Submission of Clinical and Economic Data Supporting Formulary Consideration of:

RUCONEST®
(recombinant human C1 esterase inhibitor)
for intravenous injection

Prepared by:

Salix Pharmaceuticals, Inc.

Preface

This dossier is provided in response to your unsolicited request to Salix Pharmaceuticals, Inc. for a formulary submission document for RUCONEST® (C1 esterase inhibitor [recombinant]) in accordance with the Academy of Managed Care Pharmacy (AMCP) format.

In addition to published data and information included in the Food and Drug Administration (FDA)-approved product labeling, this dossier contains information not included in the product labeling, as well as unpublished data (eg, posters, presentation, etc). These data are provided to assist pharmacist and physician managed care decision makers in formulary and coverage evaluations, following AMCP version 3.1 dossier format guidelines.

This dossier should be used only by the intended health plan, and its distribution and/or duplication is prohibited. Please consult the enclosed prescribing information for complete safety and prescribing information for RUCONEST.

If you have any additional questions, please contact Salix Pharmaceuticals, Inc. Medical Affairs.

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Abbreviations Used in Dossier

AAAAI – American Academy of Allergy, Asthma & Immunology

ACAAI – American College of Allergy, Asthma & Immunology

ACE – angiotensin-converting enzyme

AE – adverse event

AERS – AE Reporting System

AHFS – American Hospital Formulary Service

aPTT – activated partial thromboplastin time

C1INH – C1 esterase inhibitor

CI – confidence interval

CL – plasma clearance

C_{max} – maximum observed concentration

FDA – Food and Drug Administration

GI – gastrointestinal

HAE – hereditary angioedema

HAEMAB – US Hereditary Angioedema Association Medical Advisory Board

hr – hour(s)

HMV – high molecular weight

HRI – host-related impurities

IS – investigator score

ITT – intent-to-treat

IV - intravenous

MedDRA – Medical Dictionary for Regulatory Activities

min – minute(s)

NA – not available

NDC – National Drug Code

OLE – open-label extension

pdC1INH – plasma-derived human C1 esterase inhibitor

PD – pharmacodynamics

PK – pharmacokinetics

PT – prothrombin time

RCT – randomized controlled trial

rhC1INH – recombinant human C1 esterase inhibitor

SAE – serious adverse event

SC – subcutaneous

SD – standard deviation

$t_{1/2}$ – half-life

TE – thromboembolic

TEAE – treatment-emergent adverse event

TEQ – treatment effect questionnaire

VAS – visual analog scale

V_{ss} – volume of distribution at steady state

WAC – wholesale acquisition cost

1.0 EXECUTIVE SUMMARY

Hereditary angioedema (HAE) is a rare, autosomal-dominant genetic disorder caused by deficiency in functional C1 esterase inhibitor (C1INH). Attacks in patients with HAE are characterized as acute, unpredictable, and recurrent and can be painful, disabling, and in some cases life threatening, if untreated.

1.1 Clinical Benefits

RUCONEST is the first and only recombinant human C1INH approved for the treatment of acute angioedema attacks in patients with HAE. Effectiveness was not established in HAE patients with laryngeal attacks. Efficacy was demonstrated in a multi-center, randomized, placebo-controlled (RCT) clinical trial and was supported by two additional RCT (Zuraw 2010, Reidl 2014). All 3 studies demonstrated a shorter median time to onset of sustained attack-related symptom relief versus placebo. Each of these pivotal trials also included open-label extensions (OLE) that further showed efficacy of RUCONEST for treatment of repeat attacks without reports of attack relapse (Moldovan 2012, Reidl 2013, Li 2013).

The recommended dose of RUCONEST is 50 IU/kg (or 4200 IU if the patient is >84 kg) administered intravenously as a single dose, followed by a second dose if needed. There are no known drug interactions or precautions. RUCONEST is contraindicated in patients with a history of allergy to rabbits or rabbit-derived products and in patients with a history of life-threatening immediate hypersensitivity reactions to C1 esterase inhibitor preparations, including anaphylaxis.

RUCONEST restores plasma C1INH levels to normal range by replacing dysfunctional/absent protein that is the hallmark of genetic C1INH-defiency in HAE, returning levels to within the normal functional range (van Doorn 2005). RUCONEST has a favorable safety profile comparable to placebo and there have been no thromboembolic events reported to date with use of RUCONEST. The most common adverse events reported in clinical trials (≥ 2%) were headache, nausea, and diarrhea.

1.2 Economic Benefits

There are no economic studies evaluating RUCONEST for the treatment of acute attacks in adult and adolescent patients with HAE.

1.3 Conclusions

RUCONEST is a C1 recombinant esterase inhibitor indicated for the treatment of acute attacks in adult and adolescent patients with HAE. Because of the limited number of patients with laryngeal attacks, effectiveness was not established in HAE patients with laryngeal attacks. RUCONEST is a much needed treatment option for patients suffering from acute attacks of HAE since previously there has not been an FDA-approved recombinant C1 esterase inhibitor option to treat symptoms of HAE. The safety and efficacy of rhC1INH were established by 10 clinical studies of immunogenicity, PK, safety, and efficacy, and by nonclinical toxicity and pharmacology studies that provide safety and efficacy data on a total of 239 HAE patients and healthy volunteer subjects who received a combined total of 1007 administrations of RUCONEST. The pivotal RCT and OLE studies, which are supported by the results of two additional RCTs and two additional OLE studies, demonstrated the ability of RUCONEST to reduce the median time to beginning of relief of symptoms while maintaining a favorable safety profile in patients with HAE.

2.0 PRODUCT INFORMATION AND DISEASE DESCRIPTION

2.1 Product Information

2.1.1 Generic & Brand Name, Therapeutic Class

RUCONEST 2100 IU powder for solution for injection contains the active substance human C1 esterase inhibitor (recombinant) which is purified from the milk of rabbits expressing the gene encoding for human C1 esterase inhibitor.

2.1.2 Dosage Forms, Strengths & Package Sizes

RUCONEST is available as a lyophilized powder for reconstitution for injection in a single-use 25 mL glass vial. Each vial contains 2100 IU of rhC1INH. The powder for solution for injection is reconstituted with 14 mL sterile Water for Injection per vial, to prepare a solution of 150 U/mL to be administered by intravenous (IV) injection. The reconstituted solution should be administered at room temperature as a slow intravenous injection over approximately 5 minutes.

Table 2-1. Recommended dose of RUCONEST for an acute attack

Body weight	RUCONEST Dose for Intravenous Injection	Volume (mL) of Reconstituted Solution (150 IU/mL) to be Administered
< 84 kg	50 IU per kg	Body weight in kg divided by 3
≥ 84 kg	4200 IU (2 vials)	28 mL

If the attack symptoms persist, an additional (second) dose can be administered at the recommended dose level. Do not exceed 4200 IU per dose. No more than two doses should be administered within a 24 hour period.

2.1.3 National Drug Code (NDC)

Vial: 68012-350-01; Carton: 68012-350-02

2.1.4 Wholesale Acquisition Cost (WAC)

Please contact a Salix representative for current pricing.

2.1.5 American Hospital Formulary Service (AHFS) Drug Classification

92:32 - Complement Inhibitors

2.1.6 Food and Drug Administration (FDA)-Approved Indications and Usage

FDA-Approved Use

Acute HAE (FDA Approval Date: July 16, 2014)

RUCONEST is indicated for the treatment of acute attacks in adult and adolescent patients with HAE.

Limitation of use: Effectiveness was not established in HAE patients with laryngeal attacks.

Non FDA-Approved Use

In addition to the treatment of acute HAE attacks, some patients may benefit from long-term therapy to prevent HAE attacks (prophylaxis).

2.1.7 Pharmacology

Refer to the RUCONEST prescribing information (section 12.1) in Section 6.1 of the dossier.

2.1.8 Pharmacokinetics

The pharmacokinetics of RUCONEST was evaluated in a study of 12 asymptomatic HAE patients (dose ranged from 6.25 IU/kg to 100 IU/kg). Pharmacokinetics evaluation was performed by non-compartmental analysis, using functional C1INH levels. Following administration of RUCONEST (50 IU/kg) in asymptomatic HAE patients (**Table 2-2**), the mean Cmax was 1.2 IU/mL, and the elimination $t_{1/2}$ was approximately 2.5 hours. The clearance of RUCONEST was nonlinear (clearance decreased with increasing dose) over the dose range of 25-100 IU/kg.

Table 2-2. Baseline corrected pharmacokinetic parameters (Mean ± SD) following administration of 50 IU/kg and 100 IU/kg RUCONEST to asymptomatic HAE patients

Parameters	50 IU/kg	100 IU/kg
$C_{baseline}$ (IU/mL)	0.18 ± 0.12	0.14 ± 0.08
C_{max} (IU/mL)	1.2 ± 0.2	2.3 ± 0.2
T_{max} (hours)	0.31 ± 0.10	0.31 ± 0.10
AUC (IUxhr/mL)	3.3 ± 1.0	10.6 ± 2.5
CL (mL/hr)	1207 ± 414	781 ± 147
$t_{1/2}$ (hours)	2.4 ± 0.6	2.7 ± 0.3
V_{ss} (L)	3.0 ± 0.9	2.4 ± 0.5

Studies have not been conducted to evaluate the PK of RUCONEST in special patient populations, identified by, race, age (pediatric or geriatric), or the presence of renal or hepatic impairment.

2.1.9 Pharmacodynamics

The complement component (protein) C4 is a substrate for activated C1. Patients with HAE have low levels of C4 in the circulation; RUCONEST shows a dose-dependent restoration of complement homeostasis of C4 in HAE patients. A dose of 50 IU/kg of RUCONEST increases plasma C1INH activity levels to greater than 0.7 IU/mL (the lower limit of normal) in HAE patients.

2.1.10 Contraindications, Warnings and Precautions, and Adverse Effects

Contraindications

RUCONEST is contraindicated in patients with a history of allergy to rabbits or rabbit-derived products.

RUCONEST is contraindicated in patients with a history of life-threatening immediate hypersensitivity reactions to C1 esterase inhibitor preparations, including anaphylaxis.

Warnings and Precautions

Hypersensitivity

Severe hypersensitivity reactions may occur. The signs and symptoms of hypersensitivity reactions may include hives, generalized urticaria, tightness of the chest, wheezing, hypotension, and/or anaphylaxis during or after injection of RUCONEST. Should symptoms occur, discontinue RUCONEST and institute appropriate treatment. Because hypersensitivity reactions may have symptoms similar to HAE attacks, treatment methods should be carefully considered.

Thromboembolic Events

Serious arterial and venous thromboembolic (TE) events have been reported at the recommended dose of plasma derived C1 esterase inhibitor products in patients with risk factors. Risk factors may include the presence of an indwelling venous catheter/access device, prior history of thrombosis, underlying atherosclerosis, use of oral contraceptives or certain androgens, morbid obesity, and immobility. Monitor patients with known risk factors for TE events during and after RUCONEST administration.

Adverse Effects

The serious adverse reaction in clinical studies of RUCONEST was anaphylaxis.

The most common adverse reactions (≥ 2%) reported in all clinical trials were headache, nausea, and diarrhea.

2.1.11 Drug Interactions

Drug-Drug

No drug-drug interaction studies with RUCONEST have been performed.

Drug-Food

There are no known food effects for RUCONEST.

Drug-Disease

There are no known drug-disease interactions for RUCONEST.

2.1.12 Dosage and Administration

Refer to the RUCONEST prescribing information (section 2) in Section 6.1 of the dossier.

2.1.13 Access / Restrictions on Distribution

There is no restricted access for the distribution of RUCONEST.

2.1.14 Co-prescribed / Concomitant Therapies

There are no co-prescribed or concomitant therapies for RUCONEST.

2.1.15 Comparison of RUCONEST and Other Medications Used for Hereditary Angioedema

The information presented in **Table 2-3** has been derived exclusively from the respective prescribing information. Additional information may be available in the published literature but was not included in the table.

Table 2-3. Comparator Table

	RUCONEST®	BERINERT®	CINRYZE®	FIRAZYR®	KALBITOR®
Generic Name	C1INH (recombinant)	C1INH (human)	C1INH (human)	icatibant	ecallantide
Class	C1 esterase inhibitor (human), recombinant	C1 esterase inhibitor (human), plasma-derived	C1 esterase inhibitor (human), plasma-derived	bradykinin B2 receptor antagonist	plasma kallikrein inhibitor
Indications	Treatment of acute attacks in adult and adolescent patients with HAE. Limitation of Use: Effectiveness was not established in HAE patients with laryngeal attacks.	Treatment of acute abdominal, facial, or laryngeal HAE attacks in adult and adolescent patients.	For routine prophylaxis against angioedema attacks in adolescent and adult patients with HAE.	Treatment of acute attacks of HAE in adults age ≥18 years.	Treatment of acute attacks of HAE in patients age ≥12 years.
Dosing	2100 IU in a single-use vial for reconstitution with 14 mL sterile Water for Injection per vial for a solution of 150 IU/mL; for body weight <84 kg, administer 50 IU/kg; for body weight ≥84 kg, administer 4200 IU (2 vials); administer IV slowly over 5 min. Do not exceed 4200 IU per dose and no more than 2 doses in a 24-hour period.	500 IU in a single-use vial for reconstitution with 10 mL sterile Water for Injection of a 20 IU/kg dose; administer IV at a rate of 4 mL/min over 10 min.	2 single-use vials of 500 IU each reconstituted with 5 mL sterile Water for Injection of a 1000 U dose to be administered every 3 or 4 days for routine HAE attack prophylaxis; administer IV at an injection rate of 1 mL/min over 10 min.	10 mg/mL solution in 3 mL in a prefilled syringe for a 30 mg SC injection in the abdomen; administer SC injection over at least 30 sec; additional doses may be administered at intervals of at least 6 hours for no more than 3 total doses in a 24-hour period.	3 single-use vials of 10 mg/mL for three 1 mL SC injections (abdomen, thigh, or upper arm) for a total dose of 30 mg (3 mL); if attack persists, an additional dose of 30 mg may be administered within a 24-hour period.
Pharmacology	C1INH is a normal constituent of human blood and is one of the serine protease inhibitors (serpins); administration of RUCONEST (rhC1INH) to patients	C1INH is a normal constituent of human blood and is one of the serine protease inhibitors (serpins); administration of plasma-derived BERINERT (pdC1INH),	C1INH is a normal constituent of human blood and is one of the serine protease inhibitors (serpins); administration of plasma-derived CINRYZE (pdC1INH), obtained from	FIRAZYR is a synthetic decapeptide that acts as a competitive antagonist to the bradykinin B2 receptor, with an affinity similar to bradykinin (which exerts its effect in	KALBITOR is a potent, selective, reversible inhibitor of plasma kallikrein (which converts high molecular weight [HMW] kininogen to bradykinin that in turn

	RUCONEST®	BERINERT®	CINRYZE®	FIRAZYR®	KALBITOR®
	with HAE, who have C1INH deficiency, replaces the missing or malfunctioning C1INH activity in patients, thereby restoring its inhibitory effects on the complement and contact pathways to treat the symptoms of an acute episodic HAE attack.	obtained from plasma donors, to patients with HAE, who have C1INH deficiency, replaces the missing or malfunctioning protein and C1INH activity in patients, thereby restoring its inhibitory effects on the complement and contact pathways to treat the symptoms of an acute episodic HAE attack.	plasma donors, to patients with HAE, who have C1INH deficiency, replaces the missing or malfunctioning protein and C1INH activity in patients, thereby restoring its inhibitory effects on the complement and contact pathways as a means of prophylaxis for HAE attacks.	HAE via vasodilation); FIRAZYR inhibits binding of bradykinin to the B2 receptor and thereby treats the clinical symptoms of an acute episodic HAE attack.	exerts its effect in HAE via vasodilation); KALBITOR blocks plasma kallikrein's binding site, inhibiting conversion of HMW kininogen to bradykinin, and thereby treats symptoms of an acute episodic HAE attack.
Pharmacokinetics	Following administration of RUCONEST (50 IU/kg) in asymptomatic HAE patients, the mean C_{max} was 1.2 IU/mL, and the elimination $t_{1/2}$ was approximately 2.5 hours. The clearance of RUCONEST decreased with increasing dose over the dose range of 25-100 IU/kg.	After a single IV injection of BERINERT at a dose of 500 to 1500 IU, the CL was 0.60±0.17 mL/hr/kg (range: 0.34-0.96), or 1.44±0.67 mL/hr/kg (range: 0.43-3.85) when adjusted for baseline in adults (N=35) with HAE. The CL (with or without baseline adjustment) in pediatric subjects with HAE (N=5) age 6-13 years were similar, but CL on a per-kg basis was faster in children when adjusted for baseline. Adults in this study (N=35) had a BERINERT t1/2 of 21.9±1.7 hour (range: 16.5-24.4), or 18.4±3.5 hour (range: 7.4-22.8) when adjusted for baseline. The $t_{1/2}$ in children was shorter when adjusted for baseline.	Patients with non-symptomatic HAE received a single dose of 1000 IU or 1000 IU followed by a 2nd dose of 1,000 IU given 1 hour later. The mean $t_{1/2}$ of CINRYZE was 56 hour (range: 11-108 hour; n=7) for a single dose and 62 hour (range: 16-152 hour; n=9) for the double dose. The CL after a single dose was 0.85±1.07 (n=7) and 1.17±0.78 (n=9) after a double dose.	After a 30 g SC injection in healthy subjects (N=96), the CL of FIRAZYR was 245±58 mL/min with a mean elimination $t_{1/2}$ of 1.4±0.4 hour.	After a single 30 mg SC injection of KALBITOR in healthy subjects, plasma concentration declined with a mean elimination $t_{1/2}$ of 2.0±0.5 hour and CL of 153±20 mL/min.
Adverse Effects	The serious adverse reaction in clinical studies of RUCONEST	The most serious adverse reaction reported in subjects who received	The only serious adverse reaction observed in clinical studies of CINRYZE was	The most commonly reported adverse reactions were injection	The most common adverse reactions occurring in ≥3% of

	RUCONEST®	BERINERT®	CINRYZE®	FIRAZYR®	KALBITOR®
	was anaphylaxis. The most common adverse reactions (≥ 2%) reported in all clinical trials were headache, nausea, and diarrhea.	BERINERT was increased severity of HAE-associated pain. The most common adverse reaction reported in >4% of subjects and greater than placebo among subjects who received BERINERT in the placebo-controlled clinical trial was dysgeusia.	cerebrovascular accident. The most common adverse reactions observed were headache, nausea, rash, and vomiting.	site reactions, which occurred in almost all patients (97%) in clinical trials. Other common adverse reactions occurring in >1% of patients included pyrexia, transaminase increase, dizziness, and rash.	KALBITOR-treated patients and greater than placebo are headache, nausea, diarrhea, pyrexia, injection site reactions, and nasopharyngitis. Anaphylaxis occurred in 3.9% of treated patients (see Warnings / Precautions, below).
Warnings / Precautions	Hypersensitivity reactions, including anaphylaxis may occur. Should symptoms occur, discontinue RUCONEST and administer appropriate treatment. Serious arterial and venous thromboembolic events have been reported at the recommended dose of plasma derived C1 esterase inhibitor products in patients with risk factors. Monitor patients with known risk factors for TE events during and after RUCONEST administration.	Hypersensitivity reactions may occur. Epinephrine should be immediately available to treat any acute severe hypersensitivity reactions following discontinuation. Serious arterial and venous thrombotic events have been reported at the recommended dose of C1INH products, including BERINERT, following treatment of HAE. Risk factors may include the presence of an indwelling venous catheter/access device, prior history of thrombosis, underlying atherosclerosis, use of oral contraceptives or certain androgens, morbid obesity, and immobility. Thrombotic events also have been reported in association with Berinert when used off-label and at higher than labeled doses. Monitor closely	Severe hypersensitivity reactions may occur. Signs and symptoms of hypersensitivity may include appearance of hives, urticaria, tightness of the chest, wheezing, hypotension, and/or anaphylaxis experienced during or after injection of CINRYZE. Serious arterial and venous thromboembolic events have been reported at the recommended dose of C1INH products, including CINRYNZE, following administration in patients with HAE. Risk factors may include presence of an indwelling venous catheter/access device, prior history of thrombosis, underlying atherosclerosis, use of oral contraceptives, certain androgens, morbid obesity, and immobility. Monitor patients with known risk factors for thromboembolic events during and after CINRYZE	Following treatment with FIRAZYR for laryngeal attacks, advise patients to seek immediate medical attention.	Hypersensitivity reactions including anaphylaxis; anaphylaxis has occurred in 4% of 255 HAE patients within first hour after dosing. Other adverse reactions indicative of hypersensitivity reactions included pruritus (5%), rash (3%), and urticaria (2%). Patients should be observed for an appropriate period of time after KALBITOR administration. Given the similarity between hypersensitivity and acute HAE symptoms, monitor patients closely for hypersensitivity reactions. **BOXED WARNING**: Anaphylaxis has been reported after administration of KALBITOR. Because of the risk of anaphylaxis, KALBITOR should only be administered by a healthcare professional

	RUCONEST®	BERINERT®	CINRYZE®	FIRAZYR®	KALBITOR®
		patients with known risk factors. BERINERT is made from human plasma and may contain infectious agents (e.g., viruses and, theoretically, Creutzfeldt-Jakob disease agent). Following self-administration of BERINERT for laryngeal attacks, advise patients to immediately seek medical attention.	administration. Thromboembolic events have been reported following administration C1INH when used off-label at higher than labeled doses. In an open-label trial further investigating the use of CINRYZE for prevention (n=146) of HAE attacks, 5 serious thromboembolic events (including myocardial infarction, deep vein thrombosis, pulmonary embolism and 2 events of cerebrovascular accident) occurred. Subjects had underlying risk factors for thromboembolic events. CINRYZE is made from human blood and may carry a risk of transmitting infectious agents (e.g., viruses, and, theoretically, the Creutzfeldt-Jakob disease agent).		with appropriate medical support to manage anaphylaxis and HAE. Healthcare professionals should be aware of the similarity of symptoms between hypersensitivity reactions and hereditary angioedema, and patients should be monitored closely. Do not administer KALBITOR to patients with known clinical hypersensitivity to KALBITOR.
Contraindications	Known or suspected allergy to rabbits and rabbit-derived products History of immediate hypersensitivity reactions, including anaphylaxis, to C1 esterase inhibitor preparations.	BERINERT is contra-indicated in individuals who have experienced life-threatening hypersensitivity reactions, including anaphylaxis, to C1INH preparations.	CINRYZE is contra-indicated in patients who have manifested life-threatening immediate hypersensitivity reactions, including anaphylaxis, to the product.	None	Do not administer KALBITOR to a patient who has known clinical hypersensitivity to KALBITOR.
Drug Interactions	No drug interaction studies have been conducted.	No drug interaction studies have been conducted.	No drug interaction studies have been conducted.	FIRAZYR is a bradykinin B2 receptor antagonist with potential for pharmacodynamic interaction with ACE inhibitors; FIRZYR may	No drug interaction studies have been conducted.

	RUCONEST®	BERINERT®	CINRYZE®	FIRAZYR®	KALBITOR®
				attenuate anti-hypertensive effects of ACE inhibitors. Clinical trials excluded patients on ACE inhibitors.	

Abbreviations used: ACE = angiotensin-converting enzyme, C1INH = C1 esterase inhibitor, CL = plasma clearance, C_{max} = maximum observed concentration, HAE = hereditary angioedema, HMW = high molecular weight, hr = hour(s), IV = intravenous, NA = not available, min = minute(s), pdC1INH = plasma-derived C1 esterase inhibitor, rhC1INH = recombinant human C1 esterase inhibitor, SC = subcutaneous, $t_{1/2}$ = half-life, TE = thromboembolic, V_{ss} = volume of distribution at steady-state.

BERINERT is a registered trademark of CSL Behring, LLC, Kankakkee, IL, USA; CINRYZE is a registered trademark of ViroPharma Biologics, Inc., Exton, PA, USA; FIRAZYR is a registered trademark of Shire Orphan Therapies, Inc., Lexington, MA, USA; KALBITOR is a registered trademark of Dyax Corp, Burlington, MA,USA.

2.2 Place of Product in Therapy

2.2.1 Disease Description: Hereditary Angioedema

HAE is a rare, autosomal-dominant genetic disorder caused by deficiency in functional C1INH, which is encoded by a single gene on chromosome 11 (Bock 1986). Angioedema attacks in patients with HAE are characterized as acute, unpredictable, and recurrent and manifest as episodes of self-limiting, non-pruritic swelling of subcutaneous and/or submucosal tissues. Attacks can be painful, disabling, and in some cases life-threatening, if untreated.

The estimated prevalence of HAE is 1 in 50,000, and over 200 different mutations in C1INH have been reported to date (Zuraw 2008). In about 75% of HAE cases, C1INH mutations can be identified in first-degree relatives (Varga 2011). HAE may be classified as either type I or type II based on biochemical characteristics, but the two forms are clinically indistinguishable (Zuraw 2008, Cicardi 2010). Approximately 85% of HAE cases are classified as type I, characterized by heterogeneous mutations in the C1INH gene that produce truncated or misfolded protein that cannot be efficiently secreted into the plasma. Type 1 HAE is associated with low antigenic concentrations of C1INH (i.e., protein recognized by anti-C1INH antibodies) and low functional C1INH activity. The remaining 15% of HAE cases are type II, in which dysfunctional C1INH protein (transcribed from the defective gene) is secreted. Type II defects are characterized by low levels of functional C1INH (derived from the intact allele) and normal to elevated levels of antigenic C1INH. A third, even more rare type of familial angioedema has also been described; however, it does not involve C1INH mutations or deficiencies in C1INH function (Zuraw 2008, Binkley 2000).

Dysregulation of complement and contact activation due to functional C1INH deficiency is the key pathophysiological mechanism underlying acute HAE attacks of angioedema (Zuraw 2008, Cicardi 2010). Healthy subjects have functional C1INH levels of 0.7 to 1.3 IU/mL, whereas patients with HAE have functional C1INH activity that is <20% to 50% of normal (0.2 to 0.5 IU/mL). Complement cascade components C4 and C2 are the main substrates of activated C1 esterase; patients with HAE typically have low plasma levels of C4 and C2, and high levels of C4 activation products C4b/c (van Doorn 2005, Zuraw 1986, Lunn 2010, Gompels 2002). C1INH prevents auto-activation of C1 and thus inhibits its own consumption (Windfuhr 2005, Ziccardi 1982). In patients with HAE, however, low levels of functional C1INH allow continuous auto-activation of C1 that triggers activation of the classical complement pathway (Ziccardi 1982, Cugno 1990). In addition, auto-activation of C1 also leads to consumption of C1INH, with plasma C1INH levels <50% in many HAE patients (Ziccardi 1982). The functional C1INH deficit in HAE also leads to activation of the contact system and subsequent generation of the vasoactive peptide bradykinin. This, in turn, increases vascular permeability to cause extravasation of fluid to the interstitial space and the edema that is the primary clinical manifestation of HAE. Increasing levels of functional C1INH in the plasma restores homeostasis and stops the formation of the vasoactive peptides that mediate angioedema.

Clinical manifestations of HAE are often first observed in childhood, though the rarity of the disease and potential confusion of symptoms with other disorders may delay accurate diagnosis (Agostoni 1992, Bork 2006). One study showed an average delay of 13 years between initial onset of symptoms to diagnosis (Roche 2005). If a patient's medical history or symptomatic presentation, and/or family history, suggest presence of HAE, measuring complement and C1INH activity can confirm the diagnosis. Since patients with HAE typically have low C4 levels, C4 testing can be used as an initial diagnostic tool.

Angioedema attacks occur in various anatomical locations, with distal parts of extremities and intestinal mucosa being the most commonly affected sites (Varga 2011, Zuraw 2008). These attacks are associated with significant morbidity and mortality. Symptoms of abdominal attacks include localized pain, nausea, vomiting, and diarrhea and the appearance of severe non-specific symptoms may lead to unnecessary abdominal surgery in about one-third of undiagnosed HAE patients (Varga 2011, Zuraw 2008, Agostoni 1992). The most serious manifestation of HAE is laryngeal angioedema, which can lead to asphyxiation and death. Up-to-date mortality estimates for HAE are sparse; however, 20 to 50 years ago only about 60% of patients survived a laryngeal attack (Bork 2000). Until recently, mortality rates of attacks involving the upper airway leading to asphyxia remained >25% (Bork 2000). A large retrospective

study found that about 10% of patients underwent tracheostomy or intubation due to attacks at least once before HAE diagnosis (Agostoni 1992). Peripheral attacks were once considered to have limited importance, but are now recognized to be associated with a great deal of pain and dysfunction (Varga 2011, Kusuma 2012). Subcutaneous swelling of the face, hands, arms, legs, genitals, and buttocks can be disfiguring and interfere with activities of daily living, therefore warranting treatment.

The frequency of attacks is variable, on average occurring every 7-14 days. Some patients with HAE experience attacks as frequently as every 3 days; in contrast, some patients very rarely, if ever, are symptomatic (Zuraw 2008, Bork 2006, Agostoni 1992). Patients who experience frequent attacks, occurring once per month or more often, have reported quality of life impacts including decreased participation in social activities (Cicardi 1996). Attacks may be triggered by a variety of causes—minor trauma, abdominal surgery, dental procedures, emotional stress, menstruation, estrogen-containing medications and angiotensin-converting enzyme inhibitor medications appear to be relevant factors (Agostoni 1992, Bork 2009)—although most attacks begin without recognizable triggers. An attack may be preceded by prodromal signs such as tingling or non-pruritus rash (Varga 2011, Zuraw 2008). Severity and duration of attacks is also quite variable and unpredictable. Tthe swelling in an attack typically subsides spontaneously within 1-4 days, but laryngeal and gastrointestinal tract swelling can cause serious discomfort and be severe, making every attack potentially life-threatening (Zuraw 2008).

2.2.2 Approaches to Treatment of Hereditary Angioedema

Therapy for HAE focuses on rapid treatment of acute attacks (Varga 2011, Zuraw 2008, Cicardi 2010, Bowen 2010). Patients with frequent and/or severe attacks may also be placed on maintenance therapy for angioedema prophylaxis (Bowen 2010).

Maintenance therapy for angioedema consists of anabolic steroids such as danazol (Gelfand 1976) and stanozolol (Zurlo 1990), and sometimes antifibrinolytics such as tranexamic acid and epsilon-aminocaproic acid (Agostoni 1992). Maintenance therapy reduces frequency and severity of attacks, and C4 levels may rise concomitantly with functional C1INH levels. Side effects of anabolic steroids used as maintenance therapy include menstruation irregularity, altered libido, acne, virilization, weight gain, hypertension, hepatitis, myalgia, and altered lipoprotein profiles; several reports have suggested a possible association of long-term anabolic steroids use with liver tumors (Agostoni 1992, Zurlo 1990, Bork 1999, Crampon 1998). Potential side effects of antifibrinolytics include thrombosis, myonecrosis, and postural hypotension. The side effect profiles and chronic use of maintenance therapy drugs pose a health risk. Further, maintenance therapy with anabolic steroids or antifibrinolytics may be contraindicated in, refused by, or ineffective in some patients, and particularly problematic in pregnant or lactating women and young children.

Plasma-derived human C1INH (pdC1INH) products have become the standard-of-care for treatment and prophylaxis of acute angioedema attacks in patients with HAE. Administration of pdC1INH products normalize C1INH activity, restore regulation of the complement and contact systems, and ultimately lead to resolution of clinical symptoms (Cicardi 2010, Waytes 1996). Therapeutically, pdC1INH products address the C1INH functional deficit—the underlying pathophysiology in HAE—and therefore resolve the homeostasis, with clinical studies demonstrating that angioedema attacks resolve after treatment with pdC1INH products (Zuraw 2008, Craig 2009, Kunschak 1998, Visentin 1998).

BERINERT® and CINRYZE® are pdC1INH products approved in the United States (US) for IV administration to treat angioedema attacks in patients with HAE. BERINERT is indicated to treat acute attacks, whereas CINRYZE is approved for prophylaxis of HAE attacks. Both pdC1INH products maybe self-administered. CINRYZE labelling includes report of serious thromboembolic events during routine prophylactic treatment, in patients with underlying risk factors, and if used off-label at high doses; the latter is corroborated by animal studies cited in the label that indicate an increased risk of clot formation with high-dose administration. A 2011 post-marketing retrospective database study extracting thromboembolic event reports from the US FDA AE Reporting System (AERS) (dating back to CINRYZE US approval in 2008) identified 10 confirmed and 7 additional potential cases of thromboembolic events in which CINRYZE was the suspect drug (Gandhi 2012).

Despite their effectiveness in the management of acute angioedema attacks, pdC1INH products have important limitations. For example, the availability of plasma-derived medicinal products is dependent on supplies of donated human blood, and shortages of these products have been reported (Boulis 2002). If pdC1INH is unavailable, fresh frozen plasma is sometimes used to treat severe attacks or as short-term prophylaxis prior to surgery. This approach can actually exacerbate symptoms, though, as both C1INH and contact and complement system components become supplemented (Agostoni 1992).

Use of pdC1INH also poses a theoretical risk of transmission of blood-borne infections, including pathogenic viruses (Visentin 1998, Cicardi 1996) or prions, although blood screening, viral testing, and product purification processes minimize that risk (Cicardi 1995, De Filippi 1998). Some physicians still may restrict the use of pdC1INH to treatment of laryngeal and severe abdominal attacks or pre-operative prophylaxis due to concerns about a potential risk for infection with (unknown) blood-borne pathogens (Cicardi 1996, Agostoni 1992, Visentin 1998).

Two additional products, both non-C1INH products, FIRAZYR® and KALBITOR®, are approved in the US for treatment of acute angioedema attacks in patients with HAE.

FIRAZYR® (icatibant) 30 mg is a bradykinin B2 receptor antagonist for subcutaneous (SC) injection that inhibits bradykinin activity but does not address the functional C1INH deficit, permitting the upstream contact system activation to continue unabated in an attack. In some HAE studies, rescue medication was required in approximately one-fifth of patients treated with icatibant.. Most patients receiving icatibant in clinical trials experienced an injection-site reaction. Icatibant may be self-administered by patients during an attack.

KALBITOR® (ecallantide) 30 mg is a plasma kallikrein inhibitor for SC injection in three 1 mL doses that prevents activation of downstream targets of kallikrein such as bradykinin and plasmin. Of note, labelling for ecallantide includes an important boxed safety warning of the risk of anaphylaxis, which was reported as occurring in nearly 4% of treated patients in the pivotal and supporting studies included in the labelling. Ecallantide must be administered by a healthcare professional per product labelling.

Based on the limitations and potential risks of these products and therapeutic approaches, an unmet medical need has persisted for a more widely available, alternative treatment for acute attacks in patients with HAE. Any such new product should ideally address issues of both availability (i.e., nonreliance on derivation from donated human plasma) and safety (i.e., potential exposure to blood-borne pathogens), as well as correct the underlying pathophysiology (i.e., restoration of functional C1INH levels to normal range).

RUCONEST is the first, and to-date only, recombinant human C1INH (rhC1INH) approved for treatment of acute angioedema attacks in patients with HAE, and was developed using established recombinant DNA technology. Rabbits transgenic for human C1INH protein expression in the mammary glands are used as a high-yield source of purified rhC1INH from rabbit milk (van Veen 2012). Significant advantages of the rhC1INH production modality is that the recombinant material is not derived from a human source, and that production can be more easily controlled and scaled up to meet the clinical needs for treatment of acute attacks and prophylaxis of HAE. Recombinant technology also circumvents the risk of potential exposure to blood-borne pathogens posed by human-derived products; however, it should be noted that the unlikely possibility of allergic reactivity to rabbit-derived antigens should be a clinical consideration. Importantly, in addition to its manufacturing advantages, administration of rhC1INH also physiologically addresses the functional C1INH deficit, with comparable biological activity to native C1INH observed in clinical studies.

2.2.3 Treatment Guidelines and Consensus Statements

HAE treatment guidelines were defined by the US Hereditary Angioedema Association Medical Advisory Board (HAEMAB) in 2013 (Zuraw 2013a). The HAEMAB consists of 10 clinicians who have treated a large number of patients with HAE. The unanimous treatment recommendations of the HAEMAB are subdivided into four areas: (1) management plan, (2) treatment of angioedema attacks, (3) prophylaxis, and (4) patient monitoring. These are described below.

HAE Management Plan

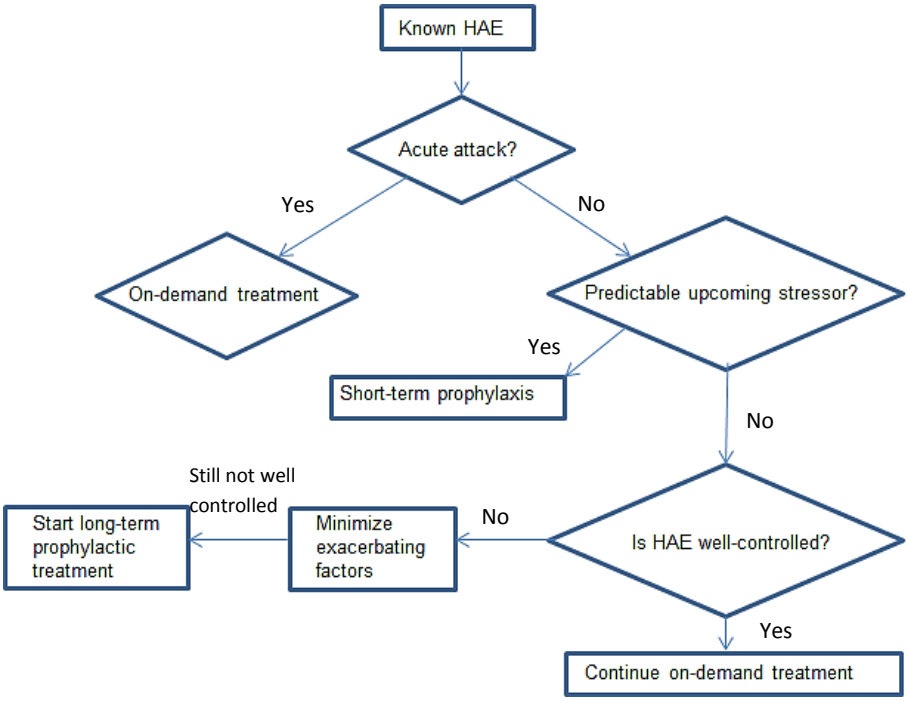
The main goals of HAE treatment are to reduce morbidity and mortality and allow patients to maintain a normal quality of life. To ensure this, the HAEMAB recommends each patient:

- be treated by an expert physician who is (1) knowledgeable about the condition, (2) experienced in managing patients with HAE, and (3) familiar with all HAE treatment options. receive education about HAE at the time of diagnosis and be offered testing for HAE for all immediate family members;
- be provided effective on-demand treatment and, if indicated, prophylactic treatment for attacks;
- coordinate with an expert physician to communicate management plan details to the healthcare providers who will care for the patient and carry an identification card that provides patient-specific treatment guidelines in case of an attack; and
- be assisted by an expert physician in creating a treatment plan for attacks that includes pre-designation of an approved therapy to treat acute attacks and contingency plans if attacks persist or are accompanied by complications requiring medical assistance.

Treatment of Angioedema Attacks

The primary goal of treating an acute angioedema attack is to minimize morbidity and prevent mortality. The treatment algorithm for patients diagnosed with HAE is shown in **Figure 2-1**, based on up-to-date guidelines as set forth by the Joint Task Force on Practice Parameters representing the American Academy of Allergy, Asthma & Immunology (AAAAI); the American College of Allergy, Asthma & Immunology (ACAAI); and the Joint Council of Allergy, Asthma and Immunology (Zuraw 2013b).

Figure 2-1. HAE attack treatment algorithm from consensus guidelines



Source: Zuraw et al. *J Allergy Clin Immunol* 2013;131:1491-1493.

Optimal treatment strategies for a patient with HAE must be individualized based on patient-specific factors and preferences because of the dramatic intra- and interindividual clinical variability of HAE, Treatment plans are focused primarily on administering on-demand therapy for acute attacks, although

prophylaxis may be considered for patients when clinically appropriate. All patients with HAE should have access to at least 2 standard doses of US Food and Drug Administration medicine for on-demand treatment of acute HAE attacks. Because not all patients respond the same to each medication, it is the responsibility of the coordinating expert physician to work with each patient to define the optimal medication(s) for that particular patient. Early treatment, as soon as possible after onset of symptoms, is considered best practice; arrangements for treatment can be prepared during the prodrome, however it is recommended that treatment commence only when an attack is clearly recognized. The efficacy of available products, location of attacks, as well as the overall disability experienced by the patient should be considered in determining the treatment plan. All attacks, irrespective of location, should be considered for treatment as soon as they are clearly recognized. There is overwhelming consensus that all abdominal, facial, oral, and upper respiratory attacks should be treated as early as possible. Extremity attacks are often disabling, and early treatment can prevent dysfunction. Laryngeal attacks, in particular, should be treated emergently as due to the substantial risk of mortality.

2.3 Evidence for Pharmacogenomic Tests and Drugs

Not applicable.

3.0 SUPPORTING CLINICAL EVIDENCE

3.1 Key Clinical Studies

3.1.1 Published and Unpublished Clinical Studies Supporting Labeled Indications

Phase 3, Pivotal Studies

Riedl M, Bernstein JA, Li H, et al. Recombinant human C1 esterase inhibitor relieves symptoms of hereditary angioedema attacks: Phase 3, randomized, placebo-controlled trial. *Ann Allergy Asthma Immunol*. 2014;112(2):163-169. (Study 1310 RCT phase).

Related Publications:

Li H, Moldovan D, Bernstein J, Reshef A, Porebski G, Stobiecki M et al. Efficacy and Safety of Recombinant Human C1 Esterase Inhibitor for Acute Attacks of Hereditary Angioedema: An Open-Label Study. Presented at American College of Allergy, Asthma, and Immunology (ACAAI) 2013; poster 243.

Study Description: A randomized, double-blind, placebo (saline)-controlled, multicenter, multinational study with an OLE phase.

Methods: Patients aged ≥13 years (age ≥18 years for patients outside the US and Canada) with a clinically-suspected and laboratory-confirmed HAE diagnosis (baseline plasma C1INH activity <50% of normal and no evidence of acquired angioedema) were randomized (3:2) to receive an IV injection of rhC1INH (50 IU/kg for patients <84 kg or 4200 IU for patients ≥84 kg; N=44) or placebo (N=31). Eligible attacks were determined by: (1) location as peripheral (extremities), abdominal, facial, and/or oropharyngeal-laryngeal; (2) onset <5 hours prior to presentation to the clinic; (3) Overall Severity Visual Analog Scale (VAS) score ≥50 mm at presentation and prior to dosing; and (4) no evidence of symptom regression (decrease of ≥20 mm in Overall Severity VAS score) between presentation and dosing. Patients presenting with life-threatening symptoms were excluded and treated per standard of care. Rescue medication (open-label rhC1INH 50 IU/kg up to maximum of 4200 IU) was permitted 4 hours post-treatment. The OLE analysis population (N=44) included all patients treated with open-label rhC1INH for an HAE attack and had any available efficacy data during the OLE phase of the study. Treatment was a single IV dose of rhC1INH 50 IIU/kg for patients <84 kg or 4200 IU for patients ≥84 kg; an additional dose could be given at the Investigator's discretion.

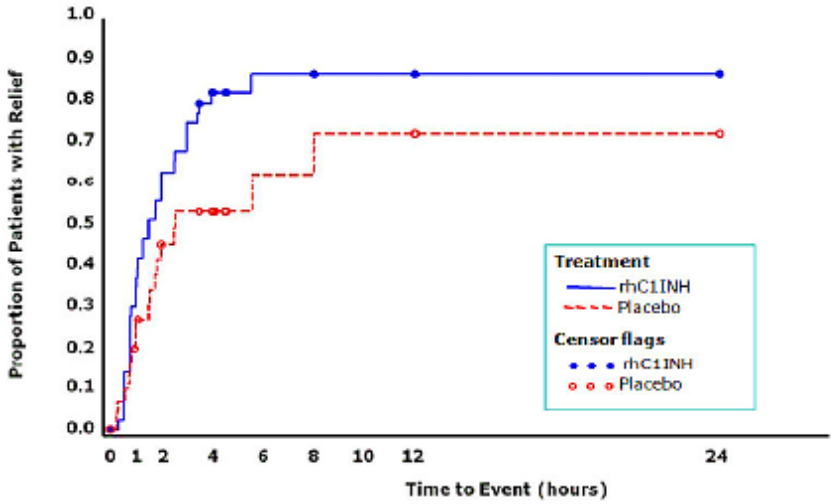
Endpoints: The primary efficacy endpoint was time to onset of sustained relief based on the Treatment Effect Questionnaire (TEQ), defined as the time between dosing and the first time point at which the patient reported all of the following for the primary attack location: (1) "better" to "much better" symptom relief; (2) notable decrease in symptoms; and (3) persistence of improvement at the next assessment time point. Secondary efficacy endpoints included time to minimal symptoms based on the TEQ (the time between dosing and the first time point at which the patient reported a response of "yes" to TEQ question 3 for all attack locations) time to minimal symptoms (time between dosing and the first time point at which the patient responded symptoms were minimal for all attack locations) and time to sustained symptomatic relief (first time point at which the Overall Severity VAS score at the primary attack location decreased ≥20 mm vs. baseline with persistence to the next time point). The Investigator Score (IS) was used to assess the severity of patient symptoms at each affected anatomic location at the same time as patient evaluations of severity. Efficacy evaluations in the OLE phase included those specified in the RCT phase. The primary safety endpoint was incidence of treatment emergent adverse events (TEAEs) (from study drug administration up to 90 days post-treatment).

Results: All 75 patients were included in primary intent-to-treat (ITT) efficacy analysis. Patient demographics and baseline characteristics were similar between the treatment groups.

Attack severity measured on the VAS was similar in both groups (rhC1INH 73.5 mm vs. placebo 77.3 mm). The most common primary attack locations in both rhC1INH and placebo groups were peripheral (44% vs. 45%) and abdominal (37% vs. 39%).

TEQ-based time to onset of sustained symptom relief of at the primary attack location was shorter in patients treated with rhC1INH (90 min) vs. placebo (152 min; *P*=0.031) (**Figure 3-1**). Multiple sensitivity analyses supported the primary efficacy analysis results, demonstrating shorter times to onset of sustained relief of symptoms in patients treated with rhC1INH vs. placebo.

Figure 3-1. Kaplan-Meier plot of TEQ-based time to onset of sustained relief of symptoms at the primary attack location



FDA data analysis of gender subgroups suggested a larger treatment effect in men than women. For women receiving RUCONEST, the median time to beginning of relief was 113 minutes [95% CI: (63, 151); n=28], and for women receiving placebo, the median time to beginning of relief was 105 minutes [95% CI: (60, 334); n=19]. The hazard ratio for women receiving RUCONEST versus placebo was 1.22 [95% CI 0.60 to 2.48]. For men receiving RUCONEST, the median time to beginning of relief was 75 minutes [95% CI: (45, 210); n=16], and for men receiving placebo, the median time to beginning of relief was 480 minutes [95% CI: (150, -); n=12]. The hazard ratio for men receiving RUCONEST versus placebo was 3.94 [95% CI 1.23 to 12.68].

FDA reported no plausible biological explanations for the regional or gender subgroup effects were found. One possible explanation is a larger-than-expected placebo response among US women. None of the subgroup confidence intervals were adjusted for multiplicity. Because almost all of the patients were Caucasian and were between 18 and 65 years of age, race and age subgroup analyses were not considered meaningful.

Additional subgroup analysis noted the mean (SD) time between onset of an attack and presentation at the site was lower for the rhC1INH group (188.4 [157.24] minutes) compared to the saline group (236.4 [193.31] minutes). The mean (SD) time between onset of an attack and iv injection was 253.4 (153.35) minutes for the rhC1INH group compared to 301.6 (193.19) minutes for the saline group. Subgroup analyses showed that these differences were especially pronounced for the abdominal attacks (233.4 [69.27] minutes, rhC1INH; 335.7 [263.24] minutes, saline), female patients (257.7 [180.09] minutes, rhC1INH; 331.2 [240.5] minutes, saline), and patients in the US (286.2 [200.42] minutes, rhC1INH; 360.6 [255.68] minutes, saline).

TEQ-based time to minimal symptoms at all attack locations was shorter in rhC1INH-treated patients (303 min) vs. placebo (483 min) (p=0.078). VAS-based time to minimal symptoms at all attack locations was

shorter in rhC1INH-treated patients vs. placebo (240 min vs. 362 min; *P*=0.005). Time to onset of sustained symptom relief was shorter in rhC1INH-treated patients vs. placebo based on the VAS (75 min vs. 303 min; *P*=0.003) and IS (60 min vs. 105 min; *P*<0.001). Recurrence of attack symptoms within 24 hours was 3% of patients in the rhC1INH group vs. 27% in the placebo group.

The most common TEAEs reported within 72 hours of dosing were respiratory and gastrointestinal events (**Table 3-1**). Only one patient reported 3 drug-related TEAEs (headache, mild skin burning sensation, and back pain at 15 min, 45 min, and 24 hours post-treatment, respectively).

Table 3-1. Treatment emergent adverse events commencing within 72 hours after dosing

MedDRA preferred term	rhC11NH (n=56)[b] n (%)	Placebo (n=18)[c] n (%)
Sinus congestion	0	1 (6%)
Sneezing	1 (2%)	0
Vasomotor rhinitis	0	1 (6%)
Diarrhea	0	1 (6%)
Dyspepsia	0	1 (6%)
Procedural headache[a]	1 (2%)	0
Fibrin D-dimer increased	1 (2%)	0
Back pain[a]	1 (2%)	0
Lipoma	1 (2%)	0
Skin burning sensation[a]	1 (2%)	0

Abbreviations used: MedDRA, Medical Dictionary for Regulatory Activities Version 15.0; rhC11NH, recombinant human C1 inhibitor.

[a] Events experienced by the same patient and all judged by the investigator to be related to study medication; [b]Includes patients treated with rhC11NH as double-blinded and/or open-label rescue medication; [c] Patients treated only with placebo.

Two patients experienced severe TEAEs (urinary tract infection and abdominal hernia) in the rhC11NH group and 1 patient (sinus congestion) in the placebo group; both were thought not to be related to study medication. One patient had a serious AE (SAE) of abdominal hernia that occurred about 80 days post-treatment and was not drug-related. No patients discontinued the study due to TEAEs.

No patients developed neutralizing antibodies to C1INH, and no anaphylaxis was reported. Confirmed anti-host-related impurity antibodies were detected in 8 patients in rhC1INH group and 3 patients in placebo group, which resulted in 6 treatment emergencies for rhC1INH-treated patients and 1 treatment emergency for placebo-treated patients. In all cases, immunogenic responses were transient and sporadic, and medical review confirmed no temporal relation between the presence of antibodies and AEs. Importantly, no thrombotic events were reported for any patients.

Open-label Extension

Forty-four patients were treated for a total of 224 HAE attacks with one intravenous injection of rhC1INH (50 IU/kg up to 4200 IU) in the OLE phase of RCT. The primary endpoint, defined as TEQ-, VAS-, and IS-based median time to onset of symptom relief at primary attack locations for the first 5 attacks, was 75 min (95% CI: 69, 89), 90 min (95% CI: 77, 100), and 75 min (95% CI: 60, 76), respectively. The secondary endpoint, defined as TEQ-, VAS-, and IS-based median time to minimal symptoms for the first 3 attacks, was 303 min (95% CI: 211, 367), 243 min (150, 272), and 244 min (95% CI: 181, 300), respectively.

Of the 44 patients, 27% experienced ≥ 1 TEAE within 72 hours of completion of rhC1INH infusion. TEAEs occurring in 5% of patients were nasopharyngitis, cough, fibrin D-dimer increase, and headache. The percentage of patients with TEAEs did not increase with rhC1INH treatments for repeat attacks. There

were no discontinuations due to AEs, no thrombotic or anaphylactic events, and no neutralizing anti-C1INH antibodies with repeat rhC1INH treatment.

Publication / Study

Zuraw B, Cicardi M, Levy RJ, et al. Recombinant human C1-inhibitor for the treatment of acute angioedema attacks in patients with hereditary angioedema. J Allergy Clin Immunol 2010;126:821-827 (Studies 1304 and 1205 pooled analysis).

Related Publications:

Moldovan D, Reshef A, Fabiani J, et al. Efficacy and safety of recombinant human C1-inhibitor for the treatment of attacks of hereditary angioedema: European open-label extension study. Clinical & Experimental Allergy 2012;42:929-935 (Study 1304 OLE).

Reidl MA, Levy RJ, Suez D, et al. Efficacy and safety of recombinant C1 inhibitor for the treatment of hereditary angioedema attacks: a North American open-label study. Ann Allergy Asthma Immunol 2013;110(4):295-299 (Study 1205 OLE).

Relan A, Bakhtiari K, van Amersfoort E, et al. Recombinant C-1 inhibitor. Effects on coagulation and fibrinolysis in patients with hereditary angioedema. Biodrugs 2012;26(1):43-52 (Study 1205 retrospective safety analysis).

Study Description: Two similar, independent, randomized, placebo-controlled, double-blind studies with OLE studies evaluated the efficacy and safety of rhC1INH to treat acute angioedema attacks resulting from C1INH deficiency in patients with HAE.

Methods: Studies 1205 (conducted in North America) and1304 (conducted predominantly in Europe) were 2 independent, randomized, double-blind, placebo (saline)-controlled, multicenter, multinational studies with OLEs. Patients with baseline plasma C1INH activity <50% of normal and eligible attacks (onset <5 hours prior to presentation to the clinic and Overall Severity VAS score ≥50 mm at presentation) were enrolled.

Study 1205: ages ≥12 years were randomized (1:1:1) to receive a single IV dose of rhC1INH 100 IU/kg (n=13) or 50 IU/kg (n=13) vs. placebo (n=13).

Study 1304: ages ≥16 years were randomized (1:1) to receive rhC1INH 100 IU/kg (n=17) vs. placebo (n=17).

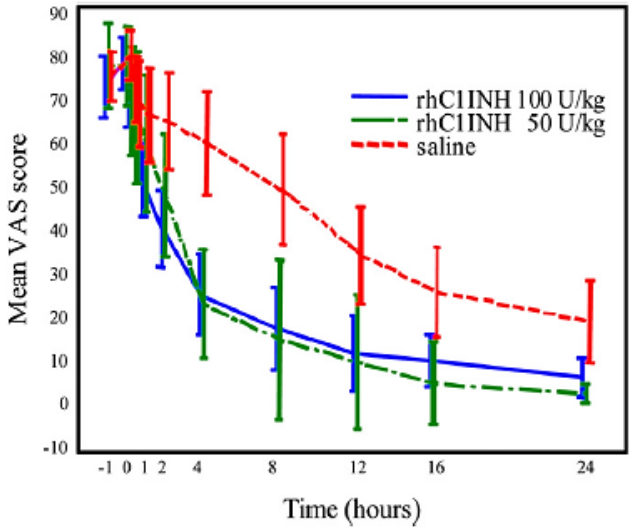
In the combined analysis, treated patients were pooled as follows: rhC1INH 100 IU/kg (N=29) or 50 IU/kg (N=12) vs. placebo (N=29).

Endpoints: The primary efficacy endpoint was time to onset of symptom relief (VAS score decreased by >20 mm at any eligible location vs. baseline for 2 consecutive VAS recordings). The secondary efficacy endpoint was the time to minimal symptoms (VAS score decreased to <20 mm for all anatomical locations of an attack). The primary safety endpoint was incidence of TEAEs (from study drug administration up to 90 days post-treatment).

Results: Overall, 70 patients across both studies received randomized treatment with rhC1INH or placebo. Treatment groups were comparable in demographics and baseline characteristics.

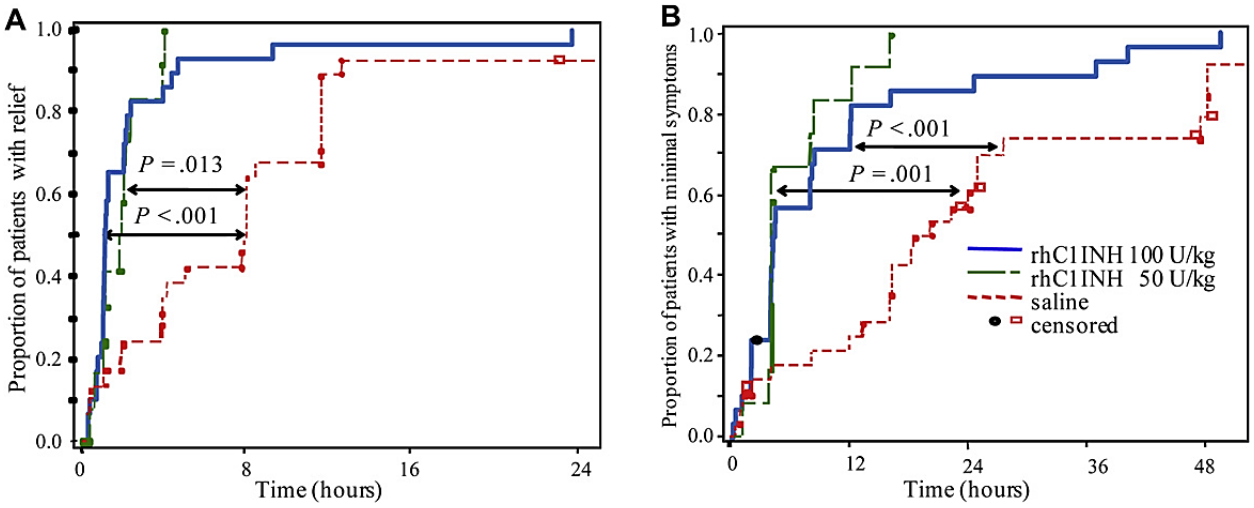
The mean overall VAS score decreased more rapidly in both rhC1INH dosing groups vs. placebo (**Figure 3-2**). Median time to onset of relief was 66 min (95% CI: 61-122 min) with rhC1INH 100 IU/kg, 122 min (95% CI: 72-136 min) with 50 IU/kg and 495 min (95% CI: 245-520 min) with placebo (P<0.001 and P=0.013, respectively).

Figure 3-2. Time course of mean VAS scores (95% CI) for rhC1INH vs. placebo groups.



Treatment with rhC1INH 100 IU/kg and 50 IU/kg also resulted in a significant reduction in time to minimal symptoms, with medians of 266 min (95% CI: 242-490 min) and 247 min (95% CI: 243-484 min), respectively, vs. a median of 1210 min (95% CI: 970-1500 min) for placebo (*P*<0.001 and *P*=0.001, respectively) (**Figure 3-3**).

Figure 3-3. Kaplan-Meier plot of VAS-based (A) time to beginning of symptom relief or (B) time to minimal symptoms



No patients in the rhC1INH 50 IU/kg group and 10% of patients in the 100 IU/kg group had therapeutic failure vs. 59% of placebo patients. Odds ratios for rhC1INH vs. placebo treatment were 0.06 (95% CI: 0.01-0.32) for 100 IU/kg and 0.13 (95% CI: 0.00-1.08) for 50 IU/kg; *P*<0.001 and *P*=0.060, respectively.

Subgroup analyses demonstrated that efficacy was achieved by both male and female patients at both rhC1INH dose levels vs. placebo, as well as for all anatomical locations of attacks and independent of Investigator assessment of symptom severity or worsening of the attack prior to treatment.

TEAEs were reported more frequently in the placebo group vs. rhC1INH groups with 33 TEAEs in 14 patients in the saline group vs. 27 TEAEs in 7 patients in the 100 U/kg and 6 TEAEs in 4 patients in the 50 U/kg group. Few TEAEs were considered drug-related (headache and vertigo in rhC1INH groups, vs. headache, injection site swelling, epistaxis, and hypotension in the placebo group) and there were no

drug-related SAEs. No patients discontinued the study due to TEAEs. No patients developed neutralizing antibodies to C1INH, and no anaphylaxis was reported.

Table 3-2. Overview of common TEAEs observed during 90 days follow-up of the study population

TEAEs, n (%)	rhC1INH 100 U/kg (N=29)	rhC1INH 50 U/kg (N=12)	Saline (N=29)
Abdominal pain	1 (3%)	0	2 (7%)
Upper abdominal pain	0	0	1 (6%)
Colitis	1 (3%)	0	0
Diarrhea	1 (3%)	0	0
Vomiting	0	0	0
Headache	3 (10%)	0	4 (14%)
Vertigo	1 (3%)	0	0
Cystitis	0	0	1 (3%)
Fungal infection	0	0	1 (3%)
Herpes simplex	1 (3%)	0	0
Sinusitis	1 (3%)	0	0
Tonsillitis	1 (3%)	0	0
Tooth abscess	0	1 (8%)	0
Urinary tract infection	0	1 (8%)	0
Pain	0	0	2 (7%)
Condition aggravated	1 (3%)	0	0
Injection site swelling	0	0	1 (3%)
Mucosal hyperemia	0	0	1 (3%)
Pyrexia	0	0	1 (3%)
Erythema	0	1 (8%)	0
Pruritus	0	1 (8%)	0
Rash erythematous	0	0	1 (3%)

Abbreviations used: rhC1INH = recombinant human C1 esterase inhibitor, TEAE = treatment-emergent adverse event.

Open-Label Extension:

Study 1304

A total of 57 patients were treated for 194 HAE attacks; 16 patients were treated for a single attack and 41 patients were treated for multiple attacks. Of those treated for multiple attacks, 34 patients were treated for 2-5 attacks and 7 patients were treated for ≥6 attacks. Of the 194 attacks treated, 57% were treated with one vial (2100 U), 35% with two vials (4200 IU) and 8% with three vials (6300 U); one patient was treated with five vials due to a protocol violation. A greater percentage of abdominal and peripheral attacks were treated with a single vial (2100 U) (74% and 64%, respectively) vs. oro-facial-pharyngeal-laryngeal attacks (28%). In attacks for which an additional dose was given, the median time at which the

second dose was administered was 65 min (range: 5-250 min) after the initial dose. For attacks 1-5, percentages of patients treated with one vial were 60%, 51%, 47%, 33%, and 50%, respectively.

Median times to onset of symptom relief for attacks 1-5 were 60, 65, 120, 60, and 61 min, respectively. Kaplan-Meier curves for attacks 1-5 were similar for time to onset of relief (**Figure 3-4**) and for time to minimal symptoms (**Figure 3-5**). Abdominal attacks had the shortest time to relief and to minimal symptoms after rhC1INH treatment (medians of 0.5 hours and 4 hours, respectively) vs. orofacial-pharyngeal-laryngeal attacks that took about 2-to 3-fold longer to resolve.

Figure 3-4. Kaplan-Meier plot of time to onset of relief for attacks 1-5

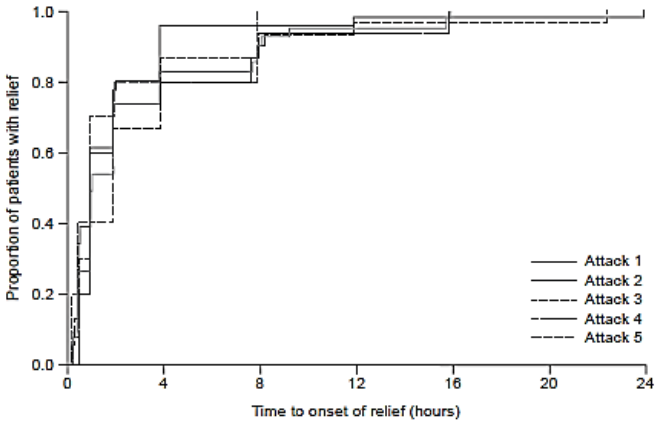
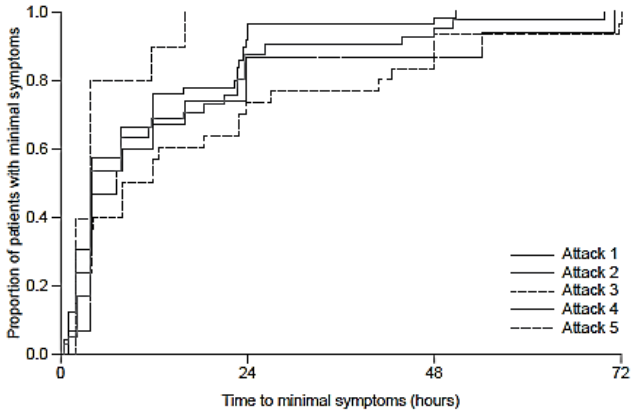


Figure 3-5. Kaplan-Meier plot of time to onset of minimal symptoms for attacks 1-5



No clinical relapses occurred during the study. Overall, rhC1INH treatment provided sustained relief of HAE symptoms within 4 hours of treatment for 87% of attacks.

The percentage of patients that reported ≥TEAE was 28% for single-dose and 26% for repeat-dose group (**Table 3-3**). Most TEAEs were mild or moderate in severity w ith headache and nausea being the most commonly reported. No SAEs were reported within 7 days of rhC1INH treatment. No patients discontinued the study due to TEAEs. No patients developed neutralizing antibodies to C1INH, and no anaphylaxis was reported.

Table 3-3. Common AEs (≥3% of the study population) with onset dates within 7 days after receiving rhC1INH treatment, n (%)

	rhC1INH 2100 U single dose (n=43) n (%)	**rhC1IN 2100 U + additional dose (n=34) n (%)**
Total number of attacks treated	112 (57%)	82 (43%)
Number of patients experiencing at least one AE	12 (28%)	9 (26%)
Headache	1 (2%)	2 (6%)
Diarrhea	1 (2%)	0
Nausea	1 (2%)	2 (6%)
Vertigo	0	1 (3%)

The safety set was analyzed for TEAEs and comprised 57 patients; 27 patients reported at least one TEAE; most events were mild-to-moderate in severity; total population = AEs occurring in all attacks, not just attacks 1–5; only those AEs occurring in > 1 patient of the total population are listed. TEAE = treatment-emergent adverse events; Counts represent number of patients, not number of events.

Study 1205

Sixty-two patients were treated for 168 attacks. Patients with eligible HAE attacks were treated with an intravenous 50 IU/kg dose of rhC11NH with an option for an additional dose of 50 U/kg based on clinical response. Twelve patients were first treated in RCT. Twenty patients were treated for 1 attack during the OLE, whereas 34 patients were treated for 2 to 5 attacks, and 8 patients were treated for 6 to 8 attacks. The mean overall severity VAS score at baseline was 74 to 83 mm. A total of 90% (151/168) of the attacks were treated with a single 50 IU/kg dose of rhClINH.

Median times to beginning of symptom relief for the first 5 attacks were 37 to 67 minutes. Median times to minimal symptoms for the first 5 attacks were 120 to 244 minutes. More than 90% of attacks responded within 4 hours after treatment with rhC11NH. There was no requirement for increased dosing with successive treatments.

Thirty-nine patients (63%) reported at least 1 treatment-emergent adverse event, with most events rated mild to moderate. Headache and nasopharyngitis were the most frequently reported AEs. Seven severe treatment-emergent adverse events were reported, and all were considered to be unrelated to treatment with rhC11NH.

Twenty five patients from the RCT phase had available plasma samples for evaluation: n=9 treated with rhC1INH 100 IU/kg, n=9 rhC1INH 50 IU/kg, and n=7 placebo. At baseline, median aPTT was similar between the 3 groups. Both thrombin activation markers were enhanced in 24 out of 25 patients and correlated with each other (r=0.57, $P<0.01$). D-dimer levels correlated significantly with PAP complexes (r=0.89, $P<0.01$) and with F1+2 levels (r=0.68, $P<0.01$), consistent with formation of D-dimers requiring both coagulation and fibrinolysis.

After infusion of rhC1INH (100 IU/kg or 50 IU/kg) or placebo, median PT was normal and remained within the normal range. After infusion, the placebo group maintained a normal level whereas a dose-dependent prolongation of aPTT was observed in the rhC1INH groups.

One patient, receiving placebo infusion and prophylactic tranexamic acid, had a remarkable course of PT and aPTT prolongation and F1+2 elevation, but reported no thromboembolic TEAEs.

3.1.2 Published and Unpublished Clinical Studies Supporting Off-label Indications

Reshef A, Moldovan D, Obtulowicz K, et al. Recombinant human C1 inhibitor for the prophylaxis of hereditary angioedema attacks: a pilot study. *Allergy.* 2013;68:118-124 (Study 1207).

Study Description: An open-label observational study of once-weekly rhC1INH administration as prophylaxis for HAE attacks.

Methods: Patients with a history of HAE attacks occurring at least every 2 weeks were treated with 8 once-weekly IV doses of 50 IU/kg rhC1INH, with additional acute treatment with rhC1INH for breakthrough attacks. HAE attack history was collected at screening and breakthrough attacks during the study were recorded at each visit. Following a 2-week run-in period, patients received 8 weekly rhC1INH administrations and were then followed for 6-weeks.

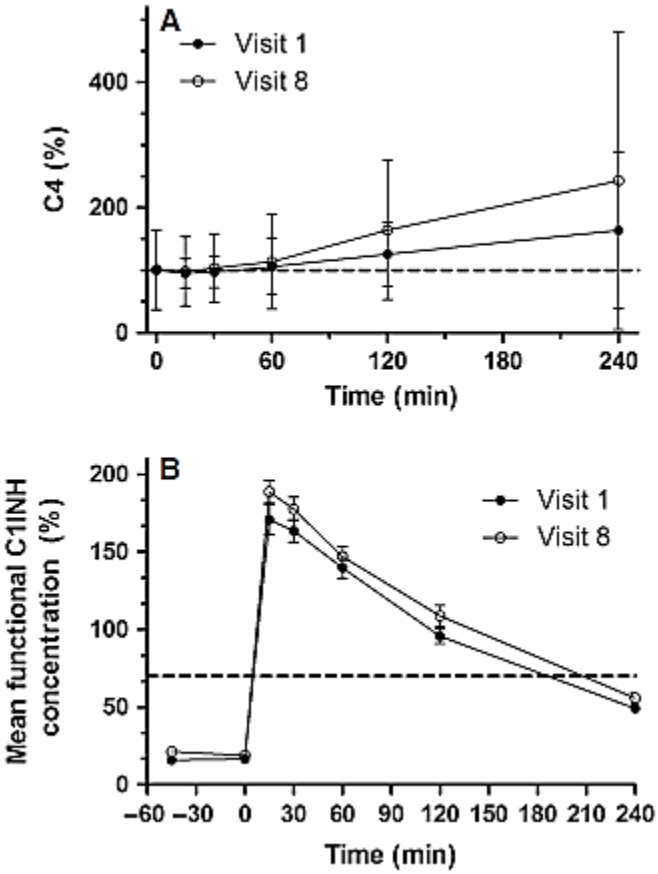
Endpoints: The primary objective was to evaluate occurrence of HAE attacks under prophylactic administration of rhC1INH 50 IU/kg/week. The secondary objective was to evaluate PK/PD parameters, immunogenicity, and safety of repeated administration of rhC1INH.

Results: A total of 25 patients reported a mean of 0.9 attacks/week over the previous 2 years, with 23 out of 25 patients reporting the impact of attacks on their quality of life to be major or a cause of disability. The mean breakthrough attack rate during the treatment period was 0.4 attacks/week (95% CI: 0.28-0.56). Of the 84% of patients that had an attack during the treatment period, 6 patients were treated with an acute dose of rhC1INH.

Twenty four out of 25 patients took concomitant medications during the study period, including 48% of patients who received a total of 20 pdC1INH treatments (12 for acute attacks, 8 as prophylactic prior to dental or surgical procedures).

There was consistency in levels of antigenic C1INH, functional C1INH, and C4 levels between the weekly treatments 1 to 8. PK/PD of C4 (normalized by using each patient's baseline value as 100%) and functional C1INH during rhC1INH treatments are shown in **Figure 3-6**.

Figure 3-6. Frequency of attacks prior to and during treatment with rhC1INH



Note: dotted line represents (A) normalized 100%, (B) lower limit of normal for healthy patients.

A total of 30 TEAEs were reported in 13 patients that were mild to moderate in severity. The only drug-related AEs were dry mouth, dizziness, and anxiety (all reported in 1 patient), and hypotension (reported in 1 additional patient). There were no allergic AEs and no neutralizing antibodies observed. One patient died from a laryngeal attack that occurred 25 days after last study drug administration.

3.1.3 Clinical Evidence Table Spreadsheets of All Published and Unpublished Studies

Study Number / Citation	Design / Sample Size / Treatments	Key Inclusion / Exclusion Criteria	Results
3.1.3.1 Published and Unpublished Studies Supporting Labeled Indications			
1310 RCT phase Riedl M, Bernstein JA, Li H, et al. Recombinant human C1 esterase inhibitor relieves symptoms of hereditary angioedema attacks: Phase 3, randomized, placebo-controlled trial. *Ann Allergy Asthma Immunol.* 2014;112(2):163-169.	Phase 3 randomized, double-blind, placebo-controlled study Treatment: rhC1INH 50 IU/kg for patients <84 kg or rhC1INH 4200 IU for patients ≥84 kg (N=44) vs. saline (N=31)	Age ≥13 years (≥18 years outside US & Canada) with HAE & acute angioedema attacks Inclusion: • functional C1INH level <50% normal • eligible attack: <5 hours from onset to clinic presentation; peripheral, abdominal, facial, or oro-pharyngeal-laryngeal • VAS >50 mm at presentation and dosing • no symptom regression [VAS decrease ≥20 mm from presentation to dosing]) Exclusion: • history of allergy to rabbits or acquired C1INH deficiency • presented with life-threatening attack (treated per standard of care)	**Primary:** TEQ-based time to onset of sustained symptom relief at primary attack location (min): 90 rhC1INH group vs. 152 placebo (P = 0.031) **Secondary:** TEQ-based time to minimal symptoms at all attack locations (min): 303 rhC1INH group vs. 483 placebo (P=0.078). VAS-based time to minimal symptoms at all attack locations (min): 240 rhC1INH vs 362 placebo (P=0.005) VAS-based time to onset of sustained relief of symptoms (min): 75 rhC1INH group vs. 303 placebo (P=0.047) Recurrence of attacks within 24 hours was 3% in rhC1INH group vs. 27% placebo **Safety:** 3 drug-related TEAEs in 1 patient (headache, mild skin burning sensation, back pain at 15 min, 45 min, and 24 hours post-treatment) Most common TEAEs within 72 hours of dosing were respiratory or GI; 1 patient had unrelated SAE of abdominal hernia about 80 days post-treatment No discontinuations due to TEAEs
1310 OLE phase Li H, Moldovan D, Bernstein J, Reshef A, Porebski G, Stobiecki M et al. Efficacy and Safety of	Open-label maintenance arm of 1310 OLE study rhC1INH 50 IU/kg for patients <84 kg or 4200 IU for		**1310 OLE Phase** **Primary:** TEQ-, VAS-, and IS-based median time to onset of symptom relief at primary attack locations for the first 5 attacks: 75 min (95% CI: 69, 89), 90 min (95% CI: 77, 100), and 75 min (95% CI: 60, 76), respectively

Study Number / Citation	Design / Sample Size / Treatments	Key Inclusion / Exclusion Criteria	Results
Recombinant Human C1 Esterase Inhibitor for Acute Attacks of Hereditary Angioedema: An Open-Label Study. Presented at American College of Allergy, Asthma, and Immunology (ACAAI) 2013; poster 243.	patients ≥84 kg (N=44) Optional 2nd dose		**Secondary:** TEQ-, VAS-, and IS-based median time to minimal symptoms for the first 3 attacks: 303 min (95% CI: 211, 367), 243 min (150, 272), and 244 min (95% CI: 181, 300), respectively **Safety:** 27% of patients experienced ≥ 1TEAE within 72 hours of completion of rhC1INH infusion TEAEs occurring in 5% of patients were nasopharyngitis, cough, fibrin D-dimer increase, and headache The percentage of patients with TEAEs did not increase with rhC1INH treatments for repeat attacks No discontinuations due to AEs, no thrombotic or anaphylactic events, and no neutralizing anti-C1INH antibodies with repeat rhC1INH treatment
1304 and 1205 (pooled) Zuraw B, Cicardi M, Levy RJ, et al. Recombinant human C-1-inhibitor for the treatment of acute angioedema attacks in patients with hereditary andioedema. *J Allergy Clin Immunol* 2010; 126:821-827.	**1304:** Phase 2/3 randomized, double-blind, placebo- controlled study rhC1INH 100 IU/kg (n=17) vs. saline (n=17) **1205:** Phase 2 randomized, double-blind, placebo-controlled study rhC1INH 50 IU/kg (n=13) or rhC1INH 100 IU/kg (n=13) vs. saline (n=13)	**1304:** Age ≥16 years with HAE & acute angioedema attacks Inclusion: • functional C1INH level <50% normal Exclusion: • history of allergy to rabbits or acquired C1INH deficiency **1205:** Age ≥12 years with HAE & acute angioedema attacks Inclusion: • functional C1INH level <50% normal Exclusion: • history of allergy to rabbits or	**Pooled analysis** **Primary:** VAS-based median reduction in time to onset of symptom relief (min): rhC1INH 100 IU/kg 66; 50 IU/kg 122; placebo 495 (P < 0.01 for 100 IU/kg vs. placebo and P = 0.013 for 50 IU/kg vs. placebo) **Secondary:** VAS-based median time to minimal symptoms (min): rhC1INH 100 IU/kg 266; 50 IU/kg 247; placebo 1220 (*P*<0.001 for 100 IU/kg vs. placebo and *P*=0.001 for 50 IU/kg vs. placebo) No patients in either rhC1INH group had therapeutic failure vs. 59% placebo; odds ratios: 100 IU/kg 0.06 (95%CI: 0.01-0.32, P<0.001), 50 IU/kg 0.13 (95%CI: 0.00-1.08, P=0.060) No relapses within 4 hours occurred in any group. **Safety:** TEAE: headache, vertigo in rhC1INH groups vs. headache, injection site swelling, epistaxis, and hypotension in placebo

Study Number / Citation	Design / Sample Size / Treatments	Key Inclusion / Exclusion Criteria	Results
		acquired C1INH deficiency	No drug-related SAEs were reported; no discontinuations due to TEAEs
1304 OLE Moldovan D, Reshef A, Fabiani J, et al. Efficacy and safety of recombinant human C1-inhibitor for the treatment of attacks of hereditary angioedema: European open-label extension study. *Clinical & Experimental Allergy* 2012;42:929-935.	Open-label arm of study 1304 2100 U rhC1INH (N=57) Optional 2nd dose of 2100 U – 4200 IU per treated attack	Age ≥16 years & acute angioedema attacks & completed preceding 1304 RCT Inclusion: • functional C1INH level <50% normal Exclusion: • history of allergy to rabbits or acquired C1INH deficiency	**Primary:** VAS-based median time to onset of symptom relief (min): 60, 65, 120, 60, and 61 min, respectively for attacks 1-5 **Secondary:** Abdominal attacks had shortest median time to relief and to minimal symptoms (0.5 hours and 4 hours) vs. oro-facial-pharyngeal-laryngeal attacks (about 2-to 3-fold longer) Response rates were similar for successive attacks (1-5) and overall response rate was 87%; no clinical relapses occurred **Safety:** 28% single-dose and 26% repeat-dose treated patients had ≥1 TEAE, most mild to moderate in severity; headache and nausea were most common No SAEs reported within 7 days of treatment; no discontinuations due to TEAEs; no neutralizing antibodies to C1INH, and no anaphylaxis; no clinically significant changes in other safety parameters
1205 OLE Reidl MA, Levy RJ, Suez D, et al. Efficacy and safety of recombinant C1 inhibitor for the treatment of hereditary angioedema attacks: a North American open-label study. *Ann Allergy Asthma Immunol* 2013;110: 295e299.	Open-label arm of study 1205 rhC1INH 50 IU/kg (N=62) Optional 2nd dose of 50 IU/kg per treated attack	Age ≥12 years & acute angioedema attacks & completed preceding 1205 RCT Inclusion: • functional C1INH level <50% normal Exclusion: • history of allergy to rabbits or acquired C1INH deficiency	**Primary:** VAS-based median times to onset of symptom relief (min): ranged from 37-67 min for attacks 1-5 **Secondary:** VAS-based median times to minimal symptoms (min): ranged from 120-244 min for attacks 1-5; 95%CIs for primary and secondary endpoints for successive treated attacks overlapped; response rates were >90% with no relapses; 1 patient had a new attack location after treatment with minimal symptoms (VAS 9 mm) **Safety:** 64% patients had ≥1 TEAE, most mild-moderate in severity; headache, naso-pharyngytis were most common 20 SAEs reported in 10 patients; 13 events were HAE attacks in

Study Number / Citation	Design / Sample Size / Treatments	Key Inclusion / Exclusion Criteria	Results
			8 patients; tremaining 7 SAEs in 4 patients included severe vertigo (3 days post-treatment), pneumonia (1 day post-treatment, urosepsis occurring twice (6 days and 46 days after second treated attack), and "itching of the lips and soft palate" shortly after the fourth treated attack (no systemic signs of allergy with negative immunology results) No discontinuation due to TEAEs
1205 Relan A, Bakhtiari K, van Amersfoort E, et al. Recombinant C-1 inhibitor. Effects on coagulation and fibrinolysis in patients with hereditary angioedema. *Biodrugs* 2012;26(1):43-52.	Randomized, double-blind, placebo-controlled studies rhC1INH 50 IU/kg (n=9) or rhC1INH 100 IU/kg (n=9) vs. saline (n=7)	Met inclusion / exclusion requirements for Study 1205, had available plasma samples before and up IV administration of rhC1INH	**Primary:** *Baseline:* 24 out of 25 patients had enhanced thrombin and activation markers that correlated with each other (r=0.57, P<0.01) D-dimer levels correlated significantly with PAP complexes (r=0.89, P<0.01) and with F1+2 levels (r=0.68, P<0.01) *Post-exposure:* Median PT was normal; aPTT was normal in placebo vs. a dose-dependent prolongation in rhC1INH groups 1 placebo patient, also on prophylactic tranexamic acid, had a remarkable course of PT and aPTT prolongation and F1+2 elevation **Safety:** No thromboembolic AEs
3.1.3.2 Published and Unpublished Studies Supporting Off-label Indications			
1207 Reshef A, Moldovan D, Obtulowicz K, et al. Recombinant human C1 inhibitor for the prophylaxis of hereditary angioedema attacks: a pilot study. *Allergy* 2013;68:118-124.	Phase 2, open-label, exploratory study rhC1INH 50 IU/kg (N=25) Optional 2nd dose of 50 IU/kg to treat breakthrough attacks 8 doses: n=22	Asymptomatic HAE patients age ≥18 years & qualifying break-through attacks (occurring at least every 2 weeks) Inclusion: • confirmed type I or II HAE diagnosis Exclusion: • history of allergy to rabbits or	**Primary:** 25 patients had mean of 0.9 attacks/ week over past 2 years; 23 out of 25 reported impact on quality as major and/or causing disability; mean breakthrough attack rate on treatment was 0.4 attacks/ week (95%CI: 0.28-0.56) 84% of patients had an attack on treatment; 6 patients received an acute dose of rhC1INH **Secondary:** Antigenic or functional C1INH and C4 levels were consistent between

Study Number / Citation	Design / Sample Size / Treatments	Key Inclusion / Exclusion Criteria	Results
	10 doses: n=2 11 doses: n=1	C1INH products, or elevated IgE against rabbit dander	weekly treatments 1-8 **Safety:** 30 TEAEs reported in 13 patients, all mild-moderate Drug-related AEs were dry mouth, dizziness, and anxiety (n=1 patient), and hypotension reported (n=1) No allergic AEs and no neutralizing antibodies; 1 patient died from a laryngeal attack 25 days after last study drug administration

Abbreviations used: aPTT = activated partial thromboplastin time, AE = adverse event, C1INH = C1 esterase inhibitor, CI = confidence interval, GI = gastrointestinal, HAE = hereditary angioedema, IS = Investigator Score; min = minute(s), IV = intravenous, OLE = open-label extension, PD = pharmacodynamics, PK = pharmacokinetics, PT = prothrombin time, RCT = randomized clinical trial, rhC1INH = recombinant human C1 esterase inhibitor, SAE = serious adverse event, TEQ = Treatment Effect Questionnaire, TEAE = treatment-emergent adverse event, VAS = visual analog scale.

4.0 ECONOMIC VALUE AND MODELING REPORT

There is currently no budget impact model with RUCONEST for the treatment of acute attacks in adult and adolescent patients with HAE.

5.0 OTHER SUPPORTING EVIDENCE

5.1 Summary of Other Relevant Evidence

5.1.1 Published and Unpublished Studies Supporting Labeled and Off-label Indications

Hack CE, Mannesse M, Baboeram A, et al. Immunogenicity assessment of recombinant human C1-inhibitor. An integrated analysis of clinical studies. *Biodrugs* 2012;26(5):303-313 (Studies 1202, 1203, 1205, 1304 pooled retrospective safety analysis).

Study Description: Retrospective safety analysis using the data pooled from Study 1202 (an open-label, single-center study), Study 1203 (a multicenter extension to 1202), and 2 multicenter, double-blind, randomized, placebo-controlled studies, 1205 and 1304, each with an OLE to assess repeat treatment of attacks.

Methods: Eligible patients had functional C1INH plasma level <50% of normal, no medical history of rabbit allergy, and presented with an eligible acute angioedema attack at the clinic. Blood samples were collected at screening, at baseline prior to rhC1INH IV administration, and on days 22 and 90 post-treatment to test for antibodies against pdC1INH or rhC1INH, or against host-related impurities (HRI) using validated assays. The effect of anti-rhC1INH antibodies on clinical efficacy was measured based on time to onset of symptom relief and time to minimal symptoms (**Table 5-1**).

Table 5-1. Overview of Studies Included in the Pooled Immunogenicity Analysis

Study number	rhC1INH dose	No. patients administered rhC1INH	Total no. rhC1INH administrations	No. rhC1INH administrations per patient
C1 1202/3-01	100 U/kg	14	21	1–2
C1 1205-01 RCT	50 or 100 U/kg	25	25	1
C1 1205-01 OLE	1–2 × 50 U/kg[a]	62[c]	168	1–8
C1 1304-01 RCT	100 U/kg	16	16	1
C1 1304-01 OLE	1–3 × 2100 U[b]	57[d]	194	1–26
All studies	All doses	155[e]	424	1–26

a Patients were treated with 50 U/kg with the option of a second 50 U/kg dose.

b Patients were treated with 2100 U with the option of a second 2100 U or 4200 U dose.

c Includes 12 patients who received first rhC1INH treatment in the RCT phase of the study.

d Includes seven patients who received first rhC1INH treatment in the RCT phase of the study.

e The total number of unique patients, corrected for the patients who participated in more than one study.

OLE = open-label extension; **RCT** = randomized control trial; **rhC1INH** = recombinant human C1-inhibitor.

Endpoints: The primary endpoint was the production of anti-drug antibodies and anti-HRI antibodies in response to multiple treatments with rhC1INH of repeated angioedema attacks.

Results: Of the 155 patients who received 424 rhC1INH treatments, 90% had received repeat treatments, including 25 treated for ≥5 attacks.

- 1.5% of all pre-exposure tests and 1.3% of all post-exposure tests were above the cut-off level.
- 3.9% of patients were positive for anti-rhC1INH antibodies in the confirmatory assay.
- 2.6% of patients overall were negative prior to rhC1INH exposure, then developed anti-rhC1INH antibodies post-exposure.
- Anti-HRI antibodies were detected in <0.7% of screening tests before rhC1INH exposure, in <1.9% after first exposure, and in <3.1% after repeat exposure to rhC1INH.
- 5 patients were positive for anti-HRI antibodies in the confirmatory assay. 1 patient had pre-existing antibodies vs. 1.9% of rhC1INH-treated patients with confirmed anti-HRI antibodies

occurring at additional time points. 9 mild or moderate AEs were identified in 4 patients and were considered not related to study drug. AEs included tooth extraction, headache, pregnancy and influenza. There were no events of hypersensitivity of anaphylaxis.

Hack CE, Relan A, Baberam A, et al. Immunosafety of recombinant human C1-inhibitor in hereditary angioedema: evaluation of IgE antibodies. Clin Drug Investig 2013;33:275-281 (Studies 1101, 1106, 1202, 1203, 1205, 1304 pooled for retrospective safety analysis).

Study Description: A retrospective safety analysis to determine the frequency and clinical relevance of pre-exposure IgE antibodies to rabbit proteins and other potentially relevant animal allergens in subjects administered rhC1INH.

Methods: Healthy volunteer subjects and patients with HAE who were treated with rhC1INH across open-label and randomized trials and their OLEs (**Table 5-2**) were retrospectively analyzed for the frequency and clinical relevance of pre-exposure and any newly-induced IgE antibodies directed against rabbit and other animal allergens, including cow's milk, using validated assays.

Table 5-2. Overview of Studies Included in the Pooled Immunogenicity Analysis

Study no.	Study population	rhC1INH dose	Subjects administered rhC1INH	rhC1INH administrations performed per subject	Total no. of rhC1INH administrations
1101	Asymptomatic HAE patients	6.25–100 U/kg	12	2	24
1106	Healthy subjects	100 U/kg	14	1–5	59
1202 and 1203	Symptomatic HAE patients	100 U/kg	14[a]	1–2	21
1205 RCT	Symptomatic HAE patients	50 U/kg or 100 U/kg	25[b]	1	25
1205 OLE	Symptomatic HAE patients	50 U/kg or 2 × 50 U/kg[c]	38[b,d]	1–7[d]	79[d]
1304 RCT	Symptomatic HAE patients	100 U/kg	16[b]	1	16
1304 OLE	Symptomatic HAE patients	2,100 U or 2–3 × 2,100 U[e]	41[b,d]	1–12[d]	76[d]

rhC1INH recombinant human C1-inhibitor, *HAE* hereditary angioedema, *OLE* open-label extension, *RCT* randomized controlled trial

[a] One patient also participated in study 1101

[b] Sixteen patients in the randomized controlled studies 1205 and 1304 also participated in the OLE studies

[c] Patients were treated with 50 U/kg with the option of a second 50 U/kg dose

[d] The OLE studies were ongoing at the time of the IgE analyses

[e] Patients were treated with one vial of 2,100 U with the option of one or two additional vials of 2,100 U

Endpoints: The primary endpoint was the production of pre-exposure IgE antibodies to rabbit and other animal allergens in subjects administered the rhC1INH product.

Results: Of the 130 patients with HAE and 14 healthy volunteers who received a total of 300 rhC1INH administrations, 47% were dosed on a single occasion and 53% on ≥2 occasions.

- 5 subjects had preexisting anti-rabbit epithelium IgE; the subject with the highest levels had a previously undisclosed rabbit allergy and developed an anaphylactic reaction upon first exposure to rhC1INH.
- No other anaphylactic reactions were identified in any subjects exposed to rhC1INH.

5.1.2 Evidence Table Spreadsheets of All Published and Unpublished Studies

Study Number / Citation	Design / Sample Size / Treatments	Key Inclusion / Exclusion Criteria	Results
1202, 1203, 1205, 1304 (pooled) Hack CE, Mannesse M, Baboeram A, et al. Immuno-genicity assessment of recombinant human C1-inhibitor. An integrated analysis of clinical studies. *Biodrugs* 2012;26(5):303-313.	**1202:** Phase 2 open-label, single-center study in symptomatic patients with HAE **1203:** multi-center 1202 extension **1205, 1304:** Phase 2 or 3 multicenter, double-blind, randomized, placebo-controlled studies each with an OLE in symptomatic patients with HAE Single or multiple doses of: rhC1INH 50 IU/kg or rhC1INH 100 IU/kg or 2100 U N=155	Met inclusion / exclusion requirements for Studies 1202, 1203, 1205, 1304 Inclusion: • functional C1INH level <50% normal • presented with eligible acute angioedema attack at the clinic Exclusion: • history of allergy to rabbits	**Primary:** 1.5% of all pre-exposure tests and 1.3% of all post-exposure tests were above the cut-off level 3.9% of patients were positive for anti-rhC1INH antibodies in the confirmatory assay 2.6% of patients overall were negative prior to rhC1INH exposure, and then developed anti-rhC1INH antibodies post-exposure Anti-HRI antibodies were detected in <0.7% of screening tests before rhC1INH exposure, in <1.9% after first exposure, and in <3.1% after repeat exposure to rhC1INH 5 patients were positive for anti-HRI antibodies in the confirmatory assay **Safety:** 9 mild or moderate AEs were identified in 4 patients and were considered not related to study drug AEs included tooth extraction, headache, pregnancy and influenza There were no events of hypersensitivity of anaphylaxis
1101, 1106, 1202, 1203, 1205, 1304 (pooled) Hack CE, Relan A, Baberam A, et al. Immuno-safety of recombinant human C1-inhibitor in hereditary angioedema: evaluation of IgE antibodies. *Clin Drug Investig* 2013;33:275-	**1101:** Phase 1 open-label, proof-of-concept study in asymptomatic patients with HAE **1106:** Phase 1 open-label study in healthy volunteers **1202:** Phase 2 open-label study in symptomatic patients with HAE	Met inclusion / exclusion requirements for Studies 1101, 1106, 1202, 1203, 1205, 1304 Inclusion: • functional C1INH level <50% normal Exclusion: • history of allergy to rabbit dander	**Primary:** 47% subjects had single-dose and 53% had ≥2 doses rhC1INH 5 subjects had preexisting anti-rabbit IgE; subject with the highest levels had a previously undisclosed rabbit allergy and developed anaphylactic reaction upon first exposure to rhC1INH **Safety:** No other anaphylactic reactions were identified

Study Number / Citation	Design / Sample Size / Treatments	Key Inclusion / Exclusion Criteria	Results
281.	**1203:** multi-center 1202 extension **1205, 1304:** Phase 2 or 3 multicenter, double-blind, randomized, placebo-controlled studies Asymptomatic (1101): rhC1INH 6.25 IU/kg to 100 IU/kg (n=12) Healthy volunteers (1106): rhC1INH 100 IU/kg (n=14) Symptomatic (1202, 1203, 1205, 1304): Single or multiple doses of: rhC1INH 50 IU/kg or rhC1INH 100 IU/kg or 2100 U (n=118)		

Abbreviations used: AE = adverse event, C1INH = human C1 esterase inhibitor, HAE = hereditary angioedema, HRI = host-related impurities, OLE = open-label extension, rhC1INH = recombinant human C1 esterase inhibitor.

6.0 SUPPORTING INFORMATION

6.1 References Contained in Dossier

Agostoni A, Cicardi M. Hereditary and acquired C1-inhibitor deficiency: biological and clinical characteristics in 235 patients. *Medicine (Baltimore)* 1992;71:206-215.

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