PHARMACEUTICALS

Cinryze™

(C1 Inhibitor, human)

for the Prophylactic Treatment of HAE

Briefing Document

Blood Products Advisory Committee Meeting

May 2, 2008

BLA 125267

Advisory Committee Briefing Materials: Available for Public Release

1.   EXECUTIVE SUMMARY

Background

Cinryze™ is a plasma-derived C1 inhibitor product for the treatment of hereditary angioedema (HAE), a rare, debilitating, life-threatening disease for which available treatment in the United States (US) is inadequate.

Cinryze is a highly purified, nanofiltered, lyophilized concentrate of C1 inhibitor made from US Source Plasma and manufactured under contract for Lev Pharmaceuticals (Lev) by Sanquin Blood Supply Foundation (formerly the Central Laboratory of the Netherlands Red Cross Blood Transfusion Services, CLB) in the Netherlands. Sanquin was the first manufacturer to produce a commercially available C1 inhibitor, and has developed successive generations of increasingly pure C1 inhibitor products for more than 35 years. Cetor, Sanquin's currently marketed product, has been available as the standard of care for the treatment of HAE in the Netherlands for the last 11 years.

Cinryze is the next evolution of the manufacturing process of Cetor. The Cinryze manufacturing process includes a second dedicated viral reduction step of nanofiltration through two serial 15 nm Planova filters, as well as ▆▆▆▆▆▆▆▆▆▆▆▆ ▆▆▆▆▆▆▆▆▆▆▆▆▆▆▆▆▆▆▆▆▆▆▆▆▆▆▆▆▆▆▆▆▆▆ Full viral inactivation and removal studies have been completed for Cinryze, demonstrating removal or inactivation of both lipid- and nonlipid-enveloped viruses and, theoretically, prions through three orthogonal steps. Additionally, a comparison study of product made with the Cinryze manufacturing process and Cetor showed they have equivalent pharmacokinetic, pharmacodynamic, and safety profiles.

Unmet Medical Need

HAE is a serious and potentially life-threatening disease. HAE is caused by a deficiency of functional C1 inhibitor, which leads to episodes of uncontrolled complement and contact activation. The disease is manifested by unpredictable attacks of nonpruritic swelling of the extremities, face, trunk, airway, or abdominal viscera, occurring spontaneously or secondary to trauma. Untreated HAE attacks typically last for 1 to 9

days. Swelling of the airway can lead to death by asphyxiation; in the past, 30% of untreated patients died from laryngeal edema. Swelling of the abdomen can lead to severe, painful, and often incapacitating illness lasting for several days. It is not unusual for HAE patients to miss up to 100 days of school or work each year because of swelling and/or pain. HAE can have a devastating impact on the lives of patients, not only from the debilitating effects of attacks, but also from the fear and uncertainty caused by the unpredictable nature of attacks.

Current therapy of HAE in the US is inadequate. There is no adequate treatment available for acute attacks other than supportive care and watchful waiting in case an emergency intubation or tracheotomy becomes necessary. Danazol, an impeded androgen, is known to increase C1 inhibitor levels and has been used for long-term prophylaxis, primarily in men. It is associated, however, with muscle toxicity, lipid abnormalities, dysphorias, menstrual disruptions, and hepatic toxicity and adenomas. It is often poorly tolerated in women and it is contraindicated in children. Epsilon aminocaproic acid (EACA) has also been used, but it has serious side effects. Short-term prophylaxis prior to dental or surgical procedures may be provided with fresh-frozen plasma (FFP). Though FFP is labeled for use in acute treatment in HAE, its use is controversial. The low concentrations of C1 inhibitor in FFP require administration of large volumes to have an effect. In addition to the risk of fluid overload, FFP can generate vasoactive proteins that can exacerbate an already serious HAE attack.

There are approximately 10 000 HAE patients in the US, of which approximately 3500 have been diagnosed. US patients continue to suffer significant morbidity and mortality because no disease-specific treatment is available. Current long-term prophylaxis options may be ineffective, intolerable, or contraindicated for many patients.

Cinryze Pivotal Trials

- Phase 3 Acute Treatment Trial: a randomized, double-blind, placebo-controlled acute treatment trial in subjects with moderate to severe HAE attacks

- Phase 3 Prophylactic Treatment Trial: a randomized, double-blind, placebo-
  controlled, crossover prophylactic treatment trial in qualified subjects who had
  completed the Acute Treatment Trial. Each patient served as his or her own control.

Cinryze Dose

The dose in each study was 1000 U (10 mL). In Europe, this is the approved dose of
Cetor both for the treatment of acute attacks as well as short-term prophylaxis. In the
Prophylactic Treatment Trial, 1000 U of Cinryze was given twice weekly by clinical
personnel. The twice-weekly dosing schedule was selected based on the half-life of C1
inhibitor and its pharmacodynamic effects on C4 levels.

Efficacy: Acute Treatment Trial

In the Acute Treatment Trial, the median time to the onset of unequivocal relief of
symptoms for an acute attack was significantly different between the Cinryze group (2
hr) and placebo group (> 4 hr) (p=0.026). The application for the treatment of acute
attacks of HAE is currently under active review at FDA and will not be addressed at this
meeting.

Efficacy: Prophylactic Treatment Trial

The focus of this meeting is the prophylaxis of HAE attacks. In the Prophylactic
Treatment Trial, Cinryze decreased the normalized number of HAE attacks compared to
placebo. The trial had a crossover design with 22 subjects in the efficacy data set. The
difference between the number of angioedema attacks during treatment with Cinryze and
the number during treatment with placebo was statistically significant (p<0.0001). During
12 weeks of prophylactic treatment with Cinryze, the number of attacks per patient
ranged from 0 to 17.6 with a mean of 6.3 (±5.5) and a median of 6 attacks. During 12
weeks of treatment with placebo, the number of attacks per patient ranged from 6 to 20.5
with a mean of 12.7 (± 4.6) and a median of 13.5 attacks. The clinically and statistically
significant results for the primary endpoint demonstrating the efficacy of Cinryze were
supported by statistically significant and clinically meaningful differences in all of the
secondary endpoints, with Cinryze demonstrating reductions in the severity and duration
of attacks, number of days of swelling, and need for open-label Cinryze rescue therapy.

Safety

The safety profile of Cinryze is favorable. In all trials, there were few treatment-emergent adverse events reported. In the Acute Treatment Trial, events reported during placebo treatment were of the same type and severity as those reported for Cinryze. In the Prophylactic Treatment Trial, four subjects reported five SAEs, none of which was related to Cinryze. All were hospitalizations for HAE or other unrelated medical conditions. In addition, another 28 SAEs have been reported in the ongoing open-label trials, and all have been classified as unrelated to Cinryze.

Conclusion

Based on its favorable safety profile and statistically significant and clinically meaningful reductions in disease burden, Cinryze has a demonstrated value in the prophylactic treatment of HAE. Cinryze at a dose of 1000 U injected twice weekly reduced the number, severity, and duration of HAE attacks along with the total days of swelling compared to placebo. Cinryze has been shown to be both safe and effective for the prophylactic treatment of HAE. Upon approval, Cinryze will address the unmet medical need for HAE patients by providing an effective option of replacement therapy for this protein deficiency disease.

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2. ABBREVIATIONS

AE	Adverse event, adverse experience
BLA	Biologic License Application
BPAC	Blood Products Advisory Committee
CBER	Center for Biologics Evaluation and Research
C1	Complement component 1
C4	Complement component 4
C1 INH	C1 inhibitor
EACA	Epsilon-aminocaproic acid
EU	European Union
FDA	Food and Drug Administration
GI	Gastrointestinal
GU	Genitourinary
HAE	hereditary angioedema
IND	Investigational New Drug
IV	Intravenous
MBL	Mannin-binding lectin
MASP	MBL-associated serine proteases
OBRR	Office of Blood Research and Review
OL	Open Label
PEG	polyethylene glycol
PD	Pharmacodynamic
PK	Pharmacokinetic
SAE	Serious adverse event
SD	standard deviation
TEAE	Treatment-emergent adverse event
U	Unit
US	United States
VAS	Visual Analogue Scale

3.   INTRODUCTION

Hereditary angioedema (HAE), also known as C1 inhibitor deficiency, is a serious, debilitating, and potentially fatal disease caused by an autosomal dominant mutation on chromosome 11 that leads to a decrease in C1 inhibitor activity (Bowen et al, 2001). Attacks of HAE follow an unpredictable course for severity, clinical presentation, and recurrence. Current treatment options in the United States (US) are limited, and there is inadequate acute and prophylactic therapy available. The unpredictable and potentially lethal nature of HAE attacks causes physical and psychological stress and significantly alters patients' lives (Agostoni et al, 2004).

HAE is a rare disease. It is estimated that 3500 people in the US are diagnosed with HAE. The diagnosis, however, is often missed for years (Frank, 1976). There are approximately 10 000 people with HAE in the US, making treatment of HAE an orphan indication for US regulatory purposes.

Lack of functional C1 inhibitor results in decreased inhibitory tone and continuous activation of the complement and kallikrein-kinin systems, which in turn lead to increased vascular permeability and edema (Davis, 2008). Attacks can involve painful and disfiguring swelling of extremities and face, painful abdominal or urogenital swelling, and potentially life-threatening laryngeal edema. Untreated HAE attacks typically last for 1 to 9 days, and frequently require hospitalization (Frank, 2008). Attacks can range from mild to severe, and any attack can be debilitating. Laryngeal attacks are life-threatening due to the potential for airway obstruction and asphyxiation. Swelling of the abdomen can lead to severe, painful, and often incapacitating illness lasting for several days, and has often been misdiagnosed as an acute abdomen, leading to unnecessary surgery (Cicardi et al, 1996). US patients continue to suffer significant morbidity and mortality because no disease-specific treatment is available.

3.1 C1 Inhibitor Replacement Therapy

3.1.1 European Experience

Replacement therapy with C1 inhibitor has been available in Europe as the standard of care to manage HAE patients for more than 35 years.

Sanquin (formerly the Central Laboratory of the Netherlands Red Cross Blood Transfusion Services, CLB) was the first manufacturer to produce a commercially available C1 inhibitor, and has developed successive generations of improved C1 inhibitor products for over 35 years. Other European plasma fractionators have also marketed C1 inhibitor preparations, leading to more than 75 published reports—including controlled trials, case reports, and review articles—describing the efficacy of C1 inhibitor in acute HAE attacks and in short-term prophylactic treatment. Replacement therapy with C1 inhibitor as long-term prophylaxis to prevent HAE attacks, while less studied, has also been described as effective.

Cetor, Sanquin's currently marketed product, is a highly purified C1 inhibitor, which has been available in the Netherlands for 11 years. Cetor has been the standard of care for the treatment of acute HAE attacks and short-term prophylactic treatment in the Netherlands, and has also been reported as effective for long-term prophylactic treatment (Levi, 2006). Cetor is pasteurized and contains hepatitis B immunoglobulin. More than ▇▇▇▇▇▇ have been distributed during this 11-year period. A single adverse event (AE) has been reported during this time, in which it originally was thought that the patient may have developed antibodies to Cetor; later it was determined that the patient had developed systemic lupus erythematosus.

3.1.2 Cinryze™

Cinryze™ is a highly purified, viral-inactivated, nanofiltered concentrate of C1 inhibitor produced from plasma collected in the US. It is manufactured under contract for Lev Pharmaceuticals (Lev) by the Sanquin Blood Supply Foundation in the Netherlands. Cinryze is the next evolution of highly purified C1 inhibitor products from Sanquin. Cinryze manufacturing includes a second dedicated viral-reduction step of nanofiltration through two serial 15 nm Planova filters and does not include the addition of hepatitis B

immunoglobulin. Lev obtained the US distribution rights to this product, and is the sponsor of the BLA currently under review by FDA for both acute and prophylactic treatment of HAE. Sanquin is concurrently developing this new nanofiltered product with European plasma as the next generation of Cetor.

Cinryze is manufactured from US Source Plasma using standard ion exchange chromatography and polyethylene glycol (PEG) precipitation. Cinryze is provided in vials containing 500 U of C1 inhibitor as a lyophilized powder that is ready for reconstitution with Water for Injection (USP), resulting in a solution for IV injection that contains 100 U/ml. One unit of Cinryze corresponds to the mean quantity of C1 inhibitor present in 1 ml of normal fresh plasma.

Two dedicated, independent, and effective viral-reduction steps are used in the manufacture of Cinryze: pasteurization at 60°C for 10 hours in an aqueous solution, and nanofiltration through two sequential 15 nm Planova filters. These viral inactivation and removal steps, as well as an additional step in the manufacturing process, PEG precipitation, have been validated in a series of in vitro experiments to inactivate and/or remove a wide range of viruses of diverse physicochemical characteristics, including Human Immunodeficiency Virus (HIV), Hepatitis A Virus (HAV), and the following model viruses: Bovine Viral Diarrhea Virus (BVDV) as a model virus for Hepatitis C Virus (HCV), Canine Parvovirus (CPV) as a model virus for Parvovirus B19, and Pseudorabies Virus (PRV) as a model virus Hepatitis B Virus (HBV). Total mean $\log_{10}$ reductions range from >8.7 to >19.1 $\log_{10}$ as shown in Table 1.

Table 1. Log_{10} Reduction Factor for Selected Viruses

Process step	Enveloped viruses			Nonenveloped viruses	
	HIV	**BVDV**	**PRV**	**HAV**	**CPV**
PEG precipitation	5.1 ± 0.2	4.5 ± 0.3	6.0 ± 0.3	2.8 ± 0.2	4.2 ± 0.2
Pasteurization	$> 6.1 \pm 0.2$	$> 6.7 \pm 0.3$	$> 6.7 \pm 0.2$	2.8 ± 0.3	0.1 ± 0.3
Nanofiltration	$> 5.6 \pm 0.2$	$> 5.5 \pm 0.2$	$> 6.4 \pm 0.3$	$> 4.9 \pm 0.2$	$> 4.5 \pm 0.3$
Total reduction	**> 16.8**	**> 16.7**	**> 19.1**	**> 10.5**	**> 8.7**

The prion reduction factor (RF) has been investigated to determine the effectiveness of the double serial dead-end 15 nm nanofiltration step to remove abnormal prion protein using hamster-adapted, sheep scrapie (strain 263K). The study was performed under the specific process conditions used in normal Cinryze manufacturing. The study shows the complete removal of 263K prion protein with reduction factors of >4.25 $\log_{10}$ and >4.54 $\log_{10}$, respectively (Table 2).

Table 2. RF ($\log_{10}$) for Prion Removal

| Agent | Run | Step | RF[1] values | |
			0.1 µm filtrate	Planova 15N filtrate
263K	2	Planova 15N	0.75	>4.25
263K	1	Planova 15N	1.25	>4.54

1 Reduction factor

3.2 Cinryze Clinical Program

Lev has studied Cinryze in two Phase 3 pivotal trials in the United States: one for treatment of acute HAE attacks (Acute Treatment Trial), and the second for prophylaxis against recurrent HAE attacks (Prophylactic Treatment Trial). A pharmacokinetic/pharmacodynamic (PK/PD) study was also performed.

In the double-blind, placebo-controlled Acute Treatment Trial, 71 subjects (36 Cinryze, 35 placebo) were randomized and treated. An additional 12 subjects received open-label Cinryze for the acute treatment of laryngeal attacks or short-term prophylaxis prior to surgery or dental procedures that were not part of the Phase 3 study.

The double-blind, placebo-controlled Prophylactic Treatment Trial randomized 24 subjects to receive Cinryze/placebo or placebo/Cinryze in a 24-week, crossover design with two treatment periods of 12 weeks each. Of these 24 subjects, 22 completed all or some of both treatment periods (ITT efficacy population); 20 subjects (10 Cinryze, 10 placebo) completed both treatment periods.

Both studies met all their primary efficacy endpoints. There has been no significant safety signal associated with Cinryze in any of the clinical studies to date in the more than 6000 injections given during these studies and in the open-label extension and Individual Treatment use studies. Adverse events for Cinryze were generally mild and similar in number, type, and severity to those occurring with placebo. Open-label trials in acute and prophylactic treatment are ongoing. The pivotal Acute Treatment Trial is under active review by FDA. The pivotal Prophylactic Treatment Trial is the subject of this BPAC.

4.   UNMET MEDICAL NEED

- US patients have inadequate options for effective treatment
  - for acute attacks or
  - for prophylaxis of attacks
- C1 inhibitor demonstrated safety and efficacy
- More than 75 publications
- 36 years of clinical experience

4.1   Hereditary Angioedema

Hereditary angioedema, also known as C1 inhibitor deficiency, is a serious, debilitating, and potentially fatal disease caused by an autosomal dominant mutation on chromosome 11 that leads to a decrease in C1 inhibitor activity. HAE patients typically have 5-30 % of normal functional C1 inhibitor activity (Davis, 1988), leading to unpredictable and spontaneous activation of complement and contact systems resulting in increased vascular permeability and a clinical presentation of edema at various locations. C1 inhibitor deficiency has been segmented into two distinct types. A decrease in the circulating quantity of C1 inhibitor is identified as Type I, and normal blood levels of a nonfunctional C1 inhibitor is identified as Type II. Both cause identical clinical disease. There is no gender or ethnic predominance (Nzeako et al, 2001). Approximately 75% of patients have a family history of swelling, while 25% of diagnosed patients have no family history and presumably have spontaneous mutations (Agostoni et al, 1992).

Epidemiology HAE is a rare disease. It is estimated that HAE affects between 1 in 10 000-50 000 people worldwide (Longhurst, 2006). There are approximately 3500 people diagnosed with HAE in the United States. The diagnosis is often missed or delayed (Frank, 1976). There may be 10 000 people with HAE in the US, making the treatment of HAE an orphan indication for US regulatory purposes.

Clinical Presentation The deficiency of C1 inhibitor results in spontaneous, nonpruritic swelling that can occur unpredictably and at random locations throughout the body. The extremities, abdomen, genitalia, face, and larynx can be affected. HAE attacks are

unpredictable in terms of the timing, location, and severity. The triggers that lead to attacks are not well understood, but attacks tend to become more frequent and/or more severe at times of physiological or psychological stress. Untreated HAE attacks can last for 1 to 9 days, and frequently require hospitalization (Frank, 2008). Swelling of the airway can lead to death by asphyxiation. Swelling of the abdomen can lead to severe, painful, and often incapacitating illness lasting for several days, and has often been misdiagnosed as an acute abdomen that has led to unnecessary surgery (Agostoni et al, 1992).

The location of the nonpruritic but often very painful swelling varies, both among patients and for a given patient. Patients may have multiple areas of involvement during an acute attack, and there is no correlation between the location of a patient's most recent attack and where the next attack will occur. Prior attacks are not predictive of the type, timing, severity, or duration of subsequent attacks.

Laryngeal attacks are the most dangerous, with most patients experiencing at least one laryngeal attack in their lifetime. Historically, untreated laryngeal attacks carried a mortality as high as 30% (Agostoni et al, 1992; Frank, 1976). Even today, HAE patients die in the US due to laryngeal attacks. Attacks can progress rapidly. In one case report, a laryngeal attack progressed to death within 20 minutes (Bork et al, 2000). More commonly, attacks peak in severity at 8 hours. Laryngeal attacks require immediate treatment. Though these attacks are the least frequent, they are unpredictable and can occur at any time in the course of the disease.

Cutaneous attacks are the most common. They typically result in edema of extremities, with functionally disabling swelling of hands or feet and swelling around joints causing loss of flexibility and discomfort. Swelling of the hands interferes with daily activities such as the use a keyboard, dialing a phone, or even buttoning clothes. Swelling of the feet can prevent a person from walking or driving. Cutaneous attacks do not generally result in hospitalization, but they are a major cause of missed work and school (Zuraw, 2006). Swelling in the extremities tends to develop gradually, and spontaneously resolves over 2-5 days.

Abdominal attacks are associated with severe pain, intestinal obstruction, nausea, vomiting, and dehydration. They frequently lead to hospitalizations. Failure to properly diagnose an abdominal attack can result in unnecessary surgeries, as the initial presentation can resemble an acute abdomen (Agostoni et al, 1992). Abdominal attacks that do not result in hospitalization still tend to be debilitating because the pain and GI symptoms prevent patients from going to work or school. The duration of the abdominal attack is typically 3 days, with symptoms peaking within the first 36 hours and gradually tapering off over the next 36 hours.

Facial attacks are the most visually striking manifestation of HAE. They are disturbing to patients, who find the temporary disfigurement embarrassing and socially inhibiting. Facial attacks often dissuade patients from leaving their homes during the attack. These attacks tend to be less painful, and patients generally do not seek hospitalization or medical care; however, facial attacks have particular clinical importance due to the potential of local extension from the face to the larynx resulting in a risk of asphyxiation.

Urogenital attacks are often triggered by intercourse, but may also occur spontaneously. They are associated with painful urination and swollen genitalia, and typically last about 3 days. Often the genitalia are swollen to such an extent that patients are unable to dress in their regular clothes or go about normal daily activities, such as sitting in a car or at a desk.

Disease burden The impact of HAE on patients' lives is multidimensional and life altering, often resulting in partial or total disability. Between 15 000 and 30 000 ER visits per year are related to HAE (Moore et al, 1988). Individual patients may lose up to 100 days of school or work annually (Nzeako et al, 2001) because of the attacks, making employment or education difficult.

Because of its unpredictability, HAE can be life altering regardless of the attack frequency. Patients live in constant fear of the next attack, and often arrange their lives around these events. If they feel an attack is imminent, they perform the common activities of daily living with urgency, knowing that they may not be able to complete these mundane tasks when they are in the midst of an attack. Some patients who have had

laryngeal attacks—or who have had family members die due to laryngeal attacks—never leave their local environment. They are afraid of being distant from the safety of their home and from the physicians who know and understand their illness (Levi et al, 2006).

In addition to the inadequacies of currently approved treatment, there is a significant potential for harm from health-care providers who do not recognize the condition. Many patients relate stories of misdiagnoses in emergency rooms, and attempts to treat attacks with drugs that are ineffective and expose patients to needless side effects. One study found that nearly one-third of patients underwent unnecessary abdominal surgery due to misdiagnosis (Agostoni et al, 1992).

Diagnosis A diagnosis of HAE is suspected with the clinical history of recurrent attacks of angioedema and abdominal pain. Clinical manifestations are variable and unpredictable. A serpiginous rash may also be seen, but it is not required for diagnosis. The edema and swelling typically develop gradually over the first several hours, increase for 12–36 hours, and then subside after 2–9 days. However, patients may experience abdominal attacks with a very sudden and severe onset of pain and no visible edema. Attacks vary in frequency among patients, and also can vary in a patient over time. The frequency can range from multiple attacks per week to one attack per year.

Patients generally experience their first attack within the first or second decade of life. Attacks typically worsen at puberty. Despite early attacks, some patients are not diagnosed with HAE for as long as 20 years (Frank, 1976).

The diagnosis of HAE is made on the basis of clinical signs and symptoms, and is supported by patient history and family history. An abnormal low result for C4 combined with either an abnormal low result for antigenic or functional C1 inhibitor confirms the diagnosis. While initially helpful in confirming a diagnosis, plasma levels of C1 inhibitor do not correlate with disease severity, and are not useful in predicting the course of the disease or onset of individual attacks (Bowen et al, 2008). The plasma level of C1 inhibitor does not correlate with the probability of an attack, but during an attack, there is an increased consumption of C1 inhibitor.

4.2 Function of C1 Inhibitor

The primary function of C1 inhibitor is to down-regulate the activation of the complement and the kallikrein-kinin contact systems. This is accomplished through the formation of pathway-specific complexes that result in inactivation of the target protease and the consumption of the C1 inhibitor on a one-to-one basis, as shown in Figure 1.

Figure 1. Inhibition of serine proteases (A) by C1 Inhibitor (B) to form a stable complex (C)
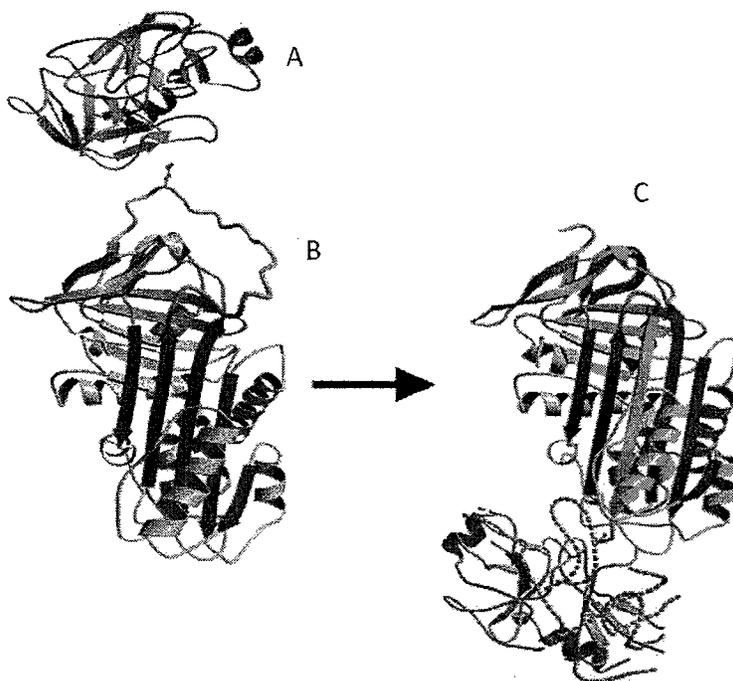
Adapted from Huntington et al, 2000

C1 inhibitor inhibits the complement system by binding C1r and C1s, two of the active enzyme subunits of the first component of the complement system in the classical pathway, as well as to mannin-binding lectin (MBL)-associated serine proteases (MASPs) in the lectin pathway. The primary substrate of the C1 enzyme is C4; uninhibited C1 can result in severely depleted levels of C4. C1 inhibitor regulates the contact system and the intrinsic coagulation pathway by binding to and inactivating kallikrein, and factors XIa and XIIa, as shown in Figure 2. Because all of these pathways are part of enzyme amplification cascades, without C1 inhibitor, spontaneous or trigger-

induced activation of these pathways can lead to unopposed activation and swelling (Davis, 2008).

Figure 2. The Effects of C1 Inhibitor in the Complement and Kallikrein-kinin Contact Pathways

X Inhibited by C1 inhibitor
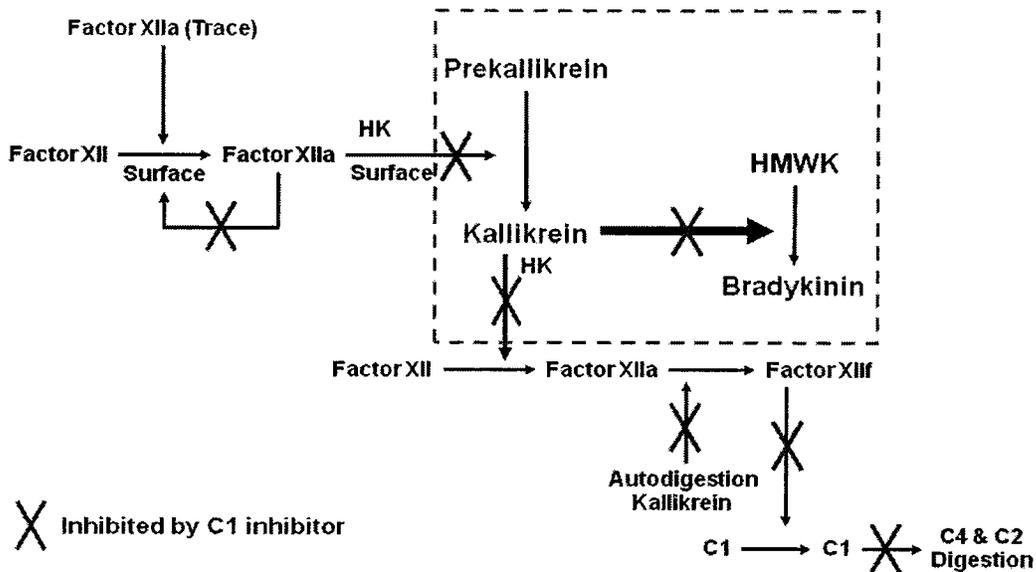
Adapted from Kaplan, 2002

In other protein deficiencies resulting from an autosomal dominant disease, one would expect that the circulating concentration of the normal protein would be decreased by 50%. In HAE, most patients have only 5-30% of normal C1 inhibitor function, probably because of continuous low-grade depletion (Davis, 2008). Deficiency of C1 inhibitor leads to chronic consumption of C4. A suspected HAE diagnosis is confirmed by a low C1 inhibitor and a low C4 (Bowen et al, 2008).

4.2.1   Pathophysiology of C1 Inhibitor Deficiency

C1 inhibitor affects the kallikrein-kinin, complement, fibrinolytic, and clotting pathways. When there is a functional deficiency of C1 inhibitor, these key inflammatory cascades are no longer controlled (Davis, 2008). The complement and kallikrein-kinin systems are continuously activated, which in turn activate other proteins of the complement system. Vasoactive components of these systems produce leakage of fluid into soft tissue, causing edema. The triggers for an attack are highly variable and include trauma, infection, and emotional stress, although most triggers are not known (Frank, 2008; Agostoni, 2004).

Hormonal fluctuations may influence attacks, and estrogens can worsen the severity of attacks.

4.3   Current Treatment

Treatment of C1 inhibitor deficiency covers long-term, short-term, and acute needs, and is aimed at management of the clinical manifestations of the disease. The threshold for treatment is usually a joint decision between clinician and patient based on an assessment of the individual clinical presentation of the disease, including the severity, frequency, or life-threatening nature of the attacks, as well as the impact on a patient's quality of life. Unlike other plasma protein deficiencies, management to clinical response rather than biochemical markers is the approach of HAE-treating physicians. This is due to the wide variation of clinical symptoms between patients and the lack of a correlation between plasma levels of C1 inhibitor and clinical manifestation of disease.

Treatment of HAE patients in the US is not adequate.

4.3.1   Therapeutic Agents

Danazol The use of danazol, an impeded testosterone derivative, was first described in 1976 when Michael Frank et al. at the NIH showed that danazol increased C1 inhibitor levels through a mechanism that is still not clear (Frank, 1976). Danazol has efficacy in some patients for the long-term prophylaxis of HAE. Patients are usually dosed to clinical response, starting at a high dose to gain control of their symptoms, and then adjusted to the lowest effective dose based on the frequency of attacks and the patient's ability to tolerate the side effects of the drugs. Patients end up on a wide range of doses because there is substantial variation in response to androgens.

Danazol is also used for short-term prophylaxis perioperatively or post-traumatically, to reduce the risk of the trauma triggering an acute attack. While danazol does increase C1 inhibitor levels in selected patients over time, the effect of danazol is not seen for at least 48 hours after treatment, and it is therefore not useful for treating acute HAE attacks. It is an imperfect mainstay of HAE prophylaxis for many people, especially women, because of the lipid abnormalities, weight gain, virilization, menstrual irregularities, hypertension,

and thrombotic events associated with its use. Long-term use has been associated with muscle toxicities as well as liver dysfunction and hepatocellular adenomas. Danazol is contraindicated during pregnancy and relatively contraindicated in children (Frank, 2008).

Antifibrinolytic agents Epsilon aminocaproic acid (EACA, Amicar) and tranexamic acid have been used as prophylactic agents for treating HAE. Their mechanism of action is thought to function through a C1 inhibitor-sparing effect, but these agents are generally no longer used unless no other therapy is available. They are not useful in treating acute attacks. Adverse effects include red-green color blindness and liver toxicity in animals.

Fresh-Frozen Plasma The only biologic product approved for the treatment of HAE is fresh-frozen plasma (FFP) that is collected from normal blood donors and frozen immediately, without any further processing or viral inactivation steps.
FFP contains all blood proteins, but the concentration of C1 inhibitor is relatively low. Large volumes of FFP can result in volume overload and elevated levels of clotting factors leading to an increased risk of thrombotic events. Treatment with FFP carries with it the danger of exacerbating an acute attack (Frank, 1976), possibly due to the replenishment of plasma proteases and substrates involved in the generation of peptides that mediate the angioedema (Agostoni et al, 2004). The use of FFP to treat acute attacks of HAE is controversial because of its potential to worsen an acute attack. It is still used for short-term prophylaxis prior to surgery.

FDA has recognized the usefulness of replacement therapy for the management of patients with rare plasma protein deficiencies such as HAE with the following labeling statements for FFP:

- Management of patients with rare specific plasma protein deficiencies, such as C-1-esterase [inhibitor]
- Management of patients with selected coagulation factor deficiencies, congenital or acquired, for which no specific coagulation concentrates are available

C1 Inhibitor Specific C1 inhibitor concentrates have not been approved for use in the US. C1 inhibitor is the standard of care in Europe, however, where it is used as the primary treatment for acute attacks, short-term prophylaxis, and increasingly for long-term prophylaxis. Purified C1 inhibitor has been available in Europe since the early 1970s. It is a disease-specific protein replacement therapy, utilizing a highly purified protein concentrate. It mitigates the use of FFP, which has a much lower concentration of C1 inhibitor and is not purified.

C1 inhibitor interrupts the cascade of the attacks at multiple points along the pathway. Replacing C1 inhibitor not only stops kallikrein-kinin system activation, but also restores normal homeostasis of the fibrinolytic and complement systems, thereby stopping an acute attack and potentially preventing further attacks. Multiple studies and publications have demonstrated the efficacy and safety of C1 inhibitor replacement therapy. Because it is a physiologic protein, present at some level in all patients, immunogenicity is unlikely and has not been reported.

4.3.2   Current Practice

Acute treatment The current treatment of acute HAE attacks is largely supportive. Abdominal attacks are often extremely painful, and may result in surgical exploration and narcotic addiction. Likewise, supportive therapy is all that is available for laryngeal attacks that may require intubation or tracheotomy. There is little evidence that antihistamines, steroids, or epinephrine are effective, though they are sometimes used.

Prophylactic treatment Current prophylactic treatment is restricted to the use of impeded androgens, such as danazol, and antifibrinolytics such as EACA (epsilon-aminocaproic acid) and tranexamic acid. While danazol can be effective in some patients, it has serious side effects and limitations as long-term therapy. Physicians who treat HAE patients with danazol will start with a relatively high dose, and then titrate the dose up or down based on the clinical response of the patient. Tranexamic acid, a cyclic derivative of EACA, has significant visual disturbances associated with its use and is generally not prescribed in the US. EACA has serious side effects and is also not commonly used in the US.

Two units of FFP infused just prior to surgery or dental procedures can be effective short-term prophylactic treatment.

5.   CLINICAL PROGRAM

To support the introduction of Cinryze into the US market, Lev performed the following series of clinical studies.

- Two pivotal safety and efficacy trials were conducted using a dose of 1000 U IV:
  - Acute Treatment Trial: A double-blind, randomized, placebo-controlled safety and efficacy trial in HAE patients for a single acute attack
  - Prophylactic Treatment Trial: A double-blind, randomized, placebo-controlled, crossover design trial of prophylactic treatment of attacks of HAE. Patients completed the Acute Treatment Trial prior to enrolling in the Prophylactic Treatment Trial
- A pharmacodynamic/pharmacokinetic study
- Open-label extension studies:
  - Open-label extension of the Acute Treatment Trial
  - Open-label extension of the Prophylactic Treatment Trial
  - Individual treatment studies

5.1   Regulatory Background

Lev filed an IND to initiate clinical studies in July 2004, after meeting with the Office of Blood Research and Review (OBRR) at the Center for Biologics Evaluation and Research (CBER) in April and June 2004 in Rockville, MD. Cinryze received orphan designation for the treatment of angioedema in July 2004 and fast-track designation in October 2005.

The Acute Treatment Trial was initiated in March 2005 and the last subject was randomized in December 2006. The first subject was enrolled in the Prophylactic Treatment Trial in September 2005, and the last subject was enrolled in December 2006 and completed participation in May 2007.

Lev submitted a BLA, STN 125267/0, on 30 July 2007 for Cinryze [C1 inhibitor (human)], for the treatment of acute attacks of HAE. This BLA was accepted for filing and granted a priority review by FDA. Lev amended the BLA on 29 October 2007 to

include prophylactic treatment to prevent or reduce HAE attacks in subjects with recurring events.

5.2 Dosing Rationale

A standard dose of 1000 U was used in these studies. This dose was based on the recommended dosing in the current Cetor label, the extensive clinical experience in Europe, and the pharmacokinetic and pharmacodynamic properties of Cetor and other C1 inhibitor products. As is the practice in Europe for Cetor administration, a repeat dose of 1000 U was administered in the Acute Treatment Trial if a subject failed to respond to the initial dose within 60 minutes.

A retrospective study was performed to identify the time to complete relief of symptoms in 35 HAE subjects who received Cetor in the Netherlands. Three subjects received 500 U, 29 subjects received 1000 U, 2 subjects received 1500 U, and 1 subject received 2000 U. The mean time to complete relief was 145 minutes for the entire group of 35 subjects. Among the 29 subjects treated with 1000 U, the mean and median times to complete relief were 140 and 120 minutes respectively (Levi, personal communication).

Data were also collected on the time to onset of relief from 206 attacks of HAE treated with 1000 U of another C1 inhibitor product (Tim3, Baxter/Immuno) in Italy. Subjects reported onset of relief within 60 minutes of treatment in 199 of the 206 attacks treated with 1000 units of Tim3. Among the 7 subjects with attacks who did not report relief within 60 minutes, 1 responded in 120 minutes, 5 responded in 180 minutes, and 1 failed to respond (Cicardi, personal communication). Taken together, the data demonstrate that the overwhelming majority of HAE subjects treated with 1000 U of C1 inhibitor show rapid clinical improvement. Furthermore, no evidence of a more rapid response was seen with higher doses of C1 inhibitor. These studies, therefore, provide a strong rationale for the dosing schedule used in this study.

Because the studies summarized above were open-label studies, it is important to ascertain how these results might compare to a placebo-controlled, blinded study. A randomized, double-blind study of C1 inhibitor (Tim3-Baxter/Immuno) versus placebo

showed that the mean and median times to onset of improvement in 11 subjects treated with placebo were 921 and 1020 minutes, respectively (Kunschak et al, 1998). Thus, it can be concluded that the rapid improvement reported in the open-label studies is not likely due to a placebo effect. The treated subjects in this study reported mean and median times to onset of improvement of 162 and 50 minutes respectively. One difference that should be noted is that the dosing scheme used by Kunschak et al. was 25 units/kg, which for a 70 kg individual would equate to approximately 1700 U.

The prophylactic dosing regimen of 1000 U administered twice weekly was based on the pharmacokinetics of Cetor, including a half-life of approximately 48 hours with a linear decay pattern. An earlier placebo-controlled study with a different C1 inhibitor product administered every 3 days demonstrated clinical efficacy, and was supported by the pharmacodynamic effects of C1 inhibitor on C4 levels.

5.3   Pharmacokinetics and Dose Selection

As part of the US development of Cinryze, a randomized, parallel group, open-label pharmacokinetics (PK) study of Cinryze was conducted in subjects with non-symptomatic HAE. Subjects received either a single dose of 1000 U intravenously (IV), or a double dose with the initial 1000 U followed by a second 1000 U 60 minutes later to mimic the dosing in the Acute Treatment Trial. The PK results for functional C1 inhibitor from this study are presented in Table 3.

Table 3. Mean pharmacokinetic parameters of Functional C1 inhibitor

Parameters	Single Dose	Double Dose
$C_{baseline}$ (U/mL)	0.31 ± 0.20 (n = 12)	0.33 ± 0.20 (n = 12)
C_{max} (U/mL)	0.68 ± 0.08 (n = 12)	0.85 ± 0.12 (n = 13)
T_{max} (hrs)	3.9 ± 7.3 (n = 12)	2.7 ± 1.9 (n = 13)
$AUC_{(0-t)}$ (U*hr/mL)	74.5 ± 30.3 (n = 12)	95.9 ± 19.6 (n = 13)
CL (mL/min)	0.85 ± 1.07 (n = 7)	1.17 ± 0.78 (n = 9)
Half-life (hours)	56 ± 36 (n = 7)	62 ± 38 (n = 9)

Single dose = 1000 U   Double dose = 1000 U followed by a second 1000 U 60 minutes later

As seen in Figure 3, the distribution and decay portions of the C1 inhibitor concentrations are first order as would be expected with the replacement of a plasma constituent.

Figure 3. C1 Inhibitor Plasma Concentration After 1 and 2 Injections of 1000 U Cinryze
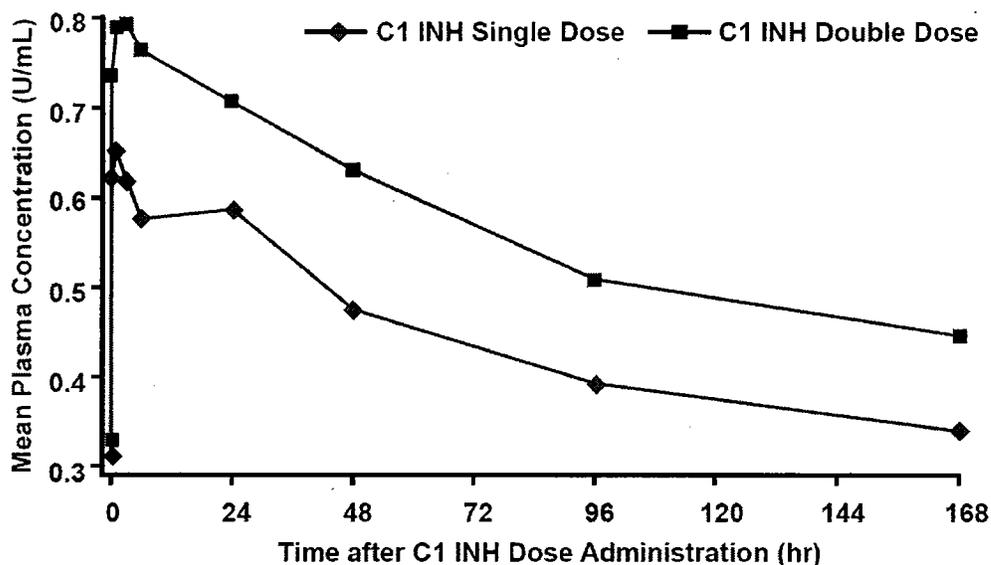
More importantly, the use of Cinryze resulted in increases in C4 levels, with the highest concentrations attained about 2 days after the injection, indicating biological activity of Cinryze and suggesting a stabilization of chronic C1 inhibitor consumption and a stabilization of the complement activation system (Figure 4).

Figure 4. Plasma C4 Levels After 1 and 2 Injections of 1000 U Cinryze
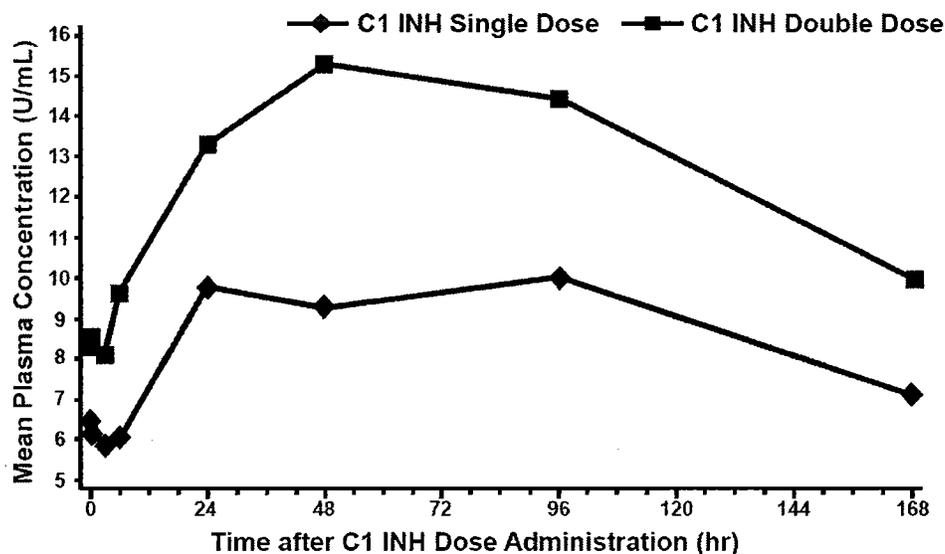
These data are also supported by an earlier study that showed the repeat dose pharmacokinetics of plasma C1 inhibitor over time as well as its pharmacodynamic marker of activity, plasma C4 levels (Waytes et al, 1996). As can be seen in Figure 5, when C1 inhibitor is administered every 3 days, there is little accumulation over time and the C1 inhibitor levels fall as expected with a T½ of approximately 50 hours. The single-dose PK data are recapitulated in the repeat-dose PK.

Figure 5. Plasma Concentration of C1 Inhibitor
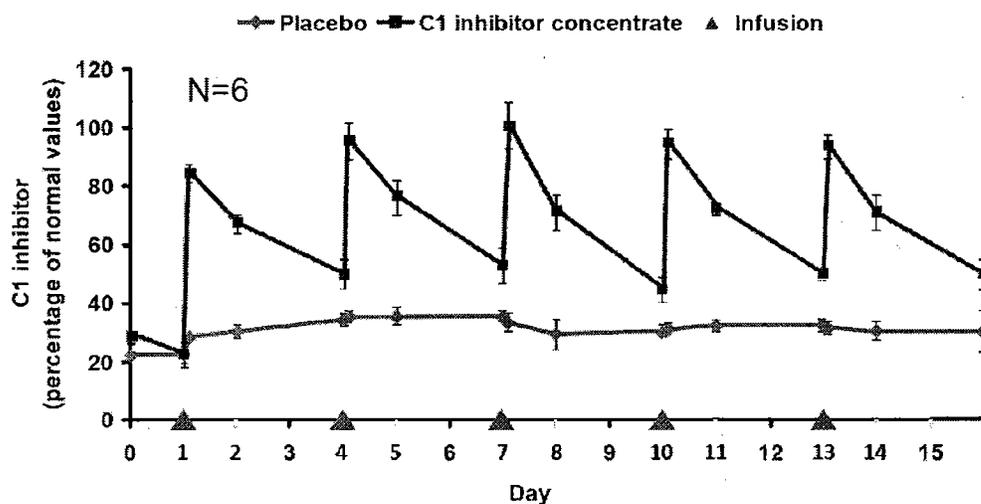
More importantly, this study showed that even though the C1 inhibitor levels continue to rise and fall with each successive administration, the C4 levels rise and stay elevated (Figure 6), suggesting that C1 inhibitor administration is able to restore control to the multiple reactive cascades seen in Figure 2 (The Effects of C1 Inhibitor in the Complement and Kallikrein-kinin Contact Pathways).

Figure 6. Normalization of C4 Level
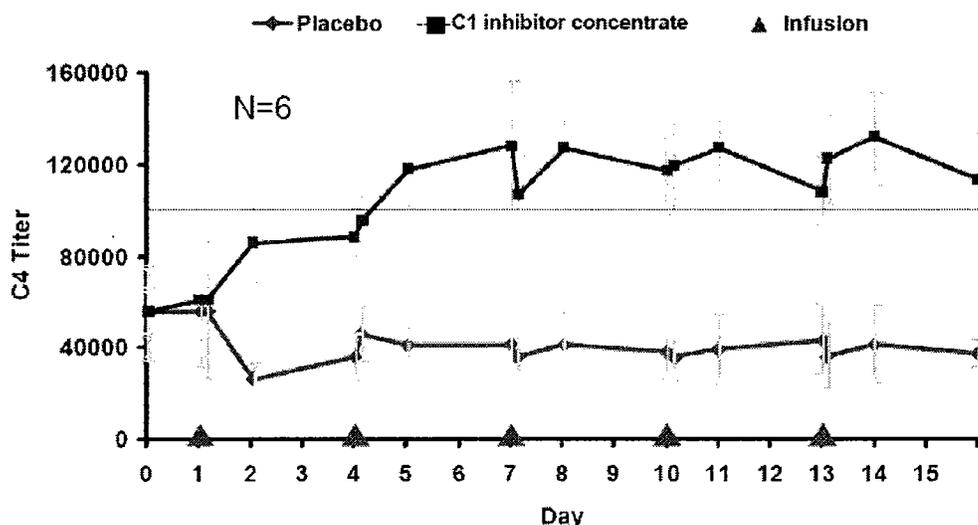
From Waytes, 1996

These PK/PD studies suggest that twice-a-week dosing is reasonable for the prophylactic treatment of HAE. These data are supported by the clinical findings of the pivotal Phase 3 study showing efficacy with a standard twice-a-week dosing schedule, where no titration based on individual clinical outcome was used.

5.4 Comparability of Cinryze Manufacturing Process with Cetor

As part of the development of the next-generation Cetor product in the EU, Sanquin performed a study comparing the pharmacokinetics of the C1 inhibitor product manufactured ▮▮▮▮▮▮▮▮▮▮ Cinryze (referred to as C1-esteraseremmer-N) with the current C1 inhibitor product Cetor. The pharmacokinetics, safety, and biological activity of C1-esteraseremmer-N were compared to the currently marketed Cetor to investigate whether ▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮▮ ▮▮▮▮▮▮▮▮▮ would affect these parameters. A randomized, double-blind,

controlled crossover study was conducted in HAE subjects without signs of an attack. Three dosages for both Cetor and C1-esteraseremmer-N were investigated. Subjects were randomly assigned to the order of administration of study medication and received 1000 U, 1500 U or 2000 U Cetor/C1-esteraseremmer-N. The same dosage was used for both products in each subject in a crossover design. Pharmacokinetic parameters, biological activity, and safety parameters were determined before administration and at several time points after administration.

5.4.1　　Pharmacokinetics

The primary pharmacokinetic parameters Clearance (CL), Volume of distribution (V), and the fraction of C1 inhibitor detected by the antigen assay relative to the functional assay (Ffunc) were estimated. No significant differences in these parameters between the two products were observed.

5.4.2　　Biological Activity

C4 levels before and after administration of Cetor and C1-esteraseremmer-N were determined. An initial decrease in C4 level was followed by an increase after approximately 6 hours for both products. The results show that in comparison with Cetor, C1-esteraseremmer-N displays an equal ability to increase C4 levels.

5.4.3　　Safety

Clinical tolerability and safety were monitored by registration of AEs, vital signs, laboratory measurements and screening for anti-C1-inhibitor antibodies. In total, 8 adverse events occurred in 5 subjects; none was considered to be related to C1-esteraseremmer-N or Cetor. With regard to laboratory data and vital signs, no differences were observed. No antibody development was detected in either group.

6. PIVOTAL STUDIES

- Phase 3 Acute Treatment Trial: a randomized, double-blind, placebo-controlled acute treatment trial in subjects with moderate to severe HAE attacks

- Phase 3 Prophylactic Treatment Trial: a randomized, double-blind, placebo-controlled, crossover prophylactic treatment trial in qualified subjects who had completed the Acute Treatment Trial. Each patient served as his or her own control.

6.1 Acute Treatment Trial

6.1.1 Study Design: Acute Treatment Trial

The Acute Treatment Trial was a randomized, placebo-controlled, double-blind study designed to evaluate the efficacy and safety of Cinryze as a therapeutic agent for treating a single acute attack of angioedema. Sixty-eight (68) subjects were planned; 71 were randomized.

6.1.2 Methodology: Acute Treatment Trial

Subjects were prequalified to confirm the diagnosis of HAE through measurement of baseline levels of C4 and exclusion of other causes of angioedema. Subjects presenting to a clinical site with an acute HAE attack of moderate or severe intensity affecting the gastrointestinal tract, face, or genitourinary system were evaluated and randomized in a blinded fashion to IV treatment with either 1000 U of Cinryze or an identical volume of normal saline placebo (Figure 7). If the attacks were only in the extremities, the subjects were not randomized and not treated. If there were any indication of laryngeal involvement, the subject was treated with open-label Cinryze and not randomized. Non-randomized subjects treated with open-label Cinryze were able to enter the Acute Treatment Trial if they presented with a qualifying attack at a later time.

Figure 7. Acute Treatment Trial -Randomization Schema
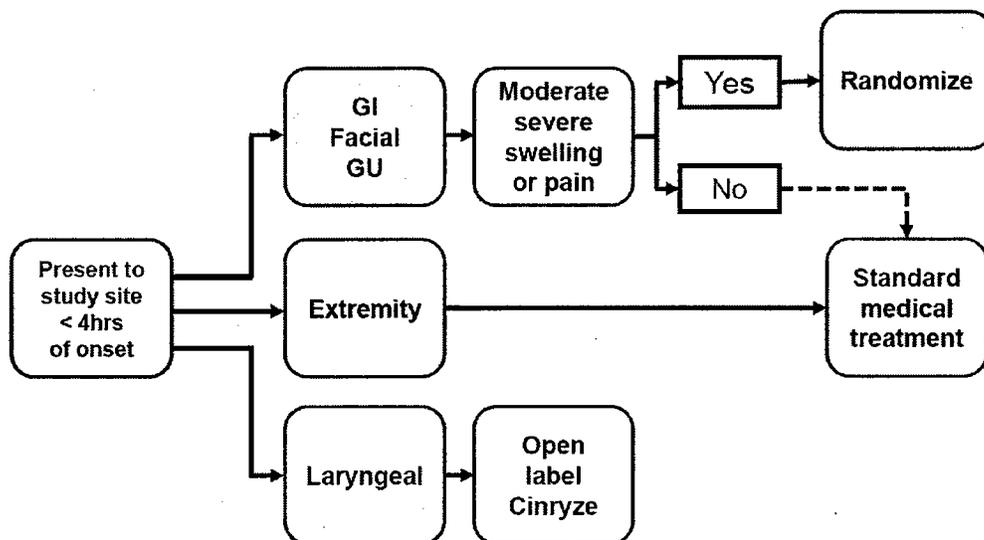
A second injection of the same study drug could be given in 60 minutes if the attack had not started to resolve or was getting worse (Figure 8). Subjects were evaluated for 4 hours following the initial injection with study drug. Open-label Cinryze could be given as rescue therapy if the subject had not reported onset of relief by 4 hours, or if the subject either presented with or progressed to airway compromise at any time. If, after 60 minutes, the attack was not starting to resolve or was getting worse, a second open-label injection of Cinryze rescue therapy could be administered.

Figure 8. Acute Treatment Trial - Treatment Schema
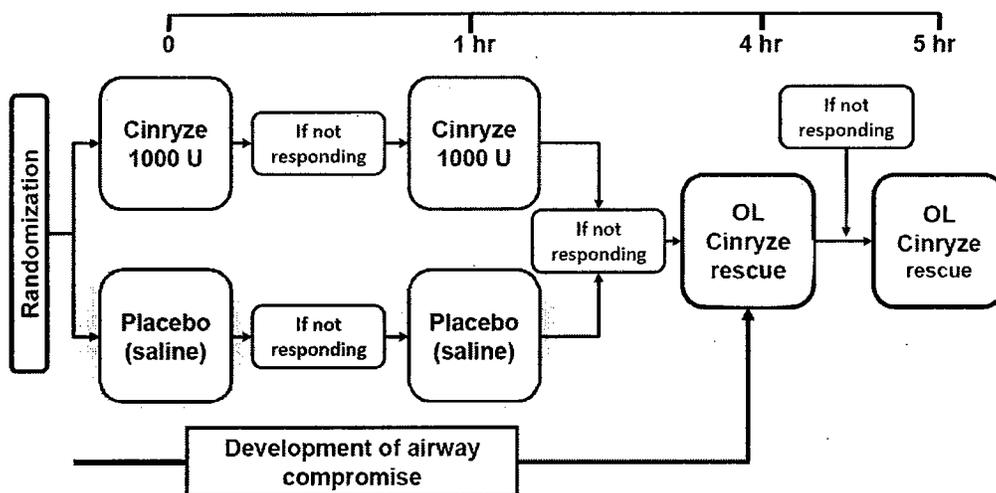
6.1.3   Subject Population: Acute Treatment Trial

6.1.3.1   Inclusion criteria

- Age ≥ 6 years
- Documented HAE based on:
  - o a low C4 level plus a low C1 inhibitor antigenic level OR
  - o a low C4 level plus a low C1 inhibitor functional level OR
  - o a known HAE-causing C1 inhibitor mutation
- Normal C1q level
- History of at least 2 HAE attacks per month (Prophylactic Treatment Trial only)
- Signed informed consent

6.1.3.2   Exclusion criteria:

- Age < 6 years
- Low C1q level (suggesting other causes of angioedema)
- B-cell malignancy
- Presence of an anti-C1 inhibitor antibody
- History of allergic reaction to C1 inhibitor or other blood products
- Narcotic addiction
- Current participation in any other investigational drug study or within the past 30 days
- Participation in a C1 esterase inhibitor trial, received blood or received a blood product in the past 90 days
- Pregnancy or lactation

- Any clinically significant medical condition, such as renal failure, that in the opinion of the investigator would interfere with the subject's ability to participate in the study

6.1.4 Efficacy Assessment: Acute Treatment Trial

The primary efficacy measure for the Acute Treatment Trial was the time from initial treatment to the beginning of unequivocal relief of the defining symptom. Secondary efficacy measures included:

- The percentage of subjects who had unequivocal beginning of relief within 4 hours following treatment;
- The time to complete resolution of the attack;
- The effects of treatment on C1 inhibitor and C4 levels;
- The effects of treatment were also rated by a Visual Analog Scale (VAS).

6.1.5 Safety Assessment: Acute Treatment Trial

Safety was assessed by an evaluation of adverse events (AEs) (including serious AEs [SAEs] and withdrawals for AEs), changes in clinical laboratory safety parameters, physical findings, and vital signs from pre- to post-injection. Local tolerance at the injection site and the immunogenicity of Cinryze were evaluated.

6.1.6 Disposition and Demographics: Acute Treatment Trial

Seventy-one (71) subjects were randomized (36 Cinryze, 35 placebo) and treated for acute attacks of moderate to severe HAE at 20 study centers in the US. Three attacks (1 Cinryze, 2 placebo) were deemed not to be due to HAE. Of the remaining 68 subjects, 35 were in the Cinryze group and 33 were in the placebo group. One subject in the placebo group received placebo as scheduled for the first dose, but received Cinryze for the second dose as a dosing error.

Demographics of the study subjects in the Acute Treatment Trial are shown in Table 4.

Table 4. Demographic Characteristics of Subjects, Acute Treatment

Variable	Statistic	Cinryze	Placebo
Age	Mean	36.7	36.2
	SD	17.9	13.8
<65 yr	n	32	33
≥65 yr	n	3	0
Gender	Male	9 (25.7%)	6 (18.2%)
	Female	26 (74.3%)	27 (81.8)
Ethnicity	Caucasian	33 (94.3%)	30 (90.9%)
	African-American	1 (2.9%)	1 (3.0%)
	Hispanic	1 (2.9%)	2 (6.1%)
Weight (kg)	Mean	80.9	77.4
	SD	28.3	22.6
Height (cm)	Mean	163.1	167.8
	SD	14.1	10.4
Years since	Mean	18.41	20.50
diagnosis	SD	11.58	13.17

6.1.7 Efficacy Results: Acute Treatment Trial

The primary endpoint of the study was time to onset of unequivocal relief of the defining symptom. The median time to onset of unequivocal relief of symptoms was 2 hours in the Cinryze group and >4 hours in the placebo group ($p=0.026$). All laryngeal attacks treated with open-label Cinryze in the Acute Treatment Trial (N=18) resolved without intubation. No open-label subject treated for short-term prophylaxis (N=7) reported HAE complications secondary to the procedure.

The application for the treatment of acute attacks of HAE is currently under active review at FDA. This briefing document addresses prophylactic treatment.

6.2 Prophylactic Treatment Trial

6.2.1 Study Design: Prophylactic Treatment Trial

The Prophylactic Treatment Trial was a randomized, placebo-controlled, double-blind, crossover study designed to evaluate the efficacy and safety of Cinryze as prophylactic treatment to prevent acute attacks of HAE. Twenty (20) subjects were planned; 24 were randomized.

6.2.2 Methodology: Prophylactic Treatment Trial

Eligible subjects were randomized to receive Cinryze or placebo as prophylactic injections 2 times per week (every 3 to 4 days) for 12 weeks with the first blinded treatment, and then crossed over and treated 2 times per week for 12 weeks with the other blinded treatment (Figure 9). All injections were given at the study site.

Subjects enrolled in the Prophylactic Treatment Trial could receive open-label treatment Cinryze for acute HAE attacks if, in the opinion of the principal investigator, treatment was required. In general, subjects were advised to seek open-label treatment at the earliest onset of an HAE attack. In the event that the next prophylactic injection was scheduled to occur within 24 hours of the open-label treatment, the injection was to be rescheduled to occur at least 24 hours after the last open-label injection. If a subject presented to the site for the regularly scheduled prophylactic injection with signs of swelling, the regularly scheduled prophylactic injection was administered. If the subject did not report onset of relief after 1 hour, an open-label treatment could be administered.

Figure 9. Patient Disposition, Prophylactic Treatment Trial
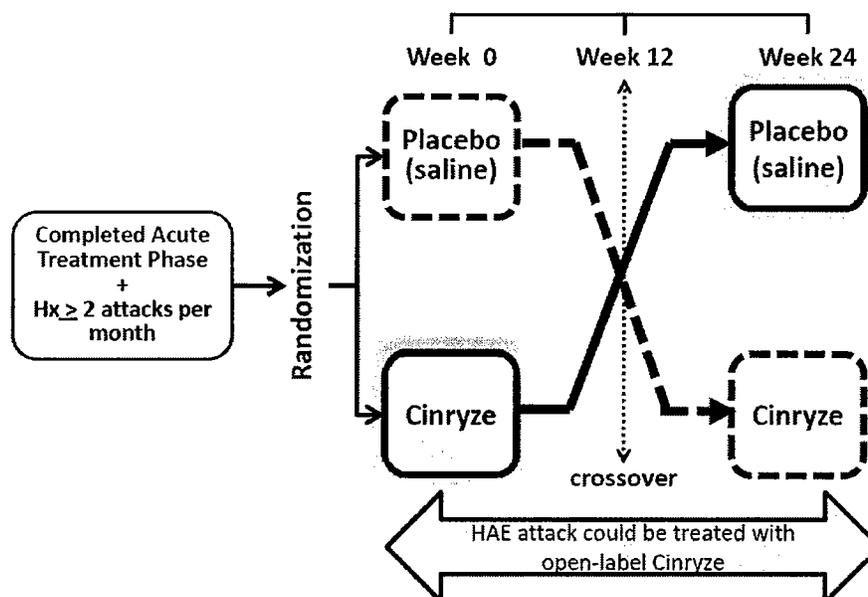
6.2.3 Subject Population: Prophylactic Treatment Trial

Subjects who completed the Acute Treatment Trial could be enrolled in the Prophylactic Treatment Trial if they had a prior history of experiencing at least 2 attacks per month. Subjects entering into the Prophylactic Treatment Trial were allowed to maintain or reduce their dose of 17-alpha-alkylated androgens prior to beginning the trial. If they chose to reduce their dose, entry into prophylactic treatment trial was delayed for 30 days. Once a subject was enrolled in prophylactic treatment trial, changes in the dose of 17-alpha-alkylated androgens were not allowed.

6.2.4 Efficacy Assessments: Prophylactic Treatment Trial

6.2.4.1 Primary Efficacy Endpoint: Prophylactic Treatment Trial

The primary efficacy endpoint for the Prophylactic Treatment Trial was the number of attacks of angioedema during each treatment period, normalized for the number of days the subject participated in that period. An attack was defined as any swelling reported by the subject at any location following a report of no swelling on the previous day. This is the most objective definition of an attack; however, it does not differentiate between types or severity of attacks.

6.2.4.2 Secondary Efficacy Endpoints: Prophylactic Treatment Trial

The secondary efficacy endpoints for the Prophylactic Treatment Trial were:

- Average severity of attacks. The severity of an attack was the highest value assigned by the subject to any location at any day during an attack. In order to calculate the average severity of attacks for each period, each mild, moderate, and severe attack was assigned a score of 1, 2, or 3, respectively. The total severity score was calculated for each period by multiplying the total number of mild attacks by 1, total number of moderate attacks by 2, and the total number of severe attacks by 3, then adding the results of these three calculations. The average severity of each period was then derived by dividing the total severity score of that period by the total number of attacks in that period. The difference between treatments was tested by a Wilcoxon Signed Rank Test.

- Number of open-label Cinryze injections. The total number of open-label Cinryze injections (counting double injections as two injections) while subjects received active treatment was compared with the total number of open-label Cinryze injections (counting double injections as two injections) while subjects received placebo by using the Wilcoxon Signed Rank Test.

- Average duration of attacks. The duration of an attack was measured from the first report of swelling at any location until the next report of no swelling at any location. Average duration of attacks for each period was calculated by first summing the duration of each attack, then dividing that sum by the total number of attacks in that period. The difference between treatments was tested by a Wilcoxon Signed Rank Test.

- Total number of days of swelling. The total number of days subjects reported swelling was compared between study treatments using the Wilcoxon Signed Rank Test.

- Number of subjects dropping out at each treatment period. This is a binary categorical endpoint. At the end of each treatment period, each subject was

assigned a Yes/No drop-out status and a 2x2 table was produced for treatment by drop-out status. A Fisher's exact test was used to compare between treatments.

6.2.5   Safety Assessment: Prophylactic Treatment Trial

Safety was assessed using the following measures: extent of exposure, AEs, vital signs, physical examinations, and laboratory tests. All safety analyses used data from subjects who received at least one dose of study medication (safety data set). Viral serology studies were also performed.

6.2.6   Statistical methods: Prophylactic Treatment Trial

Summary statistics consist of frequencies and percentages of responses in each category for discrete measures and of means, medians, standard deviations (SDs), and minimum and maximum values for continuous measures. For safety summaries, percentages were based on the number of subjects in the safety data set.

All analyses and summaries were produced using SAS® version 8.2. All significance tests were two-sided, with statistical significance assessed at the 5% level.

The Efficacy data set included all subjects who were randomized into 1 of 2 treatment sequences, and who completed the entire initial treatment phase and received at least 1 treatment in the crossover phase. The Safety data set included all subjects who received a complete or partial injection of study medication.

For crossover analyses, a standard analysis of variance (ANOVA) for crossover study design was performed with effects for treatment, period, and subject within treatment.

The primary efficacy endpoint for the Prophylactic Treatment Trial was the number of attacks of angioedema during each treatment period, normalized for the number of days the subject participated in that period. This was done by dividing the total number of attacks in each period by the number of days the subject was in that period. The crossover analysis was based on a Poisson assumption and used the GEE method as implemented in the SAS statistical procedure PROC GENMOD, and accounted for both the crossover design as well as the normalization of the time periods. The goodness-of-fit statistics,

deviance and Pearson chi-square, along with the ratios of their values to their degrees of freedom, from the initial model fitting were used to check for overdispersion.

6.2.7   Disposition and Demographics: Prophylactic Treatment Trial

Twenty-four (24) subjects were enrolled; 22 subjects who completed the first period and crossed over into the second period were included in the efficacy data set (Figure 10). To be included in the efficacy data set, subjects had to cross over and receive at least one additional dose of study drug (ITT efficacy population). All subjects were included in the safety data set.

Seven (7) subjects discontinued androgen therapy prior to randomization into the Prophylactic Treatment Trial. Three (3) continued to use androgens during the trial. Of these, one decreased the dosage prior to randomization. The other two maintained the same dosage.

Two subjects were excluded from the efficacy data set because they failed to complete the first period of the study and did not cross over to receive at least one treatment in the second period of the study. Subject 12002 was in the placebo phase and withdrew because of travel time to the site of over two hours. Subject 17001 was in the Cinryze phase and withdrew due to a major protocol violation of an interval between prophylactic treatments that exceeded twelve days.

The two subjects who dropped out during the second treatment period were included in the efficacy analysis using normalized data as per the SAP. Subject 12005 was assigned to Cinryze during this period and was no longer able to travel to the clinical site due to personal reasons and therefore withdrew. Subject 18004, who was assigned to placebo, began to experience significant HAE attacks and withdrew.

Figure 10. Time-course of subject withdrawals, Prophylactic Treatment Trial

First Period   Second Period

24 Randomized   22 Crossover   20 Complete
(Safety Data Set)   (Efficacy Data Set)

12002(P)   17001(C)   12005(C)   18004(P)
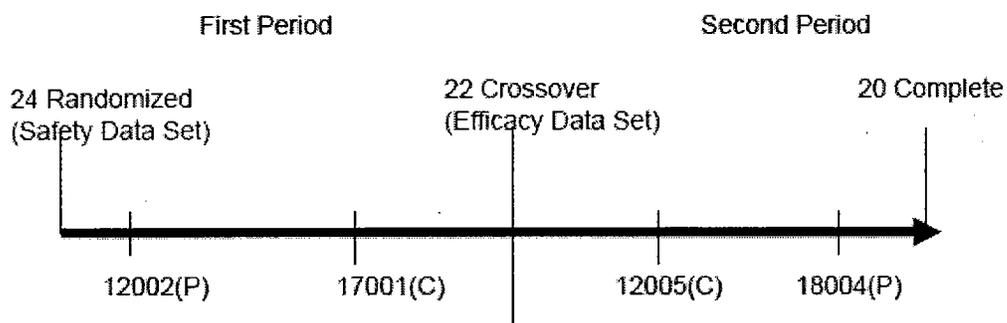
C=Cinryze, P=Placebo

Demographic characteristics of the 22 subjects in the Efficacy data set are summarized in
the following table (Table 5). In the Efficacy data set, the mean age was 38.1 years with a
range of 9 to 73 years. The majority of subjects were female (20 subjects, 90.9%) and
White (21 subjects, 95.5%).

Table 5. Demographic Characteristics of Subjects, Prophylactic Treatment Trial

Variable	Statistic	Treatment Sequence		Total
		Cinryze/ Placebo (N=11)	Placebo/ Cinryze (N-11)	(N=22)
Age (years)	n	11	11	22
	Mean	41.7	34.5	38.1
	SD	19.27	14.76	17.16
Gender, n (%)	Male	2 (18.2)	0	2 (9.1)
	Female	9 (81.8)	11 (100.0)	20 (90.9)
Ethnicity	White/ Caucasian	10 (90.9)	11 (100.0)	21 (95.5)
	Black/ African American	1 (9.1)	0	1 (4.5)
Weight (kg)	n	11	11	22
	Mean	70.5	74.80	74.84
	SD	17.15	23.20	19.92
Height (cm)	n	11	11	22
	Mean	168.51	163.17	165.84
	SD	8.09	7.93	8.28

Each day, subjects recorded information related to swelling or pain (location and severity) using standardized diary cards. They also were seen in the clinic every 3-4 days when they received their injections. Safety was assessed using standard tools and definitions to measure treatment-mediated adverse events, serious adverse events, withdrawals, clinical laboratory function, and vital signs. All participants were screened for new acute and chronic findings of HIV, HBV, HCV, and parvovirus infections at the end of the study.

6.2.8   Extent of Exposure: Prophylactic Treatment Trial

There were 24 subjects in the safety data set. Of the randomized subjects, 22 were treated

with both randomized Cinryze and placebo. During the randomized treatment periods, 1 subject received only randomized Cinryze and 1 subject received only placebo. The population exposed to either study medication was therefore 23, while the population exposed to both medications was 22.

The mean (±SD) number of randomized study medication injections per subject during treatment with Cinryze was 23.1 (±3.2). The mean (±SD) number of randomized study medication injections per subject during treatment with placebo was 22.9 (±3.76 injections). The range of number of injections per subject ranged from 8 to 25, with no notable differences between the number of injections of Cinryze and the number of injections of placebo (Table 6).

Table 6. Mean (SD) Number of Injections of Blinded Study Medication Per Subject, Prophylactic Treatment Trial

	Number of Injections Per Subject [1,2]	
	Cinryze[3] **N=23**	**Placebo** **N=23**
n	23	23
Mean	23.1	22.9
SD	3.20	2.76
Median	24.0	24.0
Min	10	8
Max	24	25

1 Subjects randomized to Cinryze or to Placebo both received open-label Cinryze for the treatment of attacks during and between treatment phases.
2 There were 2 additional subjects who received open-label Cinryze, only. These 2 subjects received 1 and 5 injections.
3 Does not include open-label injections

6.3 Efficacy Results: Prophylactic Treatment Trial

- Positive results for primary and all secondary endpoints
    - Statistically significant
    - Clinically meaningful

- Consistent reductions in disease burden
  - Frequency of attacks
  - Severity of attacks
  - Duration of attacks
  - Total days with swelling
- Confirmed by post-hoc per-subject analyses

6.3.1 Primary Analysis: Prophylactic Treatment Trial

The protocol defined the primary endpoint of the Prophylactic Treatment Trial as the normalized number of attacks of angioedema per day during each treatment period, using each subject as his/her own control. The number of attacks consisted of all angioedema attacks that occurred during treatment irrespective of whether the subject obtained open-label Cinryze or not. An angioedema attack was defined as a discrete episode during which the subject progressed from no angioedema to symptoms of angioedema. Attacks that progressed from one site to another were considered to be single attacks.

The use of Cinryze significantly decreased the normalized number of HAE attacks compared to placebo. During 12 weeks of prophylactic treatment with Cinryze, the number of attacks per patient ranged from 0 to 17.6 with a mean of 6.3 (±5.5) and a median of 6 attacks. During 12 weeks of treatment with placebo, the number of attacks per patient ranged from 6 to 20.5 with a mean of 12.7 (± 4.6) and a median of 13.5 attacks. The difference in the number of angioedema attacks during treatment with Cinryze and with placebo was statistically significant with $p < 0.0001$. The mean (SD) and median number of attacks for the two groups is shown in Table 7.

Error! Reference source not found.**Table 7. Number of HAE Attacks, 12-Week Treatment Period, Prophylactic Treatment Trial**

	Statistic	Cinryze N=22	Placebo N=22
Number of Attacks	Mean	6.3	12.7
	SD	5.5	4.6
	Median	6.0	13.5
	Min	0	6.9
	Max	17.6	20.5
GEE Analysis Results			
Effect Assessed		**p-value**	
Treatment Effect		**<0.0001**	
Sequence Effect		0.3347	
Period Effect		0.3494	

The pattern of response by individual patient demonstrates the consistency of the treatment effect, with all but two patients showing some decrease in the number of attacks (Figures 11 and 12). Figure 11 displays the number of attacks during the placebo period and the Cinryze period for each subject. Two (2) subjects had an increase in attacks while on Cinryze. Twenty (20) (90.9%) had a decrease in the number of attacks. The percentage decrease in the number of attacks is shown in Figure 12.

Figure 11. Normalized Number of Attacks by Patient
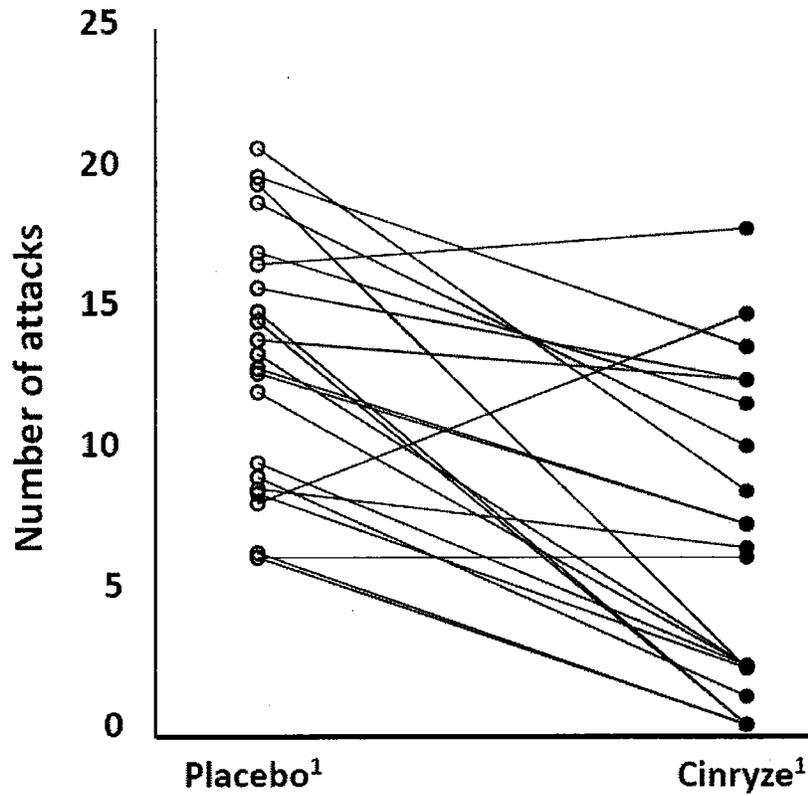
1 Each patient was his/her own control.

Individually, 20/22 (90.9%) of the subjects had fewer attacks on Cinryze than on placebo. The percent change in the number of attacks is shown by subject in Figure 12.

Figure 12. Percent (%) Change in HAE Attacks from Placebo to Cinryze by Subject, Prophylactic Treatment Trial
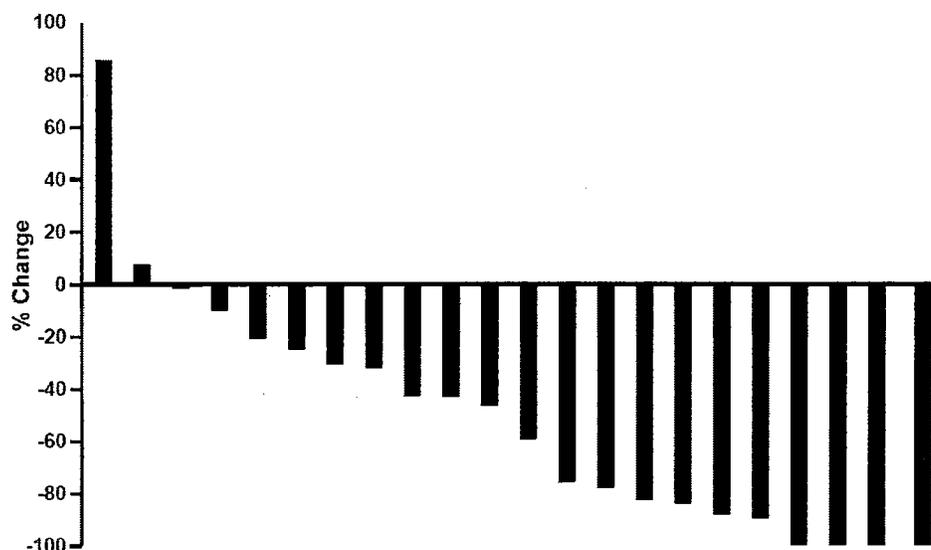
While an objective measure such as reduction in total attacks is a powerful indicator of meaningful clinical activity, it is also important to understand the effect of the treatment on the total clinical picture for subjects as well. Due to its variability both among subjects as well as within individual subjects, HAE is a disease that cannot be judged by a single criterion such as reduction in the total number of attacks. For example, a severe laryngeal attack lasting 5 days would count as one attack just as would a single day of mild hand swelling. Therefore, it is important to take other outcomes into account in assessing clinical response for a given subject in the study.

6.3.2   Secondary Endpoints: Prophylactic Treatment Trial

A number of secondary clinical endpoints were evaluated and support the primary endpoint, as well as the clinical utility of prophylactic treatment with Cinryze for HAE patients (Figure 13). The analyses of the protocol-specified secondary endpoints all achieved statistical significance and supported the conclusions of the primary analysis. Similarly, all the post-hoc analyses supported the conclusions of the primary analysis.

Figure 13. Primary and Secondary Endpoints, Median of Within-patient Percent Difference (95% Confidence Interval), Prophylactic Treatment Trial
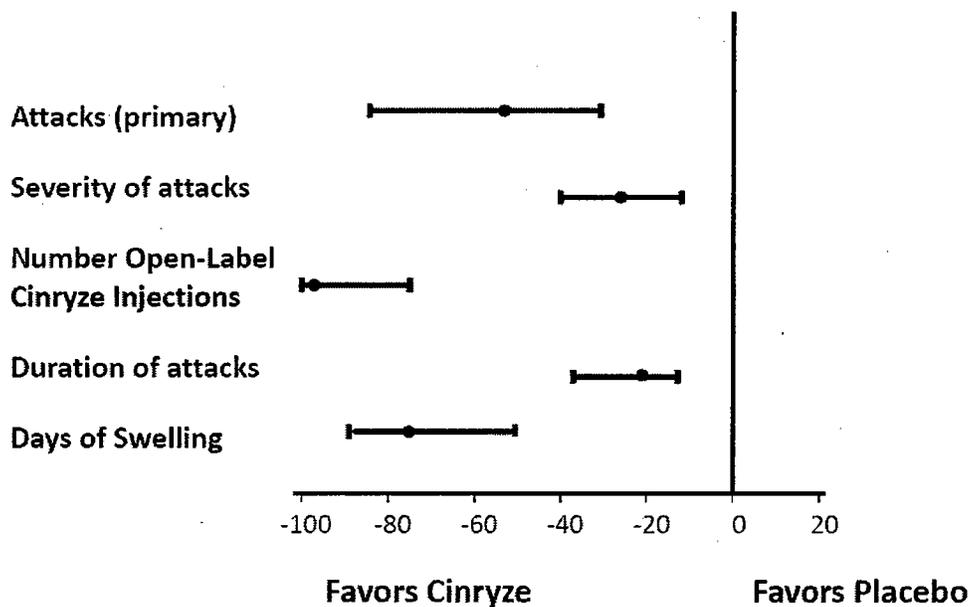
6.3.2.1   Average Severity of HAE Attacks: Prophylactic Treatment Trial

The use of Cinryze significantly decreased the average severity of HAE attacks compared to placebo. During treatment with Cinryze, the mean severity of attacks [rated by the subject as mild (1), moderate (2), or severe (3)] ranged from 0 to 3 with a mean of 1.3 (±0.85) and a median of 1.3. By comparison, during treatment with placebo, the severity of attacks ranged from 1 to 3 with a mean of 1.9 (± 0.35) and a median of 1.9. The difference in the severity of angioedema attacks during treatment with Cinryze compared to placebo was statistically significant with p=0.0008. The mean (SD) and median severity of attacks for the two groups is shown in the following table (Table 8).

Table 8. Severity of HAE Attacks, 12-Week Treatment Period, Prophylactic Treatment Trial

	Statistic	Cinryze N=22	Placebo N=22
Severity of Attacks (Score from 1 to 3)	Mean	1.3	1.9
	SD	0.85	0.35
	Median	1.3	1.9
	Min	0	1
	Max	3	3
Treatment Effect p-value		**0.0008**	

Individually, 18/22 (84.8%) of the subjects had lower average severity of attacks on Cinryze than on placebo. The percent change in the severity of attacks is shown by subject in Figure 14.

Figure 14. Percent (%) Change from Placebo in Average Severity of Attacks by Subject, Prophylactic Treatment Trial
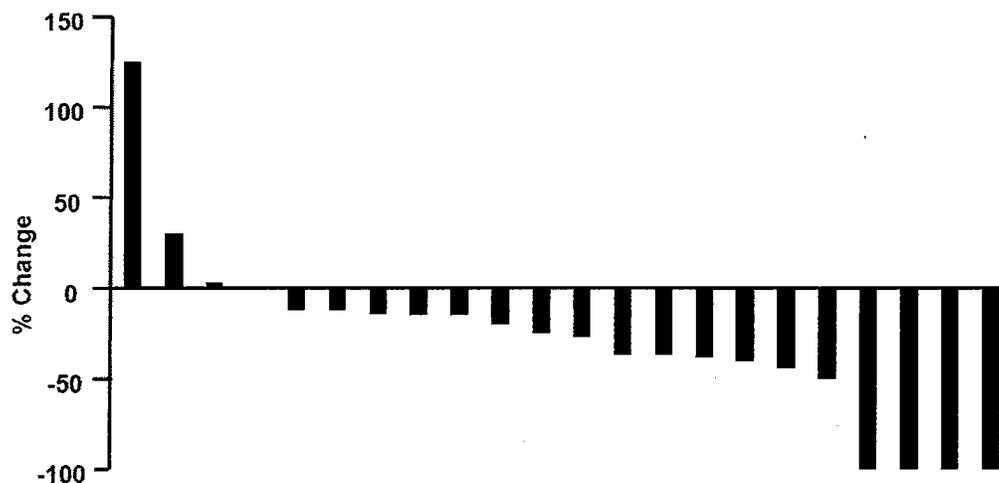
6.3.2.2 Open-label Injections: Prophylactic Treatment Trial

Open-label injections of Cinryze could be given for the treatment of acute angioedema. The number of open-label Cinryze injections was significantly different between treatment periods with p<0.0001 (Table 9). A total of 338 open-label 1000 U injections

were administered in the placebo period to treat acute attacks compared to 104 open-label 1000 U injections in the Cinryze period. Every subject received a minimum of two open-label treatments while on placebo. During treatment in the Cinryze period, 50% of subjects did not require open-label treatment. The remaining 50% required at least one open-label treatment while on Cinryze prophylactic treatment, pointing to the need for an acute therapy even for subjects on prophylactic treatment.

Table 9.   Number of Open-label Cinryze Injections, 12-Week Treatment Period, Prophylactic Treatment Trial

	Statistic	Cinryze N=22	Placebo N=22
Number Open-label Injections	Mean	4.7	15.4
	SD	8.66	8.41
	Median	0.5	13.5
	Min	0	2
	Max	36	34
Treatment Effect p-value		**<0.0001**	

### 6.3.2.3   Average Duration of HAE Attacks: Prophylactic Treatment Trial

The use of Cinryze significantly decreased the average duration of HAE attacks compared to placebo. During treatment with Cinryze, the mean duration of an attack ranged from 0 to 4 with a mean of 2.1 (± 1.13) days and a median of 2.5 days. By comparison, during treatment with placebo, the duration of an attack ranged from 2 to 8 days with a mean of 3.4 ($\pm$ 1.39) days and a median of 3.1 days. The difference in the duration of angioedema attacks during treatment with Cinryze compared to placebo was statistically significant with p=0.0004. The mean (SD) and median duration of attacks for the two groups is shown in the following table (Table 10).

Table 10. Duration of HAE Attacks, 12-Week Treatment Period, Prophylactic Treatment Trial

	Statistic	Cinryze N=22	Placebo N=22
Average Duration of Attacks (Days)	Mean	2.1	3.4
	SD	1.13	1.39
	Median	2.5	3.1
	Min	0	2
	Max	4	8
Treatment Effect p-value		**0.0004**	

Individually, 17/22 (77.3%) of the subjects had shorter average duration of attacks on Cinryze than on placebo. The percent change in the average duration of attacks is shown by subject in Figure 15.

Figure 15. Percent (%) Change in Average Duration of Attacks by Subject, Prophylactic Treatment Trial
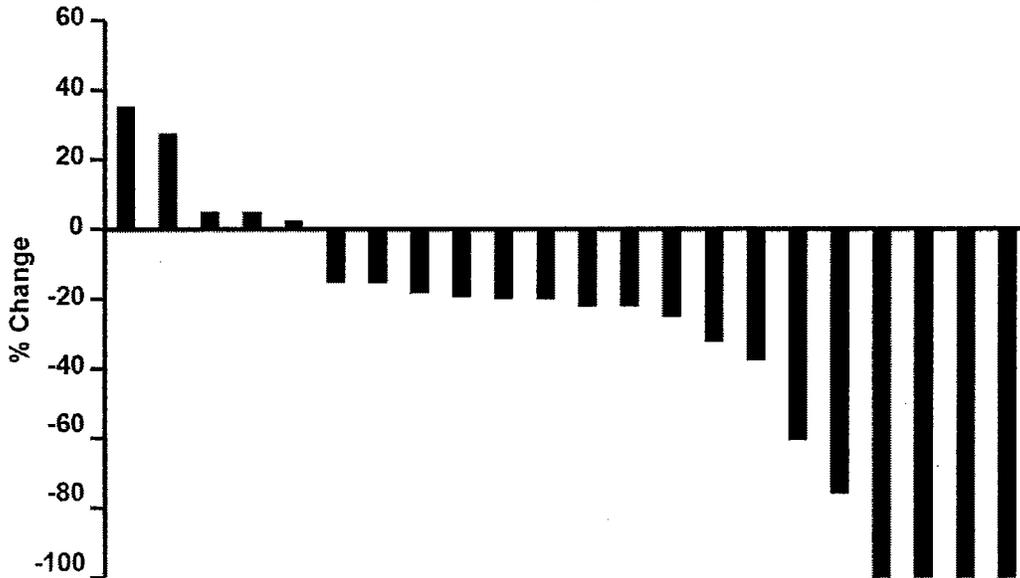
6.3.2.4 Total Days of Swelling: Prophylactic Treatment Trial

The use of Cinryze significantly decreased the total days of swelling over 12 weeks as compared to placebo. During treatment with Cinryze, the total days with swelling ranged from 0 to 38 with a mean of 10.1 (±10.73) days and a median of 6.5 days. By comparison, during treatment with placebo, the number of days with swelling ranged from 8 to 67 days with a mean of 29.6 (± 16.9) days and a median of 26.5 days. The difference in the number of days with swelling during treatment with Cinryze compared to placebo was statistically significant with $p < 0.0001$. The mean (SD) and median days of swelling for the two groups is shown in the following table (Table 11).

Table 11. Days of Swelling, 12-Week Treatment Period, Prophylactic Treatment Trial

	Statistic	Cinryze N=22	Placebo N=22
Days of Swelling	Mean	10.1	29.6
	SD	10.73	16.9
	Median	6.5	26.5
	Min	0	8
	Max	38	67
Treatment Effect p-value		**<0.0001**	

Individually, 21/22 (95.5%) of the subjects had fewer days of swelling on Cinryze than on placebo. The percent change in the days of swelling is shown by subject in Figure 16.

Figure 16. Percent (%) Change in Average Number of Days with Swelling per Subject, Prophylactic Treatment Trial
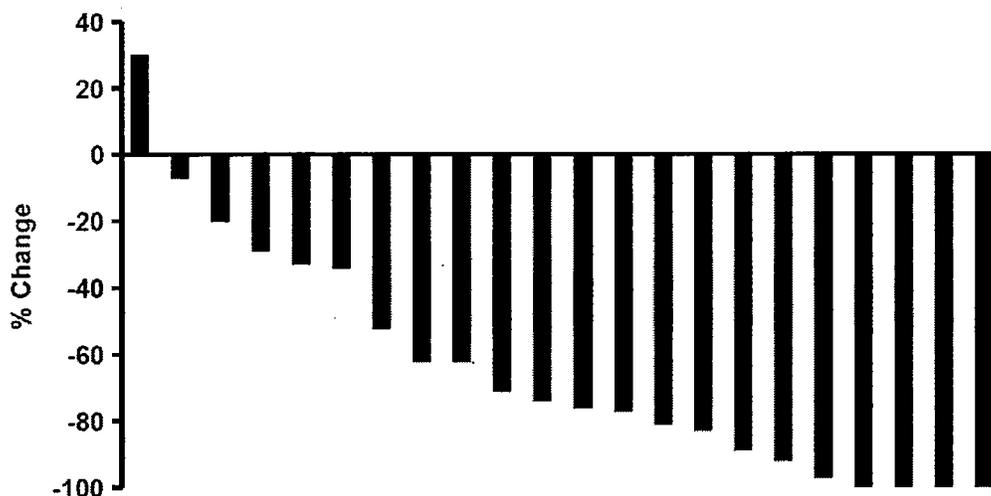
6.3.2.5   Efficacy Summary: Prophylactic Treatment Trial

Cinryze 1000 U IV given twice weekly resulted in a statistically significant and clinically meaningful reduction in the number, severity, and duration of HAE attacks, as well as the number of open-label infusions of Cinryze and the total number of days of swelling. Table 12 provides a subject-by-subject listing of the percent reduction from placebo for each of the clinical endpoints. The subjects are presented in order by the percent reduction in the number of attacks, the primary endpoint. The majority of subjects had improvements by all five measures. Some had improvements in only some of the measures. Four (4) subjects in the study were completely attack free while in the Cinryze period, and 11 subjects required no open-label treatments for acute breakthrough attacks.

Table 12. Percent (%) Change in Clinical Outcomes from Placebo, Prophylactic Treatment Trial

Subject N=22	Attacks/Day	Attack Severity	Attack Duration	Open-label Injections	Days of Swelling
06001	-100	-100	-100	-100	-100
12005	-100	-100	-100	-100	-100
24001	-100	-100	-100	-100	-100
59001	-100	-100	-100	-100	-100
16004	-90	-14	-15	-94	-92
12012	-88	-40	35	-100	-81
07001	-84	-38	-20	-100	-89
16003	-83	-37	27	-100	-76
53002	-78	125	-60	-100	-77
06018	-76	-50	-76	-100	-97
51001	-60	-12	-19	-75	-71
13002	-47	-27	-20	-83	-62
53003	-43	-44	2	-100	-83
18004	-43	-15	-38	-90	-74
53001	-32	-20	-18	-100	-52
16006	-31	-37	-32	-93	-62
56001	-25	0	-15	-57	-33
52001	-21	-15	5	-26	-20
07012	-10	3	5	-25	-7
54001	-1	-25	-20	-14	-34
16005	8	-12	-22	-52	-29
17002	85	30	-25	260	30

As expected with a disease as variable as HAE, response varied across each of the individual endpoints. However, when looking at the total clinical presentation, all but one subject showed clinical improvement on the standard regimen of twice weekly dosing with Cinryze.

For example, subject 54001 had a 1% decrease in HAE attacks. However, this subject also had a 34% reduction in the number of days of swelling, a 20% reduction in the average length of time of each attack, and a 25% reduction in the average severity of attacks while on Cinryze. Any of these individual outcomes could be classified as clinically meaningful; and, when taken together, they provide a substantial improvement in disease burden.

6.4   Safety Profile

- Safety profile of Cinryze is favorable

- 96 unique subjects in Phase 3 pivotal trials and PK study received 1413 1000 U doses of Cinryze

- 6000 injections of Cinryze in US including open-label and individual treatment studies

- No serious adverse events related to Cinryze

- 5 SAEs in Pivotal trial and 28 in OL extension studies; none related to Cinryze

- Few treatment-emergent adverse events; same type and severity as placebo

- No deaths or withdrawals for AEs during Prophylactic Treatment Trial

- No clinically relevant changes in vital signs or laboratory parameters

- No evidence of anti-C1 inhibitor antibody production found in Cinryze-treated subjects

- No seroconversion for parvovirus, Hepatitis B, Hepatitis C, or HIV

- European history is supportive of Cinryze safety

The safety profile of Cinryze was similar to the safety profile of placebo. Overall, more than 6000 injections of Cinryze have been administered to 180 unique subjects in the US, including open-label and individual treatment studies. Twelve of the subjects have received more than 100 injections. Cinryze has been administered to 96 unique subjects in the Phase 3 program. In total, these subjects received 1413 doses of 1000 U Cinryze (Table 13).

Table 13. Disposition of Subjects Receiving Cinryze in Clinical Trials or Individual Treatment Studies

Cinryze Trial Name	Total subjects treated	# Previously received Cinryze[1]	Study Treatment	Unique Subjects[1]
Pivotal Acute Treatment	71	0	Randomized Cinryze or Placebo + OL	58
		0	Non-Randomized Acute, OL	12
		0	Acute, OL	1
PK	27	6		21
Pivotal Prophylactic Treatment	24	20	Cinryze/Placebo or Placebo/Cinryze + OL	4
OL Acute Treatment	88	41	OL	47
OL Prophylaxis	63	28	OL	35
Ind Treatment	3	1		2
Total				180

1 Subjects who received Cinryze in more than one clinical setting are counted only once as "unique subjects."

6.4.1   Acute Treatment Trial

In the Acute Treatment Trial, 71 subjects were randomized to study drug (36 Cinryze and 35 placebo), and 12 received open-label Cinryze for nonrandomizable events such as acute treatment of laryngeal attacks and short-term prophylactic treatment prior to surgery or dental procedures. Of these 83 subjects, 13 had one or more treatment-emergent adverse events (TEAE) (Table 14). Six (6) subjects in the Cinryze arm reported AEs, and 7 subjects in the placebo arm reported AEs. The most common TEAE reported was sinusitis, which occurred in two subjects, both in the Cinryze arm. There were also two reports each of nausea and decreased blood pressure, which were evenly split between the two arms (Table 15). Three (3) TEAEs were considered

definitely/possibly/probably related to study drug: 2 in the placebo period (dermatitis and tetany) and one in the Cinryze period (injection site rash). There were no SAEs reported during the Acute Treatment Trial and the adverse event profile for Cinryze was no different from that for placebo. Measurements of vital signs, including HR, T, BP, and RR, were not different between Cinryze and placebo.

Table 14. Number and Percent (%) of Subjects with Adverse Events, Acute Treatment Trial

Subject TEAE Category	Number of Randomized Subjects		
	Cinryze N=36 n (%)	Placebo N=35[2] n (%)	Total N=71 n (%)
1 or more TEAE	6 (16.7)	7 (20)	13 (18.3)
TEAEs related to study drug[1]	2 (5.6)	4 (11.4)	6 (8.5)
SAEs	0	0	0
Deaths	0	0	0
Discontinuation for TEAE	0	0	0

1 Related TEAEs were events with a relationship to study drug of definitely, probably, possibly related or whose relationship to study drug was reported as unknown.
2 Most of the 35 subjects who received randomized placebo also received rescue Cinryze. Therefore, comparisons between randomized treatment groups are of limited utility.

Table 15. Adverse Events with a Total Frequency >5%, Acute Treatment Trial

TEAE	Cinryze N=36 n (%)	Placebo N=35 n (%)	Open-label N=12 n (%)
Total number (%) subjects with TEAEs	6(16.7)	7 (20.0)	0
Sinusitis	2 (5.6)	0 (0)	0 (0)
Nausea	1 (2.8)	1 (2.8)	0 (0)
Blood Pressure Decreased	1 (2.8)	1 (2.8)	0 (0)

6.4.2   Prophylactic Treatment Trial

In the Prophylactic Treatment Trial, because all subjects received open-label Cinryze for treatment for acute attacks while in the placebo period, it is not informative to compare the placebo treatment period to the Cinryze treatment period. Safety data for the

Prophylactic Treatment Trial are presented as an overall analysis, reflecting contributions throughout both periods of treatment.

There were 24 subjects in the Prophylactic Treatment Trial safety data set. Of the randomized subjects, 22 were treated in both the Cinryze and placebo periods. During the randomized treatment periods, 1 subject received randomized Cinryze but did not receive placebo, and 1 subject received placebo but did not receive randomized Cinryze. The number of subjects receiving Cinryze during the Prophylactic Treatment Trial was 23.

Twenty-one (21) of 24 subjects in the safety population had one or more TEAEs reported (Table 16). There were 9 subjects with 1 or more TEAEs that coded as related to study medication. The most common TEAE related to study medication were events that coded to the Skin and Subcutaneous Tissue Disorder system organ class (4 subjects) and Infections and Infestations (4 subjects). In the Infections and Infestations system organ class, the most common related event was viral upper respiratory tract infection (3 subjects). In the Skin and Subcutaneous Tissue Disorder system organ class, related TEAEs included rash (3 subjects), pruritus (1 subject), and erythema (1 subject). The category used to describe the causality for most events was "Unknown."

Table 16. Number (%) of Subjects Adverse Events, Prophylactic Treatment Trial

Subject TEAE category	Cinryze [1] N=23[2] n (%)	Overall N=24 n (%)
1 or more TEAEs	20 (87)	21 (87.5)
TEAE related to study medication[3]	9 (39.1)	9 (37.5)
SAEs	3 (13)	3 (12.5)
Deaths	0	0
Discontinuation for TEAE	0	0

1 Include Cinryze given for the double-blind randomization and open-label exposure
2 One subject was randomized for the Prophylactic Treatment Trial, but withdrew before receiving Cinryze
3 Related TEAEs were events with a relationship to study drug of definitely, probably, possibly related or whose relationship to study drug was reported as unknown.

6.4.2.1   Common Adverse Events: Prophylactic Treatment Trial

Infections were most commonly reported, including upper respiratory infections (7), sinusitis (7). Six (6) subjects reported skin findings including rash (5), pruritis (2), contact

dermatitis (1), and erythema (1). Four (4) subjects reported headache. Four (4) subjects

reported GI symptoms including reflux (2) and vomiting (2) (Table 14).

Table 17. Adverse Events Occurring in >5% of Subjects, Prophylactic Treatment Trial

	Subjects N=24 n (%)
Subjects with at least 1 AE	**21 (87.5)**
URI	7 (29.2)
Sinusitis	7 (29.2)
Rash	5 (20.8)
Headache	4 (16.7)
HAE	2 (8.3)
GERD	2 (8.3)
Vomiting	2 (8.3)
Bronchitis	2 (8.3)
Gastroenteritis, Viral	2 (8.3)
Nasopharyngitis	2 (8.3)
Limb Injury	2 (8.3)
Back Pain	2 (8.3)
Extremity Pain	2 (8.3)
Cough	2 (8.3)
Pruritis	2 (8.3)
UTI	2 (8.3)

6.4.2.2   Deaths and Serious Adverse Events: Prophylactic Treatment Trial

There were no deaths during Prophylactic Treatment Trial.

Three (3) subjects accounted for 4 SAEs requiring hospitalization in the study. An

additional SAE requiring hospitalization was reported for a subject (55001) who received

Cinryze in the Acute Treatment Trial but did not continue on to randomization in the

Prophylactic Treatment Trial (Table 18). All the SAEs were attributed to the underlying

HAE or other unrelated medical condition and resolved without discontinuation of

treatment.

Table 18. Serious Adverse Events, Prophylactic Treatment Trial

Subject ID Gender Age (yrs)	Preferred Term (Severity)	Relationship	Outcome
13002 Female 40	Laryngeal edema (Severe)	Not Related	Resolved
51001[1] Female 9	Lymphadenopathy (Moderate) Poor venous access (Moderate)	Not Related	Resolved
(second SAE)	Hereditary angioedema (Moderate)	Not Related	Resolved
53003 Female 64	Hereditary angioedema (Severe)	Not Related	Resolved
55001[2] Female 41	Hereditary angioedema (Moderate)	Not Related (prior)	Resolved

1   Subject was hospitalized twice during Prophylactic Treatment Trial
2   Subject 55-001 was hospitalized after completion of the Acute Treatment Trial, in which she received
    Cinryze. She was not randomized into the Prophylactic Treatment Trial.

6.4.2.3   Withdrawals for Adverse Events, Prophylactic Treatment Trial

There were no withdrawals due to adverse events from either period of the study.

6.4.2.4   Laboratory Values, Prophylactic Treatment Trial

There were no significant changes in clinical laboratory or hematology findings. No evidence of anti-C1 inhibitor antibody production was found in subjects treated with Cinryze. Viral surveillance studies demonstrated no seroconversion for parvovirus, Hepatitis B, Hepatitis C, or HIV.

6.4.2.5   Safety Summary, Prophylactic Treatment Trial

The safety profile for Cinryze in double-blind and open-label administration in the Prophylactic Treatment Trial is favorable. No Cinryze-related SAEs were recorded, and the type and severity of other AEs were similar to those reported during the placebo period. There were no deaths during the study and no withdrawals from either study period due to adverse events.

There were no significant changes in clinical laboratory or hematology findings. No evidence of anti-C1 inhibitor antibody production was found in subjects treated with Cinryze. Viral surveillance studies demonstrated no seroconversion for parvovirus, Hepatitis B, Hepatitis C, or HIV.

6.4.3   Safety Conclusions

The safety profile of Cinryze is favorable. There were few treatment-emergent adverse events reported from all studies, and those reported on Cinryze were of the same type and level of severity as on placebo. Five SAEs were reported in the prophylaxis study and another 28 SAEs have been reported in the ongoing open-label studies. All have been determined to be unrelated to Cinryze treatment. The history of Cetor use in Europe is supportive of this experience.

7.   CONCLUSION

Cinryze is a highly purified, nanofiltered, lyophilized concentrate of C1 esterase inhibitor made from US plasma and manufactured by Sanquin Blood Supply Foundation in the Netherlands. Cinryze represents the next evolution of Cetor, which has been the standard of care for the treatment of hereditary angioedema in the Netherlands for the last 11 years. The safety and efficacy of Cinryze has been demonstrated in two double-blind, placebo-controlled pivotal trials.

Cinryze was consistently efficacious by every measure for the prophylactic treatment of hereditary angioedema. Though the acute data are still under review, the results of the acute trial are supportive of the treatment effect observed in the prophylactic trial. For the treatment of acute attacks, the median time to the onset of unequivocal relief of symptoms was 2 hours in the Cinryze group and >4 hours in the placebo group (p=0.026). The Acute Treatment Trial will not be reviewed at this meeting.

In the prophylactic treatment of hereditary angioedema, the use of Cinryze significantly decreased the normalized number of HAE attacks compared to placebo. During treatment with Cinryze, the number of attacks ranged from 0 to 17.6 with a mean of 6.3 (±5.5) and a median of 6 attacks over 12 weeks. By comparison, during treatment with placebo, the number of attacks ranged from 6 to 20.5 with a mean of 12.7 (± 4.6) and a median of 13.5 attacks over 12 weeks. The difference in the number of angioedema attacks during treatment with Cinryze and with placebo was statistically significant with p<0.0001. The primary endpoint is supported by the secondary endpoints with statistically significant and clinically meaningful reductions in the severity of the attacks, number of days of swelling, the duration of attacks, and the use of open-label Cinryze.

The safety profile of Cinryze is favorable. Adverse events were mild and similar to those seen with placebo. This finding is consistent with the experience of C1 inhibitor administration in Europe. There were few TEAEs reported from all studies, and those reported by placebo-treated subjects were of the same type and level of severity as those reported by Cinryze-treated subjects. Five (5) SAEs were reported in 4 patients in the

Prophylactic Treatment Trial and another 28SAEs have been reported in the ongoing open-label studies. All have been determined to be unrelated to Cinryze treatment.

Cinryze meets an important unmet medical need and has a positive benefit-risk profile. Results of the Phase 3 trials in the US are consistent with the European experience where C1 inhibitor has been used successfully for over 35 years.

Hereditary angioedema is a serious and life-threatening disease that affects a small patient population in the US. Based on its favorable safety profile and statistically significant and clinically meaningful reductions in disease burden, Cinryze has a demonstrated value in the prophylactic treatment of HAE. Cinryze at a dose of 1000 U injected twice weekly reduced the number, severity, and duration of HAE attacks along with the total days of swelling compared to placebo. Cinryze has been shown to be both safe and effective for the prophylactic treatment of HAE. Upon approval, Cinryze will address the unmet medical need for HAE patients by providing an effective option of replacement therapy for this protein deficiency disease.

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Appendix

Hereditary Angioedema
Selected Review Articles

The following articles provide clinical and epidemiologic background information about hereditary angioedema and its treatment.

These articles can be found in the Appendix file
Lev_Cinryze_BLA125267_BPACMtg_05 02 2008_appendix.pdf

Article	Page
1. Cicardi M, Zingale LC, Zanichelli A, Deliliers DL, Caccia S. The use of plasma-derived C1 inhibitor in the treatment of hereditary angioedema. Expert Opin Pharmacother. 2007 Dec;8(18):3173-81. Review	A-3
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4. Frank MM, Jiang H. New therapies for hereditary angioedema: disease outlook changes dramatically. J Allergy Clin Immunol. 2008 Jan;121(1):272-80.	A-23