STN125267
CINRYZE (C1 Inhibitor) for routine prophylaxis against HAE attacks
Lev Pharmaceuticals, Inc.
Final Clinical Review

From: Charles Maplethorpe, OBRR/DH/CRB
Subject: Clinical Review for STN 125267/0 CINRYZE: C1 Inhibitor (Human), Intravenous, lyophilized, Lev Pharmaceuticals, Inc.
To: Felice Dagnillo, Ph.D. OBRR/DH BLA Chair
Through: Toby Silverman, M.D., OBRR/DH/CRB Chief

1. CINRYZE® BLA Clinical Review

1.1. Medical Officer's Review Identifiers and Dates

1.1.1. **BLA #:** STN 125267/0
1.1.2. **Related IND #(s):** IND --(b)(4)--
1.1.3. **Reviewer Name:** Charles Maplethorpe M.D., Ph.D.
Clinical Review Branch
Division of Hematology,
HFM 392
1.1.4. **Submission Received by FDA:** July 31, 2007
1.1.5. **Review Completed:** October 10, 2008

1.2. Product

1.2.1. **Established Name:** C1 Inhibitor (Human)
1.2.2. Proposed Trade Name: CINRYZE®
1.2.3. Product Formulation: Lyophilized white powder with following excipients: sodium chloride, sucrose, trisodium citrate, L-Valine, L-Alanine, and L-Threonine

1.3. **Applicant:** Lev Pharmaceuticals, Inc.
675 Third Ave, Suite 2200, New York, NY 11017

1.4 Pharmacologic Class or Category: Hematologic, C1 Inhibitor

1.5 Proposed Indication(s): routine prophylaxis against angioedema attacks in patients with Hereditary Angioedema (HAE)

1.6 Proposed Populations(s): Hereditary Angioedema patients

1.7 Dosage Form(s) and Route(s) of Administration:
Lyophilized white powder to be reconstituted with 5 mL Sterile Water for Injection (USP), intravenous administration

2 Table of Contents

3 Executive Summary

This Biologics License Application (BLA) contains efficacy and safety data provided by Lev Pharmaceuticals, Inc. to support approval of CINRYZE®, a C1 inhibitor indicated for routine prophylaxis against angioedema attacks in patients with Hereditary Angioedema (HAE). CINRYZE® is to be administered by intravenous injection as a 1000 Unit dose (2 vials totaling 10 mL after reconstitution) every 3 or 4 days to patients with Hereditary Angioedema. The proposed release specification for potency is 4 – 9 C1 inhibitor Units per milligram protein. After reconstitution the C1 inhibitor concentration is 100 Units per milliliter.

The Biologics Licensing Application (BLA) contains data from one phase 3 trial for routine prophylaxis (LEVP2005-1/B) and data from three supportive trials conducted in Europe with an earlier version of the product. Data from an investigational study to study the use of the product to treat HAE attacks was included in the submission, but was withdrawn by the sponsor during the review. Open-label studies are ongoing.

Efficacy

The routine prophylaxis trial LEVP2005-1/B is pivotal to the efficacy claims in this BLA. The primary objective of LEVP2005-1/B was to assess safety and efficacy of twice weekly dosing of CINRYZE (1000 Units by intravenous injection) to prevent HAE attacks over a 3 month period. The study was conducted at clinical centers (not at home) and had a prospective, randomized, double-blinded, placebo-controlled crossover study design. In the study, the According to Protocol (ATP) efficacy cohort was used for the primary efficacy analysis, and consisted of 22 HAE subjects greater than 6 years of age who experienced 3 months of routine prophylaxis with CINRYZE and placebo according to the crossover study design. The reduction of HAE attack frequency from placebo phase to active treatment phase was calculated for each subject.

In LEVP2005-1/B, an HAE attack was defined as the subject reported indication of swelling at any location following a report of no swelling on the previous day. HAE attacks were graded as mild, moderate or severe by the following definitions:

- Mild – Events that were usually transient, required no special treatment, and did not interfere with the subject's daily activities.
- Moderate – Events that introduced some level of inconvenience or concern to the subject, and may have somewhat interfered with daily activities, but were usually ameliorated by simple therapeutic measures (may have included drug therapy).
- Severe – Events that were unacceptable or intolerable, significantly interrupted the subject's usual daily activity, and required systemic drug therapy or other treatment.

The applicant demonstrated that CINRYZE, at 1000 Units per dose every 3 or 4 days, was effective in reducing the frequency of HAE attacks in patients with hereditary

angioedema. The mean number of HAE attacks was reduced from 12.7 attacks on placebo to 6.1 attacks on CINRYZE routine prophylaxis for the three month period.

Safety

In LEVP200-1/B, there were 24 subjects treated with randomized study medication. Of these, 23 subjects were treated with CINRYZE and 23 subjects were treated with Placebo. All subjects received open-label treatment with CINRYZE during their Placebo treatment phase, which confounds true attribution of adverse events to CINRYZE or placebo. There were 20 subjects (87.0%) who had a treatment-emergent adverse event (TEAE) after exposure to open-label or double-blind randomized CINRYZE. In 9 subjects, the TEAEs were categorized as related to study medication. The most common related TEAEs were viral upper respiratory infections (3 subjects) and rash (3 subjects). There were 3 subjects with 1 or more treatment-emergent SAEs and 1 subject with an SAE reported prior to randomization with study medication. None of these events were reported as related to study medication. There were no deaths or withdrawals due to AEs. There were no meaningful changes in clinical laboratory results or in evaluation of vital signs. Immunogenicity studies were flawed by technical problems with assays. Subsequent analysis using data from other testing facilities resulted in the conclusion that the product is not immunogenic; however this conclusion is being tested in a phase 4 study.

Serious adverse events - deaths

None.

Serious adverse events

In LEVP2005-1/B there were 3 subjects with a treatment-emergent SAE.

All of these subjects had an HAE attacks that required hospitalization. In addition, one subject had surgery for a cyst and the placement of a subcutaneous port put in place to improve IV access. None of these SAEs were considered related to study medication.

Solicited adverse events

Of the 24 subjects in the safety population, 21 (87.5%) had 1 or more treatment-emergent adverse events (TEAEs). There was only 1 subject who had a TEAE (sinusitis) during treatment with Placebo and prior to exposure to open-label or randomized CINRYZE. The remaining 20 subjects (87.0%) had at least 1 TEAE that followed exposure to *open-label* or randomized double-blind CINRYZE.

In subjects treated with CINRYZE, the most common TEAEs were those that coded to the Infections and Infestations system organ class (14 subjects, 60.9%). Within this system organ class, the most common individual TEAEs were sinusitis (5 subjects, 21.7%), upper respiratory tract infection (4 subjects, 17.4%) and viral upper respiratory tract infection (3 subjects, 13.0%). Gastrointestinal Disorders were experienced by 8 subjects (34.8%). The most common TEAEs in this system organ class were gastro-esophageal reflux disease (2 subjects, 8.7%) and vomiting (2 subjects, 8.7%). Treatment-emergent AEs that coded to the Skin and Subcutaneous Tissue Disorder system organ class were reported by 6 subjects (26.1%). TEAEs within this system organ class included rash (5 subjects, 21.7%), pruritus (2 subjects, 8.7%), dermatitis contact (1 subject, (4.3 %).and erythema (1 subject, 4.3 %).

In other system organ classes, headache was reported by 4 subjects (17.4%).

No other individual TEAE was reported by more than 2 subjects.

Conclusion

CINRYZE at a potency of 1000 Units per dose every 3 or 4 days by intravenous injection was effective in preventing or reducing the HAE attack frequency in patients with hereditary angioedema.

Recommendation:

The reviewer recommends that CINRYZE be approved for routine prophylaxis use in patients with hereditary angioedema to reduce the HAE attack frequency.

As part of the pre-BLA licensure agreement, the applicant will conduct a prospective US post-licensure clinical trial that will evaluate the efficacy and the safety profile of a higher than labeled dose schedule of CINRYZE for routine prophylaxis in patients who have an unacceptable clinical benefit (reduction in HAE attack frequency) at the labeled dose schedule. Other measured outcomes will include immunogenicity using validated assays.

4 Significant Findings from Other Review Disciplines

4.1 Chemistry, Manufacturing and Controls (CMC) (see CMC review)

4.2 Animal Pharmacology/Toxicology

From the proposed package insert:

13.2 Animal Toxicology and/or Pharmacology

Acute toxicity of CINRYZE was studied in a combined acute toxicity and 7-day repeat dose/ dose range finding (DRF) study in Sprague Dawley rats. Repeat dose toxicity was studied in a 7-day repeat dose follow up to the acute dose study. The acute and repeated dose toxicity study were performed with intravenous administration of CINRYZE at dose levels of 1, 7 and 28 times normal dose. No signs of toxicity were observed in the single dose study. In the repeated dose study, no signs of toxicity were observed in the two lower doses. Repeat dosing in the rat resulted in a robust neutralizing antibody response between days 1 and 14. Therefore, toxicity in animals dosed repeatedly is difficult to interpret.

In vitro and in vivo thrombogenicity studies showed a potential for clot formation when CINRYZE was administered at doses 14 times the recommended clinical dose (greater than 200U/kg).

5 Clinical and Regulatory Background

5.1 Disease or Health-Related Condition(s) Studied and Available Interventions

Background on C1 Esterase Inhibitor and Hereditary Angioedema.

C1 Esterase Inhibitor (C1INH) is a 104 kD plasma glycoprotein (35% carbohydrate) that was first described in the late 1950's as the plasma activity that inhibits the C1 proteinase activity of the complement cascade. It appears to be the only inhibitor of C1 esterase. Subsequent research demonstrated that it is a more general proteinase inhibitor of the serpin class, having inhibitory activity against C1r, C1s, kallikrein and Factor XIIa. In vitro, it inhibits plasmin; however it does not appear to be a significant inhibitor of plasmin in vivo.

C1 esterase inhibitor has the following activities, as shown in the following diagram:

- inhibition of the classical complement cascade,
- inhibition of coagulation factors XIa and XIIa
- inhibit of the conversion of plasminogen to plasmin
- inhibition of activated kallikrein in the kallikrein-bradykinin pathway.

The information in the following table presents the relative specificities of various plasma serine proteinase inhibitors (serpin) for several plasma proteinase:

From *Ann. Rev. Biochem.* **52**:655-709 (1983):

Half-time of association of proteinases with human plasma proteinase inhibitors[a]

Inhibitor	Elastase	Cat. G	Trypsin	Chymotrypsin	Kallikrein	Thrombin	Plasmin	C1r	C1s	Factor Xa
A1-Proteinase Inhibitor	0.61[c]	102[c]	3600[c]	8[c]	+	830000[c]	210000[c]	----	----	170000
A1-anti-chymotrypsin	----	5[c]	----	27000[c]	----	----	----	----	----	----
A2-Macroglobulin	7.2[c]	93[c]	19[c]	27[c]	6125	500000	+	----	----	350000
C1INH	----	----	----	----	8333	?	+	200000	47000	?
A2-Antiplasmin	----	----	617[c]	11100[c]	+	----	29[c]	----	----	+
ATIII	----	----	----	----	+	847	+	----	----	230000

[a] In milliseconds
[b] (---). No interaction; (+), inactivation but no kinetic data; (?), no data available
[c] Measured at room temperature

From A.L. Sheffer, M.D., J Allergy Clin Immunol 120:756-757 (2007):

Hereditary angioedema (HAE) is an autosomal-dominant condition [chromosome 11], characterized by episodic self-limited, occasionally life-threatening attacks of angioedema.1,2 Affected individuals lack sufficient functional inhibition of the first complement protein, the serine proteinase inhibitor C1INH.3,4 In most instances, the C1INH is absent (type I), but 15% may possess a nonfunctional C1INH (type II).5 These 2 types of HAE cannot be distinguished clinically. The incidence varies from 1:10,000 to 1:50,000 persons. The biological role of the C1INH is to regulate the intrinsic and contact coagulation pathways as well as the complement system.6,7 In the former, plasma kallikrein and coagulation factors XIa and XIIa (Hageman factor) are inhibited, and in the latter, C1r and C1s are inhibited. When C1INH is deficient or absent, bradykinin is released from the high-molecular weight kininogen by plasma kallikrein in abnormally high amounts.8-11 C1INH knockout mice have confirmed experimentally that increased vascular permeability in HAE is mediated by bradykinin via the contact system.12

1. Davis AE. C1 inhibitor and hereditary angioneurotic edema. Annu Rev Immunol 1988;6:595-628.
2. Donaldson VH, Bissler JJ. C1-inhibitors and their genes: an update J Lab Clin Med 1992;119:330-3.
3. Landerman NS, Webster ME, Becker EL, Ratcliffe HE. Hereditary angioneurotic edema, II: deficiency of inhibitor for serum globulin permeability factor and/or plasma kallikrein. J Allergy 1962;33:330-41.
4. Donaldson VH, Evans RR. A biochemical abnormality in hereditary angioneurotic edema: absence of serum inhibitor of C' 1-esterase. Am J Med 1963;35:37-44.
5. Rosen FS, Pensky J, Donaldson V, Charache P. Hereditary angioneurotic edema: two genetic variants. Science 1965;148:957-8.
6. Bowen T, Cicardi M, Farkas H, Bork K, Kreuz W, Zingale L, Varga L, et al. Canadian 2003 International Consensus algorithm for the diagnosis,

therapy, and management of hereditary angioedema. J Allergy Clin Immunol 2004;114:629-37.
7. Davis AE. Mechanism of angioedema in first complement component inhibitor deficiency. Immunol Allergy Clin North Am 2006;26:633-51.
8. Zuraw BL, Curd JG. Demonstration of modified inactive first component of complement (C1) inhibitor in the plasmas of C1 inhibitor-deficient patients. J Clin Invest 1986;78:567-75.
9. Fields T, Ghebrehiwet B, Kaplan AP. Kinin formation in hereditary angioedema plasma: evidence against kinin derivation from C2 and in support of ‘‘spontaneous’’ formation of bradykinin. J Allergy Clin Immunol 1983;72:54-60.
10. Schapira M, Silver LD, Scott CF, Schmaier AH, Prograis LJ Jr, Curd JG, et al.Prekallikrein activation and high-molecular-weight kininogen consumption in hereditary angioedema. N Engl J Med 1983;308:1050-3.
11. Nussberger J, Cugno M, Amstutz C, Cicardi M, Pellacani A, Agostoni A. Plasma bradykinin in angio-edema. Lancet 1998;351:1693-7.
12. Han ED, MacFarlane RC, Mulligan AN, Scafidi J, Davis AE. Increased vascular permeability in C1 inhibitor-deficient mice mediated by the bradykinin type 2 receptor. J Clin Invest 2002;109:1057-63.

From Zuraw, B.J., Transfusion and Apheresis Science 29:239-245 (2003):

A diagnosis of HAE requires laboratory confirmation of C1 inhibitor deficiency in addition to a compatible history. Patients suspected of having HAE are initially screened by measuring complement C4 antigenic levels which are reliably decreased during episodes of HAE swelling. The C4 level is typically decreased even when the patient is not swelling, however it may rarely be within the normal range between attacks. Measurement of the C4 cleavage product C4d is a more sensitive gauge of complement activation and is abnormal in HAE patients even when the C4 level is normal.

If the C4 level is decreased, C1 inhibitor antigenic and functional levels should be measured to confirm the diagnosis. Antigenic C1 inhibitor levels will be decreased in type I HAE patients; however the 15% of HAE patients with type II HAE will have a normal C1 inhibitor antigenic level. Functional C1 inhibitor levels will be decreased in type II as well as type I HAE patients. The tests for C1 inhibitor function that are currently available in the United States, however, are quite insensitive and may not provide accurate information. In this situation, one may need to seek more specialized testing such as measurement of C1 inhibitor function by inhibition of hemolytic complement activity or molecular diagnosis of the C1 inhibitor mutation. It may also be prudent to repeat the C1 inhibitor functional level during and attack of angioedema.

In addition to the C1 inhibitor tests, it is also useful to measure the C1q level as this component is typically decreased in acquired C1 inhibitor deficiency but normal in HAE. Complement C3 and total hemolytic complement (CH50) levels are normal or near-normal in HAE and should not be measured.

Children with a parent who has HAE have a 50% risk of inheriting the disease. If the genetic mutation is known, then it is straight forward to screen for the mutation in the cord blood of the baby. In the absence of a genetic diagnosis, it is generally advisable to wait until the infant is 1 year of age before his/her blood is tested for C1 Inhibitor deficiency.

5.2 Important Information from Pharmacologically Related Products, Including Marketed Products

There are currently several other investigational new drugs that are seeking similar indications as STN 125267, and which have been studied in clinical trials using very similar designs.

Ongoing Studies of Investigational New Drugs for HAE

Drug	Sponsor	Mechanism	Status
Berinert	CSL Behring	Plasma-derived C1INH	Phase 3 (completed)
Rhucin	Pharming LLD	Recombinant human C1INH (transgenic rabbit)	Phase 3
Ecallantide (DX-88)	Dyax	Kallikrein Inhibitor (peptide)	Phase 3 ongoing [EDEMA4]
Icantibant	Jerini AG	Bradykin Receptor (B2) inhibitor (peptide)	Phase 3 (completed)

5.3 Previous Human Experience with the Product Including Foreign Experience

The following tables present information on the clinical studies other than LEVP2005-1/B that have been conducted with CINRYZE™ or its European product version, CETOR.

The review of the results of study 2005-1 Part A (treatment of HAE attacks) is ongoing.

It should be noted that there were no adequate and well-controlled studies of CINRYZE or the European product version, CETOR, prior to study 2005-1. The European product version of CINRYZE was licensed based on data from a pharmacokinetics study.

Completed Safety and Efficacy Studies with CINRYZE (C1INH) Conducted by Lev Pharmaceuticals, Inc.

Study Number Drug Indication	Study Design	Dose	Placebo	CINRYZE	Open Label CINRYZE Only[a]	Safety	Efficacy
LEVP 2005-1 PART/A CINRYZE HAE	Phase III, multi-center, randomized, placebo-controlled, double-blind study to evaluate the efficacy and safety of CINRYZE (C1INH-nf) as a therapeutic agent for acute attacks of HAE	CINRYZE: 1000 U or 2000 U	Randomized: 35 subjects As Treated[b] 34 subjects M:6 F: 28 Age: 9-64 years Safety: 35 M:7 F:28 Age9-64 Years	Randomized: 36 subjects As Treated[b]: 37 subjects M:10 F: 27 Age: 6 -75 Years Safety: 36 M:9 F:27 Age:6-75 Years	12 subjects M: 6 F: 6 Age: 9 -73 Years Safety: 12 M:9 F:27 Age:6-75 Years	AEs clinical laboratory, vital signs local tolerance antigenicity viral serology	Primary: Time to the beginning of unequivocal relief Secondary: Percentage of subjects who had unequivocal beginning of relief within 4 hours following treatment; time to complete resolution of the attack; effects of treatment on CIINH and C4 levels.

[a] Subjects treated for non-randomizable attacks only. Randomized subjects could also receive CINRYZE for non-randomizable attacks prior to or after the attack evaluated in the double-blind part of the study

[b] Subject 22-001 randomized to the placebo treatment group received ClInh-nf in error at 60 minutes. Therefore, he was included in the CINRYZE treatment group in the "As Treated" population.

Completed Clinical Pharmacology Studies with CINRYZE (C1INH) Conducted by Lev Pharmaceuticals, Inc.

Study Number Drug Indication	Study Design	Dose	Treated Demographics	Safety Data	Other Outcomes
LEVP 2006-5 PART/B CINRYZE HAE	Phase 1, randomized, parallel-group, open-label study to compare the PK of a single dose of CINRYZE (C1INH-nf) to that of 2 doses	CINRYZE 1 or 2 doses at 1000 U	27 subjects 1 dose (13 subjects) 2 doses (14 subjects) M:10 F:17 Age:19-57 Years	AEs, clinical laboratory, vital signs, and virology	PK of antigenic and functional C1INH-nf: PK of C4

Completed Lev Pharmaceuticals, Inc. Single Subject Use Protocols

Study Number Drug Indication	Study Design	Dose Duration	Enrolled Treated Demographics	Safe Data
LEVP 2006-2 CINRYZE HAE	Open-label	CINRYZE: 1000 U twice weekly 1 or 2 doses at 1000 U	1 subject F: 1 25 Years	AEs, viral serology
LEVP 2005-4 CINRYZE HAE	Open-label	CINRYZE: 1 or 2 doses at 1000 U	1 subject M: 1 14 Years	AEs, viral serology
LEVP 2005-3 CINRYZE HAE	Open-label	CINRYZE: 1000 U twice weekly 1 or 2 doses at 1000 U	1 subject F: 1 22 ears	AEs, viral serology

Ongoing Safety and Efficacy Studies with CINRYZE (C1INH) Conducted by Lev Pharmaceuticals, Inc.

Study Number Drug Indication	Stud Design	Dose Duration	Enrolled Treated Demographics	Safety Data Data Available as of 25 Sep 2007	Efficacy
LEVP 2006-1 HAE	Phase 3, multi-center, open-label study of CINRYZETM (C1INH-nf) for the treatment of HAE attacks	CINRYZE: 1 or 2 infusions 1000 U /infusion	67 subjects 67 subjects M:18 F:49 Age: 7-81 Years	SAE s	Number of subjects with unequivocal beginning of relief within 4 hours. Time to the unequivocal beginning of relief, change in time to the unequivocal beginning of relief C1INH and C4 levels.
LEVP 2006-4 HAE	Phase 3, multi-center, open-label study that will evaluate the efficacy and safety of CINRYZE (CIINH-nf) as prophylaxis to prevent HAE attacks.	CINRYZE : 1000 U every 3 to 7 days	46 subjects 46 subjects M:5 F:41 Age:5-75 Years	SAE s	Number of attacks PK/PD analyzed under separate protocol

The following tables describe clinical studies conducted in Europe with an earlier version of the product sponsored by the European manufacturer, Sanquin:

Completed Safety and Efficacy Studies of C1-esteraseremmer-HP (Cetor) and C1INH-nf (C1-esteraseremmer-N) Conducted by Sanquin

Study Number Drug Indication	Stud Design	Drug Dose	Total Demographics	Safety Data	Efficacy
KB97002-C1-INH C 1-esteraseremmer-HP (Cetor) Myocardial infarction	Phase 2/3, multi-center, open-label, pilot safety and efficacy study of Cetor in patients with myocardial infarction	Cetor First 6 subjects: 50 U/kg bolus followed by1.25 U/kg for 48 hours Next 5 subjects: 100 U/kg bolus, followed by 1.25 U/kg for 48 hours Subsequent subjects: 100 U/kg bolus, 2.0 U/kg for 48 hours (Total doses of 4250 U to >25404 U	22 subjects M: 12 F: 10 Mean Age: 60.6 years	Laboratory values, AEs, vital signs, and physical examinations	Infarct Size of infarct vs. predicted size (planned, not done)
036-005/Part A Cetor HAE	Open-label, clinical evaluation of a pasteurized C 1 esterase inhibitor concentrate of high purity (C 1-esteraseremmer-HP); clinical tolerance	C1-esteraseremmer-HP (Cetor): Pilot Infusions 300 U to 610 U then 1200 U to 2440 U	9 subjects M: 4 F: 5 Age: 19-68 years	Laboratory safety (including coagulation), vital signs (blood pressure, heart rate, temperature), signs of allergic reactions	None

Completed Clinical Pharmacology Studies with C1-esteraseremmer-N Conducted by Sanquin

Study Number Sponsor Drug Indication	Stud Design	Drug Dose	Total Treated	Safety Data	Outcome Variables
KB2003.01/Part A C1-esteraseremmer-N and Cetor HAE	Open-label, cross-over study to compare PK of Cl-esterase-remmer-N vs. Cetor	C1-esteraseremmer-N and Cetor 1000 U (5 subjects) 1500 U (5 subjects) 2000 U (4 subjects) All subjects received one dose of Cetor and one dose of Cl-esteraseremmer-N at the dose specified	14 subjects M: 3 F: 11 Age (mean) 40.8 yrs	AEs, clinical laboratory, vitals, antigenicity	Pharmacokinetics of Cl-esteraseremmer-N versus current Cetor Biological activity of Cl-esteraseremmer-N versus current Cetor by means of C4 levels.
036-005/Part B Cetor HAE	Open-label, clinical evaluation of a pasteurized C1 esterase inhibitor concentrate of high purity (C1-esteraseremmer-HP, the in vivo recovery and the half-life of C 1-esteraseremmer-HP	C1-esteraseremmer-HP (Cetor): Pilot Infusions 300 U to 610 U then 1200 U to 2440 U	9 subjects M: 4 F: 5 Age: 44 years	Laboratory safety (including coagulation), vital signs (blood pressure, heart rate,temperature), signs of allergic reactions	In vivo recovery and the half-life of C1-esteraseremmer-HP

Ongoing Safety and Efficacy Studies with C1-esteraseremmer-N Conducted by Sanquin

Study Number Sponsor Drug Indication	Stud Design	Drug Dose	Enrolled Treated	Safety Data	Efficacy
KB2003.0I/Part B HAE and AAE	Open-label, multi-center study	Cl-esteraseremmer-N Dosed at same level as Cetor dose used in prior attacks	11 subjects	AEs, vital signs, clinical laboratory results, virology, anti-C 1 inhibitor antibodies	Time to relief, time to resolution of symptoms
KB2003.01/Part C HAE and AAE	Open-label, multi-center study	C1-esteraseremmer-N 1000 U every 5 to 7 days, with adjustments as needed. 16 weeks	14 subjects	AEs, vital signs, clinical laboratory results, virology, anti-C 1 inhibitor antibodies	Number, type, severity and duration of attacks

5.4 Regulatory Background Information (FDA-Sponsor Meetings, Advisory Committee Meetings, Commitments)

Regulatory Chronology.

13-May-2004	pre-IND meeting on manufacturing and clinical trial design
27-Jul-2004	pre-IND meeting on manufacturing and clinical trial design
28-Jul-2004	IND --(b)(4)-- submitted
07-Jan-2005	telecon on conformance lots, request for permission to do PK in phase 4, and viral safety testing
01-Feb-2005	telecon on viral safety testing
30-Oct-2005	Fast Track designation granted
21-Jun-2007	pre-BLA telecon on assay problems
31-Jul-2007	STN125267 submitted
14-Aug-2007	Review Committee: Felice D'Agnillo – Chair, Charles Maplethorpe – Clinical, Paul Buehler – Nonclinical, Boris Zaslavsky – Statistician, Robert Wesley – BIMO, Dave Doleski - CMC, Facility, Mahmood Farshid – Product (Virus Removal), Jean Makie – APLB, Elena Karnaukhova – CMC, Product, Omer Butt – CMC, Product, and Joseph Quander - Lot Release
15-Aug-2007	Priority Review granted
25-Sep-2007	FDA information request faxed to sponsor (data vetting, observation times, response modeling request, CMC, clinical pharmacology, labeling)
29-Sep-2007	Filing Date
13-Oct-2007	Deficiencies Identified
17-Oct-2007	Sponsor's response to 25-Sep-2007 FDA fax
29-Oct-2007	Sponsor submits results of Part B (prophylaxis)
27-Nov-2007	Sponsor's response to 07-Nov-2007 FDA fax
30-Jan-2008	First Action Due Date – Complete Response Letter issued
14-Apr-2008	Response to CR Letter submitted
03-Oct-2008	Sponsor withdrew treatment of HAE attacks submission
14-Oct-2008	Action Due Date for routine prophylaxis indication

6 Clinical Data Sources (both IND and non-IND), Review Strategy and Data Integrity

6.1 Material Reviewed

6.1.1 BLA/NDA Volume Numbers Which Serve as a Basis for the Clinical Review

STN125267 module 5, all volumes; response to January 30, 2008, Complete Response Letter

6.1.2 Literature, if Applicable

Not necessary.

6.1.3 Post-Marketing Experience, if Applicable

6.2 Table(s) of Clinical Studies (see 5.2)

6.3 Review Strategy

Primary data were reviewed and used to construct outcome variables. Analyses were performed according to the submitted plan for analysis, as well as *post hoc* analyses. Final results were then compared to the sponsor's narrative of the results.

6.4 Good Clinical Practices (GCP) and Data Integrity (see Bioresearch Monitoring review)

6.5 Financial Disclosures

The sponsor has submitted Form FDA 3454 (4/06) stating there were no financial conflicts of interest among the investigators for LEVP2005-1/B.

7 Human Pharmacology

From the proposed package insert:

12.2 Pharmacodynamics

In clinical studies, the intravenous administration of CINRYZE demonstrated an increase in plasma levels of C1 inhibitor within approximately one hour or less of administration.

Biological activity of CINRYZE was shown in 35 subjects by the subsequent increase in plasma C4 levels from an average of C4 8.1 mg/mL at baseline to C4 8.6 mg/mL 12 hours after infusion of CINRYZE.

12.3 Pharmacokinetics

A randomized, parallel group, open label pharmacokinetics (PK) study of CINRYZE was performed in patients with non-symptomatic hereditary angioedema (HAE). The patients received either a single dose of 1,000 units or 1,000 units followed by a second 1,000 units 60 minutes later. The PK results for functional C1 inhibitor are presented the following table:

Table 4
Mean pharmacokinetic parameters of Functional C1 Inhibitor

Parameters	Single Dose	Double Dose
$C_{baseline}$ (units/mL)	0.31 ± 0.20 (n = 12)	0.33 ± 0.20 (n = 12)
C_{max} (units/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)
$AUC_{(0-t)}$ (units*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)

Numbers in parenthesis are number of subjects evaluated
Single dose = 1000 units
Double dose = 1,000 units followed by a second 1,000 units 60 minutes later

The maximum plasma concentrations (C_{max}) and area under the plasma concentration-time curve (AUC) appeared to increase from the single to double dose, although the increase was not dose proportional. The mean half-lives of CINRYZE were 56 hours (range 11 to 108 hours) for a single dose and 62 hours (range 16 to 152 hours) for the double dose.

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

8 Clinical Studies

8.1 Indication: routine prophylaxis against HAE attacks in patients with hereditary angioedema

8.1.1 LEVP2005-1/B

8.1.1.1 CHANGE Trial (C1-Inhibitor in Hereditary Angioedema Nanofiltration Generation Evaluating Efficacy) (LEVP2005-1/B) "A Double-blind, Placebo Controlled, Clinical Study to Investigate the Efficacy and Safety of Purified C1 Esterase Inhibitor (Human) … as Prophylactic Treatment to Prevent HAE Attacks (Part B) Protocol "

8.1.1.1.1 Objective/Rationale

To investigate the efficacy and safety of CINRYZE as prophylactic treatment to prevent HAE attacks.

8.1.1.1.2 Design Overview

Phase 3, multi-center, randomized, placebo-controlled, double-blind crossover trial

8.1.1.1.3 Population

HAE subjects who had completed LEVP2005-1/A for treatment of HAE attacks

Inclusion:

- Age ≥ 6 years
- Documented HAE based on evidence of a low C4 level, AND
  - Low C1INH antigenic level OR
  - Normal C1INH antigenic level and a low C1INH functional level; OR
  - A known HAE-causing C1INH mutation.
- Normal C1q level
- Signed informed consent
- Frequent HAE attacks, at least 2 per month

Exclusion:

- Age < 6 years
- Low C1q level
- B-cell malignancy
- Presence of anti-C1INH antibody
- History of allergic reaction to C1INH or other blood/plasma products
- Narcotic addiction
- Current participation in any other investigational drug study or within the past 30 days

- Participation in a C1-esterase inhibitor trial other than LEVP 2005-1 Part A, received blood, or 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

8.1.1.1.4 Products mandated by the protocol

Subjects were randomized to receive blinded study agent i.v. (C1INH 1000 IU) 2 times per week at the study site.
Subjects could receive open-label C1INH for treatment of attacks; the next scheduled prophylactic administration of study agent would then be delayed at least 24 hours after the open-label administration

8.1.1.1.5 Endpoints

Efficacy Analyses

Primary

The primary efficacy endpoint for Part B will be the number of attacks of angioedema during each treatment period, normalized for the number of days the subject participated in that period. This will be done by dividing the total number of attacks in each period by the number of days the patient was in that period. An attack is defined as the subject reported indication of swelling at any location following a report of no swelling on the previous day. The crossover analysis will be based on a Poisson assumption and use the GEE method as implemented in the SAS statistical procedure PROC GENMOD. 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 will be used to check for over dispersion. If the Deviance/df and Pearson/df ratios are greater than 1, then there is evidence of over dispersion. In such situation, the GEE approach is able to address the over dispersion issue since it is robust to the misspecification of the covariance structure, and misspecification is occurring in the case of over dispersion.

Secondary

The secondary efficacy endpoints for Part B are

- Number of subjects dropping out at each treatment period. For the first treatment period, drop-out is defined as not having any Visit 24A records. For the second treatment period, drop-out is defined as not having any Visit 24B records. This is a binary categorical endpoint. At the end of each treatment period, each subject will be assigned a Yes/No drop-out status and a 2x2 table will be produced for treatment by drop-out status. A Fisher's exact test will be carried out to compare between treatments.
- Average severity of attacks. The severity of an attack will be the highest value assigned by the subject to any location at any day during the attack. In order to calculate the average severity of attacks for each period, each mild, moderate, and severe attack will be assigned a score of 1, 2, or 3, respectively. The total severity score will be 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 is then derived by dividing the total severity score of that period by the total number of attacks in that period. The difference between treatments will be tested by a Wilcoxon Signed Rank Test.
- Average duration of attacks. The duration of an attack will be 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 will be 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 will be tested by a Wilcoxon Signed Rank Test.
- Number of open-label C1INH-nf infusions. The total number of open-label C1INH-nf infusions (counting double infusions as two infusions) while subjects receiving active treatment will be compared with the total number of open-label C1INH-nf infusions (counting double infusions as two infusions) while subjects receiving placebo by using the Wilcoxon Signed Rank Test.
- Change from baseline in C1INH antigenic and functional levels will be compared between study treatments by using the Wilcoxon Signed Rank Test. Baseline value for the first period is defined as the Visit is pre-infusion measurement. Baseline value for the second period is defined as the Visit 1b pre-infusion measurement. C1INH antigenic and functional levels will be measured pre and post infusion at Visits la, 8a, 16a, 24a, lb, 8b, 16b, and 24b:

Other Evaluations

The total number of days of swelling in each study period will be compared between C1INH-nf and placebo. A day of swelling is defined as a day that a subject reported indication of swelling at any location. The difference between treatments will be tested by a Wilcoxon Signed Rank Test.

Safety Analyses

Safety analyses will be assessed using the following measures: extent of exposure, AEs, vital signs, physical examinations, and laboratory tests. All summary safety analyses will be carried out using subjects included in the safety dataset.

Extent of Exposure

Summary statistics for dose (mL) will be presented for each treatment and open-label drug infusions.

Adverse Events

Adverse events will be coded using the MedDRA coding dictionary version 8.0. Events will be classified by system organ class and preferred term. Only treatment emergent adverse events (TEAEs) will be summarized. Treatment-emergent adverse events are defined as those events which start on or after the time of first infusion of trial medication (or whose severity worsened on or after that time) and up to 30 days after the last infusion of study drug.

The incidence of TEAEs will be summarized by intensity ('Mild', 'Moderate' or 'Severe') at preferred term and system organ class level. For each subject and preferred term, only the most severe AE will be counted.

The incidence of AEs related to study drug will be summarized at preferred term and system organ class level. Events with a relationship to study drug classified as 'Definitely', 'Probably', 'Possibly' or 'Unknown' will be categorized as 'Related'. If a subject experiences the same event (at preferred term level) on more than one occasion, then only one event will be counted, and this event will be categorized as 'Related' if any of the events under that preferred term are categorized as 'Related'.

All AEs for each subject, including the same event on several occasions will be listed, giving both preferred term and the original term used by the investigator. Serious AEs will be presented separately on an additional listing.
Laboratory Evaluations

Summary statistics will be presented for each lab assessments. Lab value change and shift from follow-up visit to initial treatment visit will also be presented.

Physical Examination

Physical examination results at initial and final treatment visits will be listed. No summary statistics will be presented.

Vital Signs
Summary statistics for vital signs measured at each treatment visit, and the change from post-infusion to pre-infusion at each visit, will be presented by treatment.

8.1.1.1.6 Surveillance

Schedule of Laboratory Testing for Prophylactic Treatment in Part B

	Screen See Part A	**Initial Infusion**		**30 days**		**60 Days**		**90 Days Last infusion**		**Cross Over**		**120 Days**		**150 Days**		**180 Days**		**270 Days**
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	
C1INH antigenic		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
C1INH functional		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
C1INH autoantibody										X						X		X
Anti-parvo B19	X (if positive, Parvo testing complete, if negative run NAT infusion)																	
Parvo B19 NAT			X (if NAT positive post infusion, repeat AntiParvo B19)															
HBsAg		X																X
Anti-HCV		X																X
Anti-HIV		X																X
HIV NAT		X																X
HCV NAT		X																X
CBC		X																X
BUN		X																X
Reserves		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Schedule of Laboratory Testing for Open Label Treatment Part B

	Pre-Infusion	60 min	3 months
C1INH antigenic	X	X	
C1INH functional	X	X	
C4	X	X	
C1q	X	X	
C1INH autoantibody	X		
Anti-parvo B19	X		X
HBsAg	X		X
Anti-HCV	X		X
Anti-HIV	X		X
HIV NAT	X		X
HCV NAT	X		X
reserves	X	X	X

Subjects recorded the location of swelling (abdominal, genitourinary, facial, respiratory including laryngeal, extremity), attack severity (mild, moderate, severe), and duration of swelling.

Severity of swelling:

- Mild – Events that were usually transient, required no special treatment, and did not interfere with the subject's daily activities.
- Moderate – Events that introduced some level of inconvenience or concern to the subject, and may have somewhat interfered with daily activities, but were usually ameliorated by simple therapeutic measures (may have included drug therapy).
- Severe – Events that were unacceptable or intolerable, significantly interrupted the subject's usual daily activity, and required systemic drug therapy or other treatment.

8.1.1.1.7 Statistical considerations

Sample Size.

Assuming angioedema attack rates will be 1 every two weeks in the placebo phase and 1 every 12 weeks in the prophylactic C1INH-nf phase, 10 subjects per sequence provides more than 90% power to detect the treatment effect. A total of 20 subjects is planned to be enrolled into Part B.

Analysis Datasets.

The Efficacy dataset will consist of all subjects who were randomized into one of 2 treatment sequences and who completed the entire initial treatment phase (B1) and received at least 1 treatment of the crossover phase (B2). The number of attacks will be calculated on a per day basis.

The Safety dataset will consist of all subjects who received a complete or partial infusion of therapeutic treatment.

General Analysis Comments.

Descriptive summaries of measurements will be presented by treatment or by treatment sequence. Summary statistics will consist of frequencies and percentages of responses in each category for discrete measures and of means, medians, standard deviations, minimum and maximum values for continuous measures. For safety summaries, percentages will be based on the number of subjects in the safety dataset.

Efficacy analyses in Part B will be performed on the efficacy dataset; except for the analysis on the number of subjects dropping out at each treatment period, which will be

performed on the safety dataset. All safety analyses will be performed on the safety dataset.

For cross-over analyses, a standard analysis of variance for cross-over study design will be performed with effects for treatment, period, and subject within treatment.

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

By-subject listings will be provided for all data collected and entered into the study database.

8.1.1.2 Results, by Trial

Table 11-5 Number of Angioedema Attacks

	Statistic	CINRYZE (N=22)	Placebo (N=22)
Number of attacks	Mean	6.1	12.7
	SD	5.43	4.80
	Median	6.0	13.5
	Min	0	6
	Max	17	22
GEE Analysis Results			
Treatment Effect p-value		<.0001	
Sequence Effect p-value		0.3347	
Period Effect p-value		0.3494	

The mean (±SD) severity of attacks was 1.3 (±0.85) during treatment with CINRYZE and 1.9 (±0.35) during treatment with Placebo. The difference in the severity of attacks during treatment with CINRYZE and treatment with Placebo was statistically significant (p=0.0008).

Table 11-7 Severity of Attacks

Severity Statistic	**CINRYZE (N=22)**	**Placebo (N=22)**	**p-value**
Mean	1.3	1.9	**0.0008**
SD	0.85	0.35	
Median	1.3	1.9	
Min	0	1	
Max	3	3	

The mean (±SD) duration of attacks was 2.1 days (±1.13 days) during treatment with CINRYZE and 3.4 days (±1.39 days) during treatment with Placebo. The difference in the duration of attacks during treatment with CINRYZE and during treatment with Placebo was statistically significant (p=0.0004).

Average Duration of Attacks

Days Statistic	CINRYZE (N=22)	Placebo (N=22)	p-value
Mean	2.1	3.4	**0.0004**
SD	1.13	1.39	
Median	2.5	3.1	
Min	0	2	
Max	4	8	

The mean number (±SD) of open-label rescue C l INH infusions required during attacks was 4.7 (±8.66 infusions) during treatment with CI1NH and 15.4 (±8.41 infusions) during treatment with placebo. The difference in the number of open-label infusions during treatment with CINRYZE and treatment with Placebo was statistically significant (p<0.0001).

Number of Open-label Infusions: Efficacy Dataset

Number Statistic	CINRYZE (N=22)	Placebo (N=22)	p-value
Mean	4.7	15.4	**<0.0001**
SD	8.66	8.41	
Median	0.5	13.5	
Min	0	2	
Max	36	34	

The mean (±SD) total number of days of swelling was 10.1 days (110.73 days) during treatment with CINRYZE and 29.6 days (±16.9 days) during treatment with Placebo. The difference in the total days of swelling during treatment with CINRYZE and treatment with Placebo was statistically significant (p<0.0001).

Total Days of Swelling

Days Statistic	CINRYZE (N=22)	Placebo (N=22)	p-value
Mean	10.1	29.6	**<0.0001**
SD	10.73	16.90	
Median	6.5	26.5	
Min	0	8	
Max	38	67	

C1INH Levels (functional)
Pre-infusion, the mean values of ClINH functional activity were similar prior to treatment with CINRYZE (33.9 mg/dL) and prior to treatment with Placebo (31.7 mg/dL).

There was a statistically significant difference in the changes ClINH functional levels from baseline analysis in mean values at 60 post-infusion on Visits 1, 8, 16, and 24 ($p \leq 0.0001$ to 0.0002) as evaluated during treatment with CINRYZE and treatment with Placebo. During treatment with C1INH, the mean change from baseline in functional C1INH after treatment ranged from 32 to 36.6 mg/dL. During treatment with Placebo the mean change was -2.4 to 5.4 mg/dL.

C1INH Functional Levels Efficacy Dataset

Time Point	Statistic	CINRYZE (N=22)		Placebo (N=22)	
		Observed Value	Change from Baseline	Observed Value	Change from Baseline
C11NH Functional (mg/dL)					
Visit 1: Pre-infusion	n	20	-	22	-
	Mean	33.9	-	31.7	-
	SD	17.21	-	21.54	-
	Median	34.5	-	32.5	-
	Range -	1/69	-	1/79	-
Visit 1: 60 minutes	n	22	20	22	22
	Mean	62.6	32.0	29.3	-2.4
	SD	20.89	18.95	24.42	9.41
	Median	68.0	29.5	25.0	-1.5
	Range	0/95	-11/72	0/78	-20/14
	p-value [a]	<0.0001			
Visit 8: Pre-infusion	n	21	20	22	22
	Mean	40.9	5.0	36.4	4.7
	SD	25.49	23.92	23.40	25.59
	Median	37.0	2.0	36.0	4.5
	Range	0/82	-38/40	1/80	-32/56
	p-value [a]	0.6542			
Visit 8: 60 minutes	n	21	20	22	22
	Mean	71.2	36.6	37.0	5.3
	SD	12.56	17.62	22.24	26.16

	Median	70.0	33.5	35.5	2.5
	Range	48/99	8/71	1/79	-35/49
	p-value [a]	<0.0001			
Visit 16: Pre-infusion	n	20	19	20	20
	Mean	39.2	6.6	36.4	3.7
	SD	21.57	18.74	24.06	23.78
	Median	42.0	11.0	39.5	4.0
	Range	2/75	-35/43	0/93	-72/43
	p-value [a]	0.6028			
Visit 16:60 minutes	n	20	19	20	20
	Mean	65.4	32.1	36.8	5.4
	SD	12.42	19.08	22.05	15.74
	Median	65.0	30.0	34.5	5.5
	Range	46/91	0/69	0/90	-20/44
	p-value [a]	<0.0001			
Visit 24: Pre-infusion	n	21	19	21	21
	Mean	38.2	1.5	31.6	-0.1
	SD	22.46	19.04	22.18	27.96
	Median	34.0	-2.0	30.0	-8.0
	Range	0/87	-25/51	0/82	-56/66
	p-value [a]	0.7156			
Visit 24: 60 minutes	n	21	19	19	19
	Mean	69.0	33.9	33.9	0.8
	SD	12.79	21.07	21.16	23.92
	Median	68.0	26.0	29.0	2.0
	Range	45/93	-1/73	0/81	-56/39
	p-value [a]	0.0002			

[a] vs. the change from Baseline during treatment with Placebo

8.1.1.2.1 Populations enrolled/analyzed

Disposition of Subjects

There were 26 subjects enrolled. There was 1 subject (Subject 55-001) who received open-label treatment but withdrew from the study prior to randomization. Thus, there were 25 subjects who received randomization codes. However, Subject 12-010 withdrew prior to receiving any study medication. Therefore, the Subject Disposition table (below) includes 24 randomized subjects who were treated with study medication.

There were 19 subjects who completed the study. However, Subject 06-018 completed Part B and was transferred to another site for participation in LEVP 2006-04 (open label use). This was recorded, in error, as a withdrawal from LEVP 2005-1/Part B. Thus, as summarized in the Subject Disposition table (below), there were 20 subjects who completed the study (CINRYZE/Placebo, 10 subjects, Placebo/CINRYZE, 10 subjects) and 4 subjects who discontinued. All of these withdrawals were due to withdrawn consent or Investigator decision. There were no withdrawals due to AEs.

Subject Disposition

Variable	CINRYZE/ Placebo	Placebo/ CINRYZE	Non randomized	Total
Total Enrolled	12	12	2	26
Randomized and Treated	12	12	-	24 [a]
Completed Study	10 (83.3)	10(83.3)	-	20 (83.3)
Withdrew from Study	2(16.7)	2(16.7)	-	4(16.7)
Reason for discontinuation			-	
Disease Progression/ Alternative Therapy	0	0	-	0
Investigator's Decision	1 (8.3)	0	-	1 (4.1)
Adverse Event	0	0	-	0
Protocol Non-compliance	0	0	-	0
Death	0	0	-	0
Lost to Follow-up	0	0	-	0
Subject withdrew consent	0	2(16.7)	-	2(8.3)
Other	1 (8.3) [b]	0	-	1 (4.1)

a. There was 1 subject randomized, but not treated
b. 2 subjects withdrew consent. However, Subject 06-018 completed all assessments in Part B and the was withdrawal was recorded in error. Subject 17-001 withdrew for unrelated medical conditions.

Randomization to Treatment Sequences

Variable	Treatment Sequence		Total (N=24) n (%)
	CINRYZE/Placebo (N=12) n (%)	Placebo/CINRYZE (N=12) n (%)	
Efficacy	11 (91.7)	11 (91.7)	22 (91.7)

Demographics Characteristics: Efficacy Dataset

		Treatment Sequence		
Variable	Statistic	CINRYZE/Placebo (N=11)	Placebo/CINRYZE	Total (N=22)
Age (years)	n	11	11	22
	Mean	41.7	34.5	38.1
	SD	19.27	14.76	17.16
	Median	40.0	35.0	38.5
	Range	14/73	9/64	9/73
Gender, n (%)	Male	2(18.2)	0	2(9.1)
	Female	9(81.8)	11 (100.0)	20 (90.9)
Ethnic Origin n (%)	White/Caucasian	10 (90.9)	11 (100.0)	21 (95.5)
	Black/African American	1 (9.1)	0	1 (4.5)
	Hispanic/Latino	0	0	0
	Asian	0	0	0
	Native Hawaiian or Pacific Islander	0	0	0
	American Indian or Alaska Native	0	0	0
	Other	0	0	0
Weight (kg)	n	9	9	18
	Mean	70.48	76.34	73.41
	SID	9.246	25.647	18.944
	Median	70.50	64.30	69.25
	Range	58.1/87.1.	37.6/113.9	37.6/113.9
Height (cm)	n	9	9	18
	Mean	166.17	163.17	164.67
	SD	6.892	8.722	7.780
	Median	165.10	160.00	165.10
	Range	152.4/177.8	149.0/175.3	149.0/177.8

8.1.1.2.2 Efficacy endpoints/outcomes

Number of Angioedema Attacks

	Statistic	CINRYZE (N=22)	Placebo (N=22)
Number of attacks	Mean	6.1	12.7
	SD	5.43	4.80
	Median	6.0	13.5
	Min	0	6
	Max	17	22
GEE Analysis Results			
Treatment Effect p-value		<.0001	
Sequence Effect p-value		0.3347	
Period Effect p-value		0.3494	

The mean (±SD) severity of attacks was 1.3 (±0.85) during treatment with CINRYZE and 1.9 (±0.35) during treatment with Placebo. The difference in the severity of attacks during treatment with CINRYZE and treatment with Placebo was statistically significant (p=0.0008).

Severity of Attacks

Severity Statistic	**CINRYZE (N=22)**	**Placebo (N=22)**	**p-value**
Mean	1.3	1.9	**0.0008**
SD	0.85	0.35	
Median	1.3	1.9	
Min	0	1	
Max	3	3	

The mean (±SD) duration of attacks was 2.1 days (±1.13 days) during treatment with CINRYZE and 3.4 days (±1.39 days) during treatment with Placebo. The difference in the duration of attacks during treatment with CINRYZE and during treatment with Placebo was statistically significant (p=0.0004).

Average Duration of Attacks

Days Statistic	CINRYZE (N=22)	Placebo (N=22)	p-value
Mean	2.1	3.4	0.0004
SD	1.13	1.39	
Median	2.5	3.1	
Min	0	2	
Max	4	8	

The mean number (±SD) of open-label rescue C l INH infusions required during attacks was 4.7 (±8.66 infusions) during treatment with CI1NH and 15.4 (±8.41 infusions) during treatment with Placebo. The difference in the number of open-label infusions during treatment with CINRYZE and treatment with Placebo was statistically significant (p<0.0001).

Number of Open-label Infusions: Efficacy Dataset

Statistic	CINRYZE (N=22)	Placebo (N=22)	p-value
Mean	4.7	15.4	<0.0001
SD	8.66	8.41	
Median	0.5	13.5	
Min	0	2	
Max	36	34	

The mean (±SD) total number of days of swelling was 10.1 days (110.73 days) during treatment with CINRYZE and 29.6 days (±16.9 days) during treatment with Placebo. The difference in the total days of swelling during treatment with CINRYZE and treatment with Placebo was statistically significant (p<0.0001).

Total Days of Swelling

Days Statistic	CINRYZE (N=22)	Placebo (N=22)	p-value
Mean	10.1	29.6	<0.0001
SD	10.73	16.90	
Median	6.5	26.5	
Min	0	8	
Max	38	67	

C1INH Levels (functional)
Pre-infusion, the mean values of ClINH functional activity were similar prior to treatment with CINRYZE (33.9 mg/dL) and prior to treatment with Placebo (31.7 mg/dL).

There was a statistically significant difference in the changes ClINH functional levels from baseline analysis in mean values at 60 post-infusion on Visits 1, 8, 16, and 24 ($p \leq 0.0001$ to 0.0002) as evaluated during treatment with CINRYZE and treatment with Placebo. During treatment with C1INH, the mean change from baseline in functional C1INH after treatment ranged from 32 to 36.6 mg/dL. During treatment with Placebo the mean change was -2.4 to 5.4 mg/dL.

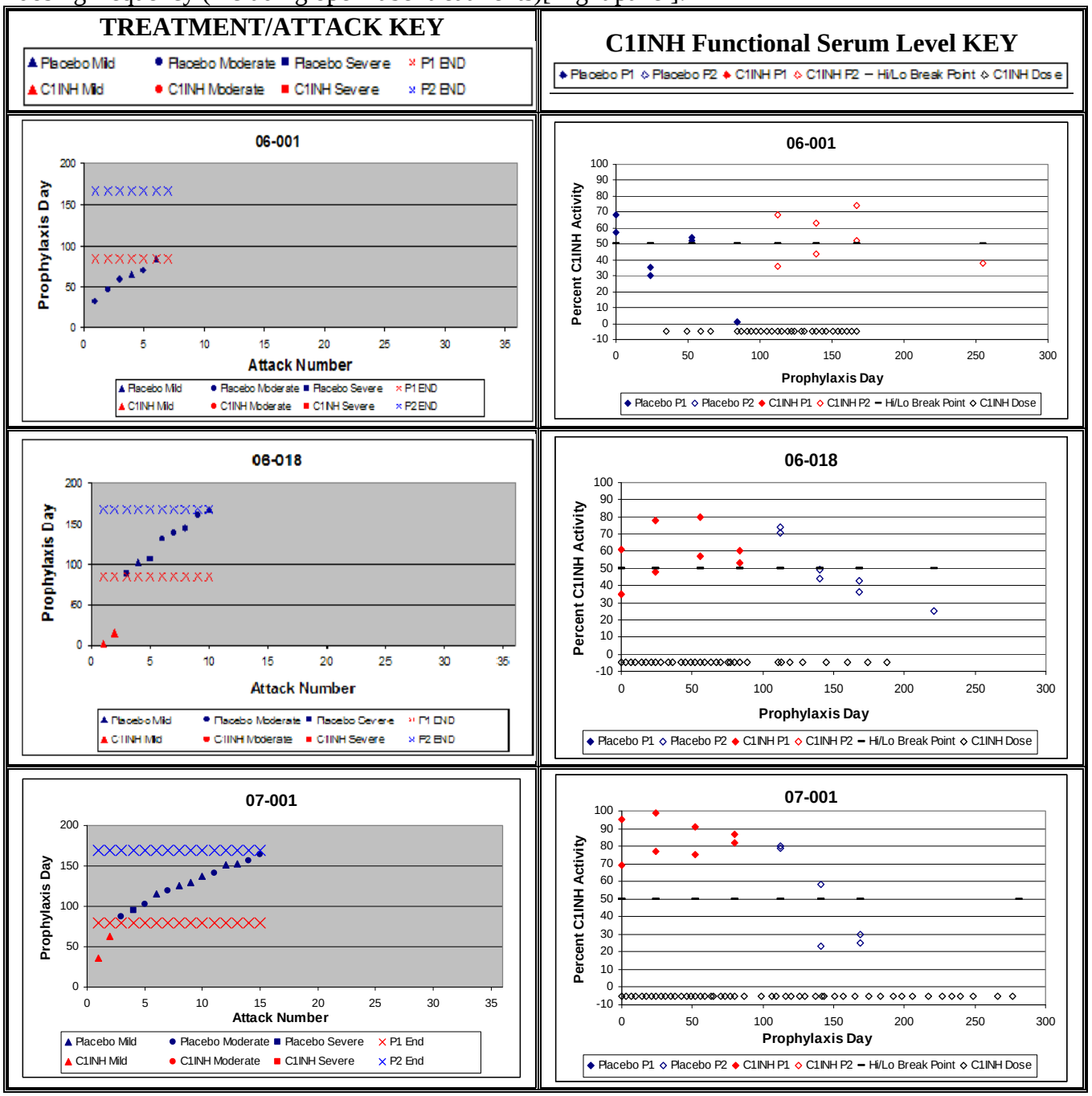
C1INH Functional Levels Efficacy Dataset

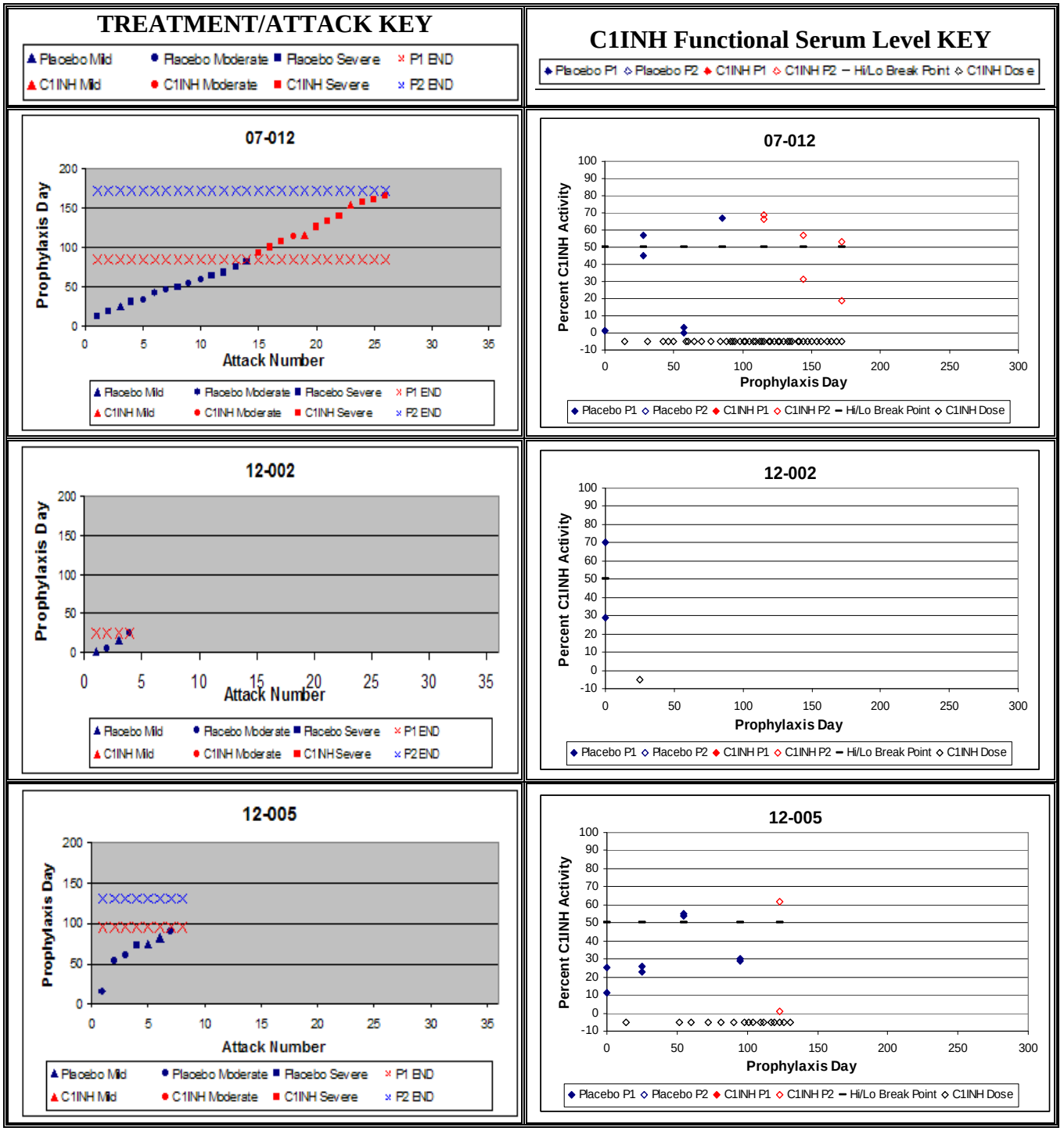
Time Point	Statistic	CINRYZE (N=22)		Placebo (N=22)	
		Observed Value	Change from Baseline	Observed Value	Change from Baseline
C11NH Functional (mg/dL)					
Visit 1: Pre-infusion	n	20	-	22	-
	Mean	33.9	-	31.7	-
	SD	17.21	-	21.54	-
	Median	34.5	-	32.5	-
	Range -	1/69	-	1/79	-
Visit 1: 60 minutes	n	22	20	22	22
	Mean	62.6	32.0	29.3	-2.4
	SD	20.89	18.95	24.42	9.41
	Median	68.0	29.5	25.0	-1.5
	Range	0/95	-11/72	0/78	-20/14
	p-value [a]	<0.0001			
Visit 8: Pre-infusion	n	21	20	22	22
	Mean	40.9	5.0	36.4	4.7
	SD	25.49	23.92	23.40	25.59
	Median	37.0	2.0	36.0	4.5
	Range	0/82	-38/40	1/80	-32/56
	p-value [a]	0.6542			
Visit 8: 60 minutes	n	21	20	22	22
	Mean	71.2	36.6	37.0	5.3
	SD	12.56	17.62	22.24	26.16
	Median	70.0	33.5	35.5	2.5
	Range	48/99	8/71	1/79	-35/49

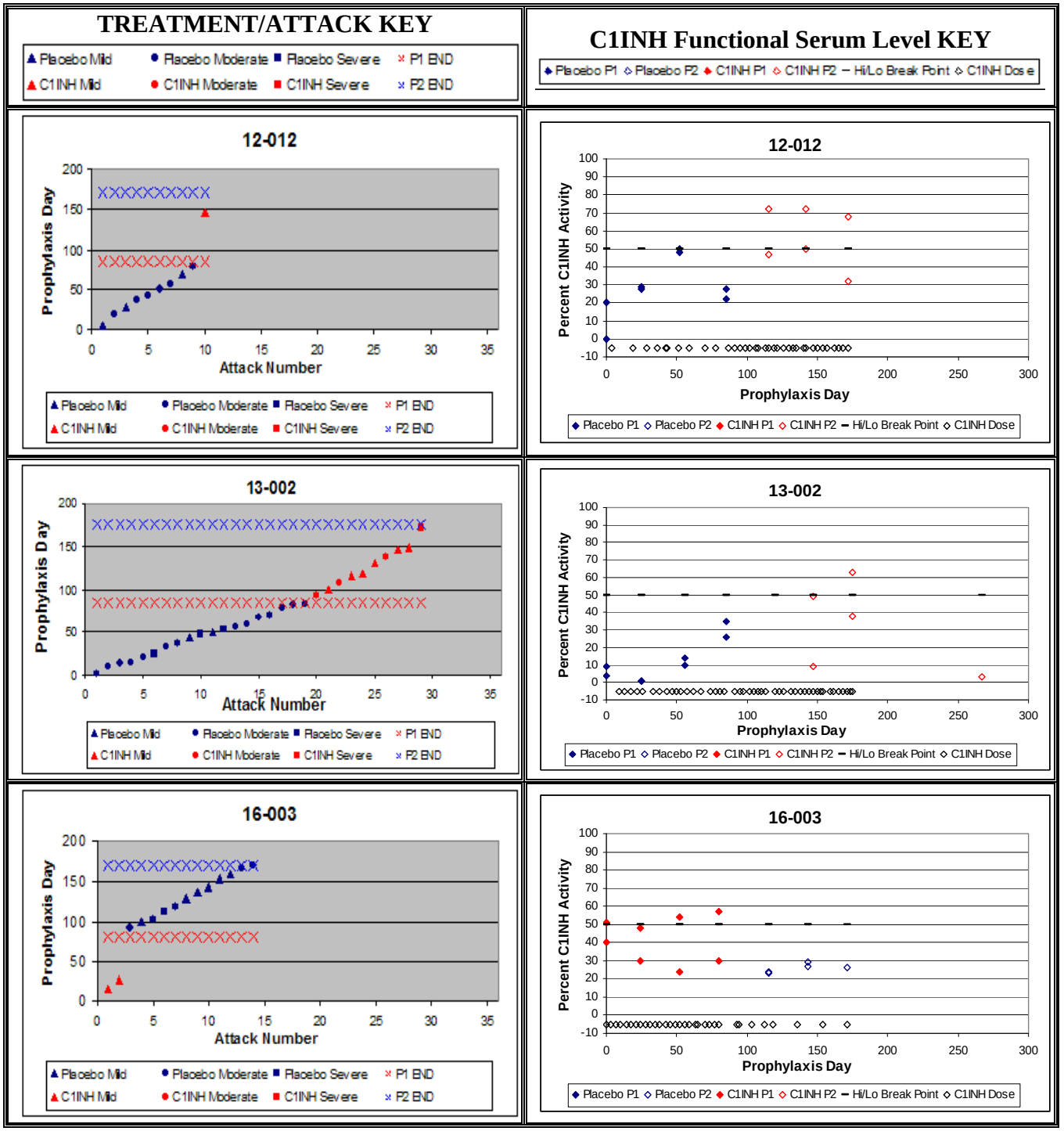
	p-value [a]	<0.0001			
Visit 16: Pre-infusion	n	20	19	20	20
	Mean	39.2	6.6	36.4	3.7
	SD	21.57	18.74	24.06	23.78
	Median	42.0	11.0	39.5	4.0
	Range	2/75	-35/43	0/93	-72/43
	p-value [a]	0.6028			
Visit 16:60 minutes	n	20	19	20	20
	Mean	65.4	32.1	36.8	5.4
	SD	12.42	19.08	22.05	15.74
	Median	65.0	30.0	34.5	5.5
	Range	46/91	0/69	0/90	-20/44
	p-value [a]	<0.0001			
Visit 24: Pre-infusion	n	21	19	21	21
	Mean	38.2	1.5	31.6	-0.1
	SD	22.46	19.04	22.18	27.96
	Median	34.0	-2.0	30.0	-8.0
	Range	0/87	-25/51	0/82	-56/66
	p-value [a]	0.7156			
Visit 24: 60 minutes	n	21	19	19	19
	Mean	69.0	33.9	33.9	0.8
	SD	12.79	21.07	21.16	23.92
	Median	68.0	26.0	29.0	2.0
	Range	45/93	-1/73	0/81	-56/39
	p-value [a]	0.0002			

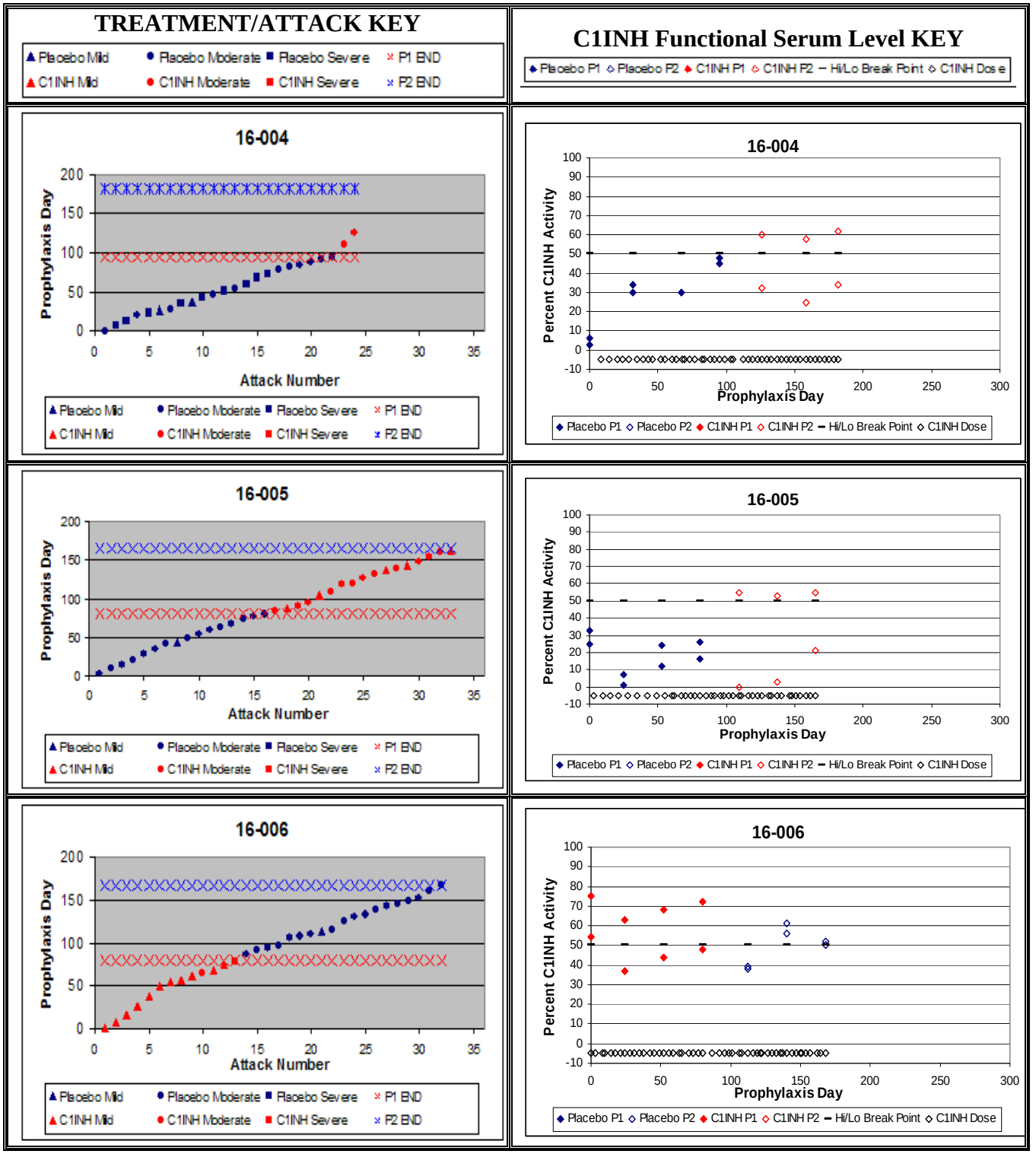
[a] vs. the change from Baseline during treatment with Placebo

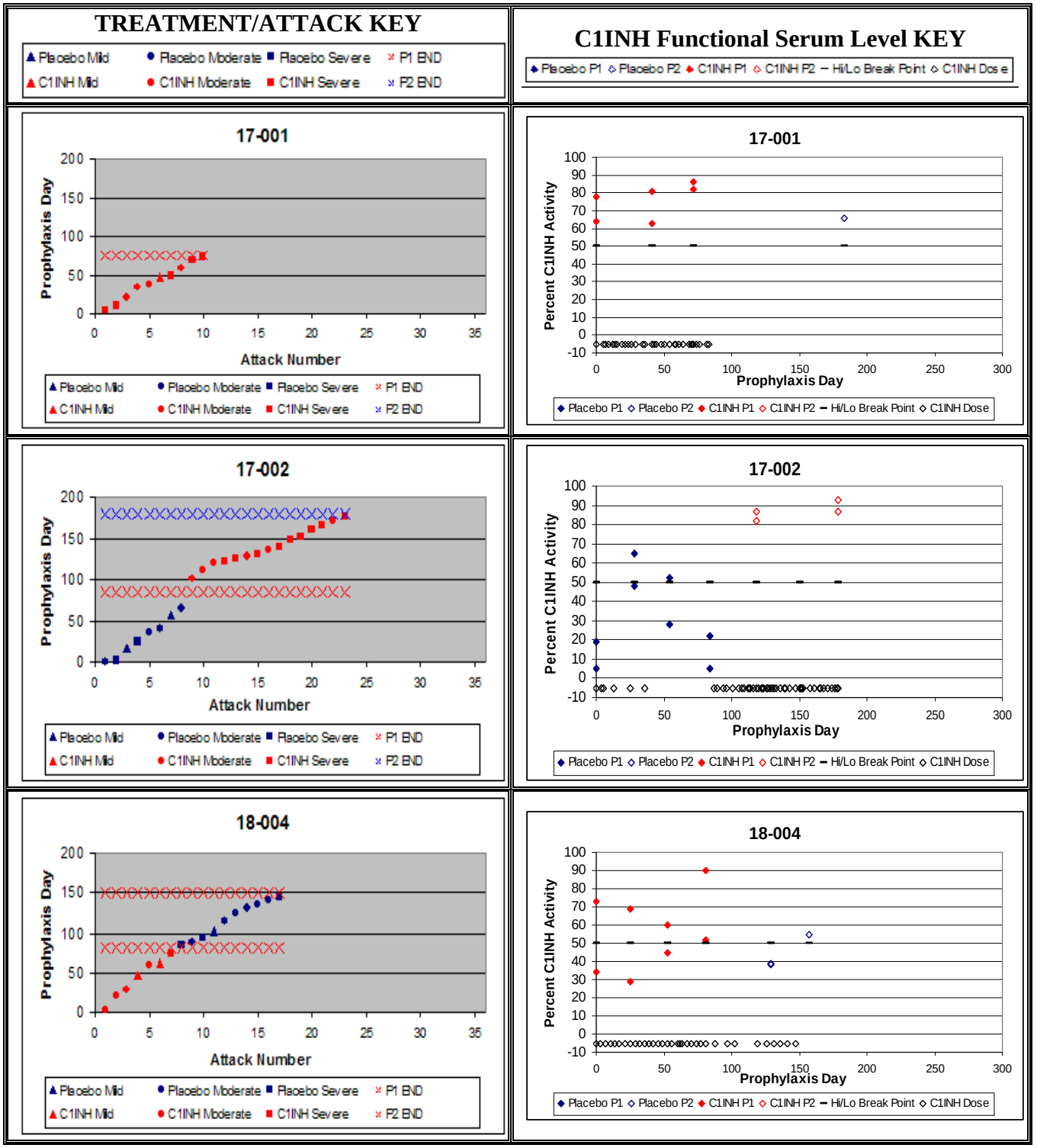
The following pages show the results of Part B for attack frequency [Left panel], severity of attack [Left Panel], functional serum C1INH level observed [Right panel], and C1INH dosing frequency (including open label treatments)[Right panel]:

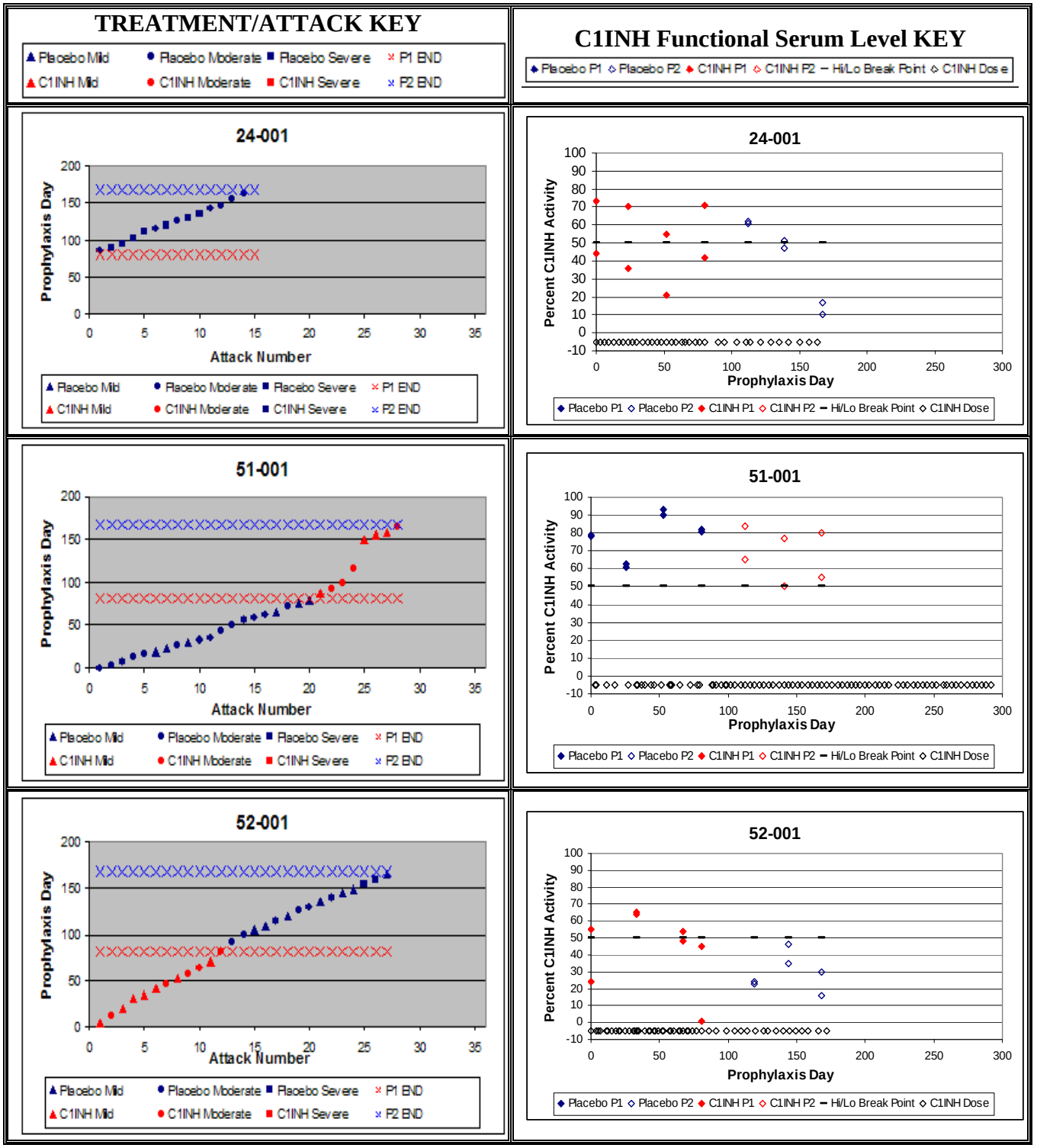


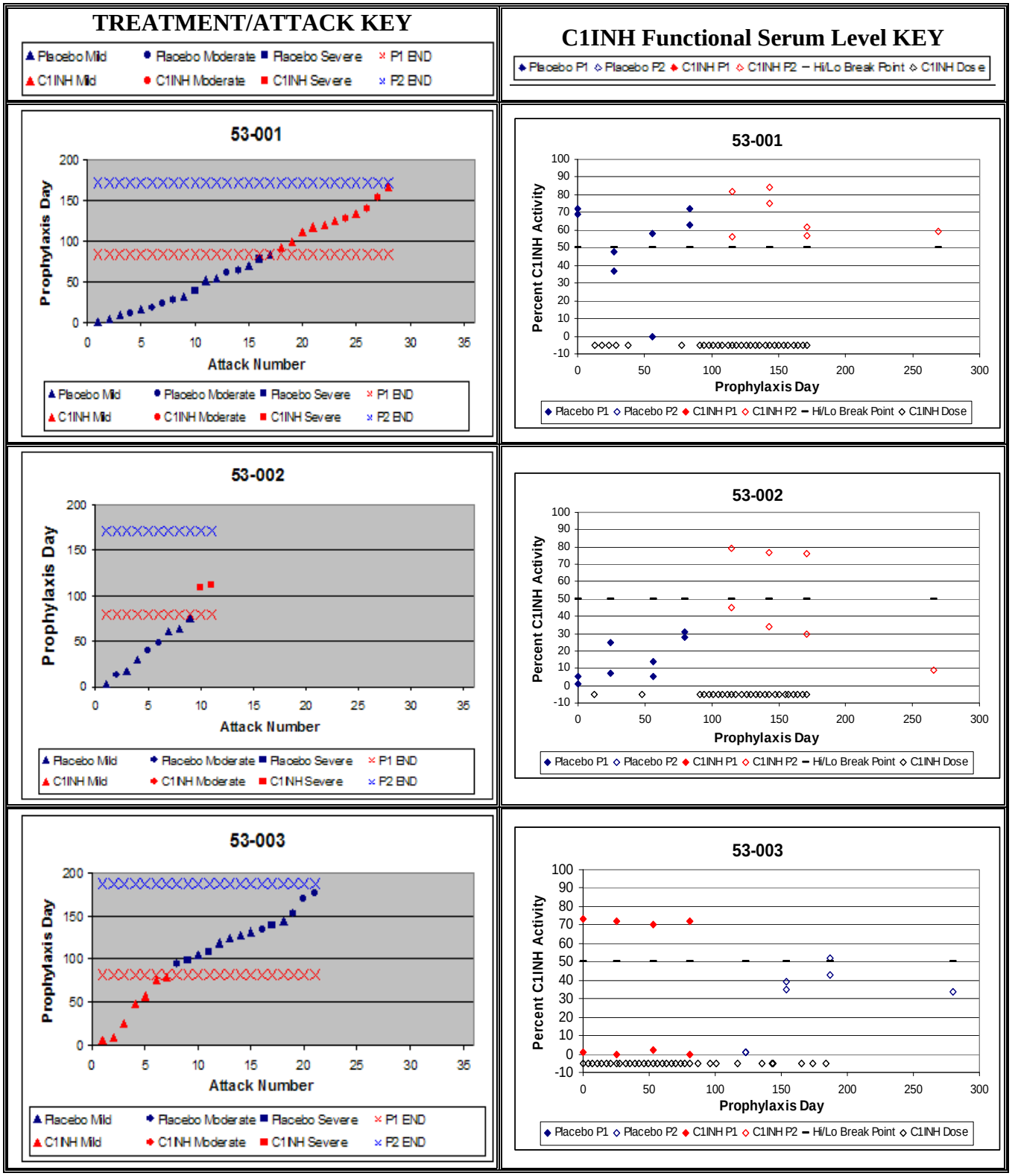

TREATMENT/ATTACK KEY
Placebo Mild
Placebo Moderate
Placebo Severe
P1 END
C1INH Mild
C1INH Moderate
C1INH Severe
P2 END
C1INH Functional Serum Level KEY
Placebo P1
Placebo P2
C1INH P1
C1INH P2
Hi/Lo Break Point
C1INH Dose
07-012
Prophylaxis Day
Attack Number
Percent C1INH Activity
Prophylaxis Day
12-002
12-005

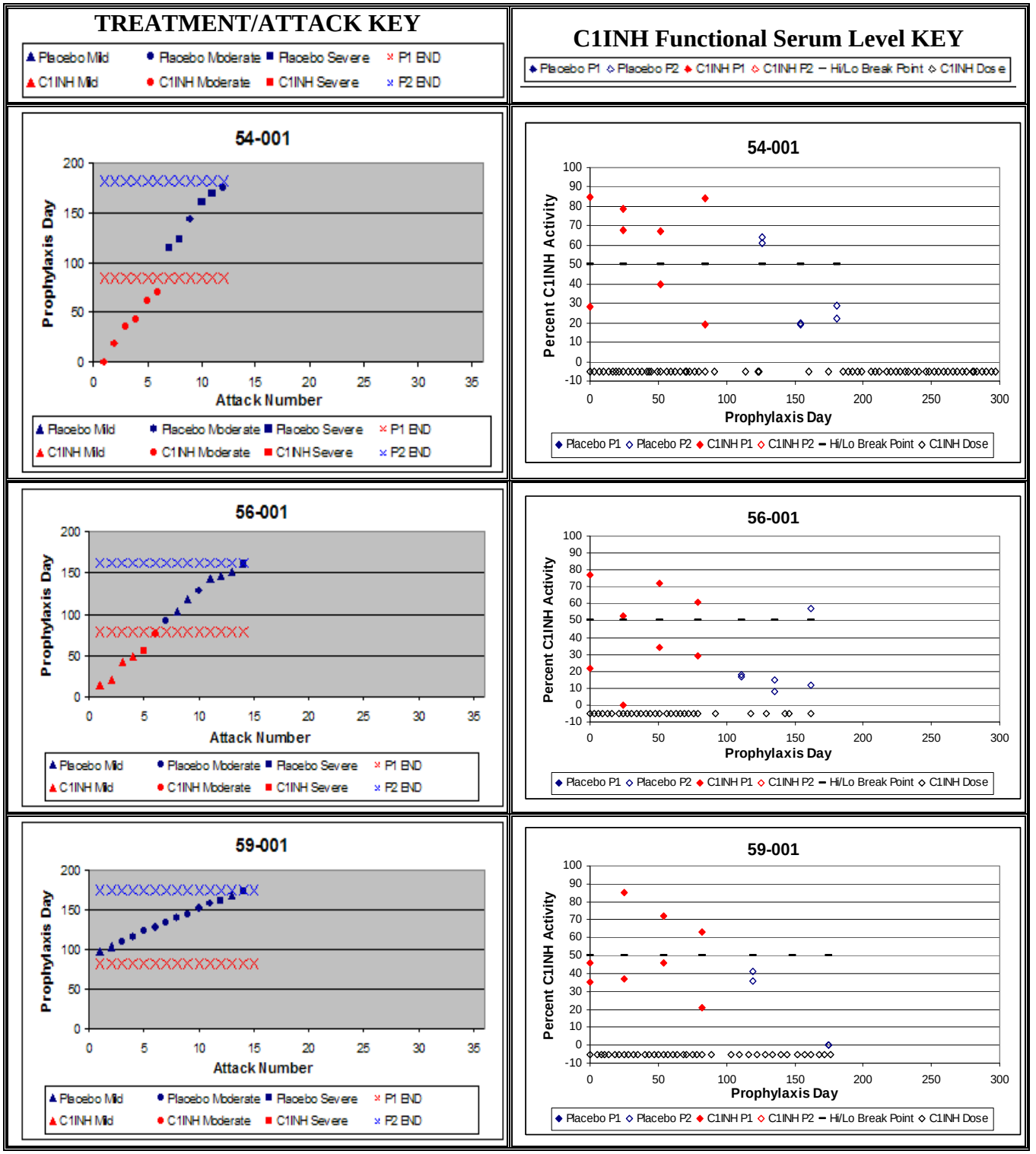

TREATMENT/ATTACK KEY
Placebo Mild
Placebo Moderate
Placebo Severe
P1 END
C1INH Mild
C1INH Moderate
C1INH Severe
P2 END
C1INH Functional Serum Level KEY
Placebo P1
Placebo P2
C1INH P1
C1INH P2
Hi/Lo Break Point
C1INH Dose
12-012
Prophylaxis Day
Attack Number
Percent C1INH Activity
Prophylaxis Day
13-002
Prophylaxis Day
Attack Number
Percent C1INH Activity
Prophylaxis Day
16-003
Prophylaxis Day
Attack Number
Percent C1INH Activity
Prophylaxis Day


TREATMENT/ATTACK KEY
Placebo Mild
Placebo Moderate
Placebo Severe
P1 END
C1INH Mild
C1INH Moderate
C1INH Severe
P2 END
C1INH Functional Serum Level KEY
Placebo P1
Placebo P2
C1INH P1
C1INH P2
Hi/Lo Break Point
C1INH Dose
16-004
Prophylaxis Day
Attack Number
Percent C1INH Activity
Prophylaxis Day
16-005
Prophylaxis Day
Attack Number
Percent C1INH Activity
Prophylaxis Day
16-006
Prophylaxis Day
Attack Number
Percent C1INH Activity
Prophylaxis Day


TREATMENT/ATTACK KEY
Placebo Mild
Placebo Moderate
Placebo Severe
P1 END
C1INH Mild
C1INH Moderate
C1INH Severe
P2 END
C1INH Functional Serum Level KEY
Placebo P1
Placebo P2
C1INH P1
C1INH P2
Hi/Lo Break Point
C1INH Dose
17-001
Prophylaxis Day
Attack Number
Percent C1INH Activity
Prophylaxis Day
17-002
Prophylaxis Day
Attack Number
Percent C1INH Activity
Prophylaxis Day
18-004
Prophylaxis Day
Attack Number
Percent C1INH Activity
Prophylaxis Day


TREATMENT/ATTACK KEY
Placebo Mild
Placebo Moderate
Placebo Severe
P1 END
C1INH Mild
C1INH Moderate
C1INH Severe
P2 END
C1INH Functional Serum Level KEY
Placebo P1
Placebo P2
C1INH P1
C1INH P2
Hi/Lo Break Point
C1INH Dose
24-001
Prophylaxis Day
Attack Number
Percent C1INH Activity
Prophylaxis Day
51-001
Prophylaxis Day
Attack Number
Percent C1INH Activity
Prophylaxis Day
52-001
Prophylaxis Day
Attack Number
Percent C1INH Activity
Prophylaxis Day


TREATMENT/ATTACK KEY
Placebo Mild
Placebo Moderate
Placebo Severe
P1 END
C1INH Mild
C1INH Moderate
C1INH Severe
P2 END
C1INH Functional Serum Level KEY
Placebo P1
Placebo P2
C1INH P1
C1INH P2
Hi/Lo Break Point
C1INH Dose
53-001
Prophylaxis Day
Attack Number
Percent C1INH Activity
Prophylaxis Day
53-002
Prophylaxis Day
Attack Number
Percent C1INH Activity
Prophylaxis Day
53-003
Prophylaxis Day
Attack Number
Percent C1INH Activity
Prophylaxis Day


TREATMENT/ATTACK KEY
Placebo Mild
Placebo Moderate
Placebo Severe
P1 END
C1INH Mild
C1INH Moderate
C1INH Severe
P2 END
C1INH Functional Serum Level KEY
Placebo P1
Placebo P2
C1INH P1
C1INH P2
Hi/Lo Break Point
C1INH Dose
54-001
Prophylaxis Day
Attack Number
Percent C1INH Activity
Prophylaxis Day
56-001
59-001

The following table shows the results for Part B – prophylaxis of HAE attacks:

Subject	Attacks on C1INH	C1INH Period Length (Days)	C1INH Attack Frequency (Attacks/Day	Attacks on Placebo	Placebo Period Length (Days)	Placebo Attack Frequency (Attacks/Day	Percent Reduction in Number of Attacks	Percent Reduction in Attack Frequency
06-001	0	81	0	6	85	0.07059	100%	100.0%
12-005	0	34	0	7	96	0.07292	100%	100.0%
24-001	0	81	0	14	82	0.17073	100%	100.0%
59-001	0	83	0	14	80	0.175	100%	100.0%
16-004	2	84	0.02381	22	96	0.22917	91%	89.6%
12-012	1	82	0.0122	9	86	0.10465	89%	88.3%
07-001	2	81	0.02469	13	83	0.15663	85%	84.2%
16-003	2	81	0.02469	12	85	0.14118	83%	82.5%
53-002	2	81	0.02469	9	81	0.11111	78%	77.8%
06-018	2	85	0.02353	8	82	0.09756	75%	75.9%
51-001	8	81	0.09877	20	82	0.2439	60%	59.5%
13-002	10	85	0.11765	19	86	0.22093	47%	46.7%
53-003	7	82	0.08537	14	93	0.15054	50%	43.3%
18-004	7	82	0.08537	10	67	0.14925	30%	42.8%
53-001	11	81	0.1358	17	85	0.2	35%	32.1%
16-006	13	81	0.16049	19	82	0.23171	32%	30.7%
56-001	6	80	0.075	8	80	0.1	25%	25.0%
52-001	12	82	0.14634	15	81	0.18519	20%	21.0%
07-012	12	82	0.14634	14	86	0.16279	14%	10.1%
54-001	6	85	0.07059	6	84	0.07143	0%	1.2%
16-005	17	81	0.20988	16	82	0.19512	-6%	-7.6%
17-002	15	86	0.17442	8	85	0.09412	-88%	-85.3%

Summary Statistics on Number of HAE Attacks in LEVP2005-1/B

	Statistic	CINRYZE N=22	Placebo N=22
Number of Attacks	Mean	6.1	12.7
	SD	5.4	4.8
	Median	6	13.5
	Min	0	6
	Max	17	22
GEE Analysis Results			
Effect Assessed		**p-value**	
Treatment Effect		<0.0001	
Sequence Effect		0.3347	
Period Effect		0.3494	
p-value is based on a test of the null hypothesis of no difference in attack frequency between prophylaxis periods. It was calculated using the Generalized Estimating Equation (GEE) method applied to Poisson distribution.			

Non-linearity of the Functional C1INH Assay (Module 2, Volume 1.1, section 2.7.1.5.3)**.**
Interpretation of the functional C1INH data presented in the above charts of the Part B results must take into account the poor operational characteristics of the assay used to produce these data. The assay used is the "--(b)(4)-- C1-Inhibitor Enzyme Immunoassay for the quantification of functional C1-Inhibitor protein (a protease inhibitor) in human serum or plasma by ---------(b)(4)----------." The assay is performed through the following steps:

1. ----------(b)(4)----------.
2. ----------(b)(4)----------.
3. ----------(b)(4)----------.
4. ----------(b)(4)----------.

The following chart shows validation data produced by the sponsor for this assay:

----------(b)(4)----------

It can be seen that there is good agreement across test samples for the amount of decrease in optical density from the undiluted samples at each dilution. However, the amount of decrease in optical density for the test samples is much less than theoretically predicted for an ideally linear assay, and also less than the results obtained by using the kit-supplied standards (each standard used undiluted and reported at the labeled concentration).

The effect of the non-linearity of the functional C1INH assay is 1) to cause higher (i.e. normal) levels of serum C1INH to appear similar in value, and 2) to decrease the apparent size of the increase from pre-dose to post-dose serum C1INH levels. The sponsor states this in the following way:

> "The results demonstrate that **this functional assay is non-linear across the entire dynamic range** but linearity is evident for results in the deficient range (<68%)."
>
> ***Reviewer's comment:*** *If the assay that is used to assign product potency has similar limitations, there may be potential problems in lot-to-lot consistency for potency.*

Product Batch Analysis by Subject for Part B -- Prophylaxis

Summary of Results by Subject for Part B – Prophylaxis

Subject	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R
06-001	X		X	X		X		X										
06-018			X	X		X		X										
07-001	X	X	X		X	X	X											
12-012							X	X	X	X			X	X			X	X
16-003								X	X	X	X							
16-004										X		X	X	X	X			
24-001							X		X	X		X	X		X			
53-002				X		X	X											
59-001										X	X		X	X			X	
07-012							X	X	X			X	X		X	X		
13-002			X					X	X	X	X	X						
16-005										X	X	X	X	X	X			
16-006								X	X	X	X							
17-002								X	X		X	X	X	X				
18-004										X		X	X					
52-001				X			X	X	X	X	X		X					
53-001				X		X	X											
54-001			X		X	X												
56-001										X		X	X					
12-002								X										
12-005							X	X	X				X	X			X	
17-001								X	X	X	X							
51-001			X	X	X	X												
53-003				X		X	X	X										

Batch Code	
A	04L15L370A
B	04L15L370B
C	05109L370A
D	05109L370B
E	05E18L370A
F	05F01L370A
G	05J06L370A
H	05K07L370A
I	05L16L370A
J	06A30L370A
K	06C02L370A
L	06E09L370A
M	06J19L370A
N	06J25L370A
O	07A29L370A
P	07B21L370A
Q	07C02L370A
R	07C08L370A

Complete Response Letter Item 22 for LEVP2005-1/B:

A complete response letter was issued January 30, 2008, for CMC and facility items, items relating to clinical trial LEVP2005-1/A (clinical trial and indication for ---(b)(4)----------withdrawn on October 3, 2008). The results of LEVP2005-1/B were unexpectedly non-uniform across all subjects; some subjects experienced complete elimination of HAE attacks, while others experienced very modest reduction in HAE attack frequency, or even an increase in HAE attack frequency.

The sponsor declined to conduct any phase 2 studies that could be informative for the plan for statistical analysis. As a result, the sponsor submitted and FDA accepted a statistical analysis plan that included a null hypothesis of no difference in HAE attack frequency, rather than a plan that specified an estimate of the expected reduction in HAE attack frequency, or one that would classify individual subject outcomes as success or failure. Given the spectrum of outcomes, the following items were included for LEVP2005-1/B in the January 30, 2008, complete response letter:

Part B – Prophylaxis of HAE Attacks

22. At the June 19, 2004, pre-IND meeting for BB-IND ---(b)(4)--, you asked FDA the following question:

    Question 5) Does FDA agree that the primary endpoint for Part B, the number of attacks of angioedema during each treatment phase, comparing each subject to himself/herself, is appropriate?

    The statistical analysis plan in the original protocol for BB-IND --(b)(4)---contains similar language about using each subject as his/her own control, as does the final analysis plan for Part B.

    Despite these questions and statements, you did not perform an analysis which uses each subject as his/her own control, rather you pooled HAE attack frequency data across subjects and compared treatment arms.

    An analysis that used each subject as his/her own control would classify outcomes for individual subjects (success, failure). If you had taken your intended approach, you would have seen that approximately half the subjects in Part B could be classified as "success" and half the subjects as "failure". A bimodal outcome such as this would not necessarily mean that the study had failed; it could mean that the product was effective in some subset of subjects that would remain to be defined.

    We note that pooling the results across all subjects and reporting that there is an approximately 50% reduction in the frequency of HAE attacks misrepresents the expected outcomes for both groups, i.e. those in the "success" category and those in the "failure" category.

> We recommend that you re-analyze the results of Part B according to your original intention to use each subject as his/her own control, and submit the analysis to STN 125267/0.
>
> We note that an additional study designed to further define responding groups of subjects under appropriate dose schedules for prophylaxis may be required. Phase 2 studies, as proposed by FDA, may have resolved this.

Sponsor's Response to Item 22 of the January 30, 2008, CR Letter:

Item 22. Part B – Prophylaxis of HAE Attacks

The basis of the question in this item is a misunderstanding of the intended analysis and how each subject can be used as his/her own control. Apparently the FDA understood this as the intent to use a responder analysis, while Lev intended an analysis of a crossover design trial in which every subject was observed during a period of drug treatment and one of placebo. The primary analysis used by Lev was a component of the protocol and prospectively defined. In response to FDA's question, we are presenting both analyses.

The prospective protocol-defined primary analysis for Part B shows clinical and statistical significance using each subject as his/her own control. The statistical analysis performed for Part B is supported by the language in the protocol, responses to FDA during the IND phase, and the pre-defined statistical analysis plan. The results of the study based on this prospective protocol-defined analysis are highly statistically significant, and the results from the study show a meaningful clinical benefit from CINRYZE administration for nearly all subjects in the study.

FDA has requested that Lev perform additional retrospective analyses on these data on a subject-by-subject basis. The results of these subject-by-subject analyses support the outcome of the primary analysis and are provided below. However, we disagree with the FDA's suggestion that classification of a subject as a "failure" using a single measurement of success, such as reduction of HAE attacks as defined in this study, means that the product was not clinically effective in that subject.

Protocol-Defined Statistical Analysis

Section 4.7.3 of the study protocol describes the anticipated analysis as the number of attacks "during each treatment phase" and explains each subject will be used as his/her own control:

> The primary endpoint for Part B will be the number of attacks of angioedema during each treatment phase, using each subject as his/her own control, thereby controlling the variability. This will enable us to attribute *the difference in the number of attacks of angioedema between*

> *the treatment groups* entirely to the treatment. Assuming angioedema attack rates will be 1 every two weeks in the placebo phase and 1 per 12 weeks in the prophylactic CINRYZE phase, 10 subjects per arm provides more than 90% power to detect the treatment effect. The analysis will be based on a Poisson assumption; a test for extra-Poisson variation will make use of generalized linear interactive modeling (GLIM). Should there be evidence of such variation, a GLIM model with a term that incorporates such variation will be used to make treatment comparisons. (emphasis added)

The language here clearly refers to the number of attacks by treatment group, not individual subject. Because this study was a cross-over design, each subject was his/her own control by definition. There was no intent to use a responder analysis.

In a response to an FDA question regarding the simulation analysis for Part B dated 17 Feb 2006, the power calculations were based on our intended primary endpoint and clearly describe using the mean number of attacks:

A simulation was performed using SAS, and repeated 10,000 times. For each simulation, data for a given sample size of 3 subjects was produced. Data for each subject include a simulated count of attacks for each of two treatment periods (as per crossover design). Simulation of attacks were based on a Poisson distribution with mean 6 (treatment group 1) and mean 1 (treatment group 2). Using Proc Genmod, with options "dist=poisson" and "link=log", and factors of subject ID and treatment group, the p-value for treatment group (based on the Chi-squared test) was assessedas being significant ($p<0.05$) or non-significant ($p\geq 0.05$). On repeating the simulation 10,000 times, the probability (and hence power) of obtaining statistical significance was found to be >90%.

Additionally, an exploratory simulation was done to evaluate the sensitivity of the above simulation to variations in the input parameters. This exploratory analysis was resampled 100 times at each of a variety of input assumptions. These assumptions include simulated sample sizes of 4, 8, 12, 18, and 24, and placebo mean of 1, 2, 3, 4, 5, and 6. Table 1 [not included here] summarizes the findings from this analysis. This exploratory analysis confirmed that a sample size of 3 is sufficient to achieve 90% or better power, given the assumptions mentioned above. A sample size of 24 maintained sufficient power, 80% or better, in the event the observed difference between observed means, treatment effect, is less than assumed.

The final SAP outlines the intended analysis:

For cross-over analyses, a standard analysis of variance for cross-over study design will be performed with effects for treatment, period, and subject within

treatment.

The primary efficacy endpoint for Part B will be the number of attacks of angioedema during each treatment period, normalized for the number of days the subject participated in that period. This will be done by dividing the total number of attacks in each period by the number of days the subject was in that period. An attack is defined as the subject reported indication of swelling at any location following a report of no swelling on the previous day. The crossover analysis will be based on a Poisson assumption and use the GEE method as implemented in the SAS statistical procedure PROC GENMOD. 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 will be used to check for over dispersion. If the Deviance/df and Pearson/df ratios are greater than 1, then there is evidence of over dispersion. In such situation, the GEE approach is able to address the over dispersion issue since it is robust to the misspecification of the covariance structure, and misspecification is occurring in the case of over dispersion.

The results of the protocol-defined primary analysis are presented in Table 22(a) and show a highly statistically significant outcome:

Table 22(a) Number of Angioedema Attacks

		Statistic	**CINRYZE (N=22)**	**Placebo (N=22)**
Number of Attacks		**Mean**	6.1	12.7
		SD	5.43	4.80
		Median	6.0	13.5
		Min	0	6
		Max	17	22
GEE Analysis Results				
Treatment Effect p-value		<0.0001		

FDA has requested that Lev re-analyze the results of Part B using each subject as his/her own control, and provides language suggesting an evaluation of outcomes for individual subjects and then classifying each as a success or failure. However, this request presupposes that using each subject as his/her own control leads to only one type of analysis (classifying subjects as “success” or “failure”) and also assumes items that are not predefined (i.e., the definition of “success” or “failure”). The protocol-defined analysis was developed to provide a simple, objective clinical endpoint to demonstrate the ability of CINRYZE to reduce the number of HAE attacks, and therefore show an objective outcome on the manifestation of the disease. It was not designed to be a responder analysis, or to make a medical determination by subject as to whether or not treatment with CINRYZE was a success or failure for them. HAE is a complicated disease

which is highly variable between subjects as well as within each individual subject. The primary endpoint, "the number of HAE attacks," does not take into account the length or severity of the attack, just the simple fact of whether or not an attack occurred. We believe that the determination of whether or not there is a clinical benefit for any individual HAE subject is a medical determination that a physician will need to make based on the total reduction in the manifestation of the disease including the reduction in the frequency of attacks, as well as the reduction in the severity and length of any breakthrough attacks.

[At this point in the response, the sponsor presents the reduction in HAE attack frequency by tables and bar charts.]

Alternative Statistical Analyses

One alternative method of analyzing the data by using each subject as his/her own control would be to use the results from Table 22(b) to test the null hypothesis that the proportion of subjects having fewer attacks while on CINRYZE is equal to the proportion with fewer attacks while on placebo. An exact two-sided 95% confidence interval on this proportion is 70.8% to 98.9%. Since the lower bound exceeds 50%, this null hypothesis would be rejected in favor of the hypothesis that the proportion of subjects having fewer attacks while on CINRYZE is greater than the proportion with fewer attacks while on placebo. Thus, the data analyzed in this manner would be seen as supporting the prophylactic use of CINRYZE to reduce the number of HAE attacks using each subject as his/her own control.

A second alternative of analyzing the data would be to classify each subject as a "success" or "failure" based on pre-defined criteria, as FDA seems to be suggesting in Item 22. As described above, this method is more subjective due to the variable nature of the disease and the factors that would need to be considered to make a determination of whether or not a subject would be classified as a failure.

Because no definition of a "success" or "failure" was defined prospectively, the resulting outcome(s) is based on the specific definition. For example, if a "success" is defined as a simple reduction in the number of HAE attacks of at least 25% from placebo, then the response rate is 17/22 (77.3%), if the definition is 40% the response rate is 14/22 (63.6%), and if the definition is 50% the response rate is 11/22 (50.0%). All of these results are supportive of the results based on the protocol-defined primary endpoint.

However, use of any of the above definitions of success relating to the primary endpoint of the study (i.e. reduction in the number of HAE attacks) does not take into account other serious sequelae of the disease which have not been defined, and should not be confused with a medical determination of whether or not the subject received a clinical benefit from the drug. Using the most liberal definition of success from the above discussion (a 25% reduction from placebo), five of the subjects would be classified as "failures" in the study. However, a "failure" under

these terms does not mean that the subject did not receive a clinical benefit from CINRYZE administration; it only means that in the simple analysis of a gross reduction in the number of attacks, the subject did not meet some arbitrarily defined endpoint.

For example, subject 54-001, located third from the bottom in table 22(b) with a response rate of 1.2% decrease in HAE attacks, is considered a "failure" under any of the above definitions. However as can be seen from Table 22(c) which provides a summary of all the measurements of efficacy, 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 outcomes could be classified as a "success" on its own, and when taken together provide a significant change in disease manifestation for this subject. At the specific request of the treating physician, this subject was subsequently enrolled in the CHANGE 3 open label prophylaxis study as soon as it was available and continues her participation to this day.

Table 22(c) Summary of all Efficacy Outcomes

Subject	Attacks/Day[a]	Attack Severity[b]	Attack Duration[c]	Days of Swelling[d]
6001	-100	-100	-100	-100
12005	-100	-100	-100	-100
24001	-100	-100	-100	-100
59001	-100	-100	-100	-100
16004	-89.6	-14	-15	-92
12012	-88.3	-40	35	-81
7001	-84.2	-38	-20	-89
16003	-82.5	-37	27	-76
53002	-77.8	125	-60	-77
6018	-75.9	-50	-76	-97
51001	-59.5	-12	-19	-71
13002	-46.7	-27	-20	-62
53003	-43.3	-44	2	-83
18004	-42.8	-15	-38	-74
53001	-32.1	-20	-18	-52
16006	-30.7	-37	-32	-62
56001	-25	0	-15	-33
52001	-21	-15	5	-20
7012	-10.1	3	5	-7
54001	-1.2	-25	-20	-34
16005	7.6	-12	-22	-29
17002	85.3	30	-25	30

[a] Percent reduction of attacks per day while on CINRYZE arm

[b] Percent reduction of average severity of attacks while on CINRYZE arm

[c] Percent reduction of average duration of attacks while on CINRYZE arm

[d] Percent reduction of numbers of days of swelling while on CINRYZE arm

FDA Comment: The response to item 22 of the January 30, 2008, Complete Response letter is acceptable.

Item 23 of the January 30, 2008, Complete Response letter is a statistical item that pertains to the routine prophylaxis study, and is included here for completeness:

Complete Response Letter Item 23 for LEVP2005-1/B (Statistical Analysis Programming):

In the study, each subject was used as his or her own control. Since it was a crossover analysis, it would be expected that the repeated measure option "REPEATED-subject" in the PROC GENMOD would be used to reflect the cross over design. In your SAS code, this option was not used. Therefore, the estimation of the treatment effect was done as if it was a parallel group design. For the parallel group design, the sample size of 22 subjects may not be sufficient to provide necessary power. Please explain your approach.

Sponsor's Response to Item 23 of the January 30, 2008, CR Letter:

> We agree with FDA that in this study each subject was used as his or her own control in a crossover analysis. We also agree that in such an analysis, it would be expected that the repeated measure option "REPEATED-subject" in the PROC GENMOD would be used to reflect the cross over design. It appears that this question relates to Table 14.6 (attached)*[**Reviewer's comment**: no Table 14.6 is attached]*. Table 14.6, along with the SAS output that supports this analysis (see 'T_14_06_OUT.RTF' attached) were both included in the complete set of data provided in the BLA amendment dated 29 October 2007 (the prophylaxis amendment).
>
> The issue seems to stem from a FDA request dated 7 December 2007 asking for text of the SAS procedures used in this analysis. The programming specifications for Table 14.6, contained in a Word document, were sent to FDA on 13 December 2007 in response to this request. Unfortunately, the option "REPEATED-subject" was inadvertently omitted from this document and most likely has led to the current confusion. However, the original analysis submitted in the prophylaxis amendment was performed using the correct programming. This can be verified by reviewing the SAS script for the actual analysis, and the SAS output that was included in the BLA amendment.
>
> We have included the SAS program, t_14_06.sas that produced Table 14.6 with this response. As can be seen in this SAS program, the statement "repeated

subject=pt/type=un;" was indeed included in the PROC GENMOD analysis. The SAS program itself was not requested in the December FDA request, and this script was not included in the response provided to FDA.

Therefore, the option was included in the original analysis. We apologize for the confusion.

FDA Comment: The response to item 23 of the January 30, 2008, Complete Response letter is acceptable, according to the FDA statistical reviewer, Dr. Boris Zaslavsky.

8.1.1.2.3 Safety outcomes

Of the 24 subjects in the safety population, 21 (87.5%) had 1 or more TEAEs. There were 20 subjects (87.0%) who had a TEAE after exposure to open-label or randomized double-blind CINRYZE.

Nine subjects had a TEAE categorized as related to study medication. There were 3 subjects with 1 or more SAEs; no SAE was related to study medication. There were no deaths and no TEAEs that led to discontinuation from the study.

Summary of Adverse Events

	Open-label or Double-blind CINRYZE n (%) (N=23)	**Overall n (%) (N=24)**
Subjects with at least 1 TEAE	20 (87.0)	21 (87.5)
Subjects with TEAE related to study medication	9(39.1)	9(37.5)
Subjects with Serious AE	3(13.0)	3(12.5)
Subjects who withdrew due to AE	0	0
Subjects who died	0	0

Treatment Emergent Adverse Events

System Organ Class Preferred Term	Open-label or Double-blind CINRYZE n (%)	Overall n (%) (N=24)
Subjects with at least 1 TEAE	20 (87.0)	21 (87.5)
Blood and Lymphatic System Disorders	2(8.7)	2(8.3)
Anaemia	1 (4.3)	1 (4.2)
Lymphadenopathy	1 (4.3)	1 (4.2)
Congenital, Familial and Genetic Disorders	2(8.7)	2(8.3)
Hereditary angioedema	2(8.7)	2(8.3)
Eye Disorders	2(8.7)	2(8.3)
Blepharospasm	1 (4.3)	1 (4.2)
Conjunctivitis	1 (4.3)	1 (4.2)
Gastrointestinal Disorders	8(34.8)	8(33.3)
Abdominal pain	1 (4.3)	1 (4.2)
Constipation	1 (4.3)	1 (4.2)
Diarrhoea	1 (4.3)	1 (4.2)
Gastrointestinal pain	1 (4.3)	1 (4.2)
Gastro-esophageal reflux disease	2(8.7)	2(8.3)
Nausea	1 (4.3)	1 (4.2)
Vomiting	2(8.7)	2(8.3)
General Disorders and Administrative Site Conditions	4(17.4)	4(16.7)
Atrophy	1 (4.3)	1 (4.2)
Chest discomfort	1 (4.3)	1 (4.2)
Pain	1 (4.3)	1 (4.2)
Pyrexia	1 (4.3)	1 (4.2)
Infections and Infestations	14 (60.9)	15 (62.5)
Acute sinusitis	1 (4.3)	1 (4.2)
Bronchitis	2(8.7)	2(8.3)
Bronchitis acute	1 (4.3)	1 (4.2)
Ear infection	1 (4.3)	1 (4.2)
Fungal infection	1 (4.3)	1 (4.2)
Gastritis viral	1 (4.3)	1 (4.2)
Gastroenteritis viral	2(8.7)	2(8.3)
Herpes simplex	1 (4.3)	1 (4.2)
Influenza	1 (4.3)	1 (4.2)

Nasopharyngitis	2(8.7)	2
Otitis media	1 (4.3)	1 (4.2)
Pneumonia	1 (4.3)	1 (4.2)
Sinusitis	5(21.7)	6(25.0)
Upper respiratory tract infection	4(17.4)	4(16.7)
Urinary tract infection	2(8.7)	2(8.3)
Vaginal candidiasis	1 (4.3)	1 (4.2)
Varicella	1 (4.3)	1 (4.2)
Viral upper respiratory tract infection	3(13.0)	3(12.5)
Vulvovaginal mycotic infection	1 (4.3)	1 (4.2)
Injury, Poisoning and Procedural	3(13.0)	3(12.5)
Contusion	1 (4.3)	1 (4.2)
Excoriation	1 (4.3)	1 (4.2)
Joint injury	1 (4.3)	1 (4.2)
Limb injury	2(8.7)	2(8.3)
Skin laceration	1 (4.3)	1 (4.2)
Thermal burn	1 (4.3)	1 (4.2)
Wound	1 (4.3)	1 (4.2)
Investigations	1 (4.3)	1 (4.2)
Antibody test abnormal	1 (4.3)	1 (4.2)
Metabolism and Nutrition Disorders	1 (4.3)	1 (4.2)
Vitamin B12 deficiency	1 (4.3)	1 (4.2)
Musculoskeletal and Connective Tissue	5(21.7)	5(20.8)
Back pain	2(8.7)	2(8.3)
Musculoskeletal pain	1 (4.3)	1 (4.2)
Musculoskeletal stiffness	1 (4.3)	1 (4.2)
Pain in extremity	2(8.7)	2(8.3)
Nervous System Disorders	5(21.7)	5(20.8)
Carpal tunnel syndrome	1 (4.3)	1 (4.2)
Dizziness	1 (4.3)	1 (4.2)
Headache	4(17.4)	4(16.7)
Psychiatric Disorders	1 (4.3)	1 (4.2)

Depression	1 (4.3)	1 (4.2)
Reproductive System and Breast Disorders	1 (4.3)	1 (4.2)
Vulvovaginal discomfort	1 (4.3)	1 (4.2)
Respiratory, Thoracic and Mediastinal Disorders	5(21.7)	5(20.8)
Cough	2(8.7)	2(8.3)
Laryngeal oedema	1 (4.3)	1 (4.2)
Nasal congestion	1 (4.3)	1 (4.2)
Pharyngolaryngeal pain	1 (4.3)	1 (4.2)
Rhinorrhoea	1 (4.3)	1 (4.2)
Sinus congestion	1 (4.3)	1 (4.2)
Skin and Subcutaneous Tissue Disorders	6(26.1)	6(25.0)
Dermatitis contact	1 (4.3)	1 (4.2)
Erythema	1 (4.3)	1 (4.2)
Pruritus	2(8.7)	2(8.3)
Rash	5(21.7)	5(20.8)
Vascular Disorders	1 (4.3)	1 (4.2)
Poor venous access	1 (4.3)	1 (4.2)

Note: Only 1 subject had a TEAE (sinusitis) after treatment with Placebo and prior to any exposure to open-label or double-blind CINRYZE.

8.1.1.3 Comments & Conclusions

In LEVP2005-1/B, routine prophylaxis using CINRYZE at a dose of 1000 Units administered every 3 or 4 days by intravenous injection was safe and effective in reducing the frequency of HAE attacks in patients with hereditary angioedema.

Outcomes varied from 100% reduction in the HAE attack frequency to an actual increase in the HAE attack frequency. The reasons for the non-uniform response across all subjects is not known. Thrombotic events have been reported in association with C1 Inhibitor products when used off-label at high doses [Arzneimittelkommission der Deutschen Aertzteschaft. Schwerwiegende Thrombenbildung nach Berinert HS. Dtsch Aerztebl. 2000; 97:B-864] . Animal studies have supported a concern about the risk of thrombosis from intravenous administration of C1 Inhibitor products [Horstick, G et al, 2002. Circulation 104:3125-3131]. If HAE patients who do not receive an adequate clinical benefit (reduction of HAE attack frequency) from the labeled routine prophylaxis dose schedule choose to intensify the routine prophylaxis dose schedule, there may be a thrombotic risk.

Therefore, the sponsor should be required, according to Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA), to conduct a post-marketing clinical trial designed to evaluate higher than labeled dose schedules of CINRYZE for routine prophylaxis of angioedema attacks in patients with Hereditary Angioedema (HAE). The objective of the clinical trial will be to define the safety profile of intensified dose schedules that may be used by patients who do not obtain an acceptable clinical benefit (reduction of HAE attack frequency) from the labeled dose schedule of CINRYZE for routine prophylaxis of HAE attacks.

9 Overview of Efficacy Across Trials

There were no European efficacy studies prior to marketing the earlier product version. LEVP2005-1/B is the only efficacy study for routine prophylaxis for CINRYZE.

10 Overview of Safety Across Trials

10.1 Safety Database - Number of Subjects, Types of Subjects and Extent of Exposure

Ninety (90) subjects have been exposed to CINRYZE in clinical trials LEVP2005-1/A & B conducted by Lev pharmaceuticals, Inc. An additional 57 subjects have been exposed to CINRYZE in open label studies and in the pharmacokinetics study LEVP2006-5 conducted by Lev pharmaceuticals, Inc. Sixty-nine (69) subjects were exposed to earlier European version of the product in European studies. The marketed European product CETOR (approved 1997) has been distributed for at least ---(b)(4)-- treatments based on units distributed and labeled dose.

10.2 Safety Assessment Methods

Standard clinical trial methodology. See **Surveillance** under the description of LEVP2005-1/B.

10.3 Significant/Potentially Significant Events

10.3.1 Deaths

There are no reported deaths for any trial conducted using CINRYZE or its earlier version European product.

10.3.2 Other Significant/Potentially Significant Events

None.

10.3.3 Dropouts

In LEVP2005-1/B, of 26 subjects enrolled, 2 subjects dropped out prior to any treatment; 2 subjects dropped out (1 CINRYZE, 1 placebo) after completing the first prophylaxis study phase, for reasons not related to treatment.

10.4 Other Safety Findings

10.4.1 ADR Incidence Tables (Local & Systemic Events)

Subjects with Treatment-emergent Adverse Events in Studies Conducted by Lev Pharmaceuticals, Inc.

Subject ID	Treatment	TEAE Preferred Term	~Severity	Relationship	Outcome
LEVP 2001 /Part A N = 83 (CINRYZE 71, Placebo 12) Number with TEAE = 13 CINRYZE 6, Placebo 7)					
01-005	Placebo + Rescue CINRYZE	Anorexia[a]	Mild	Unknown	Resolved
		Fatigue[a]	Mild	Unknown	Resolved
01-017	Placebo	Vertigo	Mild	Unknown	Resolved
02-003	Placebo + Rescue CINRYZE	Blood pressure decreased	Severe	Not related	Resolved
06-005	Placebo only	Nausea	Mild	Not related	Resolved
07-002	Placebo only	Tetany	Moderate	Possibly	Resolved
17-001	Placebo+ Rescue CINRYZE	Chest pain	Severe	Not related	Resolved
24-004	Placebo only	Dermatitis contact	Mild	Definitely	Not resolved
02-001	CINRYZE	Blood pressure decreased	Severe	Not related	Resolved
06-007	CINRYZE	Nausea	Mild	Not related	Resolved
	CINRYZE	Vomiting	Mild	Not related	Resolved
07-001	CINRYZE	Sinusitis	Moderate	Not related	Resolved
07-012	CINRYZE	Upper respiratory tract infection	Moderate	Not related	Resolved
	CINRYZE	Sinusitis	Moderate	Not related	Resolved
	CINRYZE	Vulvovaginal mycotic infection	Mild	Not related	Resolved
17-003	CINRYZE	Dizziness	Mild	Unknown	Resolved
	CINRYZE	Anxiety	Mild	Unknown	Resolved

24-001	CINRYZE	Injection site rash	Mild	Definitely	Resolved
	CINRYZE	Tooth disorder	Mild	Not related	Resolved
LEVP 2006-5					
N=27					
Number with TEAEs = 5 CINRYZE 5)					
07-007	CINRYZE single-dose	Pharyngitis-streptococcal	Moderate	Not related	Resolved
		Paraesthesia	Mild	Not related	Not resolved
12-003	CINRYZE single-dose	Lymphadenopathy	Mild	Not related	Resolved
13-004	CINRYZE single-dose	Upper respiratory tract infection	Moderate	Not related	Resolved
33-006	CINRYZE double- dose	Nasopharyngitis	Severe	Unknown	Resolved
33-010	CINRYZE single-dose	Nasopharyngitis	Moderate	Not related	Resolved
Compassionate Use Number with AE = 0					

Adverse events in Studies Conducted by Sanquin

Subject ID	Treatment	AE Preferred Term or Verbatim	Severity	Relationship
036-005/Part A N = 9 AEs = 1				
RGG2	Cetor	Fatigue	unknown	unknown
KB97002-C l-INH N=22 AEs = 17				
101	Cetor	Mitral insuff Grade II/III	mild	Not related
102	Cetor	Bleeding from wound of teeth extraction under anticoagulation	mild	Not related
		Headache	moderate	Not related
103	Cetor	Edema because of subcutaneous infusion of Cl-INH	moderate	Not related
104	Cetor	Exanthema arms & thorax mild edema fingers, all. React. to streptokinase	moderate	Not related
		Slightly elevated levels of CL, G-GT, ALAT&CRP No clinical relevance.	mild	Not related
105	Cetor	Serious complaints during infusion due to phlebitis	severe	Not related
107	Cetor	PTCA because of pending MI	severe	Not related

		Headache	mild	Not related
108	Cetor	At discharge ALAT outside normal range without clinical. relevance	mild	Not related
109	Cetor	Mitral insufficiency grade 2-3, diagnosed through echo	moderate	Not related
110	Cetor	LID, G-GT and ALAT outside normal range, no clin. relevance	mild	Not related
		Mitralis valve insufficiency grade 1 diagnosed through echo	mild	Not related
		Suspicion of hypercholesterolaemia	mild	Not related
111	Cetor	Mild allergic reaction to strepto (exanthema, itching, edemea)	severe	Not related
		ASAT&ALAT slightly outside normal range, no clinical. relevance	mild	Not related
112	Cetor	Phlebitis on site of infusion	mild	Not related
113	Cetor	Gastric complaints, subject has a history of gastic ulcers;	mild	Not related
		Reinfarction	severe	Not related
114	Cetor	Mitral valve insufficiency Grade 1-2	mild	Not related
115	Cetor	Mitralis insufficiency II/III, diagnosis through echocardiogram	moderate	Not related
116	Cetor	300-400 ML blood loss due to reopening of puncture hole	severe	Not related
127	Cetor	Compartmental syndrome in upper leg a week before the infarction	moderate	Not related
128	Cetor	Phlebitis	mild	Not related
KB2003.01/Part A N=14 AEs = 5				
103		Injection Site Thrombosis	mild	
		Influenza	moderate	Not related
		Hereditary Angioedema	severe	Not related
104		Influenza	moderate	Not related
		Hereditary Angioedema	moderate	Not related
106		Hereditary Angioedema	mild	Not related
319		Angioneurotic edema	mild	Not related
320		Angioneurotic edema	mild	Not related

10.4.2 Laboratory Findings, Vital Signs, ECGs, Special Diagnostic Studies

No subjects in studies conducted by Lev Pharmaceuticals have seroconverted for HBV, HCV, HIV, or parvovirus B19.

10.4.3 Product-Demographic Interactions (e.g., Age, Gender, etc.)

There were no pediatric or geriatric studies. Twenty of twenty-two subjects in LEVP2005-1/B were female. The reasons for this enrollment imbalance are not known. The sponsor is being asked to conduct a phase 4 study in routine prophylaxis that will be gender balanced.

10.4.4 Product-Disease Interactions

Not studied.

10.4.5 Product-Product Interactions

Not studied.

10.4.6 Immunogenicity (See CMC review for immunoassay review)

10.4.7 Carcinogenicity

Studies waived.

10.4.8 Withdrawal Phenomena/Abuse Potential (if relevant)

Not studied.

10.4.9 Human Reproduction and Pregnancy Data

No clinical studies.

10.4.10 Assessment of Effect on Growth (if relevant)

Not applicable.

10.4.11 Overdosage Exposure (if relevant)

10.4.12 Post-marketing Exposure

There are no available post-marketing data on CINRYZE to date.

10.5 Safety Conclusions

CINRYZE is safe for use as routine prophylaxis against HAE attacks in patients with hereditary angioedema when used at the labeled dose schedule.

11 Additional Clinical Issues

11.1 Directions for Use

From the proposed package insert:

2.2 Instructions for Use

The procedures below are provided as general guidelines for the reconstitution and administration of CINRYZE.

Always work on a clean surface and wash your hands before performing the following procedures. Reconstitution, product administration, and handling of the administration set and needles must be done with caution. Percutaneous puncture with a needle contaminated with blood can transmit infectious viruses including HIV (AIDS) and hepatitis. Obtain immediate medical attention if injury occurs. Place needles in a sharps container after single use. Discard all equipment, including any reconstituted CINRYZE in an appropriate container.

2.3 Preparation and Handling

- Prior to reconstitution, CINRYZE should be protected from light.

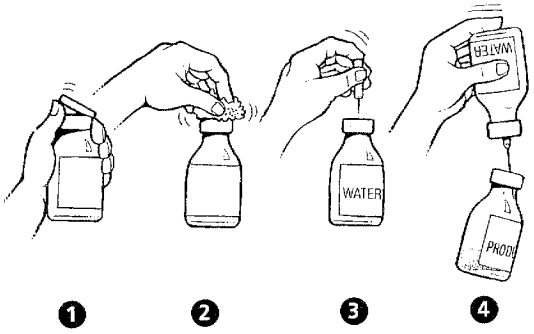
- CINRYZE should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The reconstituted solution should be colorless to slightly blue, and free from visible particles. Do not use if turbid or discolored.
- The CINRYZE vial is for single use only. CINRYZE contains no preservative. Any vial that has been entered should be used promptly. Partially used vials should be discarded in accordance with biohazard procedures.
- Do not mix CINRYZE with other materials.
- Do not freeze.
- Do not use after expiration date.

Reconstitution:

Two vials of reconstituted CINRYZE are combined for a single dose. Sterile Water for Injection, USP, is required and not supplied with CINRYZE.

1. Aseptic technique should be used during the reconstitution procedure.
2. Bring the CINRYZE (powder) and Sterile Water for Injection, USP (diluent) (not supplied) to room temperature if refrigerated.
3. Remove caps from the CINRYZE and diluent vials (Step 1).
4. Cleanse stoppers with germicidal solution, and allow them to dry prior to use. (Step 2)
5. Remove protective covering from one end of the double-ended transfer needle and insert exposed needle through the center of the diluent vial stopper (Step 3).
6. Remove protective covering from the other end of the double-ended transfer needle. Invert diluent vial containing 5 mL Sterile Water for Injection, USP, over the upright and slightly angled CINRYZE vial (Step 4); then rapidly insert the free end of the needle through the CINRYZE vial stopper at its center. The vacuum in the vial will draw in the diluent. **If there is no vacuum in the vial, do not use the product.**
7. Disconnect the two vials by removing the needle from the CINRYZE vial stopper and discard the diluent vial, along with the transfer needle directly into the sharps container. Gently swirl the CINRYZE vial until all powder is dissolved. Be sure that CINRYZE is completely dissolved.

One vial of reconstituted CINRYZE contains 5 mL of C1 inhibitor at a concentration of 100 Units/mL. Reconstitute two vials of CINRYZE for one dose.



2.4 Administration:

Two vials of reconstituted CINRYZE are combined for a single dose.

1. Use Aseptic Technique.
2. After reconstitution, the solution is colorless to slightly blue and clear. Do not use the product if the solution is turbid or discolored.
3. CINRYZE must be administered at room temperature within 3 hours after reconstitution.

4. Attach the filter needle to a sterile, disposable syringe and draw back the plunger to admit air into the syringe.
5. Insert the filter needle into the vial of reconstituted CINRYZE.
6. Inject air into the vial and then withdraw the reconstituted CINRYZE into the syringe. This should be repeated with a second vial of CINRYZE to make the complete dose.
7. Remove and discard the filter needle in a hard-walled Sharps container for proper disposal. Filter needles are intended to filter the contents of a single dose (2 vials) of CINRYZE only.
8. Attach a suitable needle or infusion set with winged adapter, and inject intravenously. As a guideline, administer 1000 Units (reconstituted in 10ml) of CINRYZE by intravenous injection at a rate of 1 mL per minute over 10 minutes *(see Clinical Studies, Section 14)*

Dispose of all unused solution, the empty vial(s), and the used needles and syringes in an appropriate container for throwing away waste that might hurt others if not handled properly.

11.2 Dose Regimens and Administration

From the proposed package insert:

2.1 Prophylaxis against HAE Attacks

- A dose of 1000 Units CINRYZE can be administered every 3 or 4 days for prophylaxis against angioedema attacks in HAE patients.
- CINRYZE is administered at an injection rate of 1 mL per minute.

Table 2 Prophylaxis Dosing

Indication	Dose (Total)	Initial Infusion rate	Maintenance infusion rate (if tolerated)
Routine prophylaxis against HAE attacks	1000 units Intravenous every 3 or 4 days	1 mL/min (10 minutes)	1 mL/min (10 minutes)

11.3 Special Populations

Pregnancy was an exclusion criterion in the routine prophylaxis study. In the open label study, one female receive CINRYZE treatments during the third trimester with no adverse effects on the labor or delivery.

11.4 Pediatrics

There are no formal studies in pediatric populations. The product has orphan drug designation, so pediatric studies under PREA have been waived.

11.5 Other

12 Conclusions – Overall

In LEVP2005-1/B, routine prophylaxis using CINRYZE at a dose of 1000 Units administered every 3 or 4 days by intravenous injection was safe and effective in reducing the frequency of HAE attacks in patients with hereditary angioedema.

13 Recommendations

13.1 Approval, Non-approval, Conditions

I recommend licensure of CINRYZE for the routine prophylaxis indication. Due to the expected home use of routine prophylaxis, I recommend that the sponsor be required to submit a Patient Package Insert (PPI) that includes Directions for Use within 30 days of licensure. The PPI does not need to be a post-marketing requirement (PMR) under Title IX section 901 of FDAAA.

13.2 Recommendation on Postmarketing Actions

Outcomes varied from 100% reduction in the HAE attack frequency to an actual increase in the HAE attack frequency. The reasons for the non-uniform response across all subjects is not known. Thrombotic events have been reported in association with C1 Inhibitor products when used off-label at high doses [Arzneimittelkommission der Deutschen Aertzteschaft. Schwerwiegende Thrombenbildung nach Berinert HS. Dtsch Aerztebl. 2000; 97:B-864] . Animal studies have supported a concern about the risk of thrombosis from intravenous administration of C1 Inhibitor products [Horstick, G et al, 2002. Circulation 104:3125-3131]. If HAE patients who do not receive an adequate clinical benefit (reduction of HAE attack frequency) from the labeled routine prophylaxis dose schedule choose to intensify the routine prophylaxis dose schedule, there may be a thrombotic risk.

Therefore, the sponsor should be required, according to Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA), to conduct a post-marketing clinical trial designed to evaluate higher than labeled dose schedules of CINRYZE for routine prophylaxis of angioedema attacks in patients with Hereditary Angioedema (HAE). The objective of the clinical trial will be to define the safety profile of intensified dose schedules that may be used by patients who do not obtain an acceptable clinical benefit (reduction of HAE attack frequency) from the labeled dose schedule of CINRYZE for routine prophylaxis of HAE attacks.

13.3 Labeling

It should be noted that the CINRYZE package insert is the first in the C1 inhibitor class to undergo review under the Physicians' Labeling Rule (PLR). Therefore, its format and content should be applied to subsequently licensed class representatives unless submitted data justify changes.

13.4 Other

13 Comments and questions for the applicant

Pursuant to section 505(o)(3) of the FDCA, the sponsor should be required to conduct a clinical trial, using the following language in the approval letter:

1. Lev Pharmaceuticals, Inc. is required to conduct a clinical trial designed to evaluate higher than labeled dose schedules of CINRYZE for routine prophylaxis of angioedema attacks in patients with Hereditary Angioedema (HAE). The objective of the clinical trial will be to define the safety profile of intensified dose

schedules that may be used by patients who do not obtain an acceptable clinical benefit (reduction of HAE attack frequency) from the labeled dose schedule of CINRYZE for routine prophylaxis of HAE attacks. The clinical trial will include the following features:

a. Gender-balanced enrollment of subjects with HAE who are receiving CINRYZE for routine prophylaxis of HAE attacks at the labeled dose schedule, and who still have an unacceptable HAE attack frequency,
b. Procedures for establishing a baseline HAE attack frequency for each subject,
c. A dose escalation algorithm that is based on a conclusion of lack of acceptable clinical benefit (reduction of HAE attack frequency) for each subject,
d. Scheduled monitoring of adverse events, with emphasis on signs and symptoms of thrombotic adverse events, and
e. Scheduled monitoring for immunogenicity using a validated assay that can detect neutralizing antibodies to CINRYZE.

The timetable you submitted on October 3, 2008, states that you will conduct this trial according to the following timetable:

Protocol Submission:	within 3 months of the date of licensure
Trial/Study Start Date:	within 9 months of the date of licensure
Final Report Submission:	within 48 months of the date of licensure