

Note to File 5

Official Title: A Phase III, Open label, Randomized, Multi-center Study of the Effects of Leukocyte Interleukin, Injection [Multikine] Plus Standard of Care (Surgery + Radiotherapy or Surgery + Concurrent Chemoradiotherapy) in Subjects with Advanced Primary Squamous Cell Carcinoma of the Oral Cavity / Soft Palate Versus Standard of Care Only

NCT Number: NCT01265849

Date: 29 April 2021

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CEL-SCI Clinical Study CS001P3

Note To File #5

The underlined Holm-Bonferroni testing text needs to be corrected to align with the three pre-defined secondary efficacy hypotheses to be tested.

The Holm-Bonferroni text follows:

“All p-values will be generated for primary, secondary, and tertiary endpoints. However, a Holm closed-sequential procedure will be used to control the probability of Type I error for the secondary hypotheses to be tested after the primary hypothesis with the exception of the individual OS, LRC, and PFS hypotheses which will simultaneously compare all three treatment groups simultaneously using contrast statements. To support registration claims, the Holm closed-sequential procedure will be used for the secondary efficacy endpoints only after the primary endpoint OS is tested statistically significant at 0.05 level. Thus, these secondary hypothesis tests will not require further Holm testing adjustment. With Holm-Bonferroni method, we will order the p-values from smallest to largest for the four comparisons of the remaining secondary endpoints, and compare the ordered p-values with  $0.05/(2-k+1)$ , where 2 is the number of secondary endpoints of interest (LRC, PFS) and k is the kth comparison in the sorted sequence, and k ranges from 1 to 3.”

The three pre-defined secondary efficacy hypotheses follow:

1. OS for Multikine + SOC vs. SOC controlling for pre-planned covariates
2. LRC for Multikine + CIZ + SOC vs. SOC controlling for pre-planned covariates
3. PFS for Multikine + CIZ + SOC vs. SOC controlling for pre-planned covariates.

Thus, the above underlined sentence needs to be corrected in three underlined places as follows:

With Holm-Bonferroni method, we will order the p-values from smallest to largest for the 3 comparisons of the remaining secondary endpoints, and compare the ordered p-values with  $0.05/(3-k+1)$ , where 3 is the number of secondary endpoints of interest (OS, LRC, PFS) and k is the kth comparison in the sorted sequence, and k ranges from 1 to 3.

In addition, it was noted that the following underlined text in Section 11.3 needs to be corrected:

### **11.3 Other Secondary Efficacy Analyses**

The planned secondary comparisons follow:

- (1) “OS in Multikine + CIZ + SOC vs. SOC
- (2) LRC in Multikine + CIZ + SOC vs. SOC
- (3) PFS in Multikine + SOC vs. SOC”

The first one is the primary endpoint (when it should be for MK + SOC) and the third one should be for MK + CIZ + SOC (not MK + SOC) so the above underlined text needs to be corrected in two places as follows:

### 11.3 Other Secondary Efficacy Analyses

The following secondary comparisons are also planned:

- (4) OS in Multikine + SOC vs. SOC
- (5) LRC in Multikine + CIZ + SOC vs. SOC
- (6) PFS in Multikine + CIZ + SOC vs. SOC

These actions do not impact the analysis or tables generation.

### Signatures:

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