Statistical Analysis Plan

CLIN_2014_TLV_001

A Post-Authorization Safety Study of the Use of Intravenous Telavancin (VIBATIV) in the Clinical Setting

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Contents

1 Introduction

As per the International Conference on Harmonisation (ICH) E9, the purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and to include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.

This Statistical Analysis Plan (SAP) assumes familiarity with the study protocol ('the protocol'). In particular, the SAP is based on the planned analysis specification as written in the protocol Section 7 "Statistical Methodology". Therefore, SAP readers may consult the protocol for more background information on the study..

2 Study Design and Objectives

This is a multi-centre, multi-national, post-marketing, retrospective chart review in 500 patients to further characterize the adverse drug reaction profile of telavancin when used in the clinical setting.

2.1 Primary Objective

The primary objective is to assess changes in renal function during and after treatment with telavancin.

2.2 Secondary Objectives

Secondary objectives are to assess telavancin in the clinical setting with respect to:

a) Fatal outcomes
b) Cardiac disorders
c) Liver and hepatobiliary disorders
d) Tinnitus and hearing loss
e) The effectiveness of risk minimization measures, including:
    a. adherence to the SmPC including:
        i. Use in the recommended indication
        ii. Avoidance of use in contraindicated conditions
        iii. Correct initial dose and dose adjustment
        iv. Renal monitoring
        v. Documentation of a negative pregnancy test in women of child-bearing potential (WCBP)
    b. Use of the pregnancy checklist

3 Observation Period

As this is a non-interventional, retrospective chart review charts will be reviewed from the patient's hospital admission until discharge. If any outcomes of interest, such as renal impairment, are not resolved at the time of discharge, then charts will be reviewed for follow-up visits for at least 6 months after the end of treatment or until resolution is observed.

4 Analysis Sets

Both efficacy and safety will be evaluated in patients who were treated with at least one dose of telavancin based upon a decision by their treating physician. Further, efficacy will be assessed in both clinically and microbiologically evaluable patients.

5 Variables for analysis

5.1 Primary Variables

The following primary variables will be evaluated in relation to renal function and disorders:

a) Absolute and change from baseline in serum-creatinine and BUN values over time
b) Number of patients with serum creatinine increases of (i) ≥ 1.5, (ii) ≥ 2 and (iii) 3 times baseline
c) Number of patients meeting RIFLE criteria for acute renal failure (as defined in Appendix 2 of the protocol)

5.2 Secondary Variables

The following secondary variables will be evaluated:

a) Mortality
    (i) All cause mortality within 28 days of starting telavancin or during treatment with telavancin, whichever is the longer
b) Cardiac disorders
    Number of patients with:
    (i) QT prolongation on ECG
    (ii) AEs of cardiac arrhythmia
    (iii) Episodes of torsade de pointes on ECG
c) Liver and hepatobiliary disorders
    (i) Absolute and change from baseline in
        1) ALT
        2) AST
        3) ALP
        4) Total bilirubin
    (ii) Number of patients with 2, 3, 5 and 10 fold increases relative to baseline in:
        1) ALT
        2) AST
        3) ALP
        4) Total bilirubin
    (iii) Number of patients with AEs relating to hepatic impairment
d) Tinnitus and hearing loss
    Number of patients with:
    (i) Positive/negative tonogram results.
    (ii) AEs relating to hearing loss and tinnitus.
e) Adherence to the SmPC:
    Will be assessed by number of patients:
    (i) correctly treated as per indication
    (ii) treated despite contra-indication
    (iii) receiving the correct Initial dosage
    (iv) with correct adherence to the SmPC renal monitoring schedule including appropriate dosage adjustment
    (v) with documentation of negative pregnancy test in WCBP

5.3 Other Variables

Other variables of interest include:

a) Total duration of hospital stay
b) Duration of stay in ICU
c) Duration of ventilation for patients with nosocomial pneumonia (NP)
d) Duration of treatment exposure

6 Statistical Methods

6.1 General

In general, all demographic, efficacy and safety variables will be summarised using descriptive statistics and graphs as appropriate. Continuous variables will be summarised by mean, SD, median, minimum, maximum and number of patients. Categorical variables will be summarized using frequency tabulations. Individual data will be presented in patient listings. Medical history and prior and concurrent medications will be summarised and listed.

AEs will be classified using the MedDRA classification system. The simple frequency and rate per patient-unit time of AEs will be tabulated by System Organ Class (SOC) and MedDRA Preferred Term. SAEs (including those defined in Section 5.5 of the protocol), AEs leading to discontinuation of telavancin and AEs leading to death will be listed and summarised separately, again by SOC and Preferred Term.

Time to first occurrence of a given AE, time to discontinuation due to AE and time to death will be summarised graphically by Kaplan-Meier curves.

Any statistical tests performed (for example in multivariate regression analyses) will be assessed at a 2-sided significance level of 5% unless otherwise specified.

6.2 Missing Data, Patient Follow-up and Exposure to Telavancin

In a retrospective chart review study missing values are to be expected, being inherent to the design. Given the nature of such a non-randomised design, methods to impute missing data (such as pattern mixture modelling or multiple imputation) are not wholly appropriate. However, within the context of the primary variables absolute and change from baseline in serum-creatinine and BUN values over time, the analysis methods described in Section 7.1.1 of this SAP automatically account for missing data.

Further, given the expected variability in individual patient follow-up, the use of simple percentages to summarise data and conventional logistic regression techniques to analyse data are problematic. To allow for variable patient follow-up, event rates per patient-unit time will be used in place of simple percentages and Negative Binomial regression analysis in place of logistic regression.

Patient exposure to telavancin will be calculated as the number of days between start and cessation of telavancin. If a patient restarts telavancin, then total exposure will be the sum of all exposures to the drug. Also the total dose of telavancin delivered will be calculated for each patient.

6.3 Visit windows

The usual concept of visit windows does not easily transfer to a retrospective chart review design. Rather, all chart data reviewed during treatment with telavancin will be included in summaries and analyses. Where serious clinical AEs (such as renal impairment) remain unresolved at the time of discharge, charts will be reviewed for any further follow-up data for a period of at least 6 months or until resolution. Data on telavancin alone and data on telavanicin plus 6 months additional chart review will be summarised separately.

7 Analysis of Efficacy

Microbiological outcome will be summarized using frequency tabulation and stratified by duration of exposure to telavancin to allow for a variable follow-up and duration of treatment between patients. Percent of patients achieving a given outcome by duration of exposure to telvancin will be displayed together with a descriptive 95% confidence interval. Efficacy data will also be similarly displayed by MIC.

7.1 Analysis of Safety

7.1.1 Analysis of Primary Variables

a) Absolute and change from baseline in serum-creatinine and BUN values over time

Serum creatinine and BUN values over time will be analysed using a mixed model repeated measures (MMRM) approach. A random slopes and intercepts model will be used to allow slopes and intercepts to vary between patients and the overall slope and standard error (SE) estimated. The corresponding statistical model can be written as follows:

$Y_{ij} = (\alpha + a_i) + (\gamma + g_i)t_{ij} + \varepsilon_{it}$

Where

- Y_{ij} is the j^{th} observation on the i^{th} patient
- t_{ij} is the time of the j^{th} observation on the i^{th} patient
- α and γ are intercept and slope fixed effects
- a_i and g_i are random specific components of the intercept and slope for the i^{th} patient
- ε_{ij} is the random error for i^{th} patient at j^{th} observation

Further, a_i and g_i are assumed to be normally distributed with mean 0 and arbitrary covariance matrix. Also, ε_{it} are assumed to be independent and normally distributed with mean 0 and variance σ_{ε}^2.

For example, for absolute serum creatinine values over time, the model may be fitted in SAS using the following code:

```
PROC MIXED data=SrCr  order=internal  covtest ;
   CLASS patient;
         MODEL creatinine= time /solution CL ddfm=KR;
         RANDOM intercept time/ type=un subject=patient solution g Gcorr;
        ODS  output solutionf=fixed solutionr=random;
RUN;
```

From this analysis, the resulting slope estimate and its SE provides a trend analysis allowing the rate of change of serum creatinine and BUN values with telavancin treatment over time to be gauged.

The slope estimate, its SE and 95% CI will be provided for the absolute and change from baseline in serum-creatinine and BUN values over time.

If the analysis fails to converge, the following covariance structures will be tested for the within patients errors: compound symmetry, autoregressive 1 and Toeplitz. The covariance structure converging to the best fit, as determined by Akaike's information criterion, will be used.

b) Number of patients with serum creatinine increases of (i) ≥ 1.5, (ii) ≥ 2 and (iii) 3 times baseline

The number of patients with serum creatinine increases of (i) ≥ 1.5, (ii) ≥ 2 and (iii) 3 times baseline will be tabulated and the rate of such increases per patient-day exposure to telavancin displayed. This tabulation will be performed for all patients and for the subset of patients with normal serum creatinine values at baseline.

Further, and to allow for patients who may experience multiple serum creatinine increases over time, the rate of serum creatinine increases per patient-day will be estimated via Negative Binomial regression modelling. In SAS, this may be achieved by fitting the following model:

```
PROC GENMOD DATA=SrCr;
   MODEL count = / DIST=NB TYPE3 LINK=LOG OFFSET=logt Scale=deviance;
   ODS OUTPUT modelfit=modelfit;
   ODS OUTPUT modelfit=modelfit (WHERE=(criterion="Deviance"));
RUN;
```

where 'count' = number of serum creatintine increases in a patient and 'logt'=natural logarithm of a patients' exposure time.

c) Number of patients meeting RIFLE criteria for acute renal failure

Will be analysed as per the number of patients with serum creatinine increases.

d) Multivariate Regression Analyses

If feasible, Primary Variables a)-c) will be explored via multivariate regression analyses with covariate factors included for:

a) baseline serum creatinine level
b) concomitant nephrotoxic medication (y/n)
c) weight (kg)
d) initial telavancin dose
e) diagnosis of diabetes mellitus (y/n)
f) baseline renal disease (y/n)
g) baseline cardiac disease (y/n)

For Primary Variable a), the MMRM model will be extended to include these covariates and both full and stepwise analyses performed with selection criteria of $p<0.05$ and deselection criteria of $p<0.10$. For Primary Variables b) and c), the Negative Binomial model will be similarly extended and full and stepwise analyses performed.

The aim of these analyses is to explore which of the listed covariate factors might me most strongly associated with renal function disorder with telavancin therapy.

7.1.2 Secondary Variables

a) Mortality

All deaths within 28 days of starting telavancin or during treatment with telavancin, whichever is the longer, will be counted and expressed as a rate per patient-day exposure to telavancin. Time to death will be displayed by Kaplan-Meier curve and median survival time estimated along with its 95% confidence interval using Greenwoods formula. Causes of death will be MedDRA coded and summarised by SOC and Preferred Term. Data will also be presented in line listings.

b) Cardiac disorders

The number of patients with QT prolongation on ECG, AEs of cardiac arrhythmia and torsade de pointes episodes will be presented relative to total patient-days exposures to Telavancin. Time these events will be displayed by Kaplan-Meier curve if possible. AE data on these and all other cardiac disorders will be listed summarised by MedDRA SOC and Preferred Term.

c) Liver and hepatobiliary disorders

Absolute and change from baseline in liver enzymes values over time will be summarised in relation to duration of telavancin exposure. The rate of change over time will also be estimates via MMRM analysis as described for the Primary Variable analysis.

Further, the number of patients with 2, 3, 5 and 10 fold increases in (i) ALT (ii) AST (iii) ALP or (iv) total bilirubin relative to baseline will be tabulated and presented relative to total patient-days exposure to Telavancin. This tabulation will be performed for all patients and for the subset of patients with normal liver enzymes values at baseline. AE data relating to liver impairment and hepatobiliary disorders will be listed summarised by MedDRA SOC and Preferred Term.

d) Hearing losses and tinnitus

The number of patient with positive/negative tonogram results along with the number of patients with AEs relating to hearing loss and tinnitus will be presented relative to total patient-days exposure to Telavancin. AE data will be listed summarised by MedDRA SOC and Preferred Term.

7.1.3 Adherence to the SmPC

Adherence to the SmPC will be assessed using descriptive statistics. The number and percentage of patients

(i) correctly treated as per indication
(ii) treated despite contra-indication
(iii) receiving the correct Initial dosage
(iv) receiving correct dosage adjustments
(v) with correct adherence to the SmPC renal monitoring schedule
(vi) with documentation of negative pregnancy test in WCBP

will be tabulated and listed. The start dose of telavancin and its adequacy with respect to baseline renal function will also be summarised.

7.1.4 Other Variables

Total duration of hospital stay, duration of stay in the ICU and duration of ventilation for NP patients will be summarised descriptively by mean, SD, median, minimum and maximum values.

7.2 Subgroup Analysis

Sufficient of data permitting, the Primary Safety Variables will be evaluated in the following subgroups:

- Each covariate factor in the multivariate regression analysis of the Primary Safety Variables
    - baseline serum creatinine level (CrCl > 50, 30-50, < 30 ml/min)
    - concomitant nephrotoxic medication (y/n)
    - weight in (BMI < 35 and ≥ 35)
    - Initial telavancin dose
    - diagnosis of diabetes mellitus (y/n)
    - baseline renal disease (y/n)
    - baseline cardiac disease (y/n)
- Indication (NP and off-label use, i.e >21 days exposure to telavancin)
- Age group (< 65 and ≥ 65 years)

In terms of Secondary Safety Variables, mortality will be evaluated by baseline serum creatinine level and baseline renal disease.

7.3 Interim Reporting

Interim evaluations will be performed yearly and provided to the regulatory authority as discussed in the PSUR.