-CONFIDENTIAL-

Research Project

The Efficacy of Acetium® Lozenges* as a Novel Method in Smoking Intervention. A double-blind, placebo-controlled trial.

Executed by:

BIOHIT Oyj (Helsinki, Finland);

Research Team:

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Background: Smoking dependence has been traditionally ascribed to nicotine, the major psychoactive component of tobacco (nicotine addiction). Dependence on smoking, however, is a much more complex issue than just nicotine addiction, and during the past several decades, a wide variety of approaches have been used in intervention for smoking cessation, with variable success.

Tobacco smoke contains several classes of carcinogens, including acetaldehyde in high concentrations. Acetaldehyde from the tobacco smoke is easily dissolved into the saliva during smoking, and thus, toxic aldehydes could mediate the carcinogenic effect of tobacco smoke through the saliva. In 2009, IARC proclaimed acetaldehyde as Group I carcinogen, equivalent to asbestos, formaldehyde and others.

It has been known for several decades that L-cysteine (a nonessential amino acid) is able to eliminate the toxicity of acetaldehyde by reacting covalently with acetaldehyde to form a stable 2-methylthiazolidine-4-carboxylic acid (MTCA). This simple principle was used in the recent innovation of Biohit Acetium® capsule containing 100mg L-cysteine. Oral administration of Acetium® was confirmed to effectively bind acetaldehyde originated from ethanol metabolism in the stomach, raising the idea that L-cysteine could also be used to eliminate acetaldehyde dissolved into the saliva during smoking. Indeed, Salaspuro et al. (2006) confirmed that orally administered L-cysteine (5mg)-containing sucking tablet (lozenge) totally inactivated acetaldehyde in the saliva during smoking.

Given the above, it is tempting to speculate that elimination of acetaldehyde in the saliva during cigarette smoking by L-cysteine sucking tablets, might effectively block (or reduce) the formation of harmans, reduce their high blood levels, and thus alleviate the acetaldehyde-enhanced nicotine addiction (by reducing MAO-inhibition) among smokers. The present study is designed to validate the novel hypothesis that regular use of Acetium® lozenges in context with smoking is an effective intervention for cessation of cigarette smoking.

Objective: To test the efficacy of Acetium® lozenges (used simultaneously with smoking) to trigger the quit from cigarette smoking as compared with similarly administered placebo preparation.

Study design: A double-blind, placebo-controlled clinical trial comparing Acetium® lozenges and placebo as triggers of cigarette smoking cessation during one-year intervention.

Methods: A cohort of 2000 current cigarette smokers will be enrolled by public invitation. Eligible subjects must be current cigarette smokers (no limitation as to pack years), who are well motivated to refrain from smoking, and who give a written consent to participate. The subjects will be randomly allocated to two groups (n=1000 in each), receiving either Acetium® lozenges or placebo, in a double-blind setting, where both the examiners and the test subjects are blinded to the test substance. All subjects must consent for not using any other measures of smoking cessation intervention. All subjects are requested to fill in a structured questionnaire recoding their detailed smoking history and assessing their nicotine dependence by FTND (Fagerström Test for Nicotine Dependence) and breath CO-monitoring. The subjects will be administered a smoking diary, to be filled on daily basis, recording the daily numbers of cigarettes, test lozenges and subjective sensations of smoking. These diaries are returned to study monitors on three-monthly FU visits, when also subjected to new FTND and CO-monitoring.

The primary study endpoints include PPA (point prevalence of abstinent rate) and PA (prolonged abstinence), used for calculating OR (95%CI) between the two study arms by logistic regression. Changes in FTND score and CO-levels represent intermediate surrogate endpoints of PPA and PA. In addition, time to quit (TTQ) and duration of quit (QT=quit time) can be used as dependent variables in univariate (Kaplan-Meier) and multivariate (Cox) survival analyses. GEE and Poisson models are used to estimate the covariates (Acetium®/Placebo) of i) persistence of abstinence, and ii) quit events (events/person time at risk), respectively, based on multiple records (panel data) in a longitudinal setting. Finally, the predictors of the multiple outcomes in this intervention trial can be estimated using the novel competing-risks regression model, where i) no effect, ii) permanent quit, iii) temporary quit with relapse, and iv) smoking reduction, represent the competing-risks events.

The power of the study can be calculated specifically for each of these statistical techniques, most simply by the two-sample proportion test for PPA and PA. This study (n=1000 in both arms) is adequately powered (Type II error 0.80, type I error 0.05) to detect a true difference (in PPA or PA) of 10% between the two arms, within the range of 10% vs. 20% quit rate in the two arms. Within this (10-20%) range, the study power is sensitive to any decrease in this difference, but allows less difference (7.5%) if the quit rate falls between 5% and 15% in the arms.

Specific aims: The null hypothesis of the study implicates that Acetium® lozenges are not superior to placebo in the intervention for smoking quit during the 1-year intervention. Rejection or not of the null hypothesis is based on comparison of the two arms by the different statistical approaches listed above.

Study execution and time-table: For execution of the study, the company has decided to set up and monitor the whole study by its own research team. This decision was based on careful consideration of the different options, with emphasis on the time-table as well as the direct and indirect project costs inherent to different options. This implies hiring of a project coordinator for taking care of the practical aspects of the project as well as its continuous monitoring.

Impact of the study: This double-blind, placebo-controlled intervention trial will test the new hypothesis (confirmed in AL-Smoquit-1 and 2 studies) whether or not Acetium® lozenges are superior to placebo as triggers of smoking quit when regularly used in context of smoking for a prolonged period. If this concept proves to be correct, the results will have a major clinical impact while providing an entirely novel approach to support regular smokers to withdraw this unhealthy habit.

1.BACKGROUND

Smoking remains the single most important preventable cause of global disease burden and premature death. Besides increasing the risk of developing cardiovascular diseases and chronic obstructive pulmonary disorders, it is a well-known major risk factor for cancers of the lung, oral cavity, larynx, esophagus, stomach, pancreas, colorectum, bladder and kidney.[1] According to the recent estimates, about one in three adults worldwide (1.1 billion) are smokers.[2] Although smoking rates fell in the higher income countries during the 1970's and 1980's, there is some evidence that this trend is currently leveling off.[3] There is little doubt about the urgency of developing, evaluating and implementing effective smoking cessation interventions and policies to reduce the major public health impact of cigarette smoking and tobacco use in any form.

Smoking cessation (colloquially quitting smoking) is the process of discontinuing the practice of inhaling a smoked substance.[4] Many of the methods attempted to prompt cessation of tobacco may also apply to cessation of smoking other substances that can be equally difficult to stop, because of the development of strong physical substance dependence or psychological dependence (addiction). Smoking cessation can be achieved by two principally different approaches; 1) with, and 2) without assistance from healthcare professionals, the latter including the use of medications.[5] The methods that have been found to be effective include interventions directed at or via health care providers and health care systems, such as i) medications including nicotine replacement therapy (NRT) and varenicline, ii) individual and group counseling, as well as iii) Web-based or stand-alone and computer programs. However, up to three-quarters of ex-smokers report having quit without assistance ("cold turkey" or cut down then quit), and cessation without professional support or medication may be the most common method reported by ex-smokers.[5] In a growing number of countries, there are more ex-smokers than current smokers. Early "failure" is a normal part of trying to quit, and more than one attempt prior to long-term success is common.

Tobacco contains the chemical nicotine, and smoking cigarettes leads to nicotine addiction.[6] In simple terms, this addiction develops when nicotine acts on nicotinic acetylcholine receptors to release neurotransmitters such as dopamine, glutamate, and gamma-aminobutyric acid. Beyond doubt, nicotine is the main psychoactive component of tobacco, particularly among adolescents, who seem to be more sensitive to the rewarding effects of nicotine, and thus more susceptible to

develop nicotine addiction. Cessation of smoking leads to symptoms of nicotine withdrawal such as anxiety and irritability. Professional smoking cessation support methods generally endeavor to address both nicotine addiction and nicotine withdrawal symptoms. Studies have shown that it takes between 6 to 12 weeks post quitting before the amount of nicotinic receptors in the brain return to the level of a non-smoker.[7] Although stopping smoking can cause short-term side effects such as reversible weight gain, smoking cessation services and activities are cost-effective because of the major public health benefits. However, dependence on smoking is a much more complex issue than just nicotine addiction. Indeed, there is experimental evidence implicating that acetaldehyde, a major constituent of tobacco smoke, enhances behavioral, endocrine, and neuronal responses to nicotine in adolescent and adult rats.[8]

1.1.Methods used for tobacco cessation intervention

Numerous reviews and meta-analyses have been carried out regarding the efficacy of a wide spectrum of tobacco cessation intervention approaches. The findings from these reviews and meta-analyses on each distinct intervention approach have to date, however, not been integrated into a mutual comparison regarding the degree of efficacy. Identification of the most successful intervention strategies that could possibly be implemented on a large scale in European countries would enable policy makers to make evidence based decisions regarding the funding of the most effective interventions.[9,10] The different intervention strategies are briefly discussed in the following.

1.1.1.Unassisted methods

Ex-smokers have usually made a number of attempts (using different approaches) to stop smoking before achieving long-term abstinence, and identifying which approach is eventually the most successful is difficult.[4] The most frequent unassisted methods reported in the literature include "cold turkey" and "gradually decreased number" of cigarettes.[11] In a meta-analysis evaluating these approaches, it was estimated that the quit rate from unaided methods was 7.3% after an average of 10 months of follow-up.[12] "Cold turkey" is a idiomatic term indicating abrupt withdrawal from an addictive drug, i.e., a sudden and complete cessation of all nicotine use.[4] In several studies, this has been the most cited method of quitting (76-88%), accompanied by comments like "not at all difficult", "fairly difficult", or “very difficult” to quit.[12]

1.1.2.Healthcare providers and system interventions

Interventions delivered via healthcare providers and healthcare systems have been shown to improve smoking cessation among people who receive this type of intervention. A 2008 Guideline meta-analysis estimated that physician advice to quit smoking led to a quit rate of 10.2%, as opposed to a quit rate of 7.9% among patients who did not receive physician advice to quit smoking.[10] For one-to-one or person-to-person counseling sessions, the duration of each session, the total amount of contact time, and the number of sessions all correlated with the effectiveness of smoking cessation. Both physicians and non-physicians increased abstinence rates compared with self-help or no clinicians.[10] In a recent systematic review and meta-analysis, multi-component interventions increased the quit rates in primary health care settings.[13]

1.1.3.Biochemical feedback

Various methods exist which allow a smoker to see the impact of their tobacco use, and the immediate effects of quitting. Using biochemical feedback methods can allow tobacco-users to be identified and assessed, and the use of monitoring throughout an effort to quit can increase motivation to quit.[14,15] In this category, two useful tools are available: breath carbon monoxide (CO) monitoring and measurement of cotinine.

Because CO is a significant component of cigarette smoke, a breath CO monitor can be used to detect recent cigarette use. The value for a smoker of demonstrating blood CO-concentration with a non-invasive breath sample is the link between smoking habit and the physiological harm associated with smoking.[15] A metabolite of nicotine, cotinine is present in smokers, and like CO, a cotinine test can serve as a reliable biomarker to determine smoking status. Cotinine levels can be tested through urine, saliva, blood, or hair samples. These two methods can be used either alone or together, for example, in a situation where abstinence verification needs additional confirmation.

1.1.4.Single medications

The American Cancer Society estimates that between about 25% and 33% of smokers who use medicines can stay smoke-free for over 6 months.[4] A wide variety of single medications have been used in smoking cessation intervention, with highly variable efficacy.

1.1.4.1.Nicotine replacement therapy (NRT):

Currently, 5 medications approved by FDA (USA) deliver nicotine in a form that does not involve the risks of smoking. NTRs are meant to be used for a short period of time and should be tapered down to a low dose before stopping. The five NRT medications, which in a Cochrane review[16] increased the chances of smoking cessation by 50 to 70% compared to placebo or no treatment include: 1) transdermal nicotine patches, which deliver doses of nicotine, thus alleviating the symptoms of nicotine withdrawal. These patches can give smaller and smaller doses of nicotine, slowly reducing the dependence. Further increased chance of success is obtained with a combination of the nicotine patch and a faster acting form.[16] Similarly, this method becomes most effective when combined with other medications and/or psychological support. The other forms nicotine administration include: 2) gum; 3) lozenges; 4) sprays, and 5) inhalers. Unfortunately, the relapse rate among over-the-counter (OTC) NRT users is very high, exceeding 90% within six months.

1.1.4.2.Bupropion

An anti-depressant, Bupropion is another FDA-approved medication in this indication, marketed under the brand name Zyban (GSK). Bupropion is contraindicated in epilepsy, seizure disorder; anorexia/bulimia, in patients using antidepressant drugs (MAO inhibitors) within 14 days, patients undergoing abrupt discontinuation of ethanol or sedatives (including benzodiazepines).[17]

1.1.4.3.Nicotinic receptor partial agonists

Cytisine (Tabex) is a plant extract used since the 1960's in countries of the former Soviet Union. It was the first medication approved as an aid to smoking cessation, and has very few side effects in small doses.[18]

Varenicline tartrate is a prescription drug marketed by Pfizer as Chantix in the U.S. and as Champix outside the U.S.[19] Synthesized as an improvement upon cytisine, varenicline decreases the urge to smoke and reduces withdrawal symptoms. Two systematic reviews and meta-analyses, one in 2006[20] and one in 2009,[21] found varenicline more effective than NRT or bupropion. According to the 2008 Guidelines, 2 mg/day of varenicline leads to the highest abstinence rate (33.2%) of any single therapy, while 1 mg/day leads to an abstinence rate of 25.4%.[10] A 2011 Cochrane review of 15 studies found varenicline being significantly superior to bupropion at one year, but varenicline and nicotine patches were equally effective in resulting abstinence at 24 weeks.[22] In a more recent review (2011)

of double-blind studies, varenicline was reported to have increased risk of serious adverse cardiovascular events as compared with placebo.[23] Varenicline may also cause neuropsychiatric side effects, e.g. possible suicidal thoughts and suicidal behavior, which should seriously limit the long-term use of this medication in smoking cessation intervention.[23]

1.1.4.4.Moclobemide

The use of moclobemide for this purpose is based on the concept that tobacco smoking could be a form of self-medication for depression, and moclobemide could therefore help increase the abstinence rates due to its mimicking the MAO-A inhibiting effects of tobacco smoke. Despite some promising short-term benefits, however, the 12 month follow-up results failed to disclose any difference between the placebo and moclobemide.[24]

Two other medications have been used in clinical trials for smoking cessation, but they are not approved by the FDA for this purpose. They may be used under careful physician supervision if the first line medications are contraindicated.[4,10] Clonidine may reduce withdrawal symptoms and, according to some studies, approximately doubles the abstinence rates when compared to placebo, but not without side effects. The latter include dry mouth and sedation, and abrupt stopping of the drug may cause high blood pressure and other side effects.[10] Nortriptyline, another anti-depressant, has success rates similar to bupropion but has side effects including dry mouth and sedation as well.[10]

1.1.5.Combinations of medications

In the 2008 US Guidelines, there are three combinations of medications that have shown some efficacy in smoking cessation intervention.[10] These include; i) long-term nicotine patch and ad libitum NRT gum or spray; ii) nicotine patch and nicotine inhaler, and iii) nicotine patch and bupropion. The latter is the only combination that FDA has approved for smoking cessation.

1.1.6.Cut down to quit

One of the used approaches in smoking cessation is a gradual reduction, based on slowly reducing one's daily intake of nicotine. This can be theoretically accomplished through i) repeated changes to cigarettes with lower levels of nicotine, ii) by gradually reducing the number of cigarettes smoked each day, or iii) by smoking only a part of a cigarette on each smoking session. A recent Cochrane

review provides evidence that an abrupt cessation and gradual reduction with pre-quit NRT produced similar quit rates, irrespective whether or not supplemented with pharmacotherapy or psychological support.[25]

1.1.7.Community interventions

There is ample evidence to suggest that community interventions using multiple channels to provide reinforcement, support and norms for not smoking, indeed, have an effect on smoking cessation outcomes among adults.[26] Specific methods used in the community to encourage smoking cessation among adults include: 1) policies making workplaces and public places smoke-free. It is estimated that "comprehensive clean indoor laws" can increase smoking cessation rates by 12%–38%; 2) voluntary rules making homes smoke-free, which are thought to promote smoking cessation; 3) initiatives to educate the public regarding the health effects of second-hand smoke; 4) increasing the price of tobacco products, e.g. by taxation. It has been estimated that an increase in price of 10% will increase smoking cessation rates by 3–5%.[26] On the other hand, the independent role of different types of mass media campaigns is difficult to establish.

1.1.8.Psychosocial approaches

The WHO's World No Tobacco Day is held on May 31 each year. In many countries, smoking-cessation support is offered over the internet, over the telephone quit-lines or in person. Three meta-analyses have concluded that telephone cessation support is effective when compared with minimal or no counselling or self-help, and that telephone cessation support with medication is more effective than medication alone.[10] Group or individual psychological support can help people who want to quit. This form of counselling can be effective alone, but combining it with medication is more effective, and the number of sessions of support with medication correlates with effectiveness.[10] Similarly, multiple formats of psychosocial interventions increase quit rates: 10.8% for no intervention, 15.1% for one format, 18.5% for 2 formats, and 23.2% for three or four formats.[10]

1.1.9.Self-help measures

The impact of different self-help measures in smoking cessation are under discussion, and in part doubtful. According to the 2008 Guidelines, the effect of self-help was weak, and many of the self-help approaches did not produce any higher abstinence rates.[10] A wide variety of self-help measures have been tested, however, but with little or no success.

1.1.10.Substitutes of cigarettes

During the past several years, a variety of measures have been developed, intended to be used as substitutes of cigarettes, aiming to trigger smoking cessation through different mechanisms. Electronic cigarettes are shaped like a cigarette to emulate the tactile experience of smoking. These contain a rechargeable battery and a heating element which vaporises liquid nicotine and other flavourings from an exchangeable cartridge. Advocates of electronic cigarettes often market them as a smoking cessation device. Many claim that electronic cigarettes deliver the experience of smoking without the adverse health effects usually associated with tobacco smoke, or at least greatly reduce those risks.[27] However, in September 2008, the WHO issued a release proclaiming that it does not consider the electronic cigarette to be a legitimate smoking cessation aid, stating that "no rigorous, peer-reviewed studies have been conducted showing that the electronic cigarette is a safe and effective nicotine replacement therapy.[28]

1.1.11.Alternative approaches

Given that a single powerful tool with a guaranteed efficacy in smoking cessation intervention is still missing, a wide variety of other measures have been tested for this purpose. These include acupuncture, aromatherapy, hypnosis and herbs. The efficacy of each of those has not been firmly documented. A recent meta-analysis showed no difference between acupuncture and placebo.[10] Only one study was found on smoking cessation and aromatherapy, in which inhalation of vapour from black pepper extract was reported to reduce smoking withdrawal symptoms. Similarly, clinical trials studying hypnosis and hypnotherapy as a method for smoking cessation have been inconclusive.[29] In one randomized trial, however, hypnosis and nicotine patches were found to favourably compete with standard behavioural counselling and nicotine patches in producing 12-month quit rates.[30] Many herbs have been studied as a method for smoking cessation, including lobelia and St John's Wort, but the results are inconclusive. Lobelia has been used for smoking cessation because of its chemical similarities to tobacco. It is now listed in the Poisonous Plant Database ((FDA), and although still found in many products sold for smoking cessation, lobelia should be used with caution.[31]

1.2.Comparison of different intervention methods

It is not easy to get an overall picture which (if any) of the plethora of intervention methods used for smoking cessation is the most effective. Probably the most comprehensive review in this respect is

the one published by Lemmens et al. (2008), where the authors analysed the Medline and Cochrane Library databases for systematic reviews and meta-analyses published since 2000.[9] Twenty-three studies met the inclusion criteria. The included intervention strategies and policies were ranked according to their effect size, taking into account the number of original studies, the proportion of studies with a positive effect and the presence of a long-term effect. Evidence of effectiveness for the following strategies was found: group behavioural therapy [odds ratio (OR) 2.17, confidence interval (CI) 1.37–3.45], bupropion (OR 2.06, CI: 1.77–2.40), intensive physician advice (OR 2.04, CI: 1.71–2.43), nicotine replacement therapy (OR 1.77, CI: 1.66–1.88), individual counselling (OR 1.56, CI: 1.32–1.84), telephone counselling (OR 1.56, CI: 1.38–1.77), nursing interventions (OR 1.47, CI:1.29–1.67) and tailored self-help interventions (OR 1.42, CI: 1.26–1.61). A 10% increase in price increased cessation rates by 3–5%. Comprehensive clean indoor laws increased quit rates by 12–38%. These results show that a wide array of smoking cessation intervention approaches and policies can have a significant impact on smoking cessation rates.[9]

1.3.Acetaldehyde, L-cysteine and smoking cessation

1.3.1.Acetaldehyde, Group 1 carcinogen (IARC)

Tobacco smoke contains several classes of carcinogens that include among others polycyclic aromatic hydrocarbons, aromatic amines, and nitrosamines. Tobacco smoke contains also high concentrations of toxic aldehydes.[32] The most abundant aldehyde in tobacco smoke is acetaldehyde, and its concentration in tobacco smoke is >1,000 times greater than those of polycyclic aromatic hydrocarbons and tobacco-specific nitrosamines.[33] Acetaldehyde is also the first metabolite of ethanol oxidation. It binds to DNA, forming stable DNA adducts that are observed in alcohol consumers. Numerous epidemiological studies in alcohol drinkers with alcohol dehydrogenase (ALDH2) deficiency or low aldehyde dehydrogenase (ADH1B) activity provide the most compelling evidence for the carcinogenicity of acetaldehyde.[34] This deficiency results in the accumulation of acetaldehyde locally into the saliva during ethanol metabolism and also in markedly increased risk for many upper gastrointestinal tract cancers.

Similarly, it was recently shown that acetaldehyde from the tobacco smoke is easily dissolved into the saliva during smoking.[35] Thus, toxic aldehydes could mediate the carcinogenic effect of tobacco smoke through saliva to oral cavity and from there further on to the larynx, the esophagus, and even to the stomach. Based on firm epidemiological and toxicological documentation, IARC proclaimed

(in 2009) acetaldehyde as Group I carcinogen, equivalent to asbestos, formaldehyde and others.[36]

1.3.2.L-cysteine eliminates acetaldehyde in the stomach and in saliva

Cysteine is a non-essential amino acid, which was shown (almost 40 years ago) to be capable of eliminating the toxicity of acetaldehyde by reacting covalently with it to form a stable 2-methylthiazolidine-4-carboxylic acid (MTCA).[37] MTCA is an inert and non-toxic compound that is eliminated from the body through feces and urine, without being absorbed into the blood circulation. This simple principle was used in the recent innovation of Biohit HealthCare's Acetium® capsule containing 100mg L-cysteine.

In the principle of concept study, oral administration of Acetium® was confirmed to effectively bind acetaldehyde originated from ethanol metabolism in achlorhydric stomach.[38] In that setting, the mean acetaldehyde level of gastric juice was 2.6 times higher with placebo than with l-cysteine (13 vs. 4.7 μM, $p<0.05$), implicating that L-cysteine can be used to decrease acetaldehyde concentration in achlorhydric stomach during alcohol exposure.

This led the authors to examine the concept, whether it would be possible to eliminate alcohol-derived acetaldehyde also from the saliva, using L-cysteine slowly released from a special buccal (Acetium®) tablet.[39] Indeed, this was shown to be the case in tested volunteers, in whom, up to two-thirds of acetaldehyde (after alcohol intake) could be removed from the saliva with a slow-releasing buccal L-cysteine formulation. This might have important implications e.g. in prevention of upper GI-tract cancers among individuals with high acetaldehyde exposure (heavy drinkers, smokers).[39]

As the logical next step, the company (Biohit Oyj) developed an Acetium® sucking tablet (lozenge) that releases L-cysteine into the oral cavity during smoking, and tested this formulation as a potential chemopreventive agent against toxicity of tobacco smoke, i.e. in harm reduction.[40] Seven volunteers smoked five cigarettes, and during every smoking period, sucked a blinded tablet containing 0, 1.25, 2.5, 5, or 10 mg of L-cysteine, followed by acetaldehyde analysis of the saliva at 0, 5, and 10 minutes from the beginning of the smoking. L-cysteine reduced highly significantly the salivary acetaldehyde. In fact, carcinogenic acetaldehyde could be totally inactivated in the saliva during smoking by the sucking tablet containing 5 mg of L-cysteine.[40]

1.3.3.L-cysteine lozenge as potential trigger of smoking quit

The idea of testing L-cysteine as potential trigger of smoking quit aroused from subjective reports by smokers who tested Acetium® lozenges in purpose of eliminating acetaldehyde in the saliva in context of smoking (see above). These emerging subjective reports among smokers suggest that Acetium® lozenges used concomitantly with smoking reduce or even totally eliminate the sensations of smoking-associated pleasure, i.e., the main cause for smoking dependence. The later has been traditionally ascribed to nicotine, the major psychoactive component of tobacco, particularly among adolescents, who seem to be more sensitive to the rewarding effects of nicotine thus leading to nicotine addiction.[6,7]

Dependence on smoking, however, is a much more complex issue than just nicotine addiction. Although nicotine is believed to be the major psychoactive substance in tobacco, nicotine replacement therapy is not highly effective as a treatment for tobacco addiction, particularly in adolescents.[4,10] As discussed, acetaldehyde is a well-known metabolite of ethanol, which is also present in tobacco smoke in a concentration half that of nicotine.[32,33] It has been previously shown that a synergistic interaction exists between nicotine and acetaldehyde in self-administration in juvenile but not in adult rats.[41] However, the underlying mechanisms are not yet clear. Although acetaldehyde has been reported to induce behavioral effects, including reward, these are usually only observed following peripheral administration of high doses of drug or following central administration.[42] Given the localization of the metabolic enzyme, aldehyde dehydrogenase (ADH) at capillary endothelial junctions, there has been considerable debate as to whether acetaldehyde can cross the blood brain barrier (BBB).

However, in recently conducted elegant experiments, Cao et al. (2007) presented experimental evidence implicating that acetaldehyde, a major constituent of tobacco smoke, enhances behavioral, endocrine, and neuronal responses to nicotine in adolescent and adult rats.[8] Although the mechanisms underlying the interaction of nicotine and acetaldehyde are still not clearly understood, these data suggest that acetaldehyde may influence habituation to stress, possibly via effects on the PVTh (paraventricular nucleus of Thalamus), which is not protected by the BBB. These experimental data also implicate that other constituents in tobacco and tobacco smoke may also contribute to the effects of nicotine and may, consequently, affect smoking behaviors.[8] It is more meaningful to study not only 'nicotine addiction' but also 'tobacco addiction' by including other tobacco components.

Clarification of the roles of tobacco components other than nicotine should aid in developing more effective smoking cessation therapies.

1.4.Study hypothesis

In all the above experiments, however, acetaldehyde was administered to animals using the i.v. or central route.[8,41,42] It is known that in concentrations reached in the saliva after cigarette smoke (or alcohol intake), acetaldehyde is not absorbed into circulation and thus has no possibility to cross BBB (Salaspuro M, personal communication; 2013). This excludes the possibility of a direct central interaction between cigarette smoke-derived i) acetaldehyde and ii) nicotine, as described in the above animal experiements.[8]

This has prompted a search for indirect mechanisms behind the suggested contribution of acetaldehyde to tobacco smoke addiction, first suggested in 2007 by Talhout et al.[43] Given that in rodents, acetaldehyde induces reinforcing effects acting in concert with nicotine, these authors hypothesized that harman and salsolinol, i.e., two condensation products of acetaldehyde and biogenic amines, may be responsible for the observed reinforcing effect of acetaldehyde. In the human, these beta-carbolines are known to be synthesized as condensation products of tryptophan and indolealkylamines with aldehydes.[44] Thus, 1-Methyltetrahydro-beta-carboline (tetrahydroharman) is formed in the body as the acetaldehyde condensate after alcohol intake and its concentration is usually greatest at the time of hang-over. Its oxidation product, 1-methyl-beta-carboline (harman), has also been found in human urine and platelets. They occur in many foods and tobacco smoke and also appear endogenously in humans.[45]

Norharman and harman are naturally occurring beta-carboline alkaloids exhibiting a wide range of biological, psychopharmacological, and toxicological actions. Harman is formed in cigarette smoke, and among smokers, blood harman levels appear to be 2-10 times higher as compared to non-smokers. Both harman and salsolinol inhibit monoamine oxidase (MAO), and some MAO-inhibitors are known to increase nicotine self-administration and maintain behavioral sensitization to nicotine.[43] Since harman readily passes the BBB and has sufficient MAO-inhibiting potency, it may contribute to the lower MAO-activity observed in the brain of smokers.[43] This led these authors to speculate that acetaldehyde may increase the addictive potential of tobacco products via the formation of acetaldehyde-biogenic amine adducts (harmans) in cigarette smoke and/or in vivo.[43]

Until now, this concept has not been systematically tested in human smokers. It is tempting to speculate, however, that elimination of acetaldehyde in the saliva after cigarette smoking using L-cysteine sucking tablets (lozenges),[40] might effectively block (or reduce) the formation of acetaldehyde-biogenic amine condensates (harmans), reduce their high blood levels, and by so doing, might alleviate the acetaldehyde-associated nicotine addiction (by reducing MAO-inhibition) among smokers.[43]

The present study design was tested in two RCTs in Finland (published in 2016-2017).[51,52] In both RCTs, Acetium® lozenge proved to be significantly more effective than placebo in assisting the smokers to quit. The present study was designed to confirm the results of the two published RCTs[51,52], by a manufacturer-independent research group. The study hypothesis is based on assumption that regular use of Acetium® lozenges concomitantly with smoking will trigger abstain from cigarette smoking.

2.STUDY DESIGN

This double-blind, placebo-controlled trial is designed to test the efficacy of intervention by Acetium® lozenges (used concomitantly with smoking) for cessation of cigarette smoking as compared with similarly administered placebo preparation. A cohort of 2000 current cigarette smokers will be enrolled by public invitation, and randomly allocated to two groups (n=1000 in each), receiving either Acetium® lozenges or placebo. All subjects will be requested to fill in a structured questionnaire recoding their detailed smoking history and other clinical data pertinent to this study. The subjects will be administered a smoking diary on daily basis, submitted to the study monitor on monthly basis for recording the compliance of each subject and the date of all eventual quits from smoking. The interim results will be analysed after 6 months of study execution, the final study endpoint being reached when all compliant subjects have completed their 12-month intervention.

2.1.Aims of the study

The single most important goal of this study is to establish whether Acetium® lozenge is an effective measure in increasing the smoking quit rate. The null hypothesis of the study implicates that Acetium® lozenges are not superior to placebo in triggering the cessation of smoking during the 1-year follow-up period. Rejection or not of the null hypothesis is based on comparison of the two

strata (Acetium® and placebo) against two primary study endpoints: Point Prevalence (PPA) abstinence rates and Prolonged Abstinence (PA). Albeit closely correlated, these two outcomes give somewhat different estimates for quit rates, and for this reason, a recent meta-analysis recommends using both PP and PA outcomes in all future smoking cessation intervention studies.[46]

In addition to these univariate primary endpoints (PPA, PA), the study also attempts to estimate the role of Acetium® lozenges as an independent covariate of smoking quit in multivariate (Cox) proportional hazards (HR) regression model, controlled for potential confounders (age, sex, pack-years, alcohol, others). Another aim is to assess whether these longitudinal data on Acetium® intervention in smoking quit can be modelled using the newly described statistical technique, competing risks regression.[47,48] In this smoking cessation intervention setting, the competing risks events (to be observed during Acetium® intervention) are: i) no effect (=smoking continues unchanged as compared with the baseline), ii) quit (=cessation of smoking since the quit date with or without grace period), iii) relapse (=cessation of smoking for a period but relapse afterwards), and iv) reduction of smoking (=number of daily cigarettes reduced at study endpoint)(more details in Methods section).

2.2.Patients

This intervention trial is conducted in collaboration between Biohit Oyj (Helsinki, Finland) and XY Clinic (X City, Y country)(hereafter called "the Partners"). The study is performed exclusively by XY, supervised by a steering committee consisting of members from both research Partners.

A cohort of 2000 current cigarette smokers (both genders, no age limit), will be enrolled by public invitation in daily newspapers. Eligible subjects must be current cigarette smokers (no limitation as to pack years), who are motivated to refrain from smoking, and who give a written consent to participate. The subjects will be randomly allocated to two groups (n=1000 in each), receiving either Acetium® lozenges or placebo, in a double-blind setting, where both the examiners and the test subjects are blinded to the test substance. All subjects must consent (for entire study period) for not using any other measures for smoking cessation (see section 1.1) than the one tested in this study, i.e., using Acetium® lozenges in context with every smoked cigarette.

In principle, subjects eligible for the study are current smokers (adult women and men), who are motivated to quit smoking, irrespective how long they have smoked, and how much they currently smoke (pack years). However, the following subjects should be considered non-eligible: 1) the individuals who smoke other type of tobacco than cigarettes, 2) those who refuse to sign written consent, 3) those who are not motivated to quit smoking, 4) those who do not commit themselves for not using other type of interventions for smoking quit during the 1-year follow-up time.

2.3.Methods

2.3.1.Baseline data

Before enrolment in the cohort, all subjects are requested to sign a written concept, after having been explained the details of the study and the commitment requested from each subject for the successful completion of the 1-year study protocol. Before study onset, each subject will be requested to fill in a structured questionnaire recoding their detailed smoking history, including the details of previous intervention approaches (**ANNEX 1).** This questionnaire also includes a more objective estimation of the nicotine dependence, evaluated by using the modified Fagerström Test for Nicotine Dependence (FTND),[49] as detailed in **ANNEX 2**.

2.3.2.Smoking quit intervention by Acetium® and placebo lozenges

The patients consenting to participate in the trial will be randomised into two groups of equal size (cases and controls) using the random number seed for a cohort of 2000 subjects. This intervention trial will be conducted using a double-blind setting, where both the examiners and the test subjects are blinded to the test substance. All subjects receive written instructions explaining the study design as well as the daily practice to be followed in usage of the test substance (Acetium® or placebo lozenges) on the occasion of every smoked cigarette. Following the randomization, all participants will receive their numbered packages of the test substance (Acetium® or placebo), equalling the need of one full month (+10% extra), calculated on the basis of their reported smoking frequency at baseline. All subjects are instructed to strictly adhere to the study protocol, most importantly, not to neglect taking one test lozenge in the context of each single cigarette, concomitantly with the smoking process. This is essential to ensure the proper function of Acetium® lozenges, intended to inactivate acetaldehyde dissolved in the saliva from the cigarette smoke.

2.3.3.Follow-up data

For accurate monitoring of the smoking practices and their eventual changes, all study subjects will be administered a smoking diary, to be filled on daily basis, recording the daily numbers of cigarettes and the test lozenges. In addition, the reported smoking abstinence will be monitored using tow objective measures: Fagerström Test for Nicotine Dependence (FTND) and breath carbon monoxide (CO) monitoring.

2.3.3.1.Smoking diary

The smoking diary (**ANNEX 3**) will provide valuable information about the smoking practices of each participant, and is also intended to assist the preparation to quit, as explained.

Careful recording of each smoked cigarette is essential on daily basis. The smoking hours tell how the smoking will dictate the smoker's daily itinerary, i.e., smoking continues evenly throughout the day or smoking is more frequent during the morning hours than in the evenings. Is the smoker able to keep longer intervals? This reflects the nicotine dependence. A person with a strong nicotine-dependence will smoke more frequently during the morning hours (before noon), to fill the nicotine deficiency that arouse during the night. This person also has to smoke at regular intervals and keeping longer breaks is difficult.

Also important is to record where and why did you smoke. That helps clarify whether one has a regular habit to smoke always on certain specific occasions, e.g. while waiting for an autobus. That might prompt one to consider alternative patterns of conduct, i.e., what else you could do after lunch or coffee break, which should assist your preparation to quit.

The question- Why- helps the smoker figure out which factors trigger the desire of a cigarette. The answer can be for example a stress or being nervous. On the other hand, one frequently goes out for smoking because of social reasons, to accompany someone, even without a personal urgency for smoking at the very moment.

Finally, into the last two columns, the test subject should enter, how she/he felt the particular cigarette, and estimate the degree of smoking pleasure, using the scale 1-10. Observing the smoking occasion itself makes it a conscious event instead of an automatic conduct. This should help breaking

one's own daily routines even before deciding to quit. Do I really need a cigarette just on this very moment? Was the smoking of this particular cigarette a true pleasure or did I light it simply because of a habit or a company? This daily diary ends up with an overall estimation of the smoking day, recording all the variables at the conclusion of the day, including the total numbers of cigarettes and lozenges used, as well as overall smoking sensations of that day.

These diaries are submitted to the study monitor on monthly basis, so as to confirm the compliance of each subject with the study protocol as well as to record the date of eventual quits from smoking, violation in the protocol or censoring due to other reasons.

2.3.3.2.Breath carbon monoxide (CO) monitoring (optional)

Because CO is a significant component of cigarette smoke, a breath CO monitor can be used to detect recent cigarette use. CO-concentration in breath is directly correlated with the CO-concentration in blood, known as per cent carboxyhemoglobin. Within hours of quitting, CO-concentrations show a noticeable decrease, and this can be encouraging for someone considering to quit. The additional value of demonstrating blood CO-concentration to a smoker through this non-invasive breath sample is that it links the smoking habit with the physiological harm associated with smoking.[15]

2.3.3.3.Fagerström Test for Nicotine Dependence (FTND)

Originally introduced in 1978, the latest modification of this test is based on six simple questions recording the key variables of the smoker's daily practices.[49] This test has been validated in several studies, and although it does not seem to bear a close correlation with the biochemical indicators of smoking, this test is valuable in monitoring the psychological dependence on nicotine. When recorded together with breath CO monitoring and smoking diary regularly during the intervention, FTND is expected to improve the objective assessment of the Acetium® lozenge's efficacy in smoking cessation intervention.

2.3.4.Study endpoints

2.3.4.1.Study compliance

Because of the study design (double-blind, placebo-controlled trial), the study endpoints can only be assessed at the stage when the randomization is unveiled. This is planned to take place after

completion of the 12-month intervention period by all those compliant subjects who are not lost to follow-up or censored for other reasons. Although it is not possible to report any interim results for test substance-specific quit rates without unveiling the randomization, it is possible to analyse some descriptive statistics e.g. at study midpoint, after 6 months of intervention.

Because of the relative complexity of the study setting, it can be anticipated that the number of subjects lost to follow-up, those not completely adherent to the study protocol, as well as those interrupting the intervention for other reasons, will not be negligible in both study arms, it is most likely that the final analyses must be run separately for two groups: 1) Per Protocol (PP), and 2) Modified intention-to-treat (mITT). The former include all subjects (in both arms) who have been compliant with the study protocol, without any major violations in i) taking the test substances (lozenges), and ii) in recording the follow-up data (Section 2.3.3). The latter category includes all subjects who were not necessarily fully compliant with the protocol, but who completed the follow-up of at least 6 months.

2.3.4.2.Primary endpoints

Due to the fact that the data are recorded by both objective and (in part) subjective means, there are several potential endpoints in this study. The two most common outcome measures in clinical trials of smoking cessation are **prolonged abstinence (PA)** and **point prevalence (PPA) abstinence**.[46] Both PA and PPA are typically tied to i) the follow-up time (that continues a variable length after a recorded quit date, but both can be tied also to ii) end of intervention, or iii) time prior to the assessment of the results. PA - a sustained or continuous abstinence - is typically defined as not smoking for a period of several months after a quit attempt. Sometimes, this is for the entire period since the quit date, and sometimes it begins after an initial "grace or charm" period. PPA is typically defined as not smoking on the day of follow-up (or for a few days before a follow-up day).

Both PA and PPA have their supporters in the literature.[46] The major benefits of PA are that it a) is more stable, b) is a better proxy for lifelong abstinence, c) is a better proxy for health benefit, and d) has a closer temporal relationship to intervention than PPA. The major benefits of PPA are that it a) has less memory bias, b) has less variability due to missing data, and c) is able to detect delayed quitting. Albeit closely correlated, these two outcomes give somewhat different estimates for quit

rates, and for this reason, a recent meta-analysis recommends using both PA and PPA outcomes in all future smoking cessation intervention studies.[46]

2.3.4.3.Surrogate intermediate endpoints

In addition to these two primary study endpoints, one can assess two other endpoints that can be considered as surrogate intermediate endpoints of PA and PPA. These are FTND score and breath CO-levels. The former is a measure on psychological nicotine dependence whereas the latter is an objective biochemical measure of exposure to tobacco smoke. When subjected to repeated measurements during the follow-up, the values of these variables in each subject are not independent but related, and as such particularly suitable measures of intra-subject variation in this longitudinal setting. Both can be considered as surrogate intermediate endpoints of PA and PPA, i.e., notable decrease in both the FTND score and CO-levels is expected to precede the decision to quit - the prerequisite of a positive rank for PA and PPA. When recorded in a panel data format, both can be used as surrogate endpoints e.g. in multivariate regression models (GEE, Panel Poisson), to estimate the role of L-cysteine lozenges as independent covariate (predictor) of smoking quit (PA, PPA) or its surrogates (FTND or CO).

2.3.5.Statistical analysis

All statistical analyses will be performed using the SPSS 25.0.0.1 for Windows (IBM, NY, USA) and STATA/SE 15.1 software (STATA Corp., Texas, USA). The descriptive statistics will be conducted according to routine procedures. Frequency tables will be analyzed using the $\chi 2$-test, with the likelihood ratio (LR) or Fisher's exact test for categorical variables. Differences in the means of continuous variables are analyzed using non-parametric (Mann-Whitney or Kruskal-Wallis) test for two- and multiple independent samples, respectively.

There are different ways to assess the primary (and secondary) endpoints of the study. The most straightforward is to calculate the risk estimates of PA and PPA in the test (Acetium®) arm versus the placebo arm, using conventional univariate regression models, where the results are expressed as crude OR (odds ratio), and their 95% confidence intervals (95% CI).

The time to quit (TTQ) in the two study arms can be compared using the life-table techniques, e.g. univariate survival (Kaplan-Meier) analysis, using the quit date as the event, and comparing the

stratum-specific estimates using the log-rank (Mantel-Cox) statistics. The same approach can be used to calculate the difference in the duration of abstinence (abstinence time, AT) between the two study arms. The dose-dependence of the Acetium®-associated quit (if relevant) can be analysed using the Cox proportional hazards regression model (in univariate), where Acetium® lozenge is used as continuous variable (i.e., quantity of lozenges consumed until quit).

In addition, using the first quit (permanent or not) as the event, the effect of Acetium® versus placebo can be modelled also using the regression techniques based on count variables, i.e., Poisson regression. In that case, quits are expressed as events per person time (months) at risk, and the two arms are compared using the incidence rate ratio (IRR) statistics. When applied to panel type of data (Panel Poisson), the covariates subject to intra-subject variation (at FU visits) can be adequately controlled, which is a definite advantage in this type of longitudinal setting. A similar type of approach based on panel data, i.e., generalized estimating equation (GEE) modelling, can be used to estimate the effect of Acetium® on persistence of the quit, using the PA (abstinence; yes/no) recorded at each follow-up visit as the dependent variable.

To estimate the effect of Acetium® lozenges as independent predictor (explanatory factor) of smoking quit, all the above analyses (logistic regression, Cox proportional hazards regression, Panel Poisson, GEE) will be repeated in multivariate mode, adjusted for potential confounders, like age, sex, alcohol use, pack-years, previous interventions, etc. according to usual practice of multivariate modelling. In addition, a completely new approach to model the complex process of smoking quit will be attempted in this trial (see 2.3.5.1).

2.3.5.1.Modelling of smoking quit by competing-risks regression

This type of smoking cessation intervention trial is more complex than merely having a single quit vs. no quit dichotomous outcome. Indeed, if carefully modeled, it can be anticipated that there are several possible outcomes to be observed during the Acetium® intervention: i) no effect at all (=smoking continues unchanged as compared with the baseline), ii) quit (=cessation of smoking since the quit date with or without a grace (charm) period), iii) relapse (=cessation of smoking for a period but relapse afterwards), and iv) reduction of smoking (=number of daily cigarettes clearly reduced at study endpoint). In addition to these primary outcomes, it can be reasoned that also the

changes in breath CO-levels and FTND scores would appear as observable outcomes, representing intermediate surrogate endpoints of PPA or PA.

Thus, another method for modeling these complex data can be used, by taking into account the fact that i) the longitudinal data be utilized in full, ii) dependence of the repeated measurements at follow-up visits be taken into account, and iii) the multiple-outcome dependent variable (no change, quit, relapse, reduction) be treated in a single statistical model. All these prerequisites are met by **the competing-risks regression**,[47,48] which will be used to model the impact of Acetium® intervention (and other covariates) on the competing risks outcomes of this trial.

Based on the method of Fine and Gray (1999), competing-risks regression provides a useful alternative to standard Cox regression for survival data in the presence of competing risks.[47,48] In contrast to the usual survival analysis measuring time-to-failure (e.g., TTQ) as a function of the covariates of interest (Acetium®/Placebo), the term competing risks refers to the chance that instead of the quit (permanent cessation), one will observe a competing event, e.g. i) no changes in smoking habits, ii) transient quit (relapse) or iii) smoking reduction. During the follow-up period, detection of any of these competing events impedes the occurrence of the other event of interest. This is basically different from the usual censoring that occurs in conventional survival analysis, i.e., loss to follow-up. Indeed, while usual censoring (exclusion) from the study (Cox) prevents you from observing the event of interest, a competing event prevents the occurrence of the event of interest. In simple terms, competing-risks regression generates hazard for (failure) events of interest, while simultaneously keeping the subjects who experience competing events still "at risk" so that they can be adequately counted as not a chance of failing.[47,48] Different from the usual Cox regression models producing HR (hazard ratio), this technique reports exponential coefficients known as sub-hazard ratios (SHR).

2.3.5.2.Power analysis

Due to the fact that several optional tools are available for statistical analysis of these data, also the power of the study can (and needs to) be analysed differently, following the algorithms specified for each of these statistical techniques. In the simplest approach (univariate logistic regression for calculating OR), the power can be calculated using the two-sample proportion test, comparing proportion of quit in the Acetium® and placebo arms. The study (n=1000 per study arm) is adequately powered (Type II error 0.80, type I error 0.05) to detect a true difference (in PPA or PA) of

10% between the two arms, within the range of 10% quit in the placebo and 20% quit in the Acetium® arm. Within this (10-20%) range, the study power is sensitive to any decrease in this difference, but allows less difference (7.5%) if the quit rate falls between 5% and 15% in the two arms.

Using univariate survival (Kaplan-Meier) analysis for TTQ, with log-rank test for comparing the study arms, this sample size (n=2000) is adequately powered to detect the true difference between the arms with HR=0.777, in other words a 22.3% difference in TTQ between Acetium® and placebo arms. This power, however, is sensitive to censoring. For the analysis by Cox proportional hazards regression, the study power estimates are the same, and also here, the power is sensitive to censoring. Using the Poisson regression for count outcomes (events/person time at risk), the cohort of 2000 subjects is also adequately powered (α=0.05; β=0.80) down to IRR 1.3 between the Acetium® and placebo study arms in producing incident quit events.

3.STUDY EXECUTION AND TIME-TABLE

For execution of the study, the company has three major options: 1) to hire a CRO (contract research organisation) to set up and monitor the whole study; 2) to find a suitable clinic or research institute, which should be willing to conduct the study on the basis of research collaboration, and 3) to set up and monitor the whole study in their own premises. In the latter case, one would necessitate hiring a project monitor, specifically devoted to this study. He/she should be responsible for taking care of all the necessary practical issues, starting from invitation of smoker volunteers, their randomization, interview of the subjects, delivery of the numbered packages of the test substances, follow-up visits on monthly bases, collecting the smoking diaries, breath CO-monitoring (monthly), recording FTND scores, to be repeated at every follow-up visit, and finally, the transfer of all collected data into the master data file.

Which one of the three options will be selected is a crucial determinant of the time-table. Most likely, the least time consuming would be the first option, but at the same time, this would be the most expensive one. Most likely, the least expensive one would be the 3rd option, i.e., conduct the whole procedure by the own research team. Probably the best balanced situation would be to find an interested third party that should be willing to conduct the intervention trial on the basis of research collaboration. In that scenario, the company would cover only the incurring direct extra costs.

Irrespective which option will be the final choice, the key elements of the project remain the same. In brief, enrolment of the cohort will be accomplished by public invitation of volunteer current smokers in local newspapers (random population sample). A cohort of 2000 volunteers is needed, randomised to the test and placebo arms in a double-blind fashion. A written consent is needed. The intervention trial necessitates regular monitoring by follow-up visits at 3-month intervals for up to 12 months. The first interim assessment of the study will be done at the point when the first 100 subjects have completed their 3-month FU, by comparing (without opening the randomization code) the two groups for their primary study endpoints (PP, PA) and for the secondary endpoints, if necessary, to disclose the eventual differences between the cases and controls. In the case that no significant differences in any of the primary, secondary and intermediate endpoints are disclosed between the two groups (code unbroken) by that time, the continuation of the project will be considered by the company's Scientific Advisory Board.

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ANNEX 1. **SMOKING HISTORY RECORD**

Date of Interview:	Day:	Month:	Year:		
Name:					
Date of Birth:	Day:	Month:	Year:		
Age:					
Gender:	Female:	Male:			
Occupation:					
Any medical problems	Yes:	No:			
Any psychological problems	Yes:	No:			
Current medication and other ongoing treatment (list)					
Alcohol consumption:					
Regularity and type	No:	Social:	Daily:	Excessive:	
Type of alcohol typically used	Beer:	Wine:	Liquors:	Spirits:	Other:
Weekly use (estimate no. of dosages/w)					
Smoking history:					
Age when started smoking					
Regular smoker ever since	Yes:	No:			
If not, describe					
Cigarettes per day (currently)					
The same number, for how long (yrs)?					
Trend in the daily numbers of cigarettes	Constant:	Increasing:	Decreasing:		
Other forms of tobacco	Cigars:	Pipe:	Smokeless:		
If any of the above, list the amounts					
Time to the first cigarette of the day:	Minutes/hours since wake-up:	Min:	Hrs:		
Daily experience of urges to smoke	Yes:	No:			
Wake-up at night for smoking	Yes:	No:			
Smoking in the household	Yes:	No:			
Smoking of first-degree relatives (Y/N)	Mother:	Father:	Sisters:	Children:	
Data on previous relapses:					
Previous quit attempts	No:	Yes:	How many:		
Time since most recent quit attempt:	Months:	Years:			
The reason to relapse? (give one)					
Longest time without smoking:	Days:	Weeks:	Months:	Years:	
Fagerström Test for Nicotine Dependence (FTND)(Score 0-10):	Score (0-2):	Score (3-4):	Score (5):	Score (6-7):	Score (8-10):
Smoke exposure validation (CO breath)	CO breath test reading (ppm):				
Previous intervention approaches:	Yes:	No:			
Type of medication (or other approach) used for quit interventions:	Unassisted:	CO-Monitoring:	NRT (any):		
	Bupropion:	Champix (Pfizer):	Moclobemide:		
	Combination:	Cut-down:	Community intervention:		
	Psychosocial:	Cigr. substitutes:	Hypnosis etc.:		
Degree of adherence to therapy:	Poor:	Moderate:	Good:		
No. of sessions offered:					
No. of sessions attended:					
Type of support offered:	Individual:	Group:			
Long-term outcome:	Duration of intervention:				
Cessation of smoking:	Yes:	No:			
Duration of temporal abstinence:	Years:	Months:	Days:		
Regular smoking continued since (date):	Day:	Month:	Year:		

ANNEX 2. **FAGERSTRÖM TEST FOR NICOTINE DEPENDENCE (FTND)**

Name:	Date of Record:	Day:	Month:	Year:

1. How soon after you wake up do you smoke your first cigarette?

[ ] Within less than 5 minutes	3 points
[ ] Within 6-30 minutes	2 points
[ ] Within 31-60 minutes	1 points
[ ] After 60 minutes	0 points

2. Do you find it difficult to refrain from smoking in places where it is forbidden, e.g., in church, at the library, cinema, etc?

[ ] No	0 points
[ ] Yes	1 point

3. Which cigarette would you hate most to give up?

[ ] The first cigarette in the morning	1 point
[ ] All others	0 points

4. How many cigarettes a day do you usually smoke?

[ ] 1 - 10	0 points
[ ] 11 – 20	1 points
[ ] 21 – 30	2 points
[ ] 31 or more	3 points

5. Do you smoke more during the first two hours of waking than during the rest of the day?

[ ] No	0 points
[ ] Yes	1 points

6. Do you smoke even when you are so ill that you are in bed most of the day?

[ ] No	0 points
[ ] Yes	1 point

In scoring the FTND, the three yes/no items are scored 0 (no) and 1 (yes). The three multiple-choice items are scored from 0 to 3. The items are summed to yield a total score of 0-10.

Classification of nicotine dependence:

0-2: Very low
3-4: Low
5: Moderate
6-7: High
8-10: Very high

ANNEX 3. **SMOKING DIARY**

Date and Hour		Where and why did I smoke?	What did I feel and how did a cigarette taste?	Level of pleasure (1-10)	Lozenge taken (Y/N)
OVERALL EVALUATION OF THE DAILY SMOKING					
No of Cigarettes		Smoking times/sites as usual (Y/N)*	Feelings about smoking (unchanged/changed)*	Level of pleasure	No. of lozenges
*Free Comments:					