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1 **Omalizumab substantially improves dermatology-related quality of**  
2 **life in patients with chronic spontaneous urticaria**

3

4 Andrew Y. Finlay, CBE FRCP,<sup>a</sup> Allen P. Kaplan, MD,<sup>b</sup> Lisa A. Beck, MD,<sup>c</sup> Evgeniya N.  
5 Antonova, PhD,<sup>d</sup> Maria-Magdalena Balp, MD, MSc<sup>e</sup> James Zazzali, PhD, MPH,<sup>d</sup> Sam Khalil,  
6 PhD,<sup>e</sup> Marcus Maurer, MD<sup>f</sup>

7

8 *<sup>a</sup> Department of Dermatology and Wound Healing, Cardiff University School of Medicine,*  
9 *Cardiff University, Cardiff, UK*

10 *<sup>b</sup> Medical University of South Carolina, Charleston, SC, USA*

11 *<sup>c</sup> Department of Dermatology, University of Rochester Medical Center, Rochester, NY, USA*

12 *<sup>d</sup> Genentech, Inc., South San Francisco, CA, USA*

13 *<sup>e</sup> Novartis Pharma AG, Basel, Switzerland*

14 *<sup>f</sup> Department of Dermatology and Allergy, Charité – Universitätsmedizin Berlin, Berlin,*  
15 *Germany*

16

17 **Short title:** Omalizumab and health-related quality of life

18

19 **Corresponding author:**

20 Andrew Y. Finlay, CBE FRCP

21 Department of Dermatology and Wound Healing, Cardiff University School of Medicine,  
22 Cardiff University, Cardiff CF14 4XN, UK. finlayAY@cardiff.ac.uk

23 Telephone: +44 2074 2615. Fax: +44 29 2074 4312

24

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53 **ABSTRACT**

54 **Background:** Chronic spontaneous/idiopathic urticaria (CSU/CIU) has substantial  
55 detrimental effects on health-related quality of life (HRQoL) with an effect comparable to or  
56 worse than many other skin diseases.

57 **Objective:** To assess the effect of omalizumab on CSU patients' HRQoL, measured by the  
58 Dermatology Life Quality Index (DLQI) in three phase III studies ASTERIA I, ASTERIA II,  
59 and GLACIAL.

60 **Methods:** A post-hoc analysis examined changes in DLQI scores, distribution of patients  
61 across DLQI bands and the proportion reaching minimal clinically important difference  
62 (MCID) following omalizumab vs placebo.

63 **Results:** Omalizumab 300 mg significantly improved total DLQI scores vs placebo, with a  
64 mean decrease from baseline to week 12 of -10.3 vs -6.1 ( $P<.0001$ ) in ASTERIA I, -10.2 vs -  
65 6.1 ( $P=.0004$ ) in ASTERIA II and -9.7 vs -5.1 ( $P<.0001$ ) in GLACIAL. A significant shift  
66 from high disease impact on life at baseline towards less impact at week 12 was seen with  
67 omalizumab 300 mg vs placebo ( $P<.001$ ; all studies). The proportion of patients where  
68 change in mean total DLQI score from baseline to week 12 reached an MCID of  $\geq 4$  was  
69 74.1%, 76.0% and 77.2% in ASTERIA I, II and GLACIAL, respectively ( $P<.01$ ; all studies).

70 **Limitations:** Maximum duration of omalizumab treatment was 24 weeks.

71 **Conclusion:** This additional analysis assessed the impact of CSU and benefit of treatment  
72 with omalizumab by exploring different facets of DLQI data by treatment arm at multiple  
73 assessment points. The original aspects of analysis included applying the concept of the  
74 recently validated score for the MCID of the DLQI, changes in DLQI domain scores and in  
75 the distribution of subjects based on validated total DLQI score bands. It showed consistently

76 that omalizumab provides significant and clinically relevant improvements in many aspects  
77 of HRQoL that are important to patients with CSU. **These results contribute to a better**  
78 **understanding of the impact of CSU and its treatment on patients and can support clinical**  
79 **decision making in routine medical practice.**

80 **Key words:** anti-IgE; chronic idiopathic urticaria; chronic spontaneous urticaria; Dermatology  
81 Life Quality Index; health-related quality of life; omalizumab.

82

### 83 **INTRODUCTION**

84 Chronic spontaneous/idiopathic urticaria (CSU/CIU) (defined as itchy wheals and/or  
85 angioedema for  $\geq 6$  weeks with no identifiable specific trigger)<sup>1-3</sup> substantially reduces health-  
86 related quality of life (HRQoL)<sup>1, 4-9</sup> with an effect comparable to or worse than many other  
87 skin diseases.<sup>10, 11</sup> CSU adversely affects many aspects of patients' lives.<sup>5, 7, 12</sup> Persistent  
88 itching can cause difficulty sleeping and the resulting chronic fatigue can impair physical and  
89 emotional well-being, work productivity and social functioning.<sup>1</sup> CSU patients feel similarly  
90 lacking in energy and are as socially isolated and emotionally upset as patients with ischemic  
91 heart disease, with even greater disturbance in their sleep.<sup>7</sup>

92 Second generation H1-antihistamines at licensed doses are the recommended first-line  
93 treatment for CSU. These doses may be increased up to four-fold in patients who do not  
94 respond.<sup>2</sup> Omalizumab is a humanized anti-IgE monoclonal antibody approved as add-on  
95 therapy for CSU/CIU in adult and adolescent ( $\geq 12$  years) patients with inadequate response  
96 to/who remain symptomatic despite H1-antihistamine treatment.<sup>13, 14</sup> It is recommended in  
97 the international EAACI/GA<sup>2</sup>LEN/EDF/WAO urticaria guideline as an add-on third-line  
98 treatment option.<sup>2</sup>

99 Patients' views on the impact of disease and benefit of treatment can be assessed through  
100 generic or disease-specific patient-reported outcome (PRO) instruments. PRO instruments  
101 developed to assess dermatology-related QoL include the Dermatology Life Quality Index  
102 (DLQI) which was validated for use in CSU.<sup>15, 16</sup> The DLQI is a well-established tool that has  
103 been used in numerous studies across multiple countries<sup>16-18</sup> and is easy to use in clinical  
104 practice.

105 Here we report a additional post-hoc analysis of the effect of omalizumab on CSU patients'  
106 HRQoL using the DLQI score in three phase III studies ASTERIA I,<sup>19</sup> ASTERIA II,<sup>20</sup> and  
107 GLACIAL.<sup>21</sup>

## 108 **METHODS**

### 109 *Study designs*

110 The DLQI was used to assess HRQoL in patients with CSU in three randomized, double-  
111 blind, placebo-controlled trials: ASTERIA I,<sup>19</sup> ASTERIA II,<sup>20</sup> and GLACIAL.<sup>21</sup> On entry  
112 into the studies, all patients aged 12-75 years (18-75 years in Germany) had symptomatic  
113 CSU, with a disease history  $\geq 6$  months. Patients in ASTERIA I and ASTERIA II were  
114 receiving H1-antihistamines at approved doses at the time of study enrolment<sup>19, 20</sup> and those  
115 in GLACIAL, H1-antihistamines at up to four times the standard dose with H2-antihistamine  
116 and/or leukotriene receptor antagonist.<sup>21</sup> In ASTERIA I and II, patients were randomized  
117 1:1:1:1 to receive omalizumab 75 mg, 150 mg, 300 mg, or placebo every 4 weeks for 24 and  
118 12 weeks, respectively (**Fig 1**). In GLACIAL, patients were randomized 3:1 to receive  
119 omalizumab 300 mg or placebo every 4 weeks for 24 weeks (**Fig 1**). The number of patients  
120 randomized in ASTERIA I, ASTERIA II and GLACIAL were 319, 323 and 336,  
121 respectively.

122 *DLQI assessments*

123 The DLQI consists of 10 questions across six domains: symptoms/feelings, daily activities,  
124 leisure, work/school, personal relationships, and treatment.<sup>17</sup> Each question is scored from  
125 ‘very much’ (score = 3) to ‘not at all’ (0), and an overall score (0–30) is calculated by  
126 summing the individual domain scores.<sup>17</sup> A higher score indicates poorer HRQoL.<sup>17</sup> DLQI  
127 was measured at baseline and at several time points during the active treatment period (weeks  
128 12 and 24 in ASTERIA I and GLACIAL; week 12 in ASTERIA II) and during the post-  
129 treatment follow-up period (week 40 in ASTERIA I and GLACIAL; week 28 in ASTERIA  
130 II).

131 Absolute (and percentage) change from baseline in mean total DLQI scores following  
132 omalizumab (at approved doses of 150 mg or 300 mg) vs placebo were measured. Change  
133 from baseline to week 12 in mean total DLQI score was a pre-specified secondary endpoint  
134 in the phase III studies.<sup>19-21</sup> The current post-hoc analysis also analysed change from baseline  
135 in scores for the 6 individual domains of the DLQI.

136 Hongbo and co-workers devised bands for DLQI scores. These relate ranges of scores to  
137 meaningful health states and reflect the impact of skin diseases on patients’ lives. Five DLQI  
138 score bands were validated based on input from 1993 patients (**Table I**), with a total DLQI  
139 score above 10 indicating a very large effect on the patient’s life.<sup>22</sup> The distribution of total  
140 DLQI scores across these descriptive bands was analysed at baseline and the different time  
141 points.

142 A minimal clinically important difference (MCID) of 3–4 points has been estimated for the  
143 DLQI in patients with CSU.<sup>23, 24</sup> The MCID is the minimum change in a score of interest  
144 considered important by the patient and mandating a change in the patient’s management.<sup>25</sup>

145 The proportion of patients whose change in mean total DLQI score from baseline reached an  
146 MCID of  $\geq 4$  was also measured at different time points.

#### 147 *Statistical analysis*

148 Least square means (LSMs) and 95% confidence intervals (CIs) were calculated for  
149 differences in mean total DLQI score between omalizumab groups and placebo using an  
150 ANCOVA model, controlling for baseline DLQI ( $<$ median vs  $\geq$ median) and weight ( $<80$  vs  
151  $\geq 80$  kg). Statistical significance was evaluated using ANCOVA t-tests. Analyses were  
152 conducted using observed data only, with no imputation for missing scores.

153 The analysis for the change in the distribution of DLQI score bands was performed for each  
154 trial and each study arm separately by assessing the number and proportion of patients in  
155 each DLQI band at baseline, week 4, 12, 24 and 40 for ASTERIA I and GLACIAL, and at  
156 baseline, week 4, 12, and 28 for ASTERIA II. Chi-square test for significant differences in  
157 the proportions of patients in each DLQI scoring band was performed for each treatment arm  
158 vs placebo.

159

160 For each trial and treatment arm, the proportion of patients who attained a MCID of  $\geq 4$  points  
161 on the DLQI total score was assessed at weeks 4, 12, 24 and 40 for ASTERIA I and  
162 GLACIAL, and weeks 4, 12, and 28 for ASTERIA II. Differences in proportions between  
163 treatment arms were analysed for significance using the one-way ANOVA test.

164

## 165 **RESULTS**

### 166 *Baseline characteristics*

167 Baseline demographics and clinical characteristics have been reported previously for the  
168 phase III studies and were similar between treatment arms (**Table SI**).<sup>19-21</sup> The mean total



169 DLQI score at baseline ranged from 12.6 to 14.0 across studies reflecting a very large impact  
170 on patients' lives (**Table SI**).

171 In more than half of patients, total DLQI scores at baseline reflected a very large or extremely  
172 large impact of CSU on their lives. The baseline proportion of patients whose disease had a  
173 very large impact on their HRQoL ranged from 42.2% to 53.8% and whose disease had an  
174 extremely large impact ranged from 10.1% to 17.7% across the phase III studies (**Figs 3, S1**  
175 and **S2**). CSU had the greatest impact on symptoms and feelings, daily activities and leisure  
176 (**Tables SII–SIV**).

#### 177 *Change in mean total DLQI score*

178 Omalizumab 300 mg showed statistically and clinically significant improvements in mean  
179 total DLQI scores vs placebo, with a mean change from baseline to week 12 of -10.3 vs -6.1  
180 [*LSM treatment difference vs placebo (95% CI) -4.1 (-6.0, -2.2);  $P < .0001$* ] in ASTERIA I, -  
181 10.2 vs -6.1 [*-3.8 (-5.9, -1.7);  $P = .0004$* ] in ASTERIA II and -9.7 vs -5.1 [*-4.7 (-6.3, -3.1);*  
182  *$P < .0001$* ] in GLACIAL. This corresponded to a percentage change of -73.6% vs -47.2%, -  
183 77.6% vs -44.0% and -72.7% vs -22.5%, respectively (**Fig 2**).

184 Omalizumab 150 mg showed statistically significant improvement vs placebo in mean  
185 change of DLQI score from baseline to week 12 in ASTERIA II, but not in ASTERIA I (**Fig**  
186 **2**).

187 Significant improvements in total DLQI scores were observed at week 24 of treatment with  
188 omalizumab 300 mg vs placebo with a mean change from baseline of -10.6 vs -8.1 [*-2.0 (-*  
189 *4.0, -0.1);  $P = .0388$* ] in ASTERIA I and -10.0 vs -6.4 [*-3.7 (-5.5, -1.9);  $P < .0001$* ] in  
190 GLACIAL (**Fig 2**).

191 In all three studies, mean total DLQI scores had increased by the end of the post-treatment  
192 follow-up period (indicating a decrease in HRQoL), although not numerically back to  
193 baseline levels (**Fig 2**).

#### 194 *Change in DLQI domain scores*

195 Omalizumab 300 mg improved scores in all but one individual DLQI domain between  
196 baseline and week 12, vs placebo; statistically significant improvements were seen in  
197 symptoms/feelings, daily activities, leisure, work and school, and treatment in all three  
198 studies (**Tables SII–SIV**). Improvement in personal relationships vs placebo was statistically  
199 significant in ASTERIA I and GLACIAL between baseline and week 12 but did not reach  
200 significance in ASTERIA II (**Tables SII–SIV**). Improvements were seen in all DLQI domain  
201 scores between baseline and week 12 with omalizumab 150 mg vs placebo but none reached  
202 statistical significance in ASTERIA I (**Table SII**), and in ASTERIA II improvements were  
203 significant only for symptoms and feelings and daily activities (**Table SIII**).

204 Improvements in individual domain scores were either continued or maintained with  
205 omalizumab 300 mg or 150 mg by week 24 of treatment in ASTERIA I and GLACIAL  
206 (**Tables SII and SIV**).

#### 207 *Change in distribution of patients across total DLQI score bands*

208 Treatment with omalizumab at either 300 mg or 150 mg doses led to a redistribution of  
209 patients across total DLQI score bands, towards bands representing better health states. In all  
210 three studies, this shift was significant vs placebo for omalizumab 300 mg at week 12  
211 ( $P < .001$  in ASTERIA I [**Fig 3**], ASTERIA II [**Fig S1**] and GLACIAL [**Fig S2**]) and at week  
212 24 for ASTERIA I and GLACIAL ( $P < .001$ ; **Figs 3 and S2**). The shift did not reach  
213 significance following omalizumab 150 mg at week 12. Following treatment with  
214 omalizumab 300 mg, the proportion of patients with DLQI scores corresponding to ‘no

215 effect' on their life at weeks 12 and 24 had increased from 1.2% at baseline to 58.9% and  
216 69.9%, respectively, in ASTERIA I (**Fig 3**), from 1.3% to 60.0% in ASTERIA II (**Figure**  
217 **S1**), and from 0.4% to 57.0% and 57.5% in GLACIAL (**Fig S2**).

218 In all three studies, by the end of the post-treatment follow-up period, there was a shift to  
219 score bands describing a greater effect on life, although not numerically back to baseline  
220 levels (**Fig 3, S1 and S2**).

221 *Changes in mean total DLQI score reaching a MCID of  $\geq 4$*

222 Significantly more patients treated with omalizumab 300 mg than placebo had changes in  
223 mean total DLQI scores reaching a MCID of  $\geq 4$  from baseline to week 4 (69.1% vs 47.5% in  
224 ASTERIA I;  $P = .015$ , 77.2% vs 50.6%;  $P = .001$  in ASTERIA II and 66.3% vs 47.6%;  
225  $P = .002$  in GLACIAL) and from baseline to week 12 (74.1% vs 46.3% in ASTERIA I;  
226  $P = .001$ , 76.0% vs 53.2%;  $P = .008$  in ASTERIA II and 77.2% vs 47.6%;  $P < .001$  in  
227 GLACIAL) (**Fig 4**). This clinically significant difference was maintained to week 24 in  
228 GLACIAL ( $P < .001$ ), but not in ASTERIA I (**Fig 4**).

229 **DISCUSSION**

230 In the phase III trials of omalizumab in CSU, the burden of disease was reflected in mean  
231 DLQI scores at baseline with most patients reporting a very large or extremely large impact  
232 on their lives. The initial planned analysis, as published in the original articles<sup>19-21</sup>, showed  
233 the change in DLQI total score from baseline to week 12. The clinical interpretation of a  
234 simple change in score, while demonstrating effectiveness, may be too simplistic in the  
235 context of clinical practice. In the further exploration reported in this study, three sets of  
236 additional analyses were included involving different aspects of the DLQI by treatment arm  
237 at multiple assessment points: assessing mean changes in individual DLQI domains;  
238 comparing mean scores on the DLQI for patients whose change in DLQI score exceeded the  
239 MCID of the DLQI; and changes in the distributions of patients across DLQI total score  
240 validated descriptor bands. Each of these analyses, representing new and alternative ways of  
241 exploring changes in dermatology-related quality of life, provide additional insights into  
242 patients' responses to treatment for CSU. The present study provides further insights relevant  
243 for decision making in clinical practice.

244 In all three studies, 12 weeks' treatment with omalizumab 300 mg significantly improved  
245 mean total DLQI scores. In ASTERIA I and GLACIAL, which evaluated omalizumab  
246 treatment beyond 12 weeks, this significant improvement was either maintained or increased  
247 vs placebo after 24 weeks (the maximum duration of omalizumab treatment studied).

248 Assessment of the individual domains of the DLQI allows further understanding of the  
249 impact of dermatological conditions on a patient's life.<sup>7</sup> In ASTERIA I and GLACIAL,  
250 omalizumab 300 mg significantly improved scores from baseline to week 12 in all DLQI  
251 domains, indicating that the improvements seen in the mean total DLQI score were due to a  
252 sum of effects on many aspects of patients' lives (symptoms/feelings, daily activities,  
253 personal relationships, leisure, work and school, and treatment). Improvement in all domains

254 but personal relationships reached statistical significance at week 12 vs placebo in ASTERIA  
255 II.

256 The beneficial effects of omalizumab 150 mg on DLQI were more modest than with  
257 omalizumab 300 mg, perhaps corresponding to the lesser effect also reported with this dose  
258 vs placebo on itch severity scores.<sup>19, 20</sup>

259 At 16 weeks after cessation of omalizumab treatment, improvements observed in both mean  
260 total DLQI scores and individual DLQI domain scores during the treatment period had  
261 lessened (although scores had not numerically increased back to baseline levels). This is in  
262 agreement with the pattern seen in the phase III studies for changes in Urticaria Activity  
263 Score (UAS7), which also increased following discontinuation of omalizumab, but did not  
264 return to baseline levels.<sup>19-21</sup> These findings support the hypothesis that longer-term treatment  
265 may be required to sustain the benefit of omalizumab on symptoms and HRQoL and reaffirm  
266 that HRQoL in CSU is linked to disease activity. A good correlation has been seen between  
267 changes in symptoms of CSU (measured using the UAS7) and changes in patients' HRQoL,  
268 as measured by the DLQI and CU-Q<sub>2</sub>oL.<sup>26</sup>

269 Analysis of the distribution of DLQI scores across descriptive bands which explain and  
270 validate the impact of disease on patients' lives support the clinical interpretation of results  
271 and advise patients regarding the expected outcomes of omalizumab treatment.<sup>22, 24</sup> In all  
272 studies, treatment with omalizumab 300 mg (but not 150 mg) led to a significant shift in the  
273 distribution of DLQI scores to bands showing less to no impact of disease on patients' lives  
274 vs placebo at week 12. In ASTERIA I and GLACIAL, the shift in DLQI score banding was  
275 still significant vs placebo for omalizumab 300 mg by week 24. Following treatment with  
276 omalizumab 300 mg, the proportion of patients with DLQI scores corresponding to 'no  
277 effect' on their life (total DLQI scores of 0-1) at weeks 12 and 24 had increased substantially

278 from baseline. In ASTERIA I and GLACIAL, 58.9% and 57% of patients, respectively,  
279 reached a DLQI of 0-1 at week 12, and 69.9% and 57.5% by week 24.

280 Across the phase III studies, significantly more patients treated with omalizumab 300 mg  
281 than placebo had changes in mean total DLQI scores from baseline reaching the published  
282 MCID of  $\geq 4$  for patients with CSU. Omalizumab 300 mg improved mean total DLQI scores  
283 from baseline to week 12 by approximately 10 points (substantially greater than the MCID of  
284 2.97–3.21 points previously estimated in CSU patients and the more stringent threshold of 4  
285 used in this study)<sup>23, 24</sup> indicating that the improvements seen in HRQoL are perceived as  
286 beneficial by patients. Indeed, this was demonstrated by the increased proportion of patients  
287 with DLQI scores corresponding to ‘no effect on their life’. While mean improvements in  
288 total DLQI from baseline to week 12 with placebo (5–6 points) also exceeded the MCID, the  
289 LSM treatment difference was significant for omalizumab 300 mg vs placebo in ASTERIA I  
290 ( $P < .0001$ ), ASTERIA II ( $P = .0004$ ) and GLACIAL ( $P < .0001$ ). The clinically significant  
291 improvement seen with omalizumab 300 mg was maintained to week 24 in both ASTERIA I  
292 ( $P = .0388$ ) and GLACIAL ( $P < .0001$ ).

293 In conclusion, our analyses demonstrate that omalizumab, particularly at a dose of 300 mg  
294 every 4 weeks, provides significant and clinically relevant improvements in many aspects of  
295 HRQoL that are important to patients with CSU. These results further validate the usefulness  
296 of the DLQI in assessing the impact of CSU and benefit of treatment.

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370 **Fig 1.** Designs of the phase III studies of omalizumab in CSU

371 *<Figure uploaded separately>*

372 Patients in ASTERIA I and ASTERIA II were receiving H1-antihistamines at approved  
373 doses at the time of study enrolment and those in GLACIAL received H1-antihistamines at  
374 up to four times the standard dose with H2-antihistamine and/or leukotriene receptor  
375 antagonist. In ASTERIA I, the introduction of an additional H1-antihistamine was allowed  
376 after week 12, with the aim of reducing patient dropout over the extended treatment period.  
377 In all of the trials, patients were permitted to take diphenhydramine 25 mg as rescue  
378 medication for symptom relief (up to a maximum of 3 doses per 24-hour period, on the basis  
379 of local regulations).

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394 **Fig 2.** Change from baseline in mean total DLQI scores during and following treatment in  
395 ASTERIA I, ASTERIA II and GLACIAL

396 *<Figure uploaded separately>*

397 Omalizumab 150 mg is not licensed for CSU in some countries. Data are for mITT  
398 population.

399 *P* values are vs placebo. <sup>NS</sup>*P* ≥ .05; \**P* < .05; \*\**P* < .01; \*\*\**P* < .001, †*P* < .0001.

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419 **Fig 3.** Change in distribution of patients across total DLQI score bands in ASTERIA I

420 *<Figure uploaded separately>*

421 DLQI is a measure of health-related quality of life, with a higher score indicating greater  
422 impairment of a patient's quality of life. An overall DLQI score is calculated by summing the  
423 score from 10 questions across six different domains, resulting in an overall score from 0 to  
424 30. The scores are then categorized into DLQI bands: 0–1 = no effect; 2–5 = small effect; 6–  
425 10 = moderate effect; 11–20 = very large effect; 21–30 = extremely large effect on the  
426 patient's life (Hongbo et al. 2005).<sup>22</sup>

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444 **Fig 4.** Proportion of patients with a change in mean total DLQI score from baseline reaching

445 a MCID of  $\geq 4$  in ASTERIA I, ASTERIA II and GLACIAL

446 *<Figure uploaded separately>*

447 *P* values are vs placebo. <sup>NS</sup>*P*  $\geq .05$ ; \**P*  $< .05$ ; \*\**P*  $< .01$ ; \*\*\**P*  $< .001$ , †*P*  $< .0001$ .

448 MCID, minimally clinically important difference of  $\geq 4$ .