)	0.653	0.238
*Placebo-Omalizumab 75 mg-Omalizumab 150 mg	0.12 (0.00-1.22)	0.832	<0.001
*Omalizumab 75 mg-Omalizumab 150 mg-Omalizumab 300 mg	0.09 (0.00-1.57)	0.903	0.159
Placebo-Omalizumab 150 mg-Omalizumab 300 mg	0.04 (0.00-1.38)	0.959	0.185
*Ligelizumab 72 mg-Ligelizumab 240 mg-Omalizumab 300 mg	0.00 (0.00-1.62)	1.000	<0.001
*Placebo-Ligelizumab 72 mg-Ligelizumab 240 mg	0.00 (0.00-2.02)	1.000	<0.001

*Note: these loops are formed only by multi-arm trial(s).

Abbreviations: CI, confidence interval; CU-Q2oL, Chronic Urticaria Quality of Life Questionnaire; HRQOL, health-related quality of life.

Table E12 Evaluation of inconsistency: loop-specific approach (continued)

Loop	Inconsistency Factor (95% CI)	P Value	Loop Heterogeneity (τ^2)
Impact on sleep			
Placebo-Ligelizumab 72 mg-Omalizumab 300 mg	0.50 (0.00-1.02)	0.061	0.001
Placebo-Ligelizumab 240 mg-Omalizumab 300 mg	0.50 (0.00-1.02)	0.060	0.001
Placebo-Omalizumab 75 mg-Omalizumab 300mg	0.18 (0.00-0.78)	0.561	0.034
Placebo-Omalizumab 150 mg-Omalizumab 300 mg	0.18 (0.00-0.77)	0.559	0.032
*Omalizumab 75 mg-Omalizumab 150 mg-Omalizumab 300 mg	0.00 (0.00-0.41)	0.996	<0.001
*Placebo-Omalizumab 75 mg-Omalizumab 150 mg	0.00 (0.00-0.42)	0.996	<0.001
*Ligelizumab 72 mg-Ligelizumab 240 mg-Omalizumab 300 mg	0.00 (0.00-0.52)	1.000	<0.001
*Placebo-Ligelizumab 72 mg-Ligelizumab 240 mg	0.00 (0.00-0.60)	1.000	<0.001
Patient-reported chronic urticaria-specific measure: CU-Q2oL			
Placebo-Omalizumab 150 mg-Omalizumab 300 mg	0.15 (0.00-0.64)	0.554	<0.001
Placebo-Omalizumab 75 mg-Omalizumab 300mg	0.15 (0.00-0.65)	0.584	<0.001
*Omalizumab 75 mg-Omalizumab 150 mg-Omalizumab 300 mg	0.00 (0.00-0.55)	1.000	<0.001
*Placebo-Omalizumab 75 mg-Omalizumab 150 mg	0.00 (0.00-0.54)	1.000	<0.001

*Note: these loops are formed only by multi-arm trial(s).

Abbreviations: CI, confidence interval; CU-Q2oL, Chronic Urticaria Quality of Life Questionnaire; HRQOL, health-related quality of life.

Table E13 Evaluation of inconsistency: design-by-treatment interaction model

Outcome	Chi-Square	P Value for Test of Global Inconsistency[†]
HRQOL (all)	2.20	0.699
HRQOL: ≤12 weeks of treatment follow-up	5.44	0.245
HRQOL: >12 weeks of treatment follow-up	1.49	0.475
Patient unacceptability	3.75	0.441
Impact on sleep	5.77	0.056
Patient-reported chronic urticaria-specific measure: CU-Q2oL	0.41	0.523

[†] $P > 0.05$ indicates that data fits consistency model, $P < 0.05$ indicates it fits inconsistency model better. Abbreviations: CU-Q2oL, Chronic Urticaria Quality of Life Questionnaire; HRQOL, health-related quality of life; NA, not applicable.

Table E14 Evaluation of the strength of the body of evidence: GRADE assessment by CINeMA: primary outcome (HRQOL)

Treatment comparison (reference: placebo)	No. of studies	No. of participants	SMD (95% CI)		Corresponding 95% PrI	Magnitudes of Effect Size [†]	Evidence certainty
			Pairwise estimate	Network meta-analysis estimate			
Canakinumab	1	20	-0.27 (-1.15 to 0.61)	-0.27 (-1.16 to 0.61)	-1.29 to 0.74	NS	Low ^{‡§¥¶*}
Cyclosporine	NA	NA	NA	-0.53 (-1.21 to 0.15)	-1.31 to 0.26	NS	Very low ^{‡£¶*}
Dapsone	1	22	0.34 (-0.50 to 1.19)	0.34 (-0.51 to 1.20)	-0.63 to 1.32	NS	Low ^{‡§£¶}
Hydroxychloroquine	1	48	-1.00 (-1.60 to -0.40)	-1.00 (-1.61 to -0.39)	-1.70 to -0.30	Large	Low ^{‡§¶*}
Ligelizumab (72 mg)	1	127	-0.45 (-0.82 to -0.08)	-0.66 (-0.96 to -0.35)	-1.02 to -0.29	Moderate	Moderate ^{‡¶}
Ligelizumab (240 mg)	1	128	-0.47 (-0.84 to -0.10)	-0.67 (-0.98 to -0.37)	-1.04 to -0.31	Moderate	Moderate ^{‡¶}
Miltefosine	1	76	-0.02 (-0.49 to 0.46)	-0.02 (-0.50 to 0.47)	-0.58 to 0.54	NS	Low ^{‡¥¶*}
Methotrexate	1	74	-0.15 (-0.61 to 0.30)	-0.15 (-0.62 to 0.31)	-0.69 to 0.39	NS	Moderate ^{‡¥¶}
Omalizumab (75 mg)	1	161	-0.19 (-0.50 to 0.12)	-0.16 (-0.43 to 0.12)	-0.49 to 0.18	NS	Moderate ^{‡¶}
Omalizumab (150 mg)	3	466	-0.27 (-0.47 to -0.07)	-0.26 (-0.44 to -0.08)	-0.49 to -0.03	Small	High
Omalizumab (300 mg)	6	1,020	-0.54 (-0.71 to -0.36)	-0.53 (-0.67 to -0.39)	-0.71 to -0.34	Medium	High

[†]To estimate treatment effects, SMD of <0.2, 0.2-0.4, 0.5-0.7, and ≥0.8 are considered to be very small, small, medium, and large, respectively.

[‡]Within study bias.

[§]Reporting bias.

[£]Indirectness.

[¥]Imprecision.

[¶]Heterogeneity.

^{*}Incoherence.

Note: See Appendix-III for full details of criteria for downgrading quality of evidence.

Abbreviations: CI, confidence interval; CINeMA, Confidence In Network Meta-Analysis; GRADE, Grading Recommendations Assessment, Development and Evaluation; HRQOL, health-related quality of life; NA, not applicable; NS, non-statistically significant; PrI, prediction interval; SMD, standardized mean difference.

Table E14 Evaluation of the strength of the body of evidence: GRADE assessment by CINeMA: secondary outcome (patient unacceptability) (continued)

Treatment comparison (reference: placebo)	No. of studies	No. of participants	OR (95% CI)		Corresponding 95% PrI	Magnitudes of effect size ^a	Evidence certainty
			Pairwise estimate	Network meta-analysis estimate			
Canakinumab	1	20	1.00 (0.02 to 55.80)	1.00 (0.02 to 61.41)	0.01 to 119.99	NS	Low ^{‡§¥¶}
Cyclosporine	NA	NA	NA	1.33 (0.04 to 49.38)	0.02 to 91.38	NS	Very low ^{‡£¶}
Dapsone	1	22	2.56 (0.08 to 85.06)	2.56 (0.07 to 94.90)	0.04 to 175.61	NS	Low ^{‡§¥¶}
Hydroxychloroquine	1	55	1.33 (0.27 to 6.61)	1.33 (0.21 to 8.29)	0.13 to 13.40	NS	Low ^{‡§¥¶}
Ligelizumab (72 mg)	1	127	0.89 (0.24 to 3.21)	0.47 (0.13 to 1.71)	0.08 to 2.78	NS	Moderate ^{‡¶}
Ligelizumab (240 mg)	1	128	1.60 (0.48 to 5.30)	0.86 (0.26 to 2.82)	0.16 to 4.62	NS	Moderate ^{‡¶}
Miltefosine	1	76	1.38 (0.39 to 4.90)	1.38 (0.29 to 6.46)	0.18 to 10.42	NS	Moderate ^{‡¥¶}
Methotrexate	1	75	0.57 (0.15 to 2.22)	0.57 (0.11 to 2.88)	0.07 to 4.65	NS	Moderate ^{‡¥¶}
Omalizumab (75 mg)	2	319	0.77 (0.31 to 1.94)	0.64 (0.27 to 1.50)	0.16 to 2.57	NS	High
Omalizumab (150 mg)	3	467	0.92 (0.50 to 1.68)	0.87 (0.41 to 1.84)	0.23 to 3.25	NS	High
Omalizumab (300 mg)	6	1,020	0.69 (0.34 to 1.40)	0.68 (0.39 to 1.20)	0.21 to 2.24	NS	High [¶]

[†]To estimate treatment effects, OR of <1.68, 1.68-3.46, 3.47-6.71, and >6.71 are considered to be very small, small, medium, and large, respectively.

[‡]Within study bias.

[§]Reporting bias.

[£]Indirectness.

[¥]Imprecision.

[¶]Heterogeneity.

* Incoherence.

Note: See Appendix-III for full details of criteria for downgrading quality of evidence.

Abbreviations: CI, confidence interval; CINeMA, Confidence In Network Meta-Analysis; GRADE, Grading Recommendations Assessment, Development and Evaluation; NA, not applicable; NS, non-statistically significant; PrI, prediction interval; OR, odds ratio.

Table E14 Evaluation of the strength of the body of evidence: GRADE assessment by CINeMA: secondary outcome (impact on sleep) (continued)

Treatment comparison (reference: placebo)	No. of studies	No. of participants	SMD (95% CI)		Corresponding 95% PrI	Magnitudes of Effect Size [†]	Evidence certainty
			Pairwise estimate	Network meta-analysis estimate			
Canakinumab	NA	NA	NA	NA	NA	NA	Insufficient
Cyclosporine	NA	NA	NA	NA	NA	NA	Insufficient
Dapsone	NA	NA	NA	NA	NA	NA	Insufficient
Hydroxychloroquine	NA	NA	NA	NA	NA	NA	Insufficient
Ligelizumab (72 mg)	1	127	-0.46 (-0.84 to -0.09)	-0.70 (-1.09 to -0.32)	-1.46 to 0.05	Medium	Moderate ^{‡¶*}
Ligelizumab (240 mg)	1	128	-0.36 (-0.73 to -0.01)	-0.60 (-0.98 to -0.21)	-1.35 to 0.15	Medium	Moderate ^{‡¶*}
Miltefosine	NA	NA	NA	NA	NA	NA	Insufficient
Methotrexate	1	64	-0.35 (-0.85 to 0.14)	-0.35 (-0.91 to 0.20)	-1.35 to 0.64	NS	Moderate ^{‡¶}
Omalizumab (75 mg)	2	263	-0.23 (-0.49 to 0.04)	-0.18 (-0.46 to 0.10)	-0.80 to 0.44	NS	High
Omalizumab (150 mg)	2	267	-0.31 (-0.56 to -0.07)	-0.27 (-0.55 to 0.01)	-0.89 to 0.35	NS	High
Omalizumab (300 mg)	4	687	-0.60 (-0.86 to -0.33)	-0.60 (-0.81 to -0.39)	-1.14 to -0.06	Medium	High [¶]

[†]To estimate treatment effects, SMD of <0.2, 0.2-0.4, 0.5-0.7, and ≥0.8 are considered to be very small, small, medium, and large, respectively.

[‡]Within study bias.

[§]Reporting bias.

[£]Indirectness.

[¥]Imprecision.

[¶]Heterogeneity.

^{*}Incoherence.

Note: See Appendix-III for full details of criteria for downgrading quality of evidence.

Abbreviations: CI, confidence interval; CINeMA, Confidence In Network Meta-Analysis; GRADE, Grading Recommendations Assessment, Development and Evaluation; NA, not applicable; NS, non-statistically significant; PrI, prediction interval; SMD, standardized mean difference.

Table E14 Evaluation of the strength of the body of evidence: GRADE assessment by CINeMA: secondary outcome (patient-reported chronic urticaria-specific measure, CU-Q2oL) (continued)

Treatment comparison (reference: placebo)	No. of studies	No. of participants	SMD (95% CI)		Corresponding 95% PrI	Magnitudes of Effect Size [†]	Evidence certainty
			Pairwise estimate	Network meta-analysis estimate			
Canakinumab	NA	NA	NA	NA	NA	NA	Insufficient
Cyclosporine	NA	NA	NA	NA	NA	NA	Insufficient
Dapsone	NA	NA	NA	NA	NA	NA	Insufficient
Hydroxychloroquine	NA	NA	NA	NA	NA	NA	Insufficient
Ligelizumab (72 mg)	NA	NA	NA	NA	NA	NA	Insufficient
Ligelizumab (240 mg)	NA	NA	NA	NA	NA	NA	Insufficient
Miltefosine	1	76	-0.11 (-0.58 to 0.36)	-0.11 (-0.58 to 0.37)	-1.15 to 0.93	NS	Moderate ^{‡¶}
Methotrexate	NA	NA	NA	NA	NA	NA	Insufficient
Omalizumab (75 mg)	1	157	0.03 (-0.29 to 0.34)	-0.02 (-0.31 to 0.26)	-0.65 to 0.61	NS	Low ^{‡¶}
Omalizumab (150 mg)	1	160	-0.18 (-0.49 to 0.13)	-0.23 (-0.51 to 0.06)	-0.85 to 0.39	NS	Moderate ^{‡¶}
Omalizumab (300 mg)	3	587	-0.66 (-0.87 to 0.46)	-0.66 (-0.84 to -0.48)	-1.05 to -0.26	Medium	High

[†]To estimate treatment effects, SMD of <0.2, 0.2-0.4, 0.5-0.7, and ≥0.8 are considered to be very small, small, medium, and large, respectively.

[‡]Within study bias.

[§]Reporting bias.

[£]Indirectness.

[¥]Imprecision.

[¶]Heterogeneity.

^{*}Incoherence.

Note: See Appendix-III for full details of criteria for downgrading quality of evidence.

Abbreviations: CI, confidence interval; CINeMA, Confidence In Network Meta-Analysis; CU-Q2oL, Chronic Urticaria Quality of Life Questionnaire; GRADE, Grading Recommendations Assessment, Development and Evaluation; NA, not applicable; NS, non-statistically significant; PrI, prediction interval; SMD, standardized mean difference.

Figure E1 PRISMA flow diagram

Abbreviations: PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses; RCTs, randomized controlled trials.

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Figure E2 Geometric network plots for secondary outcomes

(A) Patient unacceptability

(B) Impact on sleep

(C) Patient-reported chronic urticaria-specific measure: CU-Q2oL

Note: nodes indicate pharmacological treatments, and lines indicate trials performing the corresponding treatment comparison. The size of a node is proportional to the number of trials that included the corresponding treatment. The thickness of the lines corresponds to the number of trials performing each comparison (also green and yellow lines represent trials with a low risk of bias and some concerns according to the overall risk-of-bias assessment).

Abbreviations: CU-Q2oL, Chronic Urticaria Quality of Life Questionnaire

Figure E3 The surface under the cumulative ranking curve and cumulative probabilities plots

(A) Health-related quality of life

(B) Patient Unacceptability

(C) Impact on sleep

(D) Patient-reported chronic urticaria-specific measure: CU-Q2oL

Abbreviations: CAN, canakinumab; CU-Q2oL, Chronic Urticaria Quality of Life Questionnaire; CYC, cyclosporine; DAP, dapsone; HCQ, hydroxychloroquine; LIG72mg, ligelizumab 72 mg; LIG240mg, ligelizumab 240 mg; MIL, miltefosine; MTX, methotrexate; OMA75mg, omalizumab 75 mg; OMA150mg, omalizumab 150 mg; OMA300mg, omalizumab 300 mg.

Figure E4 Comparison-adjusted funnel plot

(A) Health-related quality of life

(B) Patient unacceptability

(C) Impact on sleep

(D) Patient-reported chronic urticaria-specific measure: CU-Q2oL

Abbreviations: CU-Q2oL, Chronic Urticaria Quality of Life Questionnaire.

Appendix I PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-Analysis of Health Care Interventions^{E13}

Section/Topic	Item #	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review <i>incorporating a network meta-analysis (or related form of meta-analysis)</i> .	Page 1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: Background: main objectives Methods: data sources; study eligibility criteria, participants, and interventions; study appraisal; and <i>synthesis methods, such as network meta-analysis</i> . Results: number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; <i>treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.</i> Discussion/Conclusions: limitations; conclusions and implications of findings. Other: primary source of funding; systematic review registration number with registry name.	Page 3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known, <i>including mention of why a network meta-analysis has been conducted</i> .	Page 6, 7
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 7
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	Page 8, eMethods
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. <i>Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).</i>	Page 8,9, Table E2, eMethods
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 8, eMethods
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Table E3

PICOS = population, intervention, comparators, outcomes, study design.

*Text in italics indicates wording specific to reporting of network meta-analyses that has been added to guidance from the PRISMA statement.

†Authors may wish to plan for use of appendices to present all relevant information in full detail for items in this section.

Appendix I PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-Analysis of Health Care Interventions^{E13} (Continued)

Section/Topic	Item #	Checklist Item	Reported on Page #
METHODS			
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page 10, eMethods
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 10, eMethods
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page 10, eMethods
Geometry of the network	S1	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	eMethods
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Page 10
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). <i>Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.</i>	Page 10, 11
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: • <i>Handling of multi-arm trials;</i> • <i>Selection of variance structure;</i> • <i>Selection of prior distributions in Bayesian analyses; and</i> • <i>Assessment of model fit.</i>	Page 10, 11
Assessment of Inconsistency	S2	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	Page 11
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Page 11, 12

PICOS = population, intervention, comparators, outcomes, study design.

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†Authors may wish to plan for use of appendices to present all relevant information in full detail for items in this section.

Appendix I PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-Analysis of Health Care Interventions^{E13} (Continued)

Section/Topic	Item #	Checklist Item	Reported on Page #
METHODS (continued)[†]			
Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: • Sensitivity or subgroup analyses; • Meta-regression analyses; • <i>Alternative formulations of the treatment network; and</i> • <i>Use of alternative prior distributions for Bayesian analyses (if applicable).</i>	Page 11-13
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure E1
Presentation of network structure	S3	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	Figure 1, Figure E2
Summary of network geometry	S4	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomised patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	Page 14, Table E14
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table I, Table E3-E5
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	Table I, Table E6
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. <i>Modified approaches may be needed to deal with information from larger networks.</i>	Page 14, 15, Table II, III, Figure 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. <i>In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.</i> If additional summary measures were explored (such as treatment rankings), these should also be presented.	Page 14-17, Table II, III, Table E7-E10
Exploration for inconsistency	S5	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, <i>P</i> values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	Page 16, Table E12, E13

PICOS = population, intervention, comparators, outcomes, study design.

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[†]Authors may wish to plan for use of appendices to present all relevant information in full detail for items in this section.

Appendix I PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-Analysis of Health Care Interventions^{E13} (Continued)

Section/Topic	Item #	Checklist Item	Reported on Page #
RESULTS (continued)[†]			
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	Page 14, Table E6
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses, <i>alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses, and so forth</i>).	Table E11
DISCUSSION			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	Page 18
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). <i>Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).</i>	Page 19, 20
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 20, 21
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	Page 2

PICOS = population, intervention, comparators, outcomes, study design.

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[†]Authors may wish to plan for use of appendices to present all relevant information in full detail for items in this section.

Appendix II eMethods

The pre-specified protocol for systematic review was registered at <http://crd.york.ac.uk/prospero>, an international prospective register of systematic reviews (registration number CRD42020196592). According to the pilot search result, we found a few relevant data of observational studies (cohort or case-control) with adequate adjustment for potential confounding factors. As such, we decided to include only randomized controlled trials in the present study to minimize the confounding by indication/contraindication. Based on the nature of the systematic review and meta-analysis study using the previously published information, ethical approval is not applicable. This systematic review and network meta-analysis involved no individual patient information, thus informed consent of participants was not required. In this systematic review and network meta-analysis, we followed the guidance of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA): extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions.^{E13}

Search strategy

we searched seven electronic databases in collaboration with an experienced medical librarian, including Medline, Embase, PubMed, Cochrane Library, Web of Science, Scopus, and CINAHL. We also search grey literature from Google Scholar, clinical trial register, preprints reports. The search strategy was constructed based on the combinations of main keywords or Medical Subject Headings regarding chronic spontaneous urticaria (e.g., “Chronic spontaneous urticaria” OR “Chronic idiopathic urticaria” OR “Refractory urticaria”). Moreover, search terms in relation to types of interventions were browsed according to the individual drugs or pharmacological classes. The comprehensive literature search was performed from the inception of each database to April 19, 2021, with no language restrictions. Additionally, potentially trials were also supplemented through searching reference lists of included studies, prior systematic reviews and network meta-analyses, and conference meetings from major international dermatology, allergy, and immunology congress.

Study eligibility criteria

Base on the comprehensive systematic search, a pair of investigators independently screened eligible articles according to the titles and abstracts. Next, relevant full-text articles were reviewed and selected based on the inclusion and exclusion criteria for the final set of included studies. Non-English language eligible studies were translated before the full-text appraisal. Any disagreement was resolved through a team discussion.

We included all randomized controlled trials (parallel and crossover trials) that: (i) included adolescent or adult (12 years or older) chronic spontaneous urticaria patients with an inadequate response to H1-antihistamines (standard dose or up-dosed); (ii) addressed the treatment response effects of the pharmacological interventions that account for health-related quality of life as the outcomes of interest; (iii) used validated measurement tools for health-related quality of life assessment; and (iv) comparison of intervention group against placebo, active comparator, or standard of care with study treatment period at least two weeks.

We excluded studies that: (i) were quasi- or cluster-randomized trials, non-randomized studies, n-of-one, case series/case report, reviews, systematic reviews and meta-analyses, and single-arm studies; (ii) disconnected node of interventions or used non-pharmacological interventions; and (iii) inadequately reported information or had no additional information received from the authors. We assembled the relevant information from the companion trials or post hoc analysis studies that contained overlapping participants and study periods.

Pharmacological interventions included in this systematic review and network meta-analysis were canakinumab, cyclosporine, dapsone, hydroxychloroquine, ligelizumab (72 mg and 240 mg), miltefosine, methotrexate, and omalizumab (75 mg, 150 mg, and 300 mg). Nonetheless, we excluded trials that investigate the body weight-based or immunoglobulin E (IgE) level-based dosing of omalizumab owing to the early studies among chronic spontaneous urticaria patients showed no benefit of this approach.^{E14,E15} In addition, trials that used terfenadine up-dosed or in combination with other treatments were also excluded from this review because this treatment is no longer available in the current practice. All placebo across the included trials was defined as standard dose or up-dosed of H1-antihistamines in conjunction with the rescue medications.

Outcomes of interest

The primary outcome of interest was overall changed in patient-reported health-related quality of life using the multidimensional general- or dermatology-specific measures, such as the Dermatology Life Quality Index (DLQI)^{E16}, Medical Outcomes Study Survey-Short Form 12 items (MOSS SF-12)^{E17}, or others validated instruments. When applicable, we preferred to use the DLQI as the patient-reported outcome instrument to capture the change in CSU patients' health-related quality of life. The DLQI is a well-established instrument that has been validated and used in various dermatology populations including CSU trials.^{E16,E18} Moreover, we also divided the duration study treatment with respect to the change in health-related quality of life from the baseline into 12 weeks or less and greater than 12 weeks to establish the evidence of treatment response in intermediate- and long-term effects.

The additionally secondary outcomes were (i) patient unacceptability, defined as all-cause study withdrawals; (ii) patient-reported chronic urticaria-specific or angioedema-specific measures (e.g., Chronic Urticaria Quality of Life questionnaire [CU-Q2oL]^{E19} or Angioedema QoL Questionnaire [AE-QoL]^{E20}; (iii) impact on sleep (e.g., sleep quality, insomnia, and sleep problems); (iv) symptom burden (e.g., fatigue, dyspnea, pain, difficulty in eating or swallowing); (v) psychosocial aspects, including depressive symptoms, anxiety, distress, and well-being; (vi) work impairment (e.g., absenteeism, presenteeism, work productivity and/or school performance); and (vii) healthcare utilization (e.g., emergency/unplanned visit during follow-up and costs of care).

Data extraction

Two investigators independently extracted the pre-specified information using a standardized approach to gather data as follows:

- (i) Trial characteristics (e.g., first author's name, study population [definition of H1-antihistamine-refractory chronic spontaneous urticaria], study design, study setting, country enrollment, sample size, and study treatment period)
- (ii) Participants characteristics (e.g., mean or median age of study participants, the proportion of females, race/ethnic, duration of chronic spontaneous urticaria, severity of urticaria symptoms [defined as urticaria activity score over 7 d, UAS7], body weight/body mass index, mean immunoglobulin E, positive autologous serum skin test, *Helicobacter pylori* infection, concomitant chronic inducible urticaria, history of allergy, or other systemic diseases)
- (iii) Specific pharmacological intervention and control group (individual treatments comparison, specific dose of drug, route of administration, concomitant and rescue medications)
- (iv) Predefined outcomes of interest, including details of instruments that are used to assess the outcomes of interest

Where the quantitative data were not obtained, we visualized the published figures via the WebPlotDigitizer 4.4: <https://automeris.io/WebPlotDigitizer> to extract the specific numerical values. In cases where the published information incomplete/unclear, we contacted the corresponding author for further clarification. Nevertheless, if the authors did not reply after three attempts of reach out, we decided to use the most relevant published data or excluded the study in our analyses.

In cases the mean and standard deviation (SD) values of the continuous outcome parameters were not provided, we calculated the sample mean and its SD according to the sample size, median, range, and/or interquartile range as described elsewhere.^{E21} As not all studies used the uniform instrument, we estimated treatment effects using mean change in any continuous outcome parameters from

baseline to endpoint. However, if unavailable, we calculated with the formula: $\Delta \text{value}_{\text{change}} = \text{value}_{\text{endpoint}} - \text{value}_{\text{baseline}}$, in which $\text{SD}_{\text{change}}^2 = [\text{SD}_{\text{baseline}}^2 + \text{SD}_{\text{endpoint}}^2 - (2 \times \rho \times \text{SD}_{\text{baseline}} \times \text{SD}_{\text{endpoint}})]$, where ρ indicate for the correlation coefficient. If the ρ was not available, we used a value of 0.5 for the correlation coefficient between the baseline and end of treatment follow-up, with equal variances among the intervention and control groups.^{E22} Moreover, a 0.5 cells correction was employed for any binary outcome parameters which particular studies reported with zero events.^{E23} Two investigators independently cross-checked the final set of data extraction. Any discrepancies were concluded through a team discussion.

Risk-of-bias assessment

According to the Cochrane revised tool for risk-of-bias assessment (RoB 2)^{E24}, two investigators independently critically evaluated the methodological quality of the included studies in terms of the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. We also classified the overall risk of bias rating for each included study into low, some concerns, or high risk of bias.

Statistical analysis

First, we performed a pairwise meta-analysis using DerSimonian-Laird random-effects model, which provided more conservative results and addressed the highest generalizability in the estimated treatment effects.^{E25} The effect estimates of direct treatment comparisons were pooled and expressed as standardized mean differences (SMD) and odds ratios (ORs) along with the 95% confidence interval (95% CIs). The heterogeneity in each direct comparison was assessed using the Cochran Q test with a *P*-value of less than 0.10. The degree of inconsistency across the included studies was assessed using the I^2 and tau-squared (τ^2) statistics. We categorized the degree of inconsistency as low ($I^2=20.0\%$, $\tau^2=0.04$), moderate ($I^2=50.0\%$, $\tau^2=0.16$), and high ($I^2=75.0\%$; $\tau^2=0.36$).^{E26} In cases where each outcome of interest included studies 10 or more, we visualized funnel plots and assessed publication bias using Begg's and Egger's tests, with a *P*-value of less than 0.10.^{E27,E28}

Second, we performed a random-effects model framework to incorporate direct and indirect treatment comparisons that were again expressed as SMDs or ORs with corresponding 95% CIs. The restricted maximum likelihood method was used to analyzed network effect estimates for each outcome of interest. The network meta-analysis integrates aggregated data through direct evidence and indirect evidence for every treatment comparison. For example, if there are studies that directly compare omalizumab with dapson and studies that compare omalizumab with cyclosporine, but lack of study that directly compares dapson with cyclosporine, network meta-analysis resulted in allows indirect

effect estimates of dapstone versus cyclosporine via the other treatment comparisons. The surface under the cumulative ranking curve (SUCRA) was estimated to create and rank a hierarchy of pharmacological treatment for each outcome of interest. A higher SUCRA score indicates a higher probability ranking for outcomes of interest (e.g., better treatment for change in health-related quality of life from baseline).^{E29}

We attempted to assess the transitivity assumption by exploring the distribution of participants and study characteristics across all included studies. These included mean participant age, the proportion of (female sex, angioedema, positive autologous serum skin test), the definition of H1-antihistamines-refractory chronic spontaneous urticaria, mean duration of chronic spontaneous urticaria, and baseline severity of urticaria symptoms (UAS7). A common heterogeneity estimate was reported as the between-study variance (τ^2) for each outcome of interest. Statistical incoherence assumption (disagreements between direct and indirect evidence) was evaluated using: (i) loop-specific approach in which assess for inconsistency in every closed loop of evidence; and (ii) the design-by-treatment interaction model in which assess for inconsistency through all possible sources in the network conjointly.^{E30} We assessed potential small-study effects from small trials using comparison-adjusted funnel plot symmetry. To account for a predicted range of the true treatment effect in an individual study, we estimated the 95% prediction intervals, which also provide the expected uncertainty about the estimate of a future study.^{E31}

Preplanned subgroup analysis was performed to assess the potential effect modifiers based on age (less than 18, 18 to 65, and more than 65 years), sex, baseline CSU severity (UAS7 less than 28 versus 28 or over), presence with angioedema (yes versus no), positive ASST (yes versus no), and sample size (participants less than 100 versus 100 or over). To explore reasons for heterogeneity, network meta-regression analysis was also performed by adjusting the covariates as mentioned above into the NMA model.

A set of sensitivity analyses were conducted to assess the robustness of primary findings by (i) assuming a p value of 0.7, in cases with missing correlation coefficients for continuous outcomes (ii) restricting the analysis to studies that using the DLQI for health-related quality of life measure; (iii) excluding trials with crossover design; (iv) excluding single-center trials; and (v) limiting the analysis to trials with low risk of bias.

Appendix III Criteria of GRADE assessment by CINeMA^{E32,E33}

Judgement	Criteria	Instruction for downgrading
Within-study bias	- Within-study bias was evaluated by majority of risk of bias assessment results within each comparison - We increased the concern to one level for comparisons with single study only	- Major concerns: downgrade the evidence one level - Some concerns: downgrade the evidence one level with 2 or more some concerns in other judgements
Reporting bias	- Reporting bias was evaluated by non-statistical consideration of likelihood of non-publication of evidence - We increased the concerns to one level for outcomes with evidence of small study effects in the network by comparison adjusted funnel plot	- Major concerns: downgrade the evidence one level - Some concerns: downgrade the evidence one level with 2 or more some concerns in other judgements
Indirectness	- Populations among studies were assessed by distributions of age, gender, and comorbidities - For continuous outcomes, outcomes assessment within each comparison was evaluated by the directness of validated measurement tools	- Major concerns: downgrade the evidence one level - Some concerns: downgrade the evidence one level with 2 or more some concerns in other judgements
Imprecision	- Imprecision was focused on width of CI based on a clinically important mean difference of 0.2 for continuous outcomes and odds ratio of 1.2 for binary outcomes - We increased the concern to one level if the width of CI is between 4 times and 10 times of lower limit - The concern level was increase two levels if the width of CI is above 10 times of lower limit	- Major concerns: downgrade the evidence one level - Some concerns: downgrade the evidence one level with 2 or more some concerns in other judgements
Heterogeneity	- Heterogeneity was evaluated according to the CINeMA documentation by variability of effects in relation to the clinically important size of effect and between-study variance for the network meta-analysis - We increased the concern to one level if there is no information regarding between-study heterogeneity for each direct comparison or I^2 index >50% in the direct comparison or inconsistency between 95% CI and 95% PrI	- Major concerns: downgrade the evidence one level - Some concerns: downgrade the evidence one level with 2 or more some concerns in other judgements
Incoherence	- Incoherence was evaluated by the design-by-treatment intervention model globally and the loop specific approach - We increased the concern to one level if there evidence of incoherence in the agreement between the main analysis and a set of sensitivity analyses	- Major concerns: downgrade the evidence one level - Some concerns: downgrade the evidence one level with 2 or more some concerns in other judgements

Quality of the evidence (GRADE):

High quality: further research is very unlikely to change our confidence in the estimate of effect

Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate

Very low quality: we are very uncertain about the estimate

Abbreviations: CI, confidence interval; CINeMA, Confidence In Network Meta-Analysis; GRADE, Grading Recommendations Assessment, Development and Evaluation; PrI, prediction interval.

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