PHARMING

Ruconest™
(conestat alfa)

Ein rekombinanter humaner C1-inhibitor: Klinischer Überblick

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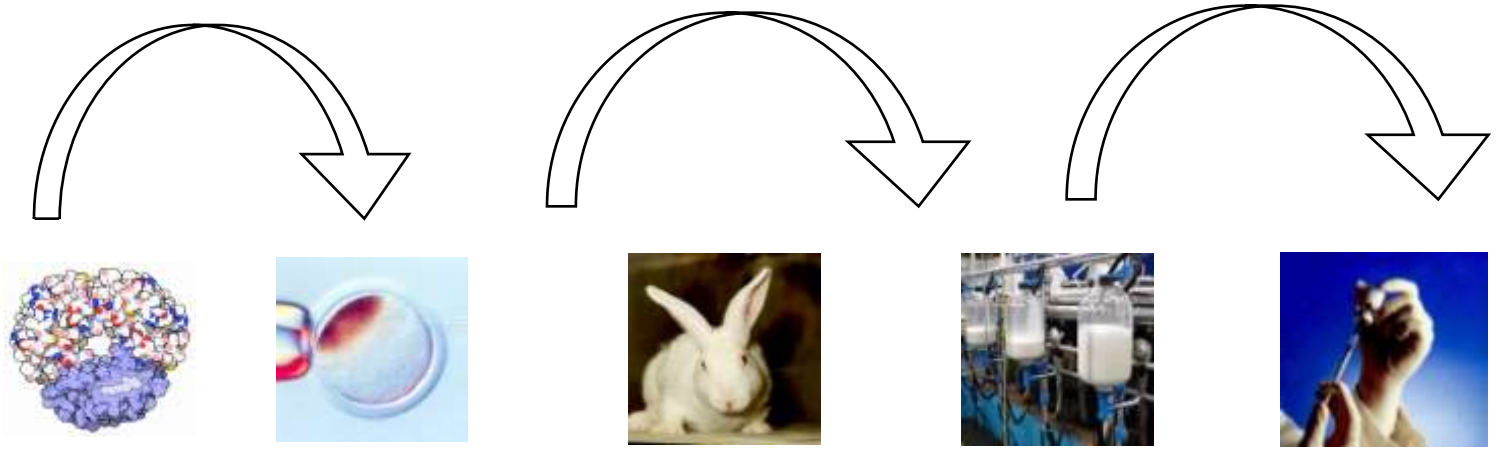
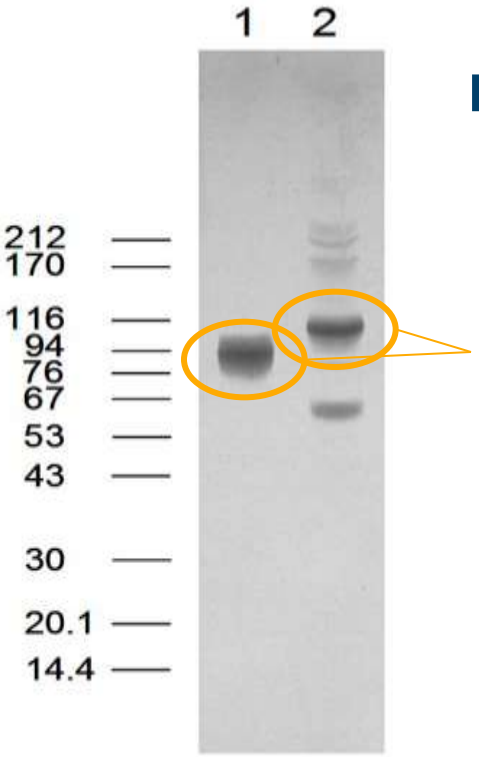
Pharming
Transgenic Technology Platform



Select protein → Generate genetic constructs → Develop founder/ mini-herd → Purify protein from milk → Formulate protein therapeutic

Ruconest® is highly purified

Non-reduced SDS-PAGE analysis of rhC1INH and native C1INH



Ruconest < 0.002% non-product related impurities

In lane 1: Ruconest

In lane 2: pdC1INH

Proteins, 100 ng/lane, were visualized by silver-staining. The migration of the standard protein markers is indicated on the left (10^{-3} x M_r).

Data on File

rhC1INH activity similar to pdC1INH

Similar affinity towards target proteins

	k_{on} ($M^{-1}.s^{-1}$)			
	C1s	Factor XIa	Factor XIIa	Kallikrein
rhC1INH[a]	$6.1 \pm 0.3 \times 10^4$	$9.8 \pm 0.5 \times 10^2$	$6.9 \pm 0.5 \times 10^3$	$9.1 \pm 0.1 \times 10^3$
h-C1INH[a]	$5.1 \pm 0.3 \times 10^4$	$9.0 \pm 0.2 \times 10^2$	$5.7 \pm 0.4 \times 10^3$	$7.6 \pm 0.3 \times 10^3$

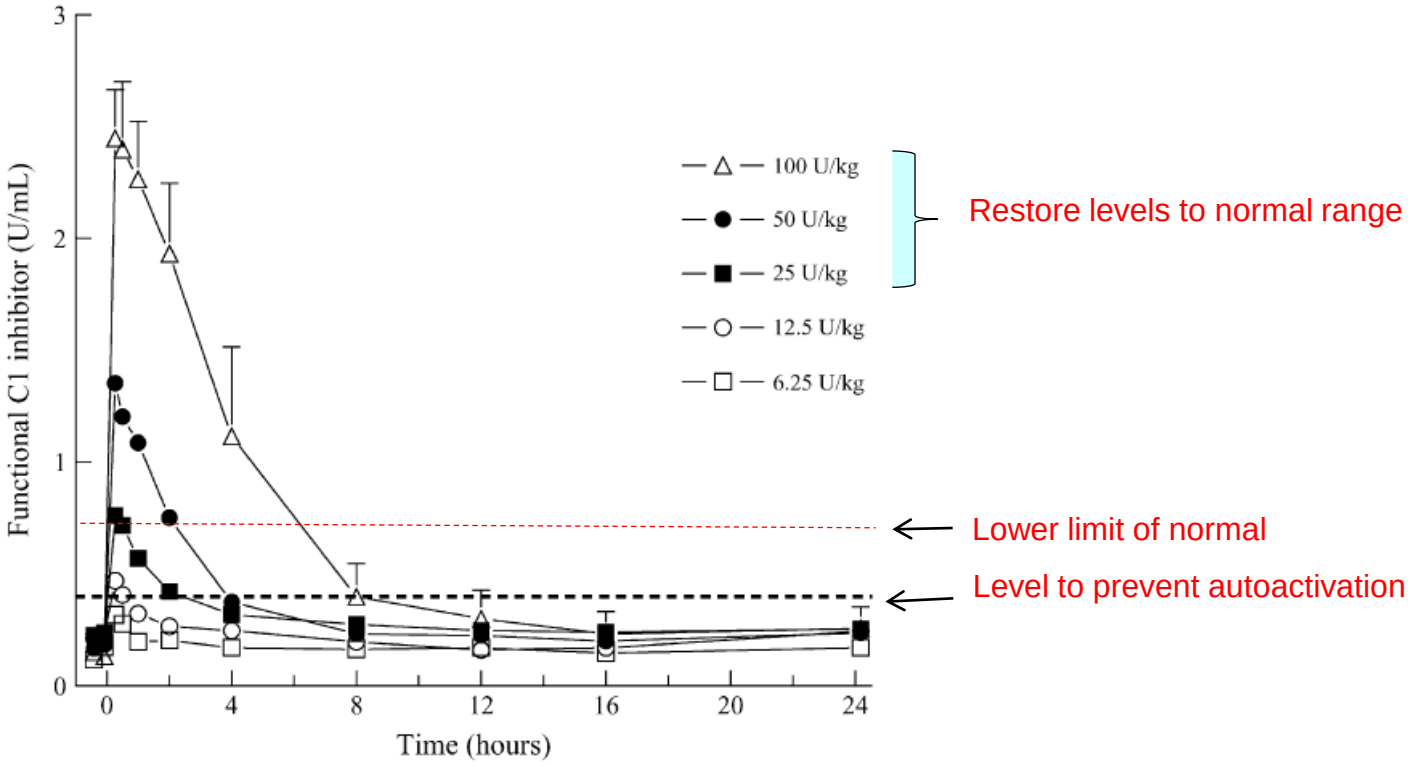
Data generated at Pharming Technologies B.V. The data are mean ± SD of three experiments.
The values for k_{off} were virtually zero.
k*on:* second-order rate constant of inhibition

rhC1INH 50 U/kg
PK parameters

Mean pharmacokinetic parameters following administration of rhC1INH 50 U/kg to asymptomatic HAE patients

Parameter	Mean value ± SD (n=6)
C_{max} (U/mL)	1.36 ± 0.306
C_{max} above baseline (U/mL)	1.18 ± 0.234
T_{max} (min)	18.3 ± 5.72
AUC above baseline (U.min/mL)	218 ± 55.6
CL (mL/min)	22.8 ± 7.34
Half life (min)	93.7 ± 8.45
Volume (L)	3.03 ± 0.794
$C_{baseline}$ (U/mL)	0.201 ± 0.108

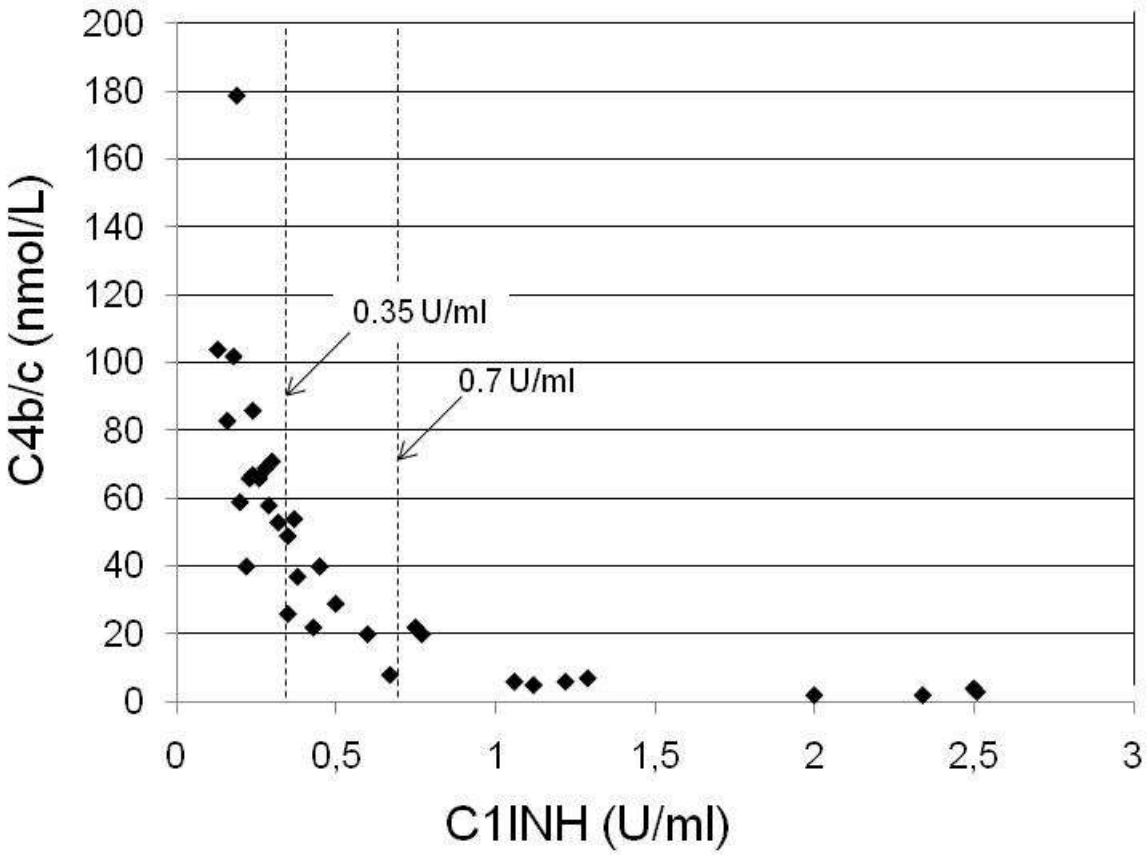
rhC1INH PK profile in asymptomatic HAE patients



Modified graph from M van Doorn et al., J Allergy Clin Immunol 2005;116:876-83

Functional C1INH target levels

No C4 cleavage at normal C1INH levels

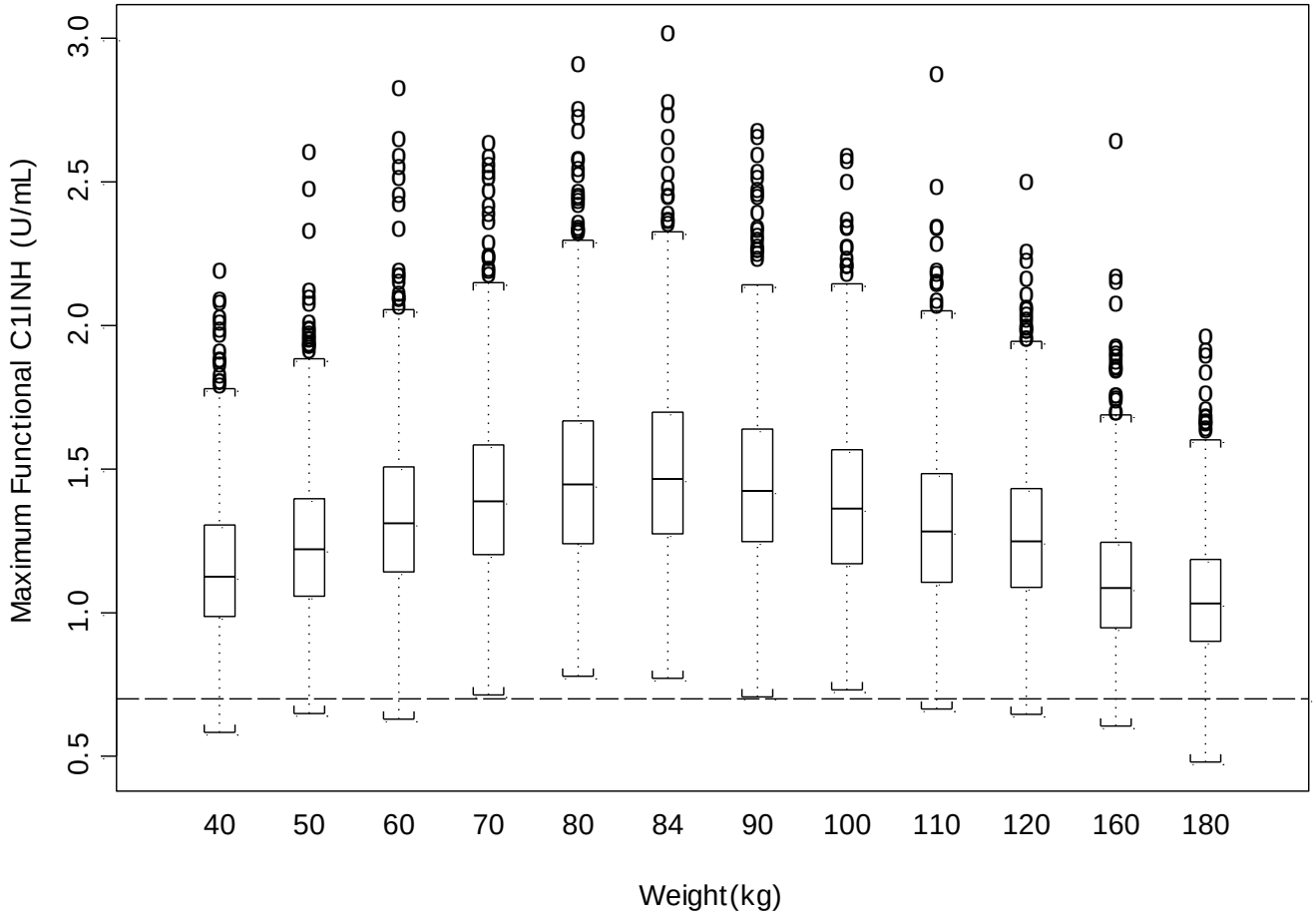


C. E. Hack et al., Allergy 2011

rhC1INH
Mechanism of Action in HAE

- Insufficient (functional) C1inh results in oedema
- Treatment requires sufficient amounts of C1Inh activity
  - 1 Unit = quantity in 1ml of normal plasma
  - 2100U > normal quantity in 2l of plasma = 4 vials of Cinryze / Berinert
- C1inh binds to target proteases as a suicide inhibitor
- Once the cascade is switched off, the edema is absorbed passively
- Dose is more important than half life

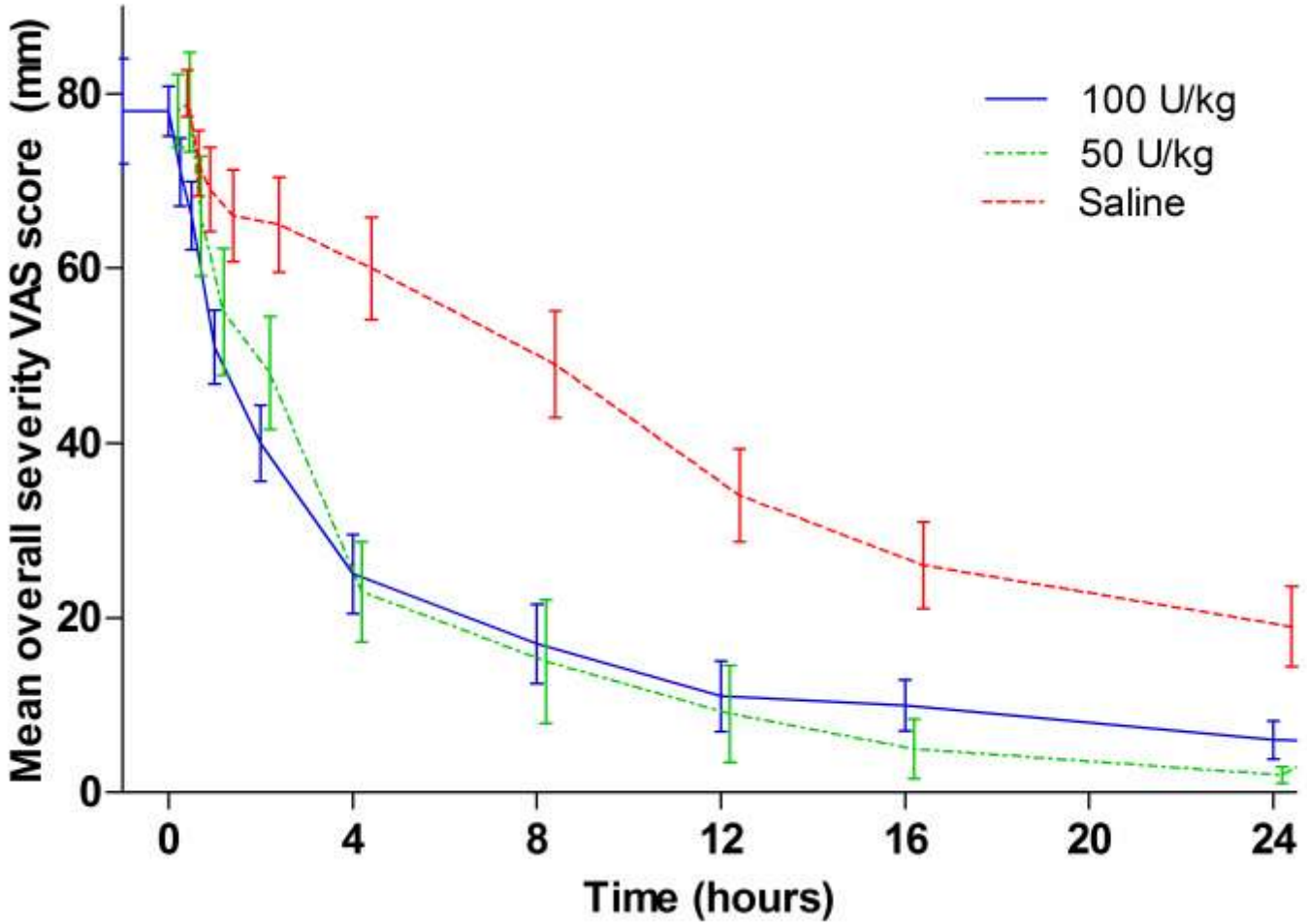
Simulated C_{max} by weight for approved dosing regimen



C.Farrell et al, BJCP 2011 in Press

Ruconest® Controlled Trials

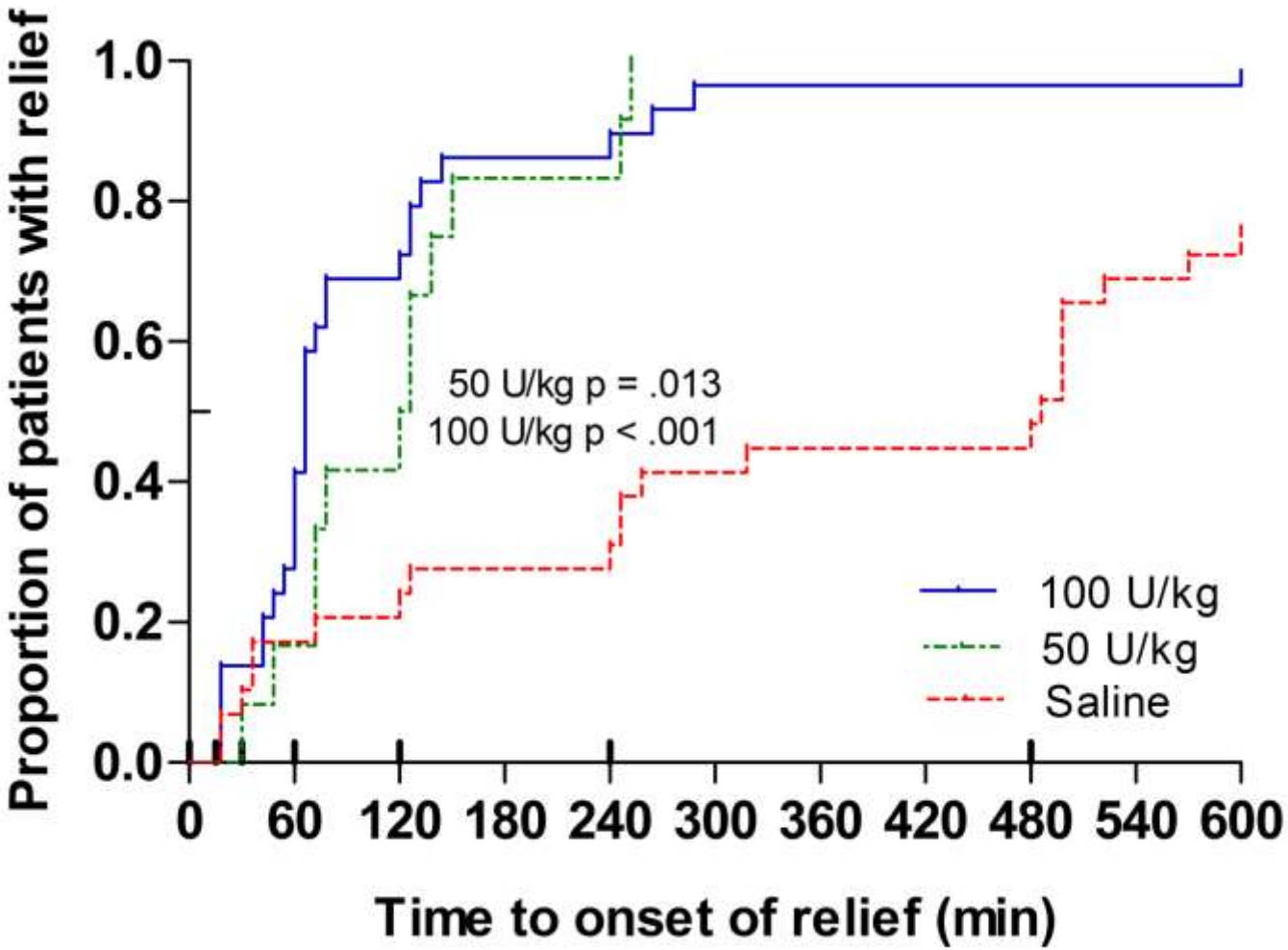
Overall VAS Scores over time at the most severe location



B. Zuraw, M. Cicardi et al., J Allergy Clin Immunol 2010;126:821-7

Ruconest ® Controlled Trials

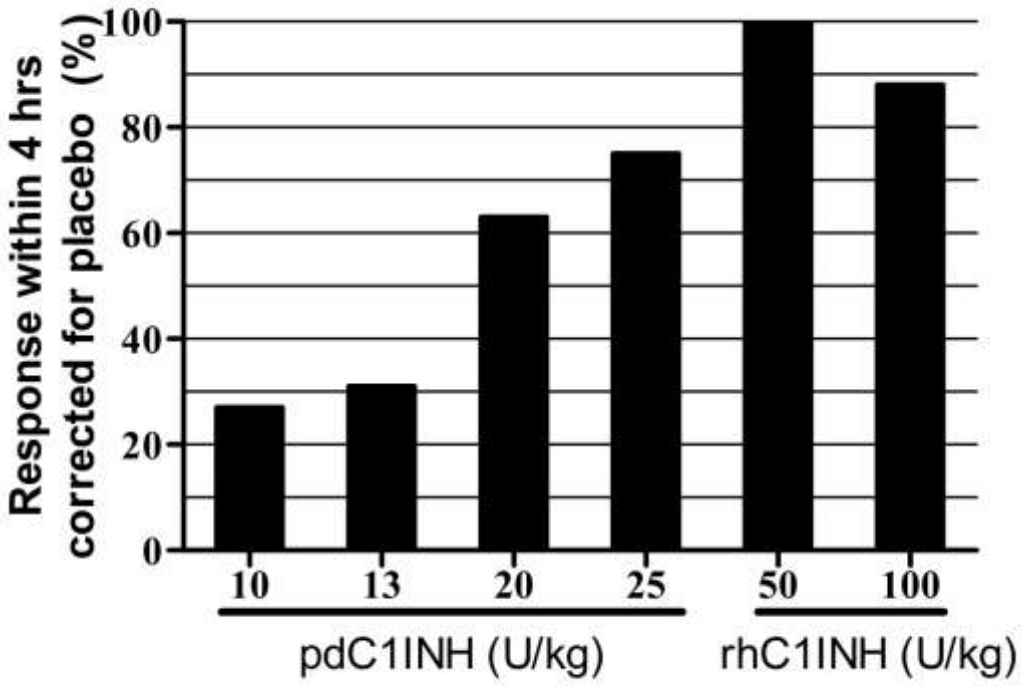
Time to onset of relief



B. Zuraw, M. Cicardi et al., J Allergy Clin Immunol 2010;126:821-7

All C1INH controlled trials

Placebo corrected dose response at 4 hours



Optimal efficacy achieved at 50 U/kg

No further improvement with 100 U/kg

Dose is more important than half-life

C. E. Hack et al., Allergy 2011

Integrated safety findings

Exposure

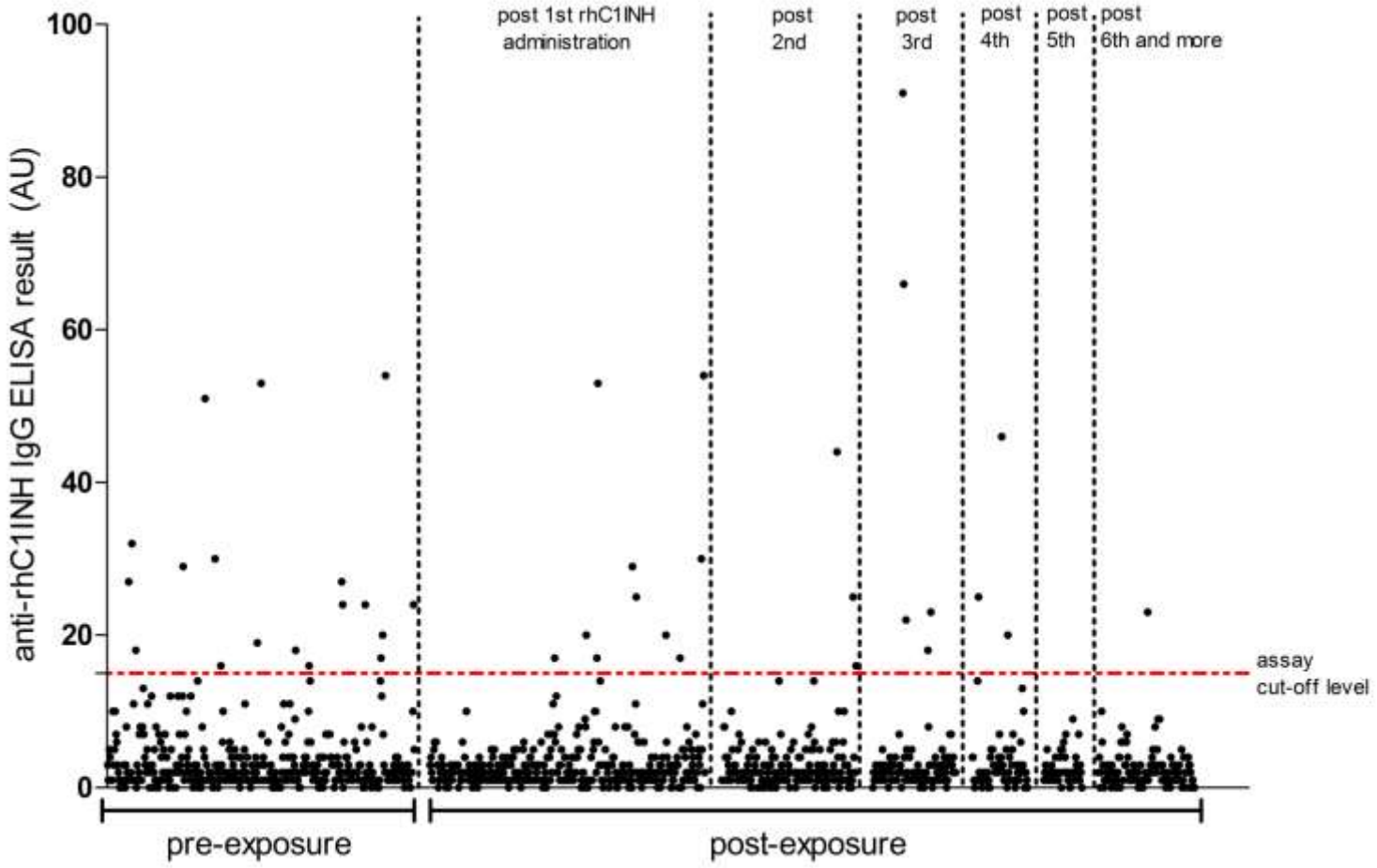
Study	Study population	Subjects (n)	Administrations (n)
C1 1202/03	Symptomatic patients	14	21
C1 1205 RCT	Symptomatic patients	25	25
C1 1205 OLE	Symptomatic patients	62	168
C1 1304 RCT	Symptomatic patients	16	16
C1 1304 OLE	Symptomatic patients	57	194
Subtotal	**Symptomatic patients**	**155**	**424**
C1 1101	Asymptomatic patients	12	24
C1 1106	Healthy Volunteers	14	59
C1 1207	Asymptomatic patients	25	207
Subtotal	**All population**	**190**	**714**

Integrated clinical safety findings
Summary

- rhC1INH up to 100 U/kg was generally well tolerated, the AE profile being similar to that of placebo
- No severe TEAEs were considered to be probable or definitely related to rhC1INH administration
- No increase in the frequency of TEAEs upon repeated rhC1INH administration

Integrated immunosafety

Antibodies to C1INH



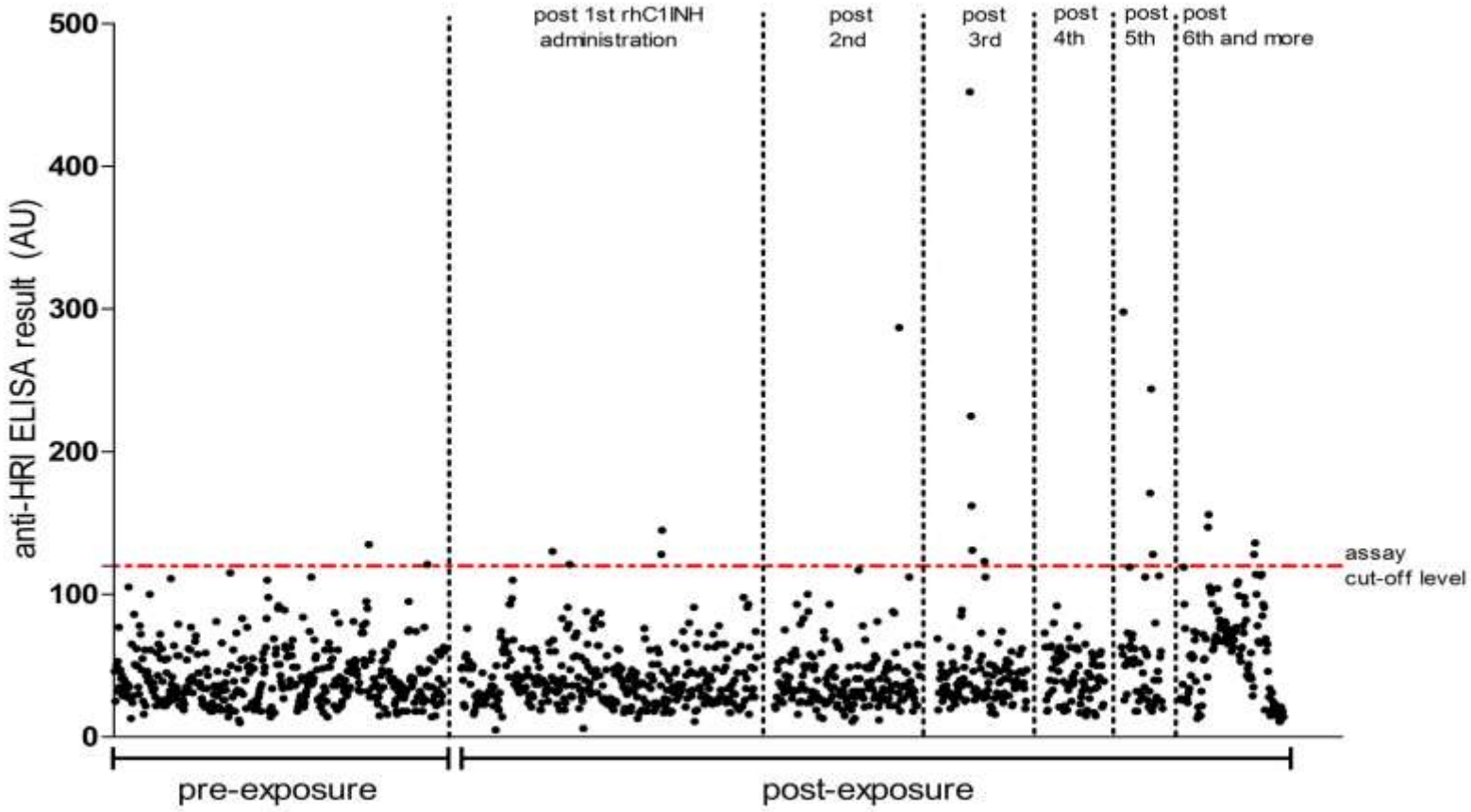
No induction of anti-C1INH antibodies

No neutralizing antibodies

Data on File

Integrated immunosafety

Antibodies to HRIs



Occasional and transient antibodies to HRIs

None associated with clinical events

Data on File

Integrated immunosafety
IgE antibodies

- Ruconest is contraindicated in patients with known or suspected rabbit allergy

- In Europe Ruconest is only administered to patients who tested negative for rabbit epithelium (dander) antibodies, and re-testing is indicated once yearly or every 10 treatments

➢Subjects exposed to rhC1inh were tested for the presence of pre-existing IgE antibodies against rabbit epithelium

- ➢No differences in pre- and post exposure blood samples.
- ➢ No induction observed of IgE antibodies

C. E. Hack et al, Poster IgE; EAACI 2010 London, Allergy 2010 Jun; 65 Suppl 92: 1- 756

Recombinant C1INH

Safety conclusions

- 714 Ruconest® exposures in 190 subjects
- No increase in adverse events with repeated exposures
- No evidence for neutralizing antibodies to endogenous C1INH
- Confirmed anti-HRI antibodies are sporadic and transient, not associated with clinical events
- No induction observed of IgE antibody

Ruconest® has an unremarkable safety profile.

Data on File

Conclusions

- Ruconest is a novel biotech alternative to plasma derived C1inh for the treatment of HAE attacks
  - Identical amino acid sequence
  - Differences in glycosylation profile
  - Highly purified
- Approved at a higher dose (50U/kg) achieving optimal efficacy
  - Similar affinity to target proteases
  - Functional units are directly comparable (1vial of Ruconest> 4 vials of plasma product)
  - Dose is more important driver of efficacy than half-life
  - No relapse
- Reassuring safety profile
  - No pharmacological AEs
  - No induction of allergies observed
  - No induction of neutralizing antibodies
  - Contraindicated in pts with rabbit allergy