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Original article

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Minimal clinically important differences in average, best, worst and current intensity and unpleasantness of chronic breathlessness

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Take Home Message:

This cohort study determined clinically important differences for current intensity and unpleasantness and the average, best and worst intensity the last 24 hours of chronic breathlessness, which is important for the design of therapeutic trials.

ABSTRACT

Background: Chronic breathlessness has devastating consequences. The minimal clinically important difference (MCID) for *current intensity* has been estimated as 9mm on a 100mm visual analogue scale (VAS). We aimed to determine MCIDs for commonly used dimensions and recall periods: the *current unpleasantness* and *current, average, best and worst intensity* of the last 24h for chronic breathlessness.

Methods: This was a secondary analysis of a randomized controlled trial of morphine vs. placebo during seven days in people with chronic breathlessness from severe disease. The breathlessness scores were self-reported using a diary each evening on 100mm VAS. The MCID for improvement in each score was estimated using anchor based and distribution based methods.

Results: 283 participants (mean age 74.2 years; 63% males; 58% COPD; 87.0% mMRC 3–4) were included. Anchor-based MCIDs for breathlessness scores ranged from -13.9mm to -9.5mm. The MCIDs were similar when using different anchors and across all participants, and participants with more severe breathlessness (mMRC 3–4), respectively. Distribution based effect sizes were: small (-4.7 to -6.3mm), moderate (-9.4 to -12.5mm) and large effect (-15.0 to -20.0mm). Sample sizes for trials using the different scores were proposed. MCIDs of absolute change were more stable than using relative change from baseline.

Conclusion: An improvement of about 10mm on a 100mm VAS is likely to be clinically meaningful across commonly used measures of chronic breathlessness (*current intensity, unpleasantness, and average, best and worst intensity* over the last 24h) – to evaluate clinical benefit and effects in therapeutic trials.

INTRODUCTION

Chronic breathlessness [1] is a key cause of suffering in advanced disease.[2] Subjective sensations of intensity and unpleasantness may be discerned as distinct aspects by individuals and their impact experienced within the context of duration of the symptom (acute *vs* chronic) and the meaning attributed by the person. Breathlessness should be measured in routine care as an essential part of disease evaluation to guide best management.[3-5] Although chronic breathlessness cannot be encapsulated in a single quantitative measure,[6] higher scores in uni-dimensional breathlessness scores do predict adverse clinical outcomes and can demonstrate change in response to an intervention, and thus are relevant for patient care and in clinical trials.[7]

Different breathlessness dimensions and recall periods have been used and assessed in trials since a consensus statement on the measurement of breathlessness in advanced disease,[5] including the current intensity (or severity), current unpleasantness, and the average, best or worst intensity during the last 24 hours. [7-15]

The minimal clinically important difference (MCID), defined as the smallest change that is meaningful to the patient, is a key concept for determining the clinical relevance of effects in therapeutic trials.[16] Data are limited on MCIDs for measures of chronic breathlessness.[7]

Using an individual pooled data analysis (n=213) of current breathlessness intensity from three trials [17-19] and one dose titration study,[20] Johnson *et al.* reported a MCID for current intensity of chronic breathlessness of 9 mm on a 100mm visual analogue scale (VAS) using both participant-anchored and distribution-based methods.[7] Distribution-based effect sizes were 5.5 mm for a small, 11.3 mm for a moderate, and 18.2 mm for a large effect.[7]

The absolute MCID, based on absolute change from baseline, was found to be more stable compared with the relative MCID (which is based on % change from baseline), and absolute MCIDs were therefore concluded to be preferable for use in trials.[21]

However, we do not know the MCIDs of chronic breathlessness for different frequently used dimensions and temporal periods – the current unpleasantness, and the average, best and worst intensity during the last 24 hours.[22] For example, measures of “current breathlessness” and “usual breathlessness” correlate poorly and likely represent different constructs,[23] and so may have different MCIDs. Further, it is not known whether MCIDs differ by underlying diagnosis (most data pertain to chronic obstructive pulmonary disease [COPD]) as seen in (acute) pain,[24] or in patients with worse activity limitation due to breathlessness, as measured by the modified Medical Research Council (mMRC) scale.[22, 25] This knowledge is of fundamental importance for choosing uni-dimensional assessment scales to reflect patients’ experiences in clinical practice and trials.

The primary aim of this paper was to determine MCIDs for improvement in current breathlessness intensity and unpleasantness, and for the average, best and worst intensity during the last 24 hours in participants with advanced disease and chronic breathlessness. Secondary aims were to evaluate MCIDs separately in participants with more severe breathlessness (mMRC 3–4).

METHODS

Study design and population

This is a secondary analysis of a randomised, parallel arm, multi-site, fixed dose, placebo controlled, phase III trial of 20mg extended release morphine daily placebo for seven days in patients with chronic breathlessness (Australian New Zealand Clinical Trials Registry, ACTRN12609000806268). The main analysis found no difference in breathlessness between the trial arms when measuring ‘*breathlessness now*’.[14] The database was also previously used to evaluate agreement between breathlessness severity and unpleasantness,[12] compare

mMRC ratings between clinicians and participants [26] and to evaluate treatment adverse events.[27]

Participants were recruited from 14 respiratory and palliative care services across Australia in the Australian Government's funded national Palliative Care Clinical Studies Collaborative (PaCCSC).[14] Main eligibility criteria were: age ≥ 18 years; chronic breathlessness defined as a mMRC [28] breathlessness score ≥ 2 at screening despite optimal management of underlying cause(s) of breathlessness; stable breathlessness medications for the previous week except 'as needed' medications; an Australia-modified Karnofsky Performance Status (AKPS) scale ≥ 40 ;^[29] expected survival ≥ 2 months; and ability to complete a daily diary.[14]

Ethical considerations

The trial was approved by the Southern Adelaide Clinical Research Ethics Committee (Dnr: EC00188) and the local ethics committee at each site prior to first recruitment at each site.

All participants gave their informed written consent to participate and the trial was monitored in accordance with Good Clinical Practice.[30]

Assessments

The mMRC breathlessness scale [25] and function using the Australia-modified Karnofsky Performance Scale (AKPS) were rated by the physician at eligibility screening.[26] Other baseline assessments are described elsewhere.[14] Breathlessness scores were rated by participants using 100mm horizontal visual analogue scales (VAS) in a diary each evening (*current intensity, current unpleasantness, and worst, best, average intensity during the last 24h*) at baseline and for the seven days of intervention (low dose morphine or placebo). The VAS is a reliable and valid scale for unidimensional measurement of breathlessness.[31,32]

Current intensity was assessed using the question “How is your breathlessness right now?” between 0 (“None”) and 100 (“Worst possible”). Current unpleasantness was then assessed using the question “Right now how would you rate the unpleasantness of your breathlessness?” between 0 (“None”) and 100 (“The most unpleasant I have ever felt”). The participant was then asked to rate the *average*, *best* and *worst* intensity of breathlessness during the last 24 hours using similar scales as the current intensity.

At the end of the study, participants were asked (double-blinded) whether they had “been less breathless during the past week” (‘less breathlessness’) and “this medication would benefit me enough to be on it long term” (‘benefit’) which were used in this current analysis as anchors for determining a participant-defined clinically meaningful change in breathlessness during the study week. The anchors were used in line with recommendations to evaluate MCIDs across several anchors and methods [16] and as the questions related to the key concept of a MCID, to measure a change in breathlessness that would be clinically important in terms of patients’ experiences and treatment decisions.

Statistical analyses

Participant baseline characteristics were summarized by descriptive statistics. For each breathlessness score (current unpleasantness and current, average, best and worst intensity), imputation was performed for those with 1) missing baseline measurements, which was imputed as their first day measurement; 2) missing day seven measurements, which was imputed as the last available value for each score at day five or six.[14] Sensitivity analysis without any imputation was firstly performed. We then imputed the missing values using multiple imputation approach (imputation model set as multivariate normal regression adjusting for baseline characteristic factors; with 20 imputations per case). Both sensitivity analyses yielded similar results.

MCIDs were calculated using anchor-based methods as recommended.[16,33] The ‘less breathless’ and ‘benefit’ questions were used as participant anchors of breathlessness change. MCIDs were calculated as the change from baseline to day seven, in the group who affirmed the anchor question (response) compared with the group that did not affirm the question (non-response) for each breathlessness scores with each of the two anchors. The estimates were reported with 95% confidence intervals (CIs). For each breathlessness score, MCIDs were calculated for all participants and separately for the subgroups with more severe breathlessness (mMRC 3–4).

Distribution-based methods were used to further explore the differences in the scores. The baseline standard deviation (SD) of 0.25, 0.5 and 0.8 were used to define small, medium and large effects.[7] Standard error of measurement (SEM),[32] defined as the baseline SD multiplied by the square root of one minus sample test-retest reliability coefficient, were also calculated for comparison purpose. One SEM can be regarded as an estimate of the MCID.[34]

Sample sizes required to detect a MCID change in each breathlessness score with assumed common baseline standard deviation, 90% power (typically used in definitive trials) and an two-sided $\alpha=0.05$ were calculated using nQuery version 8.4 (Statistical Solutions Ltd, Boston, USA). Stata version 15.1 (StataCorp LLC, USA) and R version 3.5 were used for the other statistical analyses.

Relative MCIDs using anchor based methods – defined as a change divided by the score at baseline, were calculated for comparison with the absolute MCIDs (main analysis).[21]

RESULTS

Of 284 randomised participants, 283 participants (one randomised participant did not meet the inclusion criteria of ‘Prognosis of at least 2 months in the opinion of the treating clinician’) were included for analysis: mean age 74.2 (SD 9.3) years; 63.2% males; mean AKPS 61.2 (SD 10.5); main diagnoses were COPD (58.0%) and cancer (16.6%); and 87.0% had a mMRC of 3–4 (Table 1).

Anchor based MCIDs for improvement in the breathlessness scores for the study population ranged from 9.5mm to 13.9mm (Figure 1). The MCIDs were similar when using the two different participant anchors, as shown by the largely overlapping 95% CIs (supplemental Table S1). The estimates were also largely similar to the main analysis for sub-group analyses (Supplemental Tables S2-S4).

Using distribution-based methods, the MCIDs were consistent with small to moderate changes. A small change ranged between 4.7 – 6.3 mm; moderate change 9.4 – 12.5 mm; and large change 15.0 – 20.0 mm (Table 2). The SEMs for breathlessness ranged from 9.7 to 16.4, slightly higher than the MCIDs calculated by anchor based approach.

Sample sizes required to detect a current MCID’s change in each breathlessness score (90% power and an alpha=0.05) are shown in Table 3.

The relative MCIDs ranged from -26.9% to -73.5% and varied more between the breathlessness scores than the absolute MCIDs (supplemental Table S3).

DISCUSSION

This study for the first time establishes MCIDs for improvement in a range of commonly used measures of chronic breathlessness – the current intensity and unpleasantness, and the *average*, *best* and *worst* intensity over the last 24 hours. These novel data are important to help interpret symptom response in clinical practice and for valid measurement in

interventional trials. Sample size estimations are presented and compared between the measures.

The anchor based MCIDs ranged from 9.5mm to 13.9mm, which is slightly higher than the previous estimate of 9 mm (95% CI 2.1 to 15.8) for current breathlessness.[7] However, the present 95% CIs overlapped with the earlier estimate.[7] In the present analysis, MCIDs were similar when calculated using two different participant anchors and were consistent with distribution based estimates, which supports the validity of the present findings. Another novel finding is that MCIDs were similar to in the whole population for participants with more severe breathlessness (mMRC 3–4). Consistent with the previous analysis by Johnson *et al.*[21], MCIDs for absolute change were more stable and reliable than the relative MCID (relative change compared to baseline). This study thus confirms that treatment effect should be evaluated using the absolute MCID. Sample sizes (using the present anchor based MCIDs) were calculated for a definite trial (using 90% power and an alpha of 0.05) and ranged between 61 – 143 participants for different breathlessness scores. Sample sizes were similar in participants with mMRC 3–4. Some previous research suggest that one SEM is equivalent to MCID.[34] In the present analysis, SEMs were consistent with the anchor based estimates, supporting the usage of one SEM to estimate the MCID.

When using a MCID, it should be remembered that while the estimated mean change for the population is most likely to be clinically significant for the individual [16], there is always a degree of uncertainty around the true MCID for the individual. This uncertainty is reflected in the present analysis by the confidence intervals, which were largely overlapping between the compared measures and groups. Taken together, the present findings support an MCID for the different measures of chronic breathlessness around 10mm on a 100mm VAS (Figure 1).

Strengths of the present analysis include that it is based on the largest RCT of chronic breathlessness to date with self-reported breathlessness scores at similar time points daily over one week. MCIDs were evaluated using two different participant anchors and distribution based methods, as recommended.[16]

Several potential limitations should be noted. It could be argued that the present estimates may not reflect the *minimal* important differences, as ‘minimal’ was not included in the anchors. We used available anchors that were considered to relate to a difference that was clinically important (‘*I have been less breathless during the past week*’ and ‘*This medication would benefit me enough to be on it long term*’). While the true *minimal* important differences may be slightly smaller, the present estimates are supported by the distribution based analysis that they represent small to moderate effect sizes. Sub groups were too small to evaluate MCIDs in mMRC ≤ 2 and in younger patients, which should be investigated in analyses of pooled trial data. As participants were not specifically instructed on the difference between intensity and unpleasantness, the meaning of the upper scale anchors and the ratings could be conflated between intensity and unpleasantness for some participants. The present MCIDs pertain mainly to improvement in breathlessness and cannot be assumed to apply also to deterioration in breathlessness. However, benefit is the most relevant for use in clinics and therapeutic trials.

These findings have several important implications: a change of 10mm on a 100mm VAS (or 1 unit on a 0-10 numerical rating scale) is likely to represent a change in chronic breathlessness that is clinically relevant or meaningful for the participant sufficient to inform clinical practice. MCIDs for different breathlessness dimensions and recall periods are given. When designing clinical trials, the use of an absolute MCID is preferred (over relative), and sample sizes are suggested for the different measures of chronic breathlessness. Further

research is needed on MCIDs of acute-on-chronic breathlessness, MCIDs for symptom improvement vs. worsening and how the MCID is influenced by factors including the baseline severity and history of chronic breathlessness.

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Conflicts of interest: DCC is an unpaid member of an advisory board for Helsinn Pharmaceuticals and Specialist Therapeutics, and has consulted to Mayne Pharma and received intellectual property payments from them. MJJ has consulted to Mayne Pharma with institutional payment. ME, CH and MW have no conflicts of interest to disclose.

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Table 1. Baseline characteristics

Characteristic		N=283
Age	Mean (SD)	74.2 (9.3)
	Min, max	44.3, 94.1
Gender, n (%)	Female	104 (36.8%)
Performance status (AKPS)	Mean (SD)	61.2 (10.5)
	Min, max	3, 90
BMI (kg/m ²)	Mean (SD)	25.5 (7.3)
	Min, max	12.3, 66.1
mMRC breathlessness score at baseline rated by clinician, n (%)	2	22 (7.8%)
	3	140 (49.5%)
	4	106 (37.5%)
	Missing	15 (5.3%)
Primary cause of breathlessness, n (%)	COPD	164 (58.0%)
	Cancer	47 (16.6%)
	Cardiac failure	4 (1.4%)
	Mixed	37 (13.1%)
	Other	31 (11.0%)
Charlson Co- morbidity Index	Mean (SD)	3.3 (2.5)
	Min, max	0, 13
Oxygen use	Yes n (%)	161 (56.9%)
Smoking status, n (%)	Never smoked	49 (17.3%)
	Ex-smoker	199 (70.3%)
	Current smoker	33 (11.7%)

	Missing	2 (0.7%)
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Abbreviations: AKPS, Australia modified Karnofsky performance scale; BMI, body mass index; mMRC, modified Medical Research Council scale; SD, standard deviation.

Table 2. Distribution-based analysis of clinically important differences in different breathlessness measures

Dimension	Unpleasantness	Intensity			
Focal period	Current	Current	Average	Best	Worst
Small change (0.25 SD baseline)	6.1	6.3	4.7	5.4	6.0
Moderate change (0.5 SD baseline)	12.2	12.5	9.4	10.8	12.0
Large change (0.8 SD baseline)	19.5	20.0	15.0	17.3	19.1
SEM	14.6	16.4	9.7	12.2	14.9

Estimates are mm on a 100mm visual analogue scale (VAS).

Abbreviations: SD, standard deviation; SEM, standard error of measurement;

Table 3. Sample sizes for breathlessness scores using participant-anchored MCIDs for each breathlessness score as mean difference and common baseline standard deviation as SD, at 5% two-sided significant level and 90% power

Dimension			Unpleasantness	Intensity			
Focal period			Current	Current	Average	Best	Worst
Participant preference question	Group	Parameter					
'I have been less breathless during the past week'	All	MCID	-10.9	-13.9	-9.5	-12.4	-10.9
		Baseline SD	25.1	24.4	19.8	21.3	24.3
		Sample size	113	66	92	63	106
	mMRC 3,4	MCID	-10.7	-14.5	-8.7	-12.7	-11.1
		Baseline SD	24.5	24.5	19.7	21.2	24.4
		Sample size	112	61	109	60	103
'This medication would benefit me enough to be on it long term'	All	MCID	-10.2	-9.9	-11.4	-12.2	-11.3
		Baseline SD	26.5	24.4	19.7	21.2	24.3
		Sample size	143	129	64	65	99
	mMRC 3,4	MCID	-10.1	-9.5	-10.9	-13.0	-11.4
		Baseline SD	24.5	24.4	19.7	21.2	24.4
		Sample size	125	140	70	57	98

Abbreviations: MCID, minimal clinically important difference; mMRC, modified Medical Research Council scale

Figure 1-A: Minimum clinically important difference (MCID; 95% confidence intervals) for breathlessness intensity (current, average, best, worst) and unpleasantness (current) -responding to the question 'I have been less breathless during the past week'

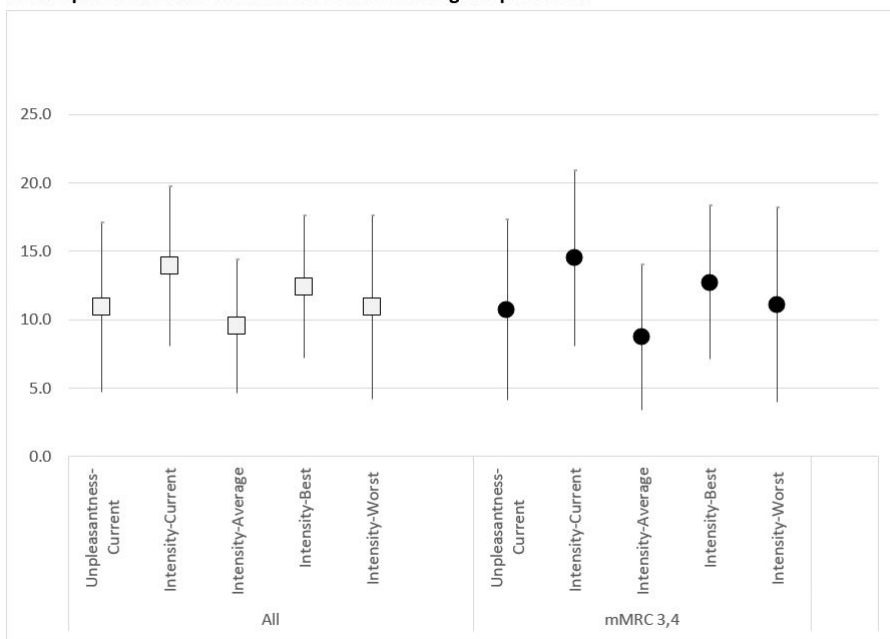
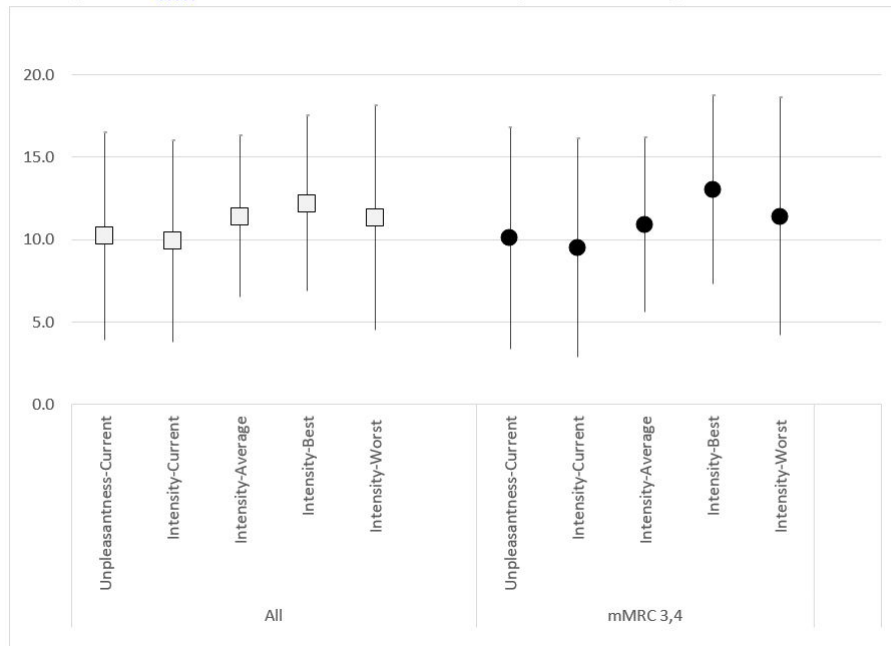


Figure 1-B: Minimum clinically important difference (MCID; 95% confidence intervals) for breathlessness intensity (current, average, best, worst) and unpleasantness (current) -responding to the question 'This medication would benefit me enough to be on it long term'



SUPPLEMENTAL MATERIAL

Minimal clinically important differences in average, best, worst and current intensity and unpleasantness of chronic breathlessness

Table S1. Minimal clinically important differences (MCIDs) calculated by anchor-based methods for all participants

Table S2. Minimal clinically important differences (MCIDs) in participants with mMRC 3-4

Table S3. Relative MCIDs (percentage change from baseline) calculated using two participant anchors

Table S1. Minimal clinically important differences (MCIDs) calculated by anchor-based methods for all participants

Dimension		Unpleasantness	Intensity			
			Current	Average	Best	Worst
Focal period		Current	Current	Average	Best	Worst
Participant preference question used						
I have been less breathless during the past week	Yes (n/N)	119/229	121/231	124/235	123/234	124/235
	Mean Changes from baseline (SD)	-7.3 (26.1)	-12.7 (23.5)	-8.1 (18.1)	-7.3 (19.5)	-11.9 (27.7)
	No (n/N)	110/229	110/231	111/235	111/234	111/235
	Mean Change from baseline (SD)	3.6 (20.9)	1.2 (21.3)	1.4 (20.1)	5.1 (20.8)	-1.0 (24.4)
	MCID (95% CI)	-10.9 (-17.1, -4.7)	-13.9 (-19.7, -8.1)	-9.5 (-14.4, -4.6)	-12.4 (-17.6, -7.2)	-10.9 (-17.6, -4.2)
This medication would benefit me enough to be on it long term	Yes (n/N)	111/223	112/225	113/229	112/228	113/229
	Mean Changes from baseline (SD)	-7.3 (23.4)	-11.0 (22.5)	-9.6 (18.9)	-7.7 (19.3)	-12.9 (26.8)
	No (n/N)	112/223	113/225	116/229	116/228	116/229
	Mean Changes from baseline (SD)	2.9 (24.4)	-1.1 (23.7)	1.8 (19.1)	4.5 (21.3)	-1.6 (25.6)
	MCID (95% CI)	-10.2 (-16.5, -3.9)	-9.9 (-16.0, -3.8)	-11.4 (-16.3, -6.5)	-12.2 (-17.5, -6.9)	-11.3 (-18.1, -4.5)

Table S2. Minimal clinically important differences (MCIDs) in participants with mMRC 3-4

Dimension		Unpleasantness	Intensity			
			Current	Average	Best	Worst
Focal period		Current	Current	Average	Best	Worst
Participant preference question used						
I have been less breathless during the past week	Yes (n/N)	109/206	111/208	114/212	113/211	114/212
	Mean Changes from baseline (SD)	-7.0 (26.3)	-13.0 (24.0)	-7.7 (18.0)	-7.2 (19.6)	-11.7 (27.7)
	No (n/N)	97/206	97/208	98/212	98/211	98/212
	Mean Changes from baseline (SD)	3.7 (20.7)	1.5 (22.2)	1.0 (20.9)	5.5 (21.3)	-0.6 (24.5)
	MCID (95% CI)	-10.7 (-17.3, -4.1)	-14.5 (-20.9, -8.1)	-8.7 (-14.0, -3.4)	-12.7 (-18.3, -7.1)	-11.1 (-18.2, -4.0)
This medication would benefit me enough to be on it long term	Yes (n/N)	103/200	104/202	105/206	104/205	105/206
	Mean Changes from baseline (SD)	-7.0 (23.3)	-10.8 (22.9)	-9.3 (19.0)	-7.8 (19.4)	-12.7 (27.2)
	No (n/N)	97/200	98/202	101/206	101/205	101/206
	Mean Changes from baseline (SD)	3.1 (24.8)	-1.3 (25.0)	1.6 (19.7)	5.2 (21.8)	-1.3 (25.3)
	MCID (95% CI)	-10.1 (-16.8, -3.4)	-9.5 (-16.1, -2.9)	-10.9 (-16.2, -5.6)	-13.0 (-18.7, -7.3)	-11.4 (-18.6, -4.2)

MCIDs were calculated using two participant anchors (questions).

Table S3. Relative MCIDs (percentage change from baseline) calculated using two participant anchors

Dimension		Unpleasantness	Intensity			
			Current	Average	Best	Worst
Focal period		Current	Current	Average	Best	Worst
Participant preference question used						
I have been less breathless during the past week	Yes (n/N)	118/225	121/229	123/233	123/228	124/233
	Relative Changes from baseline (95% CI)	26.9% (-13.8%, 67.8%)	-17.2% (-28.3%, -6.1%)	-7.8% (-23.3%, 7.7%)	16.9% (-11.8%, 45.6%)	2.5% (-21.0%, 26.0%)
	No (n/N)	107/225	108/229	109/233	105/228	109/233
	Relative Changes from baseline (95% CI)	64.1% (23.4%, 104.6%)	28.9% (8.3%, 49.5%)	33.0% (10.0%, 56.0%)	80.4% (39.2%, 121.6%)	37.4% (-3.4%, 78.2%)
	Relative MCID (95% CI)	-37.0% (-94.4%, 20.4%)	-46.1% (-68.7%, -23.5%)	-40.8% (-67.8%, -13.8%)	-63.5% (-112.4%, -14.6%)	-34.9% (-80.4%, 10.6%)
This medication would benefit me enough to be on it long term	Yes (n/N)	110/220	112/224	112/227	111/223	113/228
	Relative Changes from baseline (95% CI)	-14.0% (-39.7%, 11.7%)	-13.8% (-26.7%, -0.8)	-11.6% (-27.9%, 4.7%)	5.2% (-18.9%, 29.3%)	-1.0% (-25.6%, 23.6%)
	No (n/N)	110/220	112/224	115/227	112/223	115/228
	Relative Changes from baseline (95% CI)	76.1% (23.5%, 128.5%)	23.5% (4.0%, 43.0%)	29.5% (4.0%, 55.0%)	78.7% (39.3%, 118.0%)	25.9% (-5.3%, 57.1%)
	Relative MCID (95% CI)	-90% (-148.1%, -31.8%)	-37.3% (-60.5%, -14.0%)	-41.1% (-71.4%, -10.8%)	-73.5% (-119.4%, -27.6%)	-26.9% (-66.5%, 12.7%)

The relative MCID was defined as the change in the score divided by the score at baseline.
Abbreviations: MCID, minimal clinically important difference.