

Advancing meaningful change: generating between-group and within-person thresholds for the Asthma Daytime and Nighttime Symptom Diaries

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Background

- There is increased focus on the interpretability and meaningfulness of PROs, but the purpose and strategy for achieving such insight remains a topic of rich debate
- Evidence-based score thresholds for PROs are needed to enhance what inference is feasible, but there is heterogeneity in how these can be defined, established, and employed; for example, differentiating between change at an individual patient level from differences in change between groups
- The publication of the draft FDA Patient-Focused Drug Development Guidance 4 has renewed discussion of methods for derivation of between-group thresholds¹
- One point of increasing agreement is that there is no universal threshold for any single PRO instrument
- Two such instruments are the ADSD and ANSD – PRO measures developed and validated in a broad asthma population aged ≥12 years – which evaluate the core symptoms of asthma during the day and night^{2,3}
- Recent work has shown these measures to be valid in moderate-to-severe asthma;⁴ however, thresholds for meaningful change have not yet been defined

Conclusions

- Thresholds for meaningful within-patient change and between-group difference for the ADSD and ANSD were successfully estimated using anchor-based strategies
- Anchor adequacy evidence supported the a priori prioritisation of the PGI-S
- There was consistency in the thresholds established across two different time intervals
- These estimated thresholds will aid interpretation of data derived from the ADSD and ANSD in research settings and in real-world clinical practice
- The different threshold types can inform different research objectives. For example, while the within-patient change thresholds can inform responder definitions with the ADSD and ANSD, the between-group difference thresholds can enhance interpretation of comparisons across treatment arms in change over time

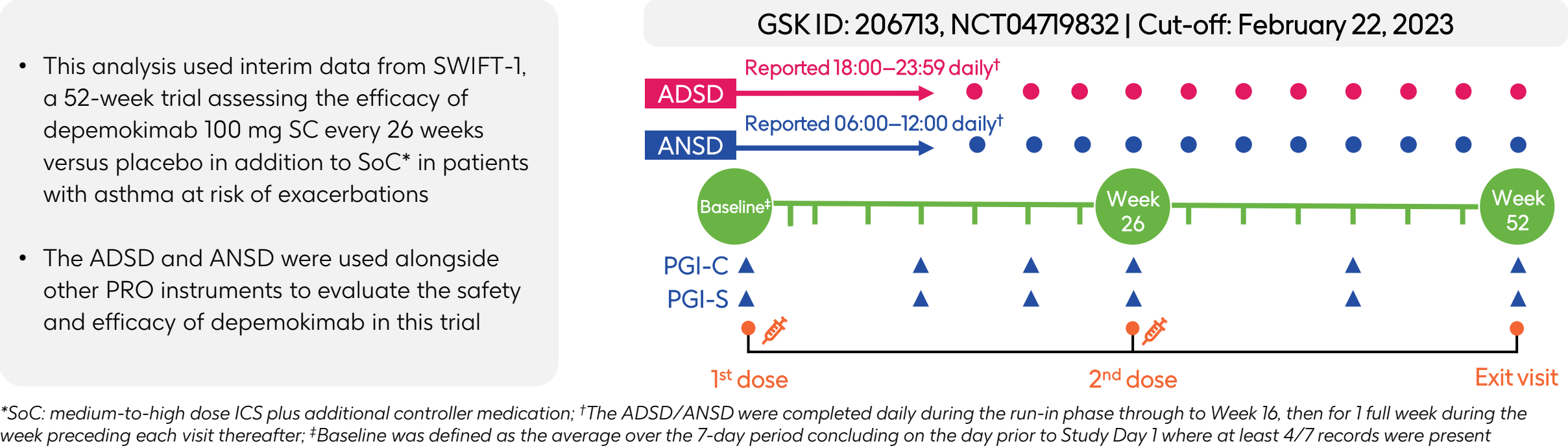
Aims



*Within-patient meaningful change is the amount of change over a predefined period that could be interpreted as meaningful benefit to the patient

†Between-group meaningful difference is the difference in change scores between two groups that can be considered meaningful to patients

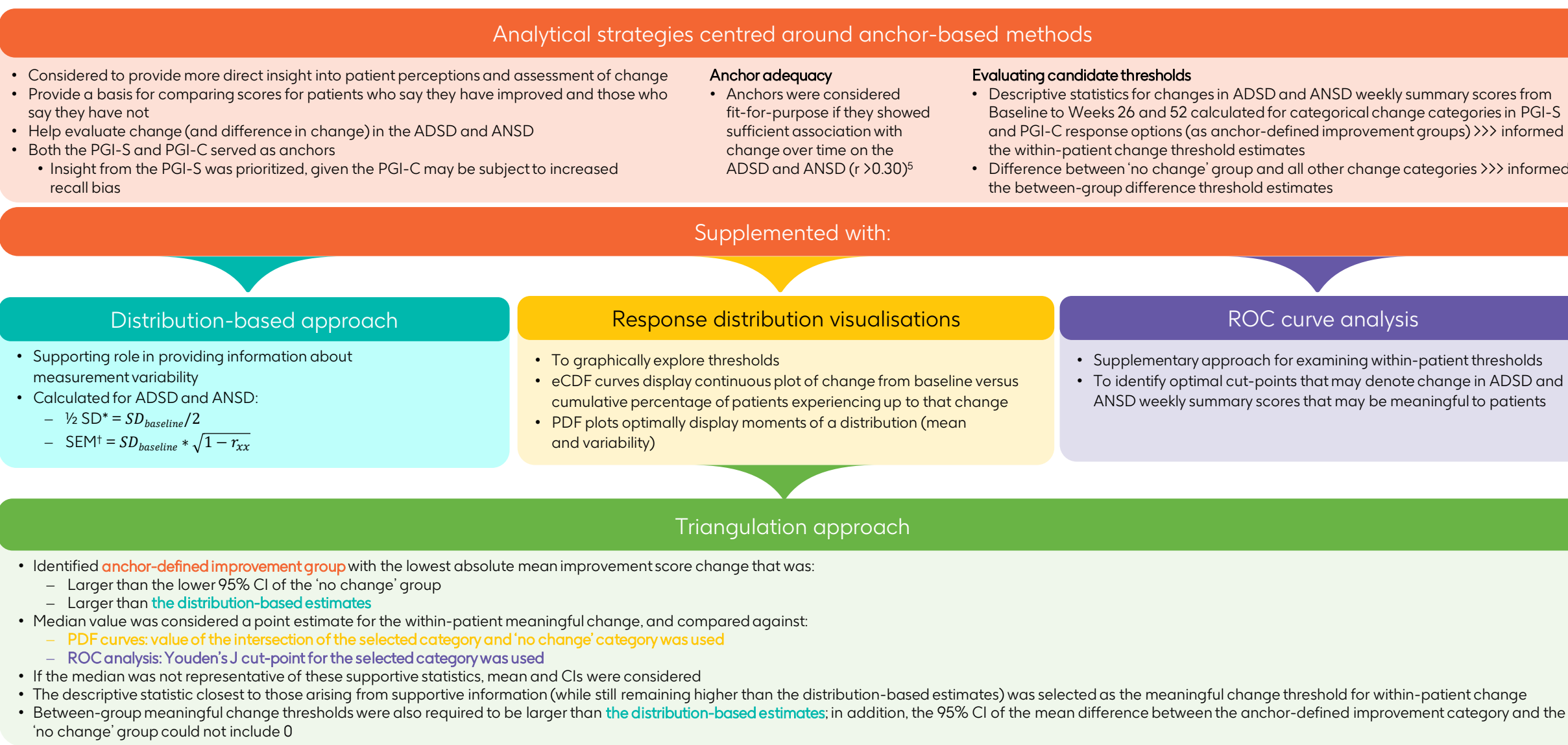
Study design



Clinical outcome assessments

	Response options and score	Measures/categories used to derive within-patient and between-group meaningful change
ADSD – completed before bed, to assess symptoms during the earlier day	6 items assessing asthma symptom severity: <ul style="list-style-type: none">Chest painChest tightnessCoughDifficulty breathingShortness of breathWheezing Daily item score: 0=none to 10=as bad as you can imagine	Daily summary score: <ul style="list-style-type: none">Average of all 6 items Weekly summary score: <ul style="list-style-type: none">Average of daily summary scoresAt least 4 out of 7 daily summary scores needed to be non-missing for a valid weekly score to be calculated
ANSD – completed on waking, to assess symptoms during the night	5-point categorical response scale: <ul style="list-style-type: none">"No symptoms""Mild""Moderate""Severe""Very severe"	Uncollapsed 9-categories: Improved 1, 2, 3 or 4 points, no change, or worsened 1, 2, 3, or 4 points
PGI-S – captures the perception of overall symptom severity over the past 7 days	5-point categorical response scale: <ul style="list-style-type: none">"Much better""A little better""No change""A little worse""Much worse"	Collapsed 7-categories: Improved >2, 2 or 1 points, no change, or worsened >2, 2 or 1 points
PGI-C – captures the perception of change in asthma symptom severity since study start	5-point categorical response scale: <ul style="list-style-type: none">"Much better""A little better""No change""A little worse""Much worse"	Collapsed 3-categories: Improvement, no change, worsening

Threshold derivation process



*SoC: medium-to-high dose ICS plus additional controller medication. †The ADSD/ANSD were completed daily during the run-in phase through to Week 16, then for 1 full week during the week preceding each visit thereafter. ‡Baseline was defined as the average over the 7-day period concluding on the day prior to Study Day 1 where at least 4/7 records were present



Robust thresholds for meaningful within-patient change and between-group difference for the ADSD and ANSD have been successfully estimated using anchor-based strategies and a triangulation approach

These thresholds could enhance interpretability and meaningfulness of the PROs when used in patients with asthma



Results

Demographics

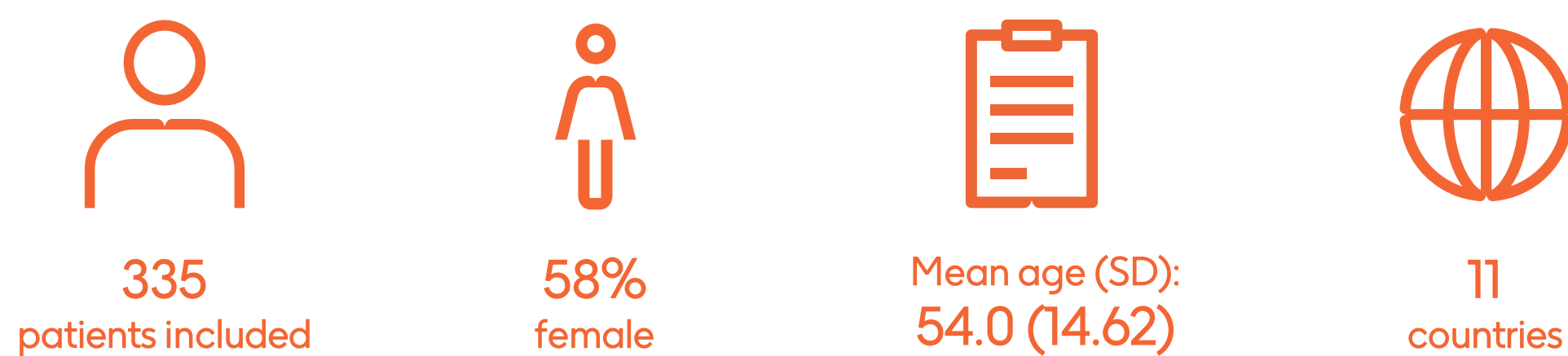


Table 1: Distribution-based estimates

Weekly summary score	N	½ SD at baseline	SEM
ADSD	335	0.967	0.410
ANSD	306	0.975	0.375

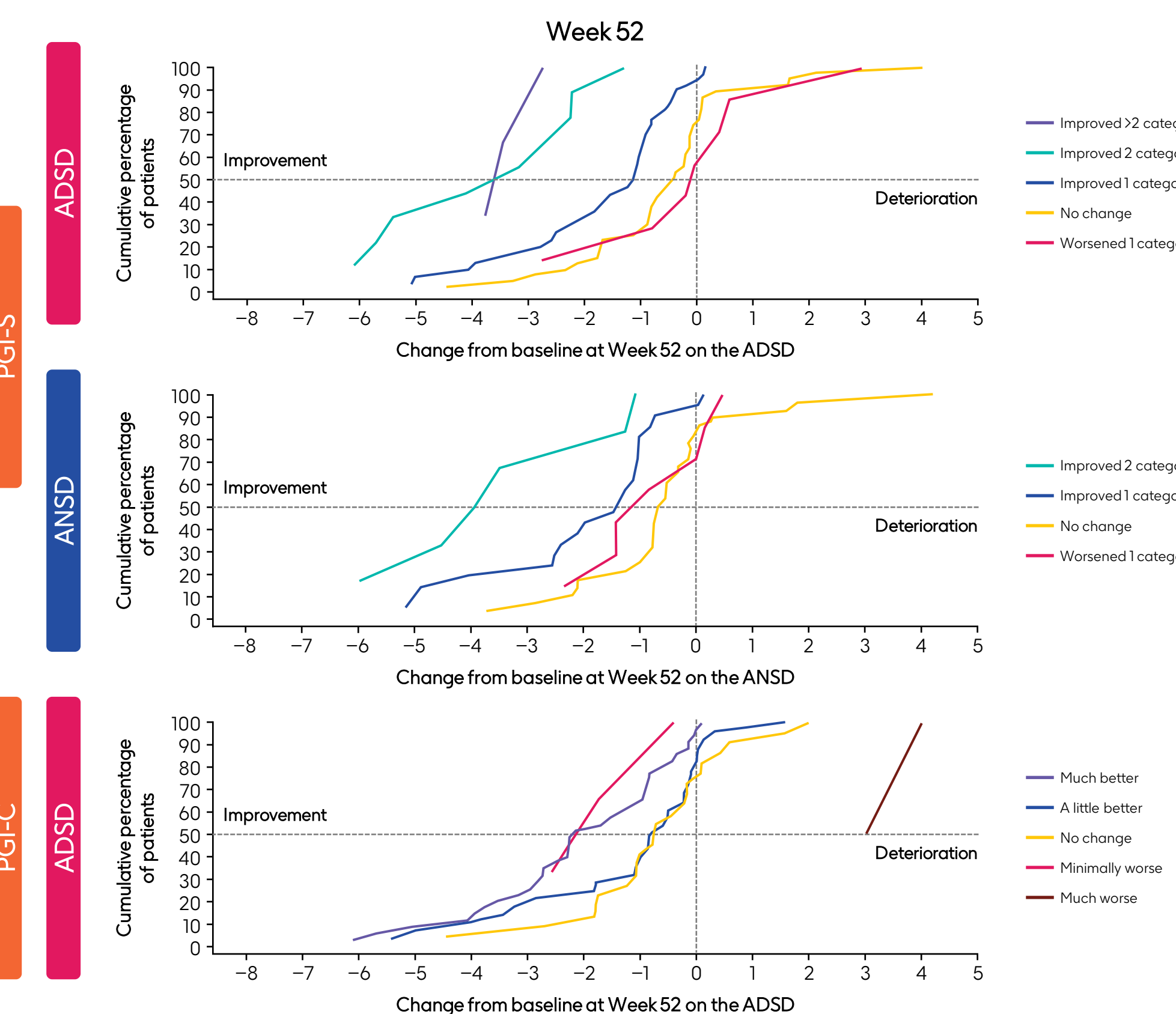
- ½ SD is mathematically equivalent to SEM if test-retest reliability is assumed to be 0.75
- ADSD and ANSD reliability exceeded 0.75, thus the SEM was deemed a more definitive distribution-based estimate

SEM prioritised in threshold triangulation

Anchor adequacy		Table 2: Evaluating candidate thresholds – key descriptive results for inferring within-patient meaningful change				
PGI-S confirmed and employed as primary anchor		Timepoint (change from baseline)	Anchor	Anchor category groups	N	Median*
Associations between the PGI-S and ADSD and ANSD were consistently high, all exceeded the a priori defined cutoff (>0.3)						Mean difference with 'No change' group (95% CI)*
Associations between the PGI-C and ADSD and ANSD were more variable						
Distribution-based approach						
Chosen thresholds are higher than the ½ SD and SEM (see Table 1)						
Response distribution visualisations						
Provided median values and degree of separation data to inform thresholds (see Figure 1)						
ROC curve analysis						
ROC-based estimates were not deemed to reflect adequate classification accuracy to inform triangulation						

*Pink/blue values in bold used to estimate thresholds and bounds for within-patient meaningful change; pink/blue values (non-bold) used to estimate thresholds and bounds for between-group change. †Collapsed PGI-C demonstrated adequate association with change on ADSD for tentative use in within-patient meaningful change threshold identification up to Week 26, and the improvement group values met the criteria for use, however, visualisations of response distributions showed limited differentiation between 'Improvement' and 'No change'. Uncollapsed PGI-C met threshold for anchor adequacy, but a 'little better' group did not meet selection criteria for within-patient meaningful change identification. ‡'much better' group tentatively considered as this showed adequate differentiation from no change. ††PGI-C did not demonstrate anchor adequacy over 26 weeks, so no inference is made for the within-patient meaningful change on the ANSD across this interval. †††PGI-C anchor met acceptability threshold for tentative use as a within-patient meaningful change on the ANSD over 52 weeks, but none of the defined improvement groups showed adequate differentiation. *Derived by rounding to 1 decimal place

Figure 1: Assessing the degree of separation in score changes from baseline at Week 52 – eCDF curves for ADSD and ANSD weekly summary scores using PGI-S and PGI-C anchors



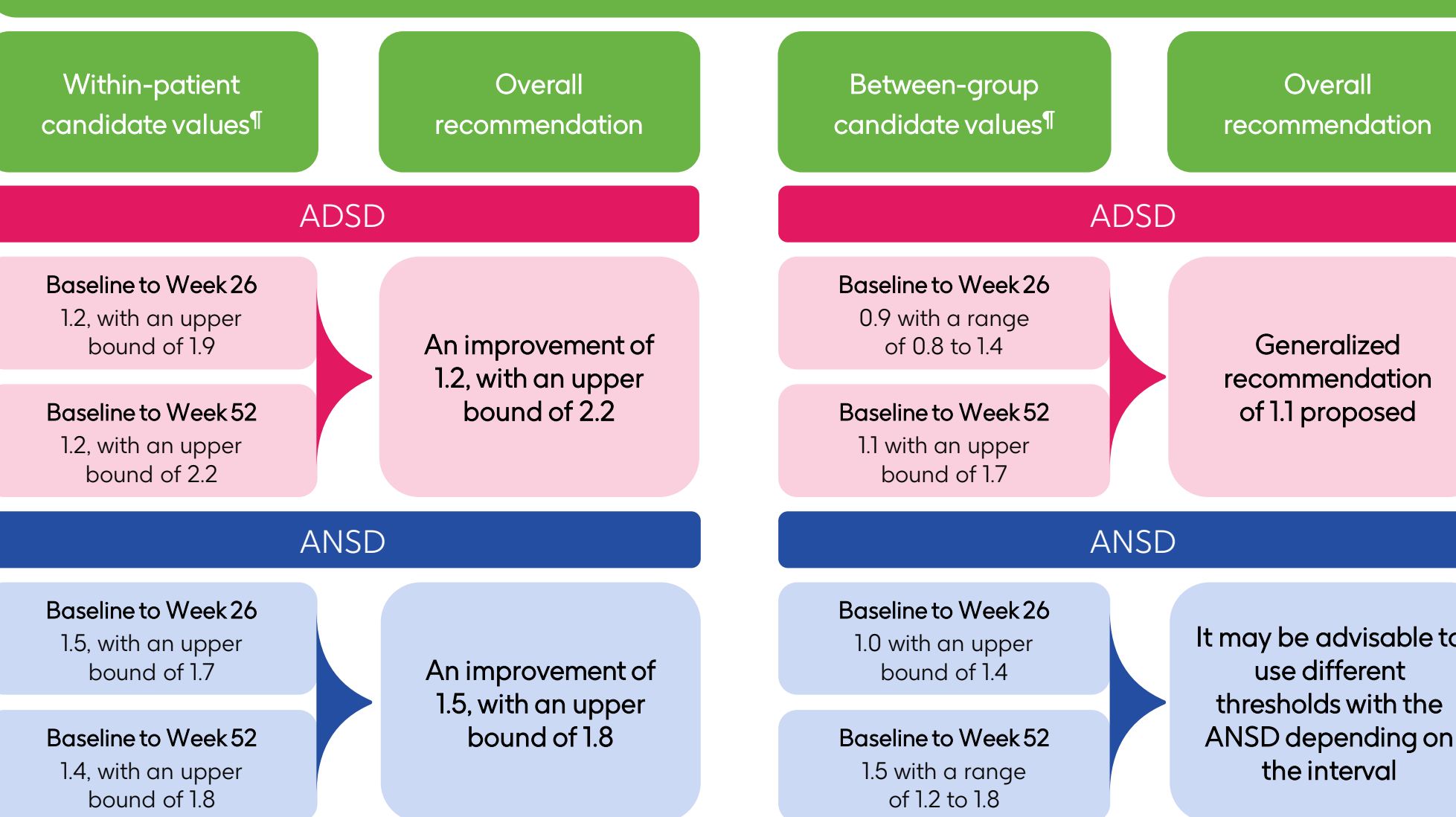
- Curves for PGI-S defined groups showed clear differentiation in ADSD and ANSD change scores between 2-point and 1-point improvement and no change at Weeks 26* and 52
- Curves for PGI-C defined groups did not show clear differentiation in ADSD and ANSD* change scores between 1-point improvement (i.e., a little better) and no change at Weeks 26* and 52
- For 2-point improvement (i.e., much better) there was clearer differentiation versus no change on ADSD, particularly at Week 52

The following median change values were used, as they met the inference criteria for deriving meaningful change:

- 1-point improvement, for ADSD and ANSD at both timepoints
- 2-point improvement (ie, much better) on PGI-C for ADSD at Week 52

*Data not shown

Figure 2: Triangulation of all data – estimated thresholds for clinically meaningful within-patient change and between-group change



Abbreviations

ADSD, Asthma Daytime Symptom Diary; ANSD, Asthma Nighttime Symptom Diary; CI, confidence interval; eCDF, empirical cumulative distribution function; FDA, U.S. Food & Drug Administration; ICC, intraclass correlation coefficient; ICS, inhaled corticosteroid; PDF, probability density function; PGI-C, Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity; PRO, patient reported outcome; ROC, receiver operating characteristic; SD, standard deviation; SEM, standard error of measurement; SC, subcutaneous; SoC, standard of care

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Acknowledgements

This study and analysis were funded by GSK (GSK ID:217640). Editorial support (in the form of writing assistance, including preparation of the draft poster under the direction and guidance of the authors, collating and incorporating authors' comments for each draft, assembling tables and figures, grammatical editing and referencing) was provided by Claire Twomey at Fishawack Indicia Ltd, UK, part of Avalere Health, and was funded by GSK.

Disclosures

TK and RAC are GSK employees and own GSK stocks/shares. GD, DO'N, and SR are employees of IQVIA, which was contracted by GSK to conduct this study. SR contributed to this study and the parent abstract and provided input on the content of this presentation but was not able to provide their final approval for this presentation.