

Amendment of the clinical study protocol SM 07-01: Serbian Smoking Reduction/Cessation Trial (2SRT): collection of data on smoking status among participants excluded from the trial at week 24

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 collection of data on self-reported smoking status at week 48 among participants who were excluded from the trial at week 24 because they failed to achieve the trial's primary end-point ("smoking reduction" as defined in the protocol). The amendment is motivated by the fact that some of these participants may have stopped smoking during week 24-48 as they were included in the trial because they wished to decrease or completely stop smoking. Availability of data on smoking status also from these participants would enhance the validity of the statistical analyses of differences in quit rates at week 48 based on the entire ITT (Intention To Treat) population.

Background & rationale: 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.

According to the protocol all participants who terminate the study prematurely for any reason are to be considered failures in analyses of both the primary and secondary efficacy analyses. This approach represents the standard in most smoking cessation trials. However, in the current study some participants are actively excluded from the trial at week 24 because of failure to achieve the primary end-point, which is, "smoking reduction" as defined above. The rationale for considering these participants as failures is that it is unlikely that they would quit smoking during week 24-48 had they continued in the study. However, although unlikely, it remains a possibility that some of them may stop smoking after week 24 as they were included in the trial because they were "motivated to substantially reduce or quit smoking" (inclusion criteria #4).

Against this background the validity of analyses of the secondary end-point "smoking cessation at week 48" as defined in the protocol would be enhanced if data were collected on self-reported smoking status from these participants.

Protocol amendment: Participants who were excluded from the trial at week 24 because they failed to achieve "smoking reduction" will be contacted by telephone at a time corresponding to the week 48 visit had they continued in the trial. If more than 48 weeks has elapsed since inclusion in the trial, the participant will be contacted as soon as possible. They will be asked to provide information on smoking status according to the following format:

1. "Have you stopped smoking completely since the week 24 visit?": yes/no
(To "stop smoking completely" means not to have a single puff on any occasion during the mentioned time period)
2. "Did you stop smoking completely during the past 12 weeks?": yes/no
3. "Have you stopped smoking completely during the past 4 weeks?": yes/no

For participants who are interviewed after their theoretical week 48 "visit window" (-/+ 1 week) the questions will be rephrased so that they relate to the week 24-48 period:

1. "Did you stop smoking completely for at least 16 weeks after the week 24 visit, that is, since you were excluded from the trial?: yes/no
2. "Did you stop smoking completely during the following period: (week 36 through 48)?": yes/no
3. "Did you stop smoking completely during the following period:(week 44 through 48)?": yes/no

Participants who answer yes to any of these questions will be offered to verify their smoking status at a clinical visit through test of CO in exhaled air (where CO < 10 ppm will be taken as evidence of non-smoking status).

In addition to these questions the date for the interview will be recorded, and how this date relates to the theoretical week 48 visit had the participant not been excluded from the trial (-/+ 1 week, +1/+4 weeks, +4/+8 weeks, +8/+16 weeks, >+16 weeks)