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Early View

Review

Definitions of non-response and response to biological therapy for severe asthma: a systematic review

Ekaterina Khaleva, Anna Rattu, Chris Brightling, Andrew Bush, Arnaud Bourdin, Apostolos Bossios, Kian Fan Chung, Rekha Chaudhuri, Courtney Coleman, Ratko Djukanovic, Sven-Erik Dahlén, Andrew Exley, Louise Fleming, Stephen J Fowler, Atul Gupta, Eckard Hamelmann, Gerard H. Koppelman, Erik Melén, Vera Mahler, Paul Seddon, Florian Singer, Celeste Porsbjerg, Valeria Ramiconi, Franca Rusconi, Valentyna Yasinska, Graham Roberts, on behalf of the 3TR definition of response working group

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ABSTRACT

Background: Biologics have proven efficacy for patients with severe asthma but there is lack of consensus on defining response. We systematically reviewed and appraised methodologically developed, defined, and evaluated definitions of non-response and response to biologics for severe asthma.

Methods: We searched four bibliographic databases from inception to 15th March 2021 (PROSPERO: CRD42021211249). Two reviewers screened references, extracted data, assessed methodological quality of development, measurement properties of outcome measures and definitions of response based on COnsensus-based Standards for the selection of health Measurement Instruments (COSMIN). Modified GRADE approach and narrative synthesis were undertaken.

Results: Thirteen studies reported three composite outcome measures, three measures of asthma symptoms, one asthma control and one quality of life. Only four were developed with patient input; none were composite measures. Studies utilised 17 definitions of response: 10/17 (58.8%) were based on Minimal Clinically Important Difference (MCID) or Minimal Important Difference (MID) and 16/17 (94.1%) had high quality evidence. Results were limited by poor methodology for development process and incomplete reporting of psychometric properties. Most measures rated 'very low' to 'low' for quality of measurement properties and none met all quality standards.

Conclusion: This is the first review to synthesize evidence about definitions of response to biologics for severe asthma. While high quality definitions are available, most are MCIDs or MIDs which may be insufficient to justify continuation of biologics in terms of cost-effectiveness. There remains an unmet need for universally accepted, patient-centred, composite definitions to aid clinical decision making and comparability of responses to biologics.

Keywords: biological therapy, treatment response, severe asthma, outcome measures, validity.

Take home message: There are no patient-centred composite measures of response to biologics for severe asthma. Single outcome measures are available but do not meet quality standards. A composite measure is required that is developed with patients.

INTRODUCTION

According to the European Respiratory Society (ERS) / American Thoracic Society (ATS) guideline, severe asthma is defined as asthma requiring treatment based on GINA steps 4–5 for the previous year or oral corticosteroids (OCS) for ≥50% of the previous year either to prevent the disease becoming uncontrolled or disease which remains uncontrolled despite this therapy[1]. Even though severe asthma only affects 5% to 10% of the total population with asthma[1], it represents a significant socio-economic[2-6], psychological[7,8], and treatment[9] burden and is also be associated with risk of mortality[10,11].

Over the past decades, new biological drugs have demonstrated positive impact on the lives of many patients with severe asthma by reducing the frequency of exacerbations and dose of OCS and by improving lung function.[12-15] Recently, in addition to total IgE, blood eosinophil count and fractional exhaled nitric oxide (FeNO) have been suggested as a guide to initiate anti-IgE treatment in adolescents and adults[16].Furthermore, blood eosinophil counts have been used to select patients for anti-IL-5[16] in adults and FeNO/blood eosinophil count for Dupilumab[17] in adolescents and adults. Several studies have described the characteristics of patients who started biologics[18,19] and characteristics of responders to treatment[20-23]. It has been shown that some patients reached a 'super response'[24] or 'partial response'[25], whereas others experienced a 'non-response'[24] or even deterioration[26] of clinical and patient-reported outcome measures (PROMs).

Although many studies have measured responses to different biologics, there are no universally accepted criteria for what constitutes response, and the absence of guidance on criteria is reported as a high priority research gap in both children and adults.[27,28] Evidence about responder definitions is critical for understanding the effectiveness of treatment for patients, clinicians and regulatory bodies, such as the European Medicines Agency (EMA)[29] and the Food and Drug Administration (FDA)[30]. Minimal Clinically Important Difference (MCID)[31] and Minimal Important Difference (MID)[32] are often used for assessing responses: these are defined as the smallest relevant within-person change or group differences between treatments, respectively. According to the FDA report, it is useful to report intra-subject responses based on *a priori* responder definition.[30] In November 2016, a Task Force reached a consensus on a traffic-light system to classify patients as non-responders, intermediate- or super-responders.[33] They suggest that patients need to be on biological treatment for at least four months before an initial assessment of response can be determined.[33] However, this proposal has neither been validated nor further developed.

Given the unmet need to use consistent definitions of response for paediatric and adult patients, we aimed to 1) synthesize evidence about definitions of non-response and response to biological therapy used in patients with

severe asthma; 2) assess the quality of the evidence for these definitions, and 3) evaluate the development, measurement properties and quality of outcome measures as supporting evidence for the included definitions. We chose to restrict our systematic review to studies where definitions were methodologically developed, defined, and evaluated. Comprehensive assessment of response in clinical practice and trials using pre-specified consensus criteria should provide useful guidance for clinical decision making, allow comparison across studies, eliminate unnecessary treatment in patients with inadequate response and ensure that the high-cost associated with biological therapies[34] is justified[35].

METHODS

This was a systematic review conducted by the 3TR (Taxonomy, treatment, targets and remission)[36] respiratory work package members and external collaborators including academic clinicians, regulatory, patient, and pharmaceutical representatives from across Europe. It is registered with the International Prospective Register of Systematic Reviews (PROSPERO registration: CRD42021211249). Our aim was to look at response in severe asthma but in anticipation that the evidence base would be limited, we initially included studies of all severities of asthma. However, given that there is evidence for definitions of response to biological therapy for severe asthma, the protocol was revised to restrict the systematic review to studies of severe asthma. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist has been used to structure this article[37] (**Appendix 1).** The methods are briefly described here. Details are available in the supplementary materials.

Search strategy

Four databases were searched (Embase (OVID); MEDLINE (OVID); CINAHL (EBSCOhost, Cumulative Index to Nursing and Allied Health Literature); ISI Web of Science (Thomson Web of Knowledge)) using a search strategy developed on EMBASE (OVID) and then adapted for other databases **(Appendix 2).** In summary, the search strategy was designed to identify papers focused on *asthma* AND *a biological therapy* AND *response/treatment outcome/minimal important difference*. Databases were searched from the inception to 15th March 2021. Additional references were searched through the references cited by the identified studies, systematic reviews, reviews, guidelines or highlighted by experts in the field.

Inclusion criteria

Studies were eligible for inclusion if they met the following criteria:

- *Population:* children/adolescents (from 6 years until 17 years) and/or adults (≥18 years) with a diagnosis of severe asthma.
- *Intervention:* any biological therapy which was investigated and/or currently used for severe asthma.

- *Comparator:* any comparator, including placebo or no comparator.
- *Outcomes:* any definitions of non-response and response to biological therapy for severe asthma which were methodologically developed, defined, and evaluated. Sole or a composite of clinical, patient reported, biological and/or imaging outcome measures were eligible for inclusion. Additional evidence about these outcome measures including development (undertaken in studies of any severity of asthma) and validation (conducted in studies with biologicals for severe asthma) was included.
- *Study types:* randomised controlled trials, cross-sectional studies, controlled before-and-after studies, non-randomised controlled studies, case-control studies in humans, cohort studies, and consecutive case series (with a minimum of 10 participants) published as full-text articles and letters published in English were eligible for inclusion. Additional evidence about development and validation of outcome measures was considered from qualitative and validation studies.

Exclusion criteria

The following manuscripts were excluded from the analysis: systematic reviews and meta-analyses, narrative reviews, discussion papers, editorials, commentaries, case reports, animal studies, conference abstracts, studies not available in full form, published in a language other than English, unpublished material, non-asthma studies such as viral bronchiolitis or viral associated wheeze. Studies were also excluded if they only used outcome measures and definitions of response to assess treatment effectiveness or efficacy.

Study selection

All references were pooled and de-duplicated in Endnote version X9, and subsequently uploaded to Rayyan (rayyan.qcri.org), where any remaining duplicates were removed. Titles, abstracts, and full texts were independently screened by two reviewers (EK, AR) according to the above selection criteria and categorized as included, excluded or unsure. Any disagreements were resolved through discussion with a third reviewer (GR).

Data extraction, risk of bias assessment, quality, and synthesis of the results

Data extraction was based on the COSMIN (COnsensus-based Standards for the selection of Measurement Instruments) guideline[38] for outcome measures. Definitions of the measurement properties provided by COSMIN are in **Table S1** and criteria for good measurement properties (GMP) in **Table S2.**

Risk of Bias (RoB) of individual studies was assessed using the COSMIN checklist for PROMs[39,40] and composite outcome measures (COSMIN RoB for non-Patient Reported Outcomes)[41]. RoB for each measurement property in the validation studies was rated as very good, adequate, doubtful, or inadequate. The certainty of evidence was assessed using the modified Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach.[38,40,42] Data extraction, RoB assessment and modified GRADE were completed independently by two reviewers independently (EK, AR). Any discrepancies were resolved by discussion or by a third reviewer (GR). A

descriptive synopsis with summary data tables were produced, and results were summarized using narrative synthesis. Detailed methods are provided in **Appendix 3**. The results were reviewed and discussed within the Core Outcome Measures for Severe Asthma (COMSA) initiative[43] that included a multidisciplinary, European group of academic clinicians, regulatory, patient, and pharmaceutical representatives. The group aimed to select the core outcome measure sets for paediatric and adult severe asthma.

RESULTS

Description of studies

Our search strategy identified a total of 11588 papers and 11553 articles were excluded after title and abstract screening. The full text of 35 papers were assessed for eligibility, including 20 articles identified through review of citations. Thirteen papers were included in the systematic review of which three were about development of the outcome measures[44-46] , five were validation papers[47-51] and five[52-56] reported development and validation data in the same manuscript. **(Figure 1)**

Development and quality of definitions of non-response and response

The approach to development of definitions and their characteristics are shown in **Tables 1 and 2**. Definitions were developed for three composite asthma outcome measures[51-53], three asthma symptoms measures[49,50], one asthma control[55], and one quality of life (QoL) measure.[48] The following methods of development were used: consensus[53,55], anchor-based[48-51] and distribution-based[52] methods. Ten definitions measured response based on MCID[48,49,51] or MID[50,52] and seven[50,55] based on responder/non-responder levels. Omalizumab[48,51,52,55], brodalumab[50], benralizumab[48,53], reslizumab[48,53] and mepolizumab[48,49,53] were predominantly used in these studies. Response was evaluated at different time points including as early as 4 weeks[48] and up to 12 months[52]. Most definitions were developed for adults[48-50,52,53] while three were for adolescents[49,51,52] and one for children[51] with severe asthma. The quality of the evidence for definitions of response was rated as 'high' for all except 'moderate' for Asthma Severity Scoring System (ASSESS)[52] due to a lower number of patients taking biologics.

Development and content validity of the outcome measures

An overview of the developmental process and its quality are shown in **Table 2, S3.** The developmental process was predominantly rated as 'sufficient', while quality of evidence was mainly 'very low' to 'low', but 'moderate' for the Severe Asthma Questionnaire (SAQ)[45,54]. Three composite outcome measures were developed by physicians, including the FEOS (FEV1, Exacerbations, Oral Corticosteroids, Symptoms Score)[53] for adults, the ASSESS[52], which was adapted from the Composite Asthma Symptom Index (CASI)[56] for adolescents/adults and children with asthma, respectively. The Global Evaluation of Treatment Effectiveness (GETE)[55] scale was also developed by physicians. Only four outcomes were developed with patient input including the SAQ[45,54], Asthma

Symptom Diary (ASD)[44], Asthma Symptom Utility Index (ASUI)[49], and Asthma Symptom Index (ASI)[46] which was adapted from ASUI by excluding questions about medication side effects. A summary of key instrument characteristics and feasibility is in **Table 4, S4.**

Risk of bias and quality of evidence for validation studies of outcome measures

Validation data including RoB are shown in **Table S5-S7** and methodological quality of the outcome measures rated against criteria for GMP in **Table 3.** Overall, almost all outcome measures had 'inadequate' RoB due to lack of involvement of patients in the development, many measurement properties not being reported and none of the studies reporting cross-cultural validity including measurement invariance.

The GETE scale has patient and physician versions which demonstrated high quality of evidence for the construct validity, although there was a positive skew towards 'complete control of asthma' and 'marked improvement of asthma' possibly due to the ceiling effect.[55] CASI[56] showed insufficient responsiveness but 'high' quality of evidence. Sufficient measurement properties were rated for ASSESS, including test-retest reliability, construct validity and responsiveness to change while the quality was mostly 'very low'. ASUI[49] and ASI[49] performed similarly and showed sufficient rating against GMP criteria and 'low' to 'high' quality. The SAQ[47,48,54] again showed sufficient properties and 'very low' to 'moderate' quality of evidence. Only responsiveness to change was evaluated for ASD[50] as assessment of other measurement properties was not performed in patients taking biologics for severe asthma. The FEOS scale [53] only contains data about inter-rater agreement which was not possible to assess based on the COSMIN methodology.

DISCUSSION

This study aimed to review the literature on definitions of response and non-response to biological therapy for severe asthma. To the best of our knowledge, the current systematic review is the first to synthesise methodologically developed, defined, and evidenced definitions. We identified eight outcome measures including three composite outcome measures, three measuring asthma symptoms, one asthma control and one QoL measure. Studies utilised a variety of definitions of response criteria, mostly using MCIDs or MIDs where available and measured at different time-points for different biologics. Only the GETE[55] defined a non-response, while the FEOS [53] is a scale ranging from 0 to 100 (best), with no established cut-off for non-responders.

One of the aims of the review was to assess the development and measurement properties of the identified outcome measures. Results were limited by 'very low' to 'low' quality of evidence for the development process except for the SAQ[45,54], and incomplete reporting of measurement properties for all outcome measures. Based on the COSMIN guideline, none of the outcome measures met all the quality standards. Only four outcome measures were developed with patient input, even though this is considered as a vital step in ensuring that the

instrument is meaningful for patients. Responsiveness to change was rated as 'low' to 'very low' while definitions of response had 'high' quality except for ASSESS[52].

Evaluation of therapeutic response in asthma has received increased attention with the introduction of biological treatments to improve disease treatment and precision management.[57] More than 70% of patients achieved good or excellent response to omalizumab based on GETE[58]; however, this relies on a single global measure to reflect the heterogeneous response to biological treatment. Thus, the GETE does not discriminate the different effects of a treatment on different response areas, such as QoL, exacerbations, maintenance corticosteroid use and lung function. Two asthma symptoms questionnaires (ASUI and ASI[49]) were designed to assess cost-effectiveness of treatment, while ASD[50] is a symptom diary and might impose too much burden on participants of biological therapy trials. The SAQ[54], which was developed with patient input, showed the best quality of evidence, and was selected in the COMSA.[43,59]

Several composite outcome measures were identified. Neither CASI[56] nor ASSESS[52] include a QoL domain and CASI[56] does not assess maintenance OCS use; even though reduction in OCS use and improvement of QoL has been shown to be the best indicators of response to treatment for patients with severe asthma[60]. The two-point MID for ASSESS showed good specificity but poor sensitivity and the authors suggested that it should be interpreted with caution until more data are available[52]. The FEOS tool to quantify response[53] was developed for adults with severe asthma using novel methodology, but patients were not involved in the selection of outcome measures, and it may not also represent the perspectives of international stakeholders. Unlike the COMSA initiative[43], the validity of the included outcome measures for severe asthma was not assessed and exclusion of aspects such as QoL may not represent a patient-centred approach.

This systematic review did not identify any studies which validated definitions of response to biological therapy using clinical outcome measures in patients with severe asthma. Some data are available from the consensus statements, for example, the MID for FEV_1 is 0.20 L[13] or 10% improvement[61] and for FeNO a reduction of at least 20% for values over 50 ppb (or $\geqslant$10ppb for values lower than 50 ppb) should be used to indicate response to anti-inflammatory therapy.[62] While a published composite definition of exacerbation has been developed and validated in patients with severe asthma taking benralizumab, no MCID data are available yet.[63]

Most outcome measures identified in the systematic review utilised MCIDs or MIDs to assess response, but we do not regard these definitions as interchangeable; for example, in one paper the term MID was used when it would seem to be more appropriate to use MCID[51]. An improvement that patients might recognise as equivalent to MCID with an inhaled asthma therapy may potentially be rated as less than the MCID in the context of high cost[34,35] biologics administered by injection. Also, to be regarded as cost-effective a biological therapy will demand a greater magnitude of response than a less expensive asthma therapy. A further critical variable may be the duration of response, given the case reports of secondary loss of response[64] i.e. the loss of response during the treatment over time despite an initial primary response[65,66].

The concept of 'super-responders' to biological treatment has emerged recently.[24,67] In order to standardise the definition, a modified Delphi exercise among healthcare professionals has been conducted but there is a need to understand patient perspectives.[68] The rate of super-responders in patients prescribed anti-IL5 depending on criteria ranges from 14% to 28%[24,67,69], forming a small but important group. Super-response should be the ultimate goal of treatment. However, patients who fail to achieve such a level of improvement may still benefit from biological therapies. Nevertheless, consideration should be given in such cases as to whether a different biological may be more beneficial. Evaluation of a complete response, as in haematological disorders[70,71], may be inappropriate in severe asthma since only a very small percentage of patients experience remission[72].

Unfortunately, some patients with severe asthma do not respond to biological therapy and may even deteriorate. Differences in treatment response may be multifactorial, reflecting medicinal and/or subject variables including mechanisms of action, target, dose and interval of the biological drug or heterogeneity of asthma phenotypes[73]. For example, non-response might reflect differences in the pharmacokinetics of biological drugs; indeed monitoring plasma monoclonal antibody levels appears useful in various chronic diseases.[74-76]

Overall, assessing the non-response and response after several months of treatment with biologics facilitates cost control by reducing the duration of ineffective therapy, and should enable better quality of care and patient experience by prescribing alternative treatments including switching to another biological[77] if appropriate. The latter is especially important given the rapidly increasing number of therapeutic options for patients with severe asthma.[1,16]

Strengths and limitations

This systematic review was conducted by a diverse group of academic clinicians, patient representatives, regulatory, and pharmaceutical representatives. This was a strength because it meant that definitions were considered on clinical and patient-centred grounds. A comprehensive search was conducted in four databases and provides a summary of the robust research. Rigorous methods were used including RoB assessment and GMP based on COSMIN followed by the modified GRADE approach to rate the certainty of the evidence. Using transparent and validated COSMIN methodology helped to standardize the quality assessment of outcome measures and reduce bias. Many studies were excluded as they used arbitrary definitions of response; only methodologically developed definitions and validated outcome measures were considered for inclusion in the systematic review. Lastly, all studies used data from large number of paediatric and adult patients with severe asthma who were treated with a variety of biological therapies such as omalizumab, brodalumab, benralizumab, reslizumab and mepolizumab.

Nevertheless, we recognise several limitations. First, only studies published in English were included; however, we screened studies included in the guidelines, previous systematic reviews, references of identified articles, and reviews which made it highly unlikely that relevant studies were missed. Second, the search was conducted in 2021 as part of the development of the COMSA which was published in 2022.[43] Third, we only searched the

literature related to biological therapies and did not look at the evidence from response to non-biological asthma therapies. Biologics have different mechanisms of action, administration approaches, cost and potential adverse effects. Therefore, response criteria could differ with different patient views on what counts as beneficial response given these considerations. However, it may be possible to also learn from the response to other therapies such as to oral and inhaled corticosteroids in severe asthma. Fourth, definitions of therapeutic response were assessed at different time points which might make it difficult to come to definitive conclusions about non-responders and responders. Moreover, COSMIN suggest using the lowest score counts method to assess measurement properties, meaning that having higher quality scores on some items of the checklist were not considered and only the 'worst score' was reported. Lastly, it was not possible to run a meta-analysis due to low number of studies per outcome measure and only narrative synthesis was undertaken.

Policy implications and next steps

This systematic review aimed to inform clinicians, regulators, and policy makers about the gaps and highlight heterogeneity of the definitions used. Even though, asthma control questionnaire/test and asthma quality of life questionnaire are widely used in the phase 3 trials of asthma biologicals and in clinical practice, definitions of response including MCID or MID have never been specifically assessed in biologics. Further research should aim to explore the identified definitions as primary and secondary outcomes in clinical trials including phase 2 and 3 efficacy studies and assess MCID/MID of well-validated questionnaires in biological trials. There is also a need to methodologically develop patient-centred definitions of non-response and response to biological therapy for severe asthma for individual PROMs and clinical as well as a composite outcome measures. For example, based on COSMIN[40]methodology for assessing the content validity of PROMs, patients should be asked about their relevance, comprehensiveness and comprehensibility. Engagement of patients is a crucial aspect of the development of outcome measures to meet their needs and preferences as well as to inform health decisions.[78,79]

Given the above, we are planning to develop definitions of non-response and response to biological therapies for paediatric and adult severe asthma trials and clinical practice based on the COMSA selected among key stakeholder groups including patients with severe asthma.[43] We aim to standardise the definitions which will allow better tailoring of individual treatment and be used in future clinical trials for documenting therapeutic response. Furthermore, looking at multiple dimensions of asthma, such as exacerbations, QoL, asthma control, lung function in one single patient-centred composite would help to determine the correct sample size for future clinical trials, assist regulators in determining whether a new biological therapy is effective and identify predictors of treatment response. Use of such definitions will also help in better understanding the applicability of novel biomarkers such as volatile organic compounds[80], peripheral blood gene expression[81,82], and serum periostin[83] in the prediction and monitoring of response which have been shown to be promising in biological treatment for severe asthma.

CONCLUSION

This systematic review is the first to evaluate the quality of evidence for definitions of response to biological therapy for severe asthma and measurement properties of associated outcome measures. There are several high-quality definitions available for use which are mostly based on MIDs or MCIDs which might not be sufficient to justify continuation of biological therapy on cost-effectiveness criteria. Even though composite outcome measures are available and able to capture the multi-dimensional nature of severe asthma, none were developed with patient input and all lack a QoL component. The quality of evidence for the development and validation of the outcome measures was rated predominantly 'low' and 'very low' and none met all the methodological quality standards, highlighting an urgent unmet need. Therefore, the forthcoming 3TR project will aim to develop the definitions of non-response and response based on COMSA[43] with involvement of patient representatives and other key stakeholders. Future research will be needed to pilot these definitions in biological trials and to address practical implications for policy makers, research, and clinical practice. Knowing how to evaluate response to biologics using universally acceptable criteria would help in assessing effectiveness of novel therapies, improve clinical decision-making and the care of patients with severe asthma.

Author contributions

EK developed a protocol and a search strategy and GR, AR reviewed; EK and AR performed abstract screening, data extraction, COSMIN evaluation; EK synthesised the evidence and wrote the first draft of the manuscript. All authors critically reviewed the manuscript and approved the final version prior to submission.

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Conflict of interests

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Advisory Board Meetings from GSK, AZ, Teva, Novartis and Sanofi; and got support for attending meetings from AZ and Novartis, all outside the present work; reports being a member Member of the steering Committee of SHARP, Secretary of Assembly 5 (Airway diseases, asthma, COPD and chronic cough), European Respiratory Society and Vice-chair of Nordic Severe Asthma Network (NSAN). Kian Fan Chung has received honoraria for participating in Advisory Board meetings of GSK, AZ, Roche, Novartis, Merck, and Shionogi regarding treatments for asthma, chronic obstructive pulmonary disease and chronic cough and has also been renumerated for speaking engagements for Novartis & AZ. Rekha Chaudhuri has received lecture fees from GSK, AZ, Teva, Chiesi, Sanofi and Novartis; honoraria for Advisory Board Meetings from GSK, AZ, Teva, Chiesi, Novartis; sponsorship to attend international scientific meetings from Chiesi, Napp, Sanofi, Boehringer, GSK and AZ and a research grant to her Institute from AZ for a UK multi-centre study. Courtney Coleman declares funding received to support this work by European Lung Foundation from European Commission's Innovative Medicines Initiative 2 Joint Undertaking (JU) under grant agreement No. 831434 (3TR). Ratko Djukanovic declares funding from ERS, TEVA, GSK, Novartis, Sanofi and Chiesi for the SHARP CRC; consulting fees for Synairgen; honorarium for a lecture from GSK; participation on a Data Safety Monitoring Board or Advisory Board for Kymab (Cambridge) and shares in Synairgen outside of the submitted work. Sven-Erik Dahlen declares funding from 3TR IMI Grant; consulting fees from AZ, Cayman Co, GSK, Novartis, Regeneron, Sanofi and Teva; honoraria for lectures from AZ and Sanofi. Andrew Exley declared being a Minority shareholder in GlaxoSmithKline PLC. Louise Fleming declares participation in advisory boards and honoraria for lectures from Sanofi, Respiri UK, Astra Zeneca, Novartis and Teva outside of the scope of this publication. All payments were made to her institution. Atul Gupta received speaker and advisory board fees from GSK, Novartis, Astra Zeneca. Boehringer Ingelheim. AG Institution received research grants from GSK, Novartis, Astra Zeneca Boehringer Ingelheim. Eckard Hamelmann declares support from German Ministry of Education and Research (BMBF) and German Asthma Net (GAN) e.V.; funding for research in Severe asthma in children (CHAMP- 01GL1742D) and for Severe Asthma Register. Gerard H Koppelman reports receiving research grants from Lung Foundation of the Netherlands, Ubbo Emmius Foundation, H2020 European Union, TEVA the Netherlands, GSK, Vertex, outside this work (Money to Institution); he reports memberships of advisory boards to GSK and PURE-IMS, outside this work (Money to institution). Erik Melen has received consulting fees from AstraZeneca, Chiesi, Novartis and Sanofi outside the submitted work. Vera Mahler has no conflict of interest but declares that the views expressed in this review are the personal views of the author and may not be understood or quoted as being made on behalf of or reflecting the position of the respective national competent authority, the European Medicines Agency, or one of its committees or working parties. Florian Singer reports being an investigator for clinical trials promoted by Vertex and having received fees for lectures from Vertex and Novartis, outside the submitted work. Celeste Porsbjerg declares grants, consulting fees and honoraria from AZ, GSK, Novartis, TEVA, Sanofi, Chiesi and ALK (paid to institution and personal honoraria); participation in the Advisory Board for AZ, Novartis, TEVA, Sanofi and ALK, outside the submitted work. Valeria Ramiconi reports grants paid to EFA from Pfizer, Novartis, Astra Zeneca, Sanofi, Chiesi Farmaceutici, Regeneron, DBV Technologies, MSD, GSK, Aimmune, LeoPharma, Abbvie, Boehringer

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Table 1. Characteristics of included studies.

Reference, year	Scale	Study design	N	Age (y), mean (SD) or range	Patient characteristics	Asthma severity (severe %)	Definition of asthma	Biological therapy (n)
Composite outcome measures								
Fitzpatrick, 2020[52]	ASSESS	Post-hoc analysis of 2 RCTs	562	44 (0.7)	F =64.1%; FEV_1 (predicted)= 74.2% (SD=0.9)	Mild to severe (58.4%)	Modified ERS/ATS	Omalizumab (n=43)
Krouse,** 2017[51]	CASI	Post-hoc analysis of RCT	419	10.8 (interquartile range, 8-14)	F=42.2%, FEV_1 (predicted)= 92.0%	Mild to severe (54.0%)	NAEPP	Omalizumab (n=208)
FEOS, 2021[53]	NR	NR	14	NR	NR	Severe (100.0%)	GINA step 5 ERS/ATS	Reslizumab (n=6) Mepolizumab (n=5) Benralizumab (n=3)
Asthma symptom outcome measures								
Shen, 2021[49]	ASUI	Post-hoc analysis of RCT	497	51.0 (13.6)	F= 59.2%; FEV_1 (predicted)= 58.8% (SD=15.7)	Severe eosinophilic (100.0%)	ERS/ATS	Mepolizumab (n=269)
Shen, 2021[49]	ASI	Post-hoc analysis of RCT	497	51.0 (13.6)	F=59.2%; FEV_1 (predicted)= 58.8% (SD=15.7)	Severe eosinophilic (100.0%)	ERS/ATS	Mepolizumab (n=269)
Globe, 2019[50]	ASD	Post-hoc analysis of RCT	417	47.3 (13.6)	F=59.0%	Moderate-severe	Doctor-diagnosed	Brodalumab (n=283)
Asthma control outcome measures								
Lloyd, 2007[55]	GETE	Post-hoc analysis of 3 RCTs	1380	12-76*	NR	Moderate-severe	GINA, ATS NHLBI	Omalizumab***
Asthma quality of life outcome measures								
Masoli, 2021[48]	SAQ	Longitudinal cohort	110	49.0	F =69.0%; FEV_1=67.0%	Severe (100.0%)	ERS/ATS	Omalizumab (n=16) Mepolizumab (n =26) Benralizumab (n=62) Reslizumab (n=2)

ACT, Asthma Control Test; ATS, American Thoracic Society; ASSESS, Asthma Severity Scoring System; ASUI, Asthma Symptom Utility Index; ASI, Asthma Symptom Index; ASD, Asthma Symptom Diary; CASI, Composite Asthma Severity Index; ERS, European Respiratory Society; FEOS, FEV1, Exacerbations, Oral Corticosteroids, Symptoms Score; GETE, Global Evaluation of Treatment Effectiveness; F, Female; GINA, Global Initiative for Asthma; FEV_1, forced expiratory volume in one second; NHLBI, National Heart, Lung, and Blood Institute; NAEPP, National Asthma Education and Prevention Program; NR, not reported; RCT, randomised-controlled trial; SAQ, Severe Asthma Questionnaire. * Inclusion criteria are reported as the mean age of the participants is unclear.**Definition was developed in mild to severe asthma and then evaluated in patients taking biological therapy.*** n=1380 patients from the randomised, placebo-controlled, double-blind studies were included in the analysis.

Table 2. Definitions of non-response and response to biological therapy for severe asthma and their quality of evidence.

Reference, year	Scale	Patient input in scale development	Time points from baseline	Method of development of definition of response	Definition of response	Range of scores	GRADE
Composite outcome measures							
Fitzpatrick, 2020[52]	ASSESS	✗	12 months	Distribution-based method	MID= 2 points	0-20 points Higher=worse	⨁⨁⨁◯[A]
Krouse,* 2017[51]	CASI	✗	60 weeks	Anchor-based method	MCID= 1 point	0-18 points Higher=worse	⨁⨁⨁⨁
FEOS, 2021[53]	NR	✗	NA	Delphi exercise, conjoint analysis	Response defined according to different thresholds for each outcome measure with respect to baseline. The response ranges from 0 (worsening) to 100 (best).	0-100 points Higher=better	⨁⨁⨁⨁
Asthma symptom outcome measures							
Shen, 2021[49]	ASUI	✓	12 weeks	Anchor-based method	MCID= 0.07 to 0.11	0-1 points Higher=better	⨁⨁⨁⨁
Shen, 2021[49]	ASI	✓	12 weeks	Anchor-based method	MCID= -0.42 to -0.26	0-3 points Higher=worse	⨁⨁⨁⨁
Globe, 2019[50]	ASD**	✓	12,24 weeks	MID (change −0.5 to −1.0 ACQ) Responder (change ≤ −1.0 ACQ)	Reported for 12 and 24 weeks: • Mean 7-day score: MID =-0.35 and -0.35; Responder= -0.54 and -0.68 • 7-day symptomatic days: MID: -1.75 and -1.98; Responder: -2.34 and -3.22 • Minimal symptomatic days 1: MID: 1.97 and 2.16; Responder: 2.43 and 3.23 • Minimal symptomatic days 2: MID: 1.02 and 1.36; Responder: 2.31 and 2.56	0-4 points Higher=worse	⨁⨁⨁⨁
Asthma control outcome measures							
Lloyd, 2007[55]	GETE	✗	28 weeks	Physician consensus	• Responder (Complete control; marked improvement of asthma) • Non-responder (Discernible, but limited improvement in asthma, no appreciable change in asthma; worsening of asthma)	0-5 points Higher=better	⨁⨁⨁⨁
Asthma quality of life outcome measures							
Masoli, 2021[48]	SAQ	✓	4,8,12 weeks	Anchor-based method	• MCID (SAQ) = 0.5 points; MCID (SAQ-global) = 11 points	SAQ:1 -7 points; SAQ-global: 0-100 points Higher=better	⨁⨁⨁⨁

ASSESS, Asthma Severity Scoring System; ASUI, Asthma Symptom Utility Index; ASI, Asthma Symptom Index; ASD, Asthma Symptom Diary; CASI, Composite Asthma Severity Index; FEOS, FEV1, Exacerbations, Oral Corticosteroids, Symptoms Score; GETE, Global Evaluation of Treatment Effectiveness; GRADE, Grading of Recommendations, Assessment, Development and Evaluation; MCID, Minimal Clinically Important Difference; MID, Minimal Important Difference; NR, not reported; SAQ, Severe Asthma Questionnaire. *Definition was developed in mild to severe using anchor-based method and then evaluated in biologicals. MID was changed to MCID by the review team. **ASD Symptomatic Days (defined as mean of the 10 ASD daily symptom items ≥1, otherwise non-Symptomatic Day); (2) Minimal Symptom Days-1 (defined as mean of the 10 ASD daily symptom items ≤1 and no single symptom item score > 1, otherwise non-Minimal Symptom Day-1); and (3) Minimal Symptom Days-2 (defined as no single ASD daily symptom item. Tick indicates 'yes' while cross is 'no'. Certainty of evidence was assessed using the GRADE approach.[38,40,42] The reason for downgrading was as follows: A, indirectness.

Table 3. Evaluation of outcome measures against good measurement properties and their quality of evidence.

	ASSESS [52]		CASI[56]**		FEOS[53]		ASUI[49,84]		ASI[49]		ASD[44,50]		GETE[55]*		SAQ [45,47,48,54]†	
	Rating	GRADE	Rating	GRADE	Rating	GRADE	Rating	GRADE	Rating	GRADE	Rating	GRADE	Rating	GRADE	Rating	GRADE
Relevance	+	⊕◯◯◯ A,B,C	+	⊕◯◯◯ A,C	+	⊕◯◯◯ A,C	±	⊕⊕◯◯ A,C	±	⊕⊕◯◯ A,C	±	⊕⊕◯◯ A,C	+	⊕◯◯◯ A,B,C	+	⊕⊕⊕◯ A
Comprehensiveness	+	⊕◯◯◯ A,B,C	-	⊕◯◯◯ A,C	±	⊕◯◯◯ A,B,C	±	⊕◯◯◯ A,B,C	-	⊕◯◯◯ A,B,C	+	⊕⊕◯◯ A,C	-	⊕◯◯◯ A,B,C	+	⊕⊕⊕◯ A
Comprehensibility	+	⊕◯◯◯ A,B,C	±	⊕◯◯◯ A,C	+	⊕◯◯◯ A,C	+	⊕◯◯◯ A,B,C	+	⊕◯◯◯ A,B,C	+	⊕⊕◯◯ A,C	+	⊕◯◯◯ A,B,C	+	⊕⊕⊕◯ A
Reliability	+	⊕◯◯◯ A,C	?		?		+	⊕⊕⊕◯ A	+	⊕⊕⊕◯ A	?		?		+#	⊕⊕◯◯ A,C
Construct validity* **	+	⊕⊕◯◯ A,C	?		?		+	⊕⊕◯◯ A	+	⊕⊕◯◯ A	?		+	⊕⊕⊕⊕	+#	⊕⊕◯◯ A,C
Responsiveness	+	⊕◯◯◯ A,C	-	⊕⊕⊕⊕	?		+	⊕⊕◯◯ A	+	⊕⊕◯◯ A	+	⊕⊕◯◯ A	?		+#	⊕⊕◯◯ A,C

ASUI, Asthma Symptom Utility Index; ASI, Asthma Symptom Index; ASSESS, Asthma Severity Scoring System; ASD, asthma symptom diary; CASI, Composite Asthma Severity Index; FEOS, FEV1, Exacerbations, Oral Corticosteroids, Symptoms Score; GRADE, Grading of Recommendations, Assessment, Development and Evaluation; GETE, Global Evaluation of Treatment Effectiveness; SAQ, Severe Asthma Questionnaire.

Good measurement properties for each measurement property were rated based on the COSMIN criteria[38,40] as either sufficient in bold (+), insufficient (-), indeterminate (?), or inconsistent (±, for development criteria only). Empty cells or indeterminate (?) ratings indicate that the measurement property was not investigated or there is insufficient information. Structural validity, internal consistency, measurement error and cross-cultural validity are not shown in the table for all outcome measures due to the same reasons.

For construct validity and responsiveness, the review team formulated *a priori* hypotheses about the expected relationships between an outcome measure and comparator instruments. Overall, ≥75% of the pooled results for the measurement property were expected to meet the criteria in order to be classified as a sufficient rating.[38]

*Physician and patient version of GETE were graded similarly. Assessment of the development was based on reviewer rating only. **Only external validation data was used for analysis as it was performed in a study with biologics. ***As there is no golden standard in asthma, data about criterion validity was combined with construct validity. †SAQ is based on a formative model; therefore, there was no need to assess structural validity and internal consistency. # Ratings apply to SAQ subscales (My Life, My Mind, My Body) and SAQ- global.

Certainty of evidence was assessed using the modified GRADE approach as 'high', 'moderate', 'low' or 'very low'.[38,40,42] The reasons for downgrading were as follows: A, risk of bias; B, inconsistency; C, indirectness.

Table 4. Summary of the characteristics of the outcome measures.

	Recall period	Outcome measure content								
		ACT	**Asthma control**	**Albuterol day/night**	**Asthma symptoms**	**Exacerbations**	**Asthma medications**	**mOCS**	**FEV_1**	**Quality of life**
ASSESS[52]	Current (FEV_1, asthma medications) 4 weeks (ACT) 6 months (exacerbations)	X				X	X		X	
CASI[56]	Current (FEV_1, asthma medications) 2 weeks (symptoms, albuterol use) 2 months (exacerbations)			X	X	X	X		X	
FEOS[53]	Baseline to current (FEV_1 and mOCS) 4 weeks (ACT) 12 months (severe exacerbations)	X				X		X	X	
ASUI[84]	2 weeks				X					
ASI[49]	2 weeks				X					
ASD[44]	Current (morning and evening)				X					
GETE[55]	Baseline to current		X							
SAQ[45]	2 weeks									X

ACT, Asthma Control Test; ASSESS, Asthma Severity Scoring System; ASUI, Asthma Symptom Utility Index; ASI, Asthma Symptom Index; ASD, Asthma Symptom Diary; CASI, Composite Asthma Severity Index; GETE, Global Evaluation of Treatment Effectiveness; FEV_1, forced expiratory volume in one second; FEOS, FEV1, Exacerbations, Oral Corticosteroids, Symptoms Score; mOCS, maintenance oral corticosteroids; SAQ, Severe Asthma Questionnaire.

ASUI and ASI measure frequency and severity of asthma symptoms (cough, wheeze, SOB, night-time awakening), while ASD measures morning and evening symptoms separately (wheeze, shortness of breath, cough, chest tightness, night-time awakening, or impairment of daily activities). GETE measures effectiveness of biological treatment based on physician and patient view separately.

Figure legends

Figure 1. PRISMA diagram demonstrating study selection.

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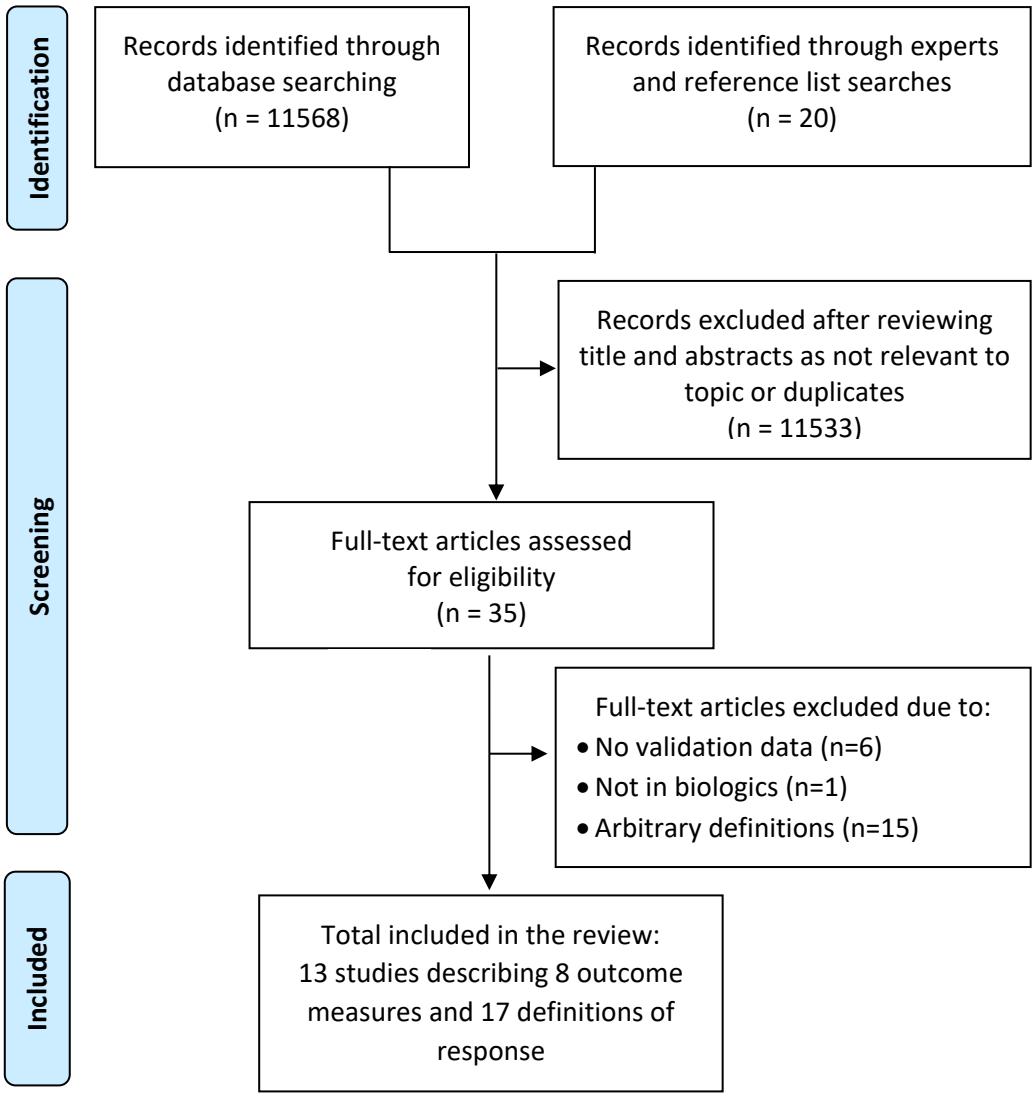

Figure 1. PRISMA diagram demonstrating study selection.

Supplementary materials

Definitions of non-response and response to biological therapy for severe asthma: a systematic review.

Ekaterina Khaleva, Anna Rattu, Chris Brightling, Andrew Bush, Arnaud Bourdin, Apostolos Bossios, Kian Fan Chung, Rekha Chaudhuri, Courtney Coleman, Ratko Djukanovic, Sven-Erik Dahlén, Andrew Exley, Louise Fleming, Stephen J Fowler, Atul Gupta, Eckard Hamelmann, Gerard H. Koppelman, Erik Melen, Vera Mahler, Paul Seddon, Florian Singer, Celeste Porsbjerg, Valeria Ramiconi, Franca Rusconi, Valentyna Yasinska, Graham Roberts on behalf of the 3TR and COMSA working group.

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Table of Contents

Appendix 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Title
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Introduction
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Introduction
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Methods- inclusion criteria; exclusion criteria
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Methods-Search strategy
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Supplementary materials
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Methods-Study selection
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Methods- Data extraction, risk of bias assessment, quality, and synthesis of the results
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Appendix 3.
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Appendix 3.
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Data extraction, risk of bias assessment, quality, and synthesis of the results
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	NA
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	NA
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	NA

Section and Topic	Item #	Checklist item	Location where item is reported
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	NA
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	NA
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	NA
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	NA
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Appendix 3.
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Methods- Data extraction, risk of bias assessment, quality, and synthesis of the results
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Figure 1
Study characteristics	17	Cite each included study and present its characteristics.	Table 1; 2; S3; S6;
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Table S7
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	NA
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Results- Development and quality of definitions of non-response and response; Development and content validity of the outcome measures; Risk of bias and quality of evidence for validation studies of outcome measures
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	NA
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	NA
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	NA
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	NA
Certainty of	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Results-Risk of bias and

Section and Topic	Item #	Checklist item	Location where item is reported
evidence			quality of evidence for validation studies of outcome measures
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Discussion
	23b	Discuss any limitations of the evidence included in the review.	Discussion: Strengths and limitations
	23c	Discuss any limitations of the review processes used.	Discussion: Strengths and limitations
	23d	Discuss implications of the results for practice, policy, and future research.	Discussion: Policy implications and next steps
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Methods
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Methods
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Methods
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Funding
Competing interests	26	Declare any competing interests of review authors.	Conflict of interests
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Supplementary materials

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

Appendix 2. Search strategies

I. Search strategy in EMBASE (OVID)

1. asthma/ or allergic asthma/ or aspirin exacerbated respiratory disease/ or asthmatic state/ or exercise induced asthma/ or experimental asthma/ or extrinsic asthma/ or intrinsic asthma/ or mild intermittent asthma/ or mild persistent asthma/ or moderate persistent asthma/ or nocturnal asthma/ or occupational asthma/ or severe persistent asthma/

2. asthma*.ti,ab.

3. 1 or 2

4. omalizumab.mp. or exp omalizumab/

5. mepolizumab.mp. or exp mepolizumab/

6. reslizumab.mp. or reslizumab/

7. benralizumab.mp. or exp benralizumab/

8. dupilumab.mp. or exp dupilumab/

9. tralokinumab.mp. or exp tralokinumab/

10. lebrikizumab.mp. or exp lebrikizumab/

11. tezepelumab.mp. or exp tezepelumab/

12. brodalumab.mp. or exp brodalumab/

13. ligelizumab.mp. or exp ligelizumab/

14. Pitrakinra.mp. or pitrakinra/

15. exp biological product/ or exp biological therapy/ or biologic*.mp.

16. (biologic* adj1 (treatment* or therap* or medicine* or drug* or agent* or product*)).mp.

17. monoclonal antibod*.mp. or exp monoclonal antibody/

18. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17

19. drug response/ or exp treatment response/ or partial drug response/

20. (responsive* or response or respond* or nonrespon*).mp.

21. treatment outcome/ or outcome assessment/

22. minimal clinically important difference/ or meaningful change.mp.

23. (Minimal* adj1 (clinical* or important or real or significant) adj1 (change or difference)).mp.

24. (Minimal* adj1 clinical* adj1 (important or significant) adj1 (change or difference)).mp.

25. (MCID or MID or MIC).mp.

26. 19 or 20 or 21 or 22 or 23 or 24 or 25

27. editorial/ or review/ or case report/ or case report*.mp.

28. editorial*.mp.

29. conference abstract*.mp.

30. conference paper*.mp. or conference paper/ or conference abstract/

31. ((systematic or narrative) adj2 review*).mp. or "systematic review"/

32. ((("semi-structured" or semistructured or unstructured or informal or "in-depth" or indepth or "face-to-face" or structured or guide) adj3 (interview* or discussion* or questionnaire*)) or ("focus group*" or qualitative or ethnograph* or fieldwork or "field work" or "key informant")).ti,ab. or survey*.ti.

33. interview/ or information processing/ or verbal communication/ or qualitative research/ or exp short survey/ or exp health care survey/ or exp health survey/

34. 27 or 28 or 29 or 30 or 31 or 32 or 33

35. 3 and 18 and 26

36. 35 not 34

37. 36 not ((exp animal/ or nonhuman/) not exp human/)

38. limit 37 to english language

II. Search strategy in MEDLINE (OVID)

1. exp Asthma, Aspirin-Induced/ or exp Asthma, Exercise-Induced/ or exp Asthma/ or exp Asthma, Occupational/ or asthma*.ti,ab.

2. omalizumab.mp. or Omalizumab/

3. mepolizumab.mp.

4. reslizumab.mp.

5. benralizumab.mp.

6. dupilumab.mp.

7. tralokinumab.mp.

8. lebrikizumab.mp.

9. tezepelumab.mp.

10. brodalumab.mp.

11. ligelizumab.mp.

12. Pitrakinra.mp.

13. biological product/ or biological therapy/ or biologic*.mp.

14. (biologic* adj1 (treatment* or therap* or medicine* or drug* or agent* or product*)).mp.

15. monoclonal antibod*.mp. or antibodies, monoclonal/ or antibodies, monoclonal, humanized/

16. 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15

17. (responsive* or response or respond* or nonrespon*).mp.

18. treatment outcome/ or Outcome Assessment, Health Care/

19. Minimal Clinically Important Difference/ or meaningful change.mp.

20. (Minimal* adj1 (clinical* or important or real or significant) adj1 (change or difference)).mp.

21. (Minimal* adj1 clinical* adj1 (important or significant) adj1 (change or difference)).mp.

22. (MCID or MID or MIC).mp.

23. 17 or 18 or 19 or 20 or 21 or 22

24. editorial/ or review/ or case report/ or case report*.mp.

25. (editorial* or conference abstract* or conference paper*).mp.

26. ((systematic or narrative) adj2 review*).mp. or "systematic review"/

27. ((("semi-structured" or semistructured or unstructured or informal or "in-depth" or indepth or "face-to-face" or structured or guide) adj3 (interview* or discussion* or questionnaire*)) or (focus group* or qualitative or ethnograph* or fieldwork or "field work" or "key informant")).ti,ab. or survey*.ti.

28. interviews as topic/ or focus groups/ or narration/ or qualitative research/ or health care surveys/ or health surveys/

29. 24 or 25 or 26 or 27 or 28

30. 1 and 16 and 23

31. 30 not 29

32. 31 not (Animals/ not (Animals/ and Humans/))

33. limit 32 to english language

III. Search strategy in CINAHL (EBSCOhost)

1. (MH "Asthma+") OR (MH "Asthma, Occupational") OR (MH "Asthma, Exercise-Induced") OR TI asthma* OR AB asthma*

2. "omalizumab" OR "mepolizumab" OR "reslizumab" OR "benralizumab" OR "dupilumab" OR "tralokinumab" OR "lebrikizumab" OR "tezepelumab" OR "brodalumab" OR "ligelizumab" OR "Pitrakinra" (MH "Biological Therapy") OR (MH "Antibodies, Monoclonal+") OR ((biologic*) N1 (treatment* OR therap* OR medicine* OR drug* OR agent* OR product*)) OR "biologic*" OR "monoclonal antibod*"

3. "responsive*" OR "response" OR "respond*" OR "nonrespon*" OR (MH "Treatment Outcomes") OR (MH "Outcome Assessment")

4. "MCID" OR "MID" OR "MIC" OR "meaningful change" OR (Minimal* N1 (clinical* OR important OR real OR significant) N1 (change OR difference)) OR (Minimal* N1 clinical* N1 (important OR significant) N1 (change OR difference))

5. TI (("semi-structured" OR semistructured OR unstructured OR informal OR "in-depth" OR indepth OR "face-to-face" OR structured OR guide) N3 (interview* OR discussion* OR questionnaire*)) OR TI ("focus group*" OR qualitative OR ethnograph* OR fieldwork OR "field work" OR "key informant"))

6. AB (("semi-structured" OR semistructured OR unstructured OR informal OR "in-depth" OR indepth OR "face-to-face" OR structured OR guide) N3 (interview* OR discussion* OR questionnaire*)) OR AB ("focus group*" OR qualitative OR ethnograph* OR fieldwork OR "field work" OR "key informant")

7. (MH "Qualitative Studies") OR (MH "Focus Groups") OR (MH "Narratives") OR (MH "Interviews") OR (MH "Surveys") OR TI Survey*

8. (MH "Literature Review") OR (MH "Scoping Review") OR PT "Systematic Review" OR PT review OR PT editorial OR PT proceedings

9. S3 OR S4

10. S5 OR S6 OR S7 OR S8

11. S1 AND S2 AND S9

12. S11 NOT S10

13. (MH "Animals+") NOT (MH "Human")

14. S12 NOT S13 Limiters - English Language

IV. Search strategy in Web of science

1. TS=(asthma*)

2. TS=(omalizumab) OR TS=(mepolizumab) OR TS=(reslizumab) OR TS=(benralizumab) OR TS=(dupilumab) OR TS=(tralokinumab) OR TS=(lebrikizumab) OR TS=(tezepelumab) OR TS=(brodalumab) OR TS=(ligelizumab) OR TS=(Pitrakinra)

3. TS=((biologic*) NEAR/1 (treatment* OR therap* OR medicine* OR drug* OR agent* OR product*)) OR TS=("monoclonal antibod*") OR TS=("biologic*")

4. TS=("responsive*") OR TS=("response") OR TS=("respond*") OR TS=("nonrespon*") OR TS=("outcome assessment*") OR TS=("treatment outcome*") OR TS=("meaningful change") OR TS=(Minimal* NEAR/1 (clinical* OR important OR real OR significant) NEAR/1 (change OR difference)) OR TS=(Minimal* NEAR/1 clinical* NEAR/1 (important OR significant) NEAR/1 (change OR difference)) OR TS=("MCID") OR TS=("MID") OR TS=("MIC")

5. #3 OR #2

6. (#1 AND #4 AND #5) NOT TS=("interview*") NOT TS=("focus group*") NOT TS=(narration) NOT TS=("qualitative research") NOT TI=(survey*)

7. #6 NOT TS=((("semi-structured" OR semistructured OR unstructured OR informal OR "in-depth" OR indepth OR "face-to-face" OR structured OR guide) NEAR/3 (interview* OR discussion* OR questionnaire*)) OR (focus group* OR qualitative OR ethnograph* OR fieldwork OR "field work" OR "key informant"))

8. (#7 NOT TS=((animal*) NOT (human* OR patient*))) AND LANGUAGE: (English)

9. (#7 NOT TS=((animal*) NOT (human* OR patient*))) AND LANGUAGE: (English)

Refined by: [excluding] DOCUMENT TYPES: (PROCEEDINGS PAPER OR EDITORIAL MATERIAL OR REVIEW OR MEETING ABSTRACT)

Appendix 3. Detailed methods

Data extraction, risk of bias assessment, quality, and synthesis of the results.

Data extraction was based on the COSMIN (COnsensus-based Standards for the selection of Measurement Instruments) guideline[1] for outcome measures. Data about study design; population characteristics and subgroups including sample size; asthma definition and severity; intervention and comparator (where appropriate); follow-up period; methodological approach to defining therapeutic response; definition of response and non-response (sole or composite outcome measures), development data, data on measurement properties (including: reliability (internal consistency, reliability, measurement error), validity (content, construct validity, responsiveness to change)) and characteristics of the outcome measurements were extracted into a template form independently by two reviewers (EK, AR). Any discrepancies were resolved by discussion or by a third reviewer (GR). The final extraction was cross-checked. Authors of included studies were contacted to provide additional data if needed.

Two reviewers (EK,AR) independently assessed the Risk of Bias (RoB) in individual studies using the COSMIN checklist for PROMs[2,3] and composite outcome measures (COSMIN RoB for non-Patient Reported Outcomes)[4]. Criterion validity was not evaluated as no gold standard exists in severe asthma.

First, development of the outcome measures was assessed based on relevance, comprehensiveness, and comprehensibility according to ten criteria.[3] Each criterion was rated as positive (+), negative (-), or indeterminate (?). The overall rating was provided as sufficient (+), insufficient (-), or inconsistent (±) which were based on the results from developmental and content validity studies as well as reviewers rating. If the developmental process for an outcome measure was not reported, then the overall rating was based only on the reviewer rating.

Second, we assessed RoB for each measurement property in the validation studies and rated it as very good, adequate, doubtful, or inadequate. The overall rating per measurement property was determined by the lowest rating for each standard.[1,2] The RoB assessment of response definitions was not undertaken as it is not part of the COSMIN RoB checklist.

Furthermore, we applied quality criteria. Each measurement property was rated as either sufficient (+), insufficient (-), or indeterminate (?) based on the predefined criteria for good measurement properties (GMP).[1] For construct validity and responsiveness, the review team formulated *a priori* hypotheses about the expected relationships between an outcome measure and comparator instruments. Overall, ≥75% of the results were expected to meet the criteria to be classified as sufficient.[1] Criteria for GMP are listed in **Table S2**.

Lastly, the certainty of evidence was assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach.[1,3,5] Quality of evidence was rated as 'high', 'moderate', 'low' or

'very low' for four factors (RoB, inconsistency, imprecision, and indirectness) for 'validity' studies while for 'developmental' studies rating was done according to three (RoB, inconsistency, and indirectness) by two reviewers (EK, AR). Papers describing development of the outcome measure were eligible for inclusion regardless of severity of asthma but subsequently downgraded for indirectness. Only inconsistency, imprecision and indirectness were assessed for the definitions of response as per the COSMIN guideline.[1] GRADE was not assessed in studies with indeterminate (?) rating based on GMP.[1] Any disagreements were resolved through the consultation with a third reviewer (GR). A descriptive synopsis with summary data tables were produced, and results were summarized using narrative synthesis.

Table S1. COSMIN definitions of domains, measurement properties, and aspects of measurement properties.

Term			Definition
Domain	**Measurement Property**	**Aspect of a Measurement Property**	
Reliability			The degree to which the measurement is free from measurement error
Reliability (extended definition)			The extent to which scores for patients who have not changed are the same for repeated measurement under several conditions: e.g. using different sets of items from the same health related-patient reported outcomes (HR-PRO; internal consistency); over time (test-retest); by different persons on the same occasion (inter-rater); or by the same persons (i.e. raters or responders) on different occasions (intra-rater)
	Internal consistency		The degree of the interrelatedness among the items
	Reliability		The proportion of the total variance in the measurements which is due to ‘‘true’’ differences between patients
	Measurement error		The systematic and random error of a patient’s score that is not attributed to true changes in the construct to be measured
Validity			The degree to which an HR-PRO instrument measures the construct(s) it purports to measure
	Content validity		The degree to which the content of an HR-PRO instrument is an adequate reflection of the construct to be measured
		Face validity	The degree to which (the items of) an HR-PRO instrument indeed looks as though it is an adequate reflection of the construct to be measured
	Construct validity		The degree to which the scores of an HR-PRO instrument are consistent with hypotheses (for instance with regard to internal relationships, relationships to scores of other instruments, or differences between relevant groups) based on the assumption that the HR-PRO instrument validly measures the construct to be measured
		Structural validity	The degree to which the scores of an HR-PRO instrument are an adequate reflection of the dimensionality of the construct to be measured
		Hypotheses	Idem construct validity

		testing	
		Cross-cultural validity	The degree to which the performance of the items on a translated or culturally adapted HR-PRO instrument are an adequate reflection of the performance of the items of the original version of the HR-PRO instrument
	Criterion validity		The degree to which the scores of an HR-PRO instrument are an adequate reflection of a ‘‘gold standard’’
Responsiveness			The ability of an HR-PRO instrument to detect change over time in the construct to be measured
	Responsiveness		Idem responsiveness
Interpretability			Interpretability is the degree to which one can assign qualitative meaning—that is, clinical or commonly understood connotations—to an instrument’s quantitative scores or change in scores.

COSMIN, COnsensus-based Standards for the selection of health Measurement INstruments; HR PRO, health related-patient reported outcomes. Taken from Mokkink LB et al.[6]

Table S2. COSMIN criteria for good measurement properties.

Measurement property (definition)	Rating	Criteria
Structural validity	+	**CTT** CFA: CFI or TLI or comparable measure > 0.95 OR RMSEA < 0.06 OR SRMR < 0.08[a] **IRT/Rasch** No violation of unidimensionality[b]: CFI or TLI or comparable measure > 0.95 OR RMSEA < 0.06 OR SRMR < 0.08 AND no violation of local independence: residual correlations among the items after controlling for the dominant factor < 0.20 OR Q3's < 0.37 AND no violation of monotonicity: adequate looking graphs OR item scalability > 0.30 AND adequate model fit IRT: χ^2 > 0.001 Rasch: infit and outfit mean squares ≥ 0.5 and ≤ 1.5 OR Z-standardized values > −2 and < 2
	?	CTT: not all information for '+' reported IRT/Rasch: model fit not reported
	-	Criteria for '+' not met
Internal consistency	+	At least low evidence[c] for sufficient structural validity[d] AND Cronbach's alpha(s) ≥ 0.70 for each unidimensional scale or subscale[e]
	?	Criteria for "At least low evidence[c] for sufficient structural validity[d]" not met
	-	At least low evidence[c] for sufficient structural validity[d] AND Cronbach's alpha(s) < 0.70 for each unidimensional scale or subscale[e]
Reliability	+	ICC or weighted Kappa ≥ 0.70
	?	ICC or weighted Kappa not reported
	-	ICC or weighted Kappa < 0.70
Measurement error	+	SDC or LoA < MIC[d]
	?	MIC not defined
	_	SDC or LoA > MIC[d]

Hypotheses testing for construct validity	+	The result is in accordance with the hypothesis[f]
	?	No hypothesis defined (by the review team)
	-	The result is not in accordance with the hypothesis[f]
Responsiveness to change	+	The result is in accordance with the hypothesis[f] OR AUC ≥ 0.70
	?	No hypothesis defined (by the review team)
	-	The result is not in accordance with the hypothesis[f] OR AUC < 0.70

AUC, area under the curve; CFA, confirmatory factor analysis; CFI, comparative fit index; CTT, classical test theory; DIF, differential item functioning; ICC, intraclass correlation coefficient; IRT, item response theory; LoA, limits of agreement; MIC, minimal important change; RMSEA, root mean square error of approximation; SEM standard error of measurement; SDC, smallest detectable change; SRMR, standardized root mean residuals; TLI, Tucker–Lewis index. Taken from COSMIN, COnsensus-based Standards for the selection of health Measurement INstruments[1].

"+" = sufficient, "–" = insufficient, "?" = indeterminate

[a]To rate the quality of the summary score, the factor structures should be equal across studies

[b]Unidimensionality refers to a factor analysis per subscale, while structural validity refers to a factor analysis of a (multidimensional) patient reported outcome measure

[c]As defined by grading the evidence according to the GRADE approach

[d]This evidence may come from different studies

[e]The criteria 'Cronbach alpha < 0.95' was deleted, as this is relevant in the development phase of a PROM and not when evaluating an existing PROM

[f]The results of all studies should be taken together and it should then be decided if 75% of the results are in accordance with the hypotheses

Table S3. Approach to development of outcome measures.

Reference, year	Scale	Approach to development of outcome measurements
Composite outcome measures		
Fitzpatrick, 2020[7]	ASSESS	Adapted from the CASI by clinicians only: removed daytime symptoms and night time symptom dimensions and replaced with the total ACT score (weighted at 30%), modified ranges for FEV_1, medications, and length for assesment of exacerbations.
Wildfire 2012[8]	CASI	Developed by physicians only. 1. Determining independent dimensions of asthma severity via factor analysis. 2. Delphi exercise: clinical weighting of the dimensions of asthma severity. 3. Scale properties of the Composite Asthma Severity Index. 4. External validation.
De Llano, 2021[9]	FEOS	Developed by physicians only. 1. Systematic literature review. 2. Selection of domains and measurement tools: Delphi exercise. 3.Weighted of selected domains: multicriteria decision analysis. 4.Face validity.
Asthma symptom outcome measures		
Shen, 2021[10] Revicki, 1998[11]	ASUI	1. Literature review, patient interviews (including ranking order the relative importance of the items) and discussion with physicians. 2. Determination of a scoring algorithm using visual analog scale and standard gamble techniques, subsequently using multi-attribute utility function.
Shen, 2021[10]	ASI	Modified version of the ASUI which includes the 4 asthma symptoms, but excludes questions about assessment of medication side effects (eg, "how many days were you bothered by side effects of your asthma medication during the past 2 weeks?," "if 1 day or more what side effects did you have?," and "on average, how severe were the side effects of your asthma medication during the past 2 weeks?").
Globe, 2015 [12] Globe, 2019[13]	ASD	1. Concept elicitation interviews in 34 adults (38.9 years (13.0), 61.8% females, ACQ≥3 in 20.6%) and 16 adolescents (15.2 years (1.6), 56.3% males, ACQ≥3 in 31.3%) with clinical diagnosis of persistent asthma. 2. Cognitive interviews in 15 adults (30.7 years (9.7), 86.7% females, ACQ≥3 in 20.0%) and 9 adolescents (14.1 years (2.2), 77.8% males, ACQ≥3 in 11.1%) with a clinical diagnosis of persistent asthma.
Asthma control outcome measures		
Lloyd, 2007[14]	GETE	Developed by physicians only
Asthma quality of life measures		
Hyland, 2018[15]	SAQ	1. Identification of domains of an instrument. 2.Focus group to seek feedback about draft instrument: patient with severe asthma defined by BTS guideline (n=16) between 24-69 y.o; mean age of 47 (SD = 13.53); female (n=12).

ACQ, Asthma Control Questionnaire; BTS, British Thoracic Society; GETE, Global Evaluation of Treatment Effectiveness; ASSESS, Asthma Severity Scoring System; ASUI, Asthma Symptom Utility Index; ASI, Asthma Symptom Index; ASD, Asthma Symptom Diary; ACT, Asthma Control Test; CASI, Composite Asthma Severity Index; FEOS, FEV1, Exacerbations, Oral Corticosteroids, Symptoms Score; SAQ, Severe Asthma Questionnaire; NR, Not reported; FEV1, Forced Expiratory Volume in 1 second.

Table S4. Summary of characteristics of the outcome measures.

Instrument (year)	Mode of administration	(Sub)scale(s) (No. of Items)	Type of response categories	Intended context of use	Target population	Time to complete (minutes)	Patient/carer report	Original language
Composite outcome measures								
Fitzpatrick, 2020[7] ASSESS	Interviewer administered, paper form (ACT[16-18]: self, at-home paper, phone, mail)	4 items: ACT (5 items), FEV_1, current medications, exacerbations.	Multiple choice questions	Clinical trials and routine clinical practice	Adolescents (≥12 years) and adults	Not reported (ACT: 2 min)	Patient and clinician	English
Wildfire,2012[8] CASI	Interviewer administered, paper form, online calculator available	5 domains: day symptoms and albuterol use, night symptoms and albuterol use, controller treatment, lung function measures, and exacerbations.	Multiple choice questions	Intervention studies and clinical practice	Children ≥ 6 years and adolescents*	Not reported	Patient and clinician	English
de Llano, 2021[9] FEOS	Paper (ACT[16-18] : self, at-home paper, phone, mail)	4-items (OCS, severe exacerbations, ACT, FEV_1)	Multiple choice questions	Clinical trials, patient monitoring	Adults	Not reported (ACT: 2 min)	Patient and clinician	English
Asthma symptom outcome measures								
Revicki, 1998[11] ASUI	Interviewer administered, paper form	11 items [four symptoms (cough, wheeze, shortness of breath, and awakening at night) and two dimensions (frequency and severity] and side effect of medications	4-point Likert scale	Clinical trials and cost effectiveness studies	Adults	Not reported	Patient	English (for the USA). Italian, French
Shen, 2021[10] ASI	Interviewer administered, paper	8 items [four symptoms (cough, wheeze, shortness of breath, and awakening at night) and two dimensions (frequency and severity]	4-point Likert scale	Clinical trials, patient monitoring	Adults	Not reported	Patient	English, Italian, French
Globe,2015[12] ASD	Self-complete, electronic device	10-items (5 morning and 5 evening)	5-point Likert scale	Clinical research	Adolescents (≥ 12 years) and adults	Not reported	Patient	English
Asthma control outcome measures								
Llyod, 2007[14] GETE	Interviewer administered, paper form	2 items	5-point Likert scale	Clinical trials and routine clinical practice	Adolescents and adults	Not reported	Patient and clinician	English
Asthma quality of life measures								
Hyland, 2018[15] SAQ	Self-complete, paper form	SAQ: 16 items SAQ-global: 1 item	7-point Likert scale	Clinical research, patient monitoring	Adults 16–78 years (reading age 11-12 years)	3-6 minutes	Patient	English (UK), Portuguese

ACT, Asthma Control Test; ASUI, Asthma Symptom Utility Index; ASI, Asthma Symptom Index; ASD, asthma symptom diary; ASSESS, Asthma Severity Scoring System; CASI, Composite Asthma Severity Index; GETE, Global Evaluation of Treatment Effectiveness; SAQ, Severe Asthma Questionnaire. FEOS, FEV1, Exacerbations, Oral Corticosteroids, Symptoms Score; FEV_1, Forced Expiratory Volume in 1 second; OCS, Oral Corticosteroids. * CASI is also validated in adults with asthma based on a conference abstract.[19]

Table S5. Summary of data for measurement properties of outcome measures.

Reference, year	Construct validity**	Reproducibility	Internal consistency	Responsiveness
Lloyd, 2007[14] GETE	1.Spearman rank-order correlation between GETE and AQLQ (physician GETE / patient GETE)*: • Activities score: –0.29 / –0.32 • Change from baseline in activities score: –0.35 / –0.37 • Emotions score: –0.36 / –0.37 • Change from baseline in emotions score: –0.31 / –0.35 • Environmental exposure score:–0.25 / –0.26 • Change from baseline in environmental exposure score: –0.27 / –0.30 • Symptom score –0.40 / –0.45 • Change from baseline in symptom score: –0.36 / –0.39 • Overall score: –0.38 /–0.41 • Change from baseline in overall score: –0.38 /–0.41 * All correlations were p<0.0001. 2. Spearman rank-order correlation between GETE and clinical characteristics (physician GETE / patient GETE)*: • Actual FEV1 value: –0.20/–0.14 • Total asthma symptom score: 0.32/ 0.34 • Change in total asthma symptom score: 0.26/ 0.31 • Nocturnal symptom score: 0.22/ 0.22 • Change in nocturnal symptom score: 0.21/ 0.23 • Daytime symptom score: 0.31/ 0.34 • Change in daytime symptom score: 0.24/ 0.29 • No. of puffs of rescue medication/day: 0.33 /0.33 • Change in no. of puffs of rescue medication/day: 0.26/ 0.29 * All correlations were p<0.0001. 3. Actual mean FEV1 (SD)/ mean total asthma symptom score (SD)/ mean nocturnal symptom score (SD) / mean daytime symptom score (SD) / mean n on puffs of rescue meds (SD)	NA	NA	NA

Reference, year	Construct validity**	Reproducibility	Internal consistency	Responsiveness
	Patient version • Complete control of asthma: 2.20 (824.58) / 1.49 (1.58) / 0.50 (0.63) / 0.68 (0.71) / 3.23 (4.49) • Marked improvement of asthma: 2.12 (776.94) / 2.14 (1.85) / 0.69 (0.81) / 1.02 (0.86) / 3.76 (4.99) • Discernible, but limited improvement in asthma: 2.07 (761.41) / 2.70 (1.99) / 0.91 (0.96) / 1.38 (0.98) / 5.47 (6.84) • No appreciable change in asthma: 2.03 (838.37) / 2.98 (2.21) / 1.01 (1.09) / 1.48 (1.05) / 5.20 (5.20) • Worsening of asthma: 1.82 (691.97) / 5.38 (3.39) / 2.06 (1.34) / 2.32 (1.46) / 13.23 (7.83) p values per clinical indicator: 0.37/ 0.0091/ <0.0001/ <0.0001/ 0.0002/ 0.0016 / < 0.0001 / 0.0009 / 0.0002 *Physician version* • Complete control of asthma: 2.37 (877.81) / 1.68 (1.73)/ 0.64 (0.70) / 0.74 (0.75) / 3.13 (4.17) • Marked improvement of asthma: 2.15 (790.23) / 2.01 (1.83) / 0.61 (0.81) / 1.00 (0.88) / 3.65 (5.66) • Discernible, but limited improvement in asthma: 2.08 (751.92) / 2.61 (1.90) / 0.83 (0.87)/ 1.27 (0.90)/ 4. 93 (5.66) • No appreciable change in asthma: 1.95 (751.86) / 3.15 (2.34) / 1.15 (1.13) / 1.58 (1.12) / 6.35 (5.98) • Worsening of asthma: 1.66 (445.85)/ 6.41 / 1.38 (1.95) / 2.63 / 16.12 (11.49) P values per clinical indicator: 0.0091; < 0.0001/ 0.0016/ <0.0001/ 0.0002 4. Data presented per GETE level by AQLQ mean activity score (SD)/Mean emotions score (SD) /Mean environment score (SD) / Mean symptoms score (SD) / Mean overall score (SD) *Patient version GETE* • Complete control of asthma: 5.74 (1.21) / 5.83 (1.19) / 5.52 (1.37) / 5.75 (1.07) / 5.73 (1.07)			

Reference, year	Construct validity**	Reproducibility	Internal consistency	Responsiveness
	• Marked improvement of asthma: 5.15 (1.21) / 5.29 (1.30) / 4.89 (1.34) / 5.15 (1.08) / 5.13 (1.06) • Discernible, but limited improvement in asthma: 4.76 (1.25) / 4.72 (1.43) / 4.56 (1.43) / 4.58 (1.13) / 4.64 (1.12) • No appreciable change in asthma: 4.45 (1.33) / 4.33 (1.47) / 4.43 (1.35) / 4.22 (1.17) / 4.31 (1.10) • Worsening of asthma: 4.40 (1.47) / 3.88 (1.57) / 4.33 (1.55) / 3.76 (1.24) / 4.03 (1.19) <u>*Physician version GETE*</u> • Complete control of asthma: 5.73 (1.22) / 5.85 (1.17) / 5.50 (1.38) / 5.72 (1.05) / 5.71 (1.06) • Marked improvement of asthma: 5.21 (1.25) / 5.38 (1.27) / 4.99 (1.35) / 5.23 (1.09) / 5.20 (1.07) • Discernible, but limited improvement in asthma: 4.79 (1.26) / 4.72 (1.49) / 4.59 (1.42) / 4.60 (1.21) / 4.67 (1.17) • No appreciable change in asthma: 4.56 (1.29) /4.54 (1.42) /4.48 (1.40) /4.37 (1.16) /4.45 (1.09) Worsening of asthma: 4.42 (1.40)/ 3.29 (1.32) /4.04 (1.46) / 3.70 (1.00) / 3.90 (1.10)			
Fitzpatrick, 2020[7] ASSESS	• AQLQ total score: r= -0.315** • AQLQ symptom: r= -0.387** • AQLQ activity: r= -0.244* • AQLQ emotion: r= -0.387** • AQLQ environment: r= -0.253* *P < .05 and **P < .01.	ICC (baseline/ 12mo; 12mo/24 mo; 24mo/36 mo) • *Entire sample* 0.764/ 0.768/ 0.813 • *12-17 ys*: 0.717/ 0.841/ 0.732 • *>18 y:* 0.768 / 0.766/ 0.816	Cronbach's alpha: *entire sample* 0.639 *12-17y:* 0.468 *≥18 y:* 0.662	<u>1. r values: AQLQ total score / symptom / activity / emotion / environment:</u> • *0-12 mo:* -0.550* / -0.579* / -0.453* / -0.488* / -0.300* • *12 - 24 mo:* -0.462* / -0.508* / -0.349* / -0.408* / -0.212* • *24 - 36 mo:* -0.468* / -0.481* / -0.396* / -0.368* / -0.265* *P < .001. <u>2. r values for changes: 0 and 12 months / 12 and 24 months/ 24 and 36 months:</u> • Change in ASSESS vs Change in ACT: -0.668* / -0.676* / -0.622

Reference, year	Construct validity**	Reproducibility	Internal consistency	Responsiveness
				• Change in ASSESS vs Change in FEV1 absolute % difference: -0.395* / -0.369* / -0.372*.
Wildfire, 2012[8] CASI*				Intervention group showed improvement in CASI & symptom days (0.67 points & 0.48-day improvement; both P < .001). CASI: 32% greater magnitude of improvement (standardized effect size: 0.25 vs 0.17 for symptom days)
Shen, 2021[10] ASUI	1.ASUI baseline/ week 12: SGRQ score: -0.68 / -0.72 SGRQ Symptom: -0.78 / -0.81 SGRQ Impact: -0.46 / -0.56 SGRQ Activity: -0.60 / -0.66 ACQ-5 score: -0.78 / -0.85 EQ-5D index score: 0.51 / 0.52 EQ-5D VAS score: 0.44 / 0.56 % FEV1 pred.: 0.19 / 0.28 FEV1 (mL): 0.15 / 0.20 No. of exacerbations: -0.15 / -0.29 Global rating of activity limitation: -0.43 / -0.51 ASD Score: -0.54 / -0.53 2.Known group validity: Group with higher ACQ-5 scores (≥1.5 indicating poorly controlled asthma) tended to have lower ASUI scores (indicative of greater symptom burden) (p<0.0001). For % pred FEV1, group with lowest FEV1 function (≤ 60%) had the lowest ASUI scores (p<0.0001).	ICC=0.87-0.90	Cronbach's alpha: Baseline=0.87 Week 12 =0.90	1.ASUI change from baseline to week 4: ΔACQ-5 score: - 0.57 ΔSGRQ score: 0.50 ΔSGRQ Symptom: -0.53 ΔSGRQ Impact: -0.25 ΔSGRQ Activity: -0.41 Δ % predicted FEV1: 0.16 No. of asthma exacerbations during on-treatment phase: -0.02 2. ASUI change from baseline to week 12: ΔACQ-5 score: -0.67 ΔSGRQ score: -0.60 ΔSGRQ Symptom: -0.67 ΔSGRQ Impact: -0.42 ΔSGRQ Activity: -0.50 Δ % predicted FEV1: 0.25 No. of asthma exacerbations during on-treatment phase: -0.05
Shen, 2021[10] ASI	1.ASI (baseline/week 12): SGRQ score: 0.67/ 0.71 SGRQ Symptom: 0.80 / 0.82	ICC=0.87-0.90	Cronbach's alpha:	1.ASI change from baseline to week: 4: ΔACQ-5 score: 0.58

Reference, year	Construct validity**	Reproducibility	Internal consistency	Responsiveness
	SGRQ Impact: 0.46 / 0.55 SGRQ Activity: 0.59 / 0.65 ACQ-5 score: 0.79 / 0.85 EQ-5D index score: -0.49/ -0.49 EQ-5D VAS score: -0.43/ -0.55 % FEV1 pred.: -0.20/ -0.28 FEV1 (mL): -0.14/ -0.19 No. of exacerbations: 0.12 / 0.28 Global rating of activity limitation: 0.43 / 0.49 ASD Score: 0.54 / 0.52 / <u>2. Known group validity:</u> Group with higher ACQ-5 scores (≥1.5 indicating poorly controlled asthma) tended to have higher ASI scores (p<0.0001). For % pred FEV1, group with lowest FEV1 function (≤60%) had the highest ASI scores (p<0.0001).		Baseline=0.89, Week 12=0.93	ΔSGRQ score: 0.50 ΔSGRQ Symptom: 0.55 ΔSGRQ Impact: 0.27 ΔSGRQ Activity: 0.39 Δ % predicted FEV1: -0.18 No. of asthma exacerbations during on-treatment phase: 0.05 <u>2.ASI change from baseline to week 12</u>: ΔACQ-5 score: 0.69 ΔSGRQ score: 0.61 ΔSGRQ Symptom: 0.70 ΔSGRQ Impact: 0.45 ΔSGRQ Activity: 0.49 Δ % predicted FEV1: -0.28 No. of asthma exacerbations during on-treatment phase*: 0.09
Hyland, 2018[20] Masoli, 2021[21] Lanario, 2021[22] SAQ	<u>1. SAQ vs</u> miniAQLQ =0.76; ACT=0.68; EQ-5D-5L score=−0.76; EQ-5D-VAS= 0.71; SAQ-global scale= 0.72; FEV1 % predicted=0.27; BMI=−0.31 <u>2. SAQ-global vs</u> MiniAQLQ= 0.71; ACT total= 0.68; EQ-5D-5L= −0.71; EQ-5D-VAS= 0.76; FEV1 % predicted=0.26; BMI=−0.22 <u>3. Data for FEV1% predicted vs SAQ domains:</u> SAQ score: 0.23; SAQ My Life: 0.29; SAQ My Mind: 0.15; SAQ My Body: 0.15; SAQ global score: 0.28 <u>4.Data for cumulative prednisolone vs SAQ domains:</u> SAQ score: -0.34; SAQ My Life: − 0.35; SAQ My Mind: − 0.23; SAQ My Body: − 0.34; SAQ global score: − 0.37 <u>5.Data for Exacerbations in the last 12 mo requiring OCS vs SAQ domains:</u>	ICC= 0.93 (SAQ) ICC= 0.93 (SAQ-global)	Cronbach's alpha= 0.93.	Change scores for different degrees of global rating of change is available for SAQ, SAQ subscales and SAQ-global.

Reference, year	Construct validity**	Reproducibility	Internal consistency	Responsiveness
	SAQ score: -0.37; SAQ My Life: − 0.37; SAQ My Mind: − 0.33; SAQ My Body: − 0.33; SAQ global score: − 0.36 6. Data for Hospital admissions in the last 12 mo vs SAQ domains: SAQ score: -0.17; SAQ My Life: − 0.16; SAQ My Mind: − 0.16; SAQ My Body: − 0.13; SAQ global score: − 0.23 7. EQ-5D-5L Index value/EQ-5D-5L item 5–Anxiety and Depression/EQ-5D VAS/ ACQ score/ACT total SAQ score:0.72/ -0.64 /0.73/ -0.75/0.71 SAQ My Life: 0.73/-0.54/0.74/-0.79/0.72 SAQ My Mind: 0.64/-0.73/0.63/ -0.62/ 0.62 SAQ My Body: 0.59/-0.56/0.62/-0.60/ 0.64 SAQ global score: 0.66/-0.50/ 0.79/ 0.77/ 0.68			
Globe, 2019[13] ASD				1. Responsiveness of the Average 7-Day ASD Score at Weeks 12 and 24 Data presented for Responders Mean (SE) Non-Responders/ Mean (SE) Difference P-Value. Effect size presented for responder / nonresponder Week 12 ACQ > 0.5: −0.49 (0.03) / 0.05 (0.03).Effect size: 0.82 / 0.08 ACQ > 1.0: −0.54 (0.03) / −0.13 (0.03).Effect size: 0.90 / 0.22 PGA: −0.48 (0.03) / −0.07 (0.03) Effect size: 0.80 / 0.12 Week 24: ACQ > 0.5: −0.59 (0.03) / −0.06 (0.03) / − 0.53. Effect size: 0.98 / 0.10 ACQ > 1.0: −0.68 (0.04) / −0.15 (0.03) / − 0.53.Effect size: 1.13 / 0.25

Reference, year	Construct validity**	Reproducibility	Internal consistency	Responsiveness
				PGA: −0.60 (0.03) / −0.10 (0.04) / −0.49.Effect size: 1.00 / 0.17 2. Responsiveness of ASD Symptomatic Days in a 7-Day Period at Weeks 12 and 24 Data presented for Responders Mean (SE) Non-Responders Mean (SE).Effect size presented for responder / nonresponder: Week 12: ACQ > 0.5: −2.21 (0.16) / −0.57 (0.18).Effect size: 0.73 / 0.19 ACQ > 1.0: −2.35 (0.20) / −0.90 (0.16).Effect size: 0.78 / 0.30 PGA: −2.34 (0.16) / −0.45 (0.17) Effect size 0.78 / 0.15 Week 24: ACQ > 0.5: −2.86 (0.18) / − 0.28 (0.28).Effect size 0.95 / 0.09 ACQ > 1.0: −3.21 (0.21) / −0.77 (0.20).Effect size 1.07 / 0.26 PGA: −2.97 (0.19) / −0.45 (0.23) Effect size 0.99 / 0.15 3. Spearman correlations between baseline to 12-week changes in ASD scores and baseline to 12-week changes in ACQ and PGA scores were 0.59 and 0.57, respectively. 4. Correlations between baseline to 24-week changes in ASD scores and

Reference, year	Construct validity**	Reproducibility	Internal consistency	Responsiveness
				baseline to 24-week changes in ACQ and PGA scores were 0.67 and 0.53, respectively.

ACQ, Asthma Control Questionnaire; ACT, Asthma Control Test; AQLQ, Asthma Quality of Life Questionnaire; ASSESS, Asthma Severity Scoring System; ASUI, Asthma Symptom Utility Index; ASI, Asthma Symptom Index; ASD, Asthma Symptom Diary; BMI, Body Mass Index; CASI, Composite Asthma Severity Index; EQ-5D-5L,EuroQol Questionnaire-5 Dimensions-5 Levels; EQ-5D-VAS, EuroQol Questionnaire-5 Dimensions Visual Analogue Scale; GETE, Global Evaluation of Treatment Effectiveness; FEV1, forced expiratory volume in 1 second; ICC, intraclass correlation coefficient; miniAQLQ, mini- Asthma Quality of Life Questionnaire; PGA, Patient's Global Assessment; SAQ, Severe Asthma Questionnaire; SGRQ, St George's Respiratory Questionnaire. *Only external validation data was used for analysis as it was performed in a study with biologics. **As there is no golden standard in asthma, data about criterion validity was combined with construct validity.

Table S6. Additional study characteristics for validation studies.

Reference, year	Scale	Study design	N	Age (years) Mean (IQR)	Patient characteristics	Asthma severity (severe %)	Definition of asthma	Biological drug
Hyland, 2018[20]	SAQ	Observational	160	51	F=66%; FEV_1 % predicted=72 (28–137)	Severe (100%)	ERS/ATS guidelines	Omalizumab =21% Mepolizumab=3%
Lanario, 2021[22]	SAQ	Cross-sectional	460	51 (50–53)	F=65%; FEV_1 % predicted, mean (CI): 71.75 (69.79–73.71) Prescribed maintenance OCS, n (%): 218 (47)	Severe (100%)	ERS/ATS guidelines	Different biologics=39%
Wildfire, 2012[8]*	CASI	RCT	419	10.8 (8-14)	F= 42%; FEV_1 % predicted (mean ± SD) = 92.1±17.1	Mild to severe (54%)	Physician-diagnosis of asthma	Omalizumab=50%

ATS, American Thoracic Society; CASI, Composite Asthma Severity Index; ERS, European Respiratory Society; FEV1, forced expiratory volume in 1 second; F, females; SAQ, Severe Asthma Questionnaire; IQR, interquartile range; CI, confidence interval; SD, standard deviation; OCS, oral corticosteroids; RCT, Randomised Control Trial. *Only external validation data was used for analysis as it was performed in a study with biologics.

Table S7. Risk of bias assessment.

	ASSESS [7]	CASI[8]*	FEOS[9]	ASUI[10,11]	ASI[10]	ASD[12,13]	GETE[14]*	SAQ[15,20-22]**
PROM development	I	I	I	D	I	D	I	V
Structural validity								
Internal consistency	I			D	V			
Cross-cultural validity								
Reliability	I			A	A			A
Measurement error	I			A	A			
Construct validity	A			D	D		V	D
Responsiveness	D	V		D	A	D		D

ASSESS, Asthma Severity Scoring System; ASUI, Asthma Symptom Utility Index; ASI, Asthma Symptom Index; ASD, Asthma Symptom Diary; CASI, Composite Asthma Severity Index; GETE, Global Evaluation of Treatment Effectiveness; FEOS, FEV1, Exacerbations, Oral Corticosteroids, Symptoms Score; SAQ, Severe Asthma Questionnaire. *Only external validation data was used for analysis as it was performed in a study with biologics. Risk of bias in individual studies was investigated using the COSMIN checklist for PROMs[2,3] and composite outcome measures (COSMIN RoB for non-PROMs)[4]. V= very good; A = adequate; D = doubtful; I = inadequate. ** SAQ is based on a formative model; therefore, there was no need to investigate the internal consistency. Empty cells indicate that the measurement property was not investigated.

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