WPIII-33

Comparison of Laboratory Safety Data from Japanese and Non-Japanese in Linezolid Phase I Studies

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ABSTRACT

Introduction. The laboratory safety data of linezolid (lzd) pooled from 6 multi-dose Phase I studies were compared in 65 Japanese (J) and 56 non-Japanese (non-J) subjects.

Methods. Hematologic parameters assessed for toxicity were hemoglobin (HGB), red blood cell (RBC), white blood cell (WBC), platelet (plt) and absolute neutrophil counts (ANC). Hepatic toxicity was assessed by alanine and aspartate amino transferases (ALT/AST) concentrations. Scatterplots of the absolute value of the safety parameter and the end of treatment (EOT) change from baseline versus the exposure measure (cumulative dose) were examined.

Results. No relationship was apparent between exposure and absolute value or EOT change from baseline for the HGB, RBC, ANC, ALT, or AST. Trends for mild decreases in plt values with increasing exposure were apparent in both populations. For WBCs, the J subjects appeared to have lower baseline values, but had response trends similar to non-J over time.

Conclusions. Overall, there were no relevant differences in hematologic or hepatic response to similar lzd exposure between J and non-J subjects. Based in part on this information, lzd was approved for use in Japan/Asia at the same dosage used in the U.S.

INTRODUCTION

- The "Ethnic Factors in the Acceptability of Foreign Clinical Data" (E5) guidance facilitates the registration of medicines among International Conference on Harmonization (ICH) regions.
- Ethnic factors include those relating to genetic, physiologic, cultural, and environmental characteristics of a population.
- The guidance provides a framework for adequate evaluation of the impact of ethnic factors on a drug's effect (i.e., efficacy and safety at a particular dosage and dose regimen), and recommends development strategies that permit this evaluation without duplication of clinical studies.
- Acceptance of foreign clinical data in the new region may be achieved by generating "bridging" data in order to extrapolate the safety and efficacy data from the population in the foreign region to the population in the new region.
- Comparison of hemopoietic and hepatic laboratory safety data from Caucasians and Japanese subjects enrolled in Phase I linezolid studies was undertaken as part of the bridging analyses performed to obtain approval for use of linezolid in Japan/Asia.

METHODS

Subjects

- Data was obtained from 56 Caucasians and 65 Japanese subjects enrolled in six Phase I studies of linezolid (Table 1).

Table 1: Phase I Studies Included in the Safety Analyses

Region	Study Design	Treatment Group, Route, Dose, & Regimen	Subjects Treated (All ITT*)
Japan	Randomized, single-blind, placebo-controlled study in healthy volunteers	Linezolid PO 125, 250, 375, 500, or 625 mg BID following breakfast or dinner; 12 subjects received 250 mg TID following breakfast, lunch, and dinner Duration: 9 days	47
Japan	Randomized, single-blind study with placebo control	Linezolid IV 300, 400, or 500 mg BID after breakfast and dinner Duration: 9 days	18
UK	Randomized, double-blind, placebo-controlled, parallel group, dose escalation assessing safety, tolerance, and PK of multiple oral doses	Linezolid PO 100, 200, 400, 625, 725 mg TID Duration: 10 days	24
UK	Randomized, double-blind, placebo-controlled, parallel group, dose escalation assessing safety, tolerance, and PK of multiple IV doses	Linezolid IV 250, 400, 500 mg TID Duration: 7 days	9
US	Randomized, double-blind, placebo-controlled, dose escalation assessing safety, tolerance, and PK for multiple oral doses	Linezolid PO 375, 500, 625 mg BID Duration: 15.5 days	12
US	Randomized, double-blind, vehicle-controlled, dose escalation assessing safety, tolerance, and PK for multiple IV doses	Linezolid IV 500, 625 mg BID Duration: 8.5 days	11

* Intention to treat

Safety Measures

- **Hematologic:** hemoglobin (HGB) values, red blood cell (RBC) counts, white blood cell (WBC) counts, absolute neutrophil counts (ANC), and platelet counts
- **Hepatic:** Alanine and aspartate aminotransferases (ALT/AST)

Trend Analysis Plots

- Absolute safety parameter value versus exposure measure
- End of treatment (EOT) safety parameter value minus the baseline value versus exposure measure
- Exposure measure: cumulative dose (mg/kg) of linezolid

RESULTS

Patient Demographics

Table 2: Subject Demographic Characteristics Stratified by Race

Parameter	Combined (N=121)	Japanese (N=65)	Caucasian (N=56)	P-Value
Age (yrs) Mean (SD) Range	25.60 (7.00) 18-48	22.48 (2.43) 20-35	29.22 (8.66) 18-48	0.0001*
Height (cm) Mean (SD) Range	174.16 (6.77) 156.6-190.5	171.91 (5.63) 156.6-182.3	176.77 (7.09) 162.6-190.5	0.0003*
Weight (kg) Mean (SD) Range	68.23 (10.30) 44.2-94.8	61.59 (6.88) 44.2-80.7	75.93 (8.00) 60.6-94.8	0.0001*

* Statistically significant difference ($p \leq 0.05$)

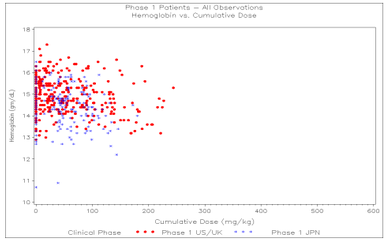
- Previous analyses showed that mean weight-corrected clearance estimates were similar in Japanese and Caucasian subjects
- Displays for all safety measures were performed; however, the displays shown for hemoglobin, neutrophil counts, platelet counts, and alanine aminotransferase were most demonstrative.

Table 3: Comparison of Safety Parameter Values in Japanese and Caucasians

Safety Parameter	All Observations		EOT Change From Baseline	
	Caucasian	Japanese	Caucasian	Japanese
Hemoglobin, gm/dL N Mean (SD)	308 14.91 (0.83)	201 14.46 (0.91)	56 -0.35 (0.61)	65 -0.34 (0.49)
Neutrophil Count, Thou/uL N Mean (SD)	290 3.04 (0.83)	201 2.83 (0.85)	55 -0.11 (1.32)	65 -0.22 (1.02)
Platelet Count, Thou/uL N Mean (SD)	308 211.1 (48.92)	201 219.14 (39.18)	56 -10 (26.81)	65 -8.72 (20.65)
Alanine Aminotransferase U/L N Mean (SD)	305 26.22 (16.35)	183 15.74 (8.13)	56 9.75 (20.5)	65 6.51 (8.45)

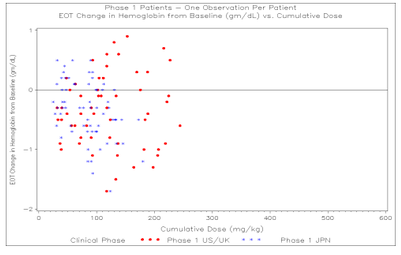
Hematologic Parameters

Figure 1: Hemoglobin (gm/dL) Versus Cumulative Dose (mg/kg)



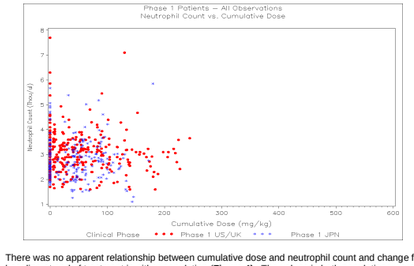
- There was no apparent relationship between cumulative dose and EOT change from baseline for HGB as shown in **Figure 2**. Japanese and Caucasian subjects had similar distributions in hemoglobin values. Although subjects had both increases and decreases from baseline values, there were slightly more subjects with declines from baseline. Most declines were < 1 gm/dL.

Figure 2: Change from Baseline at End of Treatment for HGB (gm/dL) Versus Cumulative Dose (mg/kg)



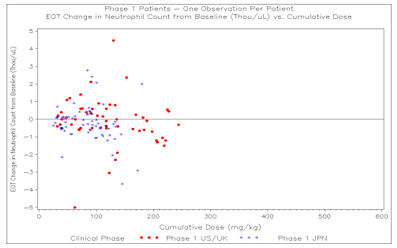
- There was a slight decrease in neutrophil counts with cumulative dose, but not considered clinically significant. Japanese and Caucasian subjects had similar distributions in values (**Figure 3**).

Figure 3: Neutrophil Count (Thou/uL) Versus Cumulative Dose (mg/kg)



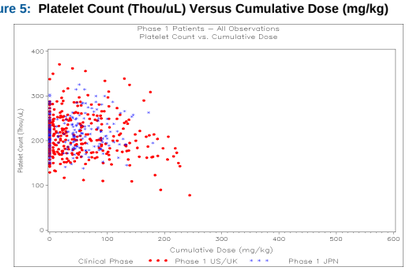
- There was no apparent relationship between cumulative dose and neutrophil count and change from baseline at end of treatment in either population (**Figure 4**). The values in both populations were similar.

Figure 4: Change from Baseline at End of Treatment in Neutrophil Count (Thou/uL) Versus Cumulative Dose (mg/kg)



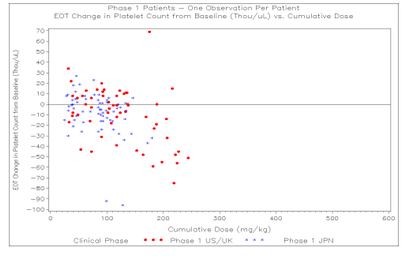
- Trends of small changes in platelet values with increasing exposure were apparent in both populations as shown in **Figure 5**. The decreases were mild, and values did not drop to a range that would put the subjects at medical risk. One subject had platelet counts below 100 x 1000 cells/μL on two occasions (78 and 90 x 1000 cells/μL), corresponding to changes from baseline of 51 and 39 x 1000 cells/μL. These changes are within the overall range for the population.

Figure 5: Platelet Count (Thou/uL) Versus Cumulative Dose (mg/kg)



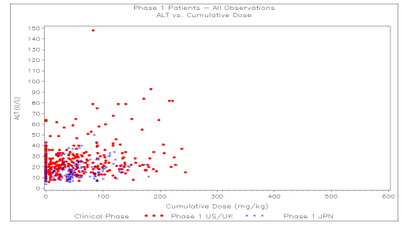
- There were downward trends in platelet counts with increasing cumulative doses. Overall, the EOT changes in platelet values were qualitatively similar in Japanese and non-Japanese subjects. Two Japanese subjects seem to have greater changes from baseline than other subjects. Both subjects had relatively high baseline platelet counts (300 and 287 x 1000 cells/μL). EOT values for the subjects were 204 and 195 x 1000 cells/μL, respectively. These changes from baseline were not clinically significant since all subjects remained within the normal range.

Figure 6: EOT Change from Baseline in Platelet Count (Thou/uL) Versus Cumulative Dose (mg/kg)



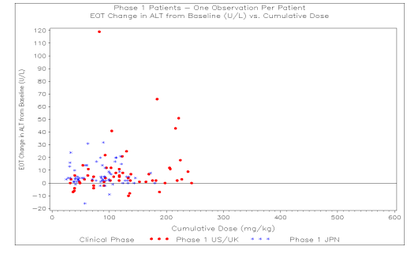
Hepatic Parameters

Figure 7: ALT (U/L) Versus Cumulative Dose (mg/kg)



- The ALT values for both populations were similar. There was no apparent relationship between cumulative dose and change from baseline at end of treatment in these values as shown in **Figure 8**.

Figure 8: Change from Baseline at End of Treatment for ALT (U/L) Versus Cumulative Dose (mg/kg)



CONCLUSIONS

- These displays were an important part of the regulatory package that led to linezolid approval in Japan/Asia at the same dosage used in the US.
- These displays helped to demonstrate that there were no relevant differences in hematologic or hepatic response to similar linezolid exposure between Japanese and non-Japanese subjects.