Biologic Drugs for Nonasthma Indications: Clinical Evidence Update

Systematic Review

Washington P&T Committee Meeting

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Presented by Wesley Lindsey, PharmD

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Overview

- Background
- PICOS
- Key Questions
- Methods
- Findings
- Discussion

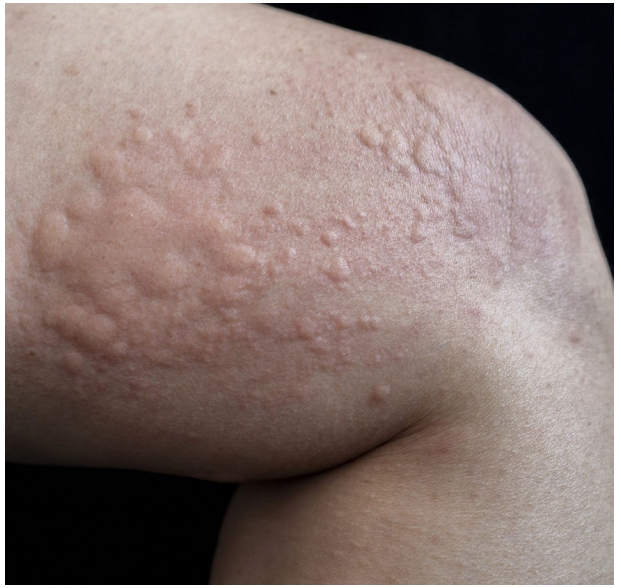
Abbreviations

- AE: adverse event
- CI: confidence interval
- CRS: chronic rhinosinusitis
- CRSwNP: chronic rhinosinusitis with nasal polyps
- CSU: chronic spontaneous urticaria
- DERP: Drug Effectiveness Review Project
- EGPA: eosinophilic granulomatosis with polyangiitis
- FDA: US Food and Drug Administration
- GRADE: Grading of Recommendations, Assessment, Development, and Evaluation
- HES: hypereosinophilic syndrome
- HR: hazard ratio
- PN: prurigo nodularis
- QoL: quality of life
- PDUFA: Prescription Drug User Fee Act
- RCT: randomized controlled trial
- RoB: risk of bias
- SAE: serious adverse event
- SQ: subcutaneous (drug delivery)

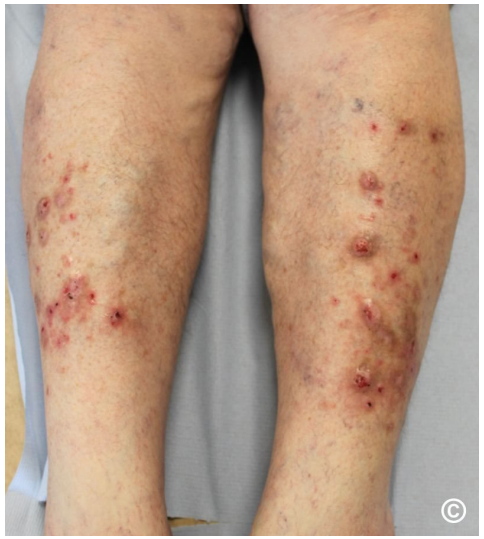
- *For common CRS measures, see slide 20*
- *For common CSU measures, see slide 30*
- *For common PN measures, see slide 48*

Background and Context

- Nonasthma inflammatory disorders can have a significant impact on patient QoL and well-being
- Associated with loss of smell/taste, impaired sleep, itching, and reduced mental and emotional health
- Biologic drugs can be used to influence the inflammation process and improve symptoms associated with these disorders



Source. oregonmedicalresearch.com



Source. pcds.org.uk/clinical-guidance

Previous Report

Biologic Drugs for Nonasthma Indications: Clinical Evidence

Systematic Review

October 2021

PICOS *(1 of 3)*

- **Populations:**
  - Adults and children with a nonasthma condition of interest
    - Chronic rhinosinusitis (CRS) with or without nasal polyps
    - Chronic spontaneous urticaria (CSU)
    - Eosinophilic granulomatosis with polyangiitis (EGPA)
    - Hypereosinophilic syndrome (HES)
    - Prurigo nodularis (PN)

PICOS *(2 of 3)*

- **Interventions:**
  - FDA-approved interventions
    - Dupilumab (Dupixent)
    - Mepolizumab (Nucala)
    - Omalizumab (Xolair)
  - Pipeline agents
    - Benralizumab (Fasenra)
    - Depemokimab
    - Lirentelimab
    - Tezepelumab (Tezspire)
- **Comparators:**
  - Another listed intervention
  - Topical prescription therapies
  - Standard of care
  - Placebo

PICOS *(3 of 3)*

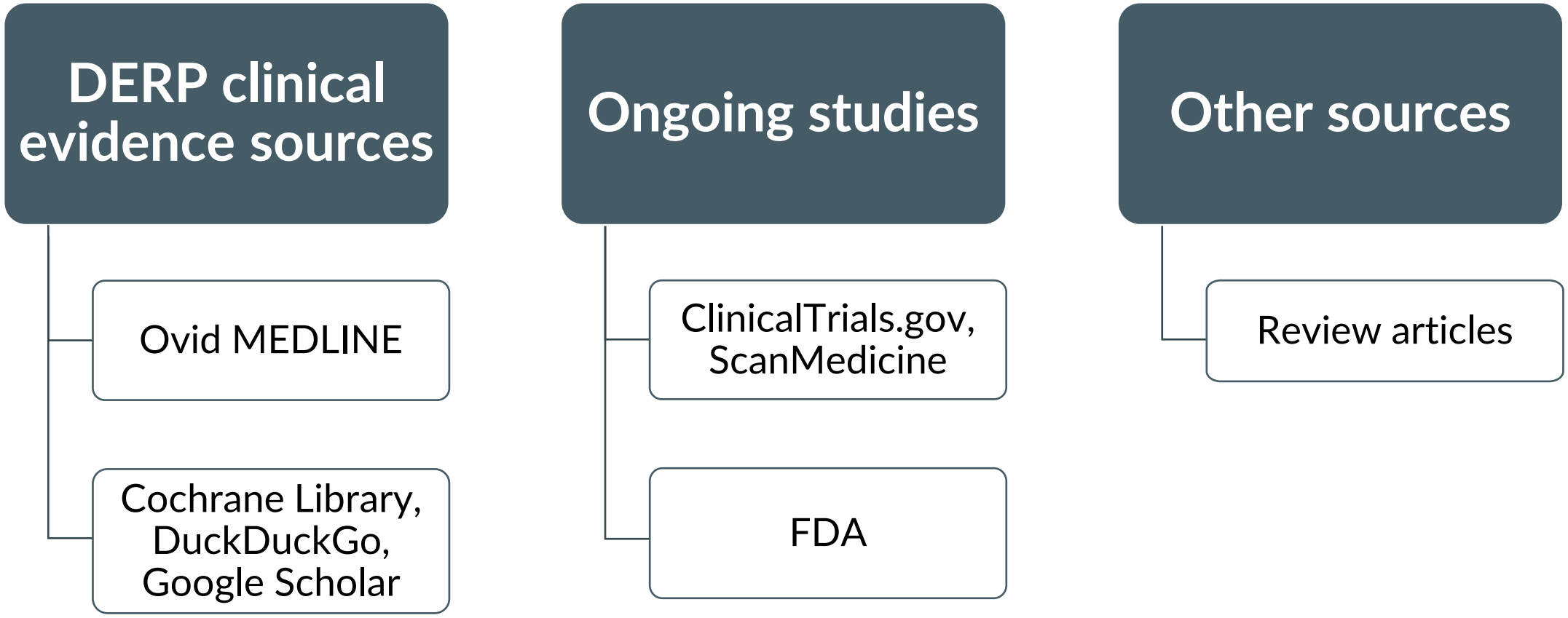
- **Outcomes:**
  - Condition-specific outcomes
  - Symptom control
  - Quality of life (QoL)
  - Severe exacerbations
  - Hospital admissions
  - Mortality
  - Adverse events (AEs)
  - Serious adverse events (SAEs)
- **Study Designs:**
  - Randomized control trials (RCTs)
  - Studies from countries that are *very high* on the United Nations Human Development Index

Key Questions

1. Effectiveness
    a. Variation by patient characteristic (e.g., age, severity of disease)
2. Harms
    a. Variation by patient characteristic (e.g., age, severity of disease)
3. Characteristics of ongoing studies and selected pipeline agents (with a PDUFA date within the next 12 months)

Methods

Methods



Methods

- Searched DERP clinical evidence sources from January 2021 to August 5, 2024, for previously reviewed therapies
- From no date limitation to August 5, 2024, for new therapies and indications
- Examined reference lists of systematic reviews
- Assessed RoB of included studies
- Used GRADE approach for overall certainty of evidence for critical outcomes
- Searched ClinicalTrials.gov, ScanMedicine, and FDA resources for ongoing studies

DERP Risk of Bias Assessment

- **Low**

  Clear reporting of methods and mitigation of potential biases and conflicts of interest

- **Moderate**

  Incomplete information about methods that might mask important limitations or a meaningful conflict of interest

- **High**

  Clear flaws that might introduce serious bias

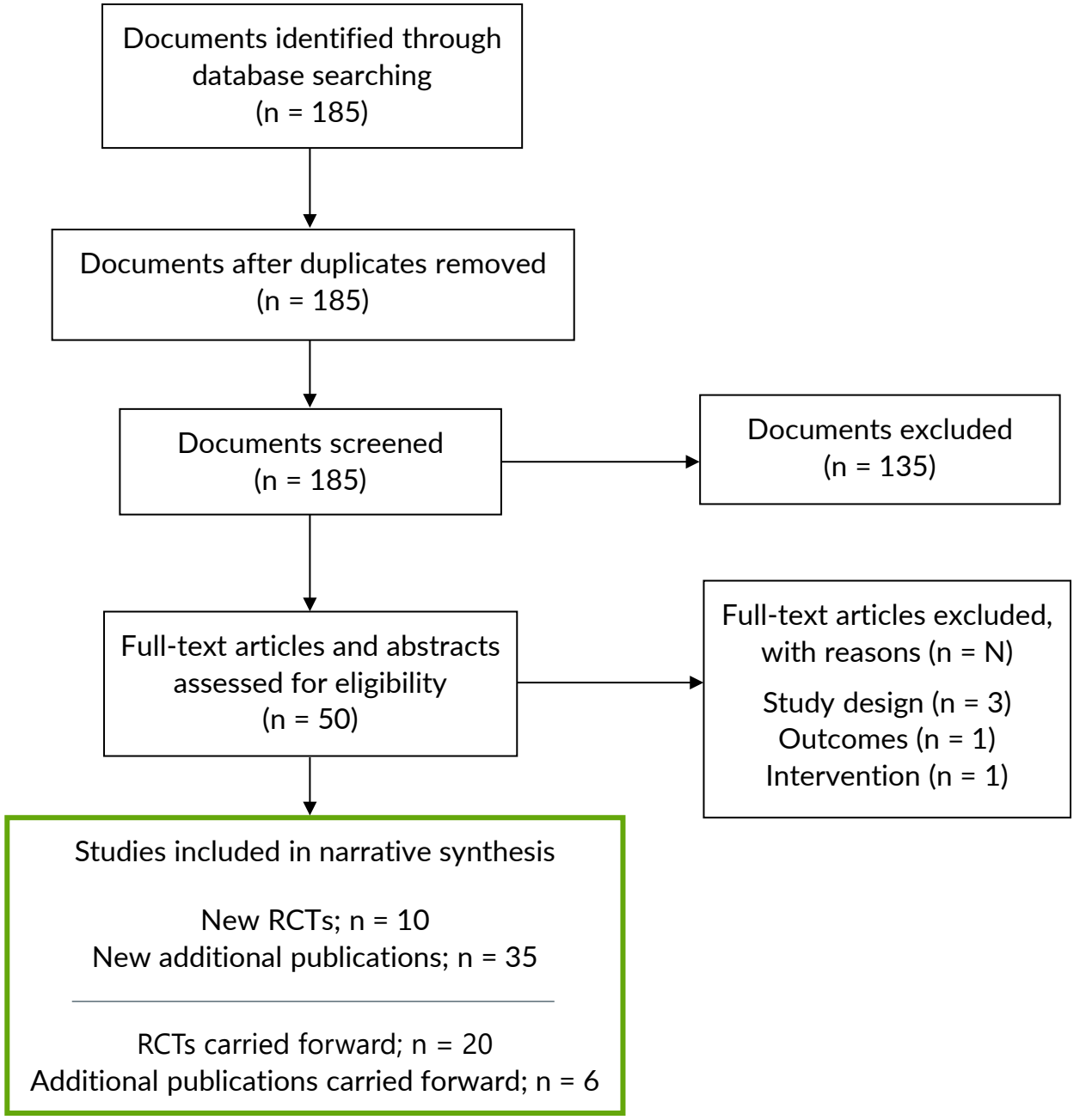
GRADE Certainty of Evidence

Outcomes rated: Various depending on nonasthma indication

- **High** *(RCTs start here)*
  Very confident that the estimate of effect of intervention on outcome lies close to the true effect
- **Moderate**
  Moderately confident in estimate of effect of intervention on outcome; true effect is likely close to estimate, but possibly different
- **Low** *(nonrandomized studies start here)*
  Little confidence in estimate of effect of intervention on outcome; true effect may be substantially different from estimate
- **Very Low**
  No confidence in estimate of effect of intervention on outcome; true effect is likely substantially different from estimate

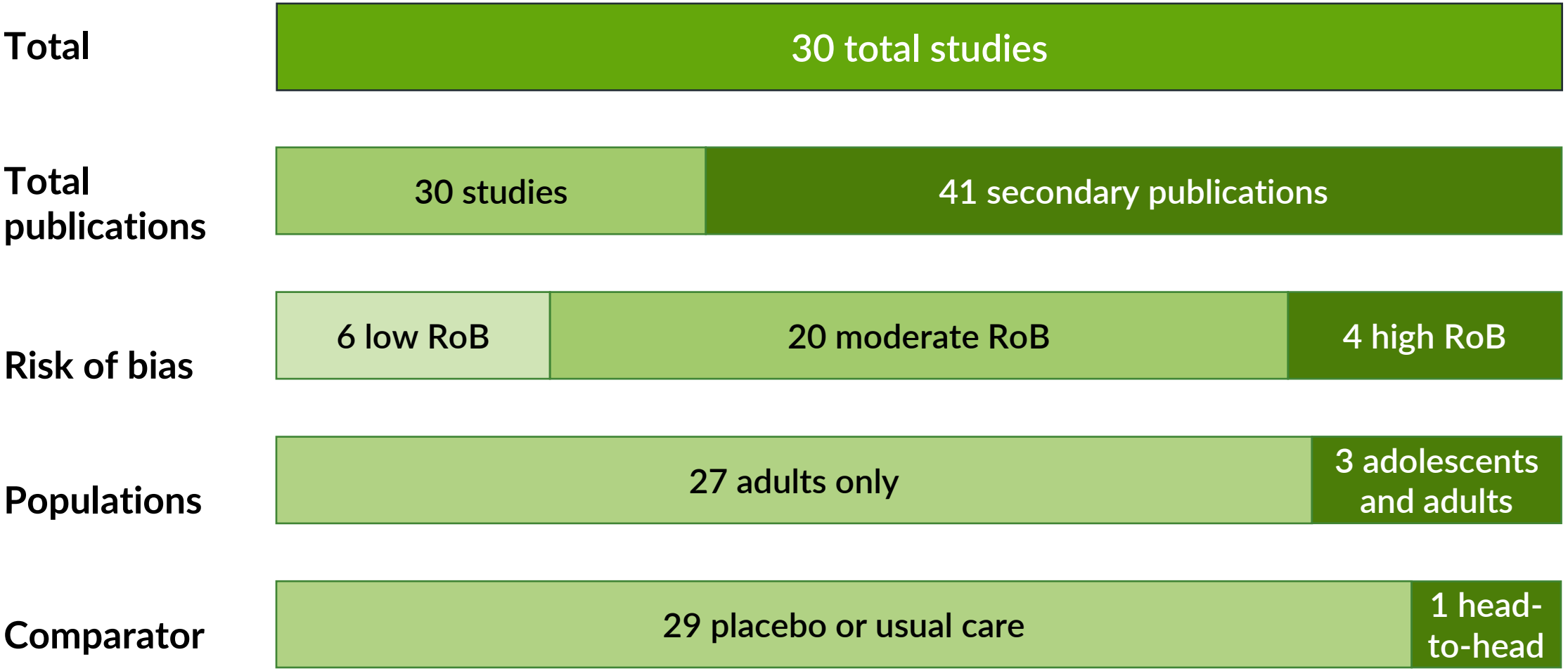
Findings

Updated Study Flow Diagram



Findings: Study Characteristics: New

Findings: Study Characteristics: Total



Findings

Chronic Rhinosinusitis (CRS) With or Without Nasal Polyps

Assessments and Questionnaires for CRS and CRSwNP

Measure	Abbreviation	Meaning	Scoring
Nasal Congestion Score	NCS	Higher score indicates worse disease state status	0 to 3
Nasal Polyp Score	NPS	Higher score indicates worse disease state status	0 to 8
Sino-nasal Outcome Test (20 questions)	SNOT-20	Lower score indicates better disease control and quality of life	0 to 110
Sino-nasal Outcome Test (22 questions)	SNOT-22	Lower score indicates better disease control and quality of life	0 to 112

Characteristics of Included Studies for CRS: New

Author, Year	Study Design	Interventions and Sample Sizes	Study Duration	Risk of Bias
Bachert et al., 2022	Randomized, double-blind, placebo-controlled, parallel group	• Benralizumab 30 mg SQ every 4 weeks for 3 doses, then every 8 weeks until endpoint: n = 207 • Placebo SQ: n = 206	56 weeks	Low
Tverskey et al., 2021	Randomized, double-blind, placebo-controlled, parallel group	• Benralizumab 30 mg SQ every 4 weeks: n = 12 • Placebo SQ every 4 weeks, n = 12	24 weeks	Moderate
Takabayashi et al., 2021	Randomized, double-blind, placebo-controlled, parallel group	• Benralizumab 30 mg SQ single dose with placebo administered every 4 weeks thereafter: n = 22 • Benralizumab 30 mg SQ every 4 weeks for 8 weeks, n = 23 • Placebo SQ every 4 weeks, n = 11	24 weeks	Moderate
Fujidea et al., 2024	Randomized, double-blind, placebo-controlled, parallel group	• Mepolizumab 100 mg SQ every 4 weeks: n = 80 • Placebo, n = 83	52 weeks	Low

Characteristics of Included Studies for CRS: Total

Comparators	Age Range	Number of RCTs	Total N	Study Duration
Benralizumab vs. placebo	Adults	3	493	24 to 56 weeks
Dupilumab vs. placebo	Adults and adolescents	3	2,686	16 to 52 weeks
Mepolizumab vs. placebo	Adults	4	707	25 to 52 weeks
Omalizumab vs. placebo	Adults and adolescents	3	299	16 to 24 weeks

Findings: Benralizumab in CRSwNP

Improvement in NPS

- 3 RCTs, N = 493
- **GRADE: Low**
  - Significant improvement in 1 larger study and no change in 2 smaller studies

Improvement in SNOT-22

- 3 RCTs, N = 493
- **GRADE: Moderate**
  - No change in SNOT-22 scores compared with placebo

Time to nasal polyp surgery after starting therapy

- 1 RCT, N = 413
- **GRADE: Moderate**
  - No change in time to surgery compared with placebo

Findings: Benralizumab in CRSwNP

AEs

- 3 RCTs, N = 493
- **GRADE: High**
  - AEs were relatively mild, and no SAEs reported

Findings: Dupilumab in CRSwNP *(1 of 2)*

Improvement in FEV-1

- 3 RCTs, N = 2,686
- **GRADE: Moderate**
  - Dupilumab inconsistently improved FEV-1 from baseline compared with placebo: mean change range, 0.12 L to 0.34 L

Change from baseline in NPS

- 2 RCTs, N = 844
- **GRADE: Moderate**
  - Dupilumab significantly improved NPS compared with placebo: mean difference range, −1.6 to −3.5

Change from baseline in NCS

- 1 RCT, N = 784
- **GRADE: Moderate**
  - Dupilumab significantly improved NCS compared with placebo: mean difference range, −0.87 to −1.2

Findings: Dupilumab in CRSwNP *(2 of 2)*

Improvement in SNOT-22

- 3 RCTs, N = 2,686
- **GRADE: Moderate**
  - Dupilumab use was associated with a significant SNOT-22 score reduction compared with placebo

AEs

- 2 RCTs, N = 844
- **GRADE: Moderate**
  - Mild AEs were common, but no differences between study groups

Findings: Mepolizumab in CRSwNP

Improvement in NPS

- 4 RCTs, N = 707
- **GRADE: Low**
  - Significant improvement compared with placebo: mean change range, −0.8 to −1.3

Improvement in SNOT-22

- 3 RCTs, N = 684
- **GRADE: Moderate**
  - Improved SNOT-22 scores compared with placebo: mean change range,–10.7 to −16.5

AEs

- 4 RCTs, N = 707
- **GRADE: Moderate**
  - Mild AEs were common, but no differences between study groups

Findings: Omalizumab in CRSwNP

Improvement in NPS

- 2 RCTs, N = 303
- **GRADE: Low**
  - Improved NPS compared with placebo: mean change range, −0.59 to −1.14

Improvement in SNOT-22

- 2 RCTs, N = 279
- **GRADE: Moderate**
  - Improved SNOT-22 compared with placebo: mean change range, −15 to −16.1

Change in NCS

- 1 RCT, N = 265
- **GRADE: Moderate**
  - Omalizumab significantly improved NCS compared with placebo: mean change range, −0.50 to −0.55

Findings

Chronic Spontaneous Urticaria (CSU)

Description of Assessments and Questionnaires for CSU

Measure	Abbreviation	Meaning	Scoring
Angioedema Activity Score	AAS	Higher score indicates more activity	0 to 105
Dermatology Life Quality Index	DLQI	Lower score indicates better QoL	0 to 30
Hives Severity Score	HSS7	High score indicates more severity	0 to 21
Urticaria Activity Score	UAS	Higher score indicates more activity	0 to 6
Weekly Urticaria Activity Score	UAS7	Higher score indicates more activity	0 to 42
Weekly Itch Severity Score	ISS7	Higher score indicates more severity	0 to 21

Characteristics of Included Studies for CSU: New

Author, Year	Study Design	Interventions and Sample Sizes	Study Duration	Risk of Bias
Altrichter et al., 2024	Randomized, double-blind, placebo-controlled, phase 2b	• Benralizumab 30 mg; n = 60 • Benralizumab 60 mg; n = 60 • Placebo; n = 40	52 weeks	Low
Maurer et al., 2024	Randomized, double-blind, placebo-controlled, parallel group	CUPID A: . Dupilumab, n = 70 . Placebo, n = 68 CUPID B: . Dupilumab; n = 54 . Placebo; n = 54	24 weeks	Low
Goswamy et al., 2022	Randomized, double-blind, placebo-controlled, proof-of-concept, exploratory	• Omalizumab 300 mg SQ; n = 5 • Placebo; n = 5	24 weeks	High

Characteristics of Included Studies for CSU: Total

Comparators	Age Range	Number of RCTs	Total N	Study Duration
Benralizumab vs. placebo	Adults	1	160	52 weeks
Dupilumab vs. placebo	Adults	1	246	24 weeks
Omalizumab vs. placebo	Adults and adolescents	9	1,510	20 to 60 weeks

Findings: Benralizumab in CSU *(1 of 2)*

Improvement in ISS7

- 1 RCT, N = 155
- **GRADE: Moderate**
  - No change in ISS7 compared with placebo

Improvement in UAS7

- 1 RCT, N = 155
- **GRADE: Moderate**
  - No change in UAS7 compared with placebo

Participants with UAS7 score ≤ 6

- 1 RCT, N = 155
- **GRADE: Moderate**
  - No change in UAS7 compared with placebo

Findings: Benralizumab in CSU *(2 of 2)*

Participants with UAS7 = 0

- 1 RCT, N = 155
- **GRADE: Moderate**
  - No change in remission compared with placebo

Improvement in HSS7

- 1 RCT, N = 155
- **GRADE: Moderate**
  - No change in HSS7 compared with placebo

AEs

- 1 RCT, N = 155
- **GRADE: Moderate**
  - No notable differences compared with placebo

Findings: Dupilumab in CSU *(1 of 2)*

Improvement in UAS7

- 1 RCT, N = 246
- **GRADE: Moderate**
  - Dupilumab showed significant improvement compared with placebo

Improvement in ISS7

- 1 RCT, N = 246
- **GRADE: Low**
  - Scores improved in CUPID A study participants, but no improvement in CUPID B study participants: mean change, −4.2

Participants with UAS7 score ≤ 6

- 1 RCT, N = 246
- **GRADE: Moderate**
  - Dupilumab showed significant improvement compared with placebo

Findings: Dupilumab in CSU *(2 of 2)*

Participants with UAS7 score = 0

- 1 RCT, N = 246
- **GRADE: Moderate**
  - Dupilumab showed significant improvement compared with placebo in CUPID A study

Improvement in HSS7

- 1 RCT, N = 246
- **GRADE: Moderate**
  - Dupilumab showed significant improvement compared with placebo in both CUPID A and CUPID B studies

AEs

- 1 RCT, N = 246
- **GRADE: High**
  - AEs were relatively mild, and no SAEs were reported

Findings: Omalizumab in CSU

Improvement in UAS7

- 8 RCTs, N = 1,746
- **GRADE: High**
  - Omalizumab showed significant improvement compared with placebo: mean change range, −9.9 to −10.3

Improvement in ISS7

- 5 RCTs, N = 1,106
- **GRADE: Moderate**
  - Omalizumab showed significant improvement compared with placebo: mean change range, −1.1 to −4.5

Improvement in DLQI from baseline

- 7 RCTs, N = 1,132
- **GRADE: Moderate**
  - Omalizumab showed significant improvement compared with placebo

Findings

Eosinophilic Granulomatosis With Polyangiitis (EGPA)

Characteristics of Included Studies for EGPA: New

Author, Year	Study Design	Interventions and Sample Sizes	Study Duration	Risk of Bias
Wechsler et al., 2024	Multicenter, randomized, double-blind, active-controlled, parallel group	• Benralizumab 30 mg SQ every 4 weeks; n = 70 • Mepolizumab 300 mg SQ every 4 weeks; n = 70	52 weeks	Low

Characteristics of Included Studies for EGPA: Total

Comparators	Age Range	Number of RCTs	Total N	Study Duration
Benralizumab vs. mepolizumab	Adults	1	140	52 weeks
Mepolizumab vs. placebo	Adults	1	136	52 weeks

Findings: Benralizumab in EGPA

Remission

- 1 RCT, N = 140
- **GRADE: Moderate**
  - Benralizumab was noninferior to mepolizumab at 36 and 48 weeks

Relapse

- 1 RCT, N = 140
- **GRADE: Moderate**
  - Benralizumab was noninferior to mepolizumab at 36 and 48 weeks

AEs

- 1 RCT, N = 140
- **GRADE: Moderate**
  - No difference in AEs between benralizumab and mepolizumab

Findings: Mepolizumab in EGPA

Remission

- 1 RCT, N = 136
- **GRADE: Low**
  - Mepolizumab increased accrued time to remission compared with placebo

Relapse

- 1 RCT, N = 136
- **GRADE: Low**
  - Mepolizumab delayed time to relapse compared with placebo

AEs

- 1 RCT, N = 136
- **GRADE: Moderate**
  - No difference in AEs between mepolizumab and placebo

Findings

Hypereosinophilic Syndrome (HES)

Characteristics of Included Studies for HES: Total

Comparators	Age Range	Number of RCTs	Total N	Study Duration
Mepolizumab vs. placebo	Adults and adolescents	2	193	32 to 36 weeks

Findings: Mepolizumab in HES

Reduction in oral corticosteroid dosage

- 1 RCT, N = 85
- **GRADE: Moderate**
  - Mepolizumab significantly reduced the use of prednisone dosage during treatment when compared with placebo
    - HR, 2.90; 95% CI, 1.59 to 5.26; *P* < .01

Time to first flare

- 1 RCT, N = 108
- **GRADE: Moderate**
  - Occurrence of flares with mepolizumab was 50% lower than with placebo

AEs

- 2 RCTs, N = 193
- **GRADE: Low**
  - Mepolizumab showed significant improvement compared with placebo

Findings

Prurigo Nodularis (PN)

Characteristics of Included Studies for PN: New

Author (Year)	Study Design	Interventions and Sample Sizes	Study Duration	Risk of Bias
Yosipovitch et al., 2023	Multicenter, randomized, double-blind, placebo-controlled, parallel-group	• Dupilumab 300 mg SQ every 2 weeks; n = 75 (PRIME) and n = 78 (PRIME 2) • Placebo every 2 weeks; n = 76 (PRIME) and n = 82 (PRIME 2)	24 weeks	Low

Description of Assessments and Questionnaires for PN

Measure	Abbreviation	Meaning	Scoring
Worst Itch Numeric Rating Scale	**WI-NRS**	Higher score indicates greater intensity	0 to 10
Skin Pain Numeric Rating Scale	**Skin Pain-NRS**	Higher score indicates greater pain	0 to 10
Sleep Numeric Rating Scale	**Sleep-NRS**	Higher score indicates better sleep quality	0 to 10
Dermatology Life Quality Index	**DLQI**	Higher score indicates higher impairment on QoL	0 to 30
Investigator's Global Assessment for Prurigo Nodularis–Stage	**IGA PN-S**	Higher score indicates greater intensity of pruritus	0 to ≥ 100

Findings: Dupilumab in PN *(1 of 2)*

Improvement in WI-NRS

- 2 RCTs, N = 311
- **GRADE: Moderate**
  - Dupilumab improved WI-NRS compared with placebo

Improvement in Skin Pain-NRS

- 2 RCTs, N = 311
- **GRADE: Moderate**
  - Dupilumab improved Skin Pain-NRS compared with placebo

Improvement in Sleep-NRS

- 2 RCTs, N = 311
- **GRADE: Moderate**
  - Dupilumab improved Sleep-NRS compared with placebo

Findings: Dupilumab in PN *(2 of 2)*

Improvement in DLQI

- 2 RCTs, N = 311
- **GRADE: Moderate**
  - Dupilumab improved DLQI compared with placebo

Improvement in IGA PN-S

- 2 RCTs, N = 311
- **GRADE: Moderate**
  - Dupilumab improved IGA PN-S compared with placebo

AEs

- 2 RCTs, N = 311
- **GRADE: Moderate**
  - AEs with dupilumab and placebo were similar

Findings

Ongoing Studies

Ongoing Studies: CRSwNP

Comparators	Estimated Enrollment	Outcomes	Estimated Completion Date
Depemokimab vs. placebo	264	• NPS • SNOT-22 • Time to nasal surgery	August 2024
Depemokimab vs. placebo	277	• NPS • SNOT-22 • Time to nasal surgery	August 2024
Mepolizumab vs. nasal polypectomy	75	• NPS • SNOT-22	December 2024
Mepolizumab vs. placebo	90	• SNOT-22 • Inflammatory biomarkers	June 2025
Mepolizumab vs. dupilumab	220	• NPS • SNOT-22 • Time to nasal surgery	March 2026
Tezepelumab vs. placebo	416	• NPS • SNOT-22 • Time to nasal surgery	December 2024

Ongoing Studies: CSU

Comparators	Estimated Enrollment	Outcomes	Estimated Completion Date
Omalizumab, multiple regimens	40	• Urticaria Control Test • UAS7 • DLQI	June 2025
Tezepelumab vs. placebo	183	• UAS7 • DLQI	April 2023

Ongoing Studies: EGPA

Comparators	Estimated Enrollment	Outcomes	Estimated Completion Date
Depemokimab vs. mepolizumab vs. placebo	160	• BVAS score • Relapse • Oral corticosteroid usage	November 2025
Dupilumab vs. placebo	64	• Eosinophil counts • Lumen imaging probe	December 2027
Mepolizumab vs. placebo vs. cyclophosphamide/ azathioprine	100	• Prednisone dosage • Relapse • SF-36 • Eosinophil counts	November 2025
Tezapelumab vs. placebo	66	• BVAS score • Relapse • Oral corticosteroid usage	October 2025

Abbreviations. BVAS: Birmingham Vasculitis Activity Score; SF-36: 36-item Short Form Survey.

Ongoing Studies: HES

- None

Ongoing Studies: PN

Comparators	Estimated Enrollment	Outcomes	Estimated Completion Date
Depemokimab vs. placebo	120	• Frequency of flares • Time to first flare • Fatigue	March 2026

Discussion

Discussion *(1 of 2)*

- Most interventions were associated with some level of improvement in their respective outcomes
  - Benralizumab outcomes were inconsistent in CRSwNP
  - Benralizumab showed a lack of efficacy in CSU
- Benralizumab was noninferior to mepolizumab for EGPA in the lone head-to-head study reviewed
- Overall lack of head-to-head studies makes relative assessments of place-in-therapy difficult
- New biologic agents are being evaluated for these disease states

Discussion *(2 of 2)*

- GRADE ratings were generally *moderate* for clinical efficacy outcomes, with ratings being performed on a relatively small number of studies
- GRADE ratings were consistently higher for AE outcomes, with studies generally reporting mild AE profiles and very few SAEs or unexpected events
- Limitations
  - Small studies
  - Variety of outcome tools used
  - Lack of head-to-head evidence

Questions?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