DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Errata and Clarifications to the FDA Briefing Document
Cardiovascular and Renal Drugs Advisory Committee (CRDAC) Meeting

September 13, 2012

NDA 203,009 (Lixivaptan)

1. Page 25 of the briefing document (page 24 of the Clinical Review) paragraph 2 states that "worsening of hyponatremia is defined as a reduction ≥3 mEq/L in serum sodium concentrations (BALANCE), not defined in the LIBRA and HARMONY trials".

The sentence should read: worsening of hyponatremia is defined as a reduction of ≥3 mEq/L in serum sodium concentration in all three trials (per final protocols).

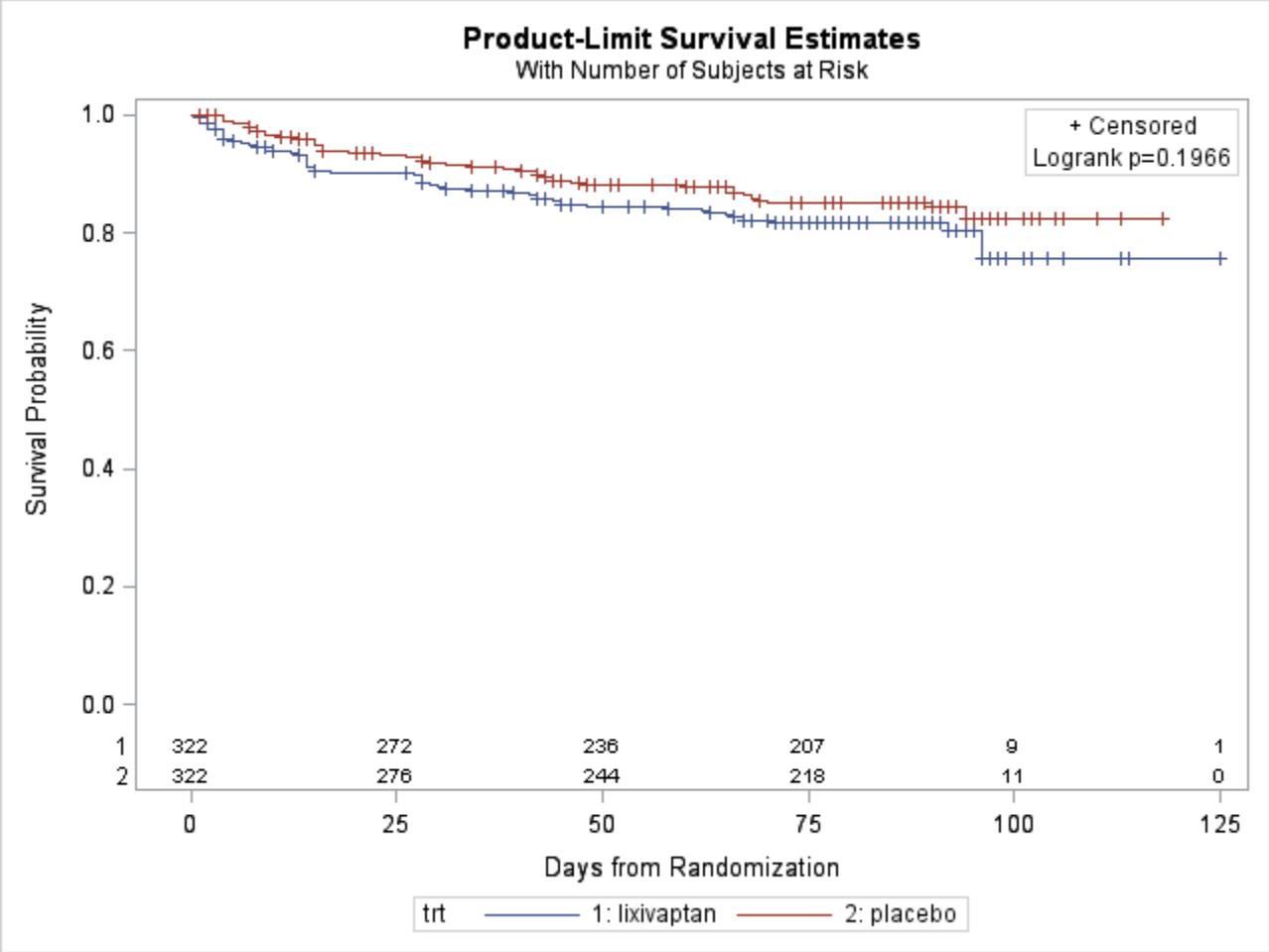
2. Page 62 of the briefing document (page 61 of the Clinical Review) states that "similar to the findings in the LIBRA trial, the percentage of subjects whose fluid restriction was initiated or tightened at end of treatment was numerically higher in the lixivaptan than placebo arm, raising the hypothesis that the efficacy may reflect, in part, the increased use of fluid restriction. Nonetheless, taking into consideration the numerically lower level of fluid restriction in lixivaptan than placebo arm at baseline (pretreatment), the level of fluid restriction on-treatment appears similar in the two treatment arms."

The sentence should read: The percentage of subjects whose fluid restriction was initiated or tightened at the end of treatment was lower in the lixivaptan than the placebo arm. Nonetheless, taking into consideration the higher level of fluid restriction in the lixivaptan compared to the placebo arm at baseline (Table 23), the level of fluid restriction on-treatment appeared similar in the two treatment arms.

3. On Page 75 of the briefing document (page 74 of the Clinical Review), a footnote states that "only subjects who died after 30 days post-treatment were counted in the above analysis".

The sentence should read: "only subjects who died within 30 days of treatment were counted in the above analysis".

4. Figure 8 on page 76 of the briefing document should be replaced with the following:



5. Page 83 of the briefing document (page 82 of the Clinical Review), Table 42 shows that 1 subject randomized to placebo died within Days 0-5, while the itemized count per Day shows a placebo subject dying on Day 4 and Day 5, respectively.

The table should be as follows:

Table 42. Deaths by day after randomization (BALANCE, per protocol safety population)

Days after randomization	Lixivaptan (N=291) n (%)	Placebo (N=289) n (%)
Day 0-5	**5 (1.7)**	**2 (0.6)**
Day 0	1 (0.3)	0 (0)
Day 1	1 (0.3)	0 (0)
Day 2	0 (0)	0 (0)
Day 3	1 (0.3)	0 (0)
Day 4	0 (0)	1 (0.3)
Day 5	2 (0.69)	1 (0.3)
Day 6-10	2 (0.69)	3 (1.0)
Day 11-30	15 (5.2)	11 (3.8)
Day 31-60	10 (3.4)	13 (4.5)
Day 61-90	10 (3.4)	7 (2.4)
Day >90	2 (0.7)	1 (0.3)
Total	44 (15.1)	37 (12.8)

[source: reviewer' analysis]

6. Page 90 of the briefing document (page 89 of the Clinical Review), immediately above Table 50 states "(see Table 51 below)".

The reference should read: (see Table 50 below).

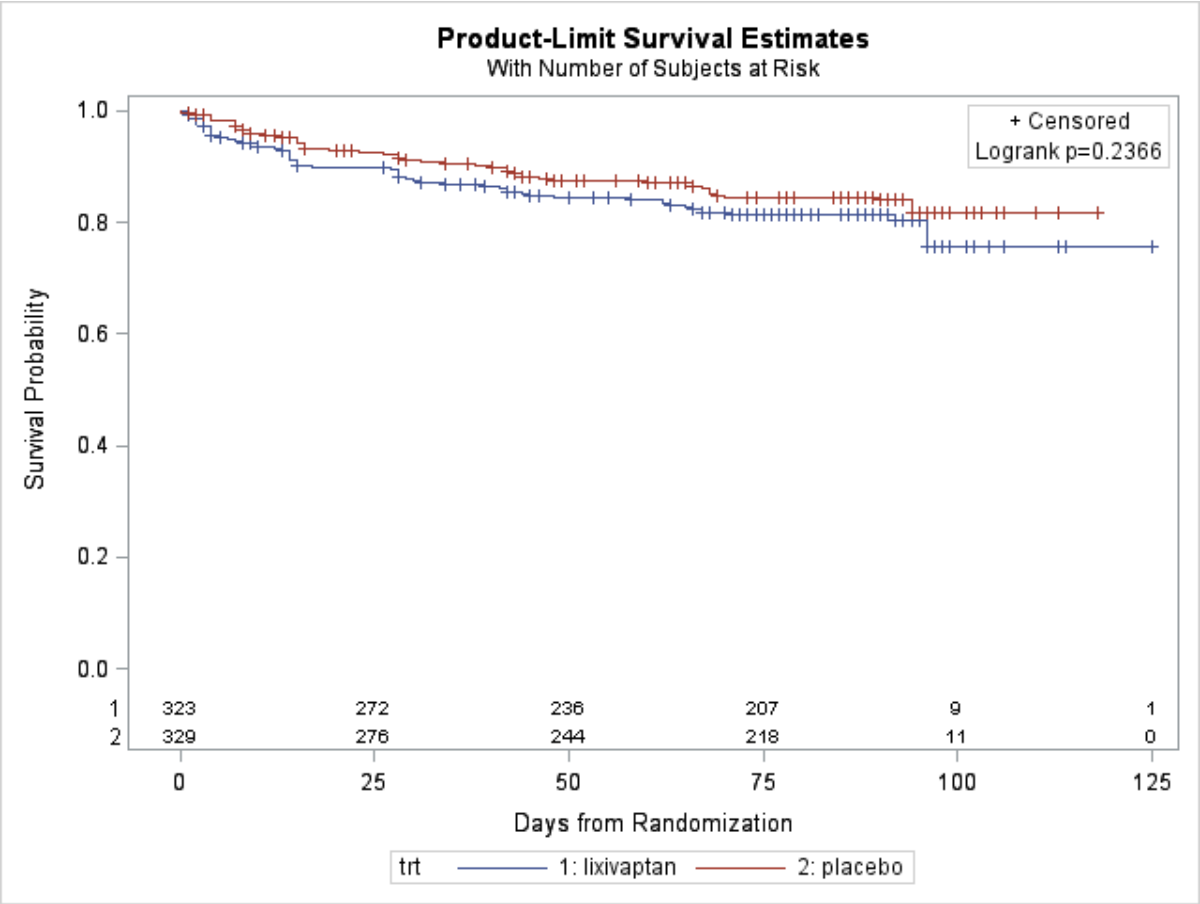
7. Page 102 of the briefing document (page 101 of the Clinical Review) states that the thorough QT studied the dose range of 25 to 100 mg BID.

The sentence should read: A thorough QT study did not show clinically significant QTc prolongation over the lixivaptan dose range studied (25 to 400 mg BID).

8. Page 157 of the briefing document (page 41 of the Statistical Review) paragraph 1 states that "The p-value from the log-rank test on time to all deaths was 0.26. If we only look at early deaths (deaths by Day 15), the log-rank test for time to all deaths up to Day 15 gives a nominal p-value of 0.036."

The sentence should read: The p-value from the log-rank test on time to all deaths was 0.24. If we only look at early deaths (deaths by Day 15), the log-rank test for time to all deaths up to Day 15 gives a nominal p-value of 0.033.

9. Figure 10 on page 157 of the briefing document should be replaced with the following:



10. Table 33 on page 160 of the briefing document (page 44 of the Statistical Review) should be as follows:

Study	Baseline Serum Sodium	Lixivaptan		Placebo	
		N	Mean Chg (Std)	N	Mean Chg (Std)
BALANCE	**missing**	**1**	**NA**	**6**	**NA**
	<=125	**31**	**6.6 (6.6)**	**36**	**6.5 (6.6)**
	>125 - <=130	53	4.9 (5.3)	61	3.2 (6.7)
	>130 - < 135	110	3.2 (4.0)	103	2.0 (4.6)
	>=135	128	0.1 (4.3)	123	-1.0 (3.9)
LIBRA	**missing**	**2**	**NA**	**1**	**NA**
	<=125	**14**	**10.4 (7.8)**	**19**	**9.4 (6.8)**
	>125 - <=130	19	5.9 (6.2)	19	2.7 (3.9)
	>130 - < 135	**17**	**3.7 (4.1)**	11	1.7 (3.8)
	>=135	**2**	**3.0 (5.7)**	**2**	**1.5 (2.1)**
HARMONY	<=125	17	5.6 (5.6)	6	3.5 (2.6)
	>125 - <=130	32	4.8 (3.5)	13	0.7 (4.6)
	>130 - < 135	69	3.2 (3.4)	18	0.8 (2.5)
	>=135	36	-0.1 (2.9)	15	-0.8 (3.1)