

# Randomized, Double-Blind, Placebo-Controlled Trial of Recombinant Human C1 Inhibitor for Prophylaxis of Hereditary Angioedema Attacks

**Marc Riedl, MD<sup>1</sup>; Vesna Grivcheva Panovska, MD<sup>2</sup>; Dumitru Moldovan, MD, PhD<sup>3</sup>; James Baker, MD<sup>4</sup>; William H Yang, MD<sup>5,6</sup>; Avner Reshef, MD<sup>7</sup>; Sladjana Andrejevic, MD<sup>8</sup>; Richard F. Lockey, MD<sup>9</sup>; Roman Haki, MD<sup>10</sup>; Shmuel Kivity, MD<sup>11</sup>; Luca Bellizzi, MD<sup>12</sup>; Joseph R Harper, PharmD<sup>13</sup>; Anurag Relan, MD<sup>12</sup>; Marco Cicardi, MD<sup>14</sup>**

<sup>1</sup>Department of Medicine, University of California-San Diego, La Jolla, CA, USA; <sup>2</sup>PHU Clinic for Dermatology, Medical University Skopje, Skopje, Republic of Macedonia; <sup>3</sup>University of Medicine and Pharmacy, Mures County Hospital, Tirgu Mures, Romania; <sup>4</sup>Baker Allergy Asthma Dermatology, Lake Oswego, OR, USA; <sup>5</sup>Ottawa Allergy Research Corporation, Ottawa, Canada; <sup>6</sup>Division of General Internal Medicine, Department of Medicine, University of Ottawa Medical School, Ottawa, Canada; <sup>7</sup>Sheba Medical Center, University of Tel Aviv, Tel-Hashomer, Israel; <sup>8</sup>Clinical Center of Serbia, Belgrade, Serbia; <sup>9</sup>University of South Florida Morsani College of Medicine, Division of Allergy and Immunology, Department of Internal Medicine, Tampa, FL, USA; <sup>10</sup>St. Anne's University Hospital in Brno, Czech Republic; <sup>11</sup>The Allergy and Immunology Unit, The Tel Aviv Medical Center, Sackler Medical School, Tel Aviv, Israel; <sup>12</sup>Department of Clinical Research and Medical Affairs, Pharming Technologies BV, Leiden, the Netherlands; <sup>13</sup>Department of Medical Affairs, Salix Pharmaceuticals, Raleigh, NC, USA; <sup>14</sup>Universita degli Studi di Milano, Milan, Italy

# Disclosures And Acknowledgments

- **Marc Riedl receives research grants from BioCryst, CSL Behring, Dyax, Ionis, Pharming Technologies, and Shire; serves as consultant for Arrowhead, BioCryst, CSL Behring, Dyax, Global Blood Therapeutics, Ionis, Salix Pharmaceuticals, and Shire; and serves on the speakers' bureaus for CSL Behring, Dyax, Salix Pharmaceuticals, and Shire**
- **Vesna Grivcheva Panovska serves as principle investigator for clinical trials sponsored by CSL Behring, Eli Lilly, and Pharming**
- **Dumitru Moldovan receives research grants from CSL Behring, Pharming Technologies, and Shire HGT, serves as consultant or advisory board member for Pharming Technologies, Shire HGT, and Swedish Orphan Biovitrum, and participates in the speakers' bureaus for Pharming Technologies and Shire HGT**
- **James Baker is researcher for BioCryst, CSL Behring, Dyax, Pharming Technologies, and Shire, serves as consultant for BioCryst, and participates in the speakers' bureau for Shire**
- **William H Yang serves as member of national and international advisory boards for CSL Behring, Shire, and Biocryst, and receives unrestricted educational grants from Shire and CSL Behring to attend continuing health education events. He also receives grants for research on acute HAE attacks from CSL Behring, Dyax, Shire, and BioCryst and for research on short-term HAE prophylaxis from CSL Behring, Shire, and BioCryst**
- **Avner Reshef receives research grants from CSL Behring, Pharming Technologies, Shire HGT, Stallergens, and Teva Pharmaceuticals, serves on the speakers' bureaus for Pharming Technologies and Shire HGT, and participates in advisory boards for CSL Behring and Shire HGT**
- **Sladjana Andrejevic, Richard F. Lockey, and Roman Hakl have no conflicts of interest to disclose**
- **Shmuel Kivity has received research support from Shire/Jerini AG**
- **Luca Bellizzi has a consultancy agreement with Pharming Technologies for research and development activities**
- **Joseph R Harper is an employee of Salix Pharmaceuticals**
- **Anurag Relan is an employee of Pharming Technologies**
- **Marco Cicardi acts as a consultant for CSL Behring, Viropharma, Dyax, SOBI, Pharming Technologies, BioCryst, Sigma Tau and receives research or educational grants from Shire and CSL Behring**
  
- **The authors would like to thank Dr. Bruno Giannetti, Pharming, for his contributions to the study.**

# Hereditary Angioedema and rhC1INH

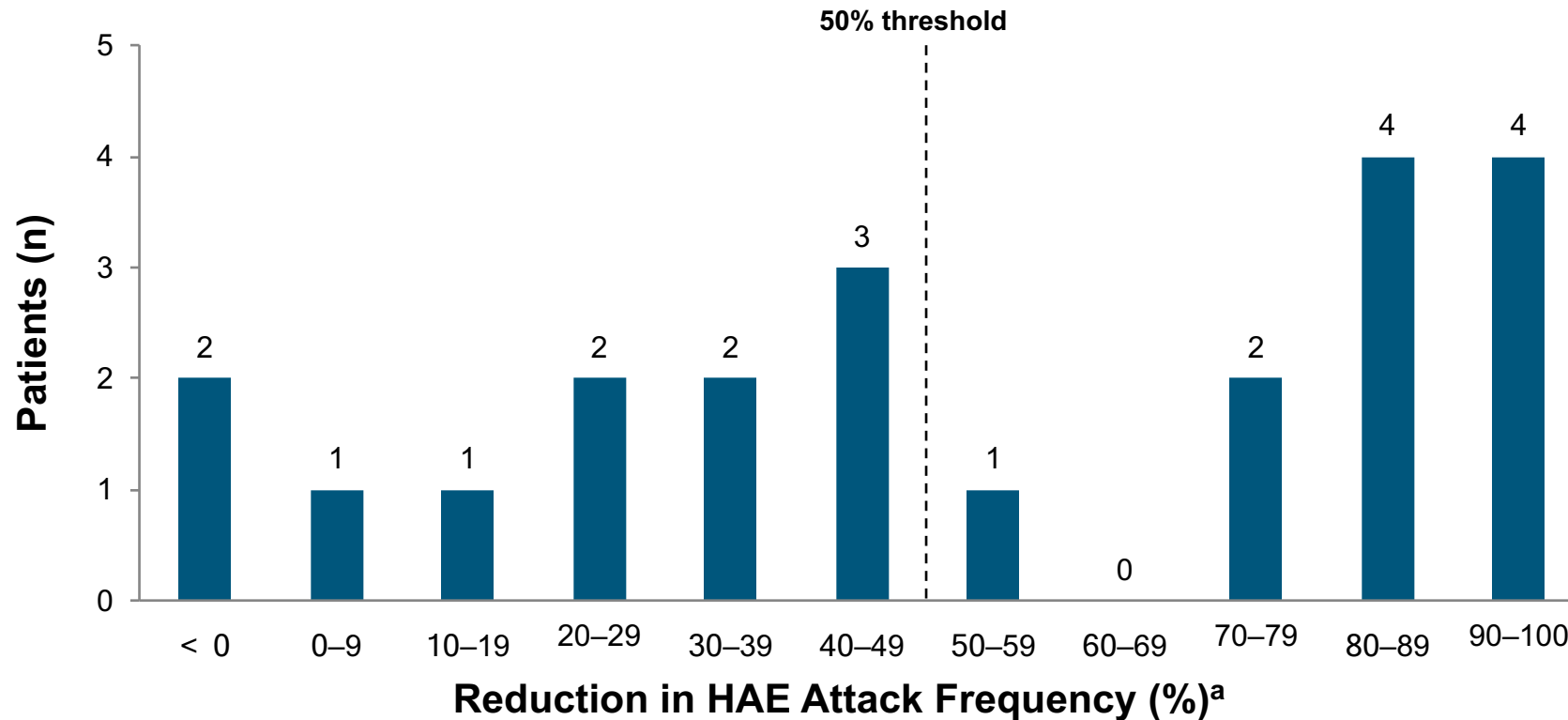
- **HAE due to C1 inhibitor deficiency is a genetic disorder characterized by episodic, unpredictable, potentially life-threatening edema and other manifestations (eg, abdominal pain)<sup>1,2</sup>**
- **rhC1INH is efficacious and well tolerated for acute HAE attacks<sup>3-7</sup>**
- **Previous open-label study suggested potential benefit of rhC1INH prophylaxis<sup>8</sup>**

HAE = hereditary angioedema; rhC1INH = recombinant human C1 esterase inhibitor.

1. Zuraw BL, et al. *J Allergy Clin Immunol*. 2013;131:1491-1493. 2. Zuraw BL. *N Engl J Med*. 2008;359:1027-1036. 3. Li HH, et al. *J Allergy Clin Immunol Pract*. 2015;3:417-423. 4. Moldovan D, et al. *Clin Exp Allergy*. 2012;42:929-935. 5. Riedl MA, et al. *Ann Allergy Asthma Immunol*. 2013;110:295-299. 6. Riedl MA, et al. *Ann Allergy Asthma Immunol*. 2014;112:163-169. 7. Zuraw B, et al. *J Allergy Clin Immunol*. 2010;126:821-827. 8. Reshef A, et al. *Allergy*. 2013;68(1):118-124.

# Plasma-derived C1INH Prophylaxis: Clinical Response

- Prophylaxis with plasma-derived C1INH (n = 22) resulted in varying reduction of HAE attack frequency



<sup>a</sup>2 patients had an increase in HAE attack frequency while receiving plasma-derived C1INH prophylaxis.  
C1INH = C1 esterase inhibitor; HAE = hereditary angioedema.

FDA Briefing Document. Blood Products Advisory Committee Meeting. <http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4355B2-1b.htm>. Published May 2008. Accessed July 26, 2016.

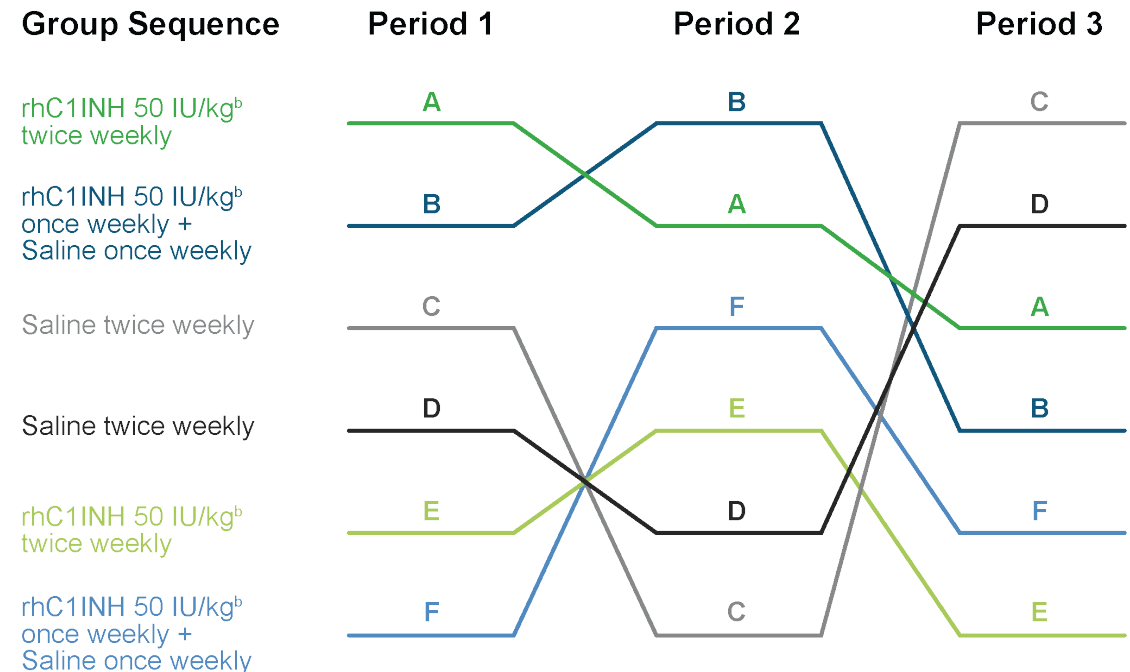
# Objective

- **To evaluate the efficacy and safety of rhC1INH as prophylaxis against angioedema attacks in adolescents and adults with HAE**

# Study Design

- **Phase 2, double-blind, multicenter, crossover study**
- **Patient population**
  - ≥13 years of age
  - Functional C1INH level <50% of normal
  - History of ≥4 HAE attacks/month for ≥3 consecutive months
  - No rabbit-related allergies
- **Randomized to 3 separate 4-week treatment periods, each separated by 1-week washout period**
  - Randomized to 1 of 6 sequences (A-F)
- **Rescue medications permitted for breakthrough HAE attacks<sup>a</sup>**
- **>99% power to detect ≥50% reduction in HAE attacks with 24 patients completing study**

## Treatment Sequences



<sup>a</sup>Rescue medications could include open-label rhC1INH, HAE specific medications (eg, icatibant), or symptomatic medications (narcotics).

<sup>b</sup>50 IU/kg for patients <84 kg; 4200 IU for patients ≥84 kg.

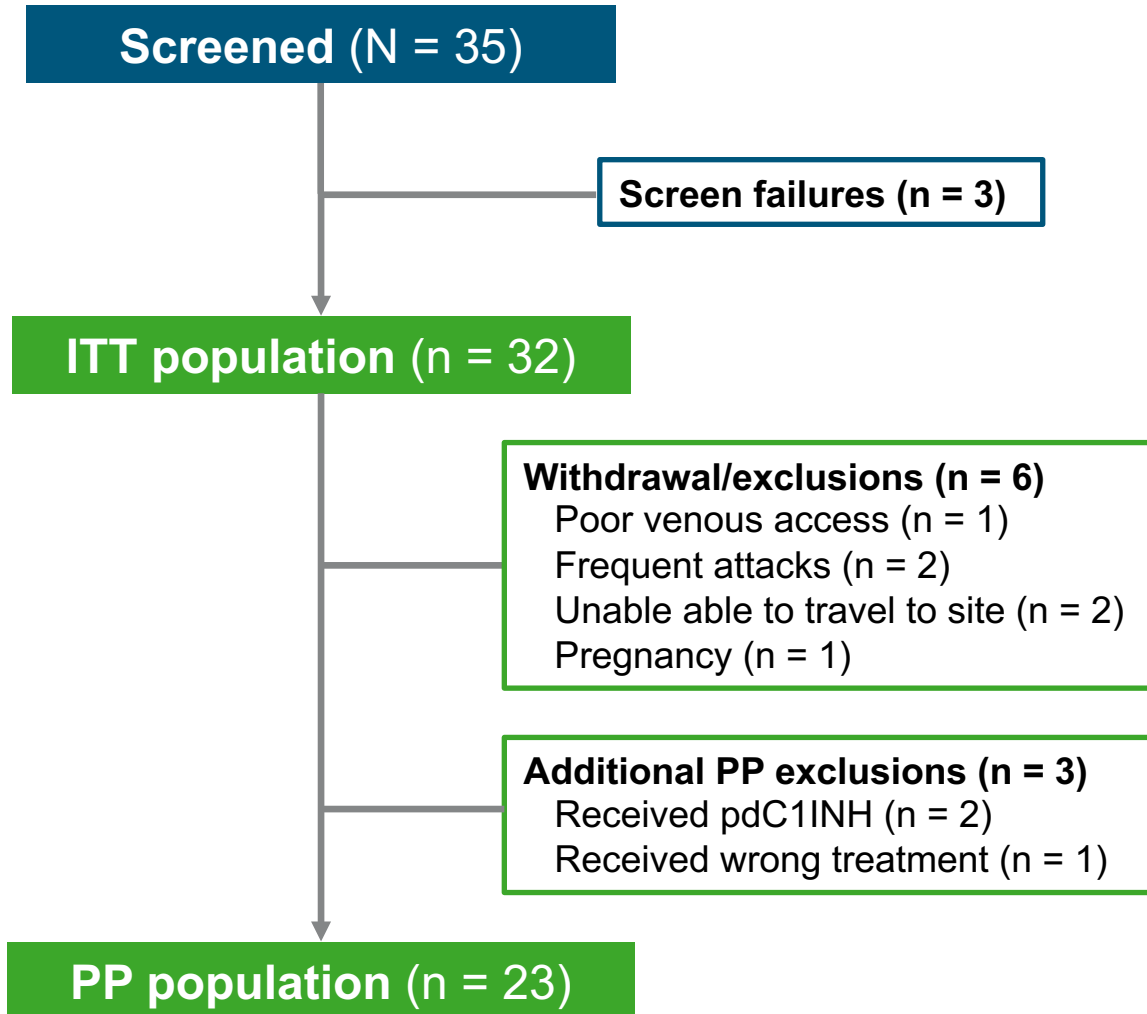
C1INH = C1 esterase inhibitor; HAE = hereditary angioedema; pdC1INH = plasma-derived rhC1INH; rhC1INH = recombinant human C1 esterase inhibitor.

# End Points

- **Primary end point**
  - Number of HAE attacks during 4-week period
- **Secondary end point**
  - Percentage of patients who had clinical response<sup>a</sup>
- **Safety**
  - AEs
  - Thrombotic events
  - Immunogenicity

<sup>a</sup>Clinical response defined as a  $\geq 50\%$  reduction in the number of attacks from the placebo treatment period to the rhC1INH-treatment period.  
AE = adverse event; HAE = hereditary angioedema; rhC1INH = recombinant human C1 esterase inhibitor.

# Patient Disposition and Demographics



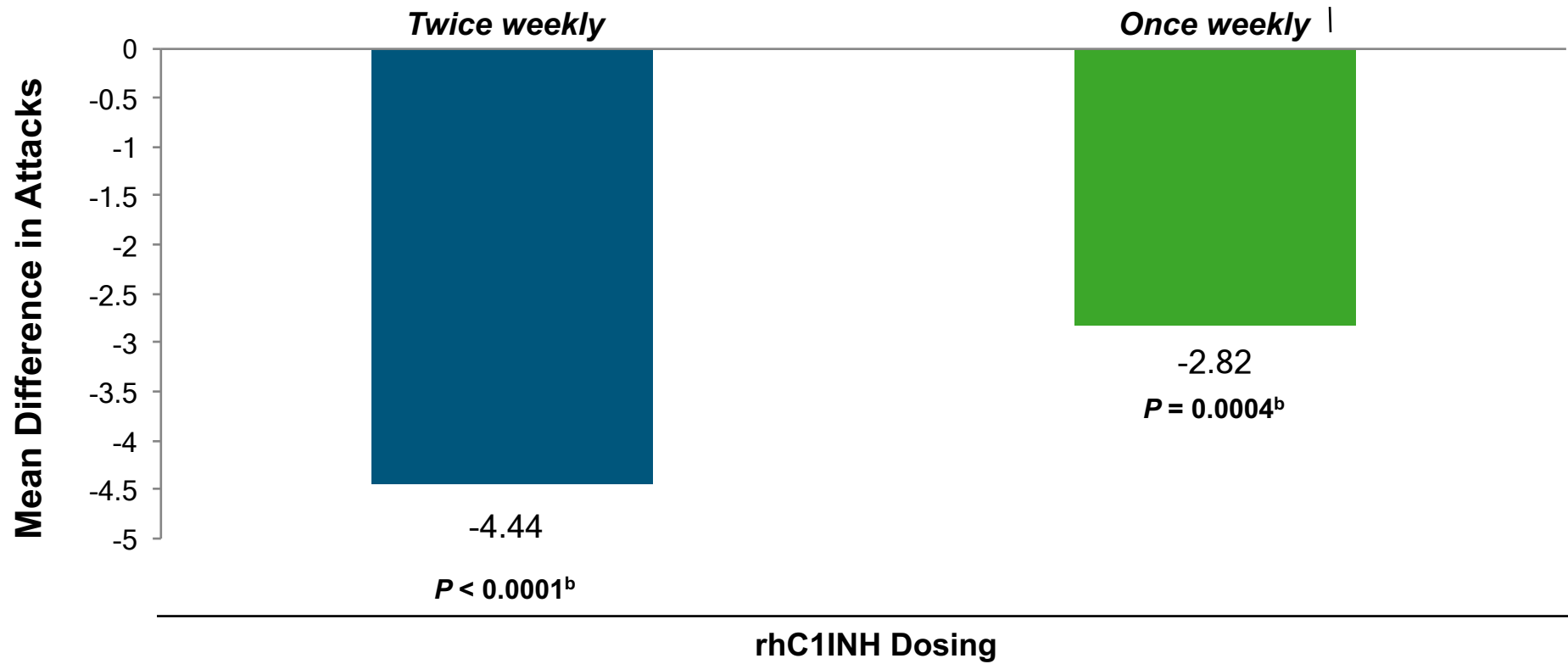
Parameter	ITT population (n = 32)
Mean age, y (SD)	45.9 (14.5)
Sex, n (%)	
Female	26 (81.3)
Male	6 (18.8)
Race, white, n (%)	32 (100.0)
Prior use of prophylaxis, n (%)	6 (18.8)
Mean attacks within last 3 months, n (SD)	17.9 (7.2)

HAE = hereditary angioedema; ITT = intention-to-treat; pdC1INH = plasma-derived C1 esterase inhibitor; PP = per protocol; SD = standard deviation.



# Reduction in Number of HAE Attacks

- rhC1INH treatment significantly reduced number of HAE attacks<sup>a</sup> versus placebo (n = 32; ITT population)



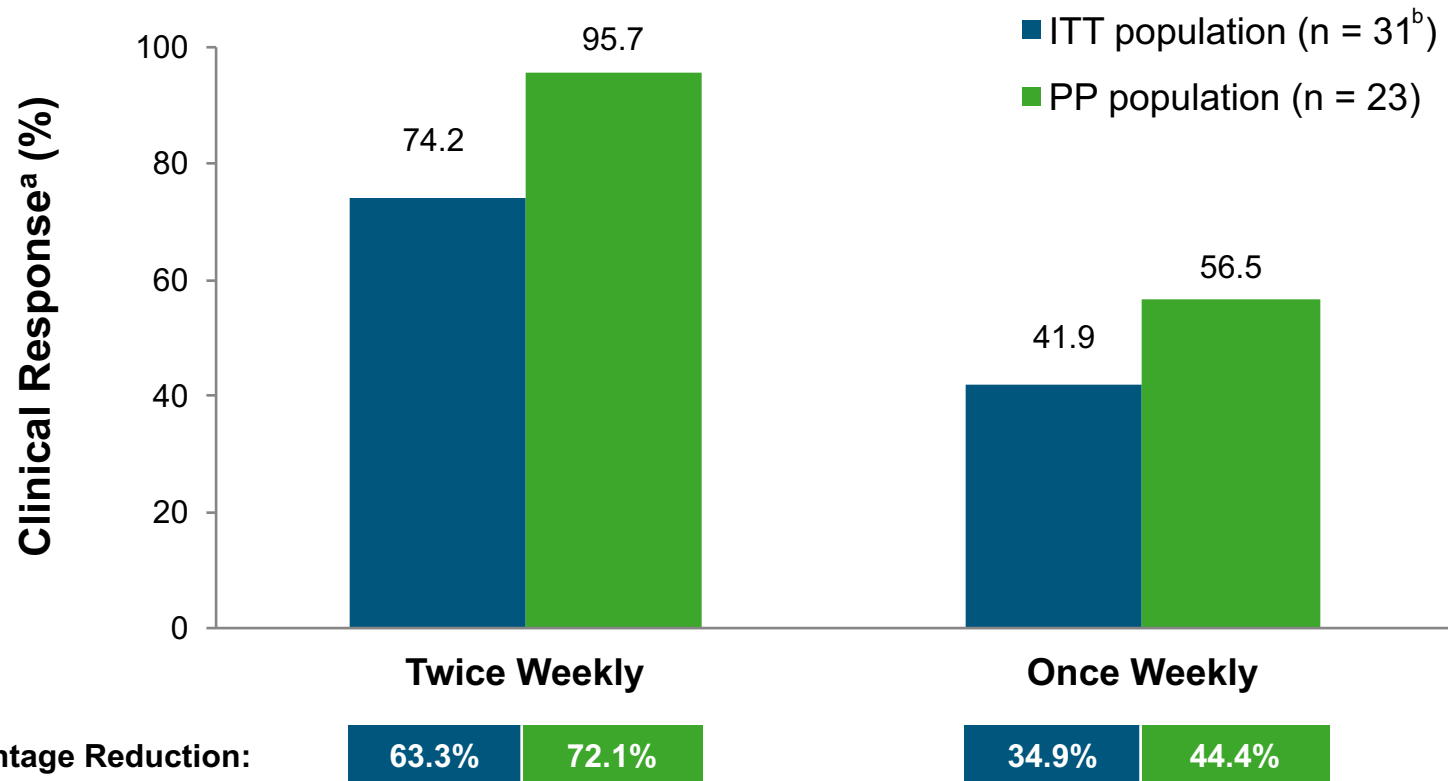
<sup>a</sup>Attack number normalized to a 28-day treatment period.

<sup>b</sup>P-values derived from negative binomial model

Error bars represent standard deviation.

HAE = hereditary angioedema; ITT = intention-to-treat; rhC1INH = recombinant human C1 esterase inhibitor.

# Clinical Response



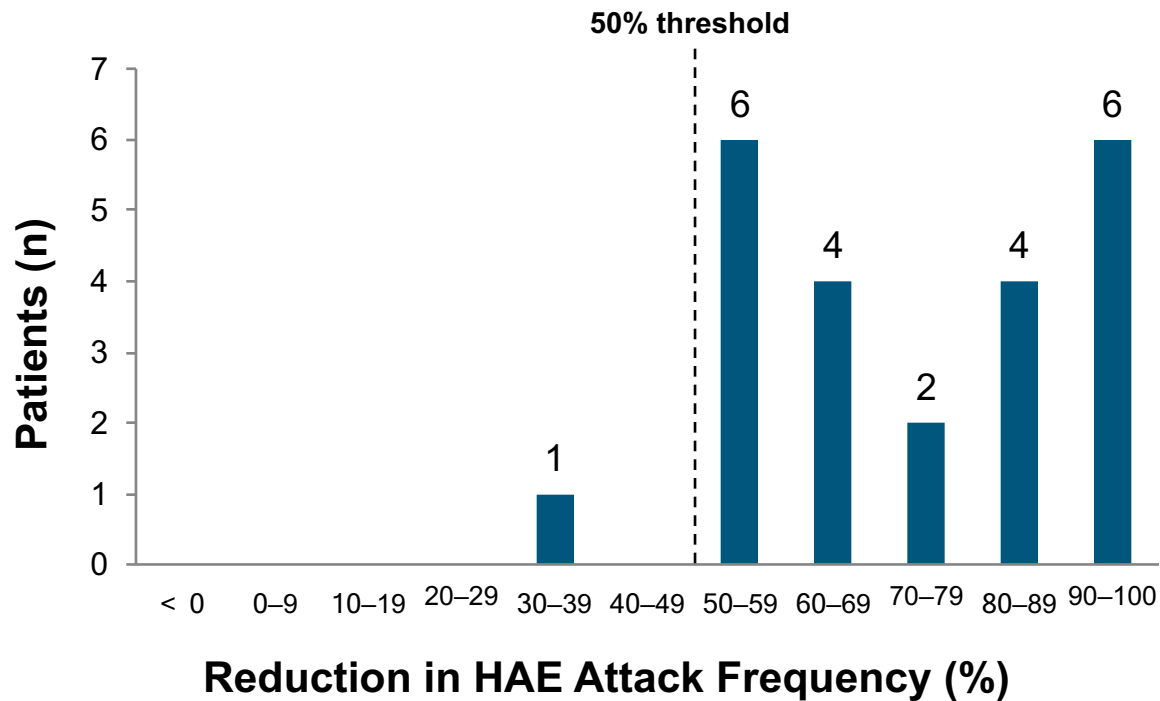
<sup>a</sup>Patients who had  $\geq 50\%$  reduction in number of HAE attacks (normalized to a 28-day treatment period) from placebo treatment period to rhC1INH treatment period.

<sup>b</sup>Excludes 1 patient who was randomized to treatment but did not receive study medication.

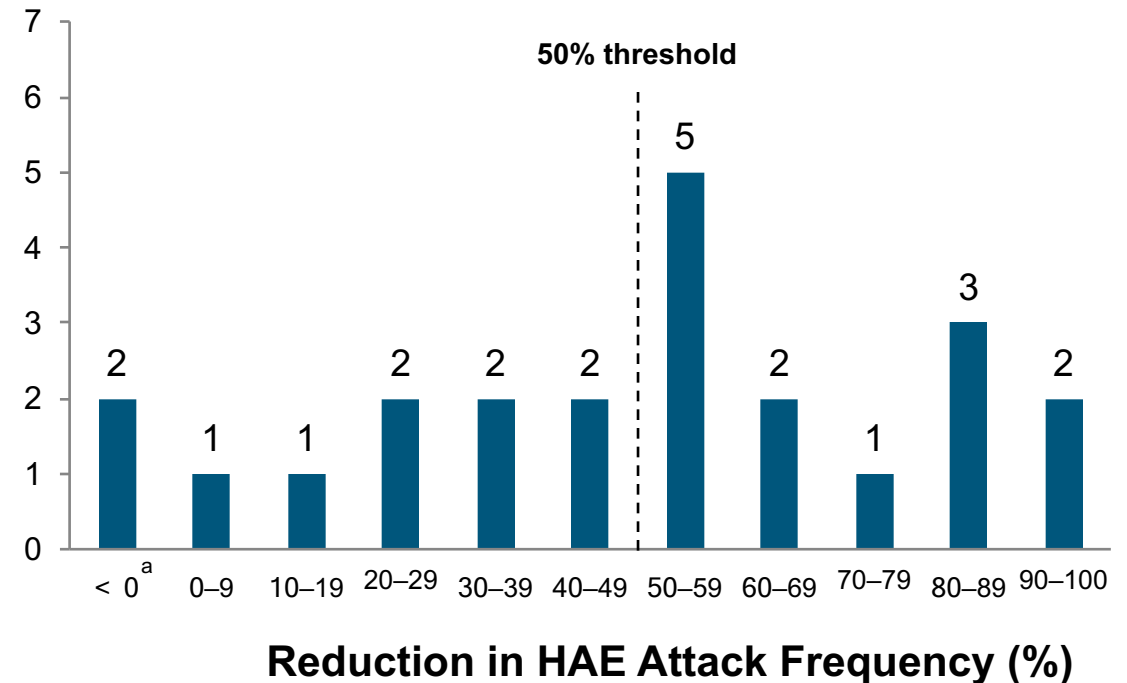
HAE = hereditary angioedema; ITT = intention-to-treat; PP = per protocol; rhC1INH = recombinant human C1 esterase inhibitor.

# Range of Percentage Reduction in Clinical Response (PP)

Twice Weekly Dosing (n=23)



Once Weekly Dosing (n=23)



<sup>a</sup>2 patients had an increase in HAE attack frequency while receiving once weekly rhC1INH prophylaxis. One patient an increase of 40% and one patient an increase of 62.5%.  
HAE = hereditary angioedema; rhC1INH = recombinant human C1 esterase inhibitor.

# Safety Assessments

Parameter	rhC1INH twice weekly (n = 29)	rhC1INH once weekly (n = 29)	Placebo (n = 28)
Any AE	10 (34.5)	13 (44.8)	8 (28.6)
Serious AE	1 (3.4) <sup>a</sup>	0	0
AE-related discontinuation	0	0	0
AEs <sup>b</sup>			
Headache	5 (17.2)	2 (6.9)	0
Nasopharyngitis	0	3 (10.3)	2 (7.1)
Anxiety	0	2 (6.9)	0
Additional assessments			
Hypersensitivity or anaphylactic reactions	0	0	0
Neutralizing antibodies	0	0	0
Thrombotic or TE events	0	0	0

<sup>a</sup>Patient underwent a urologic procedure for pre-existing phimosis.

<sup>b</sup>Adverse events that occurred in ≥5% of patients in any treatment group (safety population).

AE = adverse event; ; rhC1INH = recombinant human C1 esterase inhibitor; TE = thromboembolic.

# Conclusions

- **rhC1INH 50 IU/kg (up to 4200 IU/kg) administered once or twice weekly significantly reduced the number of HAE attacks**
  - Most patients had  $\geq 50\%$  reduction during treatment with rhC1INH
  - 22 of 23 patients (95.7%) had  $\geq 50\%$  reduction with twice weekly rhC1INH
- **Administration of rhC1INH for up to 8 weeks was generally well tolerated**
- **Further research on rhC1INH as prophylaxis for the prevention of HAE attacks is warranted**

# Back-Up Slides

# Generalized Estimating Equation Analysis<sup>a</sup>

- 1-week washout between treatment periods
- No evidence for carryover effect observed

Parameter	<i>P</i> -value
Sequence effect	0.7
Treatment effect	<0.0001
Period effect	0.6

<sup>a</sup>n = 31; excludes 1 patient who was randomized to treatment but did not receive study medication.