Food and Drug Administration

Bone, Reproductive and Urologic Drugs Advisory Committee Meeting

January 9, 2018

Errata to the FDA Briefing Materials

We have the following corrections and clarifications to the FDA briefing document for the January 9, 2018, Bone, Reproductive and Urologic Drugs Advisory Committee Meeting.

1- **Testosterone assay which required switch to new bioanalytic laboratory**. Entry into the study was based on testosterone concentrations measured in serum from plain tubes, whereas dose titration and the final efficacy analysis were based on testosterone concentrations measured in plasma from NaF-EDTA tubes. The serum testosterone assay remained constant throughout the study. The laboratory doing the plasma testosterone assay switched.

   A) On page 14 of the briefing document it states (bold-text added to identify the issue): *Once CLAR-15012 was initiated, a series of protocol changes were instituted based on the need to switch to a new bioanalytical laboratory secondary to potential issues with measurement of* ***serum*** *testosterone concentrations at the original bioanalytical laboratory. As a result of these changes, some patients had their dose titration visits delayed and thus, the median time of drug exposure for TU patients was 138 days compared to the planned median time of exposure of 105 days.*

   For the reasons explained above, the bolded word "serum" should be changed to "plasma".

   B) On page 57 of the briefing document it states:
      - *The Applicant re-analyzed stored pre-treatment testosterone samples using the new assay and confirmed that the population included in the study was appropriate.*

   As noted above, entry into the study was based on testosterone concentrations measured in serum. This assay performed as expected. The Sponsor did not re-analyze screening testosterone samples. For this reason, this bullet should be disregarded and considered to be deleted.

2- **Time interval between when ABPM was measured and final cuff BP was measured**. Both ABPM and clinic cuff pressures were measured prior to treatment initiation. ABPM was measured again at Visit 6 (placed at Visit 6 for a 24 hour monitoring period), and

cuff BP was measured at Visit 7 which occurred about 3 days after Visit 6. Hence the Visit 6 ABPM and Visit 7 cuff BP represent BP assessment after essentially the same duration of therapy.

On page 17 of the briefing document it states (bold-text added to identify the issue):

- *The FDA and Applicant agreed that the daytime SBP would be the basis of the primary ABPM analysis in that the daytime ABPM readings would most reasonably correlate with the morning cuff blood pressures that were being followed in the entire study population* ***and over a longer period of treatment****.*

For the reasons explained above, the phrase "*and over a longer period of treatment*" is an error and should be disregarded.

3- **Normal range for Axiron**. On Page 33 of the briefing document in Table 8 it indicates that the normal range against which the Axiron Cavg was assessed for efficacy was 300-1000 ng/dL (see highlight added to identify the issue).

Table 8: Comparative Testosterone and Testosterone Metabolite Exposures in CLAR-15012

End of Treatment	Clarus	
	Oral TU Arm	Topical Axiron
Testosterone Cavg (mean [SD]) (ng/dL)	402.5 (127.7); N=151	383.3 (131.4); N=48
Testosterone normal range (ng/dL)	252-907	300-1000
TU (mean [SD])	N/A	N/A
DHTU (mean [SD])	N/A	N/A
DHT Cavg (mean [SD]) (ng/dL)	73.3 (30.1); N=148	73.8 (30.9); N=52
Estradiol Cavg (mean [SD]) (pg/mL)	32.3 (13.9); N=146	33.0 (18.3); N=47

NA=not performed in study

The Axiron samples were collected in NaF-EDTA tubes, so were assessed against the relevant normal range, 252-907 ng/dL. For this reason, the Axiron normal range should be considered as 252-907 ng/dL, not 300 – 1000 ng/dL as shown in Table 8.

4- **Stability of TU in serum**. On page 46 of the briefing document it states (bold added to identify the issue)

The Applicant has proposed that ***TU is unstable in serum specimens*** *and that TU may be converted to T ex vivo when collected in serum collection tubes (the most commonly used specimen matrix for testosterone testing).*

TU is stable in serum, but it is not stable in blood from which the serum is isolated. The red blood cells are the source of the esterase activity. After the whole blood is allowed to coagulate and the tube is spun, the separation of the cell pellet from the serum stops the *ex vivo* conversion. Therefore, that sentence should read:

The Applicant has proposed that TU is unstable in **blood collected in plain (red-top) tubes ~~serum specimens~~** and that TU may be converted to T *ex vivo* when collected in **plain (red-top) ~~serum~~ collection tubes from which serum is isolat**ed (the most commonly used specimen matrix for testosterone testing).

5- **Subject 129-005**. On page 103 of the briefing document it states (bold added to identify issue)

*In addition, 1 **Oral TU** subject (129-005) was randomized in the study despite having an elevated PSA.*

Subject 129-005 was randomized and was receiving Axiron, not oral TU.