European Medicines Agency

London, 19 July 2007
Doc. Ref. CHMP/EWP/369963/05

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

DRAFT

GUIDELINE ON THE DEVELOPMENT OF MEDICINAL PRODUCTS FOR THE TREATMENT OF NICOTINE DEPENDENCE

DRAFT AGREED BY THE EFFICACY WORKING PARTY	June 2007
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	19 July 2007
END OF CONSULTATION (DEADLINE FOR COMMENTS)	31 January 2008

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KEYWORDS	Nicotine Dependence, guidance

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GUIDELINE ON THE DEVELOPMENT OF MEDICINAL PRODUCTS FOR THE TREATMENT OF NICOTINE DEPENDENCE

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EXECUTIVE SUMMARY

The aim of the present guideline is to provide guidance in the development of clinical studies for the treatment of nicotine dependence. 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 available; others are within the scope of development, i.e. cannabinoid receptor 1 antagonists and immune therapy using nicotine-conjugate antigens[1]. Because of their different mode of action, and, subsequently, different approaches in the treatment of nicotine dependence, 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 (refer to Section 3).

1. INTRODUCTION (background)

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.

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 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 irritability, anxiety, dysphoria, difficulty concentrating, restlessness, 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.

1.1 Epidemiology

Smoking is a well known risk factor for the development of cardiovascular diseases, chronic obstructive pulmonary disease (COPD) and many forms of cancer, and therefore represents a major public health concern. Toxicity is not only related to nicotine itself, but also to the presence of carbon oxide and carcinogenic polyaromates in smoke. 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.

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 to smoke 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] nicotine-conjugate antigens are also called nicotine vaccines in the literature.

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) and bupropion (Zyban). NRT, in many countries, is an OTC (over the counter) product, and is available in many forms, e.g. patches, lozenge, nasal spray and chewing gum. Bupropion is available as oral tablet formulation. Bupropion was originally developed as an antidepressant, and is a noradrenalin, dopamine, serotonin re-uptake inhibitor and a non-competitive nicotine receptor antagonist. Its mechanism of action in the treatment of nicotine dependence is not well understood.

The efficacy of both NRT and bupropion is rather similar, and in many trials it is proven that these products are superior to placebo. Varenicline appears to be a relatively more effective drug in smoking cessation thus far.

Individual preference and tolerability determines whether one or the other product will be used, albeit those contraindications may prevail treatment in special groups, e.g. NRT in cardiovascular patients and bupropion in patients with epilepsy.

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 such as cardiovascular patients and patients once diagnosed with epilepsy or psychoses.

Consequently, despite the proven 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 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 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. 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 and nitrosamine, are beyond the scope of this guidance document, as these products are not therapeutic drugs.

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

Subjects with the intention to quit smoking should fulfil the criteria for nicotine dependence as defined in the DSM IV (TR) or ICD-10. The number of previous quit attempts and former pharmacotherapy for smoking cessation should be documented. If in the study a mixed population is included (e.g. naïve and treatment resistant patients) the study should be stratified for these groups. Likewise subjects may be stratified according to their level of nicotine dependence, but in principle inclusion should be as broad as possible.

The level of dependence can be measured with the Fagerström Test for Nicotine Dependence (FTND), which is a valid instrument to be used for this purpose.

4.1.1 Baseline characeristics

The following descriptive features at least should be documented:

- demographic features (age, gender, ethnicity, social-economic class)
- 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
- the amount of craving/urge to smoke
- body weight
- general health score
- 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, point prevalence abstinence, sustained abstinence, prolonged abstinence etc). Whatever the term used, its definition should reflect total abstinence for a long enough period of time under treatment.

According to the WHO, an ex-smoker is considered a subject who has been abstinent for a period of at least 1 year. Relapse rates are highest during the first year of abstinence. Therefore the primary endpoint should be the persistent abstinence rate off drug until 1 year after the end of the initial treatment period. A smoker's diary is considered an adequate tool to measure smoking status. However, smoking status should also be verified by biomarkers i.e. carbon oxide or cotinine.

4.2.2 Definition of secondary endpoints

- Abstinence rate at the end-of-treatment period
- Abstinence rate 6 months after end-of-treatment

- Craving/urge to smoke assessment
- Withdrawal symptoms
- Weight change
- Health outcome

Nicotine withdrawal symptoms (irritability, depression, restlessness, sleep disorder, vivid dreams, difficulty concentrating, and increased appetite) can be measured by validated scales like the Wisconsin Withdrawal Scale, the Minnesota Withdrawal Form 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. Craving feelings usually persist even years after cessation, especially after certain smoking related cues, and could lead to relapse even after long-term cessation. For a specific claim regarding craving, both short-term and long-term data (e.g. 1 year after treatment) are needed.

Measuring withdrawal symptoms and craving is not only of interest during active treatment, but also in the period immediate after the subjects became off-drug. This should be taken into account in the study design.

4.3 Strategy and design of clinical trials

4.3.1 Pharmacodynamics

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). Weight gain after smoking cessation and consecutive metabolic effects may be evaluated.

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. cardiovascular products) should be investigated, unless there is clear evidence that a pharmacokinetic interaction is unlikely to occur.

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

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) is defined. Usually a TQD is set within two weeks after initiating treatment. Evaluation of the treatment effect can only take place after a patient is stabilised (e.g. titration is completed, acute withdrawal and craving has subdued, steady state is reached, etc). This period of stabilisation is called the grace period. In the grace period, no complete abstinence is expected, and this period need not be incorporated in the evaluation of efficacy.

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 trials. The comparator should be justified. For new non-oral products double dummies could be applied. Follow-up, up to 1 year off drug, is obligatory for obtaining the primary outcome (see Section 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, and 6 months and 12 months after end of therapy. Any form of therapeutic counselling should be standardised in trials that aim at a primary indication for smoking cessation.

For nicotine-conjugate antigens, the off-treatment phase may be difficult to define, as some level of immunity may persist long-term after administration of the last application. Therefore, a follow up to 1 year after the last immunisation may be acceptable.

c. Duration of Treatment

Claims that prolongation of the treatment would be beneficial in either responders or failures should be based on randomised parallel 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 1 year off drug is, again, obligatory.

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

For references to the methodological EMEA guidance documents, see Section 3.

It is important to demonstrate that the effect of the agent is specific in the treatment of nicotine dependence and not due to secondary therapeutic effects, e.g. (therapeutic) counselling. Either any kind of external non-medical support or counselling should be prospectively defined in the protocol and should remain constant during the study or formal psychotherapy with proven efficacy on smoking cessation should be excluded.

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 may come into focus.

Adolescents

Cravings and withdrawal symptoms occurs rapidly after the first experience with nicotine. Hence nicotine dependence in adolescents also develops rapidly, even before daily use. In general, adolescents may be less motivated to stop smoking, which may affect efficacy outcomes. No specific efficacy studies in adolescents are considered necessary as the pathophysiology of nicotine dependence is not considered different from that of adults. However, the generation of pharmacokinetic and safety data is relevant if adolescents are included in the labelling.

Elderly

Even after long-term smoking for decades, there is always benefit of smoking cessation. Pharmacokinetic data may be relevant as guidance for dose adjustments for this special age group. For safety assessments a sufficient number of elderly subjects should be included in the trials (see also Section 4.5.1 of this guidance document).

Psychiatric co-morbidity

The prevalence of smoking is high in patients with psychiatric disorders like (major) depression and schizophrenia. Psychiatric patients may have more problems to abstain from smoking than other

smokers. Specific efficacy studies in psychiatric patients are not needed. 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 should be evaluated if there are signs that such interactions may occur based on the safety and pharmacodynamic profile of the drug under investigation (e.g. somnolence, psychoses).

4.5 Clinical safety evaluation

4.5.1 General considerations

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

4.5.2 Specific adverse events

Pharmacodynamic interaction studies with nicotine are obligatory, since some subject will still continue to smoke during treatment with a new compound. Pharmacokinetic interaction studies with nicotine are only indicated if CYP1A2 enzyme is involved in metabolism of the drug. 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.

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. The risk of placenta-transfer of the antigens or antibodies in humans should be clear.

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

Not applicable.

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