Statistical Review and - CINRYZE

Date:
Type/Application ID/Amendment #: STN 125267/18 **Phase:** 4
Title: Cinryze
Proposed Use (Indication): to evaluate the safety and efficacy of Cinryze (Cl inhibitor [human]) replacement therapy dose escalation to lower the RAE attack rate in inadequately controlled RAE patients
Sponsor: LEV Pharmaceuticals
Product name(s)/Product Type:
Cinryze – C1 eserase inhibitor
Review Team:
Charles Maplethorpe, M.D.
Nannette Cagungun
From: Boris Zaslavsky, Ph.D.
Through: Ghanshyam Gupta, Ph.D.
cc: HFM-215/Henry Hsu
HFM-217/Ghanshyam Gupta
HFM-210/Steven Anderson
HFM-210/Robert Ball
HFM-215/Chronological File
Executive Summary: The sample size is estimated correctly for the one-sided test. The medical reviewer should decide whether the one-sided test is acceptable. If the two-sided test is recommended, the sample size should be increased to 32 patients.
Reviewer Title: Mathematical Statistician
Reviewer Signature:
Review Date:
Supervisory Concurrence:
Supervisor Title: Branch Chief
Concur _____ Not Concur _____
Supervisory Signature:

Comments to the Draft Protocol
Protocol LEVP2008-1: Phase 4 Study to evaluate the safety and efficacy of Cinryze (Cl inhibitor [human]) replacement therapy dose escalation to lower the RAE attack rate in inadequately controlled RAE patients

The primary endpoint of the study is the estimate of the probability P that a patient meeting entry criteria and initiating the dose escalation algorithm will be classified as a success. Overall study success is defined as finding evidence consistent with P≥ 20%, where P≤ 5% is regarded as ignorable. Thus, the null hypothesis is that P ≤5% and the specific alternative hypothesis is that P≥ 20%. Based on this specification of hypotheses and a target type I error probability of one-sided 0.05 and a target power of 80% the following table defines the requi£red study size and provides the statistical operating characteristics:
The sponsor wrote:

Null hypothesis (P = probability of individual patient success) P≤0.05
Alternative Hypothesis P> 0.05
Specific Alternative Hypothesis P≥0. 20
Target One Sided Type I Error Probability (alpha) < 0.05
Target Power >80%
Total Evaluable Patient Accrual Target 27 (computed from above using the binomial distribution)
Definition of Hypothesis to be tested P≤0.05
Statistical Significance level for testing hypothesis (one-sided) 0.05
Success (based on data collected) is the # successes for rejection in exactly 27 patients ≥4)
Statistical Operating Characteristics

True probability of success	**(P) Probability of study success**
0.05 (null)	0.0437 (actual alpha)
0.10	0.282
0.15	0.593
0.20 (specific alternative)	0.818 (actual power)
Maximum half-width of exact 95% confidence interval for 27 patients equals ±21% Minimum toxicity probability having Pr(occurring>1 time) ≥90% equals 9%	

Comments to CBER:
The sample size of 27 patients is correct for the one sided Type I error 0.05.
Usual CBER standard is either two-sided 0.05 or one-sided 0.025 type I error. For the two-sided test, the sample size should be 32 patients or more.
I do not understand, why 4 out of 27 (4/27 = 0.148) is defined as success.