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COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

GUIDELINE ON THE DEVELOPMENT OF MEDICINAL PRODUCTS FOR THE TREATMENT OF SMOKING

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GUIDELINE ON THE DEVELOPMENT OF MEDICINAL PRODUCTS FOR THE TREATMENT OF SMOKING

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ABBREVATIONS

CHMP	Committee for Medicinal Products for Human Use
CPMP	Committee for Proprietary Medicinal Products (now called CHMP)
COPD	Chronic Obstructive Pulmonary Disease
CYP	Cytochrome P-enzyme
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, version IV Text Revision
EMEA	European Medicine Evaluation Agency
EU	European Union
EWP	Efficacy Working Party
FTND	Fagerström Test for Nicotine Dependence
ICD-10	International Classification of Diseases version 10
ICH	International Conference on Harmonisation
NRT	Nicotine Replacement Therapy
OTC	Over the Counter
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
QSU-Brief	Brief Questionnaire of Smoking Urges
TQD	Target Quit Date
VWP	Vaccine Working Party

EXECUTIVE SUMMARY

The aim of the present guideline is to provide guidance for clinical studies in the development of medicinal product in the treatment of tobacco smoking. Different treatment modalities, such as nicotine replacement therapy (NRT), atypical antidepressants (bupropion) and a partial alpha 4-beta 2 nicotinic acetylcholine receptor agonist (varenicline) are already available; others are within the scope of development, e.g. immune therapy using nicotine-conjugate antigens[1].

Because of their different mode of action, and, subsequently, different approaches in the treatment of smoking, clinical trials may need to be adjusted in specific situations. The present document should be conceived as general guidance, and should be read in conjunction with other EU and ICH guidelines that apply to the subject, and the target population to be treated (see Section 3).

1. INTRODUCTION (background)

Smoking is a well known risk factor for the development of cardiovascular diseases, chronic obstructive pulmonary disease (COPD), many forms of cancer, and therefore represents a major public health concern. It has been estimated that smoking may shorten life expectancy by 7-10 years.

Tobacco toxicity is mainly due to smoke compounds (carcinogens like polycyclic aromates) and combustion products like carbon monoxide. Tobacco contains nicotine, which exerts cardiovascular effects like hypertension and increased hart rate. Nicotine passes the placenta and is also excreted in mother milk. In pregnant women, smoking may lead to degenerative changes of the placenta and low birth weight in the offspring. Maternal smoking is also associated with congenital malformations like facial-oral clefts, and sudden infant death syndrome.

Many smokers may be aware of the risks and motivated to stop smoking, but have severe difficulties to quit. Nicotine use may lead to dependence, though addiction to smoking is also maintained by other psychological factors associated with smoking habit.

Nicotine has affinity for the nicotinic cholinergic receptors, which are widely spread throughout the brain, the autonomic ganglia, and the neuromuscular junction. The natural ligand for the receptor is acetylcholine. Nicotine may exert both stimulating and inhibiting effects upon different organ systems. Nicotine use induces arterial constriction and affects the cardiovascular tone; nicotine induces nausea in naïve subjects and may induce metabolic changes (hyperglycaemia). Its addictive properties may arise from its pre-synaptic actions influencing neurotransmitter release in the brain (dopamine release in the nucleus accumbens reward system). Nicotine withdrawal is characterized by amongst others symptoms of irritability, anxiety, dysphoria, difficulty concentrating, restlessness, insomnia, decreased heart rate and increased appetite. Both craving and the severity of withdrawal symptoms, as well as the overall presence of smoking related cues are the strongest phenomena to retain dependency.

According to the definitions of the World Health Organisation, ICD-10, and DSM-IV-TR, dependence to substances is characterised by a cluster of physiological, behavioural and cognitive phenomena, in which the use of a substance takes on a much higher priority for an individual than other behaviours that once had greater value. Criteria for diagnosis of dependence are, among others, a strong desire or compulsion to take the substance despite knowledge or evidence of its harmful consequences, difficulty in controlling the level of its use, physiological withdrawal symptoms and development of tolerance. The primary difference between nicotine dependence and dependence to other substances may be the absence of behavioural disruption of daily life, as in contrast to illicit substances tobacco is freely available, and does not cause obvious intoxications unlike e.g. alcohol. As smoking however becomes less accepted in public places and working places, nicotine dependence may interfere with daily life functioning to a larger extent than in the last decades.

[1] nicotine-conjugate antigens are also called nicotine vaccines in the literature.

1.1 Epidemiology

The prevalence of smoking in adults is currently estimated to be between 22-47% worldwide. Most smokers start in early adolescence. Point prevalence rate of smoking in adolescents vary between 5.5 and 24.7% across Europe.. It has been estimated that 10-27% of the pregnant women in the EU continue smoking during pregnancy. Nicotine dependence is more common in groups with lower social-economic status.

It has been estimated that if 50% of the current smokers would give up smoking, 20-30 million premature deaths would be avoided in the first quarter of this century (Lancaster et al., 2000). Smoking cessation by current smokers is therefore the best option by which tobacco related mortality/morbidity can be reduced in the medium term.

1.2 Established treatment

In developed countries, smoking cessation is strongly promoted by health care professionals and the government. In addition to counselling programs, there are several options for pharmacotherapeutic intervention: nicotine replacement therapy (NRT), varenicline, a partial agonist of nicotinic acetylcholine receptor alpha4 beta2, and bupropion (Zyban®), a noradrenalin and dopamine re-uptake inhibitor. NRT, in many countries, is an OTC (over the counter) product, and is available in diverse forms, e.g. patch, lozenge, nasal spray, inhalator and gum.

Individual preference and tolerability determines whether one or the other product will be used. Despite these treatment options, many people remain having difficulty with becoming abstinent and especially maintaining abstinence over time. Craving and withdrawal symptoms are strong and persistent, whereas the risk of weight gain as a consequence of smoking cessation may be unattractive. Therefore, despite current treatment options, many attempts to quit smoking fail. Relapse may occur even after a long-term period of cessation of several years. Moreover, there are limited treatment options for some specific patients groups due to contraindications of established treatments. Consequently, despite the established efficacy of the current treatment options, the development of alternative pharmacological therapies is encouraged.

2. SCOPE

The scope of the present document is to provide guidance in the definition of treatment goals, study design, outcome measures, and data analysis for new products that will be developed to treat nicotine dependence.

The leading principle for the present guideline is that pharmacotherapy is an aid to become abstinent and remaining abstinent, preferably without drug treatment. This has been the basic principle in the development of products so far. Future developments, however (e.g. nicotine-conjugate antigens), might lead to a concept of intermittent or chronic treatment to optimize sustained abstinence throughout life. At present there is not enough data for recommendations regarding prevention. or literature to prospectively recommend on the best trial design.

Smoking reduction is not considered an indication target. The benefit of smoking reduction on health outcome is debatable. A more gradual ‘cut-down to quit’ approach may be applied in the clinical trials in patients not able or willing to quit abruptly, but abstinence is still considered as the ultimate treatment goal and hence the primary outcome should reflect abstinence.

Primary prevention of smoking, e.g. by immunisation with nicotine-conjugate antigens, is not considered a target indication in near future, as a target population for primary prevention cannot be defined.

Potential Reduced Exposure Products like cigarettes with low polycyclic aromates or nitrosamine contents, and smokeless tobacco products are beyond the scope of this guidance document, as these products are not therapeutic drugs and fall under different legislations.

3. LEGAL BASIS

This document should be read in conjunction with Directive 2001/83/EC (as amended) and all relevant CHMP Guidelines, among them:

- Dose-Response information to Support Drug Registration – CPMP/ICH/378/95 (ICH E4)
- Statistical Principles for Clinical Trials – CPMP/ICH/363/96 (ICH E9)
- Choice of Control Group in Clinical Trials – CPMP/ICH/364/96 (ICH E10)
- Adjustment for Baseline covariate CHMP/EWP/2863/99
- Missing data – CPMP/EWP/177/99
- Extent of Population Exposure to Assess Clinical Safety – CPMP/ICH/375/95 (ICH E1A)
- Studies in support of special populations: geriatrics – CPMP/ICH/379/99 (ICH E7)
- Clinical investigation of medicinal products in the paediatric population – CPMP/ICH/2711/99 ICH 11)
- Pharmacokinetic studies in man (EudraLex vol. 3C C3A)
- Note for Guidance on the Clinical Evaluation of Vaccines CHMP/VWP/164653/2005
- Guideline on the exposure to medicinal products during pregnancy: need for post-authorisation data EMEA/CHMP/313666/2005
- Note for guidance on the investigation of drug interactions EMEA/CPMP/EWP/560/95

4. MAIN GUIDELINE TEXT

4.1 Subject characteristics and selection of subjects

Smokers with the intention to quit smoking are eligible. Both males and females should be included.

The number of previous quit attempts and former pharmacotherapy for smoking cessation should be documented. In principle, inclusion should be as broad as possible. Subjects may be stratified according to their level of nicotine dependence, or the earlier use of other pharmacological treatments.

The level of dependence may be measured with the Fagerström Test for Nicotine Dependence (FTND), which is a valid instrument to be used for this purpose. Other instruments may be used as well provided that they are validated for this purpose.

4.1.1 Baseline characeristics

The following descriptive features at least should be documented:

- demographic features such as age, gender, ethnicity, and, optional, social-economic class)
- the age of onset of smoking
- the number of cigarettes smoked/day
- history of previous quit attempts and their treatment
- the level of dependence measured by the FTND or another validated instrument
- the amount of craving/urge to smoke
- general health, vital signs (e.g. blood pressure), body weight
- Co-morbidity including psychiatric disorders

4.2 Methods to assess efficacy

4.2.1 Definition of the primary endpoints

In smoking cessation studies so far, different definitions have been used to express abstinence (e.g. continuous abstinence, total abstinence, sustained abstinence, prolonged abstinence etc).

Different terms may be used for defining the primary outcome, though its definition should reflect continuous abstinence rate without slips or episodes of relapse to smoking throughout the follow-up period.

A responder is considered a subject who achieves continuous abstinence without slips for a considerable follow-up period. Long-term follow up data are required as early relapse rate is not predictive for long-term abstinence which is considered more relevant. Therefore in confirmatory studies, follow-up of one year from randomisation should be applied.

For recently approved products, a treatment period of 12 weeks was shown sufficient to see difference in abstinence rate after one year. Therefore duration on treatment would preferably 6 – 12 weeks, with the primary endpoint at 1 year. Relapse rates may increase after end of active treatment. For long-term treatment options exceeding 6 months of active treatment period, the observation period for the primary outcome should therefore cover at least six months off-treatment.

Evaluation of the treatment effect (i.e. abstinence without slips) may take place after once a patient is stabilised on active treatment (e.g. once titration is completed, steady state has been reached, or acute withdrawal symptoms and craving has subsided). This period of stabilisation is called the grace period. As slips may be allowed in the grace period, such period need not be incorporated in the evaluation of efficacy. The duration of grace-period depends on the pharmacological properties of the drug, and needs to be predefined. The grace period will be longer for gradual reduction (çut-down-to-quit) studies. Subjects who do not achieve abstinence at the end of the grace period are considered as non-responders. Subjects who are lost-to-follow-up after randomisation (including the grace period) are considered as non-responders.

Smoking status should be measured by self-reporting, by using a smoker's diary or structured forms. Smoking status should be verified by biomarkers i.e. carbon monoxide or cotinine.

4.2.2 Definition of secondary endpoints

- Abstinence rate at the end-of-treatment period
- Abstinence rate 6 months after TQD or end of grace period
- Abstinence with occasional slips allowed (less than five cigarettes per day)
- Craving/urge to smoke assessment
- Withdrawal symptoms

Nicotine withdrawal symptoms (e.g. irritability, depression, restlessness, insomnia, difficulty concentrating, and increased appetite) can be measured by validated scales like the Wisconsin Smoking Withdrawal Scale, the Minnesota Nicotine Withdrawal Scale or the Cigarette Withdrawal Scale.

Craving may be measured by validated by QSU-Brief (Brief Questionnaire of Smoking Urges) or as an item from the withdrawal scales mentioned before. Measuring withdrawal symptoms and craving is not only of interest during active treatment, but also in the period immediate after the subjects will become off-drug. This should be taken into account in the study design.

4.3 Strategy and design of clinical trials

4.3.1 Pharmacodynamics and Pharmacokinetics

PK/PD studies should be performed in accordance to guidance on Pharmacokinetic Studies in Man.

Craving studies may establish the proof of concept. Pharmacodynamic models for evaluating withdrawal of nicotine are needed. In addition, studies evaluating psychometric functions may be needed for central acting drugs, depending on the mechanism of action and duration of treatment (e.g. mood-scales). See also section 4.5.2 of this document regarding safety evaluation.

For nicotine-conjugate antigens, immunogenicity and specificity of the formed antibodies should be investigated in humans. Cross-immunity against endogenous acetylcholine and possible clinical consequences should be tested. These studies should be performed taking the Note for Guidance on the Clinical Evaluation of Vaccines CHMP/VWP/164653/2005 into account.

Pharmacokinetic interactions with drugs expected to be frequently used in this population of smokers (e.g. products for treatment of cardiovascular diseases and COPD) should be investigated, unless there is clear evidence that a pharmacokinetic interaction is unlikely to occur. Smoking and nicotine use may induce CYP enzymes (e.g. CYP1A2, 2A6), and pharmacokinetic interaction studies may be considered if a new drug is metabolised by these enzymes.

For line extensions of established products like NRT, reference may be made to earlier studies. Depending on the formulation and pharmacokinetic profile of the new formulation, additional tolerability studies may be needed.

4.3.2 Dose response studies

Dose-ranging studies should be preferably performed in a controlled, parallel fixed-dose design, using at least three dosages, to establish the optimal dose. Plasma levels may be informative.

4.3.3 Therapeutic studies

a. Exploratory trials

To assess the effect and the safety of a medicinal product in nicotine dependence, parallel group, double blind randomised placebo-controlled trials are recommended. Since medicinal products are available for this indication, it could be considered to use a comparator-controlled parallel group design. The choice and dose of the comparator should be justified on the basis of placebo-controlled evidence of efficacy of the comparator.

A range of treatment durations should be evaluated also taking into account the posology of the comparator (typically 8-12 weeks). At the start of treatment a Target Quit Date (TQD) and grace period is defined. Usually a TQD is set within two weeks after initiating treatment though a more prolonged period may be chosen depending on pharmacological properties of the product. For studies with nicotine-conjugate antigens, the number of booster applications and immunisation schedule should be justified. Moreover, the relationship between antibody-titre levels and clinical efficacy, the need for monitoring of the antibody titre and the need for booster immunisation should be explored.

b. Confirmatory trials

The confirmatory studies should be randomised placebo and active controlled three-arm trials. The comparator should be justified. For new oral or non-oral products double dummies could be applied.

As the short term quit rate is not predictive for sustained cessation which is more clinical relevant, follow-up up to 1 year after randomisation is required for obtaining the primary cessation outcome. See 4.2.1 for definition of primary outcome. Regular visits should be scheduled to verify smoking status throughout this period, at least at the end of the grace period, at the end of treatment, or monthly up till 12 months. For prolonged treatments options exceeding 6 months of treatment, off drug follow up should be at least 6 months. For nicotine-conjugate antigens with immunisation schedules with immunisation schedules of 6 months or longer, the off-treatment phase may be difficult to define, as

some level of immunity may persist long-term after administration of the last application. In that case, a follow up to 6 months after the last immunisation may be acceptable.

Any form of therapeutic counselling should be standardised in trials that aim at a primary indication for smoking cessation.

c. Duration of Treatment

As indicated in section 4.2.1, the duration of the trial will be 12 months, with treatment during the first 6–12 weeks. In case longer treatment duration is necessary, this should be justified and the off-treatment period should be at least 6 months.

Claims that prolongation of the treatment would be beneficial in relapse prevention or initial failures should be based on randomised parallel withdrawal studies, where treatment continuation after the regular prescription period is compared to placebo. For evaluation of an additional benefit of maintenance treatment, the follow-up of at least 6 months off drug is required.

Studies on repeat treatment of initial responders who relapsed after considerable period of cessation may be considered.

In the case of nicotine-conjugate antigens, the efficacy of various short-term and long-term schedules of booster injections may be compared.

d. Methodological considerations

No specific considerations other than established for other clinical trials need to be made. For references to the methodological EMEA guidance documents, see Section 3.

4.4 Studies in special populations

Children

Studies in children are not deemed necessary, since smoking is not a major public health problem of this age group. In case of the development of prevention strategies with pharmaceutical products (e.g. nicotine-conjugate antigens), this age group might come into focus.

Adolescents

Cravings and withdrawal symptoms may occur rapidly after the first experience with nicotine even before daily use. In general, adolescents may be less motivated to stop smoking, which may affect efficacy outcomes. Studies in adolescents may be considered, but preferably once broad post-marketing experience in adults has been obtained. The generation of pharmacokinetic and safety data is relevant if adolescents are included in the labelling. Depending on the pharmacology of the drug, specific safety measures regarding growth and/or sexual maturation, and mood disorders, may be considered to be monitored in adolescents.

Even in the elderly after long-term smoking the benefits of smoking cessation apply. The main aspects to be investigated in this special age group are pharmacokinetic data, relevant as guidance for dose adjustments and for safety with focus on drug interactions and cardiovascular effects related to possible concomitant/underlying cardiovascular disorders. For safety assessments a sufficient number of elderly subjects should be included in the trials. (see Studies in support of special populations: geriatrics – CPMP/ICH/379/99 (ICH E7, section 4.5.1) and the Concept Paper ICH E7(R1) published in 2008 for guidance on this point). Overall, sufficient clinical data should be available to adequately assess the risks in this special population.

Psychiatric co-morbidity

The prevalence of smoking is high in patients with psychiatric disorders like e.g. major depression and schizophrenia. Psychiatric patients may have more problems to abstain from smoking than other smokers. Potential pharmacokinetic interactions with antipsychotics and antidepressants should be evaluated, unless there are strong indications from *in-vitro* interaction studies that such interactions are unlikely to occur. Potential pharmacodynamic interactions and worsening of psychiatric symptoms should be evaluated if there are signs that these may be expected based on the safety and

pharmacodynamic profile of the drug under investigation in non-psychiatric smokers (e.g. somnolence, mood disorders, agitation or psychoses).

4.5 Clinical safety evaluation

4.5.1 General considerations

For references to the relevant safety guidance, see section 3.

4.5.2 Specific adverse events

Interactions

Pharmacodynamic interaction studies with nicotine are required, since some subject will still continue to smoke during treatment with a new compound. Pharmacodynamic interactions with other CNS medicinal products than mentioned in section 4.4 before or central active substances (e.g. alcohol) should be investigated if these are expected.

Vital signs

Body weight and vital signs should be measured at baseline and throughout the study.

Psychiatric adverse events

The effects of the drug on mood (depression), suicidal ideation and behaviour (agitation) should be monitored throughout the study, using appropriate scales. Abnormal (vivid) dreams should be monitored. Measures should be taken at least at baseline, during active treatment, immediately after end-of-treatment and after 6 or 12 months follow-up.

Cardiovascular and pulmonary compromised patients

Most subjects included in the clinical trials for smoking cessation will be relatively healthy. The safety profile of a test product should also be known for cardiovascular and pulmonary compromised smokers, as these patients form a potential users group.

Nicotine-conjugate antigens

For nicotine-conjugate antigens, compensatory smoking is a specific safety issue, and should be evaluated. In addition, local reactivity and systemic reactions should be investigated. Safety of long-term use, specifically in connection with the presence of antibodies during pregnancy should be discussed.

Rebound and withdrawal and addiction potential

Subjects should be monitored for rebound and withdrawal phenomena during treatment, especially in the grace period, and at discontinuation of the drug. These phenomena should be regularly monitored for a substantial amount of time after discontinuation of the drug. Efforts should be made to distinguish withdrawal and rebound phenomena of the drug from nicotine-withdrawal. Nicotine withdrawal symptoms should be separated from craving symptoms and measured with different (validated) tools (see section 4.2.2). Compensatory smoking should be assessed for safety reasons. Testing of reinforcing/addiction potential of the drug may be relevant for nicotine agonists or other psychoactive drugs.

DEFINITIONS

Addiction: see Dependence

Compensatory smoking: increment in smoking frequency and/or intensity during treatment, in an attempt to overcome diminished binding of nicotine to the target receptors, induced by treatment.

Craving: strong desire or compulsion to smoke

Dependence: A cluster of cognitive, behavioral, and physiologic symptoms indicating that the individual continues smoking despite significant substance-related problems or risks. Criteria for diagnosis of dependence are, among others, physiological withdrawal symptoms and development of tolerance, difficulty in controlling the level of its use, substance use continues despite the individual's realization that the substance is contributing to a psychological or physical problem, and unsuccessful efforts to cut down or quit.

Grace Period: Period where the patient is on active treatment, but not yet stabilized, as titration my not be complete or withdrawal symptoms may be severe. Slips are expected and allowed in this period.

Nicotine Conjugate Antigen: Complex of nicotine coupled to an antigen, in order to raise an antibody response to nicotine. Nicotine itself does not rise antibody forming. Also called “nicotine vaccine”.

Nicotine Replacement Therapy: medicinal products containing nicotine, as an aid for smoking cessation and diminishing craving.

Rebound: Increment of craving or smoking rate that may occur after stopping treatment compared to baseline

Target Quit Date: A date set to start a quitting attempt.

Withdrawal: typical symptoms that appear when a subject quit smoking. To be distinguished from withdrawal symptoms due to stopping therapy.

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