

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

NDA 22-156

STATISTICAL REVIEW(S)

Statistical Review and Evaluation

IND #: 65,114

Sn #: 063

Date Received: 10/19/2006

Drug Name: Clevidipine Injection (H324/38)

Indication: _____

Statistical Reviewer: Ququan Liu

Medical Reviewer: Mehul Desai

Sponsor: The Medicines Company

Protocol Title: Evaluation of Clevidipine in the perioperative treatment of hypertension assessing safety events with sodium nitroprusside (Protocol TMC-CLV-03-05) or nicardipine (Protocol TMC-CLV-03-04) as active comparator.

Trial Specification:

Trial Phase: III

Multicenter: Yes

Blinding: Open label

Control: Active control

Randomized: Yes (1:1)

Treatment Arms: Clevidipine

Sodium nitroprusside OR Nicardipine

Treatment Schedule: Study drug administration may be initiated after an arterial line is inserted and upon the occurrence of perioperative hypertension. Study drug administration may continue perioperatively by titration to effect as clinically necessary until discharge from the ICU.

Type of Hypothesis to be tested: No strict statistical hypothesis test will be conducted.

Study Objective: The primary objective of the study is to establish the safety of clevidipine in _____ when compared to sodium nitroprusside or nicardipine.

Primary Endpoint: The incidences of death, stroke, myocardial infarction, and renal dysfunction that occur within the period from initiation of study drug infusion through post-operative Day 30.

Secondary Endpoint:

- Blood pressure
- Use of alternative intravenous antihypertensive agent, if any
- Heart rate
- Incidence of reflex tachycardia
- Clinical laboratory parameters
- Incidence of hypovolemia and volume of fluids administered
- Incidence of spontaneously reported serious and non-serious adverse events

- Incidence and duration of atrial fibrillation, atrial flutter, supraventricular arrhythmia and/or supraventricular tachycardia

Sample Size: A total 250-500 patients will be enrolled into each of the studies. No formal sample size and/or study power was calculated.

Primary Safety Analysis:

Incidences of primary endpoint events will be summarized by treatment group and study site.

Secondary Analysis:

1. Blood pressure: AUC_{SBP-D} will be compared in the two groups using Wilcoxon rank-sum test.
2. Other variables: Descriptive statistics will be applied.

Statistical Issues and Comments to be conveyed to the Sponsor:

1. Since the evaluation for primary endpoints is objective and blinded, bias towards outcome evaluation due to open-label (unblinded treatment) seems to be minimal. Some statistical analysis comparing primary endpoints between treatment groups could be considered.

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10/31/2006

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/s/

Ququan Liu
11/6/2006 01:48:39 PM
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James Hung
11/6/2006 01:59:00 PM
BIOMETRICS

STATISTICAL REVIEW AND EVALUATION

IND #: 65,114, SN-032

DRUG NAME: Clevidipine (Clevelox) injections

INDICATION: _____

APPLICANT: The Medicines Company

DOCUMENTS REVIEWED: Special Protocol, dated 12/06/04

STATISTICAL REVIEWER: Valeria Freidlin, Ph.D. (HFD-710)

MEDICAL REVIEWER: Mehul Desai, M.D. (HFD-110)

STATISTICAL TEAM LEADER: James Hung, Ph.D. (HFD-710)

PROJECT MANAGER: Denise Sermon (HFD-110)

**ACTING BIOMETRICS DIVISION
DIRECTOR:** Kooros Mahjoob, Ph.D. (HFD-710)

INTRODUCTION

The sponsor submitted a Special Protocol TMC-CLV-03-01 (ESCAPE_1) to evaluate preoperative antihypertensive effect of clevidipine in cardiac surgery. The study has been completed but the datalock and unblinding have not occurred.

Study TMC-CLV-03-01 (ESCAPE_1) is a phase 3, randomized, double-blind, parallel, placebo-controlled study on patients scheduled for cardiac surgery who have preoperative hypertension (systolic BP \geq 160 mmHg). Patients are randomized in a 1:1 ratio, stratified by site to clevidipine or placebo. Approximately 10 centers will be used to enroll about 100 patients. Study drug infusion will be titrated. It will continue for at least 30 minutes and less than 1 hour.

The primary efficacy population will be MITT population defined as all patients who were randomized and met the post-randomization inclusion criteria immediately prior to the initiation of blinded study drug infusion.

The primary efficacy endpoint is the incidence of bailout, which is defined as, at any time within 30 minute period beginning with study drug initiation, either

1. the premature and permanent discontinuation of study drug infusion due to lack of efficacy or safety

2. the failure to decrease the SBP by a minimum of 15% from baseline value.

For the MITT population, missing bailout record will be imputed with YES for clevidipine group and NO for the placebo group on a worst-case scenario.

The proportion of patients who bailed out will be compared using the Chi-square test.

Secondary Efficacy endpoints.

1. Time to onset of effect. It is defined as the duration from start of the study drug infusion to the time when a first reduction of 15% from baseline in SBP occurred during the double-blind period. Kaplan-Meier survival curve will be presented by treatment. Treatment comparisons will be assessed by the log-rank test.
2. MAP, change from baseline. MAP will be derived as follows:
$$\text{MAP} = (\text{SBP} + 2 \times \text{DBP}) / 3.$$
Absolute and percent change from baseline to the minimum MAP within first 30 minutes for patients without bailout or until time to bailout for patients who bailed out will be summarized. Absolute change from baseline will be analyzed by ANCOVA with treatment as factor and baseline MAP as a covariate. Percentage change will be assessed by ANOVA model with treatment as factor. Statistical analyses of absolute and percent change at 2, 5, 10, 20, and 30 minutes following the initiation of the treatment will be also performed.
3. HR, change from baseline
Absolute and percent change from baseline to the maximum HR within first 30 minutes for patients without bailout or until time to bailout for patients who bailed out will be summarized. Absolute change from baseline will be analyzed by ANCOVA with treatment as factor and baseline HR as a covariate. Percentage change will be assessed by ANOVA model with treatment as factor. Statistical analyses of absolute and percent change at 2, 5, 10, 20, and 30 minutes following the initiation of the treatment will be also performed.
4. Incidence of bailout by causality. This will be compared using the chi-square test.

Additional analyses

Analyses of SBP, DBP, and Pulse pressure (PP=SBP-DBP) will be performed in the same manner as MAP.

Sample size

Fifty patients per group will have 85% power to demonstrate difference between the two groups at a 2-sided significance level of 0.05.

Interim analysis

The DSMB is periodically monitoring the study to ensure patient safety. Because the DSMB is for safety only, the nominal alpha level will not be adjusted.

Reviewer's Comments

1. The sponsor needs to be reminded of the usual evidence standard that, for a single pivotal study, statistical significance level should be at a level much smaller than 0.05.
2. For the primary efficacy analysis we recommend using the CMH test stratified for center instead of the chi-square test.
3. There are many secondary endpoints and secondary analyses in the SAP. To control the overall type 1 error, the SAP should either include an alpha spending algorithm or a hierarchical testing procedure which will require specification of an order in which the secondary analyses will be conducted. In the hierarchical testing procedure, the next secondary analysis is conducted only if the previous analysis gave a statistically significant result.

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/s/

Valeria Freidlin
1/3/05 10:57:41 AM
BIOMETRICS

Jim- You told me to DFS this review before
my leave. Valeria

James Hung
1/3/05 11:16:52 AM
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Kooros Mahjoob
1/3/05 03:29:37 PM
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