Original Article

Subcutaneous Icatibant for the Treatment of Hereditary Angioedema Attacks: Comparison of Home Self-Administration with Administration at a Medical Facility

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What is already known about this topic? Icatibant, a subcutaneous bradykinin-B2-receptor antagonist, is an effective on-demand therapy for treating hereditary angioedema attacks.

What does this article add to our knowledge? This is the first prospective, multicenter comparison of icatibant self-administration and HCP-administration (administration by health care professionals at medical facilities) in the United States showing that self-administration is comparable to HCP-administration with regard to efficacy and safety.

How does this study affect current management guidelines? Current US and World Allergy Organization guidelines recommend a home-based treatment plan for hereditary angioedema. This study provides prospective evidence that icatibant can be used as an effective on-demand therapy for home-based treatment plans.

BACKGROUND: Hereditary angioedema (HAE) is a life-threatening disorder characterized by recurrent angioedema. Icatibant, a subcutaneous bradykinin-B2-receptor antagonist, is an effective on-demand therapy. Data outside the United States suggest that self-administration is tolerated and patient-preferred compared with administration by health care professionals at medical facilities (HCP-administration).

OBJECTIVE: A prospective, multicenter study was conducted in the United States to compare icatibant self-administration and HCP-administration.

METHODS: Subjects 18 years or older with type I or II HAE were recruited. The first 2 HAE attacks after enrollment were treated at medical facilities. Subjects were instructed by a health care professional on self-administration during icatibant treatment for the second HAE attack. Icatibant was self-administered

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Conflicts of interest: W. R. Lumry has received research support from Shire, Viropharma, Biocryst, and CSL Behring; is on the US Hereditary Angioedema Association (HAEA) Medical Advisory Board; has received consultancy fees from Shire/Viropharma, Salix/Valeant, Biocryst, and CSL Behring; has received lecture fees from Shire/Viropharma and CSL Behring; and has received travel support from the US Hereditary Angioedema Association. H. H. Li has received research support, personal fees, and nonfinancial support from Shire/Dyax/ViroPharma, CSL Behring, and Salix/Pharming and has received research support and nonfinancial support from BioCryst. T. J. Craig is a past Interest Section Leader for American Academy of Allergy, Asthma & Immunology; is an American Lung Association of Pennsylvania board member; is a US HAEA Advisory Board member; is on the Alpha-1 Foundation Clinical Research Center Board; has received consultancy fees from CSL Behring, Dyax, Shire, Merck, Biocryst, Bellrose, Merck, and Novartis; has received research support from CSL Behring, Shire, Dyax, Pharming, Merck, Genentech, GlaxoSmithKline, Grifols, Novartis, Sanofi Aventis, Boehringer Ingelheim, and Biocryst; has received lecture fees from CSL Behring, Dyax, Shire, and Grifols; and is a coinvestigator for Asthmanet, the National Heart, Lung, and Blood Institute. M. A. Riedl is on the US HAEA Medical Advisory Board; has received consultancy fees from Shire, Dyax, CSL Behring, Salix, Arrowhead, BioCryst, Ionis, and Global Blood Therapeutics; has received research support from Shire, Dyax, CSL Behring, BioCryst, Pharming, and Ionis; and has received lecture fees from Shire, Dyax, Salix, and CSL Behring. B. L. Zuraw has received consultancy fees from Alnylan, Arrowhead, BioCryst, CSL Behring, Dyax, Ionis, Nektar, Shire, and Salix and has received travel support from US HAEA. A. Banerji has received research support from Shire and CSL and is on the Alnylam Advisory Board. The rest of the authors declare that they have no relevant conflicts of interest.

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Abbreviations used
AE- Adverse event
HAE- Hereditary angioedema
HCP-administration- Administration by health care professionals at medical facilities
ISR- Injection-site reaction
PSS- Patient symptom score
VAS- Visual analog scale

for all subsequent attacks. For each treated HAE attack, efficacy, safety, and tolerability data were recorded.
RESULTS: Nineteen patients with HAE received icatibant for 79 distinct HAE attacks. Mean attack duration was significantly shorter with self-administration (n = 50; 547 ± 510 minutes) than with HCP-administration (n = 29; 968 ± 717 minutes; $P = .006$). Mean time to treatment was significantly shorter with self-administration (143 ± 226 minutes) than with HCP-administration (361 ± 503 minutes; $P < .0001$). Shorter times to treatment were associated with shorter time from treatment to symptom resolution ($r = 0.35$; $P = .02$). Improvements in visual analog scale score and patient symptom score from pretreatment to 4 hours postinjection were comparable between self-administration and HCP-administration. There were no serious adverse events or discontinuations due to adverse events with self-administration or HCP-administration.
CONCLUSIONS: Icatibant self-administration shortened attack duration and time to treatment, with no difference in safety or local tolerability compared with HCP-administration. These findings support icatibant as an effective on-demand option for home-based treatment. © **2016 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;5:442-7)**

Key words: *Hereditary angioedema; Icatibant; Home-based treatment; Bradykinin-receptor antagonist*

Hereditary angioedema (HAE) is a potentially life-threatening disease that is characterized by recurrent angioedema of cutaneous (face, genitalia, extremities) and mucosal (abdomen, oropharynx, larynx) tissues. HAE attacks are painful, unpredictable, and vary in severity, frequency, and anatomical location between patients.[1] As a result, attacks can be debilitating and result in significant and multifaceted disease burden.[2]

Historically, treatment options for HAE have been limited, but newly approved and emerging therapies appear to provide safe and effective relief for a significant proportion of patients with HAE.[3] Despite advances in HAE treatment, the need to travel to a health care facility for on-demand treatment can subject patients to the inconvenience of travel and prolonged wait times in the emergency department and delay treatment after attack onset.[3] Home administration of on-demand treatment with C1-inhibitor concentrate has been shown to decrease attack duration and pain medication use.[4,5] Therefore, efforts have been focused on emphasizing home-based treatment to decrease the burden of disease and improve quality of life.[3,6] Current clinical HAE guidelines and consensus recommend a home-based treatment plan, where patients receive self-administration training and have at least 2 doses of HAE medications with them at all times for on-demand treatment.[7-12]

Icatibant is a bradykinin-B2-receptor antagonist with efficacy in treating acute attacks of HAE that was approved by the Food and Drug Administration in 2011 for patients 18 years or older.[13,14] Data from outside the United States suggest that icatibant self-administration has a comparable safety and efficacy profile to administration by health care professionals at medical facilities (HCP-administration).[15,16] Importantly, previous studies have reported that icatibant self-administration is patient-preferred and improves quality of life compared with HCP-administration, suggesting that self-administration would decrease disease burden.[15,17] Self-administration has also been shown to lower health care costs in Spain.[18] US data are needed to investigate the applicability of previous data to US patients. To our knowledge, this is the first prospective, multicenter study in the United States evaluating icatibant self-administration for HAE attacks.

METHODS

Study subjects

Subjects 18 years or older with documented HAE were recruited at 5 separate sites in different states. A documented diagnosis of type I or II HAE was based on the presence of all of the following: (1) family and/or medical history, (2) characteristic and recurrent attacks, and (3) low C4 with normal C1q and low C1 inhibitor function. Subjects who met the following exclusion criteria were excluded from the study: (1) participation in another clinical therapeutic trial within the past month; (2) diagnosis of angioedema other than type I or type II HAE; (3) comorbidities: symptomatic coronary artery disease, congestive heart failure New York Heart Association class 3 and 4, stroke within the past 6 months; (4) treatment with angiotensin-converting enzyme inhibitor; (5) pregnant and/or breast-feeding; (6) mental condition rendering patient unable to understand possible consequences of study; and (7) inability to comply with protocol. Recruitment was initiated after Food and Drug Administration approval of icatibant and previous use of icatibant was not specified as part of the exclusion criteria.

Study design

The first 2 HAE attacks after entry into the study were treated at a medical facility (HCP-administration). The medical facilities used for the study were the recruiting physician's offices at all 5 sites. During the first HAE attack treated at a medical facility, icatibant was administered by a health care professional while the technique was explained to the subject. Subjects were instructed on self-administration during icatibant treatment for the second HAE attack. HAE attacks treated at a medical facility were included in the HCP-administration group. Subsequent HAE attacks were treated with self-administration and were included in the self-administration group. All HAE attacks were treated according to icatibant prescribing guidelines (30 mg in 3 mL solution).

At the onset of each HAE attack, attack location site(s) and Patient Global Clinical Impression scores were recorded. The Patient Global Clinical Impression asks patients to answer the question "How severe do you consider your attack to be?" on a scale of 1 (very mild) to 5 (very severe). For each treated attack, efficacy and safety and tolerability data were recorded. Time of onset of HAE attack, time icatibant was administered, and time to complete relief of symptoms were recorded in hours and minutes. Time to complete relief of symptoms was defined as time from onset of symptoms to complete or near-complete resolution as reported by the patient.

TABLE I. Baseline characteristics of acute HAE attacks

	HCP (n = 22)		Self (n = 44)		
Attacks (locations and no.)	n	%	n	%	*P* value
Locations involved during attacks					
Face	4	18	3	7	.1
Extremities	12	55	27	61	.6
Abdomen	9	41	25	57	.3
Genital/rectal	3	14	3	7	.1
Other	1	5	0	0	
Number of locations involved per attack					
1	12	55	28	64	.6
2	9	41	13	30	
3	1	5	3	7	

The locations and number of locations involved at baseline for each attack are displayed. The "n" indicates the number of patients who reported involvement of the specified location and who reported involvement of the specified number of locations at baseline. The "%" is calculated with the denominator set as the number of total patients who recorded information about attack location site(s) at baseline.

TABLE II. Baseline symptom scores of acute HAE attacks

	Baseline symptom scores, mean ± SD				
	HCP		Self		
Scoring System	n	Score	n	Score	*P* value
PGCI	20	2.6 ± 0.8	47	2.8 ± 0.9	.1
VAS	26	82.9 ± 52.1	45	78.4 ± 54.1	.7
PSS	23	6.0 ± 4.1	48	5.5 ± 3.0	.6

PGCI, Patient Global Clinical Impression.
Symptom severity was assessed for each attack using the PGCI, VAS, and PSS. The "n" indicates the number of patients who completed the PGCI, VAS, or PSS at baseline. Not all patients completed all 3 scoring systems at baseline.

A visual analog scale (VAS)[19] and patient symptom score (PSS) was completed every 15 minutes during the first hour after subcutaneous injection of icatibant, every half hour from 1 to 4 hours, and then at 5, 6, and 12 hours (see Figure E1, *A* and *B*, in this article's Online Repository at www.jaci-inpractice.org). If symptom relief was not documented by 12 hours, an additional VAS and PSS was completed at 18 and 24 hours after injection. Local tolerability was assessed at 0.5 and 4 hours after injection. Adverse events (AEs) were recorded throughout the study.

Presentation to a medical facility was recommended for laryngeal involvement during any HAE attack. Repeat injection with icatibant was recommended if there was no symptom improvement at 6 hours after initial treatment or if an attack worsened within 48 hours of initial treatment.

Institutional review board

Institutional review board approval was obtained at each institution before initiation of the study.

Statistical analyses

Summary statistics included means with SDs or percentages. Statistical methods that accounted for repeated data clustered in study phase within subjects were used to compare attacks treated by HCP-administration versus self-administration. Mixed models were used for continuous outcomes. Binary or ordinal logistic models with generalized estimating equations were used for binary or ordinal outcomes, respectively. The natural log transform was applied to time variables to satisfy distributional assumptions, and a within-subject correlation was derived for the association between time to treatment and time from treatment to symptom resolution. SAS version 9.4 was used.

RESULTS

Baseline characteristics of HAE attacks

Nineteen patients were treated for 79 HAE attacks. Of these HAE attacks, 29 were treated with HCP-administration and 50 were treated with self-administration. Ten patients were treated with both HCP-administration and self-administration. Nine enrolled subjects reported data for only 1 type of treated HAE attacks (HCP-administration, n = 8; self-administration, n = 1). All patient-reported data were used in analysis and are reported in this article.

Subjects reported baseline descriptive characteristics for 66 HAE attacks out of the total number of 79 HAE attacks treated with icatibant (Table I). The location of swelling was not reported for 13 HAE attacks. Swelling site location(s) and number of swelling sites were comparable between HAE attacks treated with HCP-administration and self-administration. The most commonly involved sites were extremities, followed by abdomen and then face. Most HAE attacks involved 1 site (61%, 40 of 66); however, there were also HAE attacks that involved 2 sites (33%, 22 of 66) and 3 sites (6%, 4 of 66). Baseline severity assessed by Patient Global Clinical Impression, VAS, and PSS was similar between the HCP-administration and self-administration groups (Table II) for attacks for which patients reported scores.

Self-administration versus HCP-administration

The mean duration of time from onset of HAE attack to administration of icatibant was 137 minutes shorter with self-administration (143 ± 226 minutes) compared with HCP-administration (361 ± 503 minutes; $P < .0001$; Figure 1, *A*).

The mean HAE attack duration (length in minutes between onset of HAE attack and complete symptom resolution) was significantly shorter with self-administration (547 ± 510 minutes) compared with HCP-administration (968 ± 717 minutes; $P = .006$; Figure 1, *B*). Time from treatment to symptom resolution was shorter with self-administration compared with HCP-administration, although the difference was not statistically significant (402 ± 448 minutes vs 607 ± 582 minutes; $P = .23$). Percent changes in both the VAS score and the PSS 4 hours after treatment were comparable between self-administration and HCP-administration ($P = .9$ and .6, respectively).

Treatment outcomes

Looking at correlation between times to treatment and treatment outcomes among all patients, shorter times to treatment were positively associated with shorter time from treatment to symptom resolution ($r = 0.35$; $P = .02$).

Safety and tolerability

There were no serious AEs related to icatibant. Four mild AEs (fatigue, fever, dizziness, and nausea) were reported throughout the duration of the study. These 4 AEs occurred in 4 separate individual subjects after 4 distinct attacks, all treated with HCP-administration. One subject experienced a fall on ice that resulted in a broken ankle. This event was unrelated to the administration of the study medication. None of these events required discontinuation of future icatibant treatment.

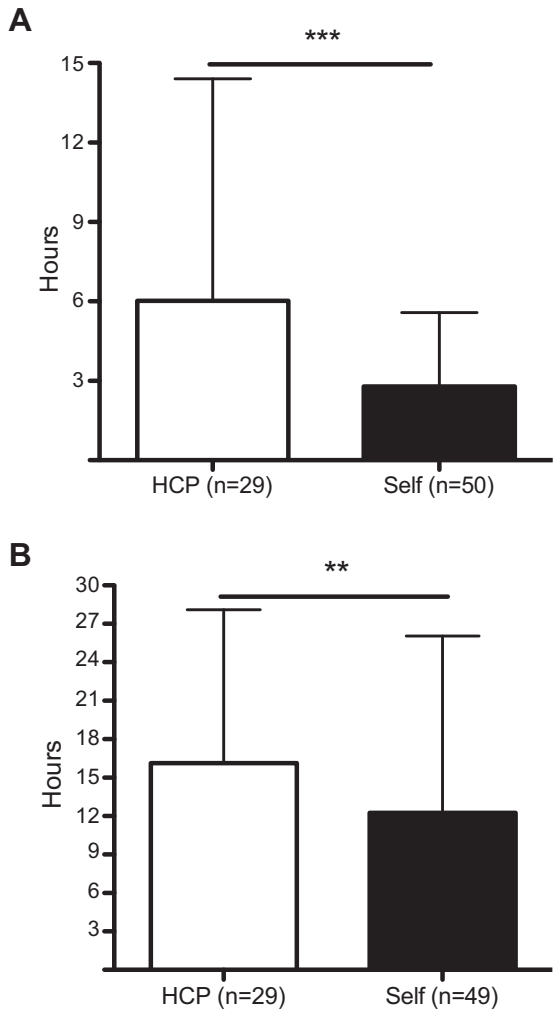


FIGURE 1. Time in minutes from attack onset to **A**, treatment and **B**, complete symptom resolution was significantly shorter for self-administration compared with HCP-administration. Data presented as mean with SD. ***$P < .0001$. **$P < .01$.

Local tolerability was comparable between HCP-administration and self-administration (Table III). Subjects reported local tolerability data at 0.5 hours for 70 HAE attacks out of the total number of 79 HAE attacks treated with icatibant. Subjects reported local tolerability data at both 0.5 hours and 4 hours for 59 HAE attacks out of the total number of 79 HAE attacks treated with icatibant. Injection-site reactions (ISRs) 0.5 hours after icatibant injection and patient-reported symptoms of swelling, erythema, and irritation were comparable between HCP-administration and self-administration. The proportion of resolved ISRs at 4 hours was comparable between HCP-administration and self-administration ($P = .7$). Similarly, patient-reported severity of skin swelling, erythema, and skin irritation was comparable between the 2 groups at 4 hours.

DISCUSSION

To our knowledge, our study is the first prospective, multicenter study to directly compare icatibant self-administration to HCP-administration among individual patients in the United States. Data from our study confirm and support previous observational and retrospective findings from outside the United States. Comparisons of icatibant treatment in a randomized clinical trial (For Angiodema Subcutaneous Treatment study [FAST-3], HCP-administration only) to real-world settings (HCP-administration and self-administration) found that time to treatment and attack duration were shorter in real-world settings.[20] A phase IIIb, open-label, multicenter trial found that the safety profile of self-administration was comparable to that of HCP-administration.[15] A retrospective analysis of data from the International Observational Study (Austria, Denmark, France, Germany, Greece, Israel, Italy, Spain, Sweden, and the United Kingdom) showed that self-administration shortened time to treatment.[16] Our study adds to these findings by providing prospective comparisons of self-administration and HCP-administration in a US population that demonstrate that self-administration shortens time to treatment and attack duration without any increase in AEs or ISRs.

With the development and Food and Drug Administration approval of several on-demand therapies for HAE since 2009, the landscape for HAE treatment has improved significantly. However, significant burden of disease for patients with HAE remains.[21,22] There is increasing recognition that this burden of disease would be improved if home-based treatment plans are more widely used.[3] Traveling to a health care facility for on-demand treatment can subject patients to the inconvenience of travel and prolonged wait times in the emergency department and delay treatment after attack onset.[3] Conversely, self-administration of home on-demand therapy facilitates rapid treatment at an early stage in an attack, limiting the amount of

TABLE III. Safety and tolerability of icatibant self-administration and HCP-administration

ISRs	HCP	Self	*P* value
0.5 h after injection			
Number of attacks with local tolerability data at 0.5 h	23	47	
Number of attacks with reactions (%)	22 (96)	42 (89)	.4
Symptoms graded on a scale of 0-4, mean ± SD			
Skin swelling	1.3 ± 0.9	1.2 ± 0.7	.9
Erythema	1.5 ± 1.0	1.4 ± 0.8	0.9
Skin irritation	1.0 ± 0.8	1.1 ± 0.9	.7
4 h after injection			
Number of attacks with local tolerability data at 0.5 and 4 h	21	38	
Number of resolved reactions (%)	14 (67)	22 (58)	.7
Symptoms graded on a scale of 0-4, mean ± SD			
Skin swelling	0.2 ± 0.5	0.3 ± 0.6	.3
Erythema	0.3 ± 0.5	0.4 ± 0.6	.4
Skin irritation	0.05 ± 0.2	0.3 ± 0.6	.2

The number of attacks for which patients answered questions regarding local tolerability (ISRs) at 0.5 h, and at both 0.5 and 4 h, is displayed. The "%" of attacks with reactions is calculated with the denominator set as the total number of attacks for which patients answered questions regarding local tolerability at 0.5 h, and at both 0.5 and 4 h. AEs other than ISRs were recorded and are reported for all treated attacks.

fluid leaked from the intravascular bed into the interstitial tissue and thereby reducing both the time to resolution and the impact the disease has on a patient's quality of life.[4,5,23] However, results from 2 sequential surveys published in 2011 and 2015 found that the percentage of patients treated in the home setting increased from 12% in 2009-2010 to only 33% in 2013.[24,25] To continue improving the delivery of home-based treatment, ongoing studies evaluating the efficacy of HAE therapies in the home setting are necessary.

One of the main goals of home-based treatment is to decrease disease burden for patients.[2,3,21] Previous studies have found that self-administration can positively affect patients' quality of life. The phase IIIb study by Aberer et al[15] found that 92% of the patients preferred self-administration to HCP-administration and that self-administration had positive impacts on quality of life as assessed by the Treatment Satisfaction Questionnaire for Medication and a convenience and satisfaction questionnaire. In a noncomparative study of icatibant self-administration, 89% of patients reported that carrying icatibant increased their confidence in managing their HAE.[17] Our findings support self-administration as an option that not only decreases disease burden for patients but also is safe and effective.

Another goal of home-based treatment is to facilitate earlier treatment of HAE attacks.[23] Current opinion is that treatment during early stages of an attack can limit the amount of fluid that leaks into interstitial tissue, thereby limiting symptoms and reducing attack duration, although this has yet to be demonstrated with mechanistic studies. Clinically, early on-demand treatment has been shown to be more effective when administered early during an attack, with improved treatment outcomes including shorter times to onset of symptoms relief and complete resolution.[5,23,26,27] Our study demonstrated that self-administration of icatibant at home did indeed lead to earlier treatment of attacks and that earlier treatment was associated with shorter time to symptom resolution. Although home treatment could also potentially result in treatment of a higher number of less severe attacks because the inconvenience of treatment is minimized, this did not seem to be the case in our study as the baseline symptom severity was similar between attacks treated with self-administration and HCP-administration.

Arranging for home-based treatment may also help decrease the significant socioeconomic burden that patients with HAE are saddled with.[18] Comparative cost-effectiveness between home-based treatment and treatment at a medical facility has not yet been performed in the United States. However, a study using an economic evaluation model in Spain found that patient self-administration of icatibant potentially results in a 9.2% cost reduction per attack.[18] Our study showed that icatibant appears to be clinically effective in the home setting, can be used as part of a home-based treatment plan, and can therefore potentially decrease economic burden for patients.

The benefits of home self-administration would be overcome by any concern regarding safety. However, our study showed icatibant self-administration and HCP-administration had similar safety and local tolerability profiles. As with previous clinical studies of icatibant, the most common AEs were ISRs that were mild to moderate in severity.[13,14] In FAST-1, FAST-2, and FAST-3, ISRs occurred in 96% to 100% of subjects treated with icatibant, with most ISRs resolving spontaneously within 4 hours.[13,14] Although previous studies outside the United States have investigated the local tolerability of icatibant self-administration, with 1 study reporting a similar percentage of patients (96.9%) experiencing ISRs compared with the FAST clinical trials, our study is the first to compare and find no difference in ISR frequency between self-administration and HCP-administration.[15-17] Similar to the FAST trials, most ISRs resolved spontaneously within 4 hours in the HCP-administration group and the self-administration group in our study.[13,14]

Our study had several limitations. Data were patient-reported, allowing bias. Patient factors that could have led to delay in treatment of HAE attacks were not recorded, although it is likely that this did not significantly affect the study results because common barriers to self-administration such as coordinating care, obtaining medications and equipment, and scheduling training sessions were obviated in the study design.[28] Patients were given the option to treat HAE attacks at home during phase 1 of the study. Rescue medication usage or need for icatibant redosing was not recorded as part of this study, limiting our ability to assess this as an efficacy outcome. However, these limitations do not detract from our study's main point. One of the main benefits of home on-demand therapy is that it can improve patients' perspectives regarding their disease.[3] At the very least, we are still able to conclude that patients perceive that their attack duration is shorter, and therefore likely less debilitating, with self-administration compared with HCP-administration.

In conclusion, icatibant self-administration demonstrated improved outcome measures compared with HCP-administration in a prospective, multicenter US study, shortening attack duration and time to treatment with no difference in safety or treatment outcomes. Earlier treatment was associated with shorter attack duration regardless of the administration method, which is consistent with previous retrospective findings for icatibant.[16] This study provides further support for icatibant as a home on-demand therapy for acute HAE attacks and for current international and US guidelines recommending early treatment for attacks.[7-12]

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A

Please draw a vertical line for each symptom assessment. Laryngeal subjects should additionally complete assessments 4 and 5 below. Please use a black ball point pen.
FOR EXAMPLE:

No complaints ——|—— **Maximum possible complaints**

1. SKIN SWELLING **How large is the swelling of your skin?**

No swelling at all —— **Maximum possible swelling**

2. SKIN PAIN **How painful is your skin swelling?**

No pain at all —— **Worst possible pain**

3. ABDOMINAL PAIN **How painful is your abdomen (stomach)?**

No pain at all —— **Worst possible pain**

B

Please rate the severity of each symptom below by placing an 'X' or a '√' in the box that best describes that symptom right now. For vomiting and diarrhea, please consider your symptoms over the last two hours. Please mark a box for each symptom.

Symptoms	Absence of Symptoms (0)	Mild (1)	Moderate (2)	Severe (3)	Very Severe (4)
Skin Swelling	☐	☐	☐	☐	☐
Erythema (Skin Redness)	☐	☐	☐	☐	☐
Skin Irritation	☐	☐	☐	☐	☐
Skin Pain	☐	☐	☐	☐	☐
Abdominal Pain	☐	☐	☐	☐	☐
Nausea	☐	☐	☐	☐	☐
Vomiting*	☐	☐	☐	☐	☐
Diarrhea*	☐	☐	☐	☐	☐

FIGURE E1. **A**, Visual Analogue Score (VAS) and **B**, Patient Symptom Score (PSS).