Evaluation of the Psychometric Properties, Scoring Algorithm, and Score Interpretation of the E-RS®: Asthma in Two Clinical Trials of Moderate to Severe Asthma

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Aims

- Literature review[1,2] and qualitative research[3,4] indicate respiratory symptom constructs included in the Evaluating Respiratory Symptoms in chronic obstructive pulmonary disease (E-RS®:COPD) are also relevant to patients with moderate/severe asthma, including breathlessness, chest symptoms, cough, and sputum.
- An electronic daily diary including the E-RS:COPD and questions on wheeze, shortness of breath with strenuous activity and overall asthma symptom severity was implemented in two clinical studies in order to test the reliability, validity, and responsiveness of this tool to measure respiratory symptoms in moderate to severe asthma and to define a responder threshold for change.

Methods

- Quantitative psychometric analyses were conducted using data from two randomised controlled clinical trials using a pre-defined analysis plan to evaluate factor structure, scoring, reliability, construct validity, and responsiveness of the E-RS:COPD for use in patients with moderate/severe asthma.
- The design of the analyses in this study was informed by previous validation work on the E-RS:COPD in COPD[5,6] and in asthma-COPD overlap syndrome (ACOS)[3] and qualitative research in patients with asthma[4].
- Data from two GSK studies in asthma were used in the analyses (N=2691): blinded interim data from GSK205715 and final data from GSK205832.
- Analytic samples were not pooled due to differences in study populations (**Table 1**). Separate analyses allowed for the evaluation of psychometric properties across patients with moderate (205832) and moderate/severe asthma (205715).
- All analyses were conducted on blinded data from a patient-reported outcome dataset, defined as intent-to-treat (ITT) patients with a minimum of 4 days of data for the week prior to baseline using SAS statistical software version 9.4 (SAS Institute Inc., Cary, NC) or STATA 15 (StataCorp LLC, College Station, TX). All statistical tests were two-sided and used a significance level of 0.05

Table 1: Summary of clinical trials 205715 and 205832

Study	205715 (interim blinded data)	205832 (final unblinded data)
Design	A Phase III, randomized, double-blind, active controlled, six-arm, parallel-group efficacy, safety, and tolerability trial	A Phase IIb, randomized, double-blind, three-arm parallel-group, efficacy, safety, and tolerability trial
Population	Patients with moderate to severe, uncontrolled asthma: ACQ-6 score ≥1.5 despite treatment with maintenance asthma medication (>250 mcg/day FP or equivalent plus LABA) N=2270	Patients with moderate, not well controlled asthma: ACQ-6 total score >0.75 at randomization despite treatment with maintenance ICS N=421
Treatment Duration	24–52 weeks*	24 weeks
PROs	E-RS: COPD SGRQ AQLQ ACQ WPAI-SHP Patient global assessments of symptom severity PGIC	E-RS: COPD SGRQ AQLQ ACQ Patient global assessments of symptom severity PGIC
Study Treatment Groups[†]	FF/UMEC/VI 100/62.5/25 mcg QD FF/UMEC/VI 200/62.5/25 mcg QD FF/UMEC/VI 100/31.25/25 mcg QD FF/UMEC/VI 200/31.25/25 mcg QD FF/VI 100/25 mcg QD FF/VI 200/25 mcg QD	UMEC 62.5 mcg QD (n=128) UMEC 31.25 mcg QD (n=128) Placebo QD (n=128) All study arms received background therapy of 100 mcg FF daily

ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; FF, fluticasone furoate; FP, fluticasone propionate; ICS, inhaled corticosteroid; LABA, long-acting β$_2$-agonist; PGIC, Patient Global Impression of Change; QD, once daily; SGRQ, St George's Respiratory Questionnaire; UMEC, umeclidinium; VI, vilanterol; WPAI-SHP, Work Productivity and Activity Impairment-Specific Health Problems Questionnaire; *Treatment duration 24 weeks (efficacy endpoints) with some patients continuing in the study for a maximum of 52 weeks.
†Blinded sample for analysis of 205715 based on interim data; final unblinded data for 205832 included.

Methods continued

- Assessments with missing item level data were excluded from the analysis. No imputation of missing data was performed as the aim was to evaluate the psychometric properties of the E-RS:COPD in asthma.

Statistical analyses

- To confirm the factor structure of the E-RS:COPD, confirmatory factor analysis (CFA) was conducted using structural equation modeling[8] to test the hypothesis that the E-RS:COPD has 3 factors and second order unidimensionality (that the 3 factors load onto a single construct). CFA was estimated at Weeks 0 and 24 in 205715 and in 205832 patients.
- Post hoc exploratory factor analysis (EFA) was also conducted to determine if there was an optimal factor structure which includes the E-RS:COPD and supplemental questions on wheeze and strenuous activity in a meaningful way. EFA was performed at Weeks 0 and 24 in 205715 and 205832. In EFA the structure or number of factors is not pre-specified; scree plots and corresponding eigenvalues are examined to empirically determine the number of factors.[7]
- Reliability was assessed as follows:
  - Internal consistency reliability assesses the extent to which individual items within each instrument or subscale of an instrument are inter-related and is typically assessed using Cronbach's α coefficient.
  - Test–retest reliability assesses the reproducibility of scores in stable patients over time.
- Construct validity was investigated to assess the degree to which the underlying construct being assessed by the instrument is supported by correlations with conceptually similar and dissimilar concepts as well as to explore scores across known-groups.
- Analysis of covariance (ANCOVA) models were utilized to examine differences in the change in total and subscale E-RS:COPD daily scores in participants classified as responders by other measures used as anchors: PGIC, SGRQ, and AQLQ to determine responsiveness.
- Anchor and distribution-based methods were then used to define a responder threshold.

Results

- Baseline demographics for the analysis population are shown in **Table 2**.

CFA

- CFA supported the fit of the data to the E-RS:COPD factor structure at baseline in 205715: comparative fit index (CFI)=0.921; standardized root mean square residual (SRMR=0.046) and in 205832 (CFI=0.872; SRMS=0.061) (**Table 3**).

EFA

- Results from EFA were similar to those in a a previous study[3] assessing the psychometric properties of the E-RS:COPD in patients with ACOS and are not presented here.
- CFA and EFA findings supported retaining the E-RS:COPD factor structure for the 11 items. Therefore, the scoring algorithm from the E-RS:COPD was retained for subsequent analyses. The resulting tool is referred to as E-RS:Asthma in this context; subscale names are consistent across both tools.

Reliability

- In both studies, internal consistency reliability was high for the RS-Total and subscale scores (Cronbach's α ranging from 0.83 to 0.96) (**Table 4**).
- Test-retest reliability results indicated stability of the RS-Total and subscale scores in both trials (intra-class correlation coefficient values >0.70 for all assessment time points).

Construct validity

- Acceptable construct and known-groups validity were demonstrated.
  - At baseline, moderate relationships (r>0.37) were observed between RS-Total score and SGRQ-Total, SGRQ symptoms and SGRQ activity domain scores; and were supported by analyses at Week 24.
  - The RS-Total and subscale scores showed evidence of convergent validity with Asthma Symptom Severity score, with high correlations ranging from r=0.58 to r= 0.88 at baseline and from r=0.59 to r=0.86 at Week 24 (all P<0.0001).
  - In support of known-groups validity, when the Global Impression of Disease Severity was used as an anchor, mean scores on the E-RS:Asthma increased linearly with increasing global severity in both trials (**Table 5**).

Responsiveness and Responder Threshold

- Responsiveness of the E-RS:Asthma was supported using PGIC, SGRQ Total and AQLQ scores as anchors (RS-Total results in **Table 6**) and distribution-based methods (results not shown).
- Triangulating the results from anchor and distribution-based methods for estimating the meaningful change threshold suggest a change of -2.0 for the RS-Total, -1.0 for RS-Breathlessness, and -0.7 for RS-Cough and Sputum and RS-Chest Symptoms constitute a meaningful change to patients in moderate to severe asthma.

Table 2. Sociodemographic and clinical characteristics at baseline (Day 0) in 205715 and 205832

Characteristics	205715 (N=2270)[a,b]	205832 (N=420)[b]
Age, mean (SD)	53.3 (13.12)	48.8 (14.65)
Gender n (%)		
Male	867 (38.2)	123 (29.3)
Female	1403 (61.8)	297 (70.7)
Ethnicity n (%)		
Hispanic or Latino	235 (10.4)	9 (2.1)
Not Hispanic or Latino	2035 (89.6)	411 (97.9)
Race n (%)		
White	1888 (83.2)	386 (91.9)
Asian	279 (12.3)	6 (1.4)
Black	84 (3.7)	26 (6.2)
Other	17 (0.7)	2 (0.5)
Missing	2 (0.1)	0 (0.0)
FEV$_1$ (L)[a], mean (SD)	2.0 (0.74)	2.2 (0.67)
FEV$_1$ % predicted[a], mean (SD)	70.7 (14.29)	70.9 (11.13)
# exacerbations in last 12 months, mean (SD)	1.4 (1.29)	0.3 (0.72)
Smoking history, n %		
Never	1835 (80.8)	388 (92.4)
Former	430 (18.9)	32 (7.6)
Missing	5 (0.2)	0 (0.0)
E-RS: Asthma Total Score, mean (SD)	8.3 (6.30)	7.2 (5.66)
ACQ-5, mean (SD)	2.0 (0.77)	1.8 (0.61)

FEV$_1$, forced expiratory volume in 1 second; SD, standard deviation.
*Interim data only; [a]2 ITT subject (715) and 1 ITT subject (832) with only 1 day or no pre-baseline data were excluded; [b]based on pre-bronchodilator spirometry

Table 3. CFA of E-RS:COPD at Week 0 in 205715 and 205832

Item	205715 (n=2244)[a]			205832 (N=420)		
	Breathlessness loadings[b]	Cough and sputum loadings[b]	Chest symptoms loadings[b]	Breathlessness loadings[b]	Cough and sputum loadings[b]	Chest symptoms loadings[b]
Chest congested (1)	-	-	0.852	-	-	**0.803**
Cough (2)	-	**0.886**	-	-	**0.829**	-
Mucus/phlegm (3)	-	**0.819**	-	-	**0.806**	-
Difficulty bring up mucus (4)	-	**0.801**	-	-	**0.846**	-
Chest discomfort (5)	-	-	**0.966**	-	-	0.958
Tight chest (6)	-	-	**0.954**	-	-	0.948
Breathlessness (7)	**0.901**	-	-	**0.897**	-	-
Describe breathlessness (8)	**0.829**	-	-	**0.813**	-	-
Short of breath personal activities (9)	**0.841**	-	-	**0.822**	-	-
Short of breath indoor activities (10)	**0.940**	-	-	**0.938**	-	-
Short of breath outdoor activities (11)	**0.914**	-	-	**0.931**	-	-
	RS-Total			RS-Total		
RS-Breathlessness	**0.901**			**0.847**		
RS-Cough and Sputum	**0.796**			**0.786**		
RS-Chest	**0.936**			**0.930**		
CFI[a]	0.921			0.872		
SRMR[a]	0.046			0.061		
RMSEA[a]	0.154			0.194		

*Interim data only; [a]factor loadings ≥0.40 appear in bold and are considered acceptable; [b]CFI of ≥0.9 indicates good model fit; SRMR of <0.1 indicates good model fit; RMSEA of <0.08 indicates good model fit
CFI, comparative fit index; RMSEA, root mean square error of approximation; SRMR, standardised root mean square residual.

Table 4. Internal consistency reliability for mean weekly E-RS:COPD total and subscale item scores at Week 0 (Cronbach's α)[7] in 205715 and 205832

Item/Total Score	Cronbach's α Week 0	
	205715* (N=2244)	205832 (N=420)
RS-Total score alpha	0.955	0.950
With item removed:		
Chest congested	0.949	0.944
Cough	0.953	0.949
Mucus/phlegm	0.956	0.951
Difficulty bring up mucus	0.954	0.947
Chest discomfort	0.949	0.943
Tight chest	0.949	0.943
Breathlessness	0.948	0.943
Describe breathlessness	0.951	0.947
Short of breath personal activities	0.951	0.945
Short of breath indoor activities	0.948	0.942
Short of breath outdoor activities	0.949	0.943
RS-Breathlessness subscale score alpha	0.947	0.944
With item removed:		
Breathlessness	0.929	0.924
Describe breathlessness	0.942	0.940
Short of breath personal activities	0.944	0.945
Short of breath indoor activities	0.924	0.921
Short of breath outdoor activities	0.932	0.925
RS-Cough and Sputum subscale score alpha	0.846	0.847
With item removed:		
Cough	0.728	0.756
Mucus/phlegm	0.811	0.803
Difficulty bring up mucus	0.807	0.795
RS-Chest subscale score alpha	0.943	0.925
With item removed:		
Chest congested	0.961	0.956
Chest discomfort	0.885	0.847
Tight chest	0.902	0.895

*Interim data only; [a]assuming a 3 factor solution.

Conclusions

- The E-RS:Asthma demonstrates good psychometric properties, including reliability, validity, and responsiveness, in patients with moderate-to-severe asthma.
- Analyses also support use of the scoring structure of the E-RS:COPD for moderate-to-severe asthma.

Table 5. Known-groups validity of mean weekly RS-total and subscales at baseline in 205715 and 205832

Patient groups	205715*				205832			
	Total (n, mean [SD])	Breathlessness (n, mean [SD])	Cough and Sputum (n, mean [SD])	Chest Symptoms (n, mean [SD])	Total (n, mean [SD])	Breathlessness (n, mean [SD])	Cough and Sputum (n, mean [SD])	Chest Symptoms (n, mean [SD])
Exacerbation history (number)								
≥2	638, 9.19 (0.25)	638, 4.44 (0.13)	638, 2.40 (0.07)	638, 2.35 (0.07)	26, 8.46 (1.11)	26, 3.95 (0.59)	26, 2.28 (0.30)	26, 2.23 (0.34)
1	1284, 7.86 (0.18)	1284, 3.76 (0.09)	1284, 2.13 (0.05)	1284, 1.97 (0.05)	71, 7.41 (0.67)	71, 3.42 (0.36)	71, 2.11 (0.18)	71, 1.88 (0.20)
0	317, 8.15 (0.35)	317, 3.85 (0.18)	317, 2.19 (0.10)	317, 2.11 (0.10)	323, 7.06 (0.31)	323, 3.43 (0.17)	323, 1.82 (0.09)	323, 1.80 (0.10)
F-test statistic	9.64	9.38	5.23	8.87	0.80	0.36	1.84	0.79
P-value	<0.0001	<0.0001	0.0054	0.0001	0.4497	0.6961	0.1608	0.4551
FEV$_1$ % predicted								
Mild (≥80%)	448, 6.59 (0.29)	448, 3.00 (0.15)	448, 1.91 (0.08)	448, 1.67 (0.09)	102, 7.06 (0.56)	102, 3.19 (0.30)	102, 1.98 (0.15)	102, 1.88 (0.17)
Moderate (50–<80%)	1469, 8.34 (0.16)	1469, 4.02 (0.08)	1469, 2.20 (0.05)	1469, 2.12 (0.05)	298, 7.09 (0.33)	298, 3.47 (0.17)	298, 1.82 (0.09)	298, 1.80 (0.10)
Severe (30–<50%)	282, 10.64 (0.37)	282, 5.17 (0.19)	282, 2.79 (0.10)	282, 2.68 (0.11)	19, 10.07 (1.29)	19, 4.92 (0.68)	19, 2.77 (0.35)	19, 2.38 (0.39)
Very severe (<30%)	9, 13.26 (2.06)	9, 6.83 (1.07)	9, 3.34 (0.58)	9, 3.09 (0.62)	0, n/a	0, n/a	0, n/a	0, n/a
F-test statistic	26.85	29.03	16.18	18.41	2.55	2.71	3.54	1.07
P-value	<0.0001	<0.0001	<0.0001	<0.0001	0.0794	0.0678	0.0300	0.3429
Global Impression of Disease Severity								
None	52, 1.87 (0.81)	52, 0.81 (0.42)	52, 0.67 (0.23)	52, 0.40 (0.24)	5, 3.40 (2.38)	5, 1.07 (1.27)	5, 1.38 (0.67)	5, 0.96 (0.73)
Mild	687, 5.36 (0.22)	687, 2.46 (0.12)	687, 1.53 (0.06)	687, 1.37 (0.07)	197, 5.34 (0.38)	197, 2.53 (0.20)	197, 1.48 (0.11)	197, 1.33 (0.12)
Moderate	1384, 9.62 (0.16)	1384, 4.64 (0.08)	1384, 2.55 (0.04)	1384, 2.43 (0.05)	213, 8.84 (0.37)	213, 4.29 (0.19)	213, 2.27 (0.10)	213, 2.28 (0.11)
Severe	97, 13.39 (0.59)	97, 6.58 (0.31)	97, 3.26 (0.17)	97, 3.55 (0.18)	5, 14.47 (2.38)	5, 7.11 (1.27)	5, 2.98 (0.67)	5, 4.38 (0.73)
Very Severe	1, 22.60 (5.82)	1, 10.00 (3.04)	1, 6.20 (1.65)	1, 6.40 (1.77)	0, n/a	0, n/a	0, n/a	0, n/a
F-test statistic	97.27	91.94	66.37	70.99	18.66	17.16	10.48	16.19
P-value	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

*Interim data only

Table 6. Responsiveness of mean weekly RS-total scores: ANCOVA of E-RS change scores from baseline (Week 0) to Week 24 in 205715 and 205832

Response to therapy	205715 interim data				205832			
	N	LS mean (se)	Overall F test value	*P* value	Effect size*	N	LS mean (se)	Overall F test value	*P* value	Effect size*
RS-Total										
Global impression of change	-	-	60.96	<0.0001	0.45	-	-	15.64	<0.0001	0.42
Significantly improved	418	-4.10 (0.18)	-	-	-	112	-3.67 (0.42)	-	-	-
Moderately improved	415	-2.58 (0.18)	-	-	-	102	-2.09 (0.44)	-	-	-
Mildly improved	410	-1.67 (0.18)	-	-	-	110	-1.19 (0.43)	-	-	-
No change	144	-0.77 (0.30)	-	-	-	43	-0.51 (0.68)	-	-	-
Mildly worse	37	-0.68 (0.59)	-	-	-	6	-1.66 (1.82)	-	-	-
Moderately worse	5	0.44 (1.60)	-	-	-	1	-4.61 (4.45)	-	-	-
Significantly worse	2	-1.03 (2.53)	-	-	-	0	-	-	-	-
SGRQ change	-	-	92.60	<0.0001	0.48	-	-	25.59	<0.0001	0.44
<-4	871	-3.01 (0.13)	-	-	-	265	-2.49 (0.28)	-	-	-
from -4 to 4	223	-1.58 (0.25)	-	-	-	65	-1.70 (0.56)	-	-	-
>4	164	-1.19 (0.29)	-	-	-	40	0.02 (0.71)	-	-	-
AQLQ change	-	-	166.88	<0.0001	0.54	-	-	35.04	<0.0001	0.45
≤0.5	747	-3.27 (0.13)	-	-	-	204	-2.62 (0.32)	-	-	-
<0.5	669	-1.66 (0.14)	-	-	-	163	-1.42 (0.36)	-	-	-

*Among patients defined as "responders" (global impression of improved change, SGRQ change <-4 or AQLQ change ≥0.5).

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- MT, RvM, ZB and AF are employees of and hold stock in GSK. LAL was an employee at the time of the study.
- EB, HK, RH are employees of Evidera. Evidera provides consulting and other research services to pharmaceutical, device, government and non-government organizations. As Evidera employees, they work with a variety of companies and organizations and are expressly prohibited from receiving any payment or honoraria directly from these organizations for services rendered.
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