

Health-Related Quality of Life with Subcutaneous C1-Inhibitor for Prevention of Attacks of Hereditary Angioedema



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What is already known about this topic? Hereditary angioedema with C1-inhibitor deficiency (C1-INH-HAE) remains a cause of health-related quality of life (HRQoL) impairments, including anxiety and productivity deficits, despite noted improvements over recent years concurrent with the availability of new targeted therapies.

What does this article add to our knowledge? This is the first analysis to evaluate HRQoL in patients with C1-INH-HAE using self-administered subcutaneous C1-inhibitor as routine prophylaxis. These findings supplement clinical efficacy outcomes reported recently from the randomized, phase III COMPACT (Clinical Studies for Optimal Management of Preventing Angioedema with Low-Volume Subcutaneous C1-Inhibitor Replacement Therapy) study.

How does this study impact current management guidelines? HAE consensus guidelines cite restoration of normal quality of life as a treatment goal, and these findings provide strong evidence that subcutaneous C1-INH has the potential to significantly improve a number of HRQoL measures.

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*Abbreviations used**C1-INH- C1-inhibitor**C1-INH-HAE- Hereditary angioedema with C1-inhibitor deficiency**CI- Confidence interval**EQ-5D-3L- European Quality of Life-5 Dimensions Questionnaire**HADS- Hospital Anxiety and Depression Scale**HAE- Hereditary angioedema**HRQoL- Health-related quality of life**HSV- Health state value**IGART- Investigator Global Assessment of Response to Therapy**IV- Intravenous**MCID- Minimal clinically important difference**PRO- Patient-reported outcome**SC- Subcutaneous**SD- Standard deviation**SF- Short Form**SGART- Subject Global Assessment of Response to Therapy**TSQM- Treatment Satisfaction Questionnaire for Medication**VAS- Visual analog scale**WPAI- Work Productivity and Activity Impairment Questionnaire*

BACKGROUND: Hereditary angioedema with C1-inhibitor deficiency (C1-INH-HAE) impairs health-related quality of life (HRQoL).

OBJECTIVE: The objective of this study was to assess HRQoL outcomes in patients self-administering subcutaneous C1-INH (C1-INH[SC]; HAEGARDA) for routine prevention of HAE attacks.

METHODS: *Post hoc* analysis of data from the placebo-controlled, crossover phase III COMPACT study (Clinical Studies for Optimal Management of Preventing Angioedema with Low-Volume Subcutaneous C1-Inhibitor Replacement Therapy). Ninety patients with C1-INH-HAE were randomized to 1 of 4 treatment sequences: C1-INH(SC) 40 or 60 IU/kg twice weekly for 16 weeks, preceded or followed by 16 weeks of twice weekly placebo injections. All HAE attacks were treated with open-label on-demand treatment as necessary. HRQoL assessments at week 14 (last visit) included the European Quality of Life-5 Dimensions Questionnaire (EQ-5D-3L), the Hospital Anxiety and Depression Scale (HADS), the Work Productivity and Activity Impairment Questionnaire (WPAI), and the Treatment Satisfaction Questionnaire for Medication (TSQM).

RESULTS: Compared with placebo (on-demand treatment alone), treatment with twice weekly C1-INH(SC) (both doses combined) was associated with better EQ-5D visual analog scale general health, less HADS anxiety, less WPAI presenteeism, work productivity loss, and activity impairment, and greater TSQM

effectiveness and overall treatment satisfaction. More patients self-reported a “good/excellent” response during routine prevention with C1-INH(SC) compared with on-demand only (placebo prophylaxis) management. For each HRQoL measure, a greater proportion of patients had a clinically meaningful improvement during C1-INH(SC) treatment compared with placebo.

CONCLUSIONS: In patients with frequent HAE attacks, a treatment strategy of routine prevention with self-administered twice weekly C1-INH(SC) had a greater impact on improving multiple HAE-related HRQoL impairments, most notably anxiety and work productivity, compared with on-demand treatment alone (placebo prophylaxis). © 2018 The Authors.

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Hereditary angioedema (HAE) with C1-inhibitor deficiency (C1-INH-HAE) is a debilitating and potentially life-threatening condition characterized by recurrent episodes of nonpruritic submucosal and/or subcutaneous edema.¹⁻⁴ C1-INH-HAE is a rare genetic disorder typified by a deficiency of C1-INH protein (HAE type 1; accounts for approximately 85% of cases) or abnormally functioning C1-INH in the presence of normal or elevated C1-INH levels (HAE type 2; approximately 15% of cases).

As a lifelong, unpredictable, and debilitating disease with an omnipresent potential for fatal laryngeal swelling, C1-INH-HAE can have profound effects on various aspects of health-related quality of life (HRQoL). A landmark study by Lumry et al,⁵ conducted before the availability of HAE-specific medications in the United States, found significant impairment of both physical and mental HRQoL in patients with C1-INH-HAE. In that study, the mean attack frequency was 27 HAE attacks per year. Since 2009, after the introduction of a number of HAE-specific therapies, some studies have indicated better overall HRQoL in patients with C1-INH-HAE as measured by the Short-Form (SF)-12 or SF-36 instruments.⁶⁻⁸ However, other research conducted among C1-INH-HAE populations with access to effective therapies has since reported continued negative impacts of HAE on various aspects of HRQoL.⁹⁻¹⁶

Anxiety continues to be a particular burden among patients with C1-INH-HAE, even in recent studies in which patients had access to current, HAE-specific medications for on-demand therapy and prophylaxis.^{10,15,17,18} The unpredictability of HAE

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attacks and the fear of pain and asphyxiation contribute to anxiety in between attacks.^{17,19} Depression is another concern, with results from recent, independent studies suggesting evidence of clinically significant depression in 8% to 39% of patients with C1-INH-HAE.^{10,18} In addition to physical and emotional effects, HAE attacks result in absences from work and school,^{5,18-22} affecting patients and potentially their family members and caregivers.

Frequency of HAE attacks in general and fear of asphyxiation in particular are frequently cited reasons for anxiety and HRQoL impairment.^{13-15,19} Thus, eliminating as many HAE attacks as possible is a highly desirable disease management goal. Until recently, prophylaxis against HAE attacks has been limited mainly to oral attenuated androgens (eg, danazol) and intravenous C1-INH (C1-INH[IV]). Androgens have a number of safety/tolerability drawbacks, including increased anxiety and depression,²³ and are not always effective, especially at presently recommended doses. Some patients using C1-INH(IV) as routine prophylaxis at the approved dose of 1000 units twice weekly have suboptimal disease control and frequent breakthrough attacks.^{11,15,24-27} Furthermore, C1-INH(IV) administration can present venous access challenges, and some patients will require central venous access devices with associated risks and complications.^{26,28,29}

A subcutaneous formulation of C1-INH (CSL830; C1-INH [SC]; HAEGARDA; CSL Behring, Marburg, Germany) was recently (June 2017) approved by the US Food and Drug Administration and offers a new option for routine prevention of HAE attacks in adolescents and adults.³⁰ Higher and more stable trough C1-INH functional activity levels have been observed with twice weekly C1-INH(SC) relative to twice weekly C1-INH(IV).³¹ Data from the “Clinical Studies for Optimal Management of Preventing Angioedema with Low-Volume Subcutaneous C1-inhibitor Replacement Therapy” (COMPACT) trial (NCT01912456) demonstrated a favorable safety profile and a high degree of attack prevention efficacy with self-administered C1-INH(SC) relative to placebo.^{31,32} In particular, COMPACT demonstrated that the approved C1-INH(SC) dose of 60 IU/kg demonstrated a 95% reduction in median attack rate and a 100% reduction in median rescue medication use versus placebo.³²

This study was a *post hoc* analysis of prespecified exploratory patient-reported outcome (PRO) endpoints related to anxiety and depression, work productivity and activity impairment, and satisfaction with treatment (collectively referred to herein as HRQoL) from the COMPACT study.

METHODS

Study design and patients

The detailed methodology and results of the COMPACT study have been reported previously³² and are briefly summarized here. The study was approved by the appropriate regulatory authorities and institutional review boards.

Eligible patients were ≥ 12 years of age with a clinical diagnosis of C1-INH-HAE type I or II, and must have experienced at least 2 HAE attacks during any consecutive 4-week period or at least 1 attack during the first 2 weeks of the run-in period (see Figure 1).

Patients were randomly assigned to 1 of 4 treatment sequences exploring 2 doses: C1-INH(SC) 40 or 60 IU/kg twice weekly for 16 weeks, preceded or followed by a placebo period (twice weekly SC

injections) for 16 weeks (Figure 1). For all treatment sequences, HAE attacks were managed using open-label, on-demand treatment of attacks (eg, C1-INH(IV), icatibant, etc.) as necessary. Thus, “placebo” treatment periods reflected HAE management using open-label, on-demand treatment of attacks with rescue medication as necessary. On-demand therapies (C1-INH(IV), icatibant, ecallantide, fresh frozen plasma) were allowed at any time during the trial as deemed necessary by the physician or patient as rescue medications. The study medication of C1-INH(SC) and corresponding placebo were volume-blinded to ensure that neither patient nor physician was able to identify the treatment assignment. Patients were trained to self-administer study medication injections at home.

Patient- and investigator-reported outcomes

Because validated HAE disease-specific HRQoL tools were not available at the time the COMPACT study was established, commonly used and validated generic HRQoL tools were completed at baseline and various time points throughout the study (Figure 1). General health and health status were measured with the European Quality of Life-5 Dimensions Questionnaire (EQ-5D-3L).³³ Anxiety and depression were assessed using the Hospital Anxiety and Depression Scale (HADS).³⁴ Health-related work productivity and activity impairment were evaluated with the Work Productivity and Activity Impairment Questionnaire (WPAI).³⁵ Lastly, the study subjects' satisfaction with medication was measured with the Treatment Satisfaction Questionnaire for Medication (TSQM).³⁶

In addition, 2 simple scales were used to assess subjective assessments of overall treatment response: the Investigator and Subject Global Assessments of Response to Therapy (IGART and SGART). Patients and investigators rated the overall response to therapy using the following direction: “Considering all of the ways HAE affects [you/your patient], please rate [your/your patient's] response to the study medication [you were given/provided] to prevent HAE attacks during this Treatment Period.” Possible answers included “none,” “poor,” “fair,” “good,” or “excellent.”

Data collection

All HRQoL data were collected using an electronic diary completed by the subjects at the study center. The IGART was completed by the investigator using the electronic case report form; whenever possible, the same investigator performed both IGART assessments for a given patient.

Data analysis

The HRQoL data were analyzed within the “HRQoL population,” consisting of all patients in the intent-to-treat population who provided at least 1 HRQoL assessment. All score values were summarized by visit and treatment. Missing values for the HRQoL assessments were not imputed.

For each HRQoL assessment, the effect of C1-INH(SC) was evaluated by the mean and median difference in within-subject scores between active and placebo treatments (40 IU/kg vs high-volume placebo, and 60 IU/kg vs low-volume placebo, and both active treatments combined vs placebo combined) and associated 95% confidence intervals (CIs) at the last assessment visit (week 14), without adjustment for multiple comparisons. Point estimates with CIs that excluded zero were considered statistically significant and interpreted to be indicative of a relevant treatment difference between C1-INH(SC) and placebo.

The minimal clinically important difference (MCID) was estimated from the data for each PRO (EQ-5D, HADS, WPAI, TSQM) using the half standard deviation (SD) approach, which has

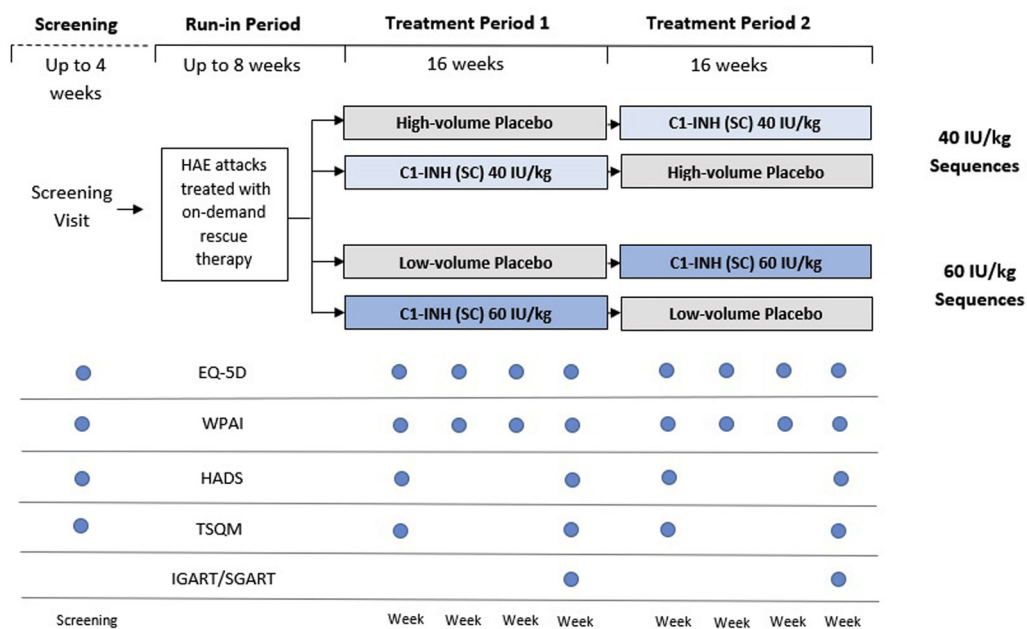


FIGURE 1. COMPACT study design and timing of health-related quality of life and productivity assessments. *C1-INH(SC)*, Subcutaneous C1-inhibitor; *COMPACT*, Clinical Studies for Optimal Management of Preventing Angioedema with Low-Volume Subcutaneous C1-Inhibitor Replacement Therapy; *EQ-5D*, European Quality of Life-5 Dimensions; *HADS*, Hospital Anxiety and Depression Scale; *HAE*, hereditary angioedema; *IGART/SGART*, Investigator and Subject Global Assessments of Response to Therapy; *TSQM*, Treatment Satisfaction Questionnaire for Medication; *WPAI*, Work Productivity and Activity Impairment Questionnaire.

been shown to approximate the threshold of discrimination for a clinically meaningful change or difference in PRO scores for patients with chronic diseases.³⁷ For the IGART and SGART, the percentage of patients with responses of none, poor, fair, good, or excellent was determined and reported descriptively.

RESULTS

Patients and treatments

A total of 90 patients with C1-INH-HAE were randomized (Table I) to study treatment, and all were included in the HRQoL population. Of the 90 subjects randomized to 1 of the 4 treatment sequences, 86 subjects received at least 1 dose of C1-INH(SC) and 86 received at least 1 dose of placebo. During the active treatment periods with C1-INH(SC), 51 of 86 (59.3%) patients experienced 219 HAE attacks in total, and 82 of 86 (95.3%) patients experienced 975 attacks during placebo periods. Rescue medication was permitted during the trial and usage was 10 and 4 times lower, respectively, when comparing C1-INH(SC) 60 IU/kg with placebo and C1-INH(SC) 40 IU/kg with placebo.

European Quality of Life-5 Dimensions

Mean and median EQ-5D health state value (HSV) and visual analog scale (VAS) scores were high at baseline (Table II) and indicative of generally good self-reported quality of life. EQ-5D VAS score changes between C1-INH(SC) and placebo at the last visit (week 14) indicated a treatment benefit with C1-INH(SC) (mean treatment difference, 8.53; 95% CI 4.10, 12.97) (Figure 2). However, changes in HSV scores from baseline to the last visit were small (mean treatment difference, 0.04; 95%

TABLE I. Baseline characteristics of patients with C1-INH-HAE in the COMPACT study

	Study population N = 90
Mean age, y (SD)	39.6 (14.9)
Range	12-72
Female, n (%)	60 (66.7)
Mean body weight, kg (SD)	81.6 (23.7)
Mean BMI, kg/m ² (SD)	28.6 (7.1)
Race, n (%)	
White	84 (93.3)
Black or African American	4 (4.4)
Asian	1 (1.1)
Other	1 (1.1)
HAE history	
C1-INH-HAE type I, n (%)	78 (86.7)
C1-INH-HAE type II, n (%)	12 (13.3)
Mean (SD) number HAE attacks in 3 mo before screening	9.8 (6.6)

BMI, Body mass index; *C1-INH-HAE*, hereditary angioedema due to C1-inhibitor deficiency; *COMPACT*, Clinical Studies for Optimal Management of Preventing Angioedema with Low-Volume Subcutaneous C1-Inhibitor Replacement Therapy; *SD*, standard deviation.

CI −0.01, 0.08) and not suggestive of a treatment benefit with C1-INH(SC) versus placebo.

Mean scores at individual study visits are shown in Figure E1 (available in this article's Online Repository at www.jaci-inpractice.org). Mean and median scores and treatment

TABLE II. Baseline (screening) health-related quality-of-life scores

Assessment	n	Study population (N = 90) Mean (SD)/median	Scoring and interpretation
EQ-5D			
HSV	80	0.89 (0.194)/1.00	HSV: 1 = “full health”
VAS	80	82.23 (17.132)/87.00	VAS: 0 (worst imaginable health state) to 100 (best imaginable health state)
HADS			
			For both domains:
Anxiety	80	6.20 (3.931)/6.00	0-7 (normal)
Depression	80	2.76 (2.843)/2.00	8-10 (suggestive of the mood disorder)
			>11 (probable presence of the mood disorder)
			(Maximum [worst] score possible per domain = 21)
WPAI			
Absenteeism	50	6.64 (16.348)/0.00	% work time missed
Presenteeism	50	24.80 (29.363)/15.00	% impairment while working
Work productivity loss	50	26.63 (31.817)/17.14	% overall work impairment
Activity impairment	80	34.13 (31.126)/30.00	% activity (nonwork) impairment
			(Higher % = greater impairment)
TSQM			
Effectiveness	76	72.08 (22.807)/77.78	
Side effects*	14	73.21 (20.863)/78.13	Each domain: scoring range = 0 to 100
Convenience	76	63.67 (21.706)/63.89	(Higher scores indicate better outcomes)
Overall satisfaction	76	75.99 (21.937)/77.78	

EQ-5D, European Quality of Life-5 Dimensions; HADS, Hospital Anxiety and Depression Scale; HSV, health state value; SD, standard deviation; TSQM, Treatment Satisfaction Questionnaire for Medication; VAS, visual analog score; WPAI, Work Productivity and Activity Impairment Questionnaire.

*A score for “side effects” was not generated for patients who indicated that they experienced none.

differences from placebo by C1-INH(SC) dose group are provided in [Tables E1–E3](#) (available in this article’s Online Repository at www.jaci-inpractice.org).

HADS domains

At screening, population HADS scores for anxiety/depression were within the range considered normal (<7)³⁴ ([Table II](#)), with little room for improvement. However, the anxiety score for all subjects (mean, 6.20; median, 6.00) was at the upper limit of normal (normal range, 0-7), indicating that some patients had some degree of anxiety burden (scores higher than 7). Nevertheless, a treatment benefit was observed in the change of the HADS anxiety score from screening to the last visit compared with placebo (mean treatment difference, −1.05; 95% CI −1.79, −0.31) ([Figure 2](#)).

At screening, mean/median population scores for depression were 2.76 and 2.00, respectively (normal range, 0-7). At the last visit (week 14), depression scores were numerically lower (direction of improvement) with C1-INH(SC) as compared with placebo and at screening ([Table E1](#), available in this article’s Online Repository at www.jaci-inpractice.org), but the mean difference in depression score between C1-INH(SC) and placebo (−0.55; 95% CI −1.11, 0.01) did not demonstrate a beneficial treatment effect ([Figure 2](#); [Table E2](#), available in this article’s Online Repository at www.jaci-inpractice.org). Mean scores at individual study visits are shown in [Figure E1 \(B\)](#) (available in this article’s Online Repository at www.jaci-inpractice.org).

Work Productivity and Activity Impairment Questionnaire

Mean scores for WPAI absenteeism suggested a low level of health-related absenteeism at screening (6.6%) ([Table II](#)), and no meaningful differences were observed for this measure between C1-INH(SC) and placebo at the last visit ([Figure 2](#)). In contrast,

scores at screening indicated substantial baseline impairment with regard to presenteeism (health-related impairment in productivity while at work), work productivity loss (overall work impairment/absenteeism plus presenteeism), and activity impairment ([Table II](#)). For each of these assessments, a treatment benefit was observed in favor of C1-INH(SC) versus placebo after 14 weeks of treatment ([Figure 2](#)).

Mean scores at individual study visits are shown in [Figure E1 \(C, D\)](#) (available in this article’s Online Repository at www.jaci-inpractice.org). Mean and median scores and treatment differences from placebo by C1-INH(SC) dose group are provided in [Tables E1–E3](#) (available in this article’s Online Repository at www.jaci-inpractice.org).

Treatment Satisfaction Questionnaire for Medication

Baseline scores for all 4 TSQM domains (effectiveness, side effects, convenience, overall satisfaction) indicated deficits ([Table II](#)), with room for improvement given effective treatment. Treatment differences between C1-INH(SC) and combined placebo for effectiveness and overall satisfaction scores indicated a treatment benefit ([Figure 2](#)). At the last visit, mean TSQM scores for the effectiveness and overall satisfaction domains worsened from baseline during placebo treatment; however, mean and median scores during C1-INH(SC) treatment were markedly improved (higher) compared with baseline and notably improved compared with placebo at the last visit ([Tables E1–E3](#), available in this article’s Online Repository at www.jaci-inpractice.org). Mean scores at individual study visits are shown in [Figure 1 \(E\)](#) (available in this article’s Online Repository at www.jaci-inpractice.org). The number of patients reporting on the side effects domain was too small for meaningful analysis (no score was generated for patients who indicated experiencing no side effects).

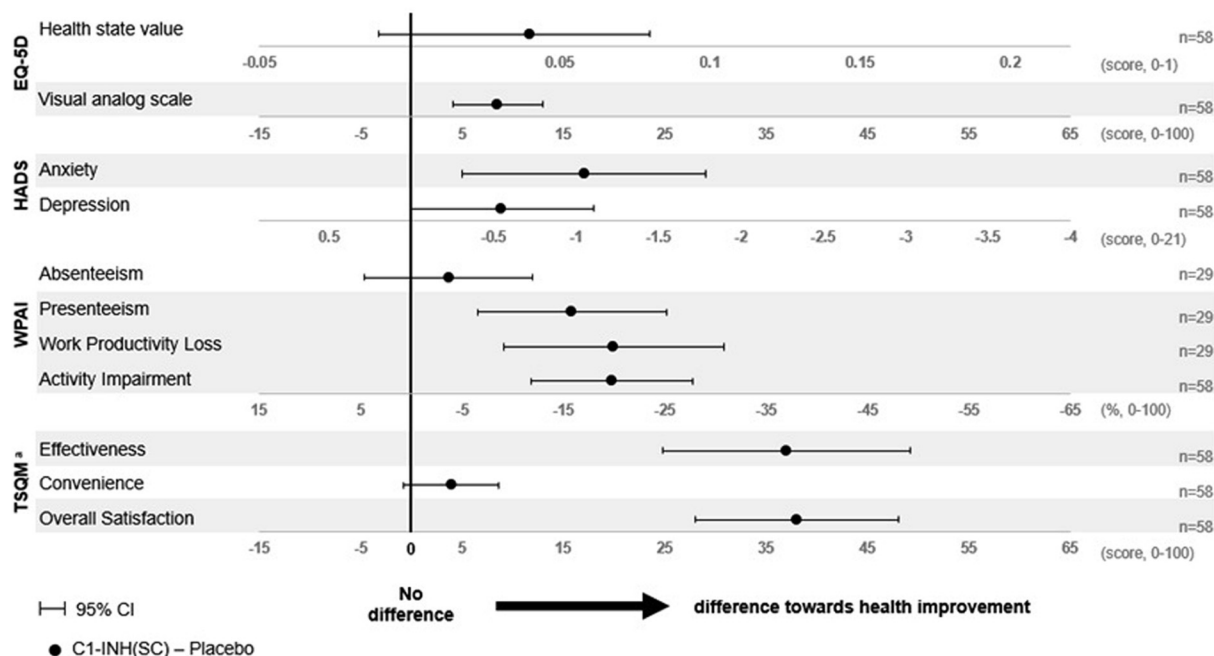


FIGURE 2. Mean difference in within-subject health-related quality of life scores between C1-INH(SC) (both doses combined) and placebo treatments and 95% CI at the last assessment visit. The gray shading indicates differences considered statistically significant (95% CI does not overlap with 0); ^aTSQM results for the side effects domain not shown; n = 1 in each sequence. Numerical data for this figure are provided in Table E2 (available in this article's Online Repository at www.jaci-inpractice.org). C1-INH(SC), Subcutaneous C1-inhibitor; CI, confidence interval; EQ-5D, European Quality of Life-5 Dimensions; HADS, Hospital Anxiety and Depression Scale; n, number of patients with data; TSQM, Treatment Satisfaction Questionnaire for Medication; WPAI, Work Productivity and Activity Impairment Questionnaire.

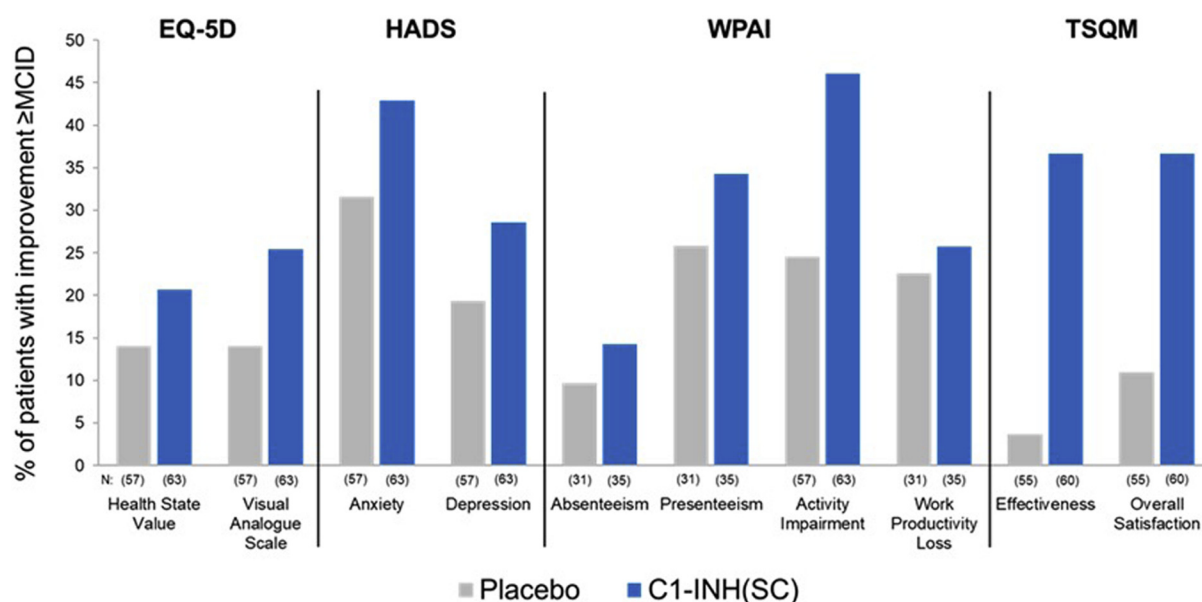


FIGURE 3. Percentage of patients demonstrating minimal clinically important difference (MCID) improvements in health-related quality of life scores—change from screening to the last assessment visit with C1-INH(SC) or placebo. C1-INH(SC), Subcutaneous C1-inhibitor; EQ-5D, European Quality of Life-5 Dimensions; HADS, Hospital Anxiety and Depression Scale; TSQM, Treatment Satisfaction Questionnaire for Medication; WPAI, Work Productivity and Activity Impairment Questionnaire.

TABLE III. Reported EQ-5D scores in C1-INH-HAE and other chronic disease states

Study	Population/disease state	Mean EQ-5D HSV scores Maximum score (full health) = 1
HAE studies		
COMPACT trial	Patients with C1-INH-HAE	
	Baseline	0.89
	Week 14 of routine prevention with C1-INH(SC)*	0.92
	Week 14 of placebo (on demand treatment)*	0.87
Nordenfelt et al ¹⁹ (Sweden)		
SWEHA-Reg	Swedish patients with C1-INH-HAE	
	“Today” score	0.83
	“Attack” score	0.51
Aygören-Pürsün et al ¹⁷ (Denmark, Germany, Spain)	Patients with C1-INH-HAE	
	In-between attacks	0.72
	HAE attack (overall)	0.44
	HAE attack, no/mild pain	0.61
	HAE attack, moderate pain	0.47
	HAE attack, severe pain	0.08
Other disease states		
Allegra et al ⁴⁴ (Italy)	Asthma	
	Controlled	0.86
	Partly controlled	0.75
Stafford et al ⁴⁵ (UK)	Chronic migraine (between attacks)	0.87
Westerhuis et al ⁴⁶ (Netherlands)	Epilepsy	0.80
Liu et al ⁴⁷ (USA)	Relapsing-remitting multiple sclerosis	0.74
Soucie et al ⁴⁸ (USA)	Severe hemophilia	0.78
Cavazza et al ⁴⁹ (Europe)	Hemophilia	0.87

C1-INH-HAE, Hereditary angioedema due to C1-inhibitor deficiency; C1-INH(SC), subcutaneous C1-inhibitor; COMPACT, Clinical Studies for Optimal Management of Preventing Angioedema with Low-Volume Subcutaneous C1-Inhibitor Replacement Therapy; EQ-5D, European Quality of Life-5 Dimensions; HSV, health state value.

*Along with on-demand treatments as necessary to treat attacks.

Minimal clinically important differences

For each of the PRO measures in the trial, a greater proportion of patients had last visit scores reflecting minimal clinically important improvements with C1-INH(SC) as compared with placebo use (Figure 3).

IGART and SGART

The proportion of patients for whom investigators rated overall response as “good” or “excellent” at the last visit was 80.0% for C1-INH(SC) therapy compared with 12.2% for placebo treatment. The proportions of patients rating treatment response as “good or excellent” therapy at the last visit was 75.6% at the last visit of C1-INH(SC) treatment compared with 23.3% of patients at the end of placebo treatment.

DISCUSSION

This analysis is one of few to evaluate the impact of an HAE-specific treatment for prevention of attacks on HRQoL and the first to evaluate the impact of routine prevention therapy on productivity measures. Our findings demonstrate that routine prophylaxis of HAE attacks using C1-INH(SC) improved many aspects of the burden of HAE, most notably self-reported anxiety, work productivity, and activity impairment. Patients also reported high levels of treatment satisfaction and perceived effectiveness with C1-INH(SC) use as routine prevention compared with on-demand treatment alone.

Access to HAE-specific treatments over recent years has brought about substantial improvements in both the physical and psychological burden of the disease. Recent studies have reported improved HRQoL scores, increased feelings of self-control, and a lessening of anxiety compared with research conducted before the availability of effective therapies for treating HAE attacks.^{8,15,24,25,38} The COMPACT study cohort reflected this trend, as evidenced by baseline scores for the EQ-5D and HADS instruments indicating good general health and little anxiety or depression. The mean EQ-5D at screening was 0.89, higher (better) than that reported in other recent studies in HAE populations.^{18,19} Yet, in the COMPACT study population, despite already high EQ-5D scores at baseline, C1-INH(SC) was associated with better mean EQ-5D VAS scores as compared with on-demand management alone after 14 weeks of treatment.

Similarly, the COMPACT study population had low anxiety and depression scores at screening. Nevertheless, the study demonstrated a benefit of C1-INH(SC) compared with on-demand treatment alone in mean anxiety scores at the last visit. Although a similar benefit was not observed with respect to mean depression scores, clinically meaningful improvements in both anxiety and depression scores were noted in 42.9% and 28.6%, respectively, of patients using C1-INH(SC), as compared with 31.6% and 19.3% during placebo treatment, respectively. Attack frequency, fear of attacks and asphyxiation, interruption of normal activities, burden of unnecessary treatments/procedures, and concerns over the impact of HAE on future goals have

been reported as hampering reported quality of life in patients with HAE, thereby potentiating feelings of anxiety and depression both between and during attacks.^{10,12,17-19,25,39-42} Thus, effective prevention of attacks by prophylactic treatment would be a major driver for improving HRQoL.

A number of recent studies have reported suboptimal disease control and psychological distress in patients with HAE.^{10,25,40,42,43} EQ-5D scores during an HAE attack suggest marked quality-of-life impairment, having been reported as 0.44¹⁷ and 0.51.¹⁹ Furthermore, attacks characterized by severe pain were associated with a mean EQ-5D score of 0.08.¹⁷ EQ-5D scores reported among patients with HAE during attack-free periods are similar to those found among other chronic diseases (eg, asthma,⁴⁴ chronic migraine,⁴⁵ epilepsy,⁴⁶ relapsing-remitting multiple sclerosis,⁴⁷ and hemophilia^{48,49}) (Table III). This illustrates the enduring emotional impact of HAE on quality of life even during attack-free intervals and despite physical recovery from acute attack symptoms, thus reinforcing the clinical importance for treatment to be able to lessen the psychological and emotional burdens of the disease.

Clear deficits in work productivity (WPAI assessment) were evident at screening in the COMPACT population, which reflected disease-related implications during nonstudy, “real-world” management scenarios using available HAE therapies. On average, patients reported approximately 25% impairment in work productivity and 34% impairment in nonwork activities at screening before study entry. Marked improvements were noted on these outcomes while using C1-INH(SC) for routine prevention compared with on-demand disease management alone, suggesting that effective prevention of attacks has important benefits with regard to minimizing disruption of work and other activities.

At screening, current treatment satisfaction scores with regard to effectiveness, convenience, and overall satisfaction were good, but reflected ample room for improvement. Overall treatment effectiveness and satisfaction ratings with C1-INH(SC) use were significantly greater compared with placebo and were at or near the maximum rating of 100. Convenience ratings were not different from placebo, which was not unexpected, given that both C1-INH(SC) and the injectable placebo in this study were administered subcutaneously and at the same weekly frequency. Yet, both placebo and C1-INH(SC) ratings for convenience were better than screening assessments, the latter of which reflected prior therapy with C1-INH(IV) or other SC medications in the majority of patients. SGART and IGART assessments corroborated the TSQM results, with a substantially greater percentage of patients reporting having “excellent” or “good-to-excellent” responses to therapy with self-administered C1-INH(SC) at home as opposed to management using on-demand treatment only.

Our analysis should be interpreted with certain limitations in mind. This was a *post hoc* analysis of exploratory PRO endpoints in a clinical trial with a relatively short observation period of 14 to 16 weeks that was not designed to demonstrate treatment benefit on these measures. Standardized, generic HRQoL assessment tools were used, rather than recently validated HAE-specific instruments that were not available at the time.^{50,51} Sequence effect is a possible confounding influence in crossover design studies; although not evaluated for the PRO data specifically, it is worth noting that a sequence effect was excluded for the primary efficacy analysis of HAE attack rate in

the COMPACT trial. In addition, the analyses were not adjusted for multiple comparisons. MCIDs have not been established in patients with C1-INH-HAE for the PROs evaluated in this study; nevertheless, the half SD approach can approximate the MCID in many/most situations.³⁷ Not all patients completed all questionnaires at all scheduled time points. For some PROs at some time points, there were substantial missing data. The work productivity questionnaire, in particular, was not relevant to all subjects, including those <18 years of age. Patients had a minimum baseline attack frequency requirement to participate in the COMPACT trial and had to be considered appropriate candidates for self-injection; thus, the study population does not represent all patients with C1-INH-HAE.

CONCLUSIONS

In patients with frequent HAE attacks, routine prevention with self-administered twice weekly C1-INH(SC) is more effective than on-demand therapy alone in alleviating certain impairments related to HAE. The HRQoL results in this analysis corroborate the objective clinical benefits observed in the COMPACT study and suggest that routine prevention of HAE attacks with C1-INH(SC) is a major advance in HAE management, improving anxiety and enabling patients with C1-INH-HAE to regain an active and productive lifestyle. Further, supporting real-world data will be needed to confirm this reported evidence from the COMPACT randomized clinical trial.

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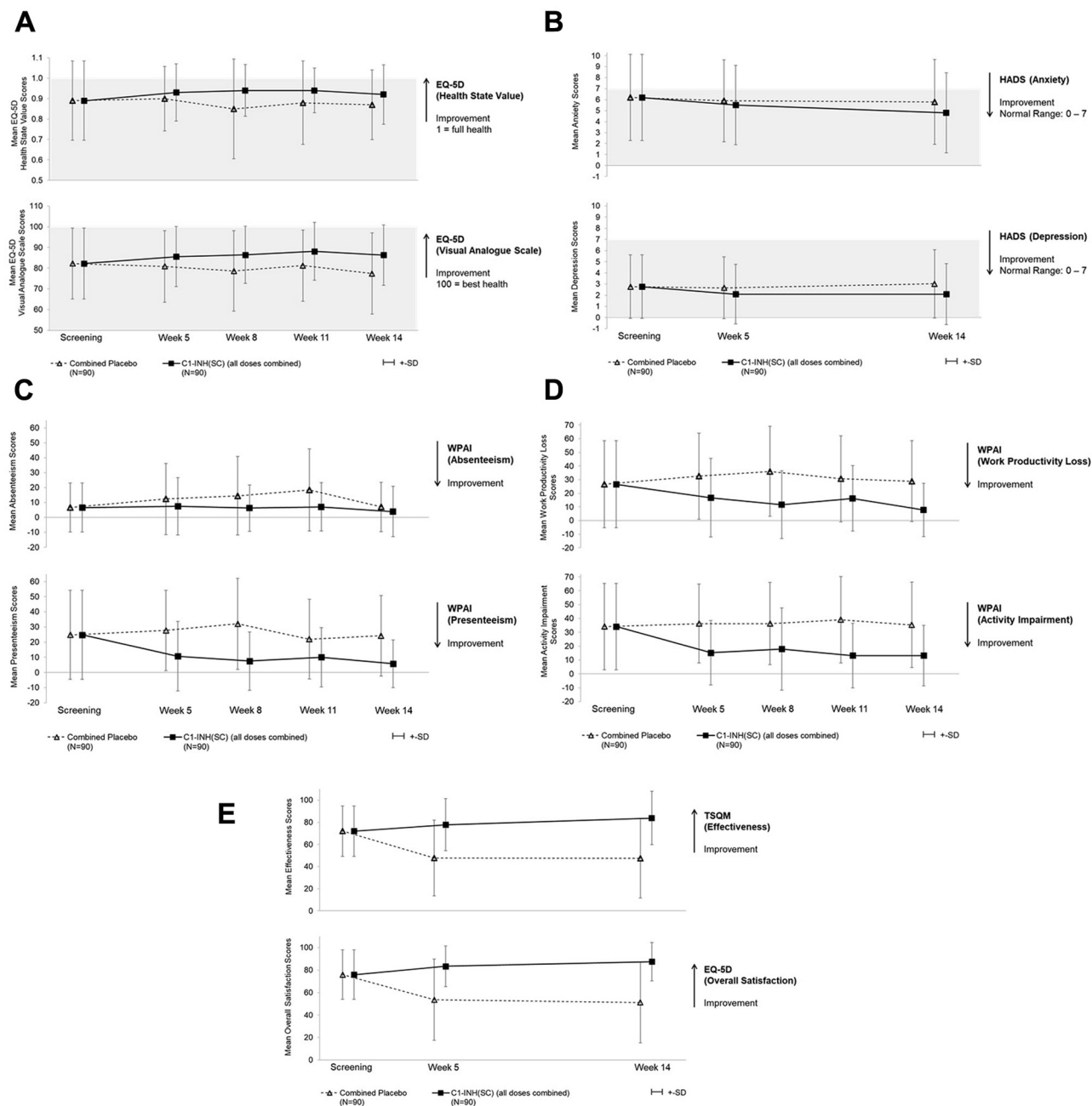


FIGURE E1. Mean scores over time by treatment group (combined placebo vs combined C1-INH(SC) 40 IU/kg and 60 IU/kg) for (A) quality of life/health status (EQ-5D), (B) anxiety and depression (HADS), (C) absenteeism and presenteeism (WPAI), (D) work productivity loss and activity impairment over time (WPAI), and (E) effectiveness and overall satisfaction (TSQM). C1-INH(SC), Subcutaneous C1-inhibitor; EQ-5D, European Quality of Life-5 Dimensions; HADS, Hospital Anxiety and Depression Scale; SD, standard deviation; TSQM, Treatment Satisfaction Questionnaire for Medication; WPAI, Work Productivity and Activity Impairment Questionnaire.

TABLE E1. Mean and median patient-reported outcome scores at screening and after 14 wk of treatment with C1-INH(SC) 40 IU/kg/high-volume placebo or C1-INH(SC) 60 IU/kg/low-volume placebo

		Mean (SD)/median scores								
Assessment	n	Screening	Last assessment visit (week 14)							
		All subjects (N = 90)	n	C1-INH(SC) 40 IU/kg (N = 45)	n	High-volume placebo (N = 45)	n	C1-INH(SC) 60 IU/kg (N = 45)	n	Low-volume placebo (N = 45)
EQ-5D*										
HSV	80	0.89 (0.194)/1.00	35	0.91 (0.169)/1.00	36	0.87 (0.185)/1.00	34	0.92 (0.145)/1.00	28	0.87 (0.153)/1.00
VAS	80	82.23 (17.132)/87.00	35	86.46 (16.656)/92.00	36	76.86 (18.037)/79.00	34	86.12 (12.323)/90.00	28	78.11 (21.767)/85.00
HADS†										
Anxiety	80	6.20 (3.931)/6.00	35	5.37 (3.727)/5.00	36	6.22 (3.855)/5.50	34	4.21 (3.488)/3.50	28	5.25 (3.874)/4.00
Depression	80	2.76 (2.843)/2.00	35	2.63 (2.745)/1.00	36	3.75 (3.541)/2.00	34	1.56 (2.654)/1.00	28	2.07 (1.980)/1.50
WPAI‡										
Absenteeism	50	6.64 (16.348)/0.00	20	0.49 (2.182)/0.00	17	3.48 (9.667)/0.00	20	7.40 (23.489)/0.00	16	10.87 (21.266)/0.00
Presenteeism	50	24.80 (29.363)/15.00	20	3.50 (8.127)/0.00	17	21.76 (28.336)/10.00	20	8.00 (20.673)/0.00	16	26.88 (25.224)/30.00
Work productivity loss	50	26.63 (31.817)/17.14	20	3.84 (9.351)/0.00	17	23.24 (29.755)/10.00	20	11.58 (25.840)/0.00	16	34.87 (29.337)/40.28
Activity impairment	80	34.13 (31.126)/30.00	35	12.86 (20.230)/0.00	36	30.56 (29.851)/30.00	34	13.53 (23.726)/0.00	28	41.43 (31.589)/40.00
TSQM§										
Effectiveness	76	72.08 (22.807)/77.78	35	86.83 (20.125)/94.44	36	45.22 (34.482)/47.22	34	80.72 (27.600)/88.89	28	50.60 (38.172)/66.67
Side effects	14	73.21 (20.863)/78.13	6	85.42 (21.164)/96.88	3	72.92 (18.042)/62.50	5	66.25 (26.369)/56.25	4	82.81 (5.984)/84.38
Convenience	76	63.67 (21.706)/63.89	35	77.46 (16.609)/77.78	36	75.77 (14.618)/72.22	34	74.18 (19.142)/75.00	28	69.25 (19.568)/72.22
Overall satisfaction	76	75.99 (21.937)/77.78	35	88.97 (16.371)/100.00	36	46.91 (36.820)/50.00	34	85.95 (17.753)/93.06	28	56.65 (34.582)/63.89

C1-INH(SC), Subcutaneous C1-inhibitor; EQ-5D, European Quality of Life-5 Dimensions; HADS, Hospital Anxiety and Depression Scale; HSV, health state value; TSQM, Treatment Satisfaction Questionnaire for Medication; VAS, visual analog scale; WPAI, Work Productivity and Activity Impairment Questionnaire.

*EQ-5D HSV: 1 = “full health”; EQ-5D VAS: 0 (worst imaginable health state) to 100 (best imaginable health state).

†HADS: maximum score possible per domain = 21: 0-7 (normal); 8-10 (suggestive of the mood disorder); >11 (probable presence of the mood disorder).

‡WPAI: absenteeism (% work time missed because of health problem); presenteeism (% impairment while working because of health problem); work productivity loss (% overall work impairment because of health problem); activity impairment (% activity non-work impairment because of health problem). Higher % = greater impairment.

§TSQM: all domains scored 0-100. Higher scores indicate better outcomes.

TABLE E2. Mean treatment differences and 95% CIs for subject-reported outcome measures at the last visit, C1-INH(SC) vs placebo

HRQoL assessment	C1-INH(SC) 40 IU/kg/placebo sequences (N = 45)			C1-INH(SC) 60 IU/kg/placebo sequences (N = 45)			All C1-INH(SC) (N = 90)		
	n	Mean diff	95% CI	n	Mean diff	95% CI	n	Mean diff	95% CI
EQ-5D									
HSV	31	0.04	−0.02, 0.10	27	0.04	−0.04, 0.11	58	0.04	−0.01, 0.08
VAS	31	7.29*	2.29, 12.29	27	9.96*	1.99, 17.94	58	8.53*	4.10, 12.97
HADS									
Depression	31	−0.55	−1.29, 0.19	27	−0.56	−1.46, 0.35	58	−0.55	−1.11, 0.01
Anxiety	31	−0.97	−2.16, 0.23	27	−1.15*	−2.05, −0.25	58	−1.05*	−1.79, −0.31
WPAI									
Absenteeism	16	−3.09	−7.80, 1.62	13	−4.41	−23.74, 14.91	29	−3.68	−12.02, 4.66
Presenteeism	16	−17.50*	−32.00, −3.00	13	−13.85*	−27.03, −0.67	29	−15.86*	−25.21, −6.52
Work productivity loss	16	−18.64*	−33.34, −3.94	13	−21.61*	−40.21, −3.00	29	−19.97*	−30.84, −9.10
Activity impairment	31	−16.45*	−26.23, −6.68	27	−23.70*	−37.15, −10.26	58	−19.83*	−27.78, −11.88
TSQM									
Effectiveness	31	43.19*	25.56, 60.82	27	30.04*	12.51, 47.57	58	37.07*	24.86, 49.28
Side effects	1	6.25	—	1	−50.00	—	2	−21.88	−379.24, 335.49
Convenience	31	0.72	−4.80, 6.23	27	7.61	−0.29, 15.52	58	3.93	−0.72, 8.58
Overall satisfaction	31	43.73*	28.94, 58.51	27	31.58*	17.83, 45.34	58	38.07*	28.08, 48.06

C1-INH(SC), Subcutaneous C1-inhibitor; CI, confidence interval; EQ-5D, European Quality of Life-5 Dimensions; HADS, Hospital Anxiety and Depression Scale; HRQoL, health-related quality of life; HSV, health state value; TSQM, Treatment Satisfaction Questionnaire for Medication; VAS, visual analog score; WPAI, Work Productivity and Activity Impairment Questionnaire. Bold indicates statistical significance ($P < .05$).

*Indicative of treatment benefit of C1-INH(SC), based on a 95% CI excluding 0.

TABLE E3. Median treatment differences and 95% CIs for subject-reported outcome measures at the last visit, C1-INH(SC) vs placebo

HRQoL assessment	C1-INH(SC) 40 IU/kg/placebo sequences (N = 45)			C1-INH(SC) 60 IU/kg/placebo sequences (N = 45)			All C1-INH(SC) (N = 90)		
	n	Median diff	95% CI	n	Median diff	95% CI	n	Median diff	95% CI
EQ-5D									
HSV	31	0.00	0.00, 0.07	27	0.00	0.00, 0.15	58	0.00	0.00, 0.00
VAS	31	4.00	0.00, 10.00	27	6.00	0.00, 21.00	58	4.00	0.00, 9.00
HADS									
Depression	31	−1.00	−1.00, 0.00	27	−1.00	−1.00, 0.00	58	−1.00	−1.00, 0.00
Anxiety	31	0.00	−1.00, 0.00	27	−1.00	−1.00, 0.00	58	−1.00	−1.00, 0.00
WPAI									
Absenteeism	16	0.00	0.00, 0.00	13	0.00	−15.09, 0.00	29	0.00	0.00, 0.00
Presenteeism	16	0.00	−30.00, 0.00	13	0.00	−40.00, 0.00	29	0.00	−20.00, 0.00
Work productivity loss	16	0.00	−30.00, 0.00	13	−10.00	−50.00, 0.00	29	0.00	−32.72, 0.00
Activity impairment	31	0.00	−30.00, 0.00	27	−30.00	−40.00, 0.00	58	−10.00	−30.00, 0.00
TSQM									
Effectiveness	31	38.89*	16.67, 83.33	27	27.78*	5.56, 66.67	58	33.33*	16.67, 61.11
Side effects	1	6.25	—	1	−50.00	—	2	−21.88	−50.00, 6.25
Convenience	31	0.00	−5.56, 11.11	27	5.56	0.00, 11.11	58	0.00	0.00, 11.11
Overall satisfaction	31	36.11*	8.33, 69.44	27	22.22*	8.33, 50.00	58	30.56*	13.89, 50.00

C1-INH(SC), Subcutaneous C1-inhibitor; CI, confidence interval; EQ-5D, European Quality of Life-5 Dimensions; HADS, Hospital Anxiety and Depression Scale; HRQoL, health-related quality of life; HSV, health state value; TSQM, Treatment Satisfaction Questionnaire for Medication; VAS, visual analog score; WPAI, Work Productivity and Activity Impairment Questionnaire.

*Indicative of treatment benefit of C1-INH(SC), based on a 95% CI excluding 0.