6 December 2012:
15:30-17:00 G.04 (HICC)

The Hyderabad International Convention Centre (HICC) in Hyderabad, India

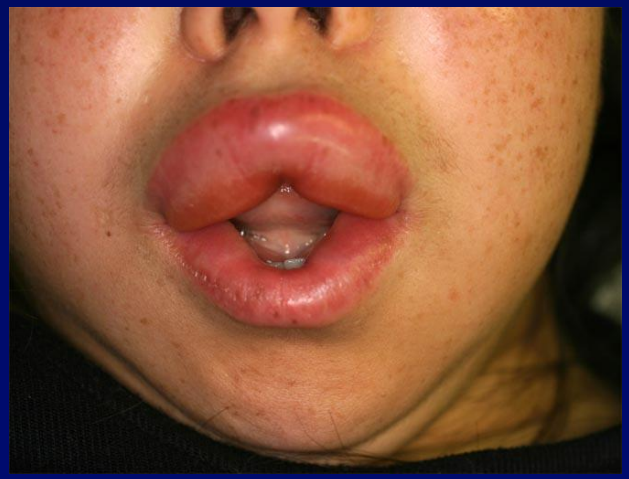
WISC 2012; WAO International Scientific Conference

Postgraduate Course 22: URTICARIA & ANGIOEDEMA TRACK
-Diagnosis and Treatment of Hereditary Angioedema (HAE)

Acute and Prophylactic Management

Since HAE is a disease due to C1-INH gene disorder, management of the symptoms, rather than cure-oriented treatment, is important in daily practice

Chairpersons: Jonathan Bernstein (United States),
Ramesh B Ramaiah (India)



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Graduate School of Biomedical Sciences
Hiroshima University

Principles for the management of HAE

- Avoid aggravating factors:

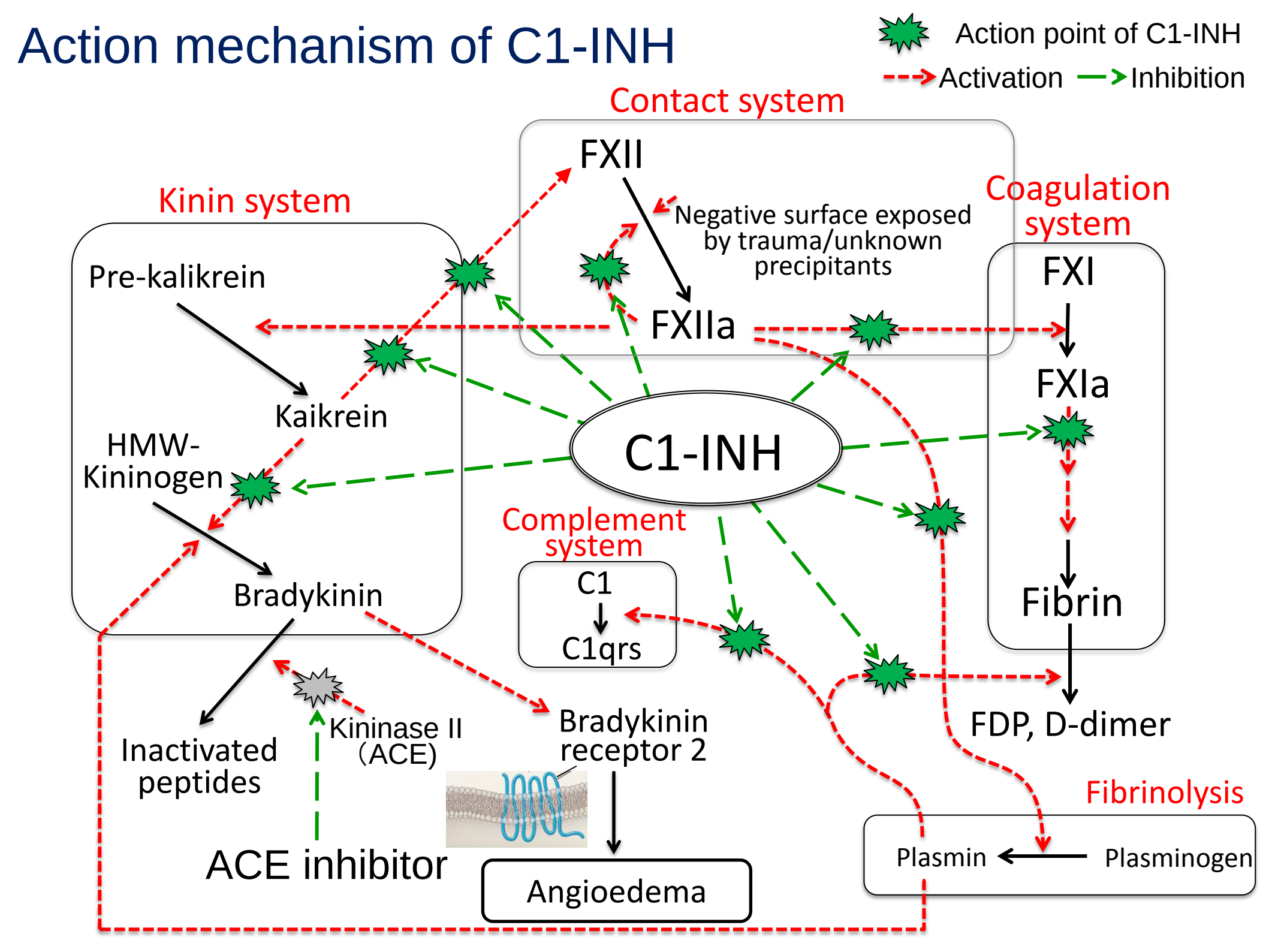
  Infection, psychological stress, fatigue, etc.

- Avoid and/or be prepared for triggering factors:

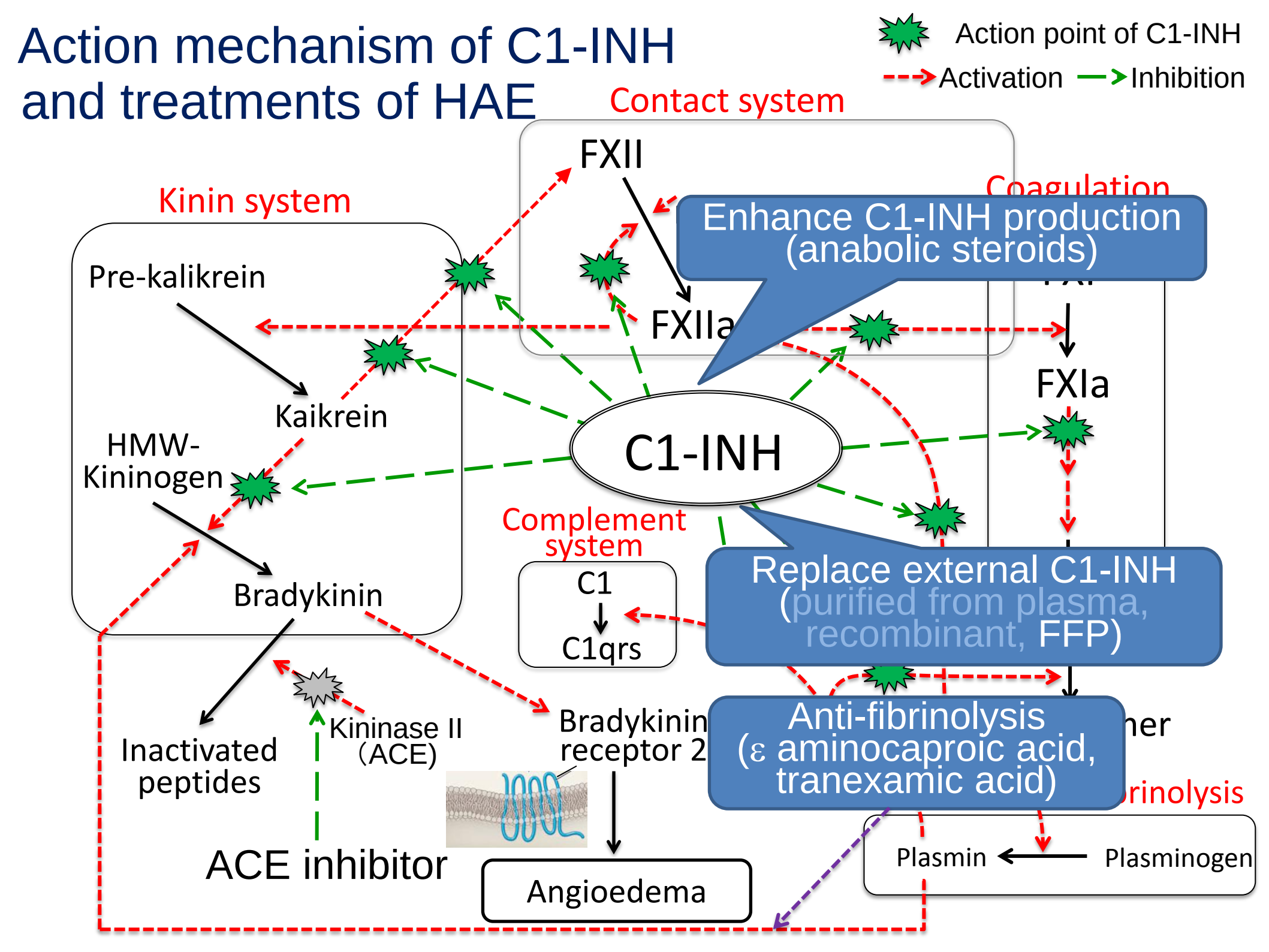
  Trauma, dental actions, surgical operation, etc.

- Medications:
  - Acute treatment for attacks: Acute on demand treatment
  - Short-term prophylaxis: For scheduled operation, special event, etc.
  - Long-term prophylaxis: For frequently occurring severe and unpredictable attacks

Action mechanism of C1-INH



Action mechanism of C1-INH and treatments of HAE



Drugs historically used for HAE

(low cost)

For long-term prophylaxis:

(1) Anabolic sterids (po)

Danazol, stanozol, oxandrolone, methyltestosterone

Efficacy and side effects are dose-related

Recommended at the lowest dose that achieves control

Side effects

Weight gain, virilization, acne, altered libido, muscle pains and cramps, headaches, depression, fatigue, nausea, constipation, menstrual abnormalities, increase in liver enzymes, hypertension, and alterations in lipid profile

(2) Anti-fibrinolytic agents (po)

ε aminocaproic acid, tranexamic acid

Less effective, but safer

(unusual side effect; enhanced thrombosis)

Nausea, vertigo, diarrhea, postural hypotension, fatigue, muscle cramps with increased muscle enzymes

For acute action:

(3) C1-INH replacement (iv)

Fresh frozen plasma (FPP)

Generally effective in treating acute attacks, but
Sometimes lacks efficacy, or can cause sudden worsening

Risk of infection by unknown microorganisms,
May worsen symptoms

Acute management of HAE attacks

Epinephrine, corticosteroids or antihistamines do not have a sufficient effect and not recommended.

		Berinert®	CINRYZE®	Ruconest® Rhucin®	Firazyr® icatibant	KAIBITOR® ecallantide
		Human C1-INH			Small protein/peptide	
		Plasma-derived human C1-INH pasteurized, nanofiltered (20nm &15nm) Berinert-unique formulation	Plasma-derived human C1-INH pasteurized, nanofiltered (15nm & 15nm) Cinryze-unique formulation	Recombinant human C1-INH	Bradykinin 2 receptor antagonis Peptide (MW 1,304)	Kallikrein inhibitor Small protein (MW 7,053)
		Human plasma	Human plasma	Extracted from transgenic rabbit milk	Synthetic	Recombinant (in yeast *Pichia pastoris*)
Half-life		22.4-36.1 hrs	56-62 hrs	2-3 hrs	1-2 hrs	2.0 hrs
Formulation / Storage		Lyophilized / 2-25ºC	Lyophilized / 2-25ºC	Lyophilized/ refrigerated (?)	Liquid, prefilled syringe/ 2-25ºC	Liquid/ refrigerated (2-8ºC)
Shelf-life		30 months	24-36 months	4 years	24 months	3 years (2-8ºC)
Pack size / Volume		500 U in 10 ml	500 U in 5 ml	2100 U in 14 ml	3ml(30mg)	3 x 1 ml(10mg)
Indica-tion	**Acute**	Label for all acute attacks	Label for all acute attacks (EU, AU, CA, IL)	Label for all acute attacks, only if negative rabbit allergy (IgE)	Label for all acute attacks	Label for all acute attacks
	Prophylaxis	Suitable (but off-label)	On Label: Long & Short Term Prophylaxis (US, EU, AU, CA, IL)	not suitable	not suitable	not suitable
Administ-ration	**Route**	i.v.	i.v.	i.v.	s.c.	s.c.
	Self-administration/ Home therapy	Approved in US, EU	Approved in US, EU, Australia, Canada & Israel	Not approved	Approved for up to 3 injections in 24hrs	Not approved

Berinert and Cinryze are in the same class therapeutics, but have different pharmacological characteristics due to different excipients.

Per-patient analysis of efficacy pdC1-INH in I.M.P.A.C.T. (Berinert-P®)

Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY EAACI

Allergy

ORIGINAL ARTICLE SKIN AND EYE DISEASES

C1 esterase inhibitor concentrate in 1085 Hereditary Angioedema attacks – final results of the I.M.P.A.C.T.2 study

T. J. Craig[1], A. K. Bewtra[2], S. L. Bahna[3], D. Hurewitz[4], L. C. Schneider[5], R. J. Levy[6], J. N. Moy[7], J. Offenberger[8], K. W. Jacobson[9], W. H. Yang[10], F. Eidelman[11], G. Janss[12], F. R. Packer[13], M. A. Rojavin[14], T. Machnig[15], H.-O. Keinecke[16] & R. L. Wasserman[17]

	I.M.P.A.C.T.2 results					
	20 U/kg bw C1-INH*					Placebo
Statistic	All attacks (n = 57)	Abdominal (n = 51)	Peripheral (n = 30)	Facial (n = 21)	Laryngeal (n = 16)	(n = 0)
Time to onset of symptom relief (h)						
Median (range)	0.46 (0.17–497.0)†	0.39 (0.17–497.0)†	0.43 (0.17–27.16)	0.48 (0.10–5.61)	0.44 (0.20–1.25)	n.a.
95% CI	0.39; 0.53	0.33; 0.48	0.29; 0.55	0.25; 0.79	0.31; 0.69	n.a.
Number (%) of patients with individual average time to onset of symptom relief of:						
<1 h	51 (89.5)	49 (96.1)	27 (90.0)	18 (85.7)	14 (87.5)	n.a.
<4 h	55 (96.5)	50 (98.0)	29 (96.7)	20 (95.2)	16 (100)	n.a.
Time to complete resolution of HAE symptoms (h)						
Median (range)	15.48 (0.64–497.0)†	12.75 (0.64–497.0)†	22.73 (5.07–497.0)†	26.63 (0.95–61.83)	5.79 (0.63–48.25)	n.a.
95% CI	11.64; 21.59	8.19, 15.19	18.73, 27.16	7.38, 43.01	2.05, 25.90	n.a.

bw, body weight; C1-INH, C1 esterase inhibitor; CI, confidence interval; HAE, Hereditary Angioedema; *N*, number of patients; n.a., not applicable.

*Of the total of 1085 attacks, the dose of C1-INH concentrate was 40–60 U/kg bw for 12 attacks (in six patients).

†The maximum time to complete resolution of 497 h occurred in a patient for whom retrospective genetic testing did not confirm the diagnosis of HAE; the patient was treated for one event. This value was also used for conservative imputations of some missing values.

‡Based on actual values recorded; see Craig et al. (9). No imputation was used for the time to onset of symptom relief. Missing values of time to complete resolution were imputed with the maximum value of 1486 h.

§Data for time to onset of symptom relief are missing for one patient.

Open Label Extension: Study 2006-1 Demographics

- Total of 113 subjects received CINRYZE
  - **101** subjects were treated for a total of **609** separate HAE attacks (GI: 353, Extremity: 86, Laryngeal: 84, Facial: 72, GU: 13, Unk: 1)
  - 12 subjects received CINRYZE only for pre-procedure prevention

(1,000 unit/attack) n=101 subjects

	Within 1 h	Within 4 h
Number of attacks with unequivocal relief of the defining symptom, relative to the start of CINRYZE dosing	412/609 (68%)	529/609 (87%)

Unequivocal Relief = 3 consecutive assessments of improvement at 15 min intervals

- Median # attacks treated per subject = 3 (range 1-57)
- For subjects with >1 HAE attack, the efficacy of CINRYZE did not diminish with subsequent repeat administrations.

LEVP 2006-1 Final Clinical Study Report. November 2008.

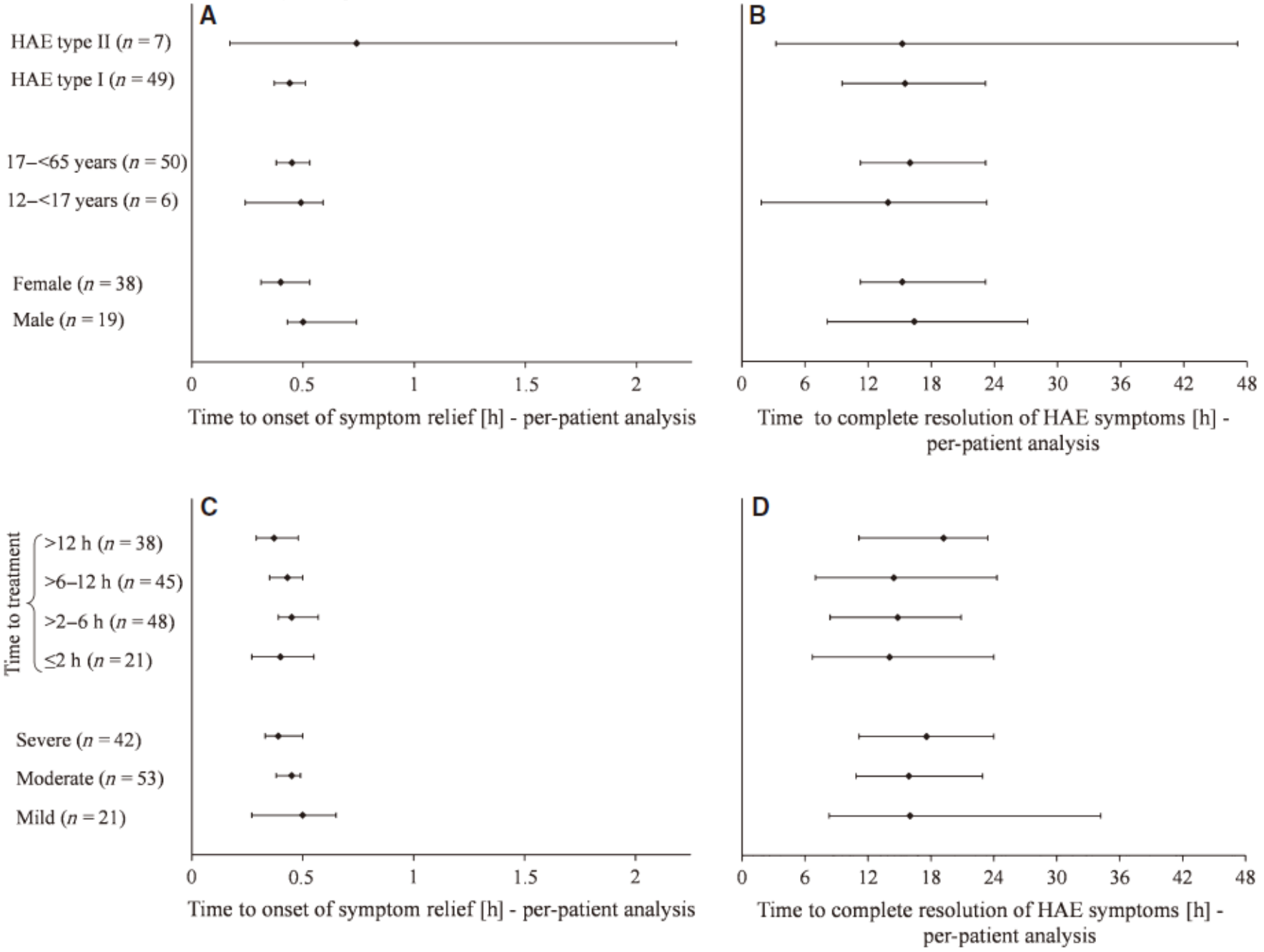
Provided by ViroPharma Inc.

Table III Assessment of treatment response, efficacy by clinical trial

Modified from Caballero T et al, J Clin Immunol 2012

Agent (Brand)	Study designation/ reference	Time to improvement	Response at 4 h		Time to complete resolution
			Percentage of responders	Other	
C1-INH, purified from sera (Berinert)	IMPACT1 (Craig et al, 2009)	0.5 h (20U/kg)	86 %		4.9 h (20 U/kg)
C1-INH, purified from sera (Cinryze)	CHANGE 1 (Zuraw et al, 2010)	2 h	60 %		12.3 h
	CHANGE 2 (Reidel et al, 2012)	0.75 h	87 %		N/A
C1-INH, recombinant (Rhucin)	(Zuraw et al, 2010)	66 min (median) (100 U/kg)	86.2 %		N/A
Ecallantide (Kalbitor)	EDEMA3 (Cicardi et al, 2010)	67 min	54.5 %		N/A
	EDEMA4 (Levy et al, 2010)	N/A	68.8 %	MSCS score improvement after 4 h vs placebo (−0.8/−0.4)	N/A
Icatibant (Firazyr)	FAST-1/FAST-2 (Cicardi et al, 2010)	2.5 h/2.0 h	66.7 %	TOS after 4 h vs placebo (54.2/8.1)	8.5 h/10.0 h
	FAST-3 (Lumry et al, 2011)	1.5 h	80.6 %		8.0 h

Subgroup analyses. Times to onset of symptom free and complete resolution of HAE symptoms in I.M.P.A.C.T.2

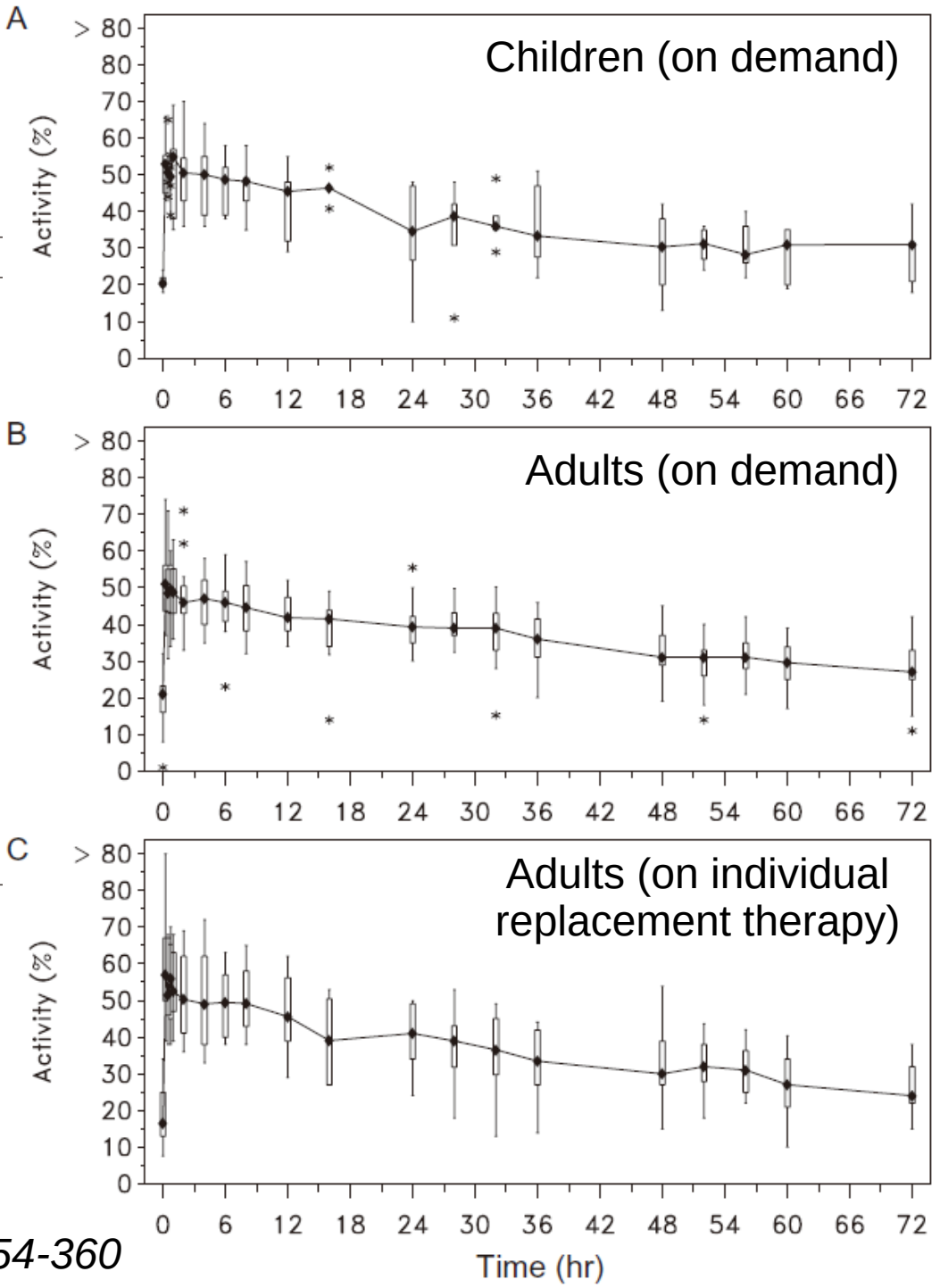


Craig TJ, et al. Allergy 2011; 66: 1604-1611

Kinetics of C1-INH plasma activity after the infusion of Berinert-P

Variable	Median	Range
Children (on demand; n = 6)		
AUC* (for dose of 15 U/kg [(U × hr)/mL])	13.4	2.9-29.4
T_{max}† (hr)	0.6	0.1-2.0
$t_{1/2}$‡ (hr)	32.9	7.3-70.5
MRT§ (hr)	47.5	10.5-101.7
Cll (mL/[kg × hr])	1.1	0.5-5.2
V_{ss}¶ (mL/kg)	50.0	41.6-62.3
Adults (IRT; n = 15)		
AUC (for dose of 15 U/kg [(U × hr)/mL])	15.7	6.3-86.1
T_{max} (hr)	0.5	0.3-8.0
$t_{1/2}$ (hr)	30.9**	10.3-96.0
MRT (hr)	44.6**	14.9-138.5
Cl (mL/[kg × hr])	1.0	0.2-2.4
V_{ss} (mL/kg)	37.5††	24.1-66.4
Adults (on demand; n = 19)		
AUC (for dose of 15 U/kg [(U × hr)/mL])	16.7	9.5-69.7
T_{max} (hr)	1.0	0.3-32.0
$t_{1/2}$ (hr)	39.1	19.4-90.4
MRT (hr)	56.5	28.0-130.5
Cl (mL/[kg × hr])	0.9	0.2-1.6
V_{ss} (mL/kg)	56.7	23.3-69.2

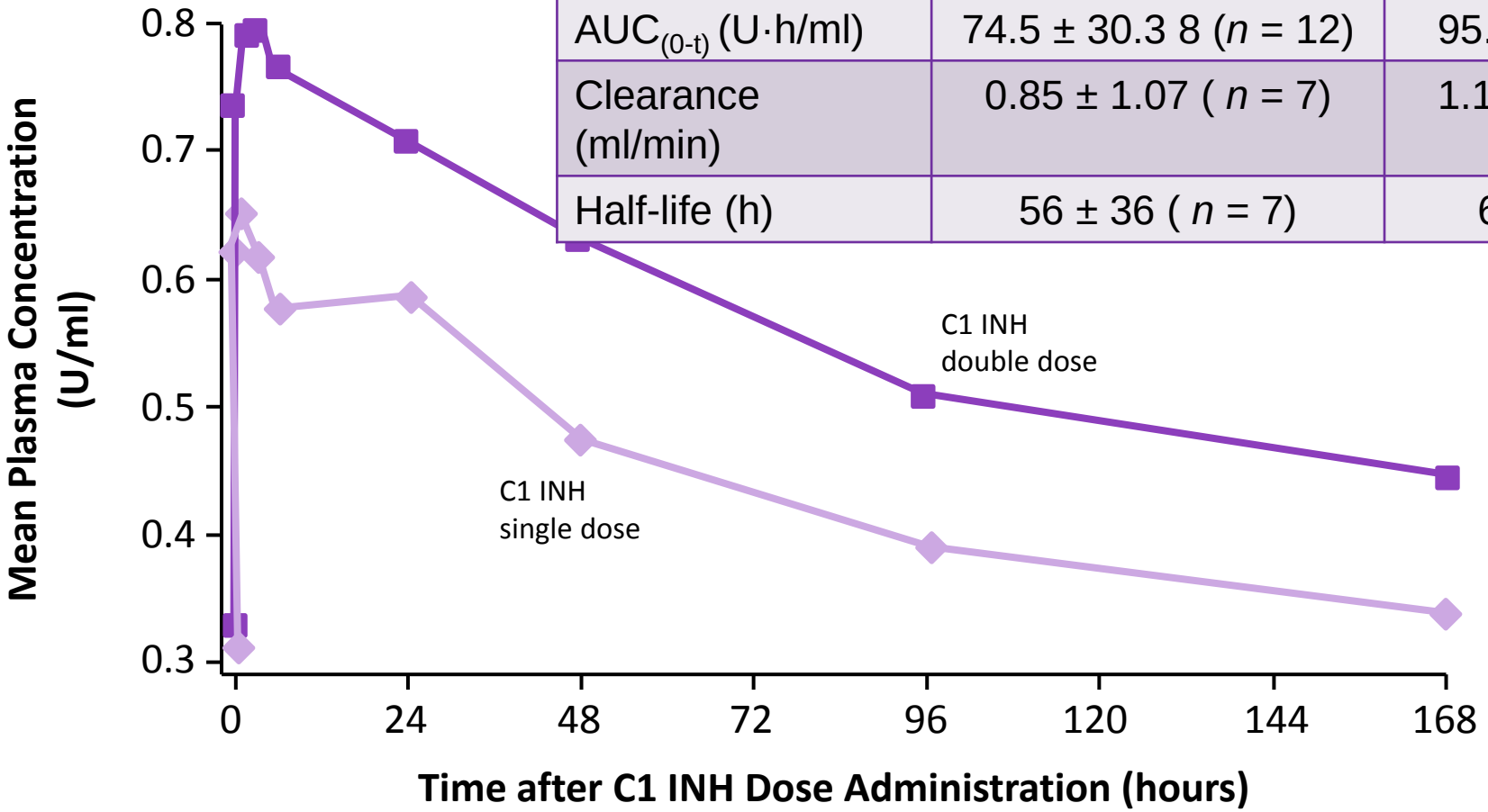
* Area under the elimination curve.
† Median time to maximum functional pC1-INH level.
‡ Terminal elimination half-life.
§ Mean residence time.
ll Total clearance.
¶ Volume of distribution at steady state.
** p = 0.052 versus adults on demand.
†† p = 0.004 versus adults on demand.



I Martinez-Saguer, et al. Transfusion 2010; 50: 354-360

C1 INH Plasma Concentration after 1 and 2 Injections of 1000 IU CINRYZE

Parameter	Single Dose	Double Dose
$C_{baseline}$ (U/ml)	0.31 ± 0.20 (*n* = 12)	0.33 ± 0.20 (*n* = 12)
C_{max} (U/ml)	0.68 ± 0.08 (*n* = 12)	0.85 ± 0.12 (*n* = 13)
T_{max} (h)	3.9 ± 7.3 (*n* = 12)	2.7 ± 1.9 (*n* = 13)
$AUC_{(0\text{-}t)}$ (U·h/ml)	74.5 ± 30.3 8 (*n* = 12)	95.9 ± 19.6 (*n* =13)
Clearance (ml/min)	0.85 ± 1.07 (*n* = 7)	1.17 ± 0.78 (*n* = 9)
Half-life (h)	56 ± 36 (*n* = 7)	62 ± 38 (*n* = 9)



Blood Products Advisory Committee Meeting, May 2, 2008. Available at: http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4355B2-2.pdf.

Failure of treatment timing may be fatal

Tranexa–mic acid 1g

Methyl predonisolon 125mg

Dyspnea hoarseness

Bonzol® 100mg/day

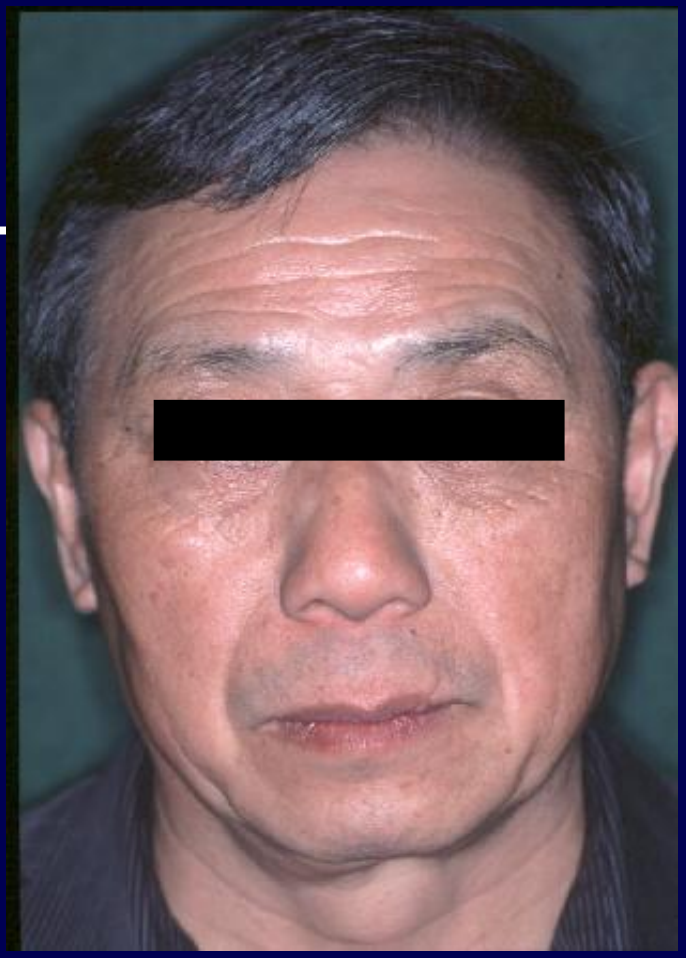
Celcect®(antihistamine) 30mg/day

edema

AM10:00 — 14:00 — 20:00 — 0:00

Admission

tooth extraction



Failure of treatment timing may be fatal

Tranexa–
mic acid
1g

Methyl
predonisolon
125mg

Dyspnea
hoarseness

Sever
laryngeal
edema

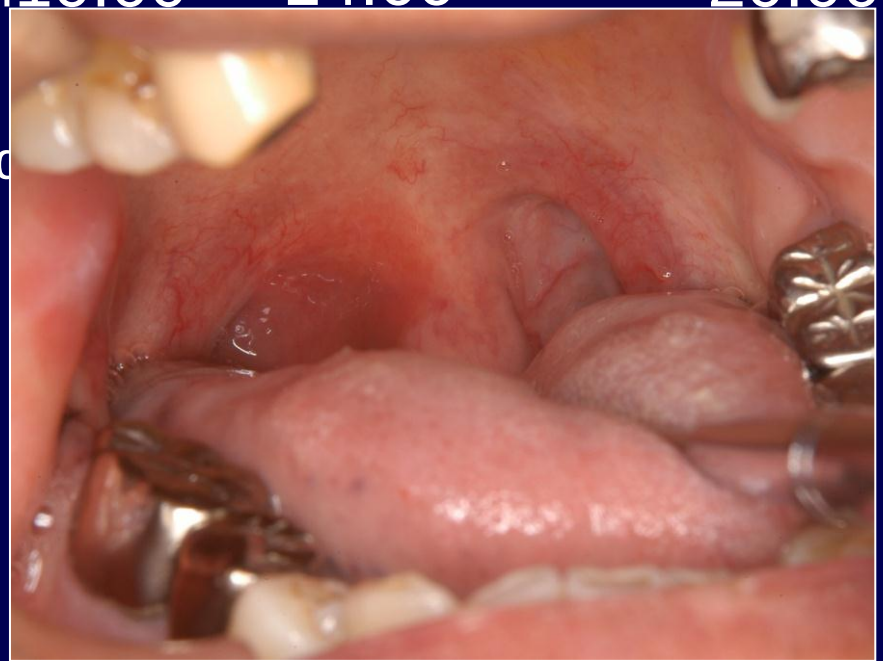
Bonzol® 100mg/day
Celcect®(antihistamine) 30mg/day

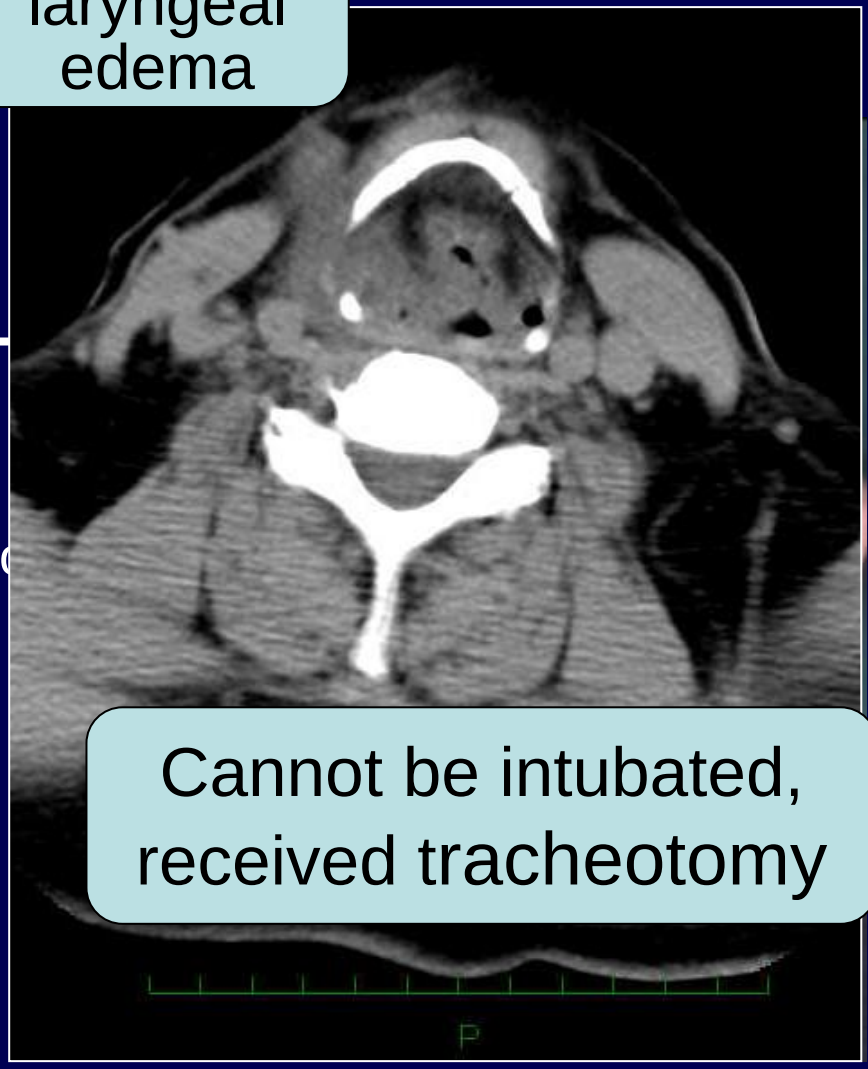
edema

AM10:00 14:00 20:00 0:00

Ac

Transfer t
ICU





Cannot be intubated,
received tracheotomy

Self-administration / home therapy for HAE

Berinert® : iv

in US, EU

Step 6: Infusion

As instructed by your healthcare provider:

- Insert the butterfly needle of the infusion set tubing into your vein (Figure 11).
- If necessary, use sterile gauze and tape or transparent dressing to hold the needle in place.
- To make sure that the needle is in a vein, gently pull back on the syringe plunger and check to see if blood is in the tubing (Figure 12). If there is blood present, then the needle is in a vein. If there is no blood present, remove the needle and repeat this step using a new needle, new administration tubing, and a different injection site.
- Remove the tourniquet.
- Inject the BERINERT solution slowly at a rate of approximately 4 mL per minute (Figure 13).

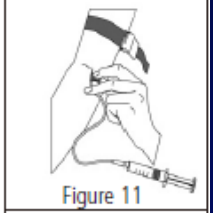


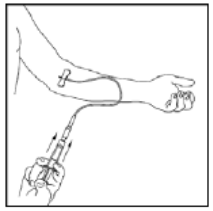
Figure 11

Figure 12

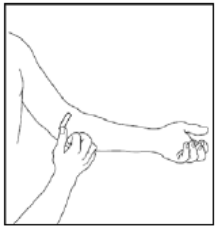
Figure 13

CINRYZE® : iv

in US, EU, Australia, Canada & Israel



4. After infusing CINRYZE, remove the infusion set and discard. Cover infusion site with an adhesive bandage. The amount of drug product left in the infusion set will not affect your treatment. Dispose of all unused solution, the empty vials, and the used needles and syringe in an appropriate container used for throwing away waste that might hurt others if not handled properly.



It is a good idea to record the lot number from the CINRYZE vial label every time you use CINRYZE.

Firazyr® :sc

US, Europe, Russia, Australia, South America

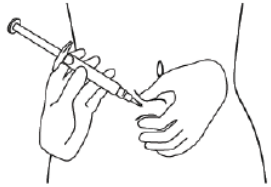


Figure L

Step 13. Push the plunger, at the top of the syringe, over at least 30 seconds until no FIRAZYR is in the syringe. See Figure M.

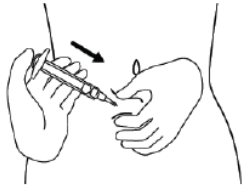


Figure M

Step 14. Release the skin fold and gently pull the needle out. See Figure N.

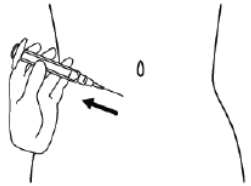


Figure N

Disposal of your used FIRAZYR prefilled syringe

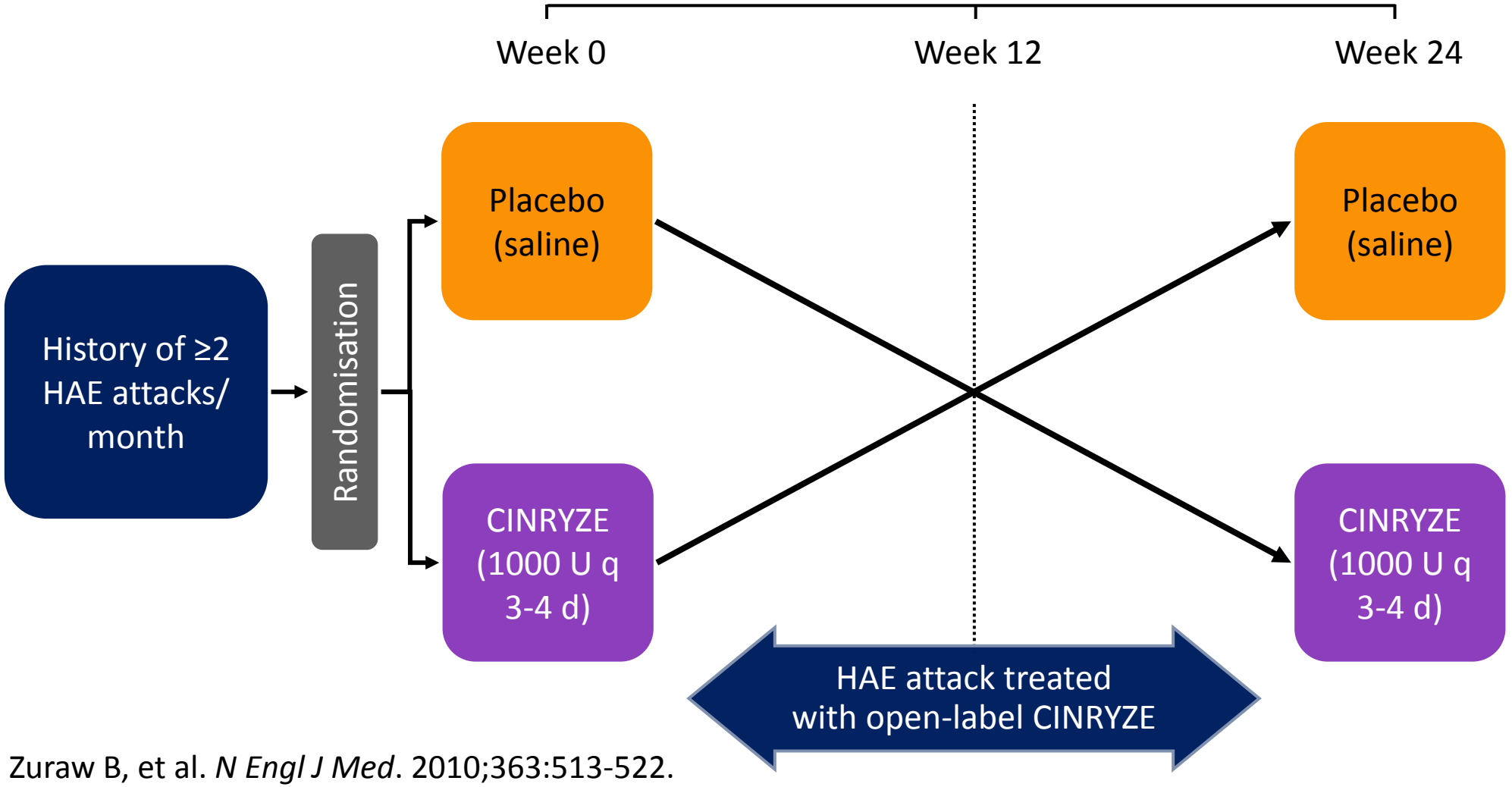
Prophylactic management of HAE symptoms

- Short-term prophylaxis: For a scheduled operation, special events, etc.
- Long-term prophylaxis: For frequently occurring unpredictable and sever attacks

Patients not managed successfully with on demand therapy should be considered for long-term prophylaxis.

Very expensive; ca $3,000 / treatment

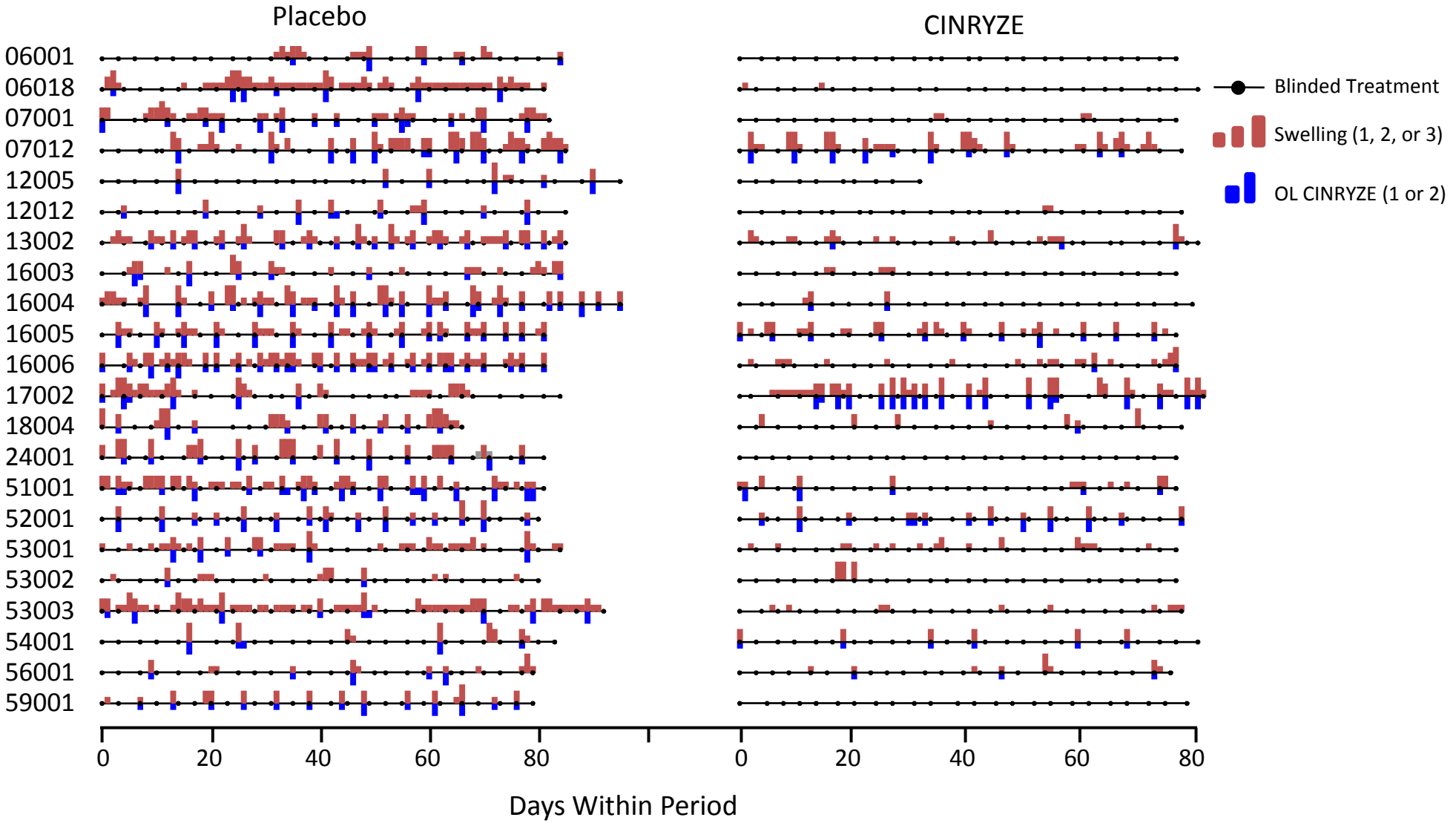
Phase 3 Study of HAE Prevention: Study 2005-1/B by C1-INH



1. Zuraw B, et al. *N Engl J Med*. 2010;363:513-522.
2. 2. LEVP 2005-1/Part B Clinical Study Report. October 2007.
3. 3. Accessed at www.clinicaltrials.gov. NCT01005888.

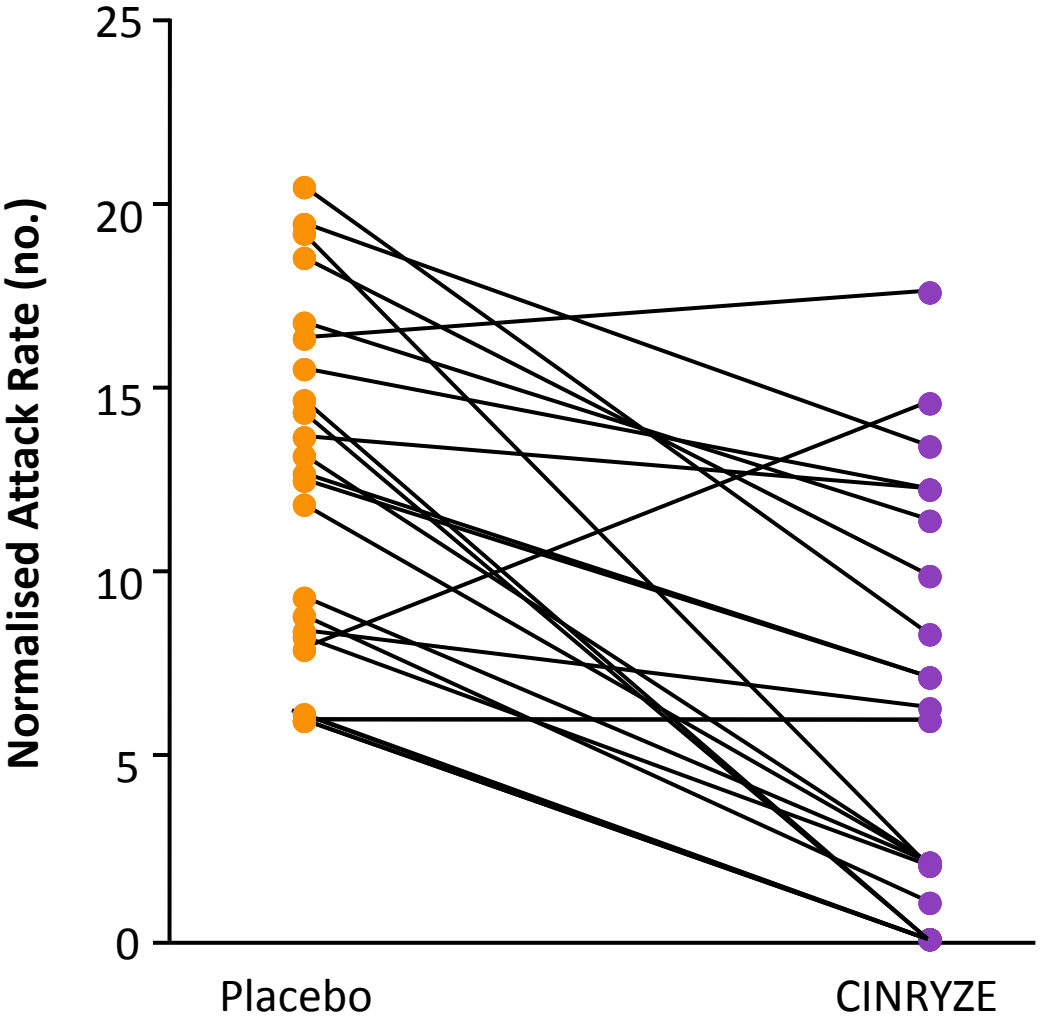
Phase 3 Study of HAE Prevention: Study 2005-1/B by C1-INH

Subject Event Chart



Zuraw B, et al. *N Engl J Med*. 2010;363:513-522.

LEVP2005-1/B: Normalized Number of Attacks by Subjects



In conclusion, prophylactic regular administration of C1-inhibitor with Cinryze twice a week largely reduces attacks of HAE. However, it is also important to take a balance between the effect and cost.

Zuraw BL, et al. *N Engl J Med.* 2010;363:513-522.

Points should be considered for the decisions of pharmacological treatment of HAE

- Severity
- Location
- Access to acute care
- Other co-morbid conditions
- Individual circumstances
- Patient values and preferences, including cost

Adapted from Lang DM, et al. International consensus on hereditary and acquired angioedema. Ann Allergy Asthma Immunol 2012; 109: 395-402

Clinical symptoms of HAE should be evaluated both in terms of severity of individual symptoms (attacks) and frequency (intervals).

- Severity of individual symptoms

  Airway obstruction: suffocation, risk of death

  Pain: intolerability

  Function: ADL, eating, finger manipulation, etc.

- Frequency of the symptoms

  How frequently they occur?

  Every few days, weekly, monthly or a few times a year

The countries where the modern five medications for HAE is licensed
(Berinert, Cinryze, Firazyr, Kalbitor, Ruconest)

Importance of

- Education: patients, physicians
- Drug access: physical, economical
- Public support: government, other organization
- Individual management plan: minimum and sufficient

Thank you for your attention

Night scene in Hiroshima