Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Cicardi M, Banerji A, Bracho F, et al. Icatibant, a new bradykinin-receptor antagonist, in hereditary angioedema. N Engl J Med 2010;363:532-41.

Icatibant, a Novel Bradykinin Receptor Antagonist, in Hereditary Angioedema

Supplementary Appendix

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Supplementary Appendix Table 1: Number of Randomized Patients per Study Site.

Country	Site No.	No. of patients	
FAST-1		***Icatibant***	***Placebo***
US			
	1	0	1
	2	1	1
	7	5	5
	9	1	1
	10	0	0
	15	2	1
	16	0	1
	17	1	0
	18	1	1
	19	0	0
	50	0	0
	51	0	0
	53	0	0
	55	2	0
	56	1	2
	57	1	0
	60	0	1
Canada			
	22	1	1
	24	0	1
	25	1	2
	26	0	0
	27	0	0
Australia			
	71	1	0
	72	1	1
	73	1	2
Argentina			
	40	6	8
FAST-2		*Icatibant*	*Tranexamic Acid*
Germany			
	10	2	3
	13	0	1
	14	2	1
	15	1	2
	16	1	1
	17	2	0
	20	3	3
	21	2	1
France			

	50	2	0
	53	0	0
	54	0	0
	55	0	0
	56	1	0
	57	0	1
	58	0	0
	59	0	0
UK			
	30	0	0
	31	0	0
	32	0	0
	33	0	0
	34	0	0
Israel			
	77	2	3
	78	1	1
	75	1	0
Hungary			
	90	3	3
Italy			
	1	3	3
	3	0	0
	4	0	2
Lithuania			
	96	1	2
	95	0	0
Poland			
	91	1	2
	92	0	0
Sweden			
	81	2	0
	82	1	2
Switzerland			
	60	1	2
	62	1	0
Austria			
	70	3	4
Ireland			
	40	0	1

Concomitant Medications

Concomitant medication was defined as any medication, other than rescue medication or the investigational agent, which was taken during the study. If a patient presenting with an attack had received treatment with replacement therapy, including C1-esterase inhibitor concentrate products within 3 days from onset of any new angioedema attack, the patient was not eligible to receive treatment with study medication for the attack. During the double-blind phase, narcotics and other pain medication were not to be used during the time between the onset of the acute attack and study treatment and avoided, if possible, for the first 8 to 9 hours following study treatment. The use of androgens for prophylactic treatment of hereditary angioedema was permitted (if the dose was stable or decreased). However, increasing the dose resulted in exclusion from the efficacy analysis of the double blind study. The use of antihistamines was to be avoided but was permitted in cases of demonstrated medical need; their use was to be recorded as concomitant medication. Routine use of antipyretics (aspirin, acetaminophen, non-steroidal anti-inflammatory drugs) and corticosteroids was avoided where possible, but were permitted in cases of demonstrated medical need. Their use was recorded as concomitant medication.

Primary End Point Assessment

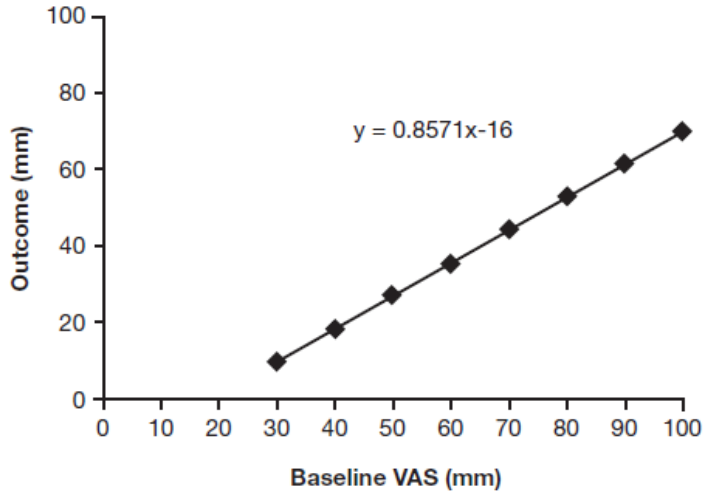
Patients presenting with cutaneous or abdominal attacks were asked to evaluate the severity of three specific symptoms (cutaneous swelling, cutaneous pain, and abdominal pain) using a visual analog scale (VAS). For each symptom, patients were instructed to draw a vertical line on an ungraduated 100 mm VAS scale, according to severity (0 mm – no symptoms; 100 mm – worst possible severity). The VAS is a validated tool for assessing a patient's perception of symptom severity, which has been widely used in clinical studies in diseases other than hereditary angioedema but with similar symptoms, to assess abdominal pain,[1-3] cutaneous pain,[4] and swelling.[5-7]

For patients presenting with cutaneous symptoms only, the primary symptom was defined either as cutaneous swelling or cutaneous pain, taking the most severe (VAS). If both were equally severe based on the VAS, 'cutaneous pain' was used. For the patients presenting with abdominal symptoms only, the primary symptom was defined as abdominal pain. Patients presenting with both cutaneous and abdominal symptoms were allocated to the abdominal group if abdominal symptoms were classified as moderate to very severe by the investigator (based on Global Assessment, which considers all abdominal symptoms combined). The patient was classified as cutaneous if the abdominal symptom(s) were mild, and at least one cutaneous symptom was moderate to very severe. The primary end point was the time to clinically significant relief of the index symptom. The time to clinically significant relief of the index symptom was determined retrospectively after symptom relief had been documented at three consecutive measurements. The earliest of the

three measurements was taken. Patients were censored when the events (symptom relief) did not occur within the observation period.

A response was any value to the right and below a line Y = 6/7 X –16 with X ≥ 30 mm, where X = pre-treatment VAS (Baseline) in mm and Y = post-treatment VAS in mm.

Supplementary Appendix Figure 1: Symptom Relief (response): Pre-treatment VAS and Outcome



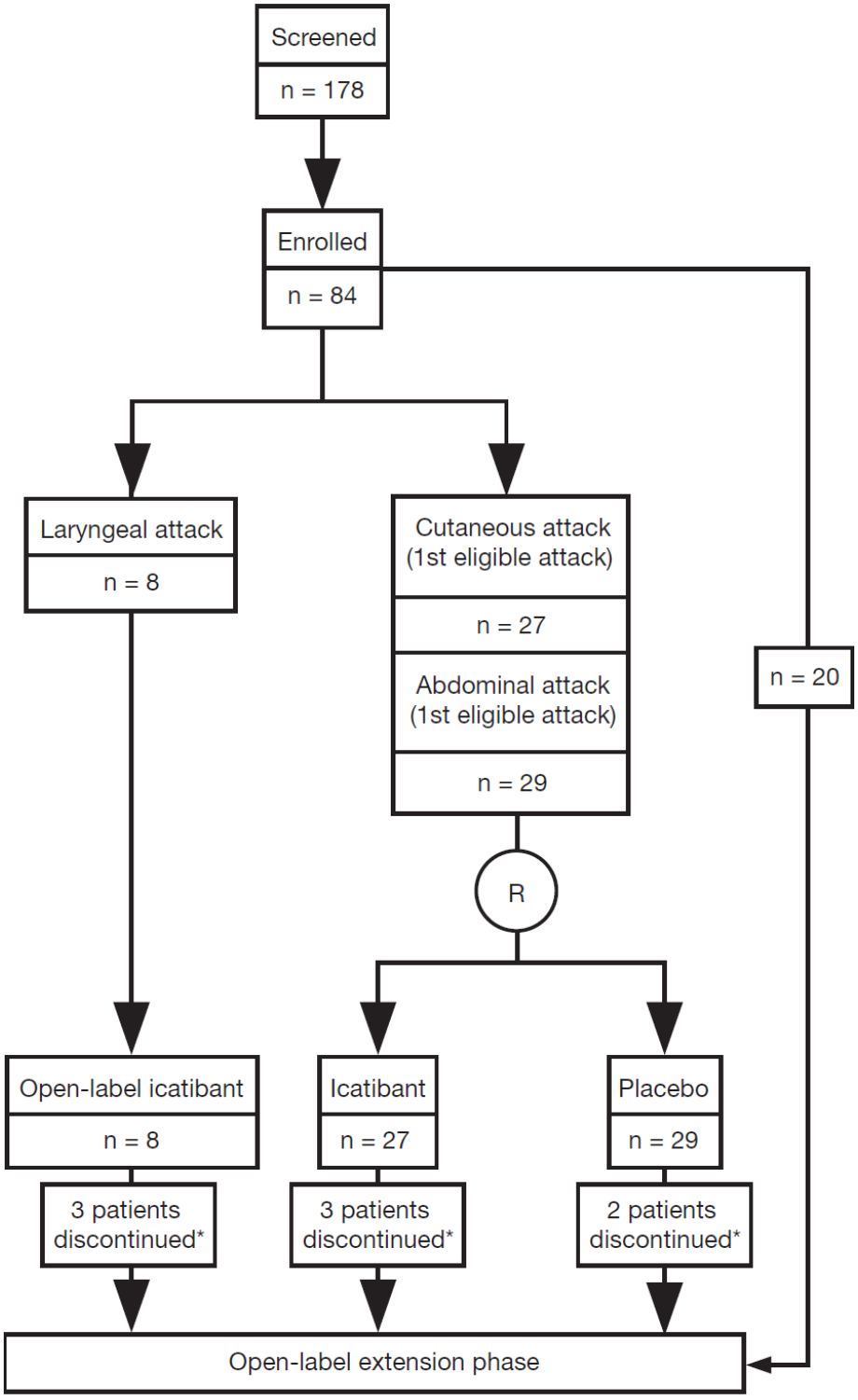
This end point was chosen to ensure detection of clinically relevant symptom improvement, and to account for potential partial unblinding of the study due to injection site reactions related to icatibant administration. The minimum clinically significant difference in VAS scores providing the basis for defining onset of clinically significant symptom relief was determined to be 9 mm in a separate study in patients with hereditary angioedema (data on file, Jerini AG). This value is consistent with values for minimum clinically significant difference in VAS scores of between 9 and 16 mm typically observed in diseases other than hereditary angioedema.[2,8,9]

Clinical Assessment of Symptoms

Global assessment of symptom severity for all abdominal, cutaneous or laryngeal symptoms was completed by the investigator using a standard 5-point scale (0=absence of symptoms, 4=very severe) prior to treatment, four and twelve hours after treatment, on day 2 and on day 14±2.[10,11] Clinical Global Improvement was completed by the investigator using a standard 7-point scale (1=very much improved, 7=very much worse)[12] four hours after treatment, and on day 2 and day 14±2. These scales were chosen due to their common use in assessing drug-related effects in various clinical conditions and the paucity of validated measurement techniques for hereditary angioedema.

The outcome of laryngeal edema was assessed by time to first symptom improvement according to the patient, and Clinical Global Improvement as assessed by the investigator.

Supplementary Appendix Figure 2: Patient Disposition in the FAST-1 Trial.

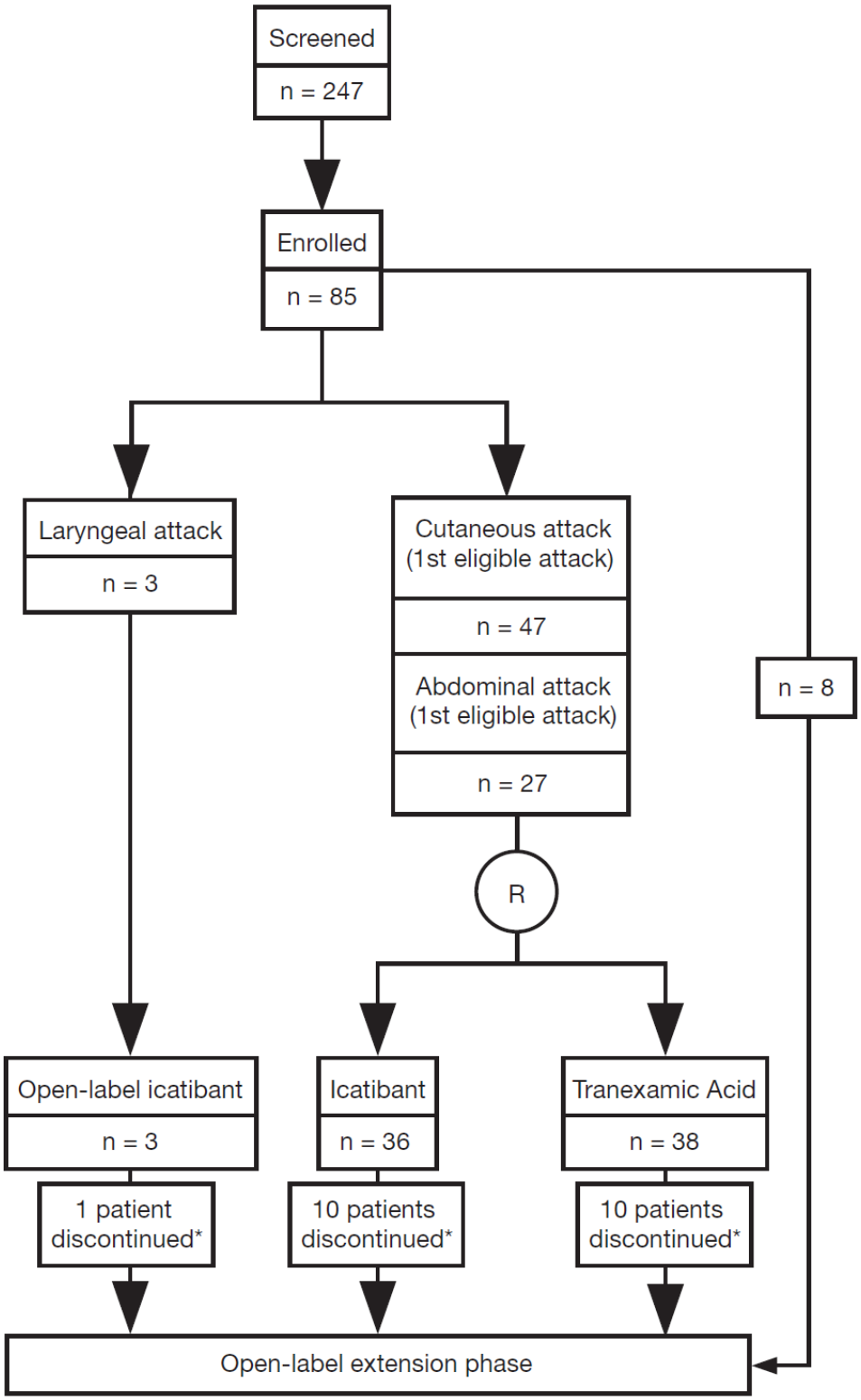


*All patients who discontinued during the controlled phase completed assessments in the controlled phase

R=randomization

- 178 patients screened, 84 patients participated in the study; 64 patients in the controlled phase.
- 29 patients excluded:
  - 25 did not meet either the inclusion or exclusion criteria at the screening visit
  - 4 failed at visit 1 due to non-compliance with either the inclusion or exclusion criteria.
- 64 patients enrolled in the controlled phase:
  - 56 randomized: 27 patients to icatibant and 29 patients to placebo
  - 8 with laryngeal attacks treated with icatibant open label.
- After completion of the double blind assessments, a total of 8 patients were discontinued during the controlled phase: 3 patients in the icatibant group, 2 patients in the placebo group, and 3 patients with laryngeal symptoms.
  Reasons for discontinuing the patients in the controlled phase:
  - 2 patients withdrew consent (1 patient in the icatibant group; 1 patient with laryngeal symptoms at baseline)
  - 3 patients lost to follow-up (1 patient in the placebo group; 2 patients with laryngeal symptoms)
  - 3 patients due to other reasons (2 patients in the icatibant group; 1 patient in the placebo group).

Supplementary Appendix Figure 3: Patient Disposition in the FAST-2 Trial.



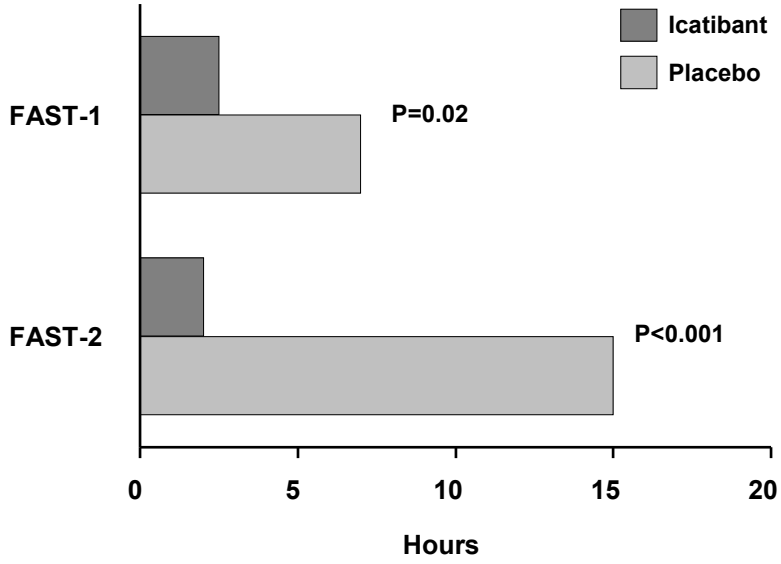
*All patients who discontinued during the controlled phase completed assessments in the controlled phase.

R=randomization

- 247 patients screened, 85 patients participated in the study; 77 patients in the controlled phase.
- 23 patients excluded due to non-compliance with either the inclusion or exclusion criteria.
- 77 patients enrolled in the controlled phase:
  - 74 patients randomized: 36 patients to icatibant and 38 patients to tranexamic acid
  - 3 patients with laryngeal attacks treated with icatibant open label.
- After completion of the double blind assessments, a total of 21 patients were discontinued during the controlled phase: 10 patients in the icatibant group, 10 patients in the tranexamic acid group, and 1 patient with laryngeal symptoms.

  Reasons for discontinuing the patients in the controlled phase:
  - 4 patients withdrew consent (2 patients in the icatibant group; 1 patient in the tranexamic acid group; 1 patient with laryngeal symptoms at baseline)
  - 6 patients lost to follow-up (4 patients in the icatibant group; 2 patients in the tranexamic acid group)
  - 8 patients due to other reasons (3 patients in the icatibant group; 5 patients in the tranexamic acid group)
  - 1 patient in the tranexamic acid group died from serious adverse events of severe aortic valve sclerosis and sudden cardiac death 41 days after receiving tranexamic acid
  - 2 patients due to significant medical conditions (1 patient in the icatibant group; 1 patient in the tranexamic acid group).

Supplementary Appendix Figure 4: Time to Onset of Symptom Relief Based on a 50% Reduction in 3-VAS Score in FAST-1 and FAST-2.



Symptom relief was defined as the earliest of three consecutive measurements where the average VAS score was reduced by >50% from baseline (average of 3 VAS scores: abdominal pain, cutaneous pain, and cutaneous swelling).

Supplementary Appendix Table 2: Time to Onset of Symptom Relief (Primary Symptom Only) - Original Primary End Point Symptom Adjusting for Rescue Medication.

	FAST-1			FAST-2		
	Median time to symptom relief (hours)			Median time to symptom relief (hours)		
	Icatibant	Placebo	P	Icatibant	Tranexamic acid	P
Time to onset of symptom relief for primary symptom (original primary endpoint) - *censoring patients taking rescue medication before onset of symptom relief at 120 hours*	2.5	9.0	0.02	2.0	16.0	<0.001
Time to onset of symptom relief for primary symptom (original primary endpoint) - *censoring patients taking rescue medication before onset of symptom relief at time rescue medication was administered*	2.5	5.0	0.07	2.0	12.0	<0.001

Rescue medication encompassed: C1-inhibitor concentrate, analgesics (opioids and non-opioids), antiemetics (5HT3R antagonists, antihistamines), prokinetic agents, anti-histamines and epinephrine.

Supplementary Appendix Table 3: FAST-1 and FAST-2 *Post-hoc* Analyses

	FAST-1		
	Icatibant	**Placebo**	**P**
1. Time to Symptom Relief Using Composite 3-VAS Score (average of the 3 VAS scores)			
Time to onset of symptom relief based on a 50% reduction in composite 3-VAS score	2.5	7.0	0.02
Time to onset of symptom relief based on a 30% reduction in composite 3-VAS score	1.6	3.8	0.03
Time to onset of symptom relief based on a 30% reduction in composite 3-VAS score censoring patients taking rescue medication before the onset of symptom relief at 120 hours	1.6	10.0	0.002
Time to onset of symptom relief based on a 30% reduction in composite 3-VAS score censoring patients taking rescue medication before the onset of symptom relief at the time rescue medication was administered	1.6	8.0	0.009
Time to onset of symptom relief based on a 40% reduction in composite 3-VAS score	2.0	6.0	0.02
Time to onset of symptom relief based on a 60% reduction in composite 3-VAS score	2.5	8.1	0.04
Time to onset of symptom relief based on a 80% reduction in composite 3-VAS score	4.0	18.0	0.04
Time to onset of symptom relief based on a 40% reduction in composite 3-VAS score censoring patients taking rescue medication before the onset of symptom relief at the time rescue medication was administered	2.0	6.0	0.006
Time to onset of symptom relief based on a 50% reduction in composite 3-VAS score censoring patients taking rescue medication before the onset of symptom relief at the time rescue medication was administered	2.5	10.0	0.01
Time to onset of symptom relief based on a 60% reduction in composite 3-VAS score censoring patients taking rescue medication before the onset of symptom relief at the time rescue medication was administered	2.5	8.0	0.02
Time to onset of symptom relief based on a 80% reduction in composite 3-VAS score censoring patients taking rescue medication before the onset of symptom relief at the time rescue medication was administered	4.0	19.8	0.05
2. Time to Symptom Relief Using Composite 4-VAS Score (average of the 4 VAS scores)			
Time to onset of symptom relief based on a 30%	1.5	3.5	0.05

reduction in composite 4-VAS score				
Time to onset of symptom relief based on a 30% reduction in composite 4-VAS score censoring patients taking rescue medication before the onset of symptom relief at 120 hours		1.5	9.0	0.01
Time to onset of symptom relief based on a 30% reduction in composite 4-VAS score censoring patients taking rescue medication before the onset of symptom relief at the time rescue medication was administered		1.5	8.0	0.02
Time to onset of symptom relief based on a 40% reduction in composite 4-VAS score		2.0	4.0	0.03
Time to onset of symptom relief based on a 50% reduction in composite 4-VAS score		2.0	5.5	0.03
Time to onset of symptom relief based on a 60% reduction in composite 4-VAS score		2.5	6.0	0.06
Time to onset of symptom relief based on a 80% reduction in composite 4-VAS score		3.5	18.0	0.03
Time to onset of symptom relief based on a 40% reduction in composite 4-VAS score censoring patients taking rescue medication before the onset of symptom relief at the time rescue medication was administered		2.0	4.2	0.01
Time to onset of symptom relief based on a 50% reduction in composite 4-VAS score censoring patients taking rescue medication before the onset of symptom relief at the time rescue medication was administered		2.0	7.9	0.01
Time to onset of symptom relief based on a 60% reduction in composite 4-VAS score censoring patients taking rescue medication before the onset of symptom relief at the time rescue medication was administered		2.5	7.9	0.04
Time to onset of symptom relief based on a 80% reduction in composite 4-VAS score censoring patients taking rescue medication before the onset of symptom relief at the time rescue medication was administered		3.5	19.8	0.05
3. Time to Symptom Relief Based on Primary Symptom				
Time to onset of symptom relief for the primary symptom (original primary endpoint) censoring patients taking rescue medication before the onset of symptom relief at 120 hours		2.5	9.0	0.02
Time to onset of symptom relief for the primary symptom (original primary endpoint) censoring patients taking rescue medication before the onset of symptom relief at the time rescue medication was administered		2.5	5.0	0.07
4. VAS score and Patient Symptom Severity Score				
Change (mean) from baseline at 4 and 12 hours in the	4 hours	-44.8	-23.5	0.002

VAS scales	12 hours	-54.2	-42.4	0.03
AUC (mean) for VAS score for primary symptom at 4, 8, and 12 hours post dose using a mixed model	4 hours 8 hours 12 hours	166.4 265.1 336.8	217.4 377.3 486.1	0.002 0.003 0.008
Composite VAS score based on 4-VAS – mean change from pre-treatment at 2, 4, 8, and 12 hours	2 hours 4 hours 8 hours 12 hours	-16.12 -22.25 -24.42 -26.92	-9.57 -13.03 -18.57 -23.91	<0.05†
Patient symptom composite score (average of 8 symptom scores) – mean change from pre-treatment at 2, 4, 8, and 12 hours	2 hours 4 hours 8 hours 12 hours	-0.58 -0.67 -0.86 -0.87	-0.39 -0.50 -0.64 -0.81	<0.05†
5. Time to Symptom Relief Based on Different Parameters				
Time to onset of symptom relief for the primary symptom - modified definition of response		2.5	8.1	0.06
Time to onset of symptom relief (primary symptom is the symptom with the highest VAS score at baseline)		2.5	5.0	0.09
Time to onset of symptom relief including all symptoms (primary and secondary)	Skin swelling Skin pain Abd. Pain	3.1 1.6 2.0	10.2 9.0 3.3	0.04 0.007 0.06
Time to onset of symptom relief in relation to severity of attack	Moderate Severe Very severe	2.0 2.0 2.7	4.2 5.0 5.6	0.69 0.06 0.85
			FAST-2	
		Icatibant	**Tranexamic acid**	**P**
1. Time to Symptom Relief Using Composite 3-VAS Score (average of the 3 VAS scores)				
Time to onset of symptom relief based on a 50% reduction in composite 3-VAS score		2.0	15.0	<0.001
Time to onset of symptom relief based on a 30% reduction in composite 3-VAS score				n/d
Time to onset of symptom relief based on a 30% reduction in composite 3-VAS score censoring patients taking rescue medication before the onset of symptom relief at 120 hours				n/d
Time to onset of symptom relief based on a 30% reduction in composite 3-VAS score censoring patients taking rescue medication before the onset of symptom relief at the time rescue medication was administered				n/d
Time to onset of symptom relief based on a 40% reduction in composite 3-VAS score				n/d

Time to onset of symptom relief based on a 60% reduction in composite 3-VAS score			n/d
Time to onset of symptom relief based on a 80% reduction in composite 3-VAS score			n/d
Time to onset of symptom relief based on a 40% reduction in composite 3-VAS score censoring patients taking rescue medication before the onset of symptom relief at the time rescue medication was administered			n/d
Time to onset of symptom relief based on a 50% reduction in composite 3-VAS score censoring patients taking rescue medication before the onset of symptom relief at the time rescue medication was administered			n/d
Time to onset of symptom relief based on a 60% reduction in composite 3-VAS score censoring patients taking rescue medication before the onset of symptom relief at the time rescue medication was administered			n/d
Time to onset of symptom relief based on a 80% reduction in composite 3-VAS score censoring patients taking rescue medication before the onset of symptom relief at the time rescue medication was administered			n/d
2. Time to Symptom Relief Using Composite 4-VAS Score (average of the 4 VAS scores)			
Time to onset of symptom relief based on a 30% reduction in composite 4-VAS score	1.1	10.1	<0.001
Time to onset of symptom relief based on a 30% reduction in composite 4-VAS score censoring patients taking rescue medication before the onset of symptom relief at 120 hours	1.1	12.0	<0.001
Time to onset of symptom relief based on a 30% reduction in composite 4-VAS score censoring patients taking rescue medication before the onset of symptom relief at the time rescue medication was administered	1.1	10.2	<0.001
Time to onset of symptom relief based on a 40% reduction in composite 4-VAS score			n/d
Time to onset of symptom relief based on a 50% reduction in composite 4-VAS score			n/d
Time to onset of symptom relief based on a 60% reduction in composite 4-VAS score			n/d
Time to onset of symptom relief based on a 80% reduction in composite 4-VAS score			n/d
Time to onset of symptom relief based on a 40% reduction in composite 4-VAS score censoring patients taking rescue medication before the onset of symptom relief at the time rescue medication was administered			n/d

Time to onset of symptom relief based on a 50% reduction in composite 4-VAS score censoring patients taking rescue medication before the onset of symptom relief at the time rescue medication was administered				n/d
Time to onset of symptom relief based on a 60% reduction in composite 4-VAS score censoring patients taking rescue medication before the onset of symptom relief at the time rescue medication was administered				n/d
Time to onset of symptom relief based on a 80% reduction in composite 4-VAS score censoring patients taking rescue medication before the onset of symptom relief at the time rescue medication was administered				n/d
3. Time to Symptom Relief Based on Primary Symptom				
Time to onset of symptom relief for the primary symptom (original primary endpoint) censoring patients taking rescue medication before the onset of symptom relief at 120 hours		2.0	16.0	<0.001
Time to onset of symptom relief for the primary symptom (original primary endpoint) censoring patients taking rescue medication before the onset of symptom relief at the time rescue medication was administered		2.0	12.0	<0.001
4. VAS score and Patient Symptom Severity Score				
Change (mean) from baseline at 4 and 12 hours in the VAS scales	4 hours 12 hours	-41.6 -54.0	-14.6 -30.3	<0.001 <0.001
AUC (mean) for VAS score for primary symptom at 4, 8, and 12 hours post dose using a mixed model	4 hours 8 hours 12 hours	137.7 202.8 247.4	205.8 376.2 517.4	<0.001 <0.001 <0.001
Composite VAS score based on 4-VAS – mean change from pre-treatment at 2, 4, 8, and 12 hours				n/d
Patient symptom composite score (average of 8 symptom scores) – mean change from pre-treatment at 2, 4, 8, and 12 hours				n/d
5. Time to Symptom Relief Based on Different Parameters				
Time to onset of symptom relief for the primary symptom - modified definition of response		2.5	21.3	<0.001
Time to onset of symptom relief (primary symptom is the symptom with the highest VAS score at baseline)		2.0	11.1	<0.001
Time to onset of symptom relief including all symptoms (primary and secondary)	Skin swelling Skin pain Abd. Pain	2.6 1.5 1.6	18.1 12.0 3.5	<0.001 0.003 0.03
Time to onset of symptom relief in relation to severity of attack	Moderate Severe Very severe	3.5 2.0 1.5	21.8 12.0 6.0	0.01 0.001 0.008

Time to onset of symptom relief shown as median hours

[†]at all timepoints

n/d, the analysis was not performed

Supplementary Appendix Table 4: **Number (%) of Randomized Patients with Adverse Events (≥5% per organ system class) by Treatment Group and Organ System Class – Controlled Phase.**

	FAST-1		FAST-2	
	Icatibant	**Placebo**	**Icatibant**	**Tranexamic acid**
	n (%)	**n (%)**	**n (%)**	**n (%)**
Patients treated in the safety population	**27 (100.0)**	**29 (100.0)**	**36 (100.0)**	**38 (100.0)**
Number of patients with at least one AE	**12 (44.4)**	**19 (65.5)**	**19 (52.8)**	**16 (42.1)**
Blood and lymphatic system disorders	0	0	0	2 (5.3)
Anaemia	0	0	0	1 (2.6)
Lymphadenopathy	0	0	0	1 (2.6)
Congenital, familial and genetic disorders	**4 (14.8)**	**5 (17.2)**	**10 (27.8)**	**6 (15.8)**
Hereditary angioedema	4 (14.8)	5 (17.2)	10 (27.8)	6 (15.8)
Gastrointestinal disorders	**1 (3.7)**	**5 (17.2)**	**2 (5.6)**	**1 (2.6)**
Abdominal pain	0	0	1 (2.8)	0
Abdominal tenderness	1 (3.7)	1 (3.4)	0	0
Diarrhea	0	0	1 (2.8)	0
Dyspepsia	0	1 (3.4)	0	0
Nausea	0	3 (10.3)	0	0
Vomiting	0	1 (3.4)	0	1 (2.6)
General disorders and administration site conditions	**3 (11.1)**	**4 (13.8)**	**5 (13.9)**	**3 (7.9)**
Asthenia	0	0	1 (2.8)	0
Fatigue	0	1 (3.4)	0	0
Feeling hot	0	0	0	1 (2.6)
Hypothermia	0	1 (3.4)	0	0
Influenza-like illness	0	1 (3.4)	0	0
Infusion site swelling	1 (3.7)	0	0	0
Injection site irritation	0	1 (3.4)	0	0

Injection site pain	1 (3.7)	0	1 (2.8)	0
Pain	0	0	0	1(2.6)
Pyrexia	1 (3.7)	0	1 (2.8)	0
Sudden cardiac death	0	0	0	1 (2.6)
Infections and infestations	**4 (14.8)**	**4 (13.8)**	**9 (25.0)**	**6 (15.8)**
Acute sinusitis	0	1 (3.4)	0	0
Blister infected	0	0	1 (2.8)	0
Borrelia infection	0	0	1 (2.8)	0
Bronchitis	0	0	0	1 (2.6)
Cystitis	0	0	1 (2.8)	0
Dental caries	0	0	1 (2.8)	0
Gastroenteritis	1 (3.7)	0	1 (2.8)	0
Gastroenteritis viral	0	1 (3.4)	0	0
Herpes simplex	1 (3.7)	0	0	1 (2.6)
Influenza	0	0	1 (2.8)	1 (2.6)
Nasopharyngitis	1 (3.7)	0	2 (5.6)	3 (7.9)
Onychomycosis	0	0	0	1 (2.6)
Pharyngitis	1 (3.7)	1 (3.4)	0	1 (2.6)
Sinusitis	0	0	1 (2.8)	0
Upper respiratory tract infection	0	1 (3.4)	0	0
Vaginal candidiasis	0	0	1 (2.8)	0
Viral upper respiratory tract infection	1 (3.7)	0	1 (2.8)	0
Injury, poisoning, and procedural complications	**0**	**0**	**3 (8.3)**	**1 (2.6)**
Fall	0	0	1 (2.8)	0
Joint sprain	0	0	1 (2.8)	0
Skin laceration	0	0	1 (2.8)	0
Wound	0	0	0	1 (2.6)
Investigations	**2 (7.4)**	**0**	**2 (5.6)**	**0**
Aspartate aminotransferase increased	1 (3.7)	0	0	0

Blood bilirubin increased	1 (3.7)	0	0	0
Blood creatine phosphokinase increased	1 (3.7)	0	0	0
Blood urine present	0	0	1 (2.8)	0
Liver function test abnormal	1 (3.7)	0	0	0
White blood cells urine positive	0	0	1 (2.8)	0
Musculoskeletal and connective tissue disorders	**0**	**0**	**2 (5.6)**	**1 (2.6)**
Arthritis	0	0	0	1 (2.6)
Chest wall pain	0	0	1 (2.8)	0
Jaw cyst	0	0	1 (2.8)	0
Nervous system disorders	**2 (7.4)**	**4 (13.8)**	**2 (5.6)**	**2 (5.3)**
Dizziness	2 (7.4)	1 (3.4)	0	0
Headache	0	2 (6.9)	2 (5.6)	2 (5.3)
Migraine	0	1 (3.4)	0	0
Respiratory, thoracic and mediastinal disorders	**3 (11.1)**	**1 (3.4)**	**0**	**0**
Nasal congestion	2 (7.4)	0	0	0
Pharyngolaryngeal pain	0	1 (3.4)	0	0
Throat irritation	1 (3.7)	0	0	0
Vocal cord disorder	1 (3.7)	0	0	0
Skin and subcutaneous tissue disorders	**2 (7.4)**	**3 (10.3)**	**0**	**0**
Hand dermatitis	1 (3.7)	1 (3.4)	0	0
Pruritus	0	2 (6.9)	0	0
Rash	1 (3.7)	0	0	0

Adverse Events

The most frequently occurring adverse events were angioedema attack, nausea, nasopharyngitis and dizziness. Other adverse events reported at a lower frequency included abdominal tenderness, pharyngitis, headache, hand dermatitis, pruritis and others (see Supplementary Appendix Table 3 for a complete list). Symptoms of angioedema were reported in 9 patients (16.1% overall, 4 icatibant [14.8%], 5 [17.2%] placebo) in FAST-1 and in 16 patients (21.6% overall, 10 icatibant [27.8%], 6 [15.8%] tranexamic acid) in FAST-2. These included patients whose angioedema symptoms worsened within 48 hours following symptom onset and those experiencing a new attack. On the day of study drug administration in FAST-2, 1 patient given icatibant experienced worsening of angioedema compared with 4 patients given tranexamic acid. Five patients given icatibant and 3 given tranexamic acid experienced worsening of angioedema on the day following administration.

Injection Site Reactions

In FAST-1, symptoms at the injection site were reported for 34 patients overall (60.7%); 26 patients (96.3%) randomized to receive icatibant and 8 patients randomized to placebo (27.6%). In the icatibant group, symptoms typically included erythema (26 patients [96.3%]); swelling (23 patients [85.2%]); warm sensation (18 patients [66.7%]); burning (6 patients [22.2%]); itching and cutaneous pain (5 patients [18.5%]). Median duration of symptoms ranged from 0.5 hours (burning) to 3.5 hours (erythema). In FAST-2, injection site reactions were reported for 45 patients overall (97%); 35 patients (97.2%) randomized to receive icatibant and 10 patients (26.3%) receiving tranexamic acid patients (26.3%). Typical symptoms were as in FAST-1. Median duration of symptoms ranged from 0.5 hours (cutaneous

pain) to 3.5 hours (erythema) in patients receiving icatibant. All patients treated for laryngeal symptoms with open-label icatibant in the controlled phase of both FAST-1 and FAST-2 experienced injection site reactions.

Laboratory Test Results

Two patients in the controlled phase of FAST-1 experienced 4 laboratory abnormalities reported as adverse events. One patient who received icatibant had mildly abnormal liver function tests (increase in ALT, AST and GGT), which were considered possibly related to icatibant and which resolved after 30 days. The second patient had a mild increase in CK, AST and total bilirubin on the day of icatibant administration.

In FAST-2, a trend was apparent at 24 hours post-treatment towards a decrease in mean CK in each treatment group, and similarly of mean uric acid level in the tranexamic acid group. Laboratory abnormalities reported as adverse events included hematuria and proteinuria (in 1 icatibant-treated patient who had proteinuria prior to and after drug administration most likely due to underlying diabetes), and leukocyturia that was evident before icatibant administration and persisted throughout the follow-up period (1 patient).

No anti-icatibant antibodies were detected in any post-treatment blood sample. There was no apparent change in complement C3a-des-Arg levels (a measure of complement activation).

Serious Adverse Events in the FAST-1 and FAST-2 Trial

No serious adverse events were reported in the Safety population of the FAST-1 trial. In FAST-2, one patient in the tranexamic acid group with preexisting

right and left ventricular hypertrophy died 41 days after administration of study drug (sudden cardiac death as a result of aortic valve sclerosis), which was the only serious AE (SAE) in this group. Five patients treated with icatibant experienced the following SAEs: (a) gastroenteritis and hypertensive crisis (blood pressure increase to 190/90 mm Hg) requiring hospitalization, occurring ~3 months after icatibant administration; (b) severe, life-threatening laryngeal HAE attack ~5 months after icatibant treatment, which required tracheotomy and hospitalization; (c) hospitalization for a new abdominal HAE attack accompanied by acute cystitis 15 days after icatibant administration; (d) severe cholelithiasis requiring hospitalization >1 year after icatibant treatment; (e) a laryngeal attack in 1 patient requiring intubation 5 minutes after icatibant administration was reported as SAE.

Adverse Events in Patients Treated for Laryngeal Edema

In patients treated with open-label icatibant for laryngeal symptoms, adverse events were reported by 75% (6/8) of patients in FAST-1 and by 33% (1/3) of patients in FAST-2. The most frequently occurring adverse event in these patients was angioedema attack (4 and 1 patient, respectively); none were considered icatibant related. One adverse event, headache, experienced by a patient in FAST-1, was possibly related to study medication. Moderate atypical chest pain due to hereditary angioedema, experienced by 1 patient, was reported as a serious adverse event but not considered related to icatibant. The patient recovered from this serious adverse event after 1 day.

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