Summary Basis for Regulatory Action Template

Date: June 20, 2018

From: Agnes Lim, M.D., Chair of the Review Committee

BLA STN: BL 125267/1356

Applicant Name: ViroPharma Biologics, Inc.

Date of Submission: December, 19, 2017

PDUFA Goal Date: June 20, 2018

Proprietary Name/ Established (USAN) names: CINRYZE /C1 Esterase Inhibitor (Human)

Proposed Indication: CINRYZE is a C1 esterase inhibitor indicated for routine prophylaxis against angioedema attacks in adults, adolescents and pediatric patients (6 years of age and above) with Hereditary Angioedema (HAE).

Recommended Action: The Review Committee recommends approval of this efficacy supplement.

Review Office(s) Signatory Authority: Tejashri Purohit-Sheth, M.D., Director, Division of Clinical Evaluation and Pharmacology/Toxicology, Office of Tissues and Advanced Therapies

☐ **I concur with the summary review.**

☐ **I concur with the summary review and include a separate review to add further analysis.**

☐ **I do not concur with the summary review and include a separate review.**

The review disciplines and respective review committee members who participated in reviewing this Biologics License Prior Approval Supplement (PAS) and developing the Summary Basis of Regulatory Action (SBRA) are shown in Table 1.

Table 1. SBRA Review Disciplines and Review Committee

Document title	Reviewer name, Document date
Regulatory Project Manager	Seameen (Jean) Dehdashti (OTAT/DRPM/RPMB2)

Document title	Reviewer name, Document date
CMC Review(s) • CMC (product office) • Facilities review (OCBQ/DMPQ)	Ewa Marszal, PhD (OTAT/DPPT/HB) Obinna Echeozo and Ellen Huang (OCBQ/DMPQ/BII)
Clinical Review(s) • Clinical (product office) • Postmarketing safety epidemiological review (OBE/DE) • BIMO	Agnes Lim, MD (OTAT/DCEPT/GMB1) Jaspal Ahluwalia, MD (OCBQ/DE/PB) Carla Jordan, MS (OCBQ/DIS/BMB)
Statistical Review • Clinical data	Jiang (Jessica) Hu, PhD (OBE/DB/TEB)
Pharmacology/Toxicology Review • Toxicology (product office) • Developmental toxicology (product office) • Animal pharmacology	Evi Struble, PhD (OTAT/DPPT/PDB)
Clinical Pharmacology Review	Xiaofei Wang, PhD (OTAT/DCEPT/GMB2)
Labeling Review • APLB (OCBQ/APLB)	Alpita Popat, PharmD (OCBQ/DCM/APLB)
Advisory Committee summary	Supplement 1356 was not presented to an advisory committee

1. INTRODUCTION

ViroPharma Biologics, Inc. submitted this Biologics License Prior Approval Supplement (PAS) for CINRYZE, C1 Esterase Inhibitor (Human) (STN 125267), for routine prevention of angioedema attacks in children aged 6 to 11 years old who have Hereditary Angioedema (HAE). Currently, CINRYZE is indicated for routine prophylaxis against angioedema attacks in adolescent and adult patients with HAE.

While data in the original BLA demonstrated that CINRYZE administered as prophylaxis against angioedema attacks is safe and effective in adults and adolescents, optimization of pediatric dosing regimens, particularly for young children, had not been evaluated. To evaluate CINRYZE as routine prophylaxis against angioedema attacks in pediatric subjects with HAE, a dedicated study (Study SHP616-301) specifically targeted enrollment of pediatric subjects aged 6 to 11 years who have HAE. This study investigated different dosing regimens of CINRYZE to identify a dose that has the most favorable benefit/risk profile in younger children.

This PAS labeling supplement contains safety and efficacy data from a randomized, single-blind, dose-ranging, cross-over, multi-center study (SHP616-301) of 12 pediatric subjects aged 6-11 years old that evaluated the use of CINRYZE (500 U and 1,000 U doses) administered via intravenous (IV) infusion for the prevention of HAE attacks and reduction in attack severity and requirement for acute treatment.

The application is not subject to the Pediatric Research Equity Act (PREA) because the product has received orphan drug designation as a therapeutic for HAE attacks.

2. BACKGROUND

Hereditary angioedema (HAE) is a rare autosomal dominant disease resulting from a gene mutation on chromosome 11 that results in a quantitative or functional deficiency of the C1 esterase inhibitor (C1 INH) enzyme. This C1 INH deficiency causes unchecked activation of the complement system and increased release of bradykinin, the primary mediator responsible for capillary leakage and the clinical manifestations associated with angioedema attacks. HAE affects an estimated 1 in 50,000 individuals in the United States. Nearly all affected individuals experience recurrent episodes of the disease; however, the symptoms vary in both their frequency and severity. HAE is characterized by relapsing skin swelling, abdominal pain attacks, and, less frequently, life-threatening laryngeal attacks. Abdominal attacks can be very debilitating and almost 80% of patients with HAE will experience a gastrointestinal attack. Episodes of laryngeal edema are the least frequent type of attack, but are the primary cause of mortality in patients with HAE because of the progression to asphyxiation. In undiagnosed laryngeal edema cases, mortality can be as high as 30% to 40%.

Cl-INH products that are administered to HAE patients with inadequate functional Cl-INH levels are intended to abort or prevent acute HAE attacks. When the product is infused to treat an acute HAE attack that has already begun, it is called "treatment." In contrast, routine prophylaxis therapy involves the administration of a Cl-INH product at regular time intervals to maintain a serum level of functional Cl-INH that would prevent or greatly reduce the frequency of acute HAE attack episodes.

3. CHEMISTRY MANUFACTURING AND CONTROLS (CMC)

a) Product Quality

No manufacturing process, process control or product control information was provided in this supplement.

Immunogenicity assay information was requested and evaluated. The sensitivity of the immunogenicity assay used is not known. Matrix interference may impact the validity of the assay, especially as the presence of the product and endogenous C1-esterase inhibitor in patient samples may interfere with antibody detection. As a PMC, the sponsor is asked to develop a new sensitive and well controlled immunogenicity assay and is advised to use 2016 *FDA Guidance for Industry Assay Development and Validation for Immunogenicity Testing of Therapeutic Protein Products* as reference.

b) Facilities review/inspection

No manufacturing or facilities-and equipment-related information/data was provided in the supplement.

c) Environmental Assessment

The PAS included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31(c). The FDA concluded that this request is justified as the manufacturing of this product will not alter significantly the concentration and distribution of naturally occurring substances and no extraordinary circumstances exist that would require an environmental assessment.

4. NONCLINICAL PHARMACOLOGY/TOXICOLOGY

There were no new animal pharmacology and toxicology studies submitted with this supplement. The review of the studies submitted to support the original BLA identified a risk for increased thrombosis following the administration of CINRYZE; the risk is clearly communicated in the label. The animal studies do not raise other toxicity concerns or any specific concerns for the pediatric population.

The active ingredients and excipients for CINRYZE and the calculated exposures to these constituents following maximum administration volumes for adult and pediatric populations are comparable to other approved therapies. For two excipients, L-valine and L-threonine, for which no comparable products were found, the exposure from the product would be a fraction of recommended or expected daily intake for these compounds, including in children. Thus, the formulation does not raise toxicologic concerns for the pediatric population.

Approval is recommended from the animal pharmacology and toxicology perspective.

5. CLINICAL PHARMACOLOGY

This supplemental BLA proposes addition of a new pediatric subpopulation (children 6 to 11 years of age) to the existing indication for use in the PI. This addition to the PI is based on results of a phase 3, randomized, single-blind, dose-ranging, crossover study (Study SHP616-301) that evaluated the safety and efficacy of IV administration of CINRYZE for prevention of angioedema attacks in children 6 to 11 years of age who have HAE. To characterize the clinical pharmacology of C1 INH in the study population, the applicant performed population pharmacokinetic modeling using data from the pivotal phase 3 study (Study SHP616-301) and two previously completed studies (Study LEVP2005-1/B and StudyLEVP2006-4) that supported approval of the original BLA submission.

Results of Study SHP616-301 showed that both studied doses (500 U and 1000 U twice weekly) of CINRYZE increased C1 INH levels (functional activity and antigenic content) in the study population (age range of enrolled subjects: 6 to 11 years).

Population pharmacokinetic modeling results indicated lower clearance and volume of distribution of CINRYZE in subjects with lower body weight. Administration of 500 U CINRYZE twice weekly (BIW) in children aged 6 to 11 years old was associated with approximately a 21% lower mean $AUC_{0\text{-}4,ss}$ (area under the concentration-time curve from time 0 to 4 h at steady state) and $C_{max,ss}$ and an 18% longer half-life than that observed in adults receiving 1000 U CINRYZE BIW. Administration of 1000 U CINRYZE BIW in children aged 6 to 11 years old was associated with an approximately 30% higher mean $AUC_{0\text{-}4,ss}$ and $C_{max,ss}$, as well as a 17% longer half-life than that observed in adults who received the comparable dose.

6. CLINICAL/STATISTICAL/PHARMACOVIGILANCE

a) Clinical Program

The main data supporting the use of CINRYZE as prophylaxis against angioedema attacks in pediatric subjects (aged 6 to 11 years) with HAE were collected in Study SHP616-301.

Summary of the Design of Study SHP616-301 Protocol
Study Title: "A Phase 3, Multicenter, Randomized, Single-blind, Dose-ranging, Crossover Study to Evaluate the Safety and Efficacy of Intravenous Administration of CINRYZE® (C1 Esterase Inhibitor [Human]) for the Prevention of Angioedema Attacks in Children 6 to 11 Years of Age With Hereditary Angioedema."

This prospective, randomized, single-blind, dose-ranging, cross-over, multi-center study of 12 pediatric subjects aged 6-11 years old was conducted at 10 study centers globally; 4 US sites, 4 European Union sites, 1 site in Mexico, and 1 site in Israel.

Primary Study Objective
The primary objective of this study was to assess the relative efficacy of 2 dose levels of CINRYZE (500 U and 1000 U) administered by IV infusion every 3 or 4 days to prevent angioedema attacks in children 6 to 11 years of age who have Type I or II hereditary angioedema (HAE).

Secondary Study Objectives
1. Assess the safety and tolerability of the 2 dose levels of CINRYZE administered by IV infusion in children 6 to 11 years of age with HAE;
2. Characterize the pharmacokinetics/pharmacodynamics of CINRYZE administered by IV infusion in children 6 to 11 years of age;
3. Assess the immunogenicity of CINRYZE following IV administration; and

Exploratory Objective
Assess the impact of treatment on health status (quality of life) in children 6 to 11 years of age with HAE.

Eligibility Criteria
Main Inclusion Criteria
- ≥6 to <12 years of age at the time of screening
- Confirmed diagnosis of Type I or II HAE and a functional C1 INH level <50% of normal
- History of ≥ 1.0 angioedema attack(s) per month (on average) that were moderate or severe or required acute treatment during the 3 consecutive months prior to screening (to enter into the 12-week observational period)

Additional Inclusion Criterion (Qualification for randomization after the 12-week observational period was completed)
- Experienced ≥1.0 angioedema attack(s) per month (on average) that were moderate or severe or required acute treatment during the 3 consecutive months during the 12-week baseline observation period

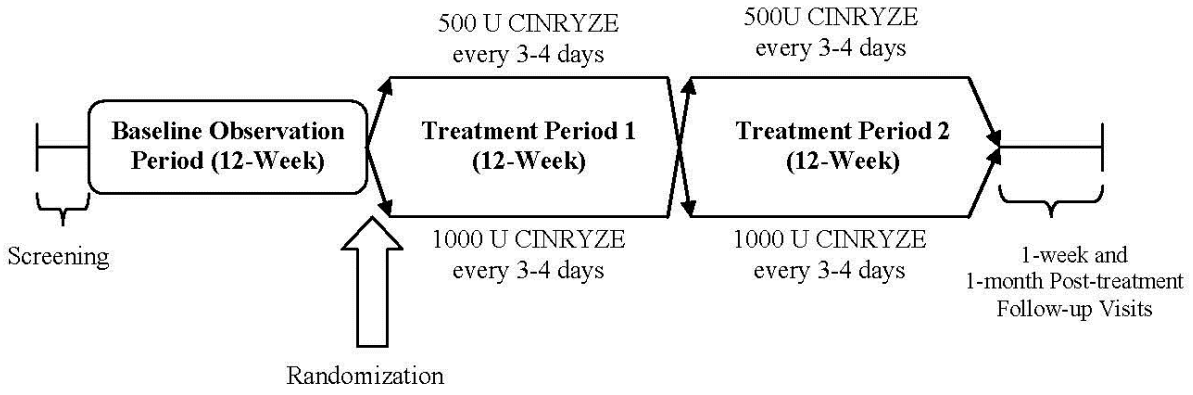
Main Exclusion Criteria
- History of hypercoagulability (abnormal blood clotting)
- Diagnosis of acquired angioedema or known to have anti-C1 INH antibodies

Additional Exclusion Criteria (Disqualification from Randomization):
- Had an active infectious illness or fever defined as an oral temperature >38°C (100.4°F), tympanic >38.5°C (101.3°F), axillary >38°C (100.4°F), or rectal/core >38.5°C (101.3°F) within 24 hours prior to the first dose of investigational product in Treatment Period 1
- Had angioedema attack signs or symptoms within 2 days prior to the first dose of investigational product in Treatment Period 1

Screening and Baseline Procedures
Potential subjects had a screening evaluation the day prior to entering the study's baseline observation period. Subjects meeting all eligibility criteria were enrolled and entered into the baseline observation period for at least 12 weeks, during which subjects could remain on any prophylactic therapy for HAE that they had been receiving prior to study enrollment.

Treatment Plan
In Treatment Period 1, subjects were to receive CINRYZE at a dose of either 500 U (Treatment A) or 1000 U (Treatment B) by IV infusion twice weekly (every 3 or 4 days) for 12 weeks. After completion of the first treatment period, subjects were crossed over to receive the alternate CINRYZE dose in Treatment Period 2 with no washout period. The dosing interval for individual subjects in Treatment Period 2 was the same as in Treatment Period 1.

Figure 1. Study Design Schematic



Source: BLA 125267, Module 5.3.5.1 Clinical Study Report, Section 9.1

Subjects and parents/caregivers were blinded to the treatment administered. Study site personnel, home healthcare professionals, and the sponsor were not blinded to dose and treatment sequence. Investigational product was administered intravenously by qualified personnel at the investigational site, or by qualified home healthcare professionals at the subject's home or other agreed upon location.

After the first 6 subjects completed the study, the protocol was amended to allow (if permitted per local regulations) subjects to self-administer CINRYZE or to receive administration of CINRYZE from a non-healthcare provider (e.g., parent), provided the subject or non-healthcare provider had been trained to do so. The option for self-administration or administration by a non-healthcare provider could only be selected at the request of the subject and with approval of the parent(s)/legal guardian and the investigator.

SHP616-301 Efficacy Results

Subject Disposition

Of the 16 subjects screened to participate in the study, four subjects failed to qualify for randomization based on the number of attacks experienced (≥1.0 angioedema attacks per month [on average] that were moderate or severe or required acute treatment) during the 12-week baseline observation period and were not randomized to a treatment sequence. A total of 12 subjects were enrolled and randomized into the study. Five subjects were randomized to treatment sequence A/B (500 U/1000 U CINRYZE) and seven subjects were randomized to treatment sequence B/A (1000 U/500 U CINRYZE). There were no dropouts or discontinuations. All 12 subjects completed the study.

Demographics

The study population consisted of 7 (58.3%) females and 5 (41.7%) males, with a median age of 10 years (range: 7 to 11 years). Eleven subjects were White and 1 subject was of mixed race (Black or African American, White). Four subjects (33.3%) were Hispanic or Latino. The median body weight was 37.2 kg (range: 23.2 to 67.6

kg) and median body mass index was 18.6 kg/m^2 (range: 13.1 to 28.2 kg/m^2) (Table 2).

Table 2. Subject Demographic and Baseline Characteristics by Treatment Sequence

Characteristic[a]	**Sequence A/B 500 U/1000 U CYNRYZE (N=5)**	**Sequence B/A 1000 U/500 U CYNRYZE (N=7)**	**All Subjects (N=12)**
Age (years)[b]			
Mean (±SD)	10.2 (±o.84)	9.4 (±1.51)	9.8 (±1.29)
Median	10.0	10.0	10.0
Min., Max.	9, 11	7, 11	7, 11
Sex, n (%)			
Male	3 (60.0)	2 (28.6)	5 (41.7)
Female	2 (40.0)	5 (71.4)	7 (58.3)
Ethnicity, n (%)			
Hispanic or Latino	2 (40.0)	2 (28.6)	4 (33.3)
Not Hispanic or Latino	3 (60.0)	5 (71.4)	8 (66.7)
Race, n (%)			
White	4 (80.0)	7 (100.0)	11 (91.7)
Multiple: Black, Caucasian	1 (20.0)	0	1 (8.3)
Weight (kg)			
Mean (±SD)	41.7 (±15.56)	41.3 (±14.16)	41.4 (±14.05)
Median	34.5	39.8	37.2
Min, Max	30.0, 67.6	23.2, 61.2	23.2, 67.6
Height (cm)			
Mean (±SD)	147.6 (±9.29)	143.2 (±13.54)	145.0 (±11.68)
Median	145.0	147.4	147.0
Min, Max	138.5, 161.0	118.0, 159.3	118.0, 161.0
BMI (kg/m^2)[c]			
Mean (±SD)	18.7 (±4.53)	19.8 (±5.32)	19.4 ±(4.82)
Median	18.0	18.6	18.6
Min, Max	14.3, 26.1	13.1, 28.2	13.1, 28.2

[a] The baseline value for a characteristic was the value form the screening visit (Day -1) or last observation on or prior to the first dose of treat, whichever was later.
[b] Age was calculated as the difference between date of birth and date of informed consent, truncated to years.
[c] Body mass index was calculated as (weight [kg]/height [m]^2).
Percentages were based on the safety set.
Treatment A = IV infusion of CYNRYZE 500 U twice weekly (every 3-4 days) for 12 weeks.
Treatment B = IV infusion of CYNRYZE 1000 U twice weekly (every 3-4 days) for 12 weeks.
Source: Module 5.3.5.1, SHP616-301 clinical study report [CSR], Table 15

Efficacy Results

The primary efficacy outcome measure assessed the difference in the change in the time-normalized number of angioedema attacks per month during the 12-week treatment period between the 1000 U and 500 U dose cohorts. The superiority of 1000 U vs 500 U was tested at the prespecified two-sided $\alpha = 0.1$. There was a statistically significantly greater reduction in the time-normalized number of angioedema attacks per month with 1000 U CINRYZE compared to 500 U CINRYZE (p=0.03). However, when compared to the baseline observational period, a reduction in the time-normalized number of angioedema attacks per month during

the 12-week treatment period was observed for both CINRYZE 500 U and CINRZYE 1000 U (mean percent reduction: 71.1% and 84.5%, respectively; see Table 3).

Table 3. Time-Normalized Number of HAE Attacks during Observational Period and during 12-week Treatment Period with CINRYZE 500 U and 1000 U

Parameter	**Observational Period N = 12**	**CINRYZE 500 U N = 12**	**CINRYZE 1000 U N = 12**
Mean (SD)	3.7 (3.15)	1.2 (1.53)	0.7 (1.35)
Min, Max	1.0, 11.8	0.0, 5.6	0.0, 4.8
Median	2.2	0.8	0.4
Mean (SD) difference compared to baseline	N/A	-2.6 (2.88)	-3.0 (2.87)
90% CI for the difference compared to baseline	N/A	(-4.1, -1.1)	(-4.5, -1.5)
Mean % reduction compared to baseline	N/A	71.1%	84.5%
Median % reduction compared to baseline	N/A	76.2%	87.4%

CI=confidence interval; HAE=hereditary angioedema; N=number of randomized subjects; SD=Standard Deviation, scaled normalized score is expressed as the score per month.
N/A=not applicable
Source: BLA Module 5.3.5.1

Secondary efficacy endpoints included cumulative attack severity, cumulative daily severity of attacks, and the number of attacks requiring treatment. Data analyses demonstrated that both doses lessened the severity of angioedema attacks and reduced the use of acute treatment compared with the baseline observational period. There was a high clinical response rate for subjects who experienced a pre-specified reduction in the number of attacks in the treatment period compared to baseline: 91.7% of subjects experienced $\geq$ 50% reduction in the number of attacks compared to baseline and 83.3% of subjects experienced ≥70% reduction in the number of attacks compared to baseline after the overall treatment (calculated as the average reduction relative to the baseline from both treatment periods). The mean ±SD and median (range) differences between treatment with 1000 U and 500 U CINRYZE in the average angioedema attack duration (scaled scores normalized per month, compared to baseline) were -0.12±0.56 (90% CI: -0.41, 0.17; p=0.47) and -0.0 (-1.0, 0.8), respectively. No statistically significant difference was observed in cumulative average attack duration for 1000 U and 500 U doses of CINRYZE. In summary, both 500 U and 1000 U of CINRYZE (administered twice weekly) during 3 months of treatment lowered the number of angioedema attacks, lessened the severity of attacks, and reduced the requirement for acute treatment compared with baseline, demonstrating a clinical benefit for children 6 to 11 years of age.

In conclusion, the SHP616-301 study data support the efficacy of CINRYZE (500 U and 1,000 U) administered via IV infusion for the prevention of HAE attacks in pediatric subjects, based on the demonstrated reductions in the per month time-normalized number of attacks, attack severity, and requirement for acute treatment.

b) Bioresearch Monitoring

BIMO Inspections: Bioresearch Monitoring (BIMO) inspections were conducted at three clinical sites that participated in the conduct of Study# SHP616-301. The inspections did not reveal any issues that impact the data submitted in this application.

7. SAFETY

The safety of CINRYZE 1000 U IV every 3 to 7 days for the routine prophylaxis to prevent acute HAE attacks in adults and adolescents was demonstrated in pivotal study LEVP2005-1 prior to the original BLA 125267/0 licensure, approved on October 10, 2008.

The safety information collected in Study SHP616-301 was monitored through the recording of AEs and changes in physical examinations, vital signs, clinical safety laboratory testing (hematology, chemistry, and coagulation). As per the clinical protocol, all angioedema attacks occurring after the first dose of investigational product were defined and reported as a treatment-emergent adverse event (TEAE). Immunogenicity testing for anti-C1 INH antibodies was also performed. A post-treatment follow-up safety visit was performed at the clinical site 1 week (±2 days) after the final dose of investigational product. If a subject discontinued prematurely from treatment and/or the study, the investigator was to perform the early discontinuation visit safety procedures as soon as possible. Subjects had a blood sample for anti-C1 INH antibody testing collected 30 (±2) days after the last dose of investigational product.

SHP616-301 Safety Results

In this study of 12 children aged 6 to 11 years with HAE, twice weekly administration of 500 U and 1000 U IV CINRYZE was shown to be generally well- tolerated. The most frequently reported TEAEs were angioedema attacks (10 [83.3%] subjects): 41 attacks in 9 (75.0%) subjects who received 500 U CINRYZE and 25 attacks in 8 (66.7%) subjects who received 1000 U CINRYZE. Six severe, 15 moderate, and 16 mild angioedema attacks were reported among study subjects during treatment with 500 U CINRYZE, and 3 severe, 15 moderate, and 7 mild angioedema attacks were reported among study subjects during treatment with 1000 U CINRYZE. A higher proportion of subjects reported severe angioedema attacks with 500 U CINRYZE (41.7%, 5/12) compared to 1000 U CINRYZE (25.0%, 3/12). Viral upper respiratory tract infection was reported by more subjects who received 1000 U CINRYZE (8 reported by 6 [50.0%] subjects) compared with those who received 500 U CINRYZE (3 reported by 2 [16.7%] subjects). TEAEs considered by the investigator to be

related to CINRYZE were fatigue, irritability, HAE attack, diarrhea, erythema, and pruritus. The TEAE profile was similar for the other common (≥ 2 subjects) TEAEs (erythema marginatum, fatigue, irritability, headache, upper respiratory tract infection, abdominal pain, nasopharyngitis, nausea, diarrhea, cough, fall, and rhinitis allergic) with 500 U or 1000 U of CINRYZE treatment. In general, the TEAE profile was similar following treatment with 500 U or 1000 U of CINRYZE.

No deaths or other SAEs were reported, and no subject discontinued investigational product due to an AE. No subjects in Study SHP616-301 experienced a TEAE that was thrombotic or thromboembolic in nature and no new adverse events were observed in this study, compared to previous clinical studies with CINRYZE. In addition, all subjects tested negative for anti-C1 INH antibodies following six months of treatment with CINRYZE. In summary, no overt safety issues were identified following 12-week IV administration of CINRYZE at a dose of either 500 U or 1,000 U in pediatric subjects aged 7 – 11 years old in Study SHP616-301.

8. ADVISORY COMMITTEE MEETING

There were no issues related to this product that prompted the need for discussion by the Blood Products Advisory Committee.

9. OTHER RELEVANT REGULATORY ISSUES

No notable regulatory issues or concerns were identified during the review of Efficacy Supplement BLS 125267/1356.

10. LABELING

The APLB Reviewer found the FULL PRESCRIBING INFORMATION and carton/container labels for CINRYZE® [C1 esterase inhibitor (human)] to be acceptable from a promotional and comprehension perspective. The review committee required revisions to the PI to improve accuracy and clarity of the safety and efficacy information in the label. The review committee also required revisions to the carton/container labels. All issues were acceptably resolved after exchange of information and discussions with the applicant.

11. RECOMMENDATIONS AND RISK/ BENEFIT ASSESSMENT

a) Recommended Regulatory Action

The review committee recommends the approval of this supplement.

Although the youngest enrolled subject in Study SHP616-301 was 7 years of age, the Clinical Reviewer recommends an indicated age range of 6-11 years in the PI, given the expected similarity of the PK profile for CINRYZE when administered to patients who are as young as 6 years of age. When compared to the baseline observational

period, a reduction in the time-normalized number of angioedema attacks per month during the 12-week treatment period was observed for both CINRYZE 500 U and CINRZYE 1000 U. Although a greater mean reduction in the normalized number of angioedema attacks per month was observed with the higher 1,000 U dose of CINRYZE compared to the lower 500 U dose (-3.0 and -2.6 attacks per month, respectively) and a greater mean percent reduction in HAE attacks (84.5% and 71.1% reduction compared to baseline) was also observed for the 1,000 U dose compared to 500 U, the differences in these outcomes between the two doses were fairly small. Given the limited sample size of the study, the Clinical Reviewer's assessment is that the primary clinical outcomes do not conclusively demonstrate that 1,000 U has superior clinical efficacy compared to 500 U, but rather that the demonstrable efficacy for the two dose levels at least appears to be comparable. Therefore, the Clinical Reviewer's opinion is that the lower dose (500 U) administered every 3 to 4 days is a reasonable starting dose for routine prophylaxis against angioedema attacks in this age group, with a maximum dose of 1000 U being reserved for patients who have an inadequate clinical response to the 500 U dose.

b) Risk/Benefit Assessment

The efficacy of CINRYZE (500 U and 1,000 U) for the prevention of HAE attacks and the reduction in the severity of attacks and the requirement for acute treatment was demonstrated in Study SHP616-301. There were no overt safety issues identified. Therefore, the Risk/Benefit profile of the product is sufficiently favorable to support licensure.

c) Recommendation for Postmarketing Activities

The review committee agrees with the pharmacovigilance plan that is specified in the Applicant's proposed pharmacovigilance plan. Standard pharmacovigilance will continue through passive reporting. FDA will continue to monitor reports of thrombotic and thromboembolic events and other potential safety signals. FDA will maintain the option of requesting additional active surveillance via a postmarketing registry if the need arises.

d) Postmarketing Requirements and Commitments

Postmarketing Commitments Subject to Reporting Requirements Under Section 506B

1. ViroPharma will re-test the available samples retained from Phase 3 Study (Protocol 0624-301) with the new immunogenicity assay and will submit the results of the study in a "Postmarketing Submission - Final Study Report" by January 1, 2020.

Postmarketing Commitments Not Subject to Reporting Requirements Under Section 506B

2. ViroPharma will develop and validate a sensitive and well controlled assay for testing CINRYZE immunogenicity. In the event a sensitivity of (b) (4) for screening and confirmation assays cannot be achieved, ViroPharma will provide data to support the highest sensitivity possible. A description of the proposed immunogenicity assays for CBER evaluation will be provided by January 1, 2019, as a "Postmarketing Study Commitments – Status Update" and the assay methods SOP and validation report will be submitted as a "Prior Approval Supplement" by (b) (4) .