

## Amendment of target sample size in the clinical study protocol SM 07-01: Serbian Smoking Reduction/Cessation Trial (2SRT)

**Summary:** This memorandum describes an amendment of the clinical study protocol SM 07-01 which is a randomized trial of the efficacy of Swedish snus to help smokers aged 20-65 years to reduce or quit smoking. The amendment consists of a decreased target sample size from 500 to 300 eligible participants. The decrease is motivated by recently published data from a Danish randomized clinical trial on the efficacy of a smokeless tobacco product for smoking cessation purposes. No such data were available when the original sample size was decided. With a sample size of 300 participants the trial will have reasonable statistical power ( $>80\%$ ,  $p<0.05$ ) to detect an effect on the primary end-point (smoking reduction at 24 weeks verified by a decrease in CO in exhaled air) and key secondary end-points (smoking cessation) corresponding to an odds ratio (active snus group versus placebo snus group) of 2.2-2.3. The original target size of 500 participants was selected to permit detection of a treatment effect corresponding to an odds ratio 1.9.

**Background:** The 2SRT is a randomized, placebo-controlled, double-blind clinical trial that examines the ability of snus, a traditional Swedish low-nitrosamine smokeless tobacco product, to help cigarette smokers reduce and eventually quit smoking. The primary end-point in the trial is smoking reduction at week 24 defined as a self-reported reduction in the number of cigarettes smoked daily during the preceding 4-week period of  $>50\%$ , verified by a decrease in CO in exhaled air of at least 1 ppm. Participants who fulfill the criteria for the primary end-point continue in the trial up to 48 weeks with the aim of complete smoking cessation (defined as self-reported total abstinence from cigarettes verified by a CO concentration in exhaled air of  $<10$  ppm). Secondary trial end-points include point prevalence estimates of smoking cessation as well as continued abstinence rates.

To reliably detect ( $p<0.05$ , statistical power  $>80\%$ ) a two-fold increase in the odds of smoking reduction at 24 weeks among the active versus placebo groups, and assuming a smoking reduction rate of 15% in the placebo group versus 25% (corresponding to an odds ratio of 1.9) the target sample size was originally estimated at 250 participants per group for a total sample size of 500 participants. This was motivated by the results of previous randomized trials of nicotine replacement therapies versus placebo showing increases in the proportion of participants achieving short- to medium term smoking cessation with odds ratios in the order of 1.5-2.5. Also, epidemiological, cross-sectional surveys in Sweden had suggested that Swedish snus might be more effective as an aid in smoking cessation than conventional nicotine replacement therapies. At the time when the protocol was developed, there were no data available from controlled clinical trials on the efficacy of Swedish snus or any other smokeless tobacco product for smoking reduction or smoking cessation purposes.

**Rationale for the protocol amendment:** The first results of a randomized smoking cessation trial with a Danish chewing tobacco product were recently published (1). The study tested the efficacy of smokeless tobacco pellets together with group support for smoking cessation in an open, randomized study. The control subjects received group support alone. The study enrolled 263 smokers of whom 143 were allocated to the smokeless tobacco group and 120 to the group support alone group.

Smokeless tobacco was provided for 7-12 weeks combined with 8 nurse-led group support sessions. The control group received group support alone. The participants were followed up to 6 months.

Self-reported smoking cessation verified by a CO concentration in exhaled air of <8 ppm was statistically significantly better in the smokeless tobacco group than in the control group during the first 7 weeks, that is, during the period of active intervention. Point prevalence of smoking cessation at week 7, for instance, were 36% versus 21% ( $p < 0.001$ ), in the two groups respectively. This difference corresponds to an odds ratio of 2.5. The continued abstinence rates from week 4 through 7 were 32% versus 19% (odds ratio 1.9,  $p = 0.023$ ), respectively. However, the 6-month point prevalence estimates of smoking cessation were not significantly different in the two groups, 23% and 21% (odds ratio 1.3). Only a small proportion of those allocated to the smokeless tobacco product continued to use such products after 6 months (18%).

Some aspects on the trial design merit consideration when judging the results this study:

- The nicotine delivery from the product tested in the trial was relatively low and protracted (c. 2 mg during 60-90 minutes) compared to Swedish snus. In addition, the recommended dose was only 5-6 pellets per day and the maximum 10-15 pellets per day.
- The intervention period was short (7-12 weeks) and the participants were instructed to try to gradually reduce their usage already after 4 weeks.
- Compliance with the tobacco pellets was low. Only 62% of those allocated to pellets used them after one week, and this proportion decreased to 20% at week 12.
- The study was not double-blind and the authors admit that the nurses responsible for the protocol interventions including delivery of the tobacco pellets probably had a negative view of the efficacy and relevance of using a smokeless tobacco product for smoking cessation purposes.
- C. 50% of the participants had made previous quit attempts and failed using nicotine replacement therapies.

There are several important design features of the Serbian trial that suggest that efficacy in terms of achieving the primary end-point probably will be higher than that illustrated by the mentioned odds ratios in the Danish trial.

- The nicotine delivery from Swedish snus is better than from the product tested in the Danish trial.
- Usage is ad libitum to avoid nicotine craving which might result in increased smoking or smoking relapse
- The study design allows for a much longer transition period from a smoking to a non-smoking behavior as the primary end-point is defined as a continued smoking reduction during the last 4 weeks of the initial 6-month intervention period, that is, during a period when the participants are still using their allocated study product.
- Primary end-point is smoking reduction, not cessation. Smoking reduction is probably easier to achieve than total abstention from smoking.
- Smoking cessation as a secondary end-point might be easier to achieve after an initial period of smoking reduction and the study design allows for a relatively long transition period.
- Study design is double-blind
- Few participants are likely to have made previous quit attempts using nicotine replacement therapies as usage of such products is still relatively limited in Serbia.

Because of these circumstances and considerations, it is reasonable to expect that the treatment effect in the Serbian trial in terms of the primary end-point will be greater than the week 4 through week 7 continued abstinence rate in the Danish trial (odds ratio 1.9).

As mentioned, the target sample size in 2SRT was originally estimated at 250 participants per group for a total sample size of 500 participants. These numbers were based on assumptions of a success rate of 25% in the active snus group and 15% in the placebo group which corresponds to an odds ratio of 1.9.

If the success rate among those allocated to snus is assumed to be slightly higher, for instance 28% or 29% (corresponding to odds ratios of 2.2 and 2.3, respectively), the required total sample size ( $p < 0.05$ , statistical power  $> 80\%$ ) would be 312 and 274, respectively.

Against this background it is reasonable to lower the target total sample size from 500 to 300 eligible participants.

#### Reference

1. Tønnesen P, Mikkelsen K, Bremann L. Smoking cessation with smokeless tobacco and group therapy: an open, randomized, controlled trial. *Nicotine & Tobacco Research* 10; 1365-1372, 2008

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