ADDENDUM to:

doi:10.21873/anticanres.16404

Syrjänen K, Eronen K, Hendolin P, Paloheimo L, Eklund C, Bäckström A and Suovaniemi O: Slow-release L-cysteine (Acetium®) lozenge is an effective new method in smoking cessation. A randomized, double-blind, placebo-controlled intervention. Anticancer Res *37(7)*: 3639-3648, 2017. PMID: 28668855. DOI: 10.21873/anticanres.11734

In the original study, the main results of this randomized controlled trial were reported only for the group of subjects who completed the study per protocol (PP). Accordingly, in the PP group (n=753), 170 (45.3%) quitted smoking in the intervention (Acetium®) arm compared to 134 (35.4%) in the placebo arm [odds ratio (OR)=1.51, 95% CI=1.12-2.02; p=0.006]. The second group analyzed, as a modified intention to treat (mITT) group (n=944), was defined as study subjects who presented with a variety of violations in the study protocol. Finally, the third group (n=301) of subjects included all those who were lost to follow-up (LTF) and did not provide information on the study endpoint (point prevalence of abstinence, PPA). This definition of the mITT group led to biased estimates on the efficacy of Acetium® in this group of subjects with incomplete data on the study endpoint, with OR=0.86 (0.36-2.04); p>0.05.

A recent review emphasizes the importance of including all the study subjects who were originally randomized in the analysis of randomized controlled trials (1). This is called an ITT analysis and is considered equally important as the PP analysis, both having different scopes and interpretations depending on the context (1). Because of their substantial impact on the results of our original study, we feel it important to include the results of the ITT analysis of the original data in this ADDENDUM to complement the results of the PP analysis.

When all study subjects originally randomized in the study (n=1,998) are included in the ITT group, the results on the efficacy of Acetium® will be different as compared with the originally presented mITT analysis (see above), in our case, significantly different. The data on the study endpoint (PPA) are available from 1,697 subjects: 840 in the Acetium® arm and 857 in the placebo arm (no PPA data for the LTF group). The numbers of study subjects that stopped smoking in the Acetium® and placebo arms were 181/840 (21.5%) and 149/857 (17.4%), respectively. This translates to an (unadjusted) OR of 1.305 [95 confidence interval (CI)=1.025-1.661; p=0.030].

Because the new ITT group (n=1,998) is the same as the entire cohort originally used (PP + mITT + LTF group, n=1,998), the common OR for the ITT group can be calculated in a Cochran–Mantel–Haenszel test using the stratum-specific estimates of the three compliance categories originally used. From this, we obtain the common OR of 1.384 (95% CI=1.053-1.819; p=0.020) for the efficacy of Acetium® versus placebo in the ITT analysis.

Accordingly, the original results of PP analysis presented in the Abstract of our Acetium® intervention study: "In the PP group, 170 (45.3%) quitted smoking in the intervention arm compared to 134 (35.4%) in the placebo arm (OR=1.51, 95% CI=1.12-2.02; p=0.006)", should be supplemented with the following statement: In the ITT analysis (n=1,998), the efficacy of Acetium® compared with placebo had an OR of 1.38 (95% CI=1.05-1.81; p=0.020).

This new analysis provides additional evidence that use of Acetium® lozenge is an effective new method in smoking intervention, and this efficacy is not dependent on the compliance of the study subjects, i.e., whether analyzed by PP or ITT.

Reference

1. Tripepi G, Chesnaye NC, Dekker FW, Zoccali C and Jager KJ: Intention to treat and per protocol analysis in clinical trials. Nephrology 25(7): 513–517, 2020. PMID: 32147926. DOI: 10.1111/nep.13709