

# **Firazyr<sup>®</sup> (icatibant) SC Injection for The Treatment of Acute Attacks of Hereditary Angioedema (HAE) in Adults**

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Pulmonary - Allergy  
Drugs Advisory Committee  
June 23, 2011

# Introduction

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**Philip Vickers, PhD**

Senior Vice President

Head of Research & Development

Shire Human Genetic Therapies (HGT)

## Proposed Indication for Icatibant

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- Firazyr<sup>®</sup> (icatibant) 30 mg SC Injection Is Indicated for The Treatment of Acute Attacks of Hereditary Angioedema (HAE) In Adults.

# HAE is a Rare and Debilitating Disease

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- < 30,000 HAE patients in US
- Icatibant was granted orphan status in Nov 2003
- Icatibant received Fast Track designation in Dec 2004

# Agenda

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## Introduction

### **Philip Vickers, PhD**

Senior Vice President  
Head of Research and Development  
Shire HGT

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## Unmet Medical Need

### **William Lumry, MD**

Clinical Professor of Medicine, Allergy Division  
University of Texas, SW Medical School  
Director, AARA Research Center  
Private Practice, Dallas, TX

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## Clinical Efficacy and Safety

### **Sue Cammarata, MD**

Vice President, Clinical Research  
Shire HGT

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## Clinical Perspective for Patient & Physician

### **Marc Riedl, MD, MS**

Assistant Professor of Medicine  
Section Head, Clinical Immunology & Allergy  
David Geffen School of Medicine, UCLA

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## Benefit-Risk Assessment Concluding Remarks

### **Sue Cammarata, MD**

# Icatibant – A First-in-Class Treatment

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- Potent and selective bradykinin (B2) receptor antagonist
- Bradykinin induces HAE edema
- Bradykinin receptor antagonism is a promising therapeutic approach
- Icatibant delivered by subcutaneous injection
- Icatibant provided in a pre-filled syringe that can be stored at room temperature

# Development History of Icatibant

- Icatibant discovered by Hoechst Marion Roussel
- Jerini AG conducted 2 Ph III trials (FAST-1, FAST-2)
  - NDA submitted (October 2007)
  - Initial trials were insufficient for efficacy and safety (April 2008)
  - FDA was uncertain about the validity of the primary endpoint
  - FDA requested 3rd Ph III study to establish efficacy and safety
- Shire acquired Jerini AG and discussed trial design with FDA
  - Shire conducted the definitive Phase III trial (FAST-3)
  - Shire submitted response to FDA (February 2011)
  - EMA approved icatibant for the treatment of HAE (July 2008) and self-administration (February 2011)

# HAE Unmet Medical Needs

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**William R. Lumry, M.D.**

Clinical Professor, Internal Medicine/Allergy Division  
University of Texas Southwestern Medical School  
Medical Director - Allergy & Asthma Research Center  
Private Practice - Dallas, Texas

# Hereditary Angioedema – Prevalence

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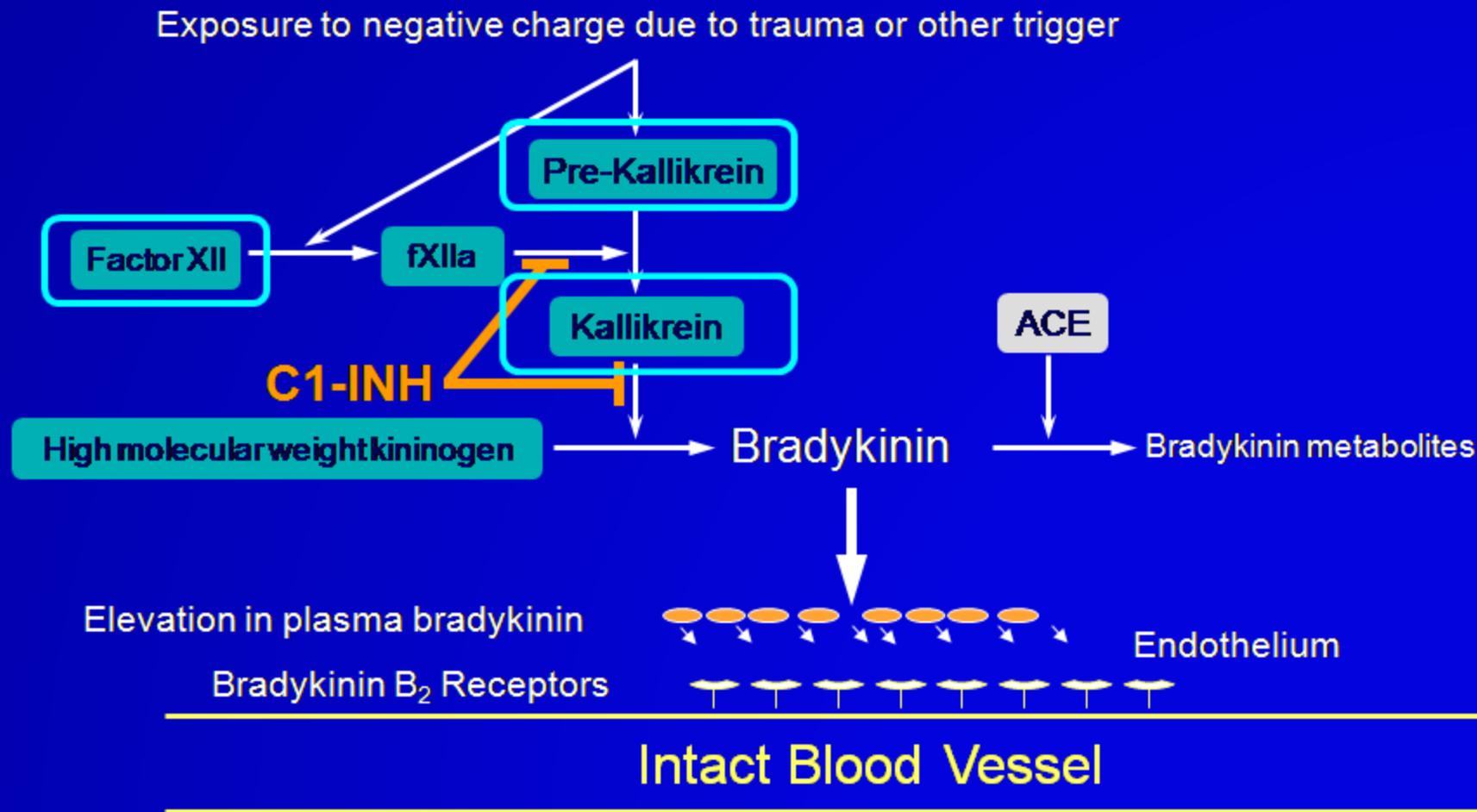
- HAE is a rare disorder
- HAE represents about 2% of all angioedema cases
- Global prevalence of 1/10,000 to 1/50,000
- US HAE patients estimated to be 6,000 - 30,000

# Hereditary Angioedema – Etiology

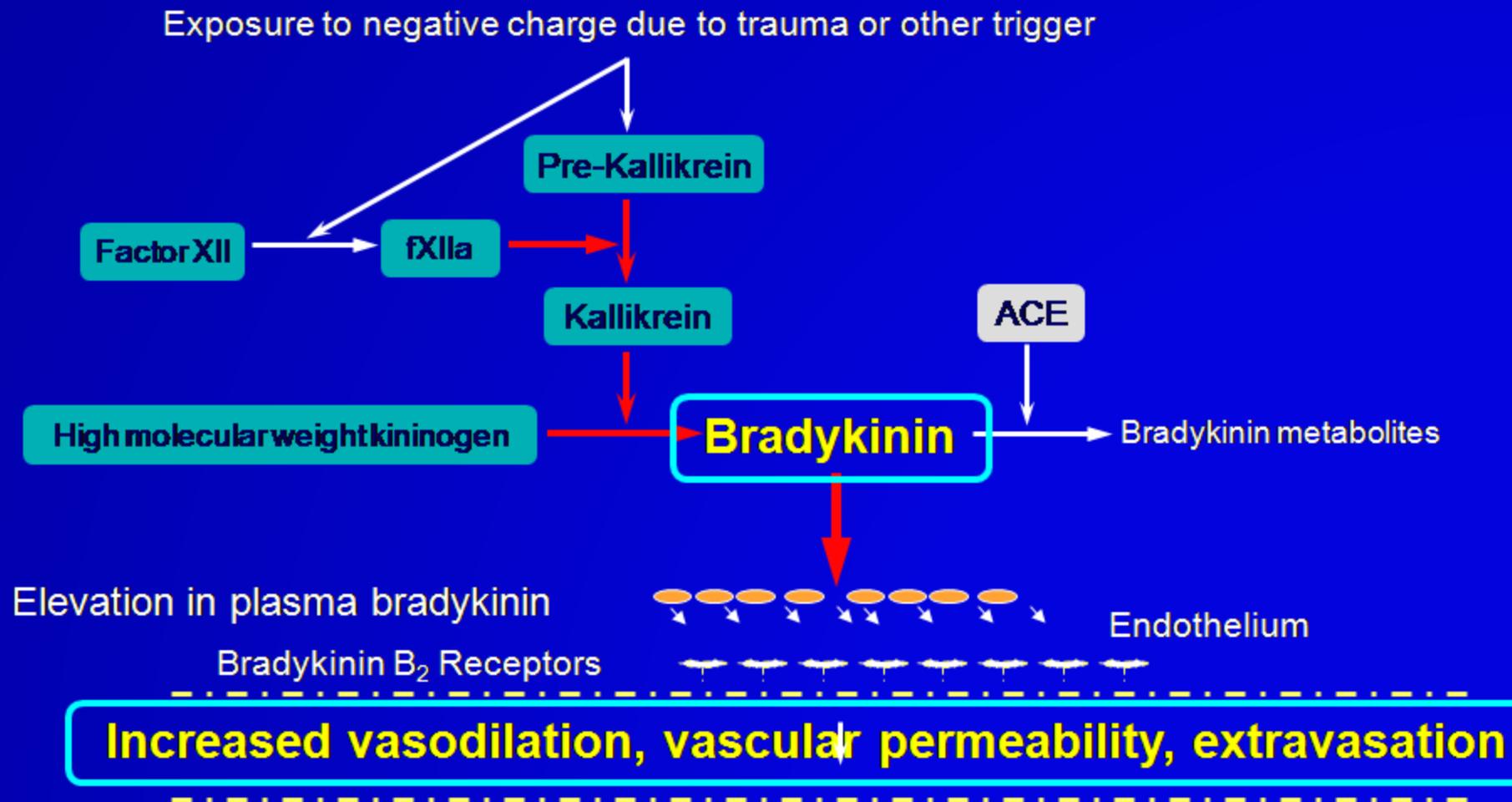
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- HAE is a genetic disorder with autosomal dominant transmission
- Mutations lead to C1-INH deficiency or dysfunction
- C1-INH regulates complement, coagulation, fibrinolytic and kinin pathways
  - C1-INH is the most important inhibitor of kallikrein
  - Kallikrein liberates bradykinin from HMW kininogen
- Bradykinin causes vasodilation, vascular leakage and serum extravasation resulting in angioedema

# C1-INH Controls Bradykinin Production



# C1-INH Deficiency May Increase Bradykinin Production



# HAE Attacks Present as Recurrent, Unpredictable Bouts of Swelling

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- HAE edema commonly affects several anatomical sites
  - Cutaneous tissues – hands, feet, face, genitalia
  - Mucosal tissues - lips, tongue, larynx, abdominal viscera

# Abdominal and Laryngeal HAE Attacks Have Important Clinical Presentations

- Abdominal attacks may present without peripheral edema
  - Severe colicky pain, nausea and vomiting
  - Dehydration, hemoconcentration, leukocytosis
  - Abdominal attacks often misdiagnosed
- Laryngeal attacks present as airway constriction or blockage
  - Mouth, tongue, pharyngeal and laryngeal swelling
  - Dysphagia, voice change, throat tightness, stridor
  - 2% of total attacks, but are life-threatening
  - 50% of HAE patients will experience laryngeal attack

## HAE Attacks - Duration and Course

- Typically bradykinin levels rise in affected tissue
- Edema develops gradually over 2–24 hours without treatment
- Attacks resolve within 2-5 days without treatment
- Attacks can move from one area to another
- Frequency can vary from  $> 1/\text{week}$  to  $< 1/\text{year}$
- Attacks are unpredictable, disruptive and disabling

# Patients Have an Understanding of Their HAE Condition

- Most attacks seem to occur spontaneously<sup>1</sup>
- Known triggers include<sup>1,2</sup>
  - Stress
  - Trauma, medical and dental procedures, surgery
  - Febrile illness
  - Menses and pregnancy
  - Treatment with ACE inhibitors and estrogens
- HAE patients are aware of signs and symptoms of an attack and often can predict onset<sup>3</sup>

1.HJ Longhurst, K Bork. Br J Hosp Med 2006; 67(12): 654-657.

2.M Bas et al. Allergy 2007; 62: 842-856. ; 3. Cicardi M et al. Am J Med Sci 1982 284:2-9

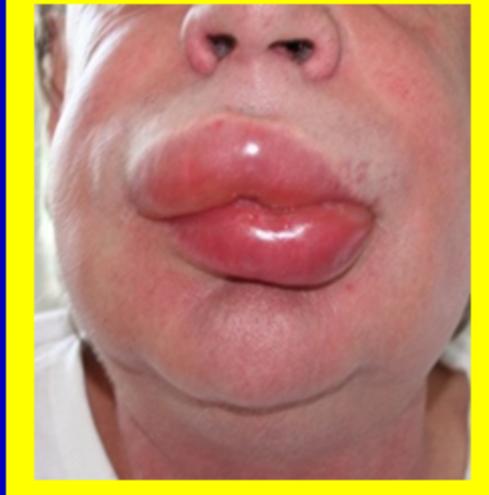
# HAE Attacks Presentations



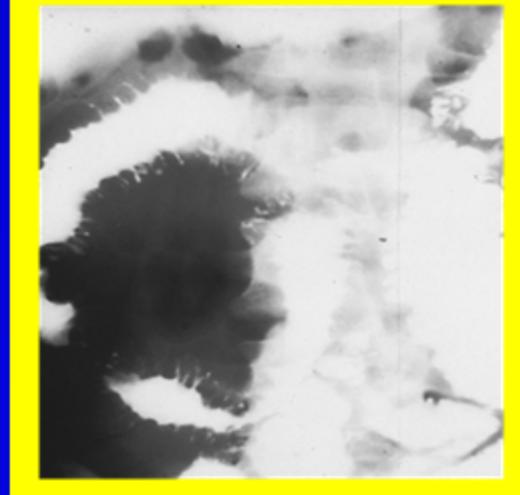
1



2



1



3

1..Photos courtesy of M Bas, Klinikum Rechts der Isar der Technischen Universität München, Munich, Germany

2..M Bas et al. Allergy 2006; 61: 1490-1492.

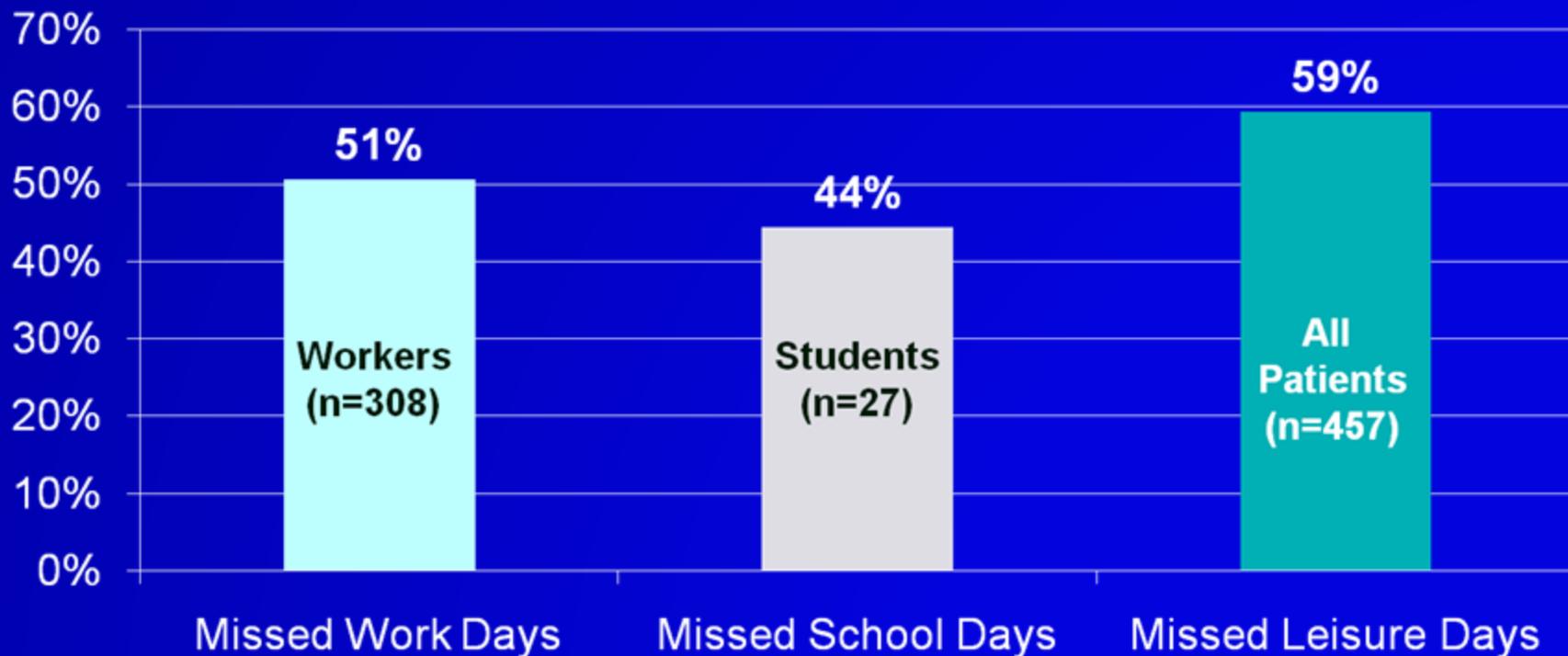
3..Photo courtesy of Michael Frank

# Laryngeal HAE Attack



# HAE Patients Often Miss Work, School or Personal Time Until Attack Resolves

**% of Patients Reporting Lost Days Following Most Recent HAE Attack**



# HAE Treatment Guidelines

- Currently no consensus guidelines in the US
- Treatment based on International & Canadian guidelines<sup>1,2</sup>
- These treatment guidelines address –
  - Prophylactic treatment -
    - Pre-dental and medical procedures
    - Chronic
  - Treatment of attacks
    - Access to therapy
    - Early intervention
    - Self-administration<sup>3</sup>

1 Bowen T et al. Allergy, Asthma & Clin Immunol 2010, 6:24

2 Bowen T et al. Allergy, Asthma & Clin Immunol 2010, 6:20

3. Longhurst HJ et al. Allergy, Asthma & Clin Immunol 2010, 6:10

# Literature Supports the Benefit of Early Intervention

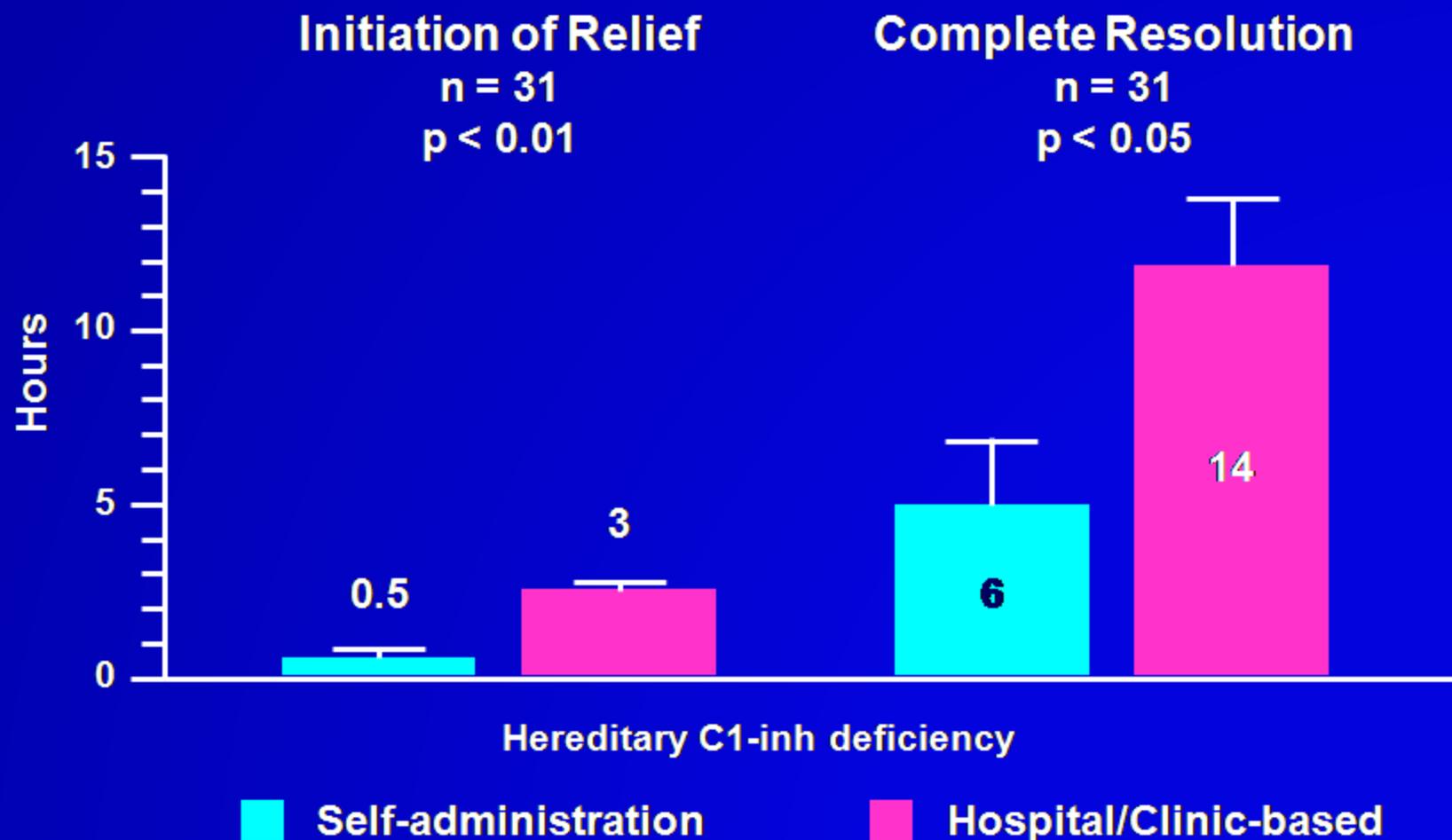
- Limited data available that examines early intervention
  - Immediate treatment recommended for acute attacks<sup>1</sup>
  - HAE clinical focus on demonstration of efficacy/safety
- Literature from plasma-derived C1-INH<sup>2,3</sup>
  - Attacks treated early are typically less severe
  - Attacks treated early begin to subside within 1 hour
  - Delayed treatment extends duration of attack

1. Bowen et al. Allergy Asthma Clin Immunol. 2010 Jul 28;6(1):24

2. Levi et al. J Allerg Clin Immunol 2006 117(4):904.

3. Longhurst, et.al., Clin & Exp Immunol Jan 2007

# Improved HAE Outcomes with Patient Self-Administered Therapy



# Acute HAE Treatments are Frequently Delayed by Lack of Ready Access

- Therapies for acute HAE attacks usually provided by healthcare professional<sup>1</sup>
- Most physicians are unfamiliar with HAE<sup>1</sup>
  - Mis-diagnosis as allergic angioedema or acute abdominal event
  - Administration of ineffective therapies based on mis-diagnosis
  - Delayed interventions caused by ER triage or diagnostic testing
- Patients often unable to convince HCP regarding diagnosis

# HAE: Unregulated Bradykinin Production Leading to Debilitating Edema

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- Patients suffer debilitating edema, pain; sometimes death
- Patient QOL disrupted at work, school and home
- Need for effective and safe treatment for immediate use
  - Prompt onset of efficacy
  - Shortened attack duration
  - Acceptable benefit-risk profile for on-demand self-administration

# Efficacy and Safety

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**Sue Cammarata, MD**

Vice President, Clinical Research

Shire Human Genetic Therapies (HGT)

# Review of Icatibant Efficacy and Safety

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- Dose selection
- Phase III study design
- Phase III efficacy
  - FAST-3, then FAST-1 and FAST-2
  - Laryngeal attacks
  - Repeat attack treatment
- Phase III safety
  - 1<sup>st</sup> attack (comparator controlled)
  - Repeat attack treatment (open label)
- EASSI self-administration study

# Large Database for Orphan Indication in Treatment of Acute Attacks of HAE

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- 236 patients received icatibant 30mg
  - Ph II-III and extensions
- 1055 acute HAE attacks
  - 60 patients with laryngeal attacks
  - 38 patients treated for > 5 attacks
- 56 patients who self-administered icatibant

# Phase I and II Studies to Support Clinical Development of Icatibant in HAE

<b>Study</b>	<b>Study Objective</b>
1001 (Ph I)	Dose ranging PK/PD for IV (Bradykinin challenge)
1101 (Ph I)	IV infusion times
1102 (Ph I)	Bioavailability SC vs IV
1103 (Ph I)	PK, safety (including QTc)
061 (Ph I)	Single SC dose QT study
065 (Ph I)	PK
2101 (Ph II)	Efficacy, safety, tolerability, PK, PD (30 mg & 45mg)

# Icatibant Phase III Program Evaluates Use for Acute Attacks of HAE

**FAST-3**

Icatibant  
30 mg SC  
vs.  
Placebo

**FAST-1**

Icatibant  
30 mg SC  
vs.  
Placebo

**FAST-2**

Icatibant  
30 mg SC  
vs.  
Tranexamic  
Acid

**EASSI**

Icatibant  
30 mg SC  
Open Label  
Self  
Administered

Open-label Extension Trials for Repeat  
Attacks with icatibant 30 mg SC

# Phase III Trials Used Consistent Overall Method for Data Collection

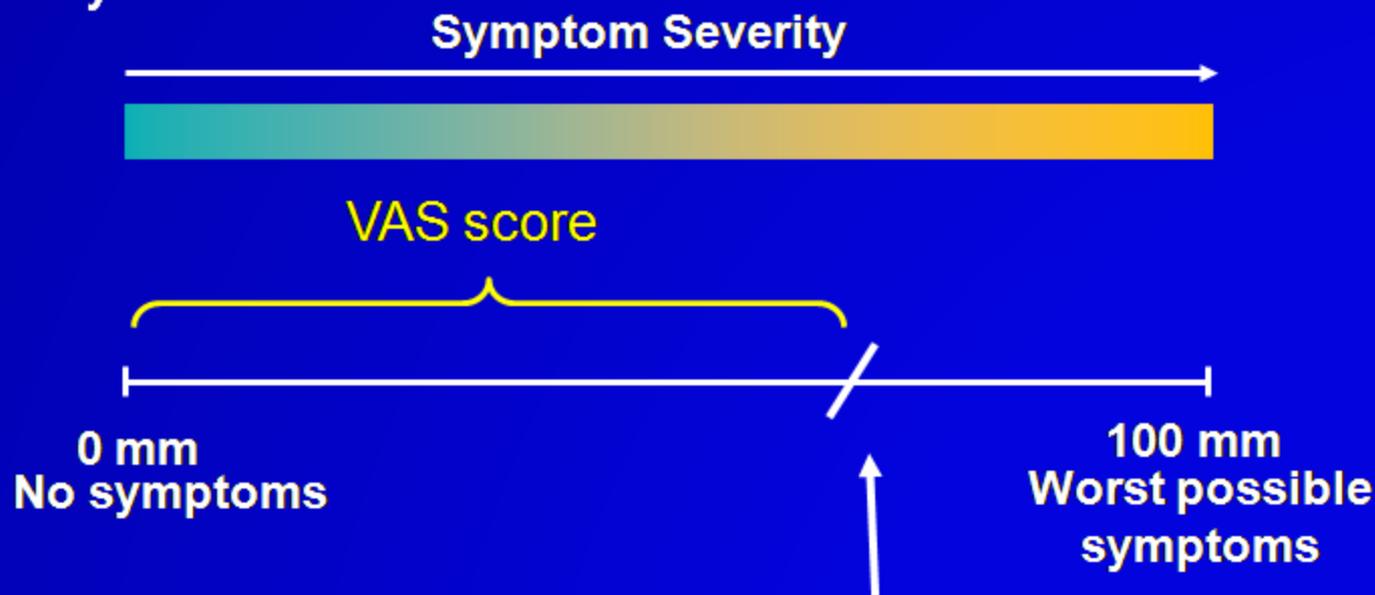


## VAS & Symptom Score Measures

1st measure occurred at 1 hour  
Then every 30 min from hour 1-4  
Then every 1 hour for hour 5-12  
Measures at 24 & 48 hours

# Primary Endpoint Used Validated Visual Analog Scale (VAS) Design

- Standardized, clinically validated measure of symptom severity



*Mark made by patient pre-treatment  
and at pre-defined time points post-treatment*

# Assessments Used Scoring Relevant to HAE Patients and Physicians

## Single VAS

- Skin Swelling
- Skin Pain
- Abdominal Pain
- Difficulty Swallowing
- Voice Change
- Nausea

## VAS-3

- Skin Swelling
- Skin Pain
- Abdominal Pain

## VAS-5

- Skin Swelling
- Skin Pain
- Abdominal Pain
- Difficulty Swallowing
- Voice Change

# Assessments Used HAE Relevant Scoring By Patient or Physician

## Symptom Score

- Skin Swelling
- Erythema
- Skin Pain
- Skin Irritation\*
- Abdominal Pain
- Abdom. Tender †
- Nausea / Vomiting
- Diarrhea
- Diff. Swallowing
- Voice Change
- Breathing Difficulty†
- Stridor†
- Asphyxia†

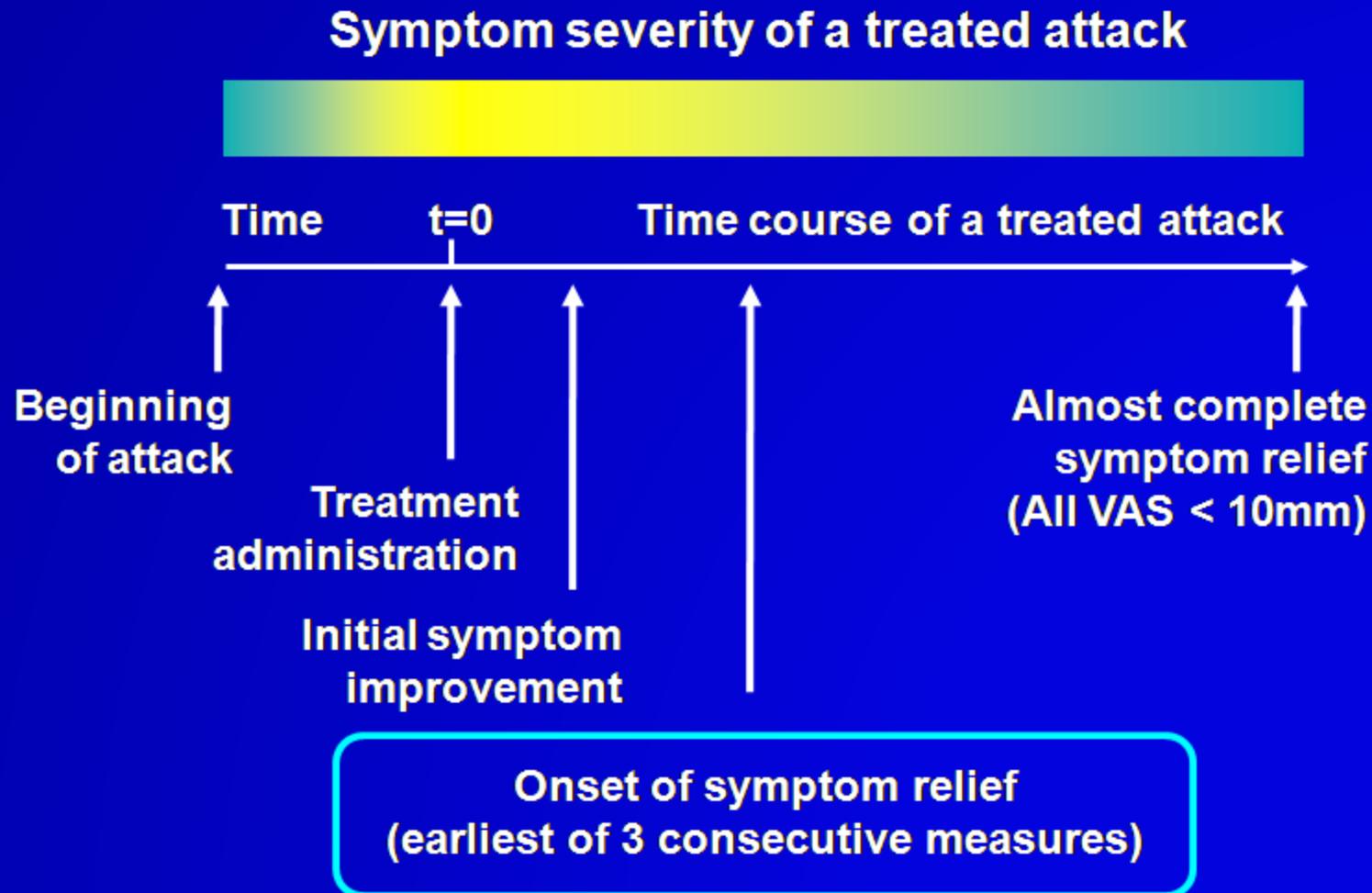
## Global Assess

- Cutaneous Symptoms
- Abdominal Symptoms
- Laryngeal Symptoms

† Physician only rated

\* Patient only rated

# Endpoints Measure Onset and Resolution of Symptoms



# Time to Onset of Primary Symptom Relief Was Common VAS Endpoint in Ph III Trials

<u>Ph III Study</u>	<u>Primary Endpoint</u>	<u>Key Endpoint</u>	<u>Supportive Endpoints</u>
FAST-3	Time to symptom relief - Composite VAS-3	Time to symptom relief - Single primary VAS	<ul style="list-style-type: none"> <li>• Time to initial symptom improvement</li> <li>• Mean composite VAS over time</li> <li>• Time to almost complete symptom relief</li> </ul>
FAST-1	Time to symptom relief - Single primary VAS	Time to symptom relief - Composite VAS-3 (post-hoc)	
FAST-2	Time to symptom relief - Single primary VAS	Time to symptom relief - Composite VAS-3 (post-hoc)	

# Icatibant Ph III Data Segmented by Non-laryngeal, Laryngeal and Repeat Attacks

**FAST-3**  
Non-  
laryngeal  
Attacks

**FAST-1**  
Non-  
laryngeal  
Attacks

**FAST-2**  
Non-  
laryngeal  
Attacks

**All Laryngeal Attacks**  
(FAST-1 + FAST-2 + FAST-3 + Extension)

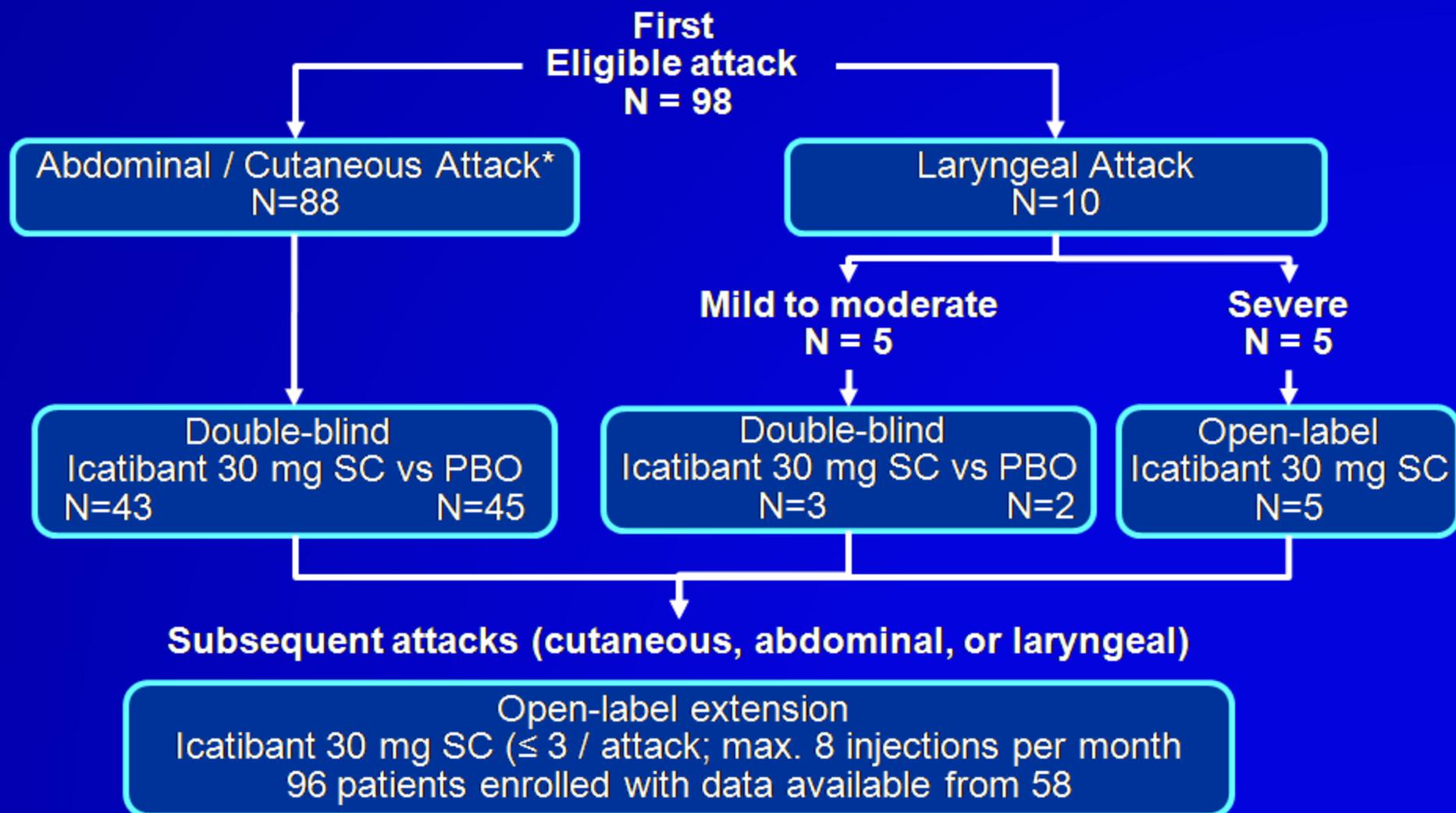
**Open Label Extension Trials for Repeat  
Attacks with icatibant 30 mg SC**

## **FAST-3 Efficacy**

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Non-laryngeal attacks

# FAST-3 Assessed 98 HAE Patients



\*Moderate to very severe.

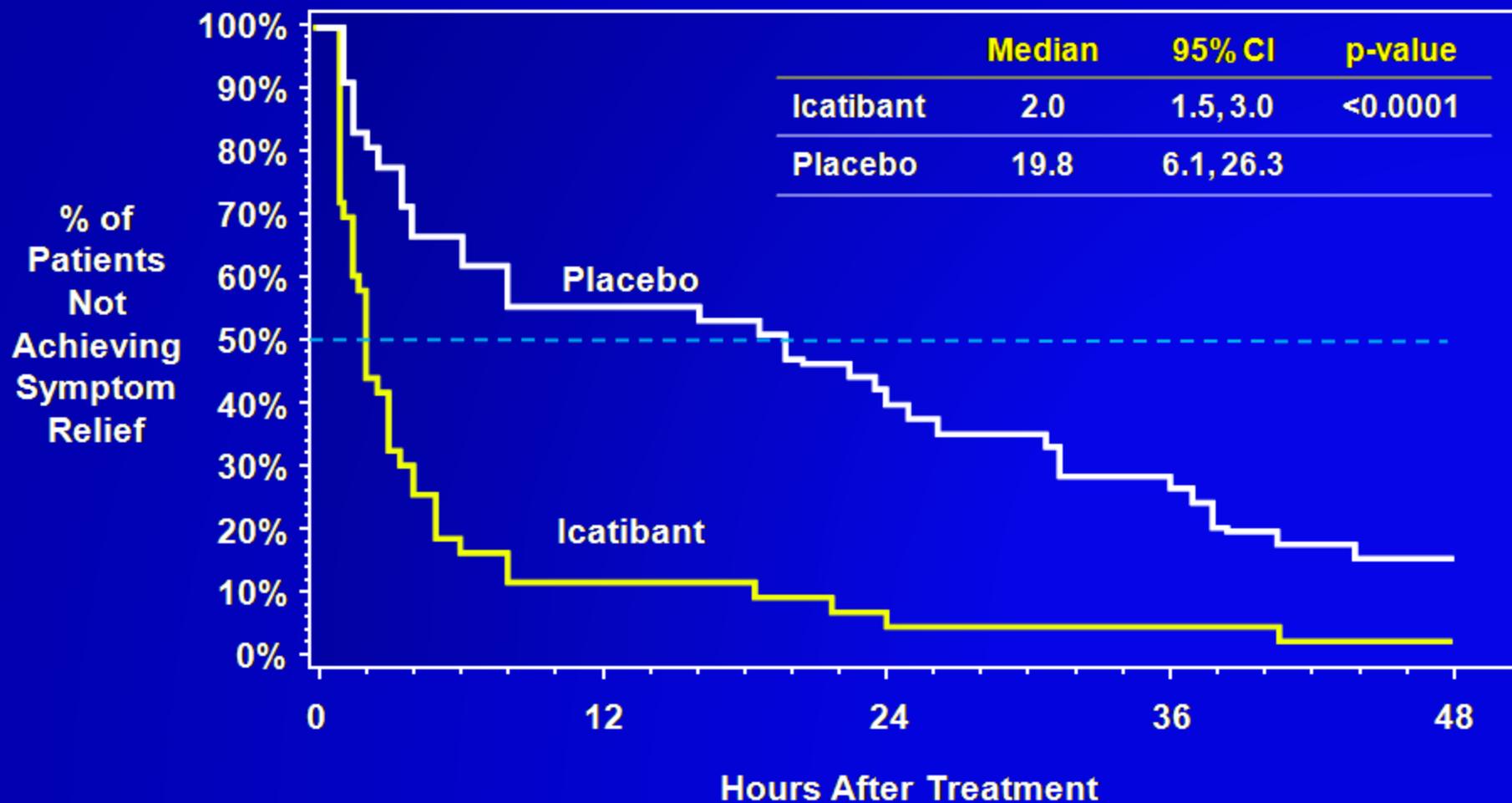
# Patient Disposition for Double-blind Non-laryngeal Population in FAST3

	Icatibant N=43		Placebo N=45	
	n	%	n	%
<b>Completed assessments up to Day 14</b>				
Yes	33	77%	37	82%
No	10	23%	8	18%
<b>Reason patient did not complete up to Day 14</b>				
Withdrawal of consent	-	-	-	-
Significant medical conditions	-	-	1	2%
Additional HAE attack	9	21%	6	13%
Lost to Follow-up	-	-	-	-
Death	-	-	1	2%
Other	1	2%	-	-

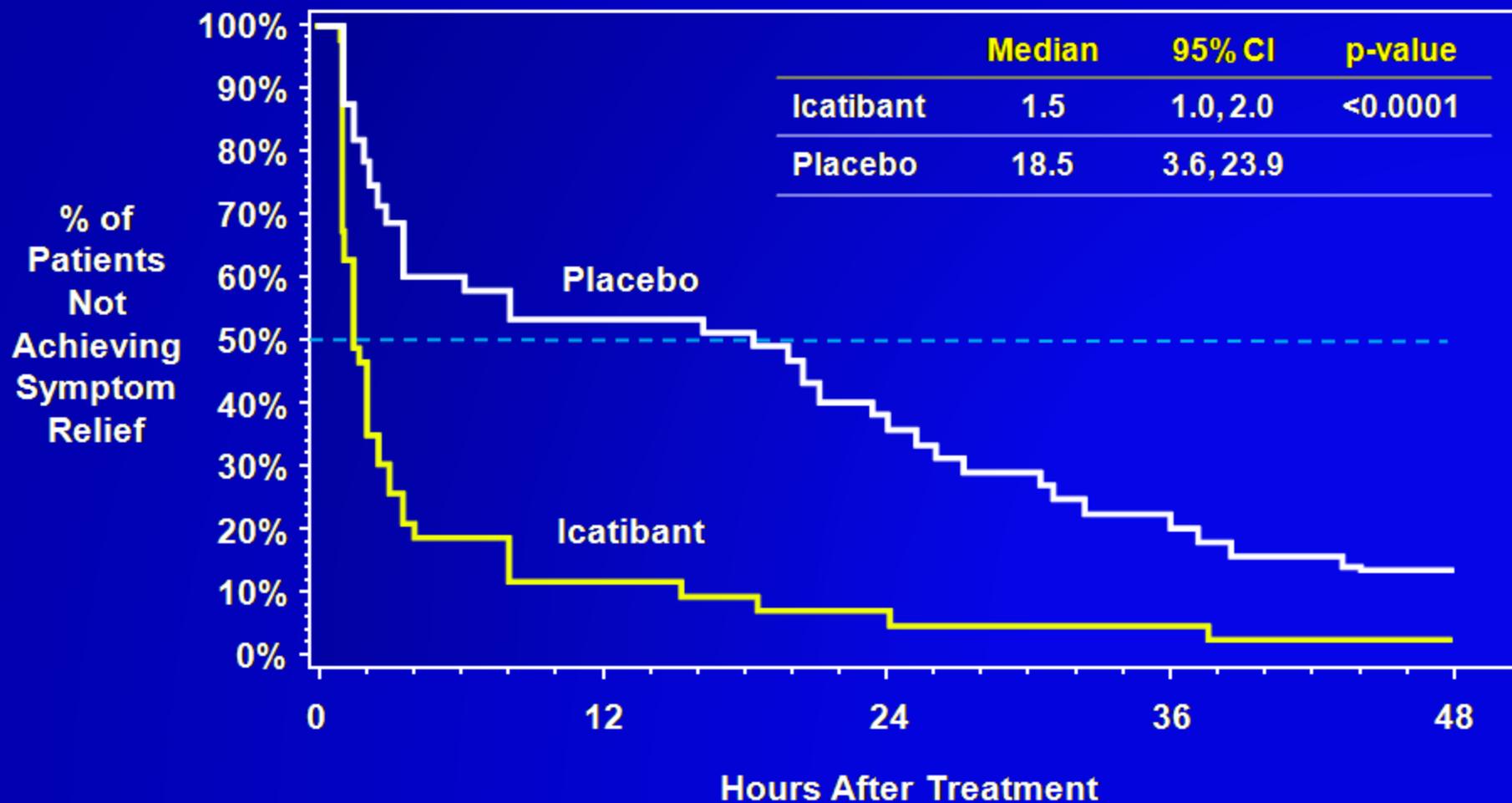
# FAST-3 Non-Laryngeal Patient Demographics

	Icatibant N=43	Placebo N=45
<b>Age (years)</b>		
Mean	36.1	36.6
<b>Sex - n (%)</b>		
Male	16 (37%)	16 (36%)
Female	27 (63%)	29 (64%)
<b>Race - n (%)</b>		
White	38 (88%)	40 (89%)
Other	5 (12%)	5 (11%)
<b>Weight (kg)</b>		
Mean	81.7	80.7

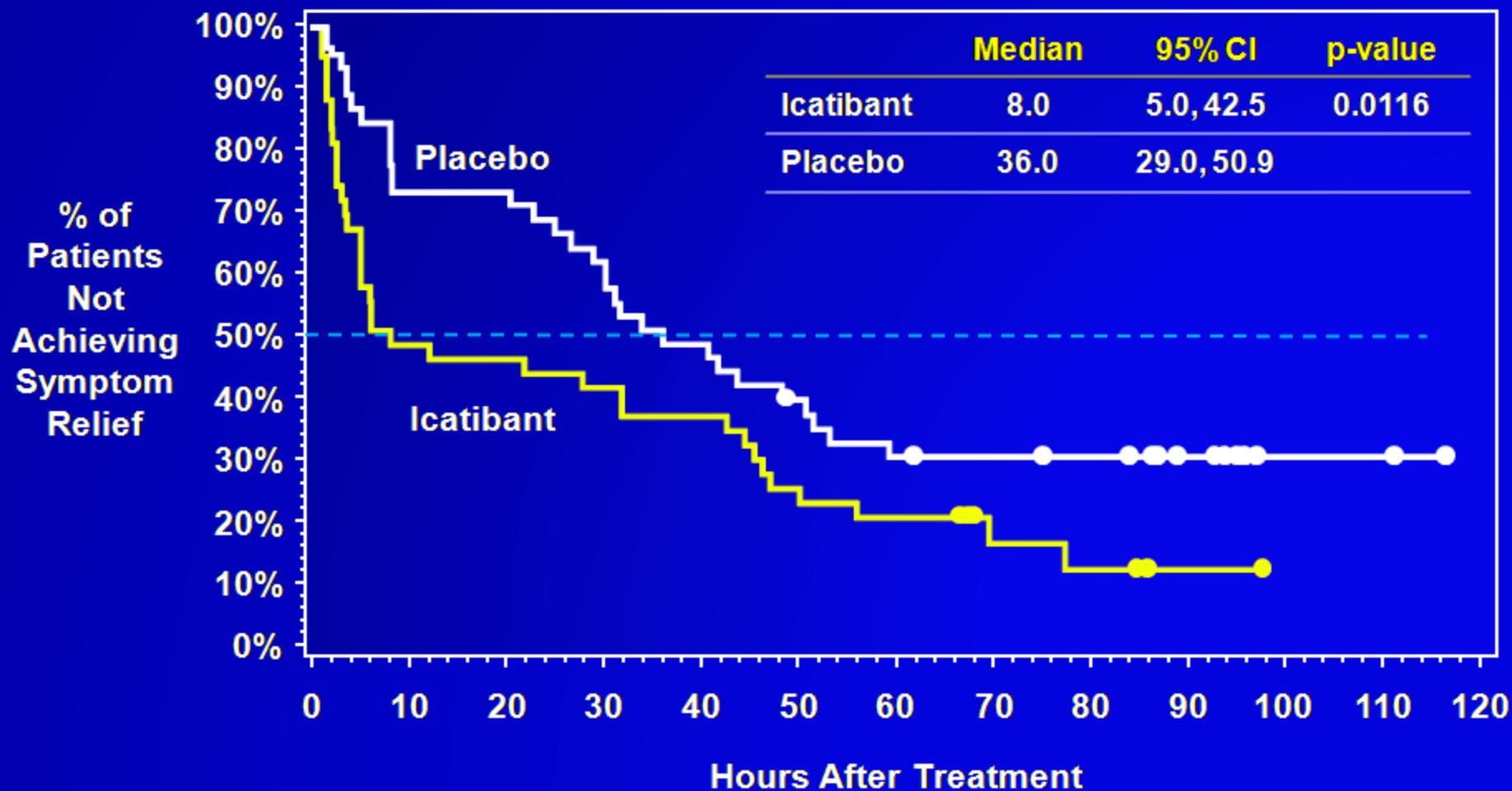
# FAST-3: Time to Onset of Symptom Relief (Composite VAS-3)



# FAST-3: Time to Onset of Primary Symptom Relief (Single VAS)



# FAST-3: Time to Almost Complete Symptom Relief

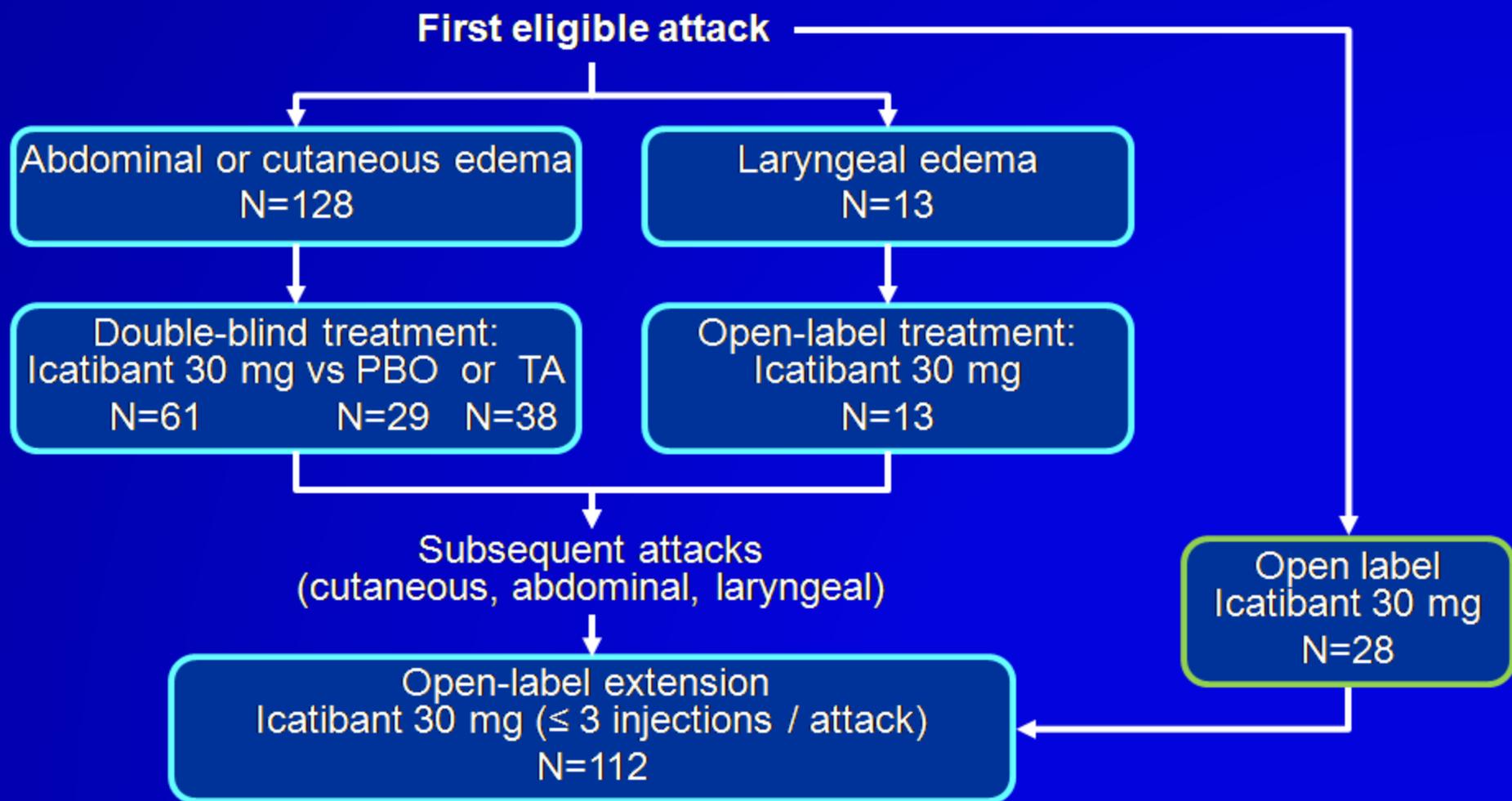


# FAST-1 and FAST-2 Efficacy

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Non-laryngeal attacks

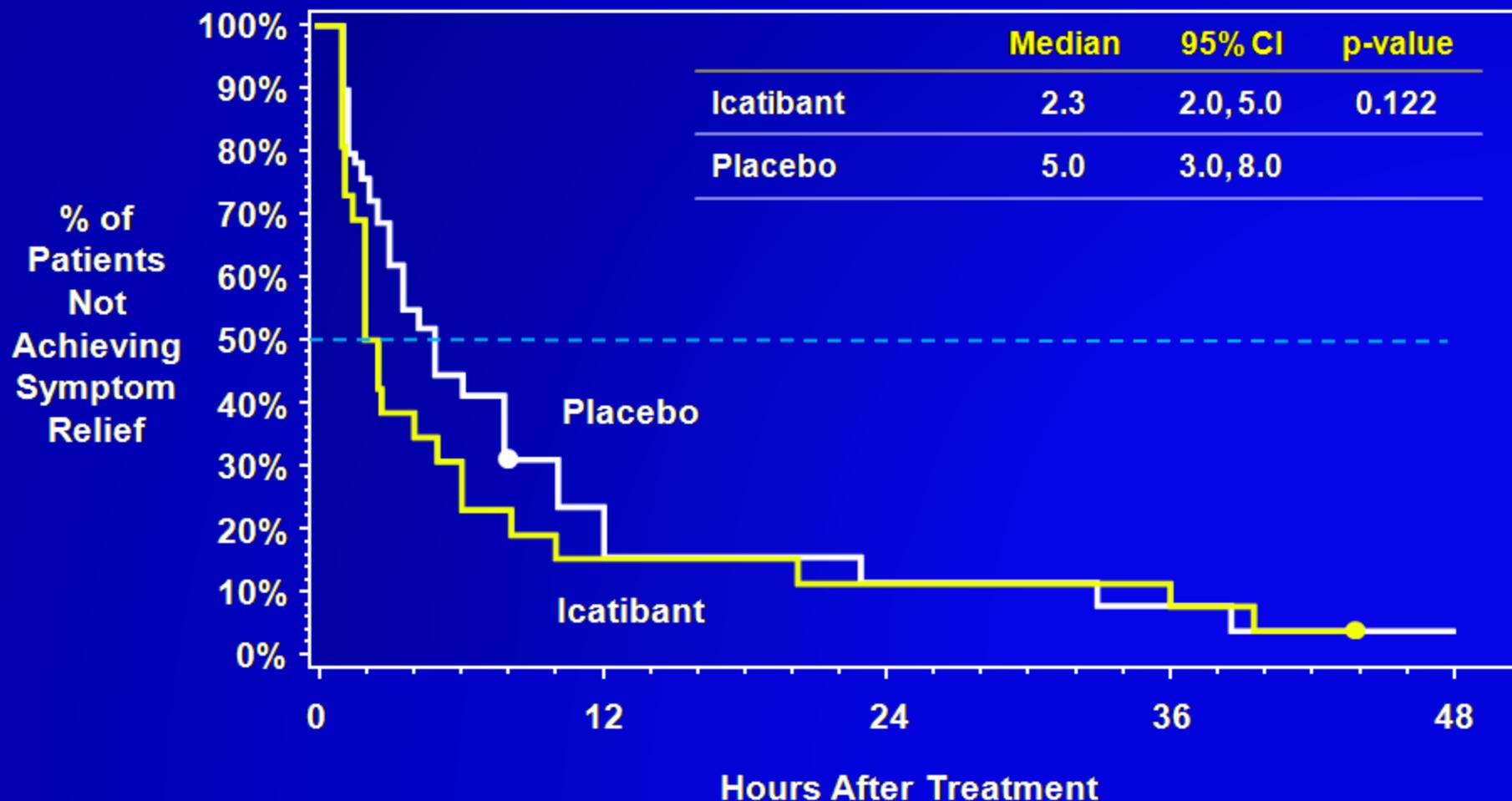
# FAST-1 & FAST-2 Assessed 141 HAE Patients



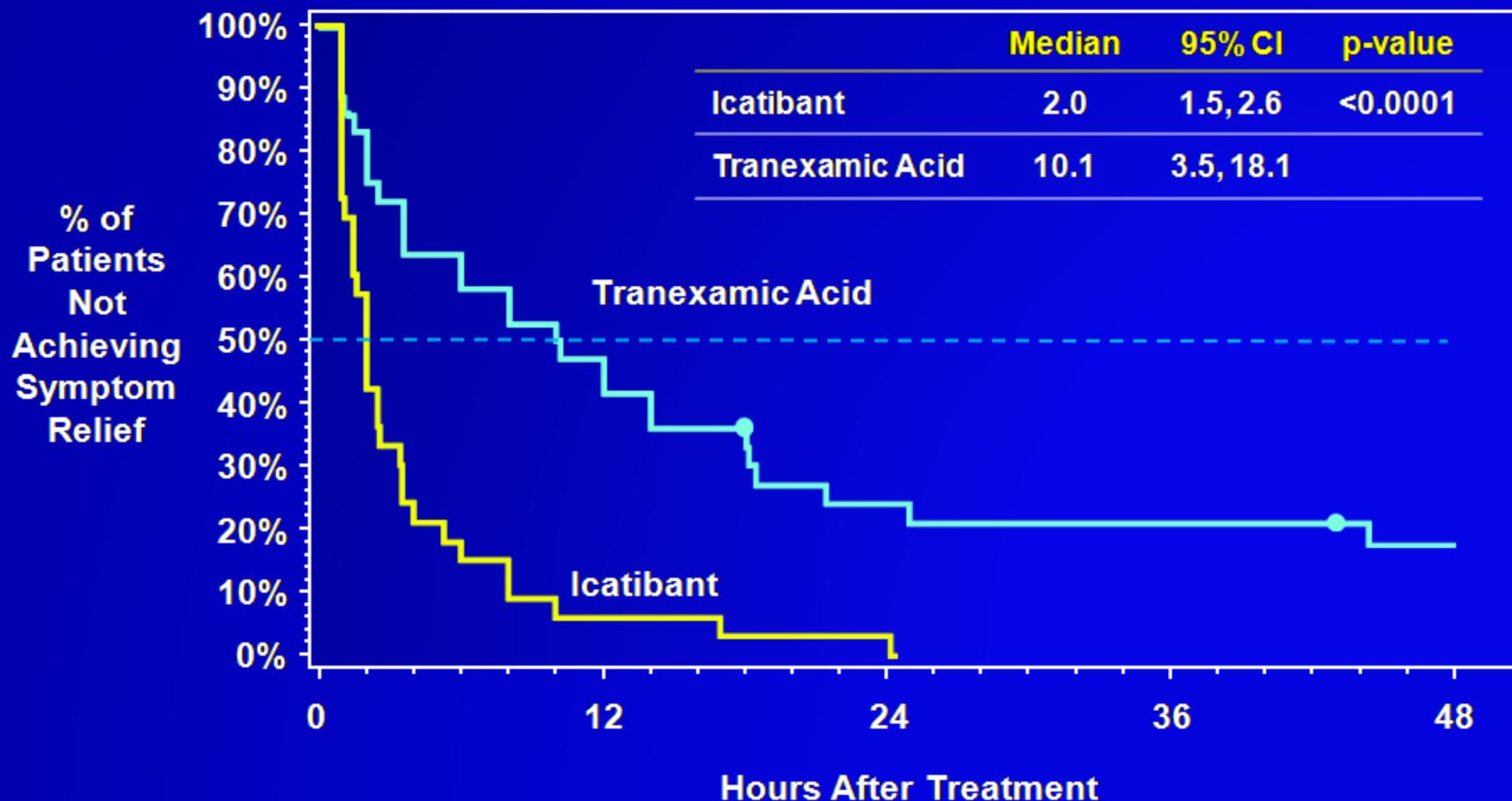
# Patient Disposition for Double-blind Non-laryngeal Population in FAST-1 & FAST-2

	FAST 1				FAST 2			
	Icatibant N=26		Placebo N=29		Icatibant N=35		TA N=38	
	n	%	n	%	n	%	n	%
<b>Completed assessments up to Day 14</b>								
Yes	20	77%	27	93%	29	83%	31	82%
No	6	23%	2	7%	6	17%	7	18%
<b>Reason patient did not complete up to Day 14</b>								
Withdrawal of consent	-	-	-	-	-	-	-	-
Significant med. conditions	-	-	-	-	-	-	-	-
Additional HAE attack	4	15%	2	7%	6	17%	6	16%
Lost to Follow-up	-	-	-	-	-	-	1	3%
Death	-	-	-	-	-	-	-	-
Other	2	8%	-	-	-	-	-	-

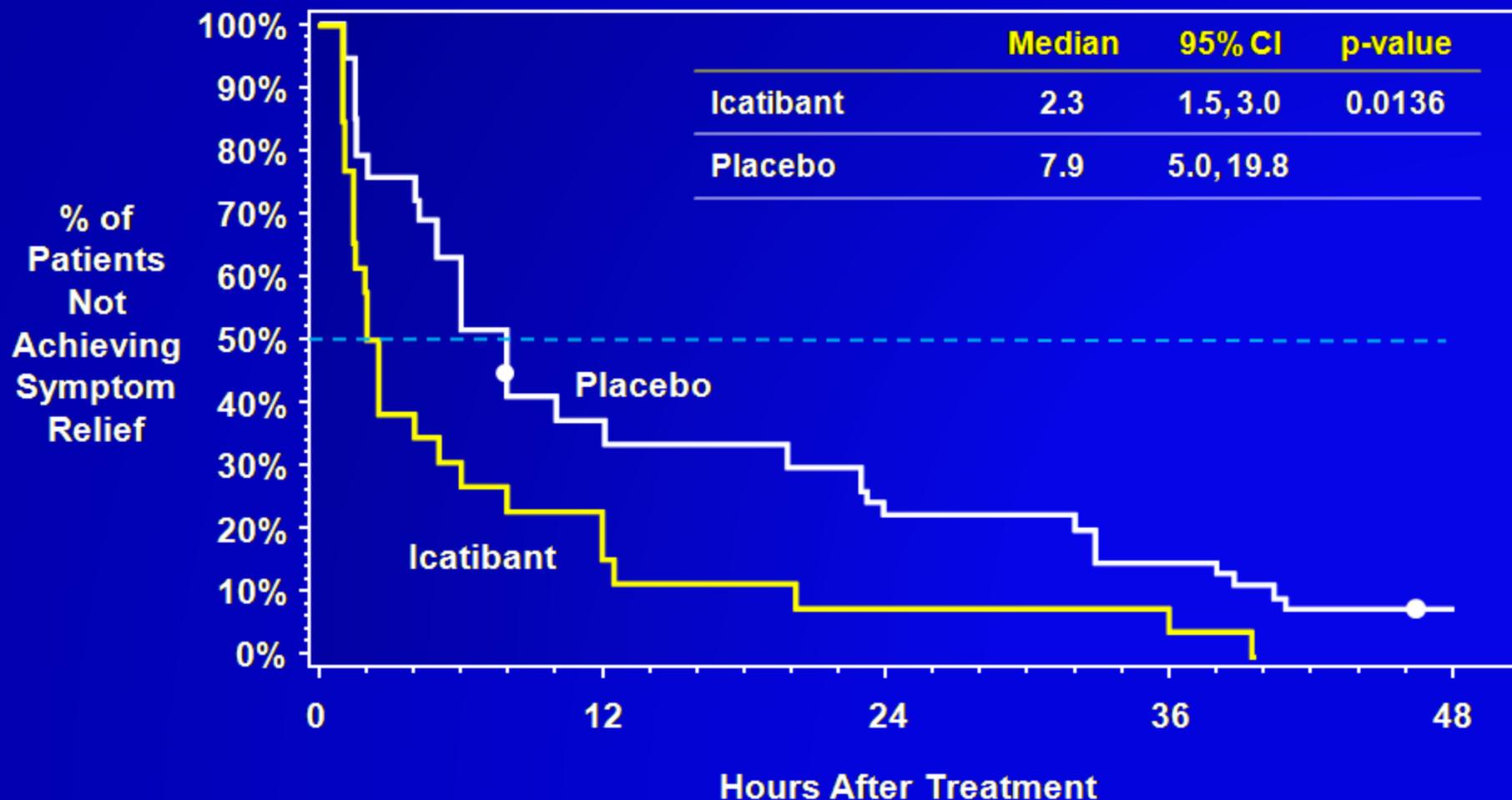
# FAST 1: Time to Onset of Primary Symptom Relief (Single VAS)



# FAST 2: Time to Onset of Primary Symptom Relief (Single VAS)

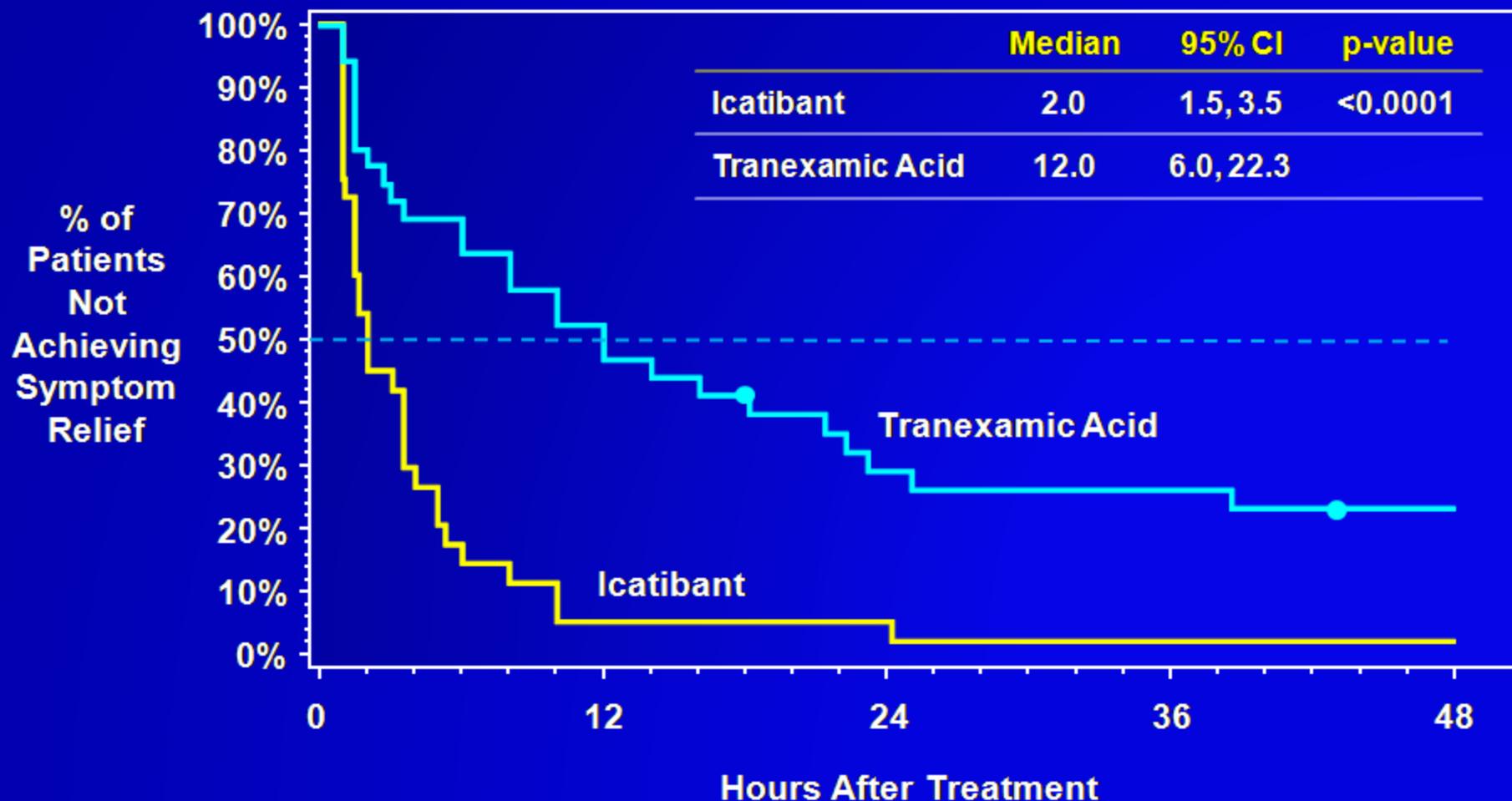


# FAST 1: Time to Onset of Symptom Relief (Composite VAS-3)



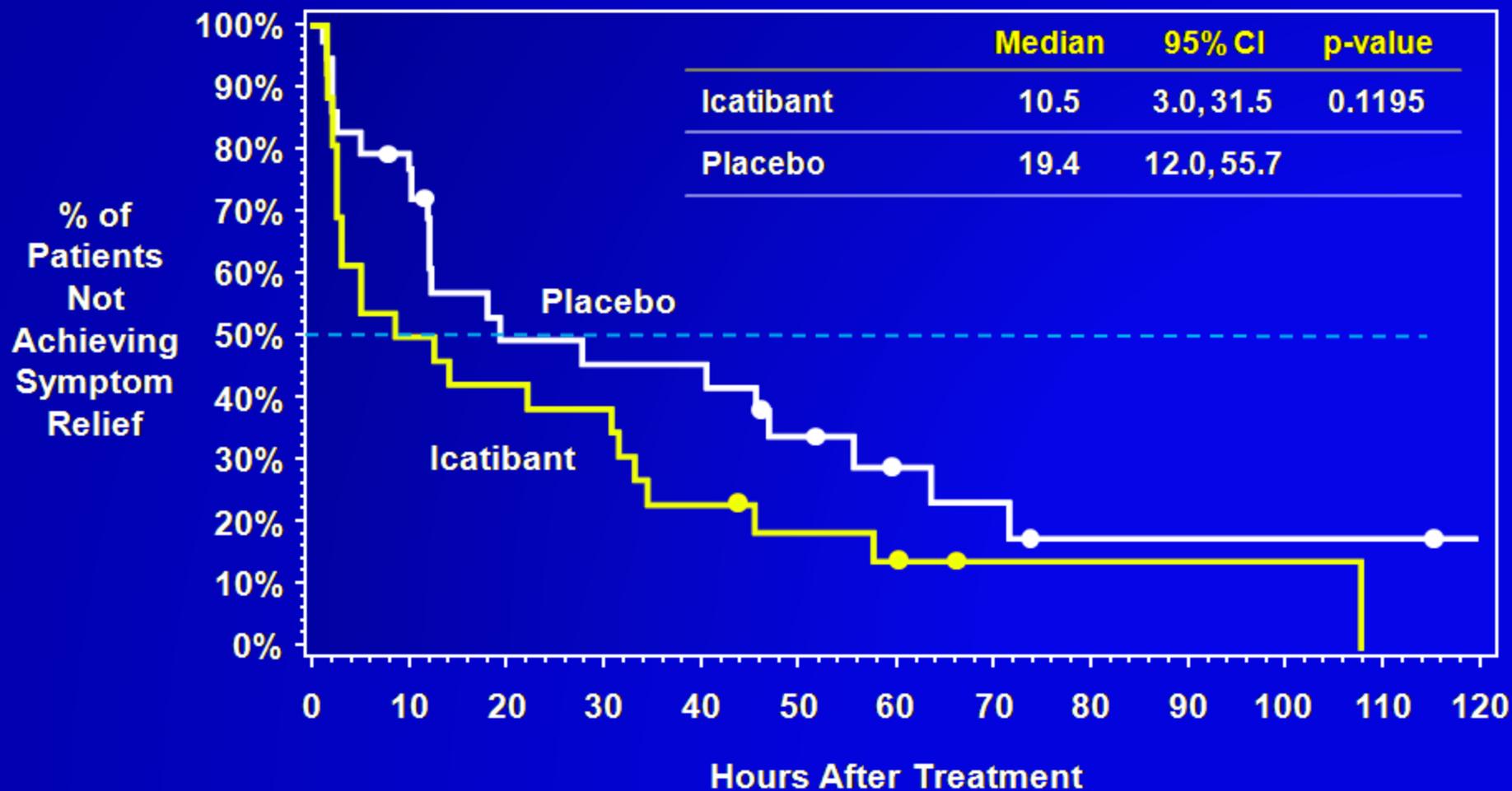
Source: Post-hoc calculation from prospectively collected single VAS scores

# FAST 2: Time to Onset of Symptom Relief (Composite VAS-3)

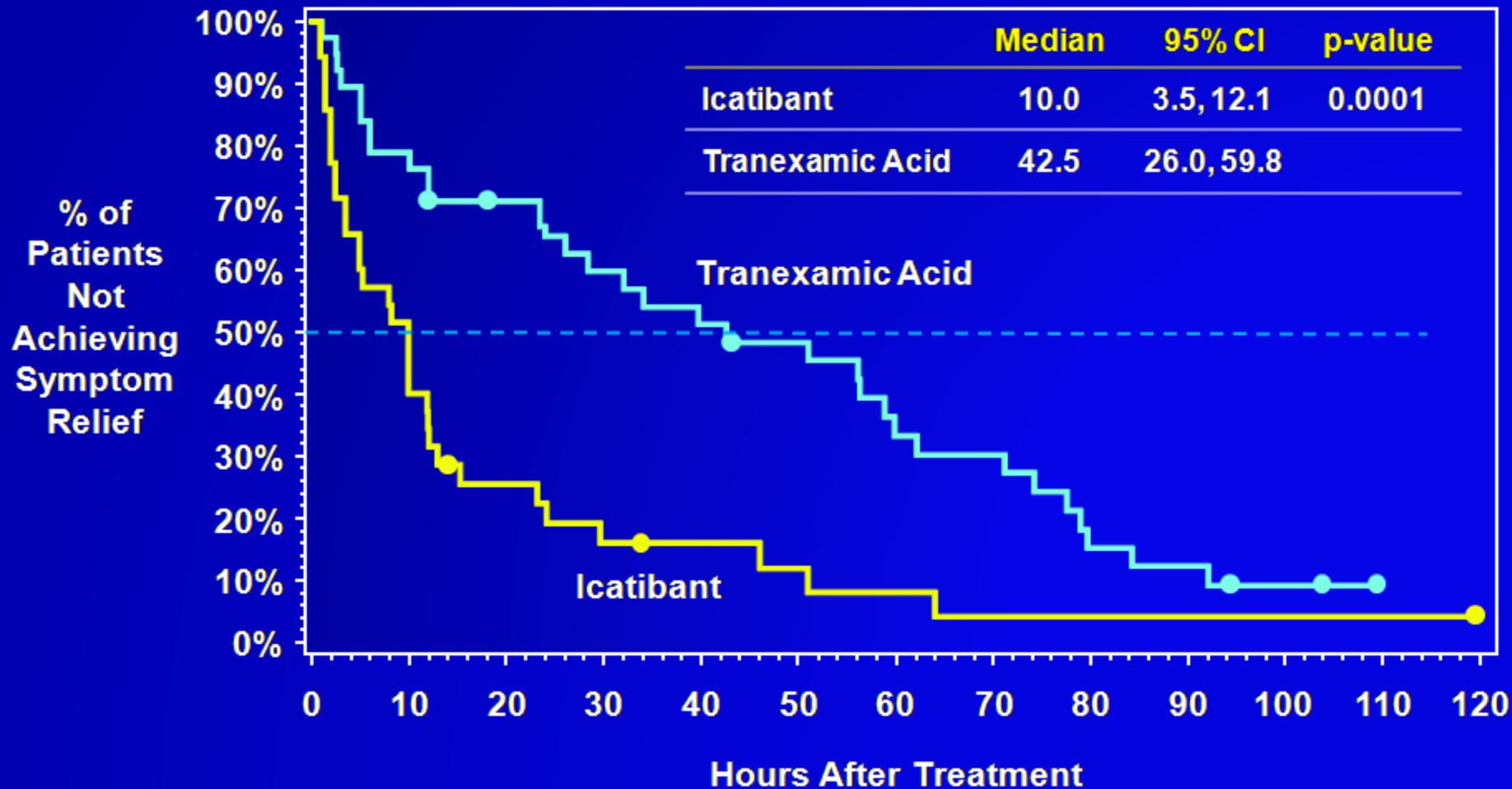


Source: Post-hoc calculation from prospectively collected single VAS scores

# FAST 1: Time to Almost Complete Symptom Relief



# FAST 2: Time to Almost Complete Symptom Relief



# The FAST-1 Placebo Group Had Some Differences that May Affect Results

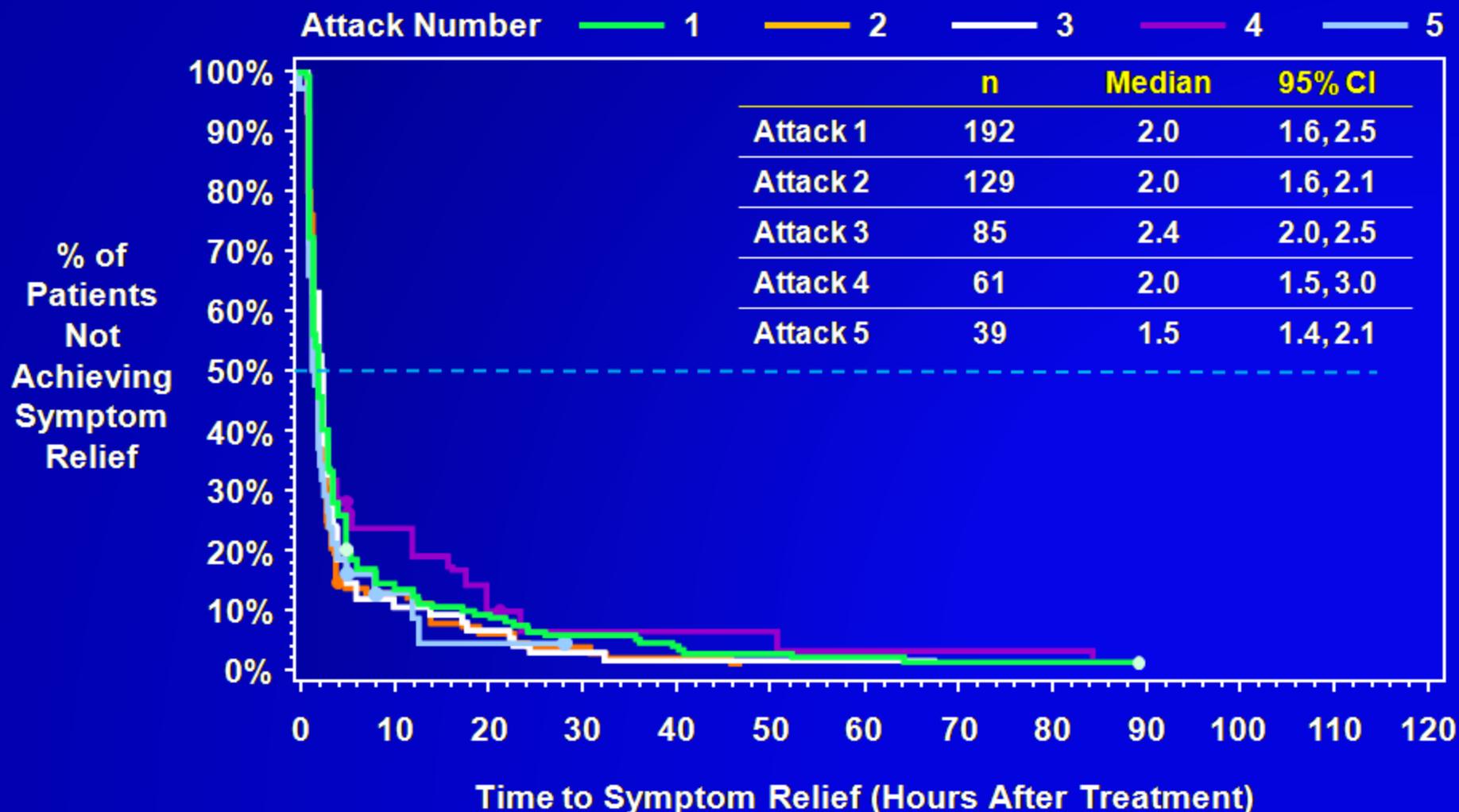
Placebo Group Attack Characteristic	FAST-1 N=29		FAST-3 N=45	
	n	%	n	%
<b>Primary Attack</b>				
Cutaneous	13	45%	26	58%
Abdominal	16	55%	19	42%
<b>Severity</b>				
Moderate	12	41%	28	62%
Severe	17	59%	17	38%
Median hours from attack onset to dose	10.0		5.5	
Used rescue meds any time during attack	15	52%	18	40%

# Repeat Attack Efficacy

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Non-laryngeal attacks

# Time to Onset of Symptom Relief Composite VAS-3 Repeat Treatment Attacks 1-5



Attacks 2-5 are open label data

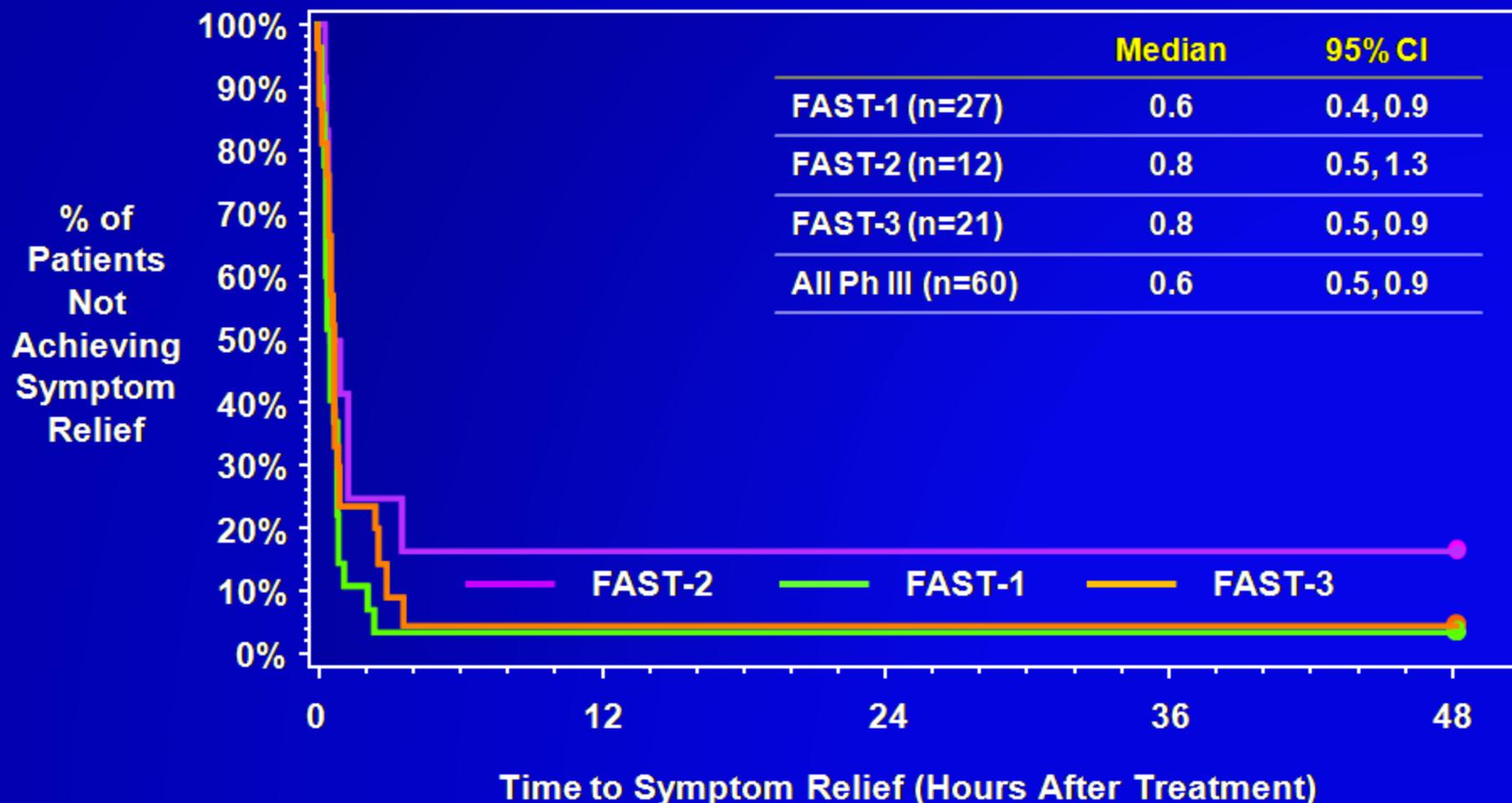
# Laryngeal Attack Efficacy

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# FAST-3: Icatibant Laryngeal Attack Efficacy Comparable to Abdominal or Cutaneous

Events including open label extension trial	Laryngeal Treated Icatibant (N=21 attacks)
Median time to onset of symptom relief as measured by VAS-5; hours (95% CI)	2.2 (1.5, 3.5)
Median time to onset of primary symptom relief; hours (95% CI)	2.2 (1.5, 3.5)
Median time to almost complete symptom relief; hours (95% CI)	6.2 (3.0, 24.3)

# Laryngeal Attacks Time to Onset of Initial Symptom Improvement

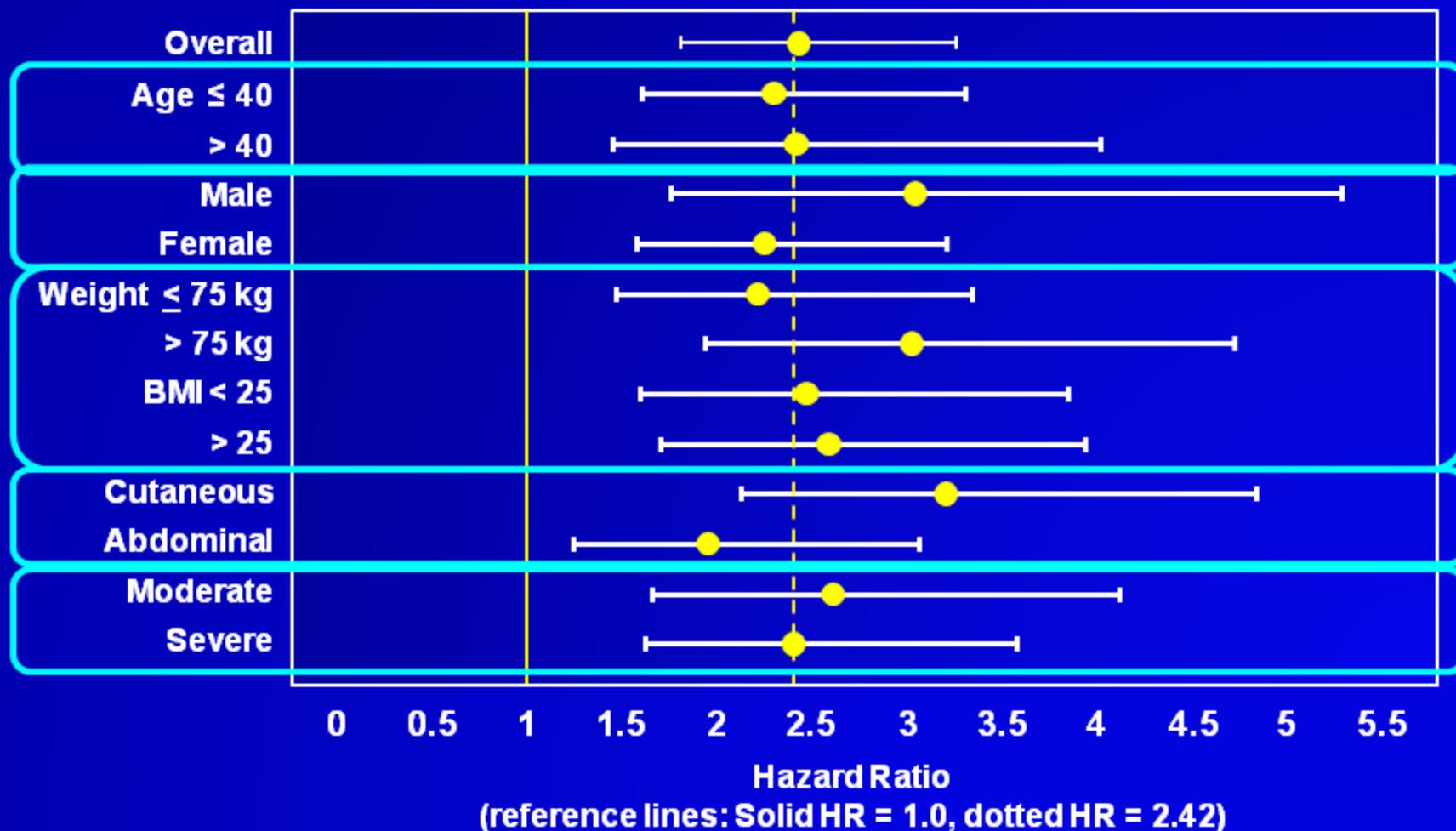


# Efficacy in Subgroups

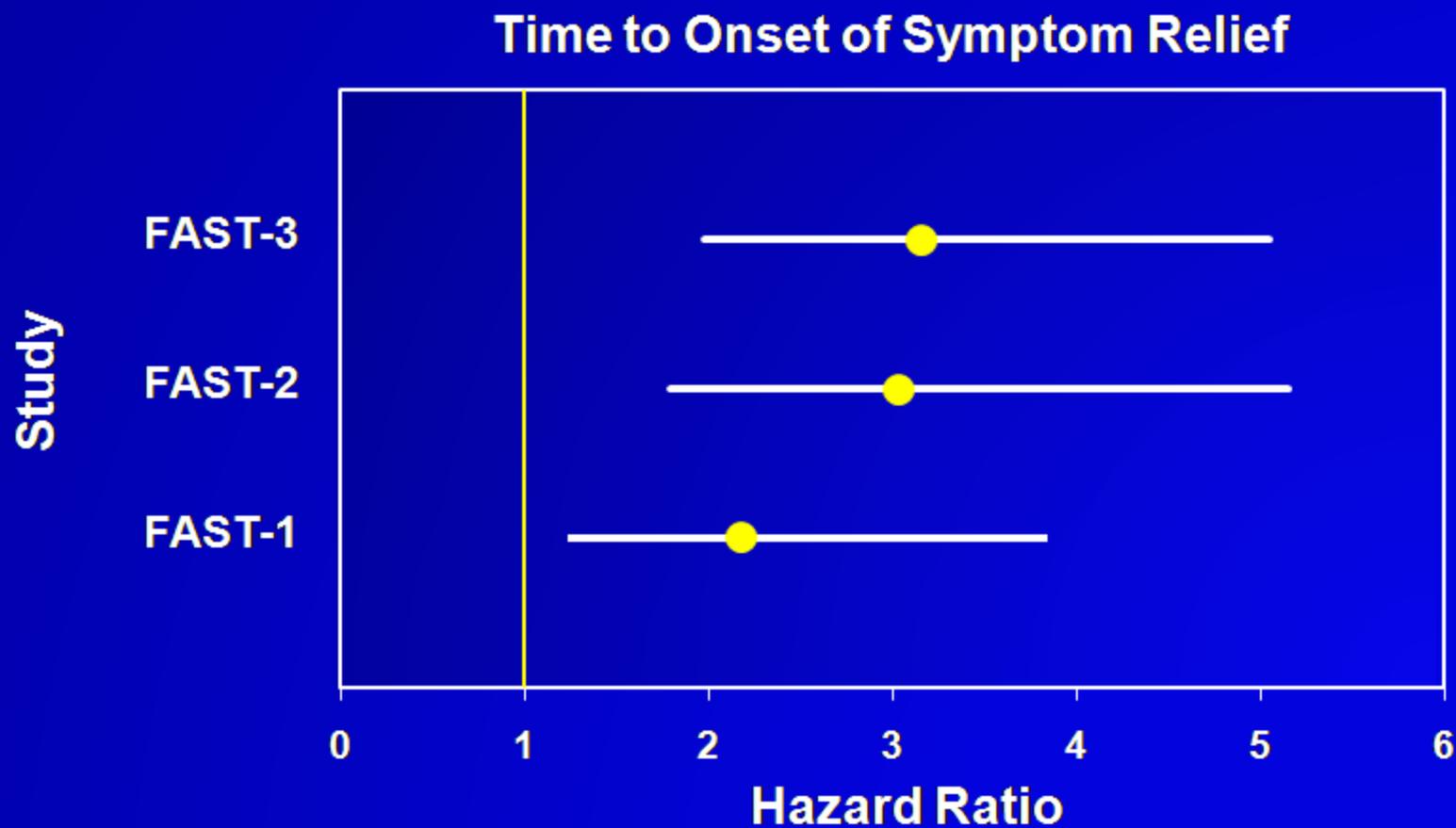
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# Hazard Ratios from Pooled Data Show that Icatibant has Consistent Response

Hazard ratios for time to onset of primary symptom relief  
Pooled data from FAST-1, FAST-2 and FAST-3



# Hazard Ratios for Time to Onset of Symptom Relief (VAS-3)



# Icatibant Produces a Rapid & Durable Response for Acute HAE Attacks

- Consistent results from 3 Phase III trials
  - Cutaneous, abdominal, and laryngeal attacks
  - Multiple endpoints and analyses
  - Multiple attacks
- A single Icatibant 30 mg SC injection is generally sufficient for relief of HAE symptoms

# Icatibant Safety

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# Icatibant Phase III Program Defines Use for Acute Attacks of HAE

**FAST-3**

Icatibant  
30 mg SC  
vs.  
Placebo

**FAST-1**

Icatibant  
30 mg SC  
vs.  
Placebo

**FAST-2**

Icatibant  
30 mg SC  
vs.  
Tranexamic  
Acid

**EASSI**

Icatibant  
30 mg SC  
Open Label  
Self  
Administered

Open Label Extension Trials for Repeat  
Attacks with icatibant 30 mg SC

# Exposure to SC Icatibant in Clinical Studies

Study	Number of HAE patients Exposed to SC Icatibant		Number of HAE Attacks Treated with SC Icatibant	
	HCP	Self	HCP	Self
	30 mg	30 mg	30 mg	30 mg
Phase II	4	-	4	-
JE049-2101	4	-	4	-
Phase III	225	-	987	-
FAST-2	68	-	413	-
FAST-1	81	-	376	-
FAST-3	76	-	198	-
EASSI	8	56*	8	56*
<b>Total</b>	<b>236</b>	<b>56*</b>	<b>999</b>	<b>56*</b>

\* Subset of HCP (all previously administered by HCP)

# Demographics & Baseline Characteristics (Ph III Controlled Population)

	Icatibant 30 mg (N=113)	Placebo (N=75)	Tranexamic Acid (N=38)
<b>Age (years)</b>			
Mean	37.6	35.9	41.9
<b>Sex</b>			
Male	42 (37%)	24 (32%)	15 (40%)
Female	71 (63%)	51 (68%)	23 (61%)
<b>Race n(%)</b>			
White	105 (93%)	66 (88%)	38 (100%)
Non-White	8 (7%)	9 (12%)	0
<b>Weight (kg)</b>			
mean	81	79	74

# Erythema and Swelling Were the Predominant Injections Site Reactions

<b>Injection Site Reaction n (%)</b>	<b>Icatibant 30 mg (N=113)</b>	<b>Placebo (N=75)</b>	<b>Tranexamic Acid (N=38)</b>
<b>Any reaction</b>	<b>110 (97%)</b>	<b>25 (33%)</b>	<b>10 (26%)</b>
<b>Erythema</b>	<b>108 (96%)</b>	<b>15 (20%)</b>	<b>4 (11%)</b>
<b>Swelling</b>	<b>93 (82%)</b>	<b>12 (16%)</b>	<b>6 (16%)</b>
<b>Burning</b>	<b>41 (36%)</b>	<b>3 (4%)</b>	<b>2 (5%)</b>
<b>Itching</b>	<b>35 (31%)</b>	<b>-</b>	<b>-</b>
<b>Warm Sensation</b>	<b>60 (53%)</b>	<b>2 (3%)</b>	<b>1 (3%)</b>
<b>Cutaneous (Skin) Pain</b>	<b>29 (26%)</b>	<b>3 (4%)</b>	<b>-</b>

# Injection Site Reactions are Common but Transient and Self-resolving



# Injection Site Reactions Did Not Lead to Withdrawal or SAEs

Injection Site Reaction n (%)	Icatibant 30 mg (N=113)	Placebo (N=75)	Tranexamic Acid (N=38)
Any severe reactions	30 (26.5%)	2 (2.7%)	-
Erythema	28 (24.8%)	-	-
Swelling	7 (6.2%)	-	-
Burning	5 (4.4%)	1 (1.3%)	-
Itching	3 (2.7%)	-	-
Warm Sensation	-	1 (1.3%)	-
Cutaneous (Skin) Pain	2 (1.8%)	1 (1.3%)	-
Withdrawals	0	0	0
Any SAEs	0	0	0

# Summary of Adverse Events During the 14-Day Observation Period

Parameter n (%)	Icatibant 30 mg (N=113)	Placebo (N=75)	Tranexamic Acid (N=38)
Any AE	48 (42.5%)	41 (54.7%)	13 (34.2%)
Any serious AE	1 (0.9%)	3 (4.0%)	1 (2.6%)
Any severe AE	7 (6.2%)	14 (18.7%)	4 (10.5%)
Deaths due to AE	0	1 (1.3%)	0
Hospitalizations due to AE	0	2 (2.7%)	0
Study discontinuation due to AE	0	1 (1.3%)	1 (2.6%)

# Most Common Adverse Events are Related to the Underlying HAE

	Icatibant 30 mg (N=113)		Placebo (N=75)		Tranexamic Acid (N=38)	
	Patients	%	Patients	%	Patients	%
Any AE	48	42.5%	41	54.7%	13	34.2%
HAE	18	15.9%	15	20.0%	6	15.8%
Headache	4	3.5%	4	5.3%	2	5.3%
Pyrexia	4	3.5%	-	-	-	-
Sinusitis	3	2.7%	1	1.3%	-	-
Abdominal pain	3	2.7%	-	-	-	-
Nausea	2	1.8%	3	4.0%	-	-
Nasopharyngitis	2	1.8%	-	-	1	2.6%
Pharyngitis	1	0.9%	2	2.7%	-	-
Pruritus	-	-	3	4.0%	-	-

*Excludes injection site reactions*

Phase III Safety Population

# Observation Period Severe Adverse Events (Phase III Safety Population)

	Icatibant (N=113)		Placebo (N=75)		Tranexamic Acid (N=38)	
	n	%	n	%	n	%
<b>Any Severe Adverse Event</b>	<b>7</b>	<b>6.2%</b>	<b>14</b>	<b>18.7%</b>	<b>4</b>	<b>10.5%</b>
<b>HAE</b>	<b>5</b>	<b>4.4%</b>	<b>11</b>	<b>14.7%</b>	<b>3</b>	<b>7.9%</b>
Dyspepsia	1	0.9%	-	-	-	-
Headache	1	0.9%	-	-	-	-
Pain	-	-	-	-	1	2.6%
Pregnancy	-	-	-	-	1	2.6%
Aphonia	-	-	1	1.3%	-	-
Migraine	-	-	1	1.3%	-	-
Myocardial infarction	-	-	1	1.3%	-	-

## Few Serious Adverse Events were Noted in the 14 Days Post Dosing

- 1 patient in the icatibant group (cystitis)
- 1 patient in the tranexamic group (pregnancy)
- 3 patients in the placebo group
  - Myocardial infarction
  - Worsening or recurrence of HAE
  - Gastroenteritis
- No SAE was considered treatment-related

# Repeat Attack Safety

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# Safety Profile of Icatibant is Maintained with Repeat Use

## Icatibant 30 mg Treated Attack

	Attack 1 (N=225)		Attack 2 (N=146)		Attack 3 (N=96)		Attack 4 (N=67)		Attack 5 (N=48)	
	n	%	n	%	n	%	n	%	n	%
	<b>Any AE</b>	95	42.2%	56	38.4%	34	35.4%	20	29.9%	12
<b>Any serious AE</b>	2	0.9%	3	2.1%	3	3.1%	2	3.0%	1	2.1%
<b>Any severe AE</b>	14	6.2%	9	6.2%	7	7.3%	1	1.5%	2	4.2%
<b>Hospitalizations due to AE</b>	-	-	-	-	1	1.0%	1	1.5%	-	-
<b>Study discontinuation due to AE</b>	-	-	-	-	-	-	-	-	-	-

Excludes Injection Site Reactions

Phase III Treated Population

# Icatibant Appears to Have Low Immunogenicity Potential

- 3 patients tested positive for anti-icatibant antibodies
  - 1 patient (FAST-1) tested positive at pre-treatment and after initial icatibant treatment
  - 2 patients (FAST-2) tested positive after repeated icatibant treatment, but results were transient
- All 3 patients maintained efficacy over the treatment period
- No patients in FAST-3 tested positive for anti-icatibant antibodies

# Icatibant Self-administration Safety Assessment

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EASSI Study

# EASSI was Designed to Study Self-Administration of Icatibant

- Self-administration for a single acute HAE attack
- Previous icatibant patients were trained to self-administer (n=48)
- Icatibant-naïve patients (n=8)
  - First dose given at study site by HCP
  - Trained to self-administer, and self-treated for subsequent attack
- A second dose could be administered at study site if required

# The Safety Profile of Self-administered Icatibant is Similar to the Phase III Trials

Self-administration Preferred Term ( <i>excl. injection site reaction</i> )	Total (N=56)	
	n	%
Any AE	18	32.1%
HAE	13	23.2%
Abdominal pain	2	3.6%
Headache	2	3.6%
GI pain	1	1.8%
Dizziness	1	1.8%
Migraine	1	1.8%
Rhinitis	1	1.8%
Back pain	1	1.8%
Skin swelling	1	1.8%

No reported SAEs or hypersensitivity

Self-administered Population

# Patient Questionnaire Supports Patient Desire for Self-administration

- HAE patients are very familiar with presentation of HAE attacks
- Questionnaire from 56 icatibant self-administration patients
- 100% of patients said it was easy or very easy to prepare the injection site before injection
- 98% of patients said it was easy or very easy to assemble and handle the syringe
- 95% of patients said that self-administration was preferable or very preferable to clinic administration

# Icatibant Demonstrates a Consistent Safety Profile During Ph III and Self-administration

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- Self-limiting, localized injection site reactions occurred in most patients treated with icatibant
- No AEs led to discontinuation or hospitalization
- Non-immunogenic
  - No hypersensitivity or anaphylactic reactions were reported
- Repeated treatment safety profile consistent with controlled Phase III studies

# Icatibant Clinical Data - Relevance

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**Marc Riedl , MD, MS**

Assistant Professor of Medicine

Section Head, Clinical Immunology & Allergy

David Geffen School of Medicine, UCLA

# HAE Guidelines Supports Access to On-Demand Self-Administration

- Self-administration can facilitate early intervention
- Literature supports self-administration
  - Reduces attack severity and duration
  - Improves HAE-related QOL; time at work & school
- Endorsed by guidelines from UK, Denmark, Canada and International
  - Every patient should be considered for self-administration
  - Benefit-risk for every patient should be weighed

1 Levi et al. J Allerg Clin Immunol 2006;      2 Bowen T et al. Allergy, Asthma & Clin Immunol 2010

3 Longhurst HJ et al. Allergy, Asthma & Clin Immunol 2010

# HAE Prophylaxis Treatment Paradigm

- HAE therapy focused on prophylaxis and acute treatment
- Long-term prophylaxis can reduce HAE attack frequency and severity
  - 40-50% of US HAE patients receive prophylaxis
- Prophylaxis candidates include<sup>1,2</sup>
  - Frequent HAE attacks (>1 / month)
  - Frequent debilitating attacks that interfere with daily activities, work or school
  - Inability to maintain acceptable quality of life

<sup>1</sup> Zuraw BJ. N Engl J Med. 2008;359:1027-1036

<sup>2</sup> Zuraw BJ. Allergy, Asthma & Clin Immunol 2010, 6:23

# Treatments are Available for HAE Prophylaxis

- Available prophylactic treatments
  - Attenuated androgens
  - Anti-fibrinolytics
  - Fresh-frozen plasma (IV) – pre-medical/dental procedure only
  - Human plasma-derived C1-INH Cinryze (IV)

<sup>1</sup> Zuraw BJ. N Engl J Med. 2008;359:1027-1036

<sup>2</sup> Zuraw BJ. Allergy, Asthma & Clin Immunol 2010, 6:23

# Limitations With HAE Prophylaxis

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- Currently available prophylaxis agents
  - Androgens
  - Nano-filtered plasma-derived C1-INH
- Long-term prophylaxis effective for many patients
- Concern for long-term side effects
- Incomplete prevention of HAE attacks
  - Need for on-demand therapy

# Current Therapies for Acute HAE Attacks

- Fresh-Frozen Plasma (IV)
  - Risks for anaphylaxis, exacerbation, viral transmission
- Human plasma-derived C1-INH – Berinert<sup>®</sup> (IV)
  - Facial & abdominal attacks in adolescents & adults
  - Infusion by healthcare provider
  - Risks for vascular events or viral & prion transmission
- Kallikrein inhibitor - Kalbitor<sup>®</sup> (SC)
  - All attacks in age 16 years and older
  - Injection by professional in healthcare setting
  - Risks for hypersensitivity reactions - anaphylaxis

# All HAE Patients Need Rapid Access to Acute Treatments

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- Effective acute treatments are available
- Current products have barriers for gaining rapid access to treatment
  - Trips to physician or hospital for administration
  - Need for IV administration

# HAE Patients Have an Understanding of Attack Symptoms

- HAE patients are diagnosed based upon repeat attacks and family history
- Patients recognize the symptoms that signal onset of an HAE attack
  - Distinct repeatable symptoms
- Patients can correctly self-administer
  - Levi, et.al. (2006), EASSI, Zuraw, et.al. (2011)

# The Goal of Acute Treatment is to Accelerate the Initiation of Intervention

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- Early HAE attack intervention can reduce hospitalizations and duration of attack
- Early interventions help patients become self-sufficient
- Acute therapies need to reduce access barriers
  - Remove need to travel for care
  - Ensure ready availability of medication
  - Eliminate admission and diagnostic delays
  - HAE clinical trials under-represent access barriers

## Icatibant – Impact on Unmet Need

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- Icatibant Phase III data support HAE efficacy
- Icatibant appears to be well tolerated
- SC injection facilitate self-administration
  - Supported by proper patient management

# Self-administration Should Include Physician-Patient Discussion

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- Available treatment options for acute attacks
- Recognizing when to use icatibant
- Recognizing potential side-effects of icatibant
- Appropriate action if icatibant not effective
- Proper storage, preparation and administration
- Plan for recording attacks and injections
- Periodic physician follow up and review

## HAE and Icatibant - Summary

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- HAE is a life-altering and life-threatening chronic condition
  - Adversely affects physical, psychological, social health
- Prophylactic and acute treatments are suboptimal
- Need for early intervention and self-administration
- Icatibant capable of addressing unmet medical needs

## Conclusions

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**Sue Cammarata, MD**

Vice President, Clinical Research

Shire Human Genetic Therapies (HGT)

# Icatibant 30 mg SC Benefit-Risk Assessment

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- FAST-3 demonstrates HAE benefit
  - FAST-1 and FAST-2 support benefit
  - Time to symptom relief (VAS-3)
  - Time to almost complete symptom relief
- Phase III studies support a consistent safety profile
  - Injection site reactions in most patients
  - No hypersensitivity
- Shire post-approval activities will support self-administration

# Patient Education and Targeted Surveillance

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- Patients actively participate in HAE treatment
- Patient instructions included with packaging
  - Support self-administration
  - Seek assistance following laryngeal attack treatment
- Available injection training
  - Disease-state and product training by partner(s)
- Training kit to be used during injection training
  - Artificial abdomen for injection practice
- Surveillance, including identified and potential AEs of interest

## Substantial Database for HAE Indication

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- 236 patients with HCP administration
- 56 patients who self-administered icatibant
- 1055 acute attacks of HAE
- 60 patients with laryngeal attacks
- 38 patients treated for more than 5 attacks
- Approximately 8000 post-marketing patient exposures from EU approval to January 2011

# **Firazyr<sup>®</sup> (icatibant) SC Injection for The Treatment of Acute Attacks of Hereditary Angioedema (HAE) in Adults**

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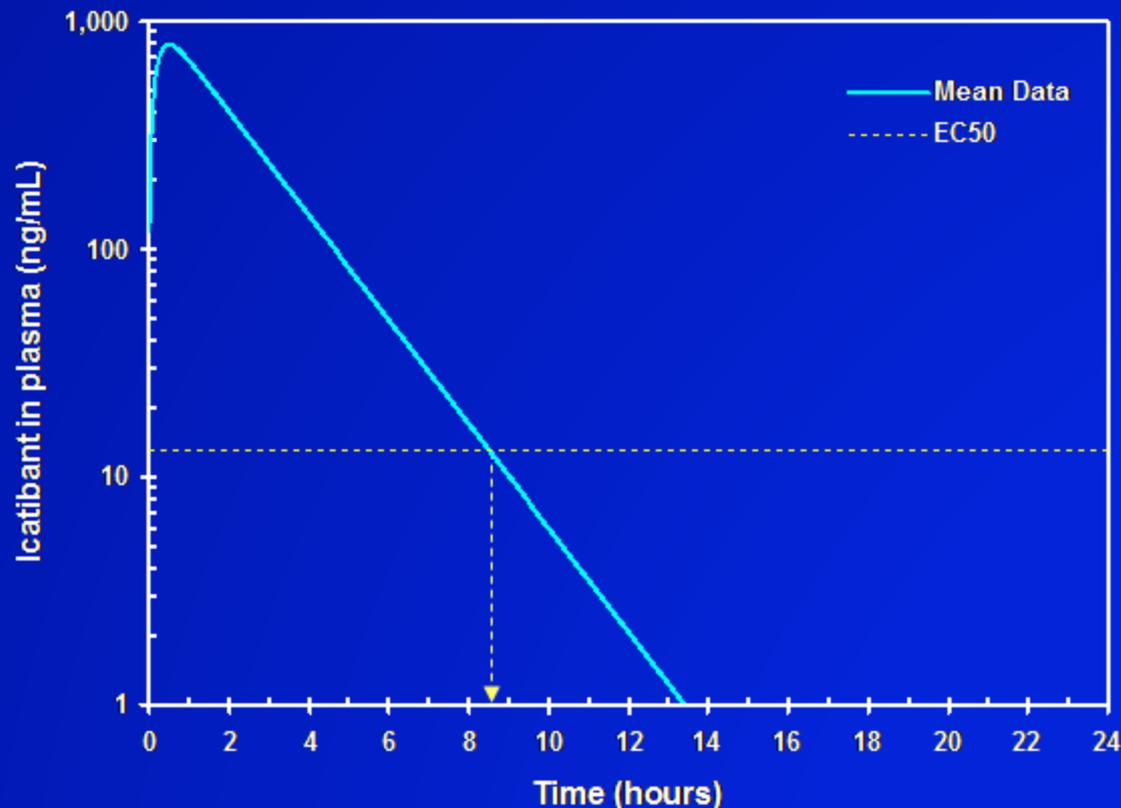
Pulmonary - Allergy  
Drugs Advisory Committee  
June 23, 2011

**Backup Slides Shown**

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# Plasma Concentration & Duration of Action in Healthy Volunteers after 30 mg SC Icatibant



- Duration of action → plasma concentration  $\geq$  EC50 ~ 6-8 hours
- $C_{max}$  at 30 mg SC is 50-100 fold greater than the EC50 for BK inhibition

# FAST-1 Ab+ Patient

Weeks from Screening	Status	Attack Type	TOSR-P (hrs)	TACSR (hrs)	TISI (hrs)
0	-				
4	-	Skin Swelling	2.6	5.1	0.6
6	+				
9	-				
19	-	Abdominal Pain	1.0	3.0	0.2
21	-				
31	-				

# First FAST-2 Ab+ Patient (abbreviated)

Weeks from Screening	Status	Attack Type	TOSR-P (hrs)	TACSR (hrs)	TISI (hrs)
0	-				
4, 5, 9	-	Skin Swelling	17, 1, 3	64, 5, 6	0.3, 0.5, 0.5
11	+				
17	+	Skin Pain	1.5	12	0.5
31	+				
36	-	Skin Pain	1	3	0.4
45, 46, 70	-	Skin Swelling	2, 1, 2	20, 2, 6	1.2, 0.3, 0.4
47, 64, 67	-	Skin Pain	3., 1.5, 1	6, 3, 3	0.5, 0.5, 0.5
75, 83	-	Skin Pain	1, 1	2, 4	0.8, 0.5
100, 112	-	Skin Pain	1, 1.7	10, 4.2	0.8, 0.9
120, 127	-	Skin Swelling	2, 14.2	3.5, 29.2	0.8, 144.7

## Second FAST-2 Ab+ Patient

Weeks from Screening	Status	Attack Type	TOSR-P (hrs)	TACSR (hrs)	TISI (hrs)
0	-				
17	-	Abdominal Pain	1.0	1.0	0.8
19	-				
22	-	Skin Swelling	3.0	23.5	1.5
24	-				
44	<b>+</b>				
70	-				
82	-	Abdominal Pain	0.9	0.9	0.3
85	<b>+</b>				
96	-	Abdominal Pain	0.8	13.8	0.7
98	-				

# Self-administered Icatibant had Shorter Overall Attack Duration

Time Interval	Median Time (Hours)	
	Pooled Phase III Icatibant (N = 104)	EASSI (N = 56)
<b>Attack Onset to Treatment</b>	<b>7.6</b>	<b>4.5</b>
Treatment to Onset of Symptom Relief	2.0	2.6
Treatment to Onset of Primary Symptom Relief	2.0	2.0
Treatment to Almost Complete Symptom Relief	9.3	8.0
<b>Attack Onset to Almost Complete Symptom Relief</b>	<b>18.7</b>	<b>14.0</b>

# Patients Self-Administered Icatibant Sooner

## Hours from Attack Onset to Icatibant Treatment

<b>Study</b>	<b>N</b>	<b>Mean</b>	<b>SD</b>	<b>Median</b>	<b>Range</b>
<b>Fast-1</b>	<b>24</b>	<b>12.0</b>	<b>11.1</b>	<b>7.6</b>	<b>3.7 – 53.4</b>
<b>Fast-2</b>	<b>35</b>	<b>10.2</b>	<b>6.1</b>	<b>10.5</b>	<b>3.4 – 27.1</b>
<b>Fast-3</b>	<b>43</b>	<b>7.1</b>	<b>3.2</b>	<b>6.5</b>	<b>2.2 – 12.4</b>
<b>Pooled</b>	<b>102</b>	<b>9.3</b>	<b>7.0</b>	<b>7.6</b>	<b>2.2 – 53.4</b>
<b>EASSI</b>	<b>56</b>	<b>6.7</b>	<b>8.3</b>	<b>4.5</b>	<b>0 – 47.0</b>

# Packaging

- Primary Packaging:
  - One pre-filled syringe
  - No measuring/ calculations for dosing
  - Single injection per dose



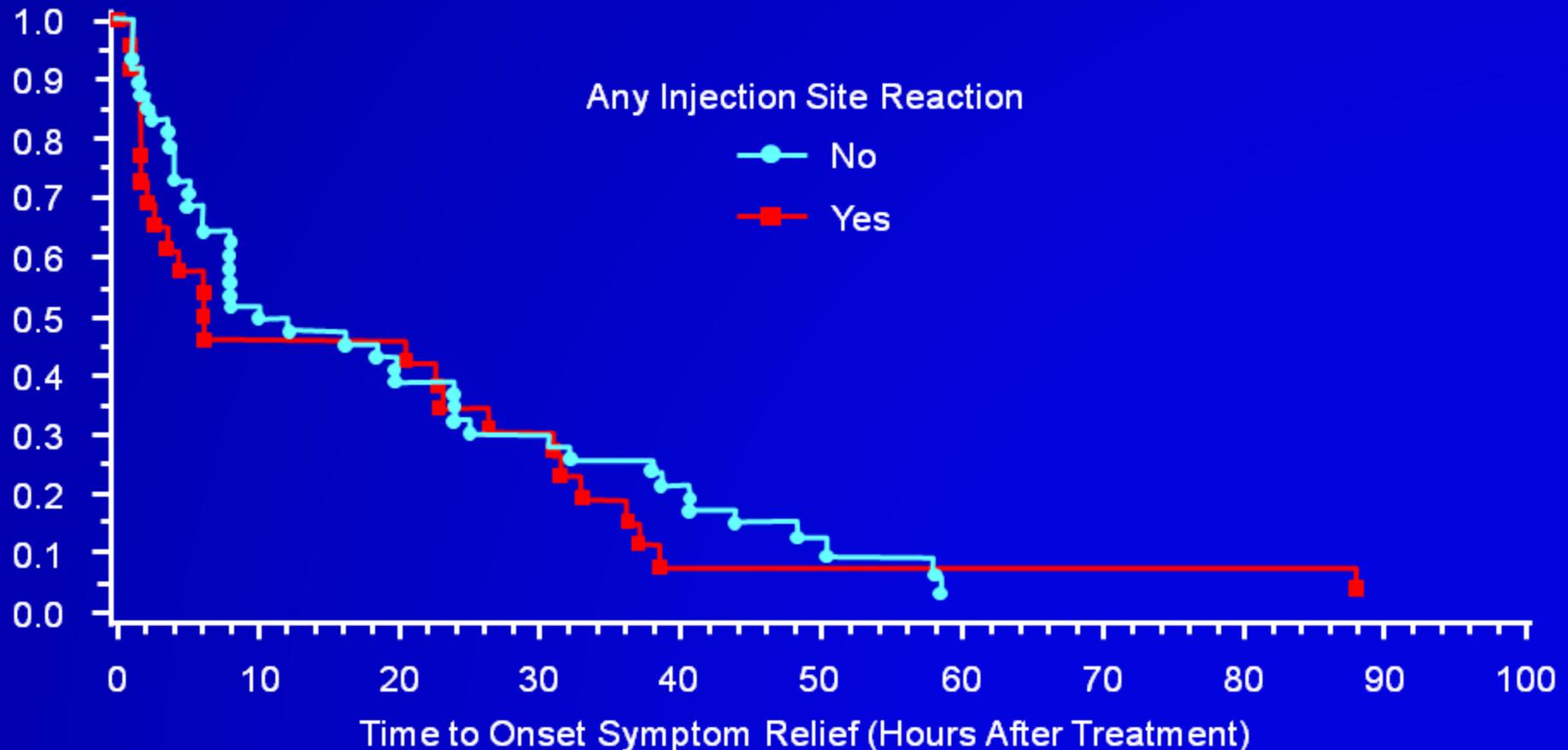
# Packaging

- Secondary Packaging
  - Industry standard materials
  - Zipper opening
  - Offered in single (1) and multi (3) packs



# Time to Symptom Relief in Placebo Group by ISR Status

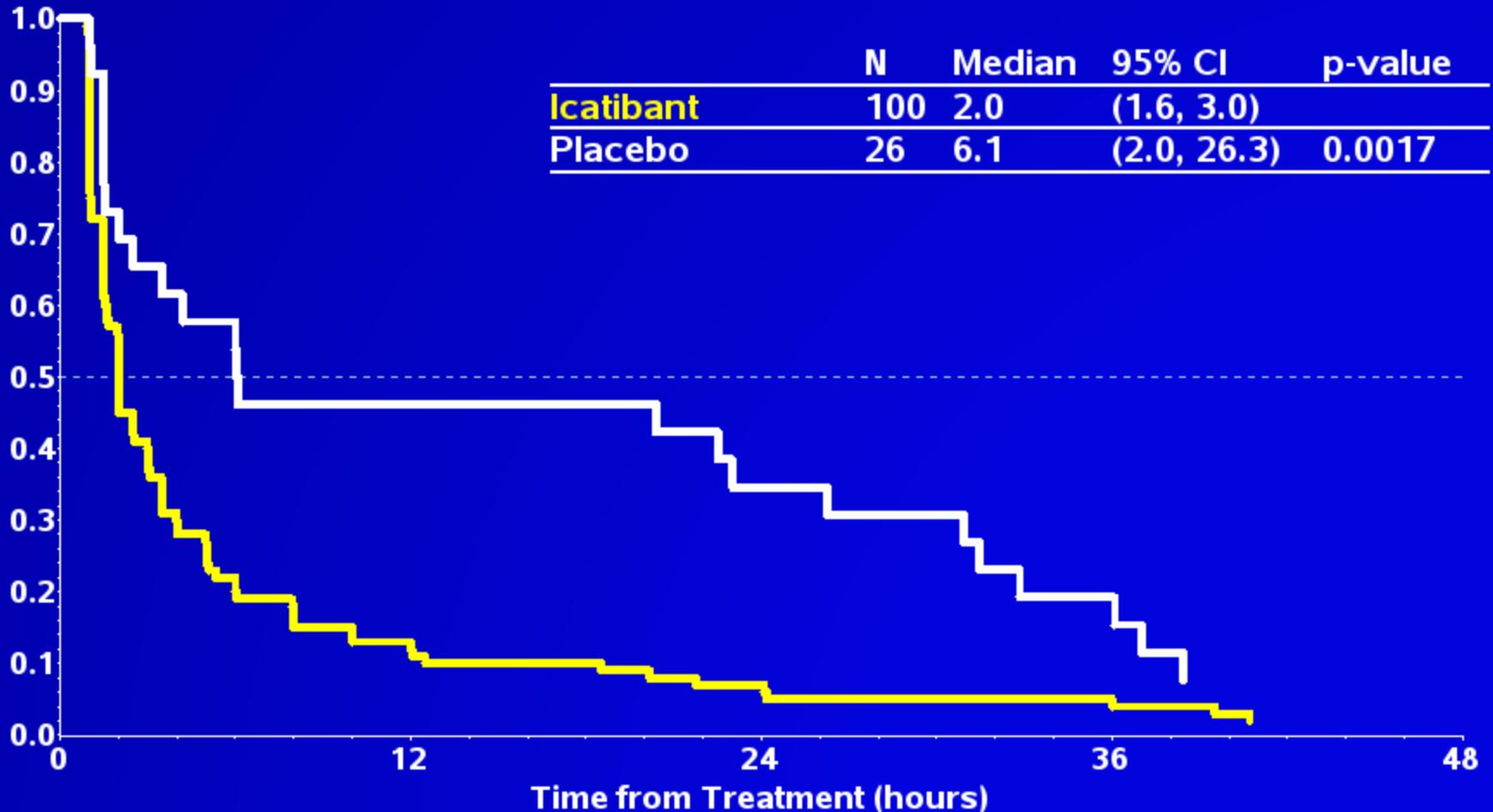
% of Subjects Not Achieving Symptom Relief



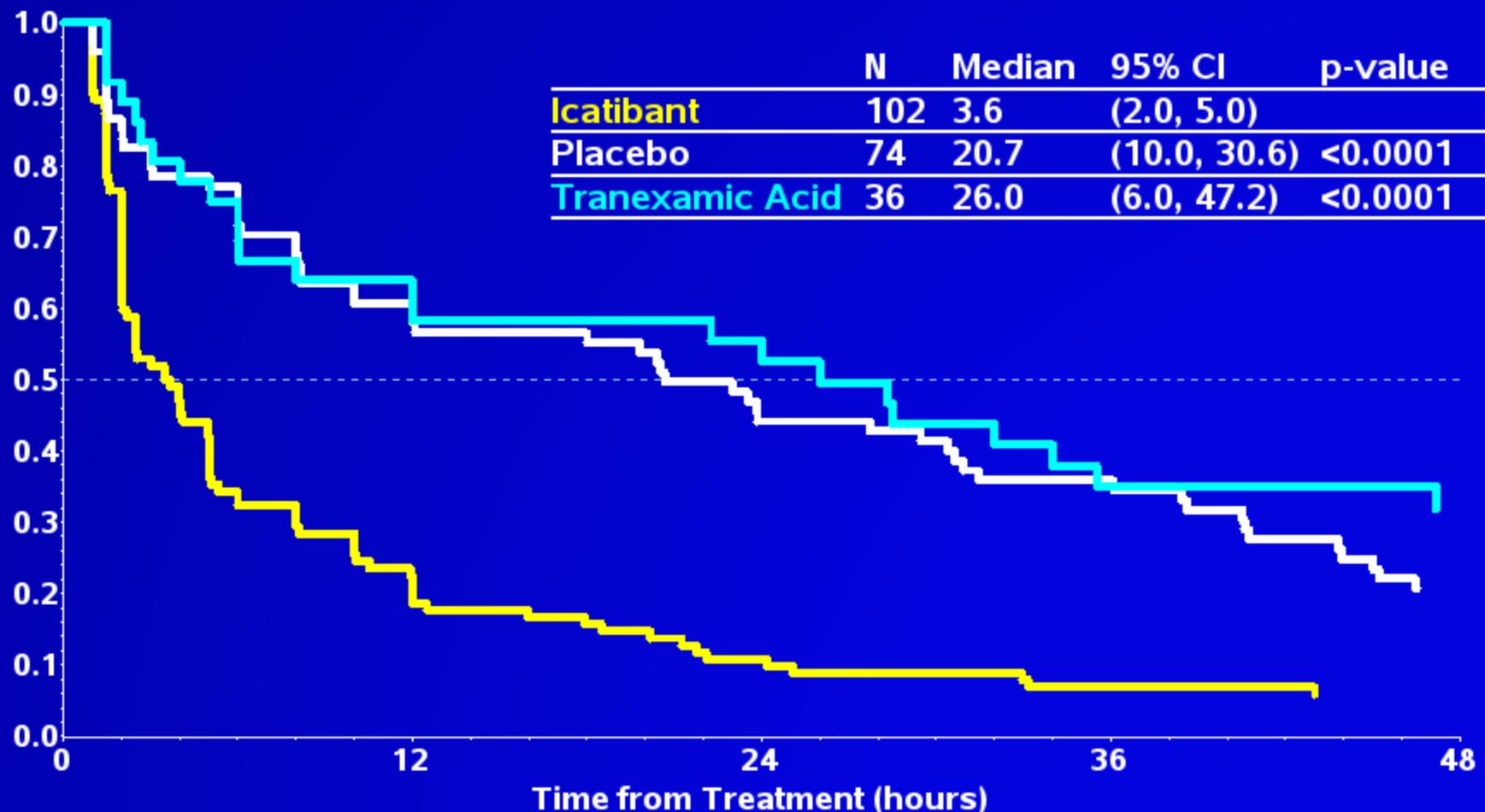
Note: Symptom relief is defined as a 50% reduction from pretreatment in the 3-symptom composite VAS score. Subjects who did not achieve symptom relief within the observation period were censored at the last observation time.

# TOSR in those with ISRs

## Non-Laryngeal ITT Population



# TOSR-70 - Pooled Non-Laryngeal ITT Population



# Rescue Medications Used for Worsening or Recurrence of HAE - Phase III Safety Population

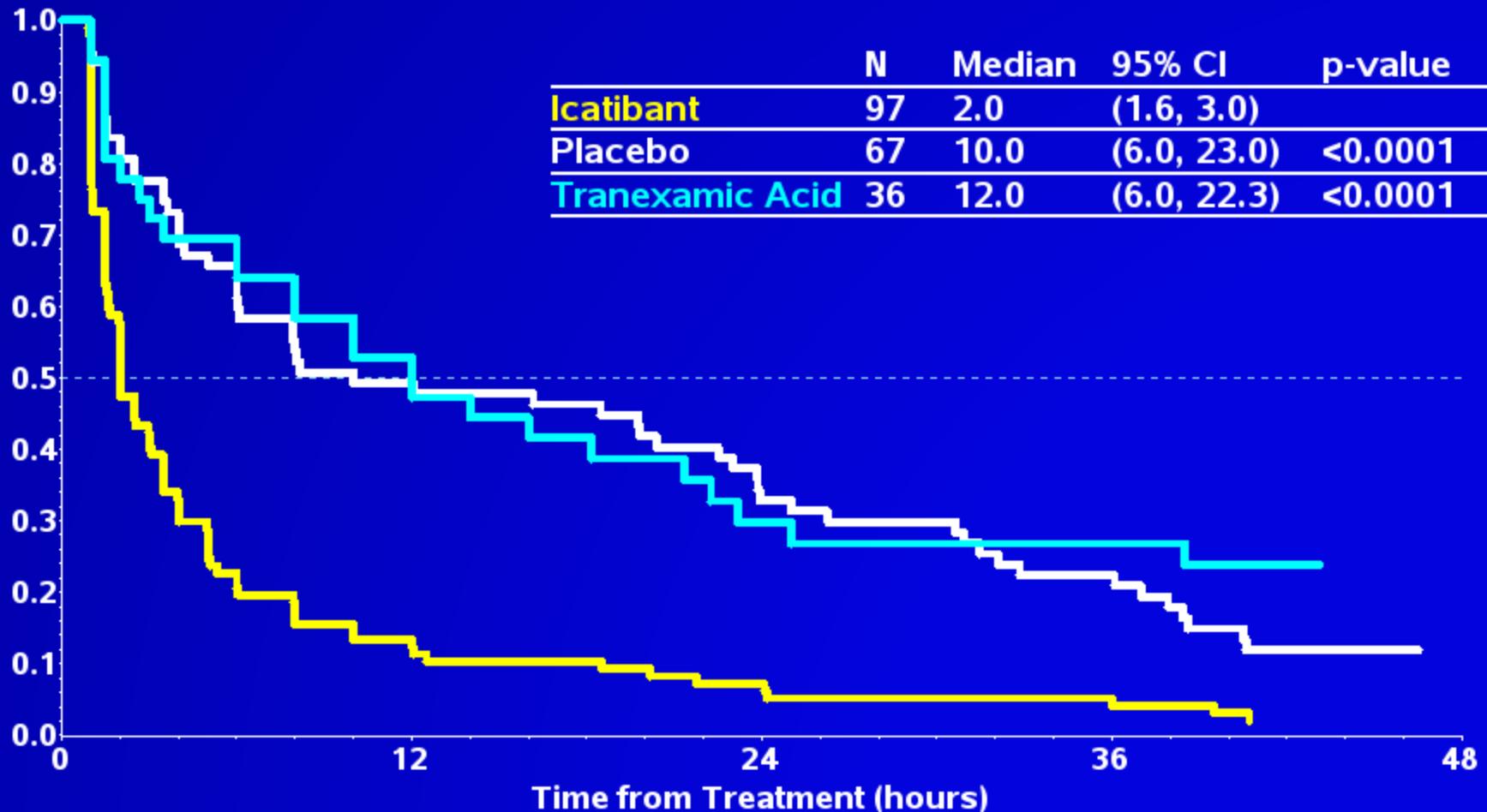
Preferred Term	Subjects who Had Worsening or Recurrence of HAE		
	Icatibant	Tranexamic Acid	Placebo
	N=18 n (%)	N=6 n (%)	N=15 n (%)
No Rescue Medication Use	8 (44.4)	0	4 (26.7)
Any Rescue Medication Use	10 (55.5)	6 (100.0)	11 (73.3)
Danazol	0	1 (16.7)	1 (6.7)
Diphenhydramine	0	0	2 (13.3)
Hydromorphone hydrochloride	2 (11.1)	0	0
Investigational drug	0	0	3 (20.0)
Methylprednisolone	0	0	1 (6.7)
Metoclopramide	0	0	1 (6.7)
Morphine	0	0	2 (13.3)
Nalbuphine	1 (5.6)	0	1 (6.7)

# Pregnancies in Patients Exposed to Icatibant

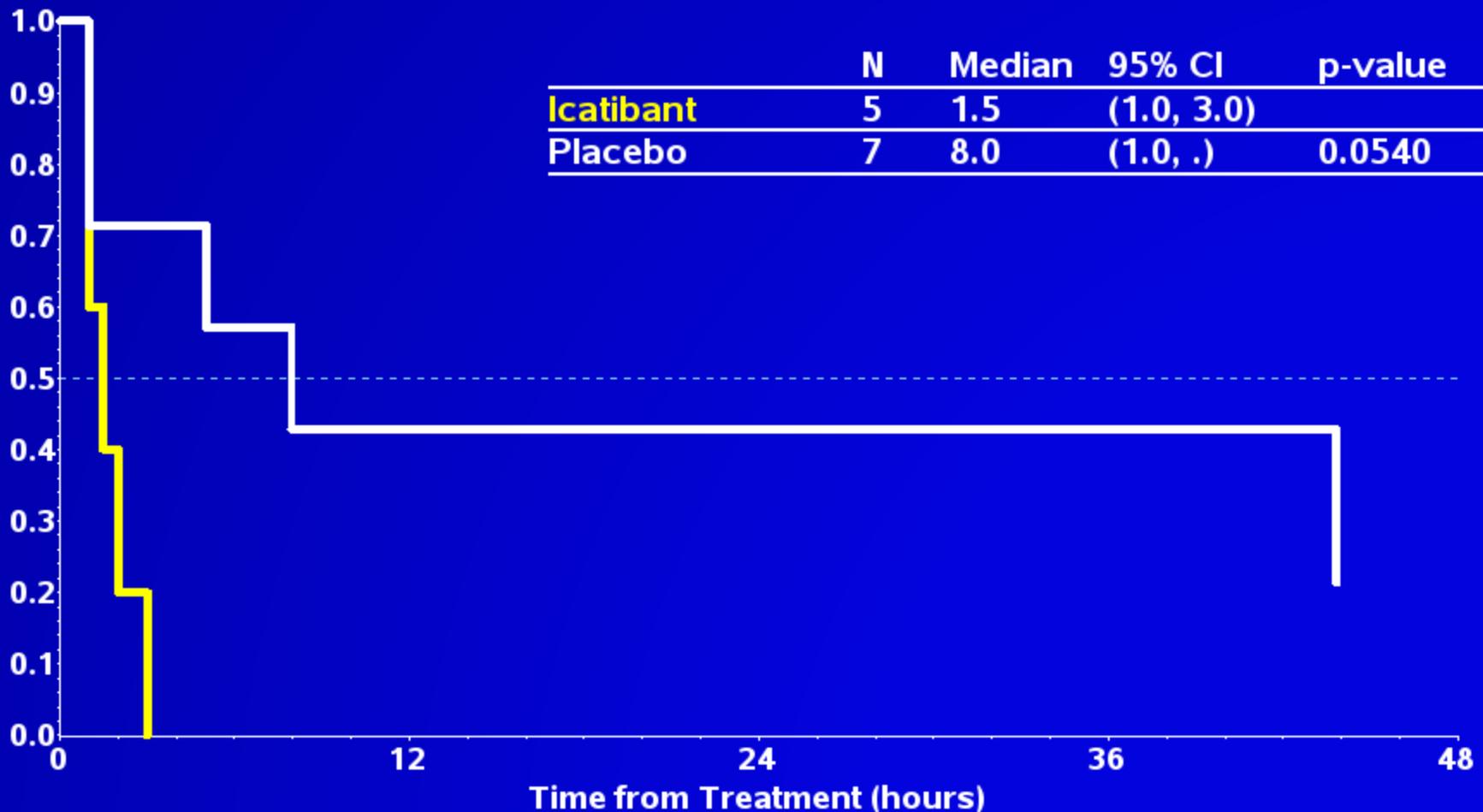
- 7 pregnancies in patients exposed to icatibant (5 Clinical Trials + 2 Post-marketing)
  - Healthy newborn (4 cases)
  - Newborn, awaiting health status (1 case)
  - Elective termination (1 case)
  - Unknown outcome, awaiting follow-up (1 case)

# TOSR by Race: White

## Pooled Non-Laryngeal ITT Population

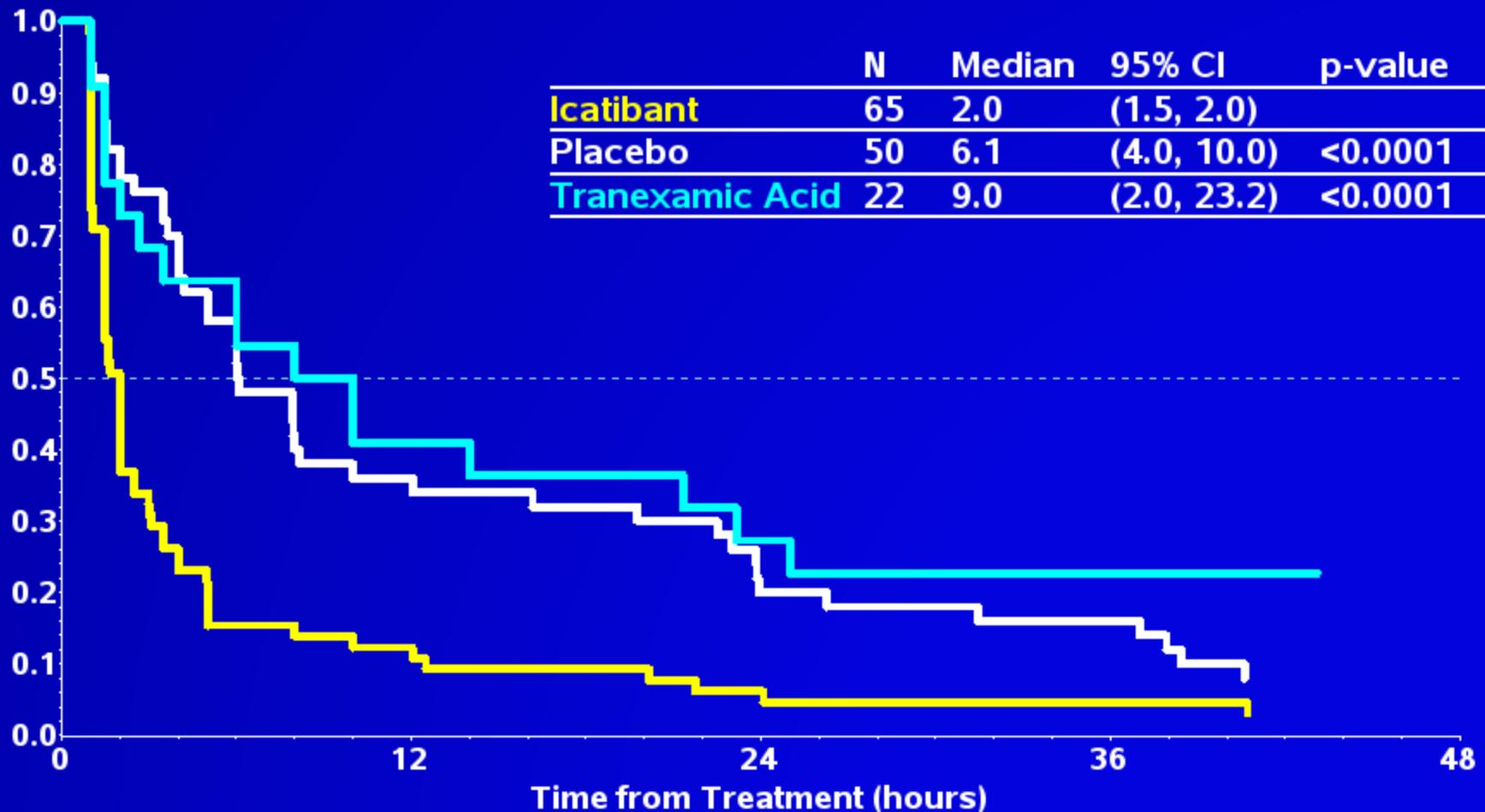


# TOSR by Race: Non-White Pooled Non-Laryngeal ITT Population



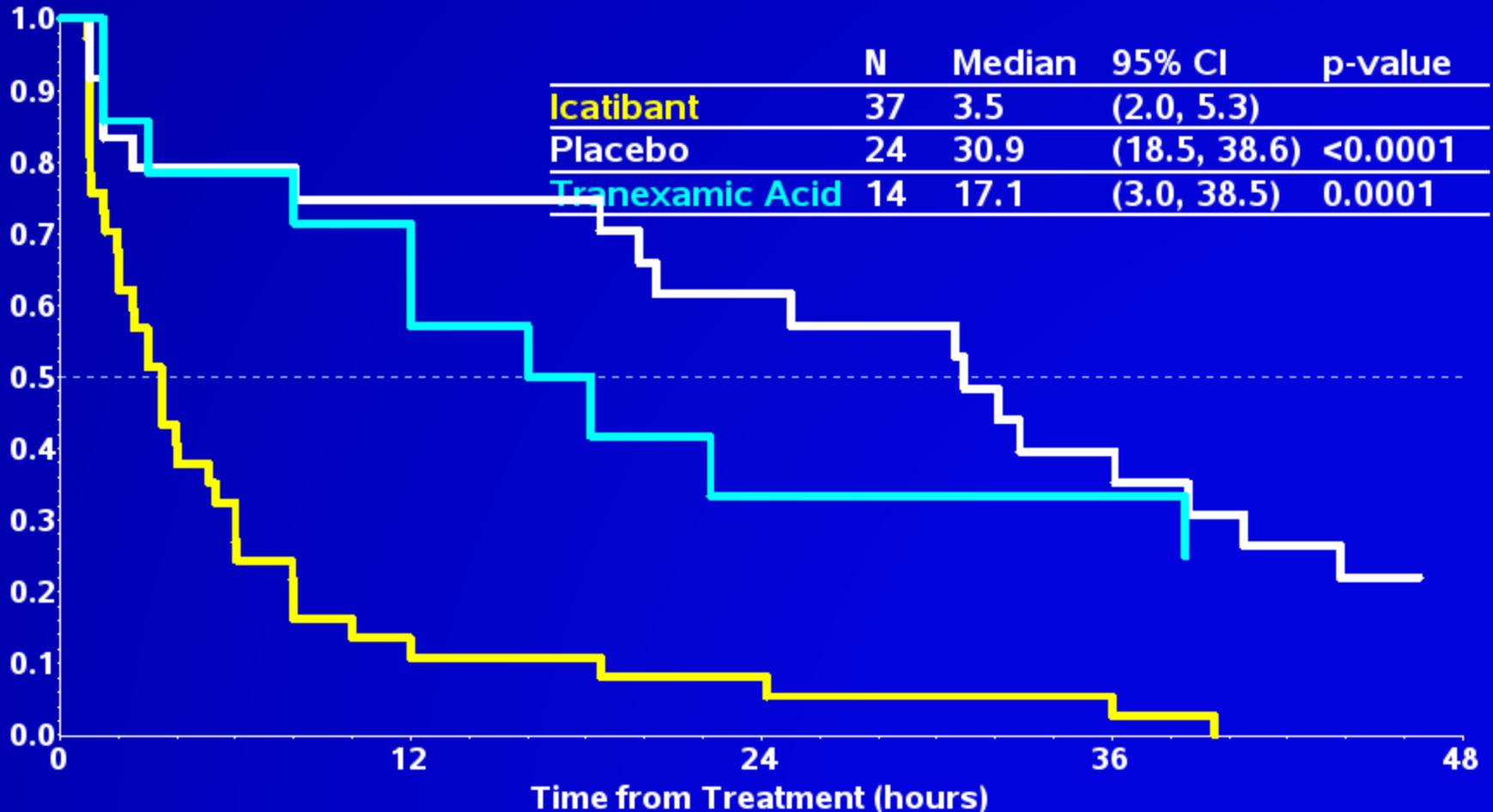
# TOSR by Sex: Females

## Pooled Non-Laryngeal ITT Population



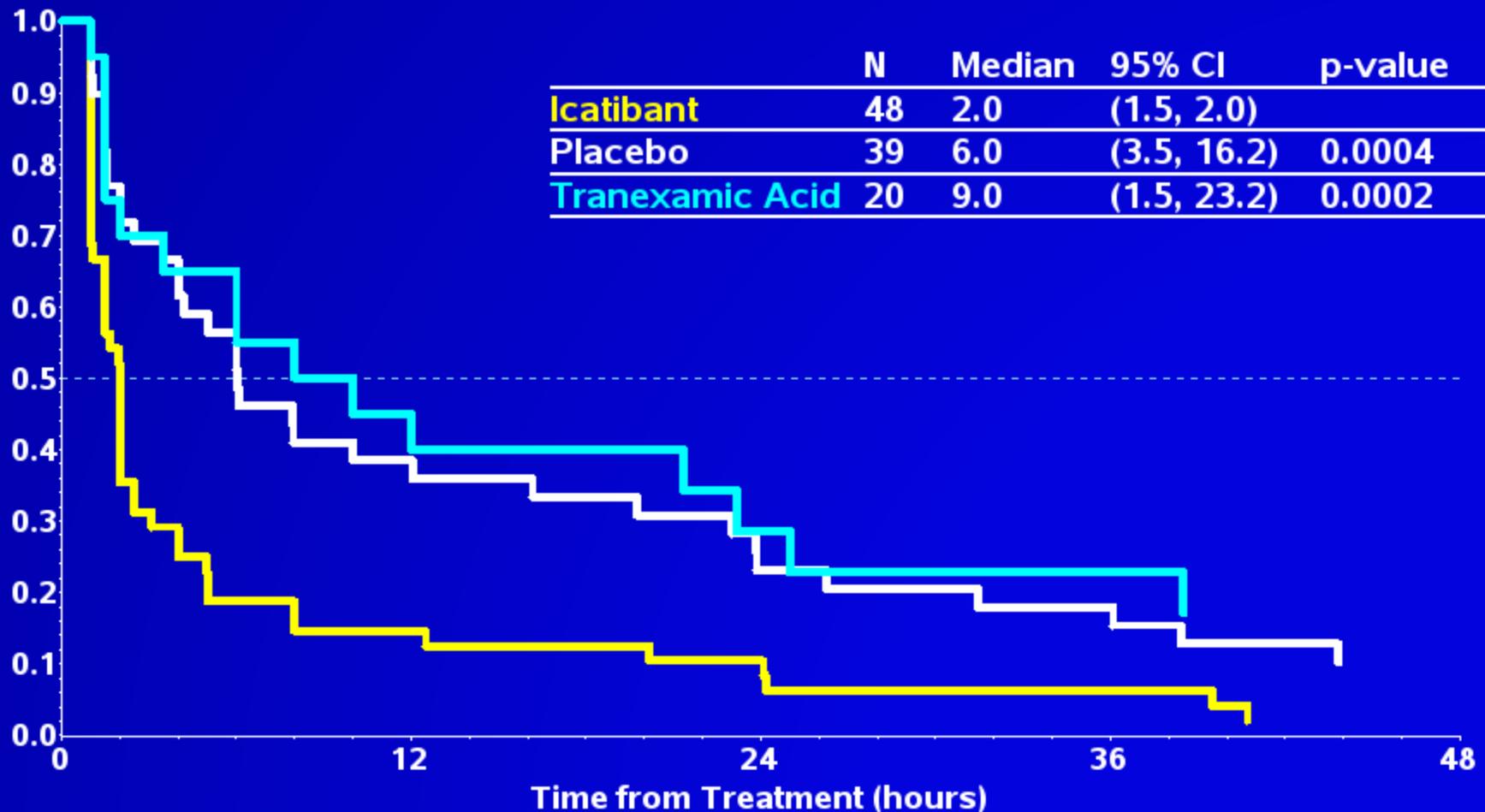
# TOSR by Sex: Males

## Pooled Non-Laryngeal ITT Population



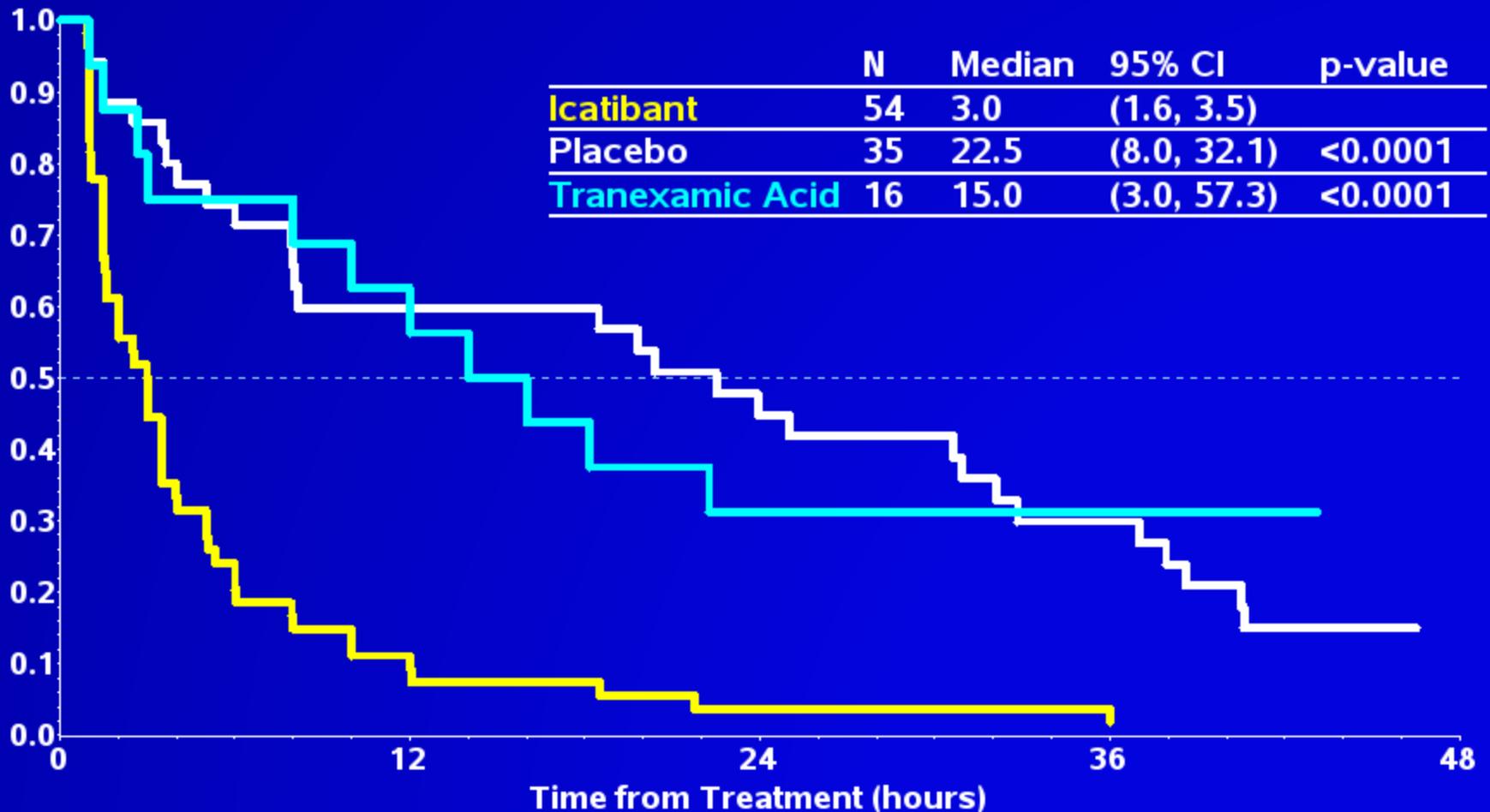
# TOSR by Weight $\leq 75$ kg

## Pooled Non-Laryngeal ITT Population

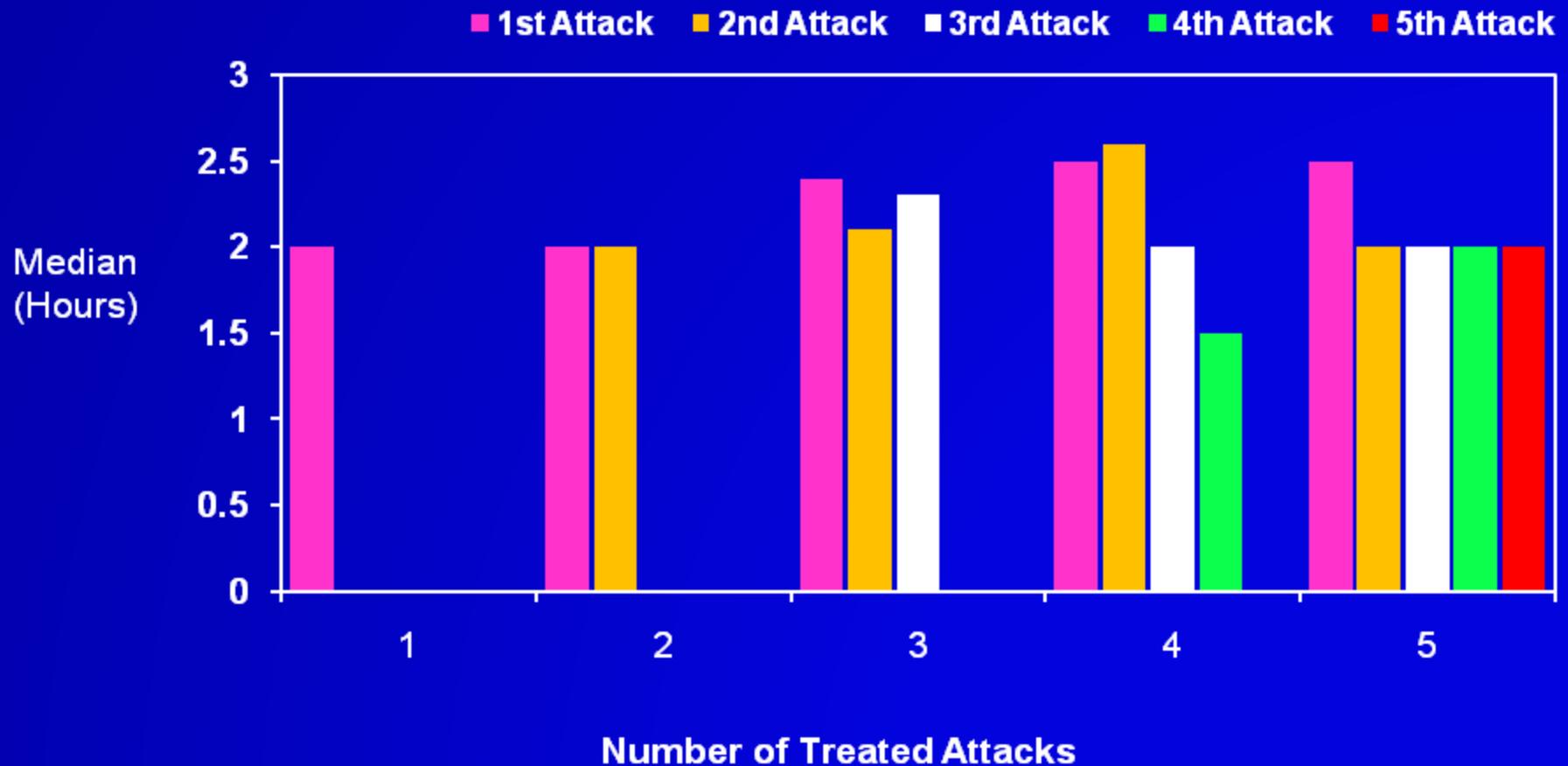


# TOSR by Weight > 75 kg

## Pooled Non-Laryngeal ITT Population



# TOSR Relief Across Repeat Attacks



# Composite VAS - Pooled Treated Population (Non-Laryngeal Attacks)

