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ORIGINAL ARTICLE

Allergen-Specific Immunotherapy and Biologics

Determining the minimal important differences in the RQLQ score with grass and tree allergy immunotherapy versus placebo in adults with moderate-to-severe allergy

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Abstract

Background: Pollen from grasses and trees can trigger allergic rhinitis (AR), where the symptoms and associated consequences can negatively affect quality of life (QoL). The Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) is frequently used in clinical trials of AR to assess QoL. To help interpret RQLQ data, the minimal important difference (MID) can be used to assess whether a mean difference in QoL between treatment groups is clinically meaningful. In seasonal allergy, an MID differs according to the allergen, pollen exposure, symptom severity, patient age and treatment; the same MID cannot be applied to all scenarios.

Methods: Using data from four Phase III clinical trials of SQ sublingual immunotherapy-tablets in adults with moderate-to-severe allergy, between-group MIDs were derived for the RQLQ in grass pollen allergy (during the peak [n = 501] and entire [n = 514] pollen seasons), and in tree pollen allergy (during the birch [n = 516] and tree [n = 518] pollen seasons), using anchor-based methodology, supported by distribution-based methods.

Results: For grass pollen allergy, anchor-based derived between-group MIDs were 0.22 for the entire pollen season (n = 343) and 0.10 for the peak pollen season (n = 335). For tree pollen allergy, anchor-based derived between-group MIDs were 0.26 for the tree pollen season (n = 306) and 0.16 for the birch pollen season (n = 305) (representative of peak season). Distribution-based derived MIDs were supportive of the anchor-based values.

Conclusions: This analysis has derived between-group MIDs specific to the trial populations evaluated and to the conditions under which the data were obtained, and highlights the need for a range of MIDs to reflect the unique nature of seasonal allergic disease.

KEYWORDS
Allergy, immunotherapy, minimal important difference, quality of life, Rhinoconjunctivitis Quality of Life Questionnaire

Abbreviations: AR, allergic rhinitis; MID, minimal important difference; QoL, quality of life; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire; SLIT, sublingual immunotherapy.

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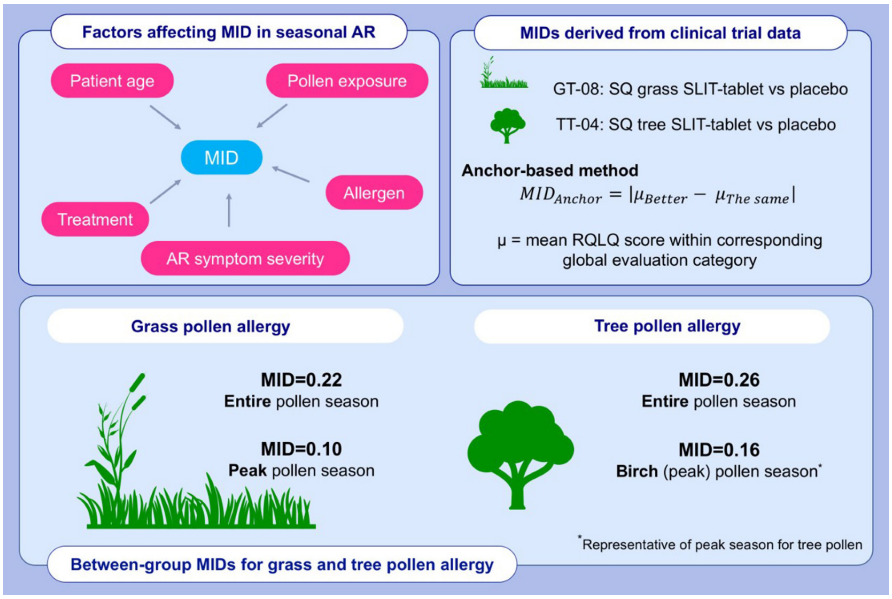

GRAPHICAL ABSTRACT

The RQLQ evaluates QoL in trials of AR; an MID for the RQLQ represents a clinically meaningful difference in QoL between treatment groups. There is no single MID that applies to all seasonal allergies and severity of disease. These analyses provide an estimation of between-group MIDs for the RQLQ in grass and tree pollen-induced AR, considering different pollen exposures.
Abbreviations: AR, allergic rhinitis; MID, minimal important difference; QoL, quality of life; RQLQ, rhinoconjunctivitis quality of life questionnaire; SLIT, sublingual immunotherapy

1 | BACKGROUND

Pollen from grasses and trees is a common source of allergens that trigger allergic rhinitis (AR).[1] Sensitised individuals can experience the symptoms of AR throughout the relevant pollen season each year – for example during late spring and summer for grasses and during spring for trees.[1] Pollen levels vary from year to year between seasons and can also fluctuate within any one pollen season;[2,3] an inter-annual variability in the seasonal pollen index of approximately 5–15% has been reported for grass and approximately 15–25% for birch.[2] Such changes can influence the symptomatic burden of AR in sensitised individuals. The European Academy of Allergy and Clinical Immunology (EAACI) Task Force has published a report confirming a positive correlation between grass and birch pollen concentration and the symptoms of AR – the maximum level of AR symptoms occurred mostly within the peak pollen periods.[4]

The symptoms of AR, combined with the subsequent negative effect on various emotional and social aspects of everyday life, can have a considerable detrimental impact on an affected individual's quality of life (QoL),[5] which worsens with increasing severity of AR.[6,7] In the development of treatments for AR, regulatory authorities and reimbursement agencies are, increasingly, requesting evidence for the translation of clinical benefit into a positive, and clinically relevant, effect on patients' QoL. The Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) has been identified as the most frequently used instrument to assess health-related QoL (HRQoL) in clinical trials of AR.[5] To help interpret the RQLQ clinical data from a treatment benefit perspective, it is important to understand the smallest degree of improvement that can be considered clinically beneficial to patients.[8,9] This is known as the minimal important difference (MID).[8,9]

Allergy immunotherapy (AIT) is an effective treatment for AR induced by pollen from grass, and from birch trees.[10-13] However, MIDs based on mean RQLQ data from confirmatory randomised controlled trials (RCTs) of AIT have not been derived for either type of allergy. Juniper and colleagues (who developed the RQLQ) derived a within-patient MID of 0.5 using data from patients with ragweed pollen-induced AR who were treated with conventional pharmacotherapy.[14] Although a within-patient MID is widely used and is the type of MID preferred by the US Food and Drug Administration (FDA),[15] it does not reflect the minimal difference that is considered clinically meaningful at the group level[16,17] (and which is relevant for trials of AIT versus placebo). An MID derived at the individual level is unlikely to be the same as a between-group MID; indeed, a between-group MID is likely to be smaller than a within-patient MID.[17] In addition, calculating a within-patient MID for the RQLQ requires data from a baseline assessment, which are difficult to obtain in clinical trials of AIT conducted under natural conditions where pollen exposure is variable. Unlike environmental exposure chamber trials where pollen exposure is controlled and, therefore, a baseline assessment can be performed, field trials to confirm the efficacy of AIT must initiate treatment before the pollen season starts, to induce immunomodulation during subsequent pollen exposure. Therefore, it is not possible to perform a baseline assessment of RQLQ in this situation.

In general, an MID (independent of type) can vary across patient groups with respect to factors such as disease type and severity.[18,19] In allergy, for example, an MID for the effect of grass pollen AIT would not necessarily be the same as the MID for tree pollen AIT, even in patients with similar disease severity. Similarly, for individuals sensitised to the same allergen, an MID for mild disease would

not be the same as that for moderate or severe disease. An added complexity is that symptom severity can be driven by the pollen concentration, meaning that the level of pollen exposure can also influence the MID. Age can also affect MID values, such that the MID may differ in younger versus older individuals.[20] Furthermore, the type of allergy treatment under consideration may impact the MID. For example, conventional pharmacotherapy is designed to have a short time to effect, whereas the onset of effect is longer for AIT. In clinical trials of AIT, it is common practice to permit the use of pharmacotherapy (as 'rescue medication') alongside the AIT, resulting in a combined effect of the two medications. Therefore, an MID calculated using data from trials of pharmacotherapy alone, as was done by Juniper and colleagues, is expected to be different to an MID calculated from trials of AIT. Given the variety of influential factors, it is not possible to derive one MID for the whole allergy field – it would be more prudent to define a range of MID values according to different scenarios. Therefore, deriving a between-group MID for the mean RQLQ in grass pollen allergy and tree pollen allergy requires separate ranges of MID.

Various methodologies can be used to establish the MID for HRQoL instruments (or any other patient-reported outcome [PRO]). The anchor-based method is characterised by comparing ('anchoring') the target outcome measure, such as the RQLQ, to an external clinically relevant measure, which serves as the anchor.[15,17,21] This external measure is usually a PRO,[15,17,21] such as the global rating of change or the global evaluation. The distribution-based method is characterised by establishing the MID based on the statistical characteristics of the obtained sample.[17,21] Therefore, an MID can also vary depending on the derivation method used.[21]

Although there is no clear consensus regarding which method to use, anchor-based methods most often serve as the primary analysis to derive an MID, supported by distribution-based methods.[15,17,22]

The present analysis aimed to derive between-group MIDs for the mean RQLQ in patients with moderate-to-severe allergy to grass pollen and, separately, in patients with moderate-to-severe allergy to tree pollen using an anchor-based method, supported by distribution-based methodology.

2 | METHODS

2.1 | Data used in the analysis

The MID analyses used data from four Phase III, randomised, double-blind, placebo-controlled trials of SQ sublingual immunotherapy (SLIT)-tablets, conducted by ALK – three in grass pollen allergy[10-12] and one in tree pollen allergy (Table 1).[13] All four trials were confirmatory RCTs conducted under natural conditions; data from one pollen season in each trial were used for the analyses. For trials evaluating more than one pollen season, data from the first pollen season were used. An additional trial (GT-14) was excluded from this analysis, due to a lack of relationship between pollen count and symptoms.[23]

The four trials were selected as they each included the RQLQ as a measure of QoL. Two trials (GT-08 and TT-04) also included an assessment of global evaluation, which provides the PRO measure required by the anchor-based method for deriving an MID. Table 2 shows the timings of the RQLQ and global evaluation assessments in these two trials. GT-08 and TT-04 were designed to evaluate the safety and efficacy of SLIT-tablets; RQLQ was included as a secondary outcome and global evaluation as an exploratory outcome. The between-group MID values were derived by *post hoc* analyses using the data from the RQLQ and global evaluation assessments as they were performed in the trials.

An MID was calculated for the entire and peak pollen seasons in the grass allergy trials, and for the tree and birch pollen seasons in the tree allergy trial. The birch pollen season was used to represent the peak pollen season for tree allergy, since birch pollen is the major allergenic tree pollen across parts of Europe (and representative of the cross-reactive tree pollens in the birch homologous group). Pollen seasons were defined according to the threshold of the relevant pollen. In the grass allergy trials, the start of the entire grass pollen season was defined as the first day of three consecutive days with a pollen count ≥10 grains/m^3.[11,12] The end of the grass pollen season was defined as the last day of the last occurrence of three consecutive days with a pollen count ≥10 grains/m^3.[11,12] The peak grass pollen season was defined as the period of 15 consecutive days within the entire pollen season with the highest average pollen count among all possible 15 consecutive-day averages across the grass pollen season.[11,12]

For the tree allergy trial, the tree pollen season included the alder, hazel and birch pollen seasons.[13] The start and end of the alder, hazel and birch pollen seasons were defined as described for the grass pollen season, with the same pollen count threshold of ≥10 grains/m^3 for alder and hazel, but a higher threshold of ≥30 grains/m^3 for the birch pollen season.[13]

According to best practice for the derivation of an MID, the anchor-based method was applied to the mean RQLQ data from the GT-08 and TT-04 trials. Corresponding analyses using the distribution-based method were used to support the anchor-based analyses.

2.2 | Anchor-based methodology

To derive a between-group MID using anchor-based methodology (MID_{Anchor}), the mean RQLQ scores obtained from the GT-08 and TT-04 trials were anchored to the global evaluation assessment.

In adults, the RQLQ is graded on a 7-point scale (0=not troubled to 6=extremely troubled).[24,25] The mean value for each domain is calculated and the overall RQLQ score is expressed as the mean of the 28 item scores;[25] higher RQLQ scores indicate poorer HRQoL.[24] For each patient, the RQLQ was assessed several times during each trial (Table 2), and the overall RQLQ scores were averaged for the entire grass/tree pollen season, as well as for the peak grass/birch pollen season; the overall RQLQ data were used in the analyses.

TABLE 1 Overview of the grass and tree pollen allergy SQ SLIT-tablet clinical trials used in the MID analyses

Trial	Trial objective(s)	Patient population	Patients randomised, n	Description of pollen season	Key outcome(s)
Grass pollen allergy trials					
GT–08 NCT00227279 EudraCT: 2004–000083–27[10]	To confirm the efficacy of SQ grass SLIT-tablet in patients with grass pollen-induced ARC	Moderate-to-severe ARC Mean age: 34 years Onset of ARC: 18 years Mean duration of ARC: 16 years	SQ grass SLIT-tablet: 316 Placebo: 318	Mean duration: Entire pollen season: 58 days Peak pollen season: 15 days Average daily pollen count: Entire pollen season: 53.5 grains/m^3 Peak pollen season: 105.1 grains/m^3	SQ grass SLIT-tablet reduced ARC symptoms by 30% and medication use by 38% during the entire pollen season ($p < 0.0001$ vs placebo)
P05238 NCT00562159[11]	To investigate the safety and efficacy of SQ grass SLIT-tablet in patients with grass pollen-induced ARC	Moderate-to-severe ARC Mean age: 36 years Onset of ARC: 15 years Mean duration of ARC: 21 years	SQ grass SLIT-tablet: 213 Placebo: 225	Mean duration: Entire pollen season: 53 days Peak pollen season: 15 days Average daily pollen count: Entire pollen season: 26.8 grains/m^3 Peak pollen season: 48.0 grains/m^3	SQ grass SLIT-tablet reduced combined ARC symptoms and medication use by 20% during the entire pollen season ($p = 0.005$ vs placebo) Similar improvements were observed during the peak pollen season
P08067 NCT01385371[12]	To evaluate SQ grass SLIT-tablet treatment in patients with grass pollen-induced AR/C	Moderate-to-severe AR/C Mean age: 33 years Onset of AR/C: 15 years Mean duration of AR/C: 18 years	SQ grass SLIT-tablet: 752 Placebo: 749	Mean duration: Entire pollen season: 54 days Peak pollen season: 15 days Average daily pollen count: Entire pollen season: 23 grains/m^3 Peak pollen season: 53 grains/m^3	SQ grass SLIT-tablet reduced combined AR/C symptoms and medication use by 23% during the entire pollen season, and by 29% during the peak pollen season ($p < 0.001$ vs placebo)
Tree pollen allergy trial					
TT–04 EudraCT: 2015–004821–15[13]	To evaluate the safety and efficacy of SQ tree SLIT-tablet in patients with tree pollen-induced AR/C	Moderate-to-severe AR/C Mean age: 36 years Onset of AR/C: 20 years Mean duration of AR/C: 16 years	SQ tree SLIT-tablet: 320 Placebo: 314	Mean duration: Tree pollen season: 50 days Birch pollen season: 24 days Average daily pollen count: Alder: 100 grains/m^3 Hazel: 40 grains/m^3 Birch: 284 grains/m^3	SQ tree SLIT-tablet reduced combined AR/C symptoms and medication use by 36.5% during the tree pollen season and by 39.6% during the birch pollen season ($p < 0.0001$ vs placebo)

Note: AR/C = allergic rhinitis with or without conjunctivitis, ARC = allergic rhinoconjunctivitis, SLIT = sublingual immunotherapy.

Based on the assumption that symptomatic burden would be greatest during peak pollen levels, the RQLQ scores were mapped to the pollen count in order to assess the MID_{Anchor} for the peak grass pollen season and the birch pollen season.

For the global evaluation in the GT-08 and TT-04 trials, patients were asked to state how their allergy symptoms during the pollen season within the trial compared with their allergy symptoms in the previous pollen season(s). Patients could answer, 'much better', 'better', 'the same', 'worse' or 'much worse'.

For each pollen allergy (grass and tree) and each treatment group (SQ SLIT-tablet and placebo), to represent minimal improvement, the mean RQLQ score corresponding to the global evaluation categories 'better' and 'the same' was considered in the analyses of MID_{Anchor}, based on the formula:[26,27]

$$MID_{Anchor} = \left|\mu_{Better} - \mu_{The\ same}\right|$$

where μ is the mean RQLQ score within the corresponding global evaluation category.

The formula above determines the difference between two patient groups – those who felt better and those who had not improved – as captured by the global evaluation. For each trial, the derived MID_{Anchor} values for the active and placebo groups were averaged to determine one between-group MID_{Anchor} for each pollen season within each type of allergy (entire and peak grass pollen seasons, and tree and birch pollen seasons). An average was calculated to ensure an equal contribution of active and placebo data to the estimation of MID (the number of patients in each group was not equally distributed).

2.3 | Distribution-based methodology

In contrast to the anchor-based method, distribution-based derivation of an MID ($MID_{Distribution}$) is based on statistical properties of the observed distribution (and, by definition, does not consider the patient's perspective that is captured by the global evaluation).[17,18,21] The $MID_{Distribution}$ helps to put the MID_{Anchor} values into perspective.

Cohen (1992) proposed operational benchmarks for standardised effect sizes.[28] The defined standard benchmarks are 0.2 (small effect), 0.5 (medium effect) and 0.8 (large effect),[28] which are now generally accepted values across various disciplines.[18] Samsa et al. (1999) suggest that a standard benchmark of 0.2 can be used as an initial value for $MID_{Distribution}$.[18] In the present analysis, standardised effect sizes were calculated for the RQLQ between SQ SLIT-tablet (grass and tree) and placebo, using data from each of the four clinical trials, by dividing the treatment difference (ie, raw effect size) by the pooled standard deviation from the relevant pollen season of the corresponding clinical trial:

$$ES_{Standardised} = \frac{\mu_{Placebo} - \mu_{SQ\ SLIT-tablet}}{\sigma_{pooled}} = \frac{ES_{Raw}}{\sigma_{pooled}}$$

where μ is the mean RQLQ score, σ_{pooled} is the mean of the standard deviations from the individual trials, and ES is effect size.

The $ES_{Standardised}$ values for the RQLQ in grass, and tree, pollen allergy calculated from the trial data can then be compared with 0.2 to determine if Samsa's value of $MID_{Distribution}$ is met.

Samsa et al. (1999) recommend that the standard benchmark of 0.2 is compared with the results of anchor-based analyses if possible.[18] To allow for this comparison in the present analysis, the benchmark value on the standard scale was converted to the corresponding benchmark value for the raw scale (ie, RQLQ), using the formula:[18]

$$Benchmark_{Raw} = Benchmark_{Standard} \bullet \sigma_{pooled}$$

where σ_{pooled} is the mean of the standard deviations from the relevant pollen season.

In addition to Samsa's proposed initial $MID_{Distribution}$ of 0.2, the MID_{Anchor} values were also compared with standard benchmarks of 0.1 and 0.3 to refine the data within these parameters and to allow further understanding of the results from the analyses.

In the AIT trials included in this analysis, the RQLQ data were not normally distributed. Therefore, according to common practice, square root transformation of the data was performed before analysis.

3 | RESULTS

Table 3 shows the mean RQLQ data anchored to the global evaluation categories for the SQ SLIT-tablet and placebo treatment groups in the grass and tree pollen AIT trials. The anchor-based derived MID values are presented in Table 4, showing that the MID values for the peak grass pollen season and the birch pollen season were lower than those derived for the corresponding entire grass pollen season or the tree pollen season.

ES_{Raw} and $ES_{Standardised}$ values for the different pollen seasons in the individual clinical trials are presented in Table S1. For all trials except one (P08067), the $ES_{Standardised}$ values are above the initial value of $MID_{Distribution}$ (0.2) proposed by Samsa et al. (1999).[18]

The $Benchmark_{Raw}$ values converted from Samsa's standard benchmark of 0.2 and the wider parameters, 0.1 and 0.3, are presented in Table S2. The MID_{Anchor} values in Table 4 were compared with the $Benchmark_{Raw}$ values in Table S2 to assess how well the MIDs derived from the clinical trial data aligned between the two derivation methods. For the entire grass pollen season, the MID_{Anchor} was closest to the $Benchmark_{Raw}$ corresponding to a $Benchmark_{Standard}$ of 0.2; for the peak grass pollen season, the corresponding $Benchmark_{Standard}$ value was 0.1. For the tree pollen season, the MID_{Anchor} was closest to the $Benchmark_{Raw}$ corresponding to a $Benchmark_{Standard}$ of 0.3 and for the birch pollen season, the value corresponds to values for $Benchmark_{Standard}$ between 0.1 and 0.2.

4 | DISCUSSION

The analyses presented have derived a set of between-group MIDs for the RQLQ using data from SQ SLIT-tablet trials in grass and tree

TABLE 2 RQLQ and global evaluation assessments in (A) GT-08 and (B) TT-04 trials

(A) GT-08

Visit	1 Screening	2 Randomisation (1 week after Visit 1)	3 Off season (~8 weeks after Visit 2)	4 Off season (~16 weeks after Visit 2)	5 Pre-season (~2 weeks before anticipated start of GPS)	6 On season (in GPS)	7 End of treatment (~1 week after end of GPS)	Follow-up Post season (1 week after Visit 7)
RQLQ					X[†]----------			
Global evaluation						X[‡]		

(B) TT-04

Visit	1 Screening	2 Randomisation	3 Off season	4 Pre-tree pollen season	Telephone consultation Start of tree pollen season	5 Pre-birch pollen season	6 End of trial
RQLQ	X				X	X[†]----------	
Global evaluation							X[§]

Note: GPS = grass pollen season, RQLQ = Rhinoconjunctivitis Quality of Life Questionnaire.

[†]RQLQ assessments were performed on a weekly basis from Visit 5 onwards.

[‡]Question asked: Compared to your rhinoconjunctivitis symptoms in previous grass pollen seasons, how have you felt overall in this grass pollen season?

[§]Question asked: Compared to your rhinitis and/or conjunctivitis symptoms in the previous birch/tree pollen season, how have you felt overall in this birch/tree pollen season?

pollen allergy, across different pollen seasons. This is the first demonstration of a clinically relevant impact of SQ SLIT-tablet therapy on QoL evaluated using the RQLQ in patients with grass or tree pollen allergy. The derived between-group MID values can be used to reassure physicians and payers that the treatment is having a worthwhile beneficial effect on the patient's QoL. However, it is important to note that each of the between-group MIDs derived are specific to the patient population of the trials included in the analyses (adults with moderate-to-severe grass or tree allergy) and for the natural pollen seasons during the trial (duration and pollen concentration). Evidence from clinical studies indicates that the RQLQ is responsive to different levels of pollen exposure,[29,30] meaning that pollen levels can influence the QoL of patients with pollen-induced AR. The between-group MIDs derived in this analysis may be applicable to other scenarios under similar conditions, but not necessarily to pollen seasons with markedly different pollen levels and associated symptom severity. Such considerations emphasise the need for a range of MIDs that can be applied to different pollen concentrations and varying degrees of symptom severity among patients, and which also account for differences in patient age. The present analyses were based on the evidence available and provide an initial exploration into defining between-group MIDs for seasonal allergy. It is reassuring to know that although the trials were not designed to derive an MID for the RQLQ, the sample size used in these analyses was relatively large in comparison with other studies that have derived MIDs within the allergy field[31,32]; this observation lends an element of robustness to the findings presented here.

The anchor-based derived between-group MID values for the peak grass pollen season and for the birch pollen season (representative of the peak pollen season for tree allergy) were lower than the values derived for the corresponding entire grass pollen season and tree pollen season. In peak season, symptoms are expected to be most intense.[4] Therefore, even relatively small changes in QoL would be worthwhile to patients, and would explain the lower anchor-based MIDs derived for the peak pollen seasons. Another possible explanation is the 'priming' effect of pollen earlier in the season, which may cause patients to be more symptomatic during peak pollen exposure;[3,33,34] again, even a small relief from symptoms would be meaningful to patients. A comparison of the findings from the anchor-based and distribution-based methods suggests that, for seasonal pollen allergy, the expected MID during the most intense period of the pollen season is between the standard benchmarks 0.1 and 0.2, and during the entire pollen season is between the standard benchmarks 0.2 and 0.3. Until more specific MIDs are available, these benchmark values can, potentially, be applied to other seasonal pollen allergies treated with AIT, or other populations, when a PRO anchor is not available.

To place the derived MID values into perspective, it is important to consider that an average 'off-season' RQLQ score may not be zero and, similarly, an average 'in-season' RQLQ score may not be 6, despite prolonged severe symptoms. Data from AIT trials are limited, but one study of SQ grass SLIT-tablet reported RQLQ scores that can be used to derive estimates for the two seasons.[29] In this study, the

off-season value was approximately 1.0 and the in-season value was approximately 2.5 – a range of 1.5 points.[29] It is important to highlight that, even during the grass pollen season when patients were sufficiently bothered by their symptoms to contact their doctor, the RQLQ score was 2.5, on a 7-point scale.[29] Based on these data, a fully-effective treatment could be expected to maintain QoL at the off-season level and prevent a 1.5-point increase in RQLQ. Applying this principle to the present analysis, achieving an MID of 0.1–0.3 on a 1.5-point scale is more meaningful than if it was evaluated on a 7-point scale. It is possible that participants in the Horn et al. study had allergies other than to grass pollen affecting their QoL, which may explain why the off-season RQLQ value was not zero. However, even if this was the case, the overall principle would still apply.

Theoretically, a between-group MID will be smaller than a within-patient MID.[17] The derived between-group MID values in this analysis are lower than the within-patient MID of 0.5 for the RQLQ that was proposed by Juniper and colleagues,[14] and which has been widely used for between-group comparisons considering different disease severities, pollen exposure and patient age groups. However, there is evidence to suggest that a value of 0.5 may be unachievable as a universal between-group threshold for all therapies. For example, a network meta-analysis of various effective asthma treatments has shown that a within-patient MID of 0.5 (also suggested by Juniper and colleagues for an asthma QoL scale[35]) was not achieved as a between-group threshold for either of two outcome measures.[16] Additionally, an analysis of four RCTs of grass AIT versus placebo reported that the between-group difference for the RQLQ was less than 0.5.[36]

Considering the study limitations, firstly, the between-group MIDs were derived through *post hoc* analysis of data from clinical trials that were not designed to measure MID. Secondly, determination of an MID is most often carried out using the anchor-based method, and it is important to consider the timing of the anchor assessment (in this case, global evaluation) relative to the RQLQ evaluation. In the trials included in the present analyses, the global evaluation asked patients to compare their symptoms during the pollen season under investigation with symptoms experienced during previous pollen seasons (a recall period of ≥1 year). Not only can the global evaluation be influenced by changes in pollen levels (and, therefore, symptomatic burden) from year to year, it can also be affected by recall bias. Recall can be influenced by forgetfulness, recent or salient events and by mood which, over an extended time period, can lead to an inaccurate picture of change.[17] Different recall periods can be defined for different situations, but it has been recommended that the recall period used in clinical trials should be ≤1 year.[37] Outside of the allergy field, the global evaluation has been included in a trial using a recall period of 2 years.[26] However, the global evaluation has not been extensively used in allergy trials, and it could be questioned if patients can reliably compare their current symptoms with symptoms experienced during a previous pollen season, which would have been 1 year previously. Although recognised as a limitation of the analyses, the delay between RQLQ assessment and the global evaluation reflects the intended use of the instruments. Additionally, whilst the global evaluation is not a validated PRO, global assessment scales have been shown to be very responsive to change, both positive and negative.[26] Questions may also be raised in relation to the granularity of the global evaluation (five categories) used in the trials included in the analyses. In contrast, the Juniper et al. (1996) analysis used the global scale, which is a more detailed 15-point system.[14] It may be that using a PRO with finer increments of difference would have produced smaller MID values with the anchor-based method. However, in this analysis, increased granularity within the global evaluation would have resulted in even fewer patients in each category and, potentially, greater imbalance in patient numbers between categories (global evaluation category 'the same' included a low number of patients and fewer patients than in the 'better' category; Table 3). It is

TABLE 3 Anchoring of mean RQLQ scores to global evaluation categories used in the anchor-based method for deriving an MID

	Much worse	Worse	The same	Better	Much better
Global evaluation category	**Mean RQLQ score (N)**				
Entire grass pollen season					
SQ SLIT-tablet	0.56 (2)	2.30 (7)	1.30 (38)	1.03 (124)	0.87 (88)
Placebo	2.22 (8)	2.04 (23)	1.54 (81)	1.36 (100)	1.0 (43)
Peak grass pollen season					
SQ SLIT-tablet	0.73 (2)	2.63 (6)	1.37 (38)	1.36 (120)	1.14 (84)
Placebo	2.57 (8)	2.52 (23)	1.89 (79)	1.71 (98)	1.17 (43)
Tree pollen season					
SQ SLIT-tablet	– (0)	1.42 (5)	1.42 (19)	1.01 (105)	0.71 (129)
Placebo	– (0)	1.57 (5)	1.27 (69)	1.40 (113)	0.92 (73)
Birch pollen season					
SQ SLIT-tablet	– (0)	1.67 (5)	1.51 (18)	1.20 (105)	0.80 (128)
Placebo	– (0)	2.02 (5)	1.61 (69)	1.61 (113)	1.10 (73)

Note: RQLQ = Rhinoconjunctivitis Quality of Life Questionnaire, SLIT = sublingual immunotherapy.

TABLE 4 MIDs for the RQLQ in grass and tree pollen allergy derived using anchor-based method

	MID_{Anchor} (SE)[a]
Entire grass pollen season	0.22 (0.09)
Peak grass pollen season	0.10 (0.09)
Tree pollen season	0.26 (0.11)
Birch pollen season	0.16 (0.11)

Note: MID = minimal important difference, SE = standard error.
[a]Standard errors were estimated using a nonparametric bootstrap method, as defined in Efron and Tibshirani (1993).[40]

important to note that the trials included in the present analysis reflect the data that were available at the time. Furthermore, the trials were not designed for use in determining an MID (the data from the PRO assessments were used as they were performed in the trials). Consequently, the patient numbers in each global evaluation category were not optimised for the purpose of the analysis, potentially resulting in reduced accuracy of the estimated MID.

A third limitation concerns the suitability of the RQLQ for assessing QoL in trials of AIT, given that it does not consider medication use or the burden on the patient of different treatment regimens. The validation of the RQLQ and an estimation of MID were obtained from clinical trials evaluating allergy pharmacotherapy (intranasal steroids and/or antihistamines).[14,24,38,39] To the best of our knowledge, the RQLQ has not been validated, specifically, in clinical trials of AIT. However, the RQLQ remains a well-known tool in AR that has been validated in other situations and which is widely used in clinical research today.

In conclusion, the present analyses provide a first exploration and estimation of between-group MIDs for the RQLQ in grass and tree pollen-induced allergic disease, considering different pollen exposures. Seasonal allergy is a unique disease area that is dependent on nature and is subject to uncertainty. Consequently, the between-group MIDs derived here can be applied to scenarios with a similar study population and trial conditions, to evaluate if a treatment has a clinically beneficial effect on patients. Further investigation is required to determine MIDs that reflect differences in pollen levels, symptom severity, type of allergy, patient age and treatment.

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Author contributions: RGJ and EH were involved in planning and conduct of the analysis. All authors had access to the data and were involved in interpretation of results, writing of the manuscript, critically evaluating revisions and approval of the final submission draft.

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CONFLICTS OF INTEREST

MB has received consulting fees from ALK-Abelló, Stallergenes Greer, Perrigo, and Merck, speaker/writing fees from ALK-Abelló and Merck, and has participated on a Data Safety Monitoring Board/Advisory Board for ALK-Abelló and Merck. LS has no conflicts of interest to declare. PD has received personal fees, speaker/writing fees, and meeting attendance support from ALK-Abelló, consulting fees from ALK-Abelló, Stallergenes Greer, GlaxoSmithKline, AstraZeneca, Chiesi, Novartis, and Mylan/Meda Pharma. RGJ and EH are employees of ALK-Abelló.

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REFERENCES

1. European Academy of Allergy and Clinical Immunology (EAACI). Global atlas of allergic rhinitis and chronic rhinosinusitis. 2015.
2. Sofiev M. On impact of transport conditions on variability of the seasonal pollen index. *Aerobiologia (Bologna)*. 2017;33(1):167-179.
3. D'Amato G, Cecchi L, Bonini S, et al. Allergenic pollen and pollen allergy in Europe. *Allergy*. 2007;62(9):976-990.
4. Pfaar O, Karatzas K, Bastl K, et al. Pollen season is reflected on symptom load for grass and birch pollen-induced allergic rhinitis in different geographic areas – An EAACI Task Force Report. *Allergy*. 2020;75(5):1099-1106.
5. Wise SK, Lin SY, Toskala E, et al. International Consensus Statement on Allergy and Rhinology: Allergic Rhinitis. *Int Forum Allergy Rhinol*. 2018;8(2):108-352.
6. Petersen KD, Kronborg C, Gyrd-Hansen D, Dahl R, Larsen JN, Løwenstein H. Quality of life in rhinoconjunctivitis assessed with generic and disease-specific questionnaires. *Allergy*. 2008;63(3):284-291.
7. Bousquet J, Neukirch F, Bousquet PJ, et al. Severity and impairment of allergic rhinitis in patients consulting in primary care. *J Allergy Clin Immunol*. 2006;117(1):158-162.
8. Jaeschke R, Singer J, Guyatt GH. Measurement of health status. Ascertaining the minimal clinically important difference. *Control Clin Trials*. 1989;10(4):407-415.
9. Stratford PW, Binkley JM, Riddle DL, Guyatt GH. Sensitivity to change of the Roland-Morris Back Pain Questionnaire: part 1. *Phys Ther*. 1998;78(11):1186-1196.
10. Dahl R, Kapp A, Colombo G, et al. Efficacy and safety of sublingual immunotherapy with grass allergen tablets for seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol*. 2006;118(2):434-440.
11. Nelson HS, Nolte H, Creticos P, Maloney J, Wu J, Bernstein DI. Efficacy and safety of timothy grass allergy immunotherapy tablet treatment in North American adults. *J Allergy Clin Immunol*. 2011;127(1):72-80.
12. Maloney J, Bernstein DI, Nelson H, et al. Efficacy and safety of grass sublingual immunotherapy tablet, MK-7243: a large randomized controlled trial. *Ann Allergy Asthma Immunol*. 2014;112(2):146-153.
13. Biedermann T, Kuna P, Panzner P, et al. The SQ tree SLIT-tablet is highly effective and well tolerated: Results from a randomized, double-blind, placebo-controlled phase III trial. *J Allergy Clin Immunol*. 2019;143(3):1058-1066.
14. Juniper EF, Guyatt GH, Griffith LE, Ferrie PJ. Interpretation of rhinoconjunctivitis quality of life questionnaire data. *J Allergy Clin Immunol*. 1996;98(4):843-845.
15. McLeod LD, Coon CD, Martin SA, Fehnel SE, Hays RD. Interpreting patient-reported outcome results: US FDA guidance and emerging methods. *Expert Rev Pharmacoecon Outcomes Res*. 2011;11(2):163-169.
16. Bateman ED, Esser D, Chirila C, et al. Magnitude of effect of asthma treatments on Asthma Quality of Life Questionnaire and Asthma Control Questionnaire scores: Systematic review and network meta-analysis. *J Allergy Clin Immunol*. 2015;136(4):914-922.
17. Crosby RD, Kolotkin RL, Williams GR. Defining clinically meaningful change in health-related quality of life. *J Clin Epidemiol*. 2003;56(5):395-407.

18. Samsa G, Edelman D, Rothman ML, Williams GR, Lipscomb J, Matchar D. Determining clinically important differences in health status measures: a general approach with illustration to the health utilities index mark II. *Pharmacoeconomics*. 1999;15(2):141-155.
19. Jayadevappa R, Cook R, Chhatre S. Minimal important difference to infer changes in health-related quality of life – a systematic review. *J Clin Epidemiol*. 2017;89:188-198.
20. Devillier P, Chassany O, Vicaut E, et al. The minimally important difference in the Rhinoconjunctivitis Total Symptom Score in grass-pollen-induced allergic rhinoconjunctivitis. *Allergy*. 2014;69(12):1689-1695.
21. Copay AG, Subach BR, Glassman SD, Polly DW, Schuler TC. Understanding the minimum clinically important difference: A review of concepts and methods. *Spine J*. 2007;7(5):541-546.
22. Rai SK, Yazdany J, Fortin PR, Aviña-Zubieta JA. Approaches for estimating minimal clinically important differences in systemic lupus erythematosus. *Arthritis Res Ther*. 2015;17(1):143.
23. Murphy K, Gawchik S, Bernstein D, Andersen J, Pedersen MR. A phase 3 trial assessing the efficacy and safety of grass allergy immunotherapy tablet in subjects with grass pollen-induced allergic rhinitis with or without conjunctivitis, with or without asthma. *J Negat Results Biomed*. 2013;12(1):10.
24. Juniper EF, Guyatt GH. Development and testing of a new measure of health status for clinical trials in rhinoconjunctivitis. *Clin Exp Allergy*. 1991;21(1):77-83.
25. Measurement of Health-Related Quality of Life and Asthma Control. Standardised rhinoconjunctivitis quality of life questionnaire (RQLQ[S]). https://www.qoltech.co.uk/rqlq_s.html. Accessed December 23, 2020.
26. Hägg O, Fritzell P, Nordwall A. The clinical importance of changes in outcome scores after treatment for chronic low back pain. *Eur Spine J*. 2003;12(1):12-20.
27. Kulkarni AV. Distribution-based and anchor-based approaches provided different interpretability estimates for the Hydrocephalus Outcome Questionnaire. *J Clin Epidemiol*. 2006;59(2):176-184.
28. Cohen J. A power primer. *Psychol Bull*. 1992;112(1):155-159.
29. Horn A, Zeuner H, Wolf H, Schnitker J, Wüstenberg E. GRAZAX LQ-study group. Health-related quality of life during routine treatment with the SQ-standardised grass allergy immunotherapy tablet: A non-interventional observational study. *Clin Drug Investig*. 2016;36(6):453-462.
30. Laforest L, Bousquet J, Pietri G, et al. Quality of life during pollen season in patients with seasonal allergic rhinitis with or without asthma. *Int Arch Allergy Immunol*. 2005;136(3):281-286.
31. Higaki T, Okano M, Kariya S, et al. Determining minimal clinically important differences in Japanese cedar/cypress pollinosis patients. *Allergol Int*. 2013;62(4):487-493.
32. Meltzer EO, Schatz M, Nathan R, Garris C, Stanford RH, Kosinski M. Reliability, validity, and responsiveness of the Rhinitis Control Assessment Test in patients with rhinitis. *J Allergy Clin Immunol*. 2013;131(2):379-386.
33. Connell JT. Quantitative intranasal pollen challenges: III. The priming effect in allergic rhinitis. *J Allergy (Cairo)*. 1969;43(1):33-44.
34. Juliusson S, Bende M. Priming effect of a birch pollen season studied with laser Doppler flowmetry in patients with allergic rhinitis. *Clin Allergy*. 1988;18(6):615-618.
35. Juniper EF, Guyatt GH, Willan A, Griffith LE. Determining a minimal important change in a disease-specific Quality of Life Questionnaire. *J Clin Epidemiol*. 1994;47(1):81-87.
36. Serrano E, Wahn HU, Didier A, Bachert C. 300IR 5-Grass pollen sublingual tablet offers relief from nasal symptoms in patients with allergic rhinitis. *Am J Rhinol Allergy*. 2014;28(6):471-476.
37. Stull DE, Leidy NK, Parasuraman B, Chassany O. Optimal recall periods for patient-reported outcomes: Challenges and potential solutions. *Curr Med Res Opin*. 2009;25(4):929-942.
38. Juniper EF, Guyatt GH, Andersson B, Ferrie PJ. Comparison of powder and aerosolized budesonide in perennial rhinitis: validation of rhinitis quality of life questionnaire. *Ann Allergy*. 1993;70(3):225-230.
39. Juniper EF, Thompson AK, Ferrie PJ, Roberts JN. Validation of the standardized version of the Rhinoconjunctivitis Quality of Life Questionnaire. *J Allergy Clin Immunol*. 1999;104(2 Pt 1):364-369.
40. Efron B, Tibshirani RJ. An Introduction to the Bootstrap. Monographs on statistics and applied probability 57. *Springer Science+Business Media Dordrecht*. 1993;1-436.

SUPPORTING INFORMATION

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