SCIENTIFIC DISCUSSION

1. Introduction

The claimed indication for CHAMPIX (varenicline) 0.5 mg and 1 mg film-coated tablets is smoking cessation in adults.

Varenicline is a highly selective partial agonist of the nicotinic acetylcholine receptor α4β2 subtype. In animal models, the α4β2 nicotinic receptor has been shown to be responsible for the reinforcing properties of nicotine. Both nicotine and varenicline bind to this receptor subtype. Binding of nicotine to this receptor subtype causes dopamine release in the mesolimbic "reward" system *(nucleus. accumbens*). It is hypothesized that varenicline, a partial agonist, blocks the full-agonist activity of nicotine by competitive binding. As varenicline has this partial agonistic action it may cause relief of withdrawal and craving symptoms. Withdrawal and craving symptoms are thought to maintain nicotine addiction, and diminishing these symptoms would promote smoking cessation.

The European Commission has estimated that more than 650,000 (i.e. 1 in 7) Europeans die prematurely every year due to smoking related diseases while an additional 13 million suffer from a serious, chronic disease as a result of smoking. The economic burden due to smoking was in EU conservatively estimated at 98-130 billion Euros per year or between 1.04% and 1.39% of the region's Gross Domestic Product for 2000.

According to World Bank estimates the number of smokers worldwide exceeded 1.3 billion in 2003. The worldwide prevalence of smoking was estimated at 47% of men and 10% of women. Smoking prevalence overall and by gender varies by country and/or region). In 2002-2003, the average prevalence of adult smoking in the 25 EU member states was 29% overall, 35% for men and 22% for women. Reducing the current smoking rate by 50% would avoid 20-30 million premature deaths in the first quarter of this century.

Population-based surveys in the United States and United Kingdom indicate that approximately 70% of smokers say they are interested in giving up smoking. Reports indicate that 35% to 45% of smokers actually try to abstain each year but only 3.5% succeed without assistance. Relapse within days to weeks is common and most smokers make multiple attempts to stop, often waiting 2 to 3 years between attempts.

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). The craving and withdrawal symptoms, which include depressed mood, irritability, difficulty concentrating, restlessness, increased appetite, and sleep disturbance, cause significant distress to the smoker and threaten the quit attempt

Current pharmacotherapies for smoking cessation are presently various forms of nicotine replacement therapy (NRT) and the non-nicotinic agent, sustained release bupropion. Meta-analyses of controlled clinical trials have consistently shown that both NRT (any form) and bupropion approximately double the odds of smoking cessation compared with placebo.

2. Quality aspects

Introduction

Champix is presented as immediate release film-coated tablets containing 0.5 mg and 1 mg of varenicline (as varenicline tartrate) as active substance. The other ingredients are cellulose, microcrystalline, calcium hydrogen phosphate, anhydrous, croscarmellose sodium, silica, colloidal anhydrous and magnesium stearate. The film consists of hypromellose, titanium dioxide, macrogols, Purified Water and colorants.

The film-coated tablets are marketed either in opaque blue-white HDPE bottle with an aluminum foil/polyethylene induction seal and a child-resistant polypropylene closure or in clear PVC / Aclar film with an aluminum foil backing.

Active substance

The drug substance is varenicline as varenicline tartrate and its chemical name is 7,8,9,10-tetrahydro-6,10-methano-6*H*-azepino[4,5-*g*]quinoxaline (2*R*,3*R*)-tartrate according to the IUPAC nomenclature. Varenicline tartrate is white to off-white to slightly yellow solid and is non-hygroscopic. It is moderately soluble in dimethylacetamide, acetronitrile, methanol, hexane and ethyl acetate. Varenicline freebase is an achiral molecule, however varenicline tartrate, which is formed through the reaction of varenicline freebase and L-tartaric acid is optically active, and has the absolute configuration of the counter ion 2R, 3R.

- **Manufacture**

Varenicline is synthesised in six chemical steps followed by purification (filtration) and milling.

The manufacturing process has been adequately described. Critical parameters have been identified and adequate in-process controls included.

Specifications for starting materials, reagents, catalysts and solvents have been provided. Adequate control of critical steps and intermediates have been presented.

Structure elucidation has been performed by infrared absorption spectroscopy, mass spectrometry, ^{1}H-NMR spectroscopy, ^{13}C-NMR spectroscopy, X-ray spectroscopy, ultraviolet spectroscopy and optical rotation spectroscopy, and these data confirm the structure of the active substance. The established structure of varenicline tartrate was in agreement with the method of synthesis, analytical and spectroscopic data. The molecular weight determined by mass spectroscopy was in agreement with the expected molecular weight. Definite proof of structure was provided by X-ray crystallography.

- **Specification**

The active substance specifications include test for Appearance (Visual Inspection), identification (IR and HPLC), assay (98.00 – 102% HPLC), tartaric acid content (HPLC), water content (Karl Fisher), Residue on Ignition, heavy metals, residual solvents (GC) Impurities (HPLC) and particle size.
The specifications reflect all relevant quality attributes of the active substance. The analytical methods which were used in the routine controls were described and their validations are in accordance with the ICH Guidelines. Impurities have been extensively described, classified as process related impurities and possible degradation products, and qualified. Furthermore, some of the genotoxic impurities were reduced resulting in levels in the active substance in accordance with CHMP Guideline on the Limits of Genotoxic Impurities. Residual solvents have been satisfactorily controlled in the active substance. Limits are in accordance with ICH requirements. Batch analysis results for the active substance comply with the specifications and show a good uniformity from batch to batch.

- **Stability**

The stability results from long-term accelerated and stress studies which were completed according to ICH guidelines demonstrated adequate stability of the active substance. It was confirmed that the active substance is very stable when exposed to a variety of stressed conditions such as acid, base, oxidation, thermal, humidity and light exposure. The results of the long-term and accelerated studies support the retest period.

Finished product

- **Pharmaceutical Development**

All information regarding the choice of the drug substance as a tartaric acid salt and the excipients are sufficiently justified. Well known excipients were used in the formulation, selected based on their suitability for use in a dry granulation process. Microcrystalline cellulose is used as a diluent and binder, anhydrous calcium hydrogen phosphate as a diluent, croscarmellose sodium as a disintegrant, anhydrous colloidal silica as a glidant and magnesium stearate as lubricant. The compatibility of the active substance was demonstrated with the results of stability studies performed on the finished product.
A film-coating system was added and the tablet shape was changed to capsular tablet shape. In order to differentiate the two strengths the colorant use in the film-coating system was slightly different.
The bioequivalence studies which were performed confirmed bioequivalence between the commercial tablets (1 mg) and the phase 3 tablets, as well as between phase 3 tablets and phase 2B tablets (tartrate salt) and phase 2A tablets (succinate salt). The same core formulation (common blend) has been used for the 0.5 mg tablets as has been used for the 1 mg tablets.
Comparative dissolution profiles are presented for the two strengths of six primary stability batches manufactured by the site. All batches demonstrated similar dissolution profiles with nearly 100 % dissolved after 5 minutes.

- **Manufacture of the Product**

The proposed commercial manufacturing process involves standard technology using standard manufacturing process such as blending, milling (deagglomeration), roller compaction and milling, compression, aqueous-based film-coating unit operations. Furthermore the equipment used is commonly available in the pharmaceutical industry. A dry granulation process was selected based on the improved process robustness gained by the resulting properties of the granulate, including improvements to flow and drug uniformity.
The process validation scheme for manufacture commercial batches was provided.

The batch analysis results show that the medicinal product can be manufactured reproducibly according the agreed finished product specifications.

- **Product Specification**

The drug product specifications were established according the ICH guidelines and include the following tests: appearance, identification (TLC and HPLC), content per tablet of the active substance (HPLC), uniformity of dosage units (Ph Eur), disintegration (Ph Eur), water content (Ph Eur), individual degradation products (HPLC), microbial limits (Ph Eur).
All analytical procedures which were used for testing the drug product were properly described. Moreover, all relevant methods were satisfactorily validated in accordance with the CHMP and ICH guidelines.
The batch analysis data obtained from the analysis of six batches for each strength manufactured by the commercial manufacturing process confirmed satisfactory uniformity of the product at release.

- **Stability of the Product**

The stability studies were conducted according to the ICH guideline. Three production scale batches of each strength have been stored at long term and accelerated conditions in the proposed market packaging.
One production batch per strength was stored under elevated temperature and humidity conditions for 3 months and at ICH photostability conditions and degradation conditions.
Based on available stability data, the proposed shelf life and storage conditions as stated in the SPC are acceptable.

Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture, control of the active substance and the finished product have been presented in a satisfactory manner and justified in accordance with relevant Guidelines. The results of tests carried out indicate satisfactory consistency and uniformity of the finished product. Therefore, this medicinal product should have a satisfactory and uniform performance in the clinic.
At the time of the CHMP opinion, there were a number of minor unresolved quality issues which do not have impact on the Benefit/Risk ratio of the medicinal product. The applicant gave a letter of undertaking and committed to resolve these as Follow Up Measures after the opinion, within the agreed timeframe.

3. Non-clinical aspects

Introduction

The non-clinical programme is in reasonable agreement with EU/ICH guidelines. The majority of safety pharmacology studies were not conducted in compliance with GLP-regulations. The toxicology studies were GLP-compliant. As several pivotal toxicokinetic bioanalyses were performed by a laboratory not listed in the Cumulative Overview of GLP inspections in OECD Member countries of 2001, its GLP-status was verified by the EMEA.

Pharmacology

In vitro varenicline displayed high affinity for the rat cortex $\alpha_4\beta_2$ nicotine receptor in radioligand displacement binding assays with a Ki value of 0.17 nM. It is believed that the nicotinic $\alpha_4\beta_2$ receptor mediates dopamine release in the nucleus accumbens and thus is involved in the motivational effects of smoking. Both nicotine and varenicline both reversibly bind to the same receptor binding site. Considering the 15-fold higher affinity of varenicline for the $\alpha_4\beta_2$ nicotinic acetylcholine receptor as compared with nicotine, very high nicotine brain concentrations would be required to fully displace varenicline and produce nicotine rewarding in the subject.

Ex vivo, varenicline only partially activates the mesolimbic dopamine system, in comparison to activation induced by nicotine: varenicline released ^{3}H-dopamine from rat striatal slices with a maximal response of 51% (relative to the release evoked by nicotine) at 1 μM, indicating that varenicline acts as a partial agonist at the nicotinic acetylcholine receptor. Additionally, 10 μM varenicline reduced the response induced by nicotine by 53%, down to levels induced by varenicline.

An EC_{50} value of 3.5 μM was obtained for varenicline in HEK293 cells expressing human $\alpha_4\beta_2$ receptors. The maximal effect of varenicline was 43% of what was observed for nicotine. Concurrent application of 10 μM varenicline and nicotine reduced the inward current by 53% at steady state.

In vivo microdialysis showed that p.o varenicline treatment caused moderate increases in dopamine release in the nucleus accumbens of freely moving rats. Maximal extracellular dopamine concentrations were reached 2 hours following dosing and the level started to normalise 4 to 5 hours after varenicline administration. The maximal dopamine response of varenicline was around 63% of the full agonist nicotine.

In drug discrimination studies, varenicline (0.01-1 mg/kg p.o.) dose-dependently generalized to nicotine, with complete generalization at 1 mg/kg. However in self-administration studies, rats self-administered varenicline significantly less than nicotine, demonstrating that varenicline is not as reinforcing as nicotine. Furthermore, varenicline pretreatment (1-3 mg kg s.c.) reduced the amount of nicotine by 50% that rats self-administered.

Varenicline displayed binding affinity towards the 5-HT_{3A}-receptor subunit with a Ki value of 350 nM. The Ki for HT_{3A} is approximately 10-fold higher then the human C_{max}. The HT_3-receptor is involved in the mediation of nausea/emesis and irritable bowel; symptoms which are observed clinically during varenicline treatment. According to the Applicant, varenicline could cause emesis peripherally by affecting afferent signaling pathways from the gastrointestinal tract to the emetic center in the mid-brainstem, most likely by activation of 5-HT_3 receptors and/or $\alpha_3\beta_4$ nAChRs. Furthermore, varenicline could possibly have a central action that contributes to emesis through the activation of $\alpha_4\beta_2$ nAChRs in brain nuclei that control the activity of the emetic center.

- Secondary pharmacodynamics and safety pharmacology

In the safety pharmacology studies, high doses of varenicline induced various CNS effects; however, they all occurred with safety margins of at least 50. The only exception is a treatment-related decrease in body temperature, which occurred with a safety margin of 16.

In vitro, 17 μM varenicline inhibited the hERG current by 17%. Additionally, 10 μM varenicline increased the action potential duration in dog cardiac purkinje fibers. In both cases, the findings occurred with a safety margin of more than 90. When evaluated in six monkeys, there were no significant differences between ECG data obtained during vehicle and varenicline treatment. However, one monkey experienced a 30% decrease in heart rate and a slight increase in P-R-interval. In the repeat-dose toxicity studies conducted in monkeys, no treatment-related effects were observed with respect to heart rate, blood pressure, ECG or respiration rate. Since no effects on ECG were observed in the 9 month repeat dose toxicity study in monkeys at the highest dose (1.2 mg/kg/day), this dose may be considered as NOAEL for QT-prolongation. Comparing clinical C_{max} and C_{max} in the monkeys gives a safety margin of approximately 15. No noteworthy changes in the QT interval or any ECG parameters were observed in the clinical studies and there appears to be no need for further investigations.

A dose-dependent increase in the urinal excretion of sodium and chloride was observed in rats but this finding occurred with a safety margin of 50. An inhibiting effect on gastrointestinal motility was observed with a safety margin of 10. Based on an emesis study conducted in ferrets, varenicline has the potential to induced emesis in humans possible via both a local effect on the gut wall as well as a central effect.

Overall, other pharmacodynamic effects caused by varenicline treatment were observed with large safety margins and the only observations of clinical relevance are nausea and emesis.

- Pharmacodynamic drug interactions

Glaucoma, mydriasis, anti-Parkinson, local anesthetics, anti-psychotics, anti-depressants and anxiolytic/hypnotic drugs show low to very low affinity for the nicotinic α4β2 AChRs. In turn, varenicline displays very low affinity for the target receptors of these classes of drugs. Pharmacodynamic interactions are therefore unlikely to occur.

Pharmacokinetics

Absorption: overall, varenicline is characterised by high absorption, negligible first-pass effect, moderate distribution across many tissues, moderate half-life and extensive renal excretion. In rats and monkeys there was no evidence of gender differences with respect to plasma exposure following repeated p.o. varenicline administration. The systemic exposure (AUC) appeared to be higher following repeated p.o. dosing of rats, indicating that accumulation occurred to a minor extent. Mean

varenicline C_{max} and AUC values increased in a less than dose-proportional manner following repeated p.o. dosing of rats and monkeys.

Distribution: the percent of drug bound to plasma proteins was 18%, 45%, 19%, 41% and 20% in mouse, rat, dog, monkey and human plasma, respectively. The tissue distribution of varenicline was investigated using whole-body autoradioluminography in male and female Long-Evans rats following oral dosing of ^{14}C-varenicline. In the majority of tissues, maximal radioactivity concentrations were measured at the first sampling point, which was 1 hour post dosing. Varenicline distributed into all collected tissues except the lens and vitreous humor. Still, varenicline displayed a high affinity for ocular tissues since (besides the GI tract) maximal radioactivity was measured in ciliary body, uvea, iris and choroid. Moreover, high concentrations of radioactivity were detected in ocular tissues at the last sampling point (168 hours). There were no apparent gender differences with respect to tissue distribution. Varenicline displays affinity for melanin containing tissues.

Metabolism: the metabolites of varenicline were identified in circulation and in excreta of laboratory animals and healthy human subjects. In mice, rats, monkeys, and humans the vast majority (75%-93%) of drug-related material in circulation and excreta was comprised of unchanged drug, indicating that metabolism is not a primary route of varenicline clearance in these species. In rabbits, metabolites were present in greater abundance than varenicline. A total of 13 metabolites were observed in all species and were products of oxidation and conjugation pathways. Three metabolites in animal studies remain unidentified (designated as M3, M3a, and M6), but all were present at less than 3.3% and none were detected in humans. In excreta, there was no single metabolite that was more than 4.6% of dose in any species, while unchanged varenicline comprised at least 75% or more of dose in excreta in all species. Overall, the metabolism of varenicline in laboratory species and humans is very similar and all metabolites observed in humans were observed in one or more animal species used in preclinical safety evaluations.

Excretion: the organic cation transporter 2 (OCT-2) is involved in renal elimination of varenicline and the risk of pharmacokinetic drug interactions with OCT-2 inhibitors has been evaluated clinically. Drug interactions on the level of CYP mediated metabolism are not likely. In vitro studies showed that glucuronyl transferase 2B7 (UGT2B7) is responsible for the N-carbamoylglucuronidation of varenicline but this pathway represents only a very small portion of the total clearance.

Toxicology

- Single dose toxicity

Single-dose toxicity studies were conducted in Sprague-Dawley rats, Beagle dog and Cynomolgus monkeys. The results are summarised in the Table below. The dose is expressed as free base. All the listed findings were reversible. No mortality was observed after PO administration of 300 mg/kg/day and 0.2 mg/kg/day varenicline to rats and monkeys, respectively.

Study ID	Species/ Number/ Sex/ Group	Dose/ Route	NTEL/ NTEL animal:human Exposure ratio (AUC)	Major findings
97-1545-06 GLP but not TK	rat/3/sex/group	30, 100, 200, 300 mg/kg /PO	100 mg/kg/ 100	≥200 mg/kg: labored respiration, ↓activity, uncoordinated gait, splayed hindlimbs, tremor, ptosis, loose stool, hunched posture, rough haircoat. ↓body weight, ↓WBC, ↓lymphocytes, ↑blood glucose. 300 mg/kg: convulsions (clonic & tonic)
00-1545-26 non-GLP	rat/6/sex/group	3, 30 mg/kg /PO	30 mg/kg/ 50	No toxicity

97-1545-05 non-GLP Dose escalation study	Dog/1/sex/group	Fasted: 0.05, 0.1, 0.3, 1 mg/kg/PO Fed: 1 mg/kg/PO	<0.05 mg/kg (clinically relevant exposure levels)	≥0.05 mg/kg: multiple episodes of emesis ≥0.1 mg/kg: body tremors, ↓activity, salivation, loose stool, ≥0.3 mg/kg: ↑ALT 1 mg/kg: unsteady gait, prolapsed nictitating membrane, ↑neutrophil, monocytes
98-1545-14 GLP	monkey/2/sex/ group	3 mg/kg/PO	<3 mg/kg (2)	Emesis, recumbency, ↓activity, tremors, ↓food intake Day 1, ↓HR &QT ↑PRQ,
00-1545-27 non-GLP	monkey/2/sex/ group	0.1/day or 0.1 BID/PO	0.1 mg/kg BID/ 0.9	No toxicity
745-03502 GLP but not TK Dose escalation study	monkey/1/sex/ group	Day 1: 80, Day 2: 200, Day 3: 300 µg/kg/day/ IV	80 µg/kg/day (C_{max} ≈ 20.5 – ratio ≈ 2)	200 µg/kg/day: emesis, tremors, ↓activity, muscle rigidity 300 µg/kg/day: as above and generalised tremors (dosing stopped), ↑AST, ALT, ↓total protein, albumin
745-03516 GLP	monkey/4/sex/ group	180 µg/kg /IV	<180 µg/kg (1.5)	↓food consumption, 48(♂)-57(♀)-fold increase in skeletal muscle specific CK, ↑AST, ALT No ECG findings

Human AUC is 194 ng*h/mL following administration of the maximum recommended dose (2 mg/day);The listed exposure ratios have been adjusted for plasma protein binding.

- Repeat dose toxicity (with toxicokinetics)

Repeated dose toxicity of varenicline was evaluated after oral administration in mice, rats, dogs and monkeys. Two studies of 14-days and 3 months duration were conducted in mice, four studies with durations of 10 days, 6 weeks, 3 months and 6 months in rats, one 7-day study in dogs and seven oral studies with durations of 7 days to 9 months were conducted in monkeys. In each study, systemic exposure to varenicline was evaluated for relationship to dose level, sex, and duration of dosing.

Decreased body weight, body weight gain and food consumption were observed in rats at varenicline plasma exposure levels around 50-fold higher than is observed in the clinic. Body weight loss, dehydration and inappetance were dose-limiting factors in the monkey repeat-dose toxicity study, where weight loss and reduced food consumption occurred at AUC values approximately 10 times the human systemic exposure. Anorexia and decreased appetite are uncommon findings in the clinic. In contrast, most patients experience increased appetite, which is commonly observed following cessation of smoking.

Effects on the central nervous system (e g tremors, laboured respiration, unsteady gait) were seen in mice, rats (both at 100 mg/kg/day), and dogs (at ≥0.1 mg/kg/day). At 150mg/kg/day, convulsions were seen in mice. Salivation was a common finding in varenicline-treated rats and monkeys, which occurred at a 6-fold higher AUC values than observed in the clinic.

Gastrointestinal effects (gastric/cecal/colonic dilatation and/or emesis, and loose stools/dehydration) occurred in mice, rats and/or monkeys and were expected findings based on known pharmacological effects of nicotine. Enlarged stomach with or without enlarged pylorus was observed in mice (at 150 mg/kg/day) and jejunal/cecal/colonic dilatation were observed in rats (at ≥30 mg/kg/day, effects that might be related to decreased gastrointestinal transit. One monkey died due to megacolon (at 0.2 BID mg/kg/day). It cannot be excluded that varenicline contributed to pathology in this animal that showed prior to and during treatment various episodes of gastrointestinal disorders. Emesis occurred in dogs (at ≥ 0.05 mg/kg/day) and in monkeys (at ≥0.25 mg/kg/day QD and ≥0.2 mg/kg/day BID). Loose stools and dehydration occurred in rats (at ≥100 mg/kg/day) and dogs (at 1 mg/kg/day). The reduced blood glucose levels, observed in mice (at 150 mg/kg/day) and rats (at ≥10 mg/kg/day), might be secondary and related to the gastrointestinal effects.

The liver was identified as a target organ in mice and rats on the basis of hepatocellular (single-cell) necrosis and moderate elevations in ALT, AST, total bilirubin and decreased 5'nucleotidase activity at 100 mg/kg/day. Liver weight was also increased by varenicline treatment at 10 mg/kg/day in rat but caused smaller increases in mean transaminase elevations without a microscopic correlate. At 30 mg/kg/day, an increase of hepatic microsomal enzymes was seen (CYP1A, CYP2E, CYP3A). Serious effects like necrosis were only seen at high doses in the short term studies. Elevated liver enzymes were observed at lower doses but still these findings occurred with a large margin of exposure. The lack of similar findings in dogs and monkeys may be due to the dose-limiting emesis observed in these species.

Hematopoietic effects consisted of increases in red blood cell counts (RBC) and haemoglobin levels and decreases in white blood cell counts (WBC) and lymphocyte counts in rats (at 100 mg/kg/day) and decreases in RBC, haemoglobin levels, WBC, and lymphocyte counts in mice (at 100 mg/kg/day). In addition there was minimal to mild cellular depletion of the bone marrow at 30 mg/kg/day in the 3 month rat toxicity study. The bone marrow changes might be related to a decrease in food consumption and body weight. Treatment-related changes in erythroid parameters (decreases in mean RBC count, haemoglobin, and haematocrit; increases in mean corpuscular volume, mean corpuscular haemoglobin, and reticulocyte count in rats (at ≥30 mg/kg/day) and mice (at ≥100 mg/kg/day) might be related to increased RBC turnover. These effects were not seen in dogs and monkeys. An increase in total bilirubin was seen in rats and occasionally also in monkeys.

Based on plasma AUC values obtained at the NOAEL and adjusted for species differences in plasma protein binding, the overall safety margins ranged from 6 to 15 in rats and from 1 to 6 in monkeys.

- Genotoxicity

Varenicline was neither mutagenic nor clastogenic when tested in assays for gene mutations in bacteria and mammalian cells or for chromosome aberrations *in vitro* and *in vivo*.

- Carcinogenicity

Carcinogenic potential was investigated in two-year studies in mice and rats.

In mice no treatment-related increase in tumor incidence was noted at any dose tested. Based on toxicokinetic data from a 3-month study, systemic exposure in the mice of the high dose group (20 mg/kg/day) is estimated to be at least 58 times the expected systemic exposure in humans at the maximum recommended therapeutic dose.

In rats, 1 benign hibernoma (brown fat tissue (BAT) tumour) were seen in the mid-dose males and 2 malignant hibernomas in the high-dose males. According to the applicant, varenicline, at exaggerated multiples of efficacious levels, could act like nicotine, and increase sympathetic stimulation/β-oxidation/UCP-1 expression in brown adipocytes. The resulting sustained stimulation of β-oxidation in mediastinal BAT could lead to the formation of reactive oxygen species may cause sufficient local oxidative damage to DNA and decreased apoptosis for development of BAT neoplasia (hibernoma) in rodents.

The exposure multiple at the NOAEL in the rat carcinogenicity study was 5 and at the mid dose where one benign hibernoma was observed the exposure multiple was 17. In rodents, BAT is present at birth, develops rapidly postnatally, and is important in thermogenesis. In contrast, in humans, BAT is present at maximal amounts at birth, after which its metabolic activity and thermogenic capacity decrease to minimal levels. Based on these arguments it is considered that the risk for humans to develop hibernomas following treatment with varenicline is theoretical and most probably non-existent.

- Reproduction Toxicity

Varenicline was tested for reproductive and developmental toxicity in conventional studies in the rat (Segment I, II and III) and the rabbit (Segment II). Toxicokinetics were included in all studies. Exposure margins were up to 37-133 times the human C_{max} or AUC at the MRHD.

Separate female and male fertility studies were conducted with varenicline. In either sex, toxicity consisted of decreases in body weights at 15 mg/kg/day. There were no findings on fertility or reproductive parameters in females and no treatment-related effects on copulation, pregnancy rates, reproductive parameters or the reproductive tract in males. Thus, the NTEL for reproduction and fertility was 15 mg/kg/day. Based on the toxicokinetic part of the 6-week rat study, this dose level would correspond to an AUC value of 36 times the AUC at the MRHD.

Varenicline was not teratogenic in rats or rabbits at any of the doses evaluated. In the rat study, maternal toxicity (decrease in body weight) was observed at doses of 5 and 15 mg/kg/day with a NOAEL of 0.3 mg/kg/day. The NTEL for fetotoxicity and teratogenicity was 15 mg/kg/day, corresponding to a safety margin of 36. In the rabbit study, maternal toxicity (decrease in body weight) was observed at 30 mg/kg/day. The only finding was a significant decrease in fetal and placental weights at the maternally toxic dose of 30 mg/kg/day. Thus, the NTEL for fetotoxicity was 10 mg/kg/day, corresponding to a safety margin of 50. Pre- and postnatal development was studied in rats at doses of 0.3, 3 and 15 mg/kg/day. The NTEL for maternal systemic toxicity (reduced body weight and food consumption) was 0.3 mg/kg/day.

Based on the toxicokinetic part of the rat Segment II study, this dose level would correspond to an AUC value of 0.85 times the AUC at the MRHD. In the offspring, treatment-related developmental findings were observed at 15 mg/kg/day and included reduced body weights, a reduction in the number of rearings, increased maximum amplitude of the auditory startle response (ASR) in males only, and reduced fertility; therefore, the NTEL for F_1 developmental toxicity was 3 mg/kg/day. The fertility rate at 15 mg/kg was 80% compared to 95% for the control, which is outside the historical control range (90%-100%). An association between treatment on the one hand and the increase in ASR amplitude and reduced number of successful F_1 mating pairs on the other hand cannot be excluded, but is considered to pose minimal risk to humans as maternal AUC exposures were 36 times the AUC at the MRHD, based on the toxicokinetic part of the rat Segment II study. Moreover, perinatal nicotine exposure also alters postnatal behavioral function in experimental animals and it is well known that maternal smoking is detrimental to human fetal development, with the most notable effect being intra-uterine growth retardation. Therefore, although varenicline is classifiable as a developmental toxicant, this is not considered a cause for concern and it is duly reflected in the SPC.

There are no studies in juvenile animals as a pedriatric indication is not being sought.

- Local tolerance

Varenicline has been tested for dermal toxicity, eye and skin irritation, delayed contact hypersensitivity and phototoxicity. These studies show the drug product to be well tolerated by dermal application, minimally irritating to the skin and eye, unlikely to cause contact dermatitis and devoid of phototoxic potential.

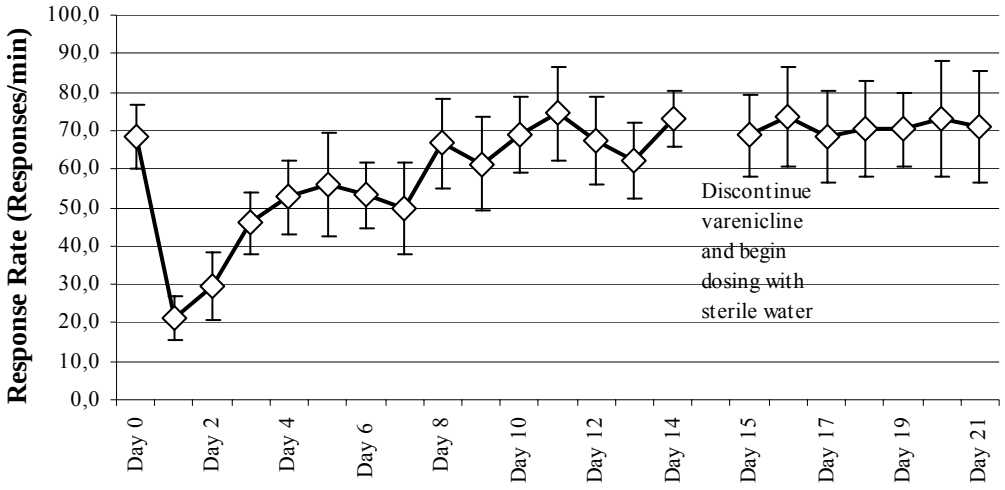
- Other toxicity studies

Antigenicity and immunotoxicity studies were not conducted. Nevertheless, it is known that nicotine alters a wide range of immunological functions and may impair both the immune and inflammatory responses.

- Dependence

The comparatively lower release of dopamine in striatal slices, lower dopamine turnover and release in nucleus accumbens and the lower potential of varenicline to maintain self-administration behavior as compared to nicotine suggests that varenicline should have a lower dependence potential when compared to nicotine. Yet, the functional and behavioral effects were not absent and varenicline generalized to nicotine in a drug discrimination study, suggesting varenicline has similar subjective effects as nicotine. Thus, based on the non-clinical studies, it may be concluded that varenicline has dependence potential due to its reinforcing properties.
Male rats were trained to discriminate 0.4 mg/kg SC nicotine from saline. On days with nicotine administration, 30 consecutive responses on the nicotine-associated lever produced a food pellet delivery (reward). On alternate days, vehicle was used and the other lever was activated. After varenicline administration to trained rats, the percentage of responding on the nicotine-associated lever was taken as an indication of the degree of nicotine stimulus exerted. In this model, SC varenicline produced dose-dependent substitution for nicotine with complete substitution at 1.0 mg/kg. Treatment did not compromise the animals' ability to respond. Mecamylamine attenuated the varenicline-treated animals' preference for the nicotine lever.
Varenicline was tested in male rats trained to self-administer (via lever pressing) 30 µg/kg/infusion nicotine through a catheter placed in the jugular vein. The animals were trained according to two different nicotine treatment protocols: 1) reinforcement was allowed after the rats had pressed the lever 5 times (Fixed ratio) and 2) a schedule that investigated how hard an animal would work (lever pressing) for reinforcement (Progressive ratio). Pre-treatment with PO and SC varenicline decreased nicotine intake under a fixed ratio schedule at doses that did not compromise the animals' ability to respond. The reductions in nicotine intake were approximately 50% and 35% following SC and PO administration of 3 mg/kg varenicline, respectively. Similarly, SC pre-treatment with varenicline reduced the number of nicotine infusions earned per minute in animals working on a progressive ratio schedule by up to 50% (at 1.78 and 3.2 mg/kg). Under the progressive ratio schedules, animals worked harder for a nicotine infusion than they did for varenicline. However, animals on the fixed ratio schedule were not able to differentiate between nicotine and varenicline. Consequently, varenicline's reinforcing properties are the same as or lower than nicotine's.

Male rats were trained in a lever-pressing paradigm, where 10 lever presses resulted in a reward food pellet being dispensed. Based on an acute-dose response curve, it was chosen to administer 1.7 mg/kg varenicline (decreased response rate by ~ 50%) daily for 14 days. As expected the response rate was decreased the first days of treatment but tolerance/neuroadaptation to treatment developed and the response rate returned to the baseline level by Day 10 (see Figure below). Potential withdrawal effects were investigated by dosing with sterile water on Days 15 through 21. Discontinuation of varenicline dosing after 14 days and substitution with sterile water on Days 15 through 21 resulted in no change in response rate, and no-observable behavioural effects. Discontinuation of dosing with varenicline did not cause any behaviour that have been observed previously following discontinuation of nicotine, including teeth chattering, chewing, gasping, writhing, head shakes, body shakes, tremors, and ptosis. Additionally, no changes in response rate or body weight were observed during the 1-week abstinence period.



SC administration of varenicline 1.7 mg/kg produced a reduction of response rate of 78% on Day 1. Dosing was continued for 14 consecutive days, and toleration was achieved by Day 10 and maintained through Day 14. Administration of varenicline was discontinued after Day 14, and rats were dosed with sterile water from Day 15 through Day 21 with no observed effect on response rate or behavior.

Overall, the negative results in the rat withdrawal study and the results obtained at the end of the 9-months monkey toxicology study suggest that varenicline has little or no potential to cause physical dependence. The positive reinforcing effects of varenicline, however, should be judged in view of the chemical-pharmaceutical properties of varenicline (difficulty to synthesize varenicline outside of an industrial setting; bitter taste), clinical experience (emetic properties at higher doses), and the wide availability of a full α4β2 nicotinic receptor agonist (nicotine).

Metabolite, impurity and special studies were not conducted and are not required.

Ecotoxicity/environmental risk assessment

The environmental risk assessment was carried out in accordance with the current draft CHMP guideline. Given a maximum daily dose of 2 mg and a default market penetration of 1%, the calculated $PEC_{surfacewater}$ was equal to the action limit of 0.01 μg/L. As a result, a Phase II fate and effects analysis was provided. Varenicline did not meet the criteria for PBT/PvBv substances. Based on a 7-day survival and reproduction study in *Ceriodaphnia dubia*, the lowest NOEC was 0.003 mg/L and the PEC/PNEC ratio equal to 0.03. Therefore, varenicline is unlikely to represent a risk to the aquatic environment and no further testing or specific labelling is required.

Discussion on the non-clinical aspects

Varenicline plasma levels were not addressed in the submitted pharmacodynamic studies. However, varenicline plasma concentration data are available from the dopamine turnover study (1997-38271). The provided data cover studies were varenicline's intrinsic activity as a nicotinic partial agonist has been investigated. In this study, the oral ED50 for varenicline was derived to be 6 μg/kg and following extrapolation the provided plasma data support the chosen clinical dose.

The CHMP was also concerned as all the safety pharmacology studies (except for cardiac purkinje fiber study IC/001/02), were not performed in compliance with GLP. During the procedure, the Applicant clarified that all safety pharmacology studies (CNS, CV, cardiopulmonary, gastrointestinal and renal) were performed between November 1997-August 1998, i.e. before the release of ICHS7A and data were compiled in a report that was signed off by management on 4 September 1998. After that date additional data were generated (rat colon assay) and/or were repeated (binding assays) and these new data were combined with the safety pharmacology data from 1997-1998 into a new report that was included in the original submission (CP526555/0705/GP).

Finally, the CHMP was also concerned by the lack of any functional immunological evaluation of varenicline in an animal model and the lack of convincing evidence that the Immunosuppressive effects of nicotine are solely mediated through nicotinic acetylcholine receptors (non-α4β2 subtypes) in human lymphocytes. Therefore, the Applicant will perform a functional immunotoxicity study as a post-approval commitment. The protocol for the study will be provided before the end of 2006. The final report for that study will be provided within one year of the protocol being agreed (see letter of undertaking.

4. Clinical aspects

Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

All plasma samples were analyzed for varenicline concentrations using a fully validated assay employing liquid-liquid extraction followed by HPLC/MS/MS. The analytical methods are suitable for their purposes and well validated. It is agreed, that the results from the two evaluated analytical laboratories are comparable.

Overview of Clinical Pharmacology Studies

The clinical pharmacology program has been studied in healthy volunteers (men and women), in patients with varying degrees of renal or hepatic impairment, in elderly people and in adolescents.

The program consists of:

- 16 clinical pharmacology studies that used only IR formulations;
- 2 clinical pharmacology studies that contained IR arms as part of an evaluation of controlled release (CR) formulations
- 5 bioavailability and bioequivalence studies
- 1 abuse potential study

Table 1- Clinical Pharmacology Program

Type of Study	Study Number
Biopharmaceutics Program	
Relative bioavailability/food effect	A3051001; A3051006[a] (food effect arm); A3051042[b]
Bioequivalence	A3051006[a] (bioequivalence arm); A3051026; A3051030[c]
Clinical Pharmacology Program	
ADME	
Single/multiple dose pharmacokinetics	305-001[a]
Human mass balance	A3051004[a]
Special populations	A3051008[a] (renal impairment); A3051009 (elderly); A3051029 (adolescent); A3051027 and A3051041 (Japanese subjects)
Drug-drug interaction	A3051010 (cimetidine); A3051031 (digoxin); A3051032 (warfarin) A3051033 (NRT patch); A3051034 (Zyban); A3051038 (metformin)
Pharmacodynamics	A3051005 (craving); A3051014, A3051015 (tolerability) A3051012; A3051013
Abuse potential	A3051039[a]

[a]Enrolled nonsmokers (42/102 in single-dose 305-001; 3/6 in A3051004; 10/15 in Study A3051006, 14/30 in Study A3051008; 22/45 in Study A3051039) or exsmokers (2/15 in Study A3051006; 10/30 in Study A3051008)
[b]Definitive food effect study [c]Pivotal bioequivalence study

Pharmacokinetics

- Absorption

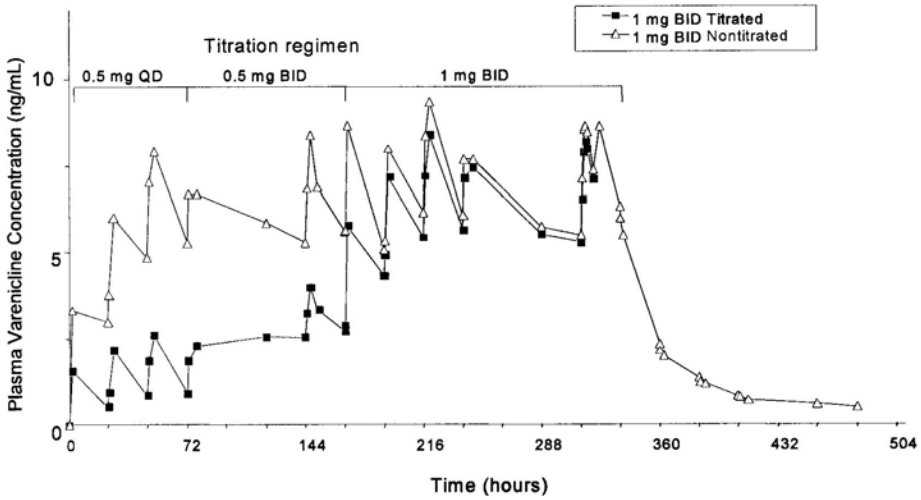
Varenicline (tartrate) oral formulations are virtually completely absorbed. Since varenicline is no substrate for glycoprotein-P transporter enzymes and is practically not metabolised by CYP enzymes in humans, there is no first pass- effect and varenicline is therefore highly available systemically. There was no interaction with food and absorption. Varenicline plasma exposure (AUC, Cmax) is dose-linear.

Table: Multiple dose studies in male and female smokers with normal renal function (mean, SD, for tmax; median, range)

study	dose	$AUC_{0\text{-}inf}$ NG/ML*HR	$AUC_{0\text{-}\tau au}$ NG/ML*HR	$AUC_{0\text{-}t}$ ng/ml*hr	Cmax ng/ml	Tmax h	t½ h
A3051008	0.5 mg QD	NA	56.8 (13.8)	NA	4.13 (1.28)	1(1-2)	34.4 (27.5)
305-001	1 mg QD	271 (75)	144 (24)	NA	7.93 (0.9)	4 (1-8)	23.8 (4.9)
305-001	1 mg BID	504 (101)	105 (16)	NA	10.2 (1)	2 (1-4)	31.5 (7.7)
A3051013	1 mg BID	NA	NA	t=24 h 208 (44.8)	10.8 (2.6)	3 (2-5)	NA
A3051014	1 mg BID	NA	NA	t=8 h 59.3 (10.7) t=24 h 184 (41.3)	8.54 (1.51)	3 (1-8)	NA
A3051014	1.5 mg BID	NA	NA	t=8 h 96.9 (24.6) t=96 h 418 (113)	13.9 (3.3)	3 (1-4)	27.3 (8.5)
A3051015	2 mg QD	NA	188 (31)	-	12.4 (1.9)	3 (2-4)	NA
305-001	2 mg QD	589 (112)	280 (33)	NA	15.1 (1.8)	2 (2-4)	24.8 (2.9)
305-001	3 mg QD	756 (268)	352 (87)	NA	19.8 (3.8)	4 (2-8)	25.2 (3.8)

NA= not available

Figure 2. Mean Plasma Concentration-Time Profiles Following Repeated Oral Administration of 1 mg BID Varenicline Using Titration and Nontitration Dosing Regimens in Healthy Adult Smokers: Study A3051014



Source: Study Report A3051014 Figure 1.1

- Distribution

Varenicline is a basic amine. In animals, varenicline is distributed throughout the body, including the brain, and varenicline passes the placenta. In rodents, varenicline accumulated in melanine containing cells and the eyes. Whether this also occurs in humans is unknown. Protein binding of varenicline in humans is low (≤20%), and therefore no major interactions regarding protein binding are expected. The volume of distribution (V/F) is estimated as 337 l in adults. Vd was significantly related to body weight. Steady-state is achieved after 4 days repeat dosing.

- Elimination

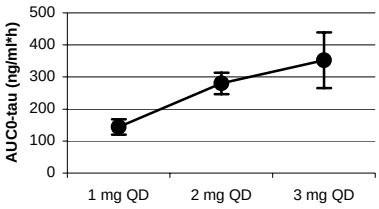
Metabolism: Varenicline is not significantly metabolised oxidatively by liver CYP enzymes. It is therefore not expected that varenicline metabolism and exposure would be affected by hepatic disorders. In minor quantities, conjugates are recovered in plasma and urine (approximately 10% of the total dose). Whether these conjugates are biological active is yet unknown.

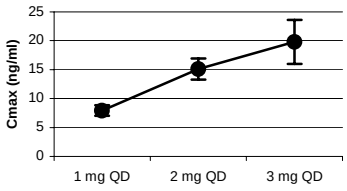
Excretion: Varenicline, and its conjugates, are virtually completely excreted renally, primarily by passive glomerular filtration and to minor extent by active secretion in the proximal tubulus.

- Dose proportionality and time dependencies

Dose proportionality
In the multiple dose regimen in study 001, varenicline exposure increased linearly with dose (range 1-3 mg QD). In the single dose regimens in the same study, varenicline exposure was dose proportional from 0.01-3 mg. The Cmax and AUC after 10 mg were however similar to 3 mg dose. However, as vomiting was common after the 10 mg single dose, and this may have biased the estimation of Cmax or AUC after 10 mg single dose.

Study 305-001 Multiple dose regimens (n=7-8)





Study 305-001 Single dose regimens, smokers (n=4)

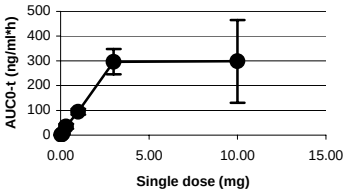
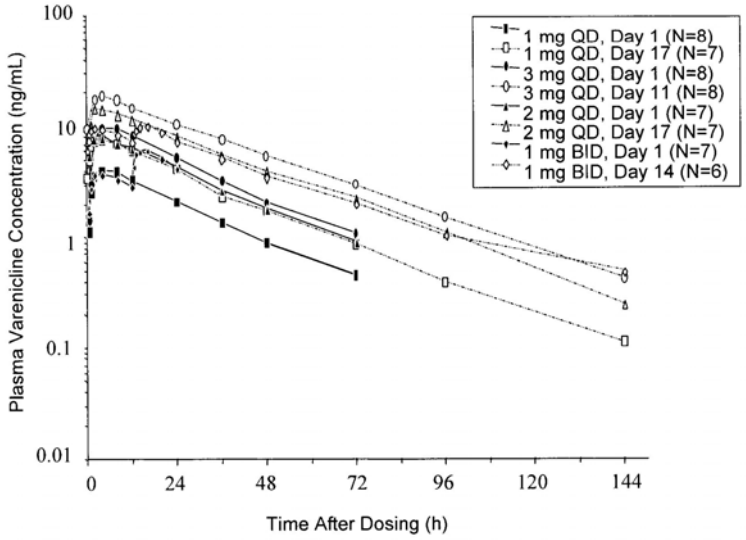


Figure 1. Mean Varenicline Plasma Concentration-Time Profiles following Single and Multiple Oral Doses given QD or BID: Study 305-001



Exposure of varenicline in plasma is linearly related to the dose.

Time dependency
There was no diurnal variability in varenicline levels. Varenicline exposure was virtually completely similar when a single dose of 2 mg varenicline was administered in the morning or before bedtime (Study A3051015, 90% CI AUC_{0-24} 95-103%)

Renal varenicline clearance was consistent over a study period of 1-14 days. This was confirmed in the population PK model; there were no trends observed in the WRES-time plots.

- Special populations

In the conducted population PK analysis renal function (on systemic clearance, CL/F) and bodyweight (on volume of distribution, V2/F) were the important factors leading to interindividual variability in the pharmacokinetics of varenicline. Plasma concentration time data were fitted to a two-compartmental model, with first-order absorption and elimination. Model parameters were central compartment (V2/F), clearance from central compartment (Cl/F), peripheral compartment (V3/F) and inter-compartmental clearance (Q/F), dosing compartment V1 and absorption constant (Ka) and a lag-time for absorption (Alag).

The table below provides estimated ranges of expected variability in CL/F and V2/F relative to the typical value based on the covariate effects and the observed range of age, weight, and CRCL values in the dataset. Observed covariate factors in the final PK model described a large fraction of the total observed inter-individual variability in both the apparent clearance (44.5%) and central volume of distribution (45.6%) of varenicline.

Table 16. Covariate Effect Ranges on Varenicline Final Model Pharmacokinetic Parameters

Pharmacokinetic Parameters (units)	Estimated Effect Relative to Typical Parameter Value[a]
CL/F (10.4 L/hr)	
Renal Function (16 - 150 mL/min)[b]	(0.38 - 1.24)
Black	1.16
Other	1.11
V2/F (337 L)	
Body weight (40 - 130 kg)	(0.65 - 1.61)
Age (18-75 yrs)	(0.89 - 1.07)
Black	0.92
Other	0.71
Overall Range (extremes fixed effects)	
CL/F (L/hr)	(0.38 - 1.97)
V2/F (L)	(0.41 - 1.72)
Individual Range (observed fixed effects)	
CL/F (L/hr)	(0.37 - 1.44)
V2/F (L)	(0.50 - 1.58)
Individual Range (observed fixed and	
CL/F (L/hr)	(0.23 - 2.93)
V2/F (L)	(0.31 - 3.99)

[a] Given the reference covariates effects (Caucasian, 45 years old, 70 kg, 100 mL/min)
[b] Estimated glomerular filtration rate (Cockroft-Gault method). Range extends to estimated GFR = 150 mL/min for clinical relevance; the highest value in the dataset was 268 mL/min.

Weight was shown to influence the volume of distribution, thus, plasma concentration fluctuations will be affected by weight.

The clearance of varenicline is linearly related to GFR (glomerular filtration rate), and varenicline exposure increased in patients with limited GFR. It is therefore recommended to adjust the regular varenicline dose if the patient has moderate or severe renal impairment. Varenicline is not recommended in patients with ESRD, based on insufficient clinical experience.

Varenicline was cleared by haemodialysis.

Varenicline plasma exposure was similar in elderly with normal renal function for their age (aged 65-75, creatinine clearance > 70 ml/min) and adults, in different ethnic groups, and between males and females.

In conclusion, there are no major problems expected based on the PK profile of varenicline regarding interactions, gender and ethnicity, though dose adjustments are necessary for patients with severe renal dysfunction.

It should be noted that this product is currently not indicated for children or adolescents. Limited data in adolescents suggests that Cmax was 30% higher than in adults and elimination was 50% shorter, probably because of a limited Vd in adolescents compared to adults.

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- Pharmacokinetic interaction studies

The active tubular secretion is mediated by human organic cation transporter proteins type 2 (hOCT2). Cimetidine is a substrate and inhibitor of this renal transporter, and concomitant use of cimetidine and varenicline caused an increase of varenicline exposure of approximately 30%. Administration of varenicline did not cause inhibition of renal elimination of another hOCT2 substrate, metformin. There were no significant PK interactions found between varenicline and narrow therapeutic drugs like digoxin and warfarin, and other smoking cessation agents like nicotine replacement and bupropion.

Pharmacodynamics

- Mechanism of action

Varenicline acts as a competitive, partial agonist for nicotine binding to nicotinic acetylcholine receptor α4β2. Both nicotine and varenicline binds to this receptor subtype. In animal models, the α4β2 nicotinic receptor has been shown to be responsible for the reinforcing properties of nicotine. It is hypothesized that varenicline, as it is a partial agonist, blocks the full-agonist activity of nicotine by competitive binding. On the other hand, the partial agonist action of varenicline may cause relief of withdrawal and craving symptoms on its own.

- Primary and Secondary pharmacology

The following pharmacodynamic studies were performed:

Study number	**objective**	**N**	**Dose varenicline (mg)**
A3051005	Proof of concept, relief of craving	40	2 SD
A3051039	Abuse potential	23	1 and 3 SD
A3051014	Tolerability, titration	120 (3x40)	1 BID non-titrated/ 1.5BID non-titrated / 1.5 BID titrated
305-001	*Tolerability, food interaction*	102 SD, 44 MD	SD:0.01-10 MD:1-3 QD,1 BID (14 days)
A3051015	Effect of dosing time on PK/PD (nausea)	44	2 QD 7 days (AM + PM)
A3051033	Drug-Drug Interaction with Nicotine Replacement Therapy (21 mg patch QD)	24	1 BID , 14 days

BID=twice daily/ MD=multiple dose/ SD=Single dose/ QD= once daily/AM=in the morning/ PM=before bedtime

A laboratory craving study was performed in smokers not intending to quit, who were exposed to a smoking related cue after an abstinence period of 12 hours. A single dose of either placebo or 2 mg varenicline was given to each participant. Varenicline significantly reduced the cue-stimulated craving and withdrawal symptoms in comparison with placebo. Results of a PK/PD analysis indicated that increasing plasma varenicline concentration was associated with reduced cigarette craving.
A study was performed to test the abuse potential of varenicline in non-smokers and smokers. Varenicline was compared to amphetamine and placebo in a group of regular amphetamine users, in a double-blind, randomised study. Amphetamine (15/30 mg), varenicline (1/3 mg) or placebo was administered to 21 tobacco smokers + 21 non-smokers. The VAS Drug Liking scale was used to assess the subjective appreciation of the offered drug. Smokers could not distinguish 1 mg varenicline from placebo. The 3 mg varenicline dose could be distinguished from placebo, but the drug was considered as unpleasant. Non-smokers could distinguish 1 mg varenicline from placebo, but like in smokers, the drug was considered unpleasant, especially at 3 mg doses. Varenicline did not induce euphoria in any subject in this study. Higher dose of amphetamine were most appreciated, indicating the validity of the chosen test method. Considering the fact that high doses of varenicline induce nausea and the rewarding effects were low, it is unlikely that varenicline would become a drug of abuse.

Finally, 4 studies were performed in smokers and non-smokers to investigate the maximum tolerated dose and dose titration and timing on dose toleration. The dose-limiting factor was nausea. Smokers were more tolerant to varenicline than non-smokers with respect to nausea. In smokers, the maximum tolerated single dose and multiple dose is 3 mg and 1 mg BID, respectively. Nausea was less severe when varenicline is up-titrated, when varenicline is administered under fed conditions and when the dose was divided over the day. Results from studies A3051014 and A3051015 indicate that the burden of nausea might be reduced by titrating the dose. The results do not enlighten any dose-response effect.

The incidence of nausea increased when varenicline was concomitantly used with nicotine replacement therapy. The interaction between varenicline and other psychotropic agents like alcohol and benzodiazepines is however only briefly investigated by the Applicant. However, varenicline use induced somnolence and abnormal dreams, indicating that this compound could be psychoactive. This is further addressed in the RMP.

Clinical efficacy

In total, seven Phase II/III studies were performed which provided efficacy data from 5944 subjects. Subjects were eligible if they were current smokers of more than 10 cigarettes per day, willing to quit, and if they had no successful quit attempt that lasted more than 3 months in the year before entrance.

Table: Overview of Phase II Efficacy studies

Study ID	Study location	Study Objectives	Design	duration	Varenicline dose	N ITT population*	Primary Endpoint
A3051007 /18	US	Dose finding Titration	R, PG, DB, PC	12 wks treat + 40 wks non-treat	0.5 mg BID NTitr 0.5 mg BID Titr 1 mg BID NTitr 1 mg BID Titr	VNC 124 VNC 129 VNC 124 VNC 129 Plac 121	4-week CQR (Wks 9-12) CAR wks 9-52
A3051002	US	Dose finding	R,PG,DB,PC, AC	6 wks treat + 45 wks non-treat	0.3 mg QD 1 mg QD 1 mg BID	VNC 126 VNC 126 VNC 125 Bupropion** 126 Plac 123	4-week CQR floating or fixed (Wks 3-6) or (Wks 4-7)
A3051016 /19	US	Dose finding	PC,DB,R	12 wks treat + 40 wks non-treat	Flexible 0.5 QD-1 mg BID	VNC 157 Plac 155	4-week CQR (wks 9-12) CAR Wks 9-52

Table: Overview of Phase III Efficacy Studies

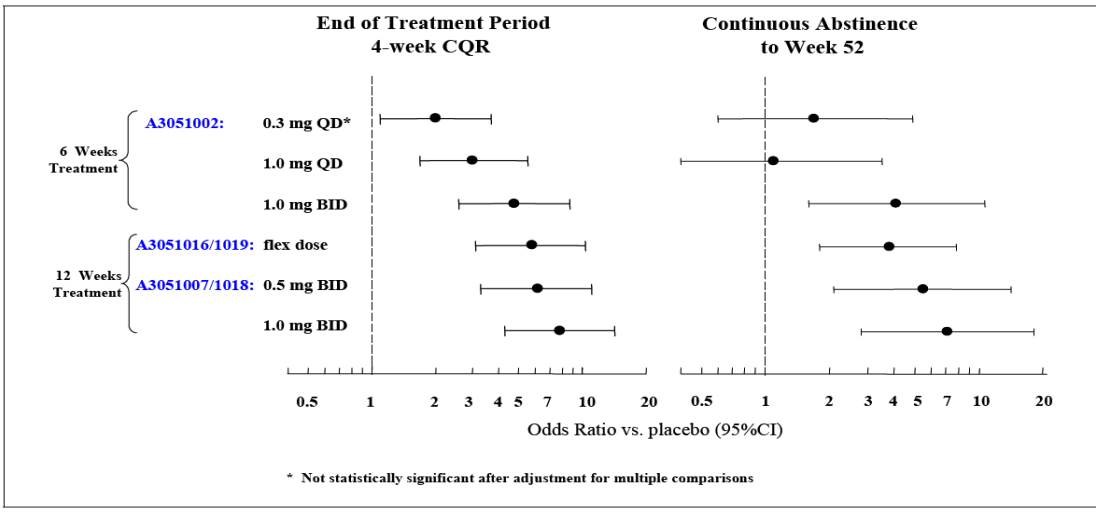
Study ID	Study Location	Study Objectives	Design	duration	Varenicline dose	N ITT population*	Primary Endpoint
A3051028	US	Smoking Cessation	R, PG, DB, PC, AC	12 wks treat + 40-wks non-treat	1 mg BID Titr	VNC 349 Bupropion** 329 Plac. 344	4-week CQR (Wks 9-12)
A3051036	US	Smoking Cessation	R, PG, DB, PC, AC	12 wks treat + 40 wks non-treat	1 mg BID Titr	VNC 343 Bupropion** 340 Plac. 340	4-week CQR (Wks 9-12)
A3051035	US, Eur, Can	Maintenance		12 wks treat OL (I) + 12 wks treat R,DB,PC (II) + 40 wks non-treat	I: 1 mg BID titr II: 1 mg BID	VNC 1927 VNC 602 Plac 604	CAR Wks 13-24
A3051037	US, Aus	Safety	R, DB, PC	52 wks treat	1 mg BID, Titr	VNC 251 Plac 126	7 days PP

AC = Active-controlled; BID = Twice per day; CAR = Continuous Abstinence Rate; CQR = Continuous Quit Rate; DB = Double-blind; NTitr = Nontitrated; OL = open label; PC = Placebo controlled; Plac = placebo; PG = Parallel Group; PP = 7-days Point Prevalence Abstinence; QD = Once daily; R = Randomized; Titr = Titrated; treat=treatment duration; VNC = varenicline. * all subject who took at least one dosage of study treatment, **Bupropion Dose 150 mg BID

- Dose response study(ies)

Based on the Phase II dose-finding studies, the following conclusions could be drawn; Varenicline, in dosages > 0.3 mg, was superior to placebo (see figure 17 below). Abstinence-rates were higher after 12-weeks than after 6-weeks continuous varenicline treatment. Dose titration was useful to prevent nausea.

Figure 17. Summary of Treatment Effect (as Odds Ratio) for End of Treatment and Long-Term Abstinence in Phase 2 Dosing Studies A3051002, A3051016/1019, A3051007/1018



In pooled data analyses, continuous cessation rate at the end of treatment at week 12 was approximately 45% in both the 0.5 and 1 mg BID treatment arms (see table III.4.1. below). At week 52, the long-term continuous abstinence rate was 22.6% after 1 mg BID dose and 19.0% after 0.5 mg BID dose.

Table III.4.1.: 4-Week Continuous Quit Rate (CQR) over Week 9-12 and Continuous Abstinence Rate (CAR) over Week 9-24 and Week 9-52 in pooled Phase III studies A3051028 and -36, and -07/18:

	Short term		Long-term			
	1 mg BID (pooled from studies A3051028, -36 and -07/18)					
	CQR Wks 9-12	**OR (95% CI)**	**CQR Wks 9-24**	**OR (95% CI)**	**CAR Wks 9-52**	**OR (95% CI)**
Varenicline	**45.9%** (434/945)	**4.13** (3.29-5.18)	**29.7%** (281/945)	**3.51** (2.6-4.5)	**22.6%** (214/945)	**3.17** (2.36-4.24)
Placebo	**16.9%** (136/805)	-	**10.9%** (88/805)	-	**8.6%** (69/805)	-
0.5 mg BID (study A3051007/1018 only)						
Varenicline	**45.1%** (114/253)	**6.07** (3.32-11.1)	**24.1%** (61/253)	**5.29** (2.3-12.0)	**19.0%** (48/253)	**5.56** (2.1-14.4)
Placebo	**12.4%** (15/121)	-	**5.8%** (7/121)	-	**4.1%** (5/121)	-

In a patient-controlled dosing study (A3051016), patients could choose a dose of 0.5/1/1.5/2 mg a day. The overall median auto-regulated total daily dose was 1.3 mg. At the end of the 12-weeks treatment period, a higher proportion of study participants were taking the 0.5 mg BID dose than the 1 mg BID dose. These data indicate that most patients would benefit from a 1 mg BID dose regime. However, every patient that would stop varenicline use prematurely due to adverse events can be considered as a loss, as varenicline is an effective drug to promote smoking cessation. Intolerant patients should be given the opportunity to change to a regimen of 0.5 mg BID.

- Main studies

METHODS

Design of pivotal studies: A3051007/1018, A3051028 and A3051036

In Studies A3051028, -36, and –07/18, varenicline was administered for 12 weeks at 1 mg BID with subsequent non-treatment follow-up for one year from the start of treatment. Based on a comparison of titrated and non-titrated regimens in Study A3051007/18, the Phase III studies titrated varenicline from 0.5 mg QD to 1 mg BID during the first week of treatment to improve tolerability. The one-year follow-up period from the start of treatment is an established design element, widely used in the smoking cessation field. Up to 10 minutes of counselling on smoking cessation was provided at each visit in accordance with Agency for Healthcare Research and Quality guidelines.

The identical Phase III trials (A3051028 and -36) were designed to demonstrate the superior efficacy of varenicline compared with bupropion and placebo. Bupropion was selected as an active control because it is an efficacious, widely prescribed, oral pharmacotherapy for smoking cessation. Nicotine replacement therapy was another alternative.

Studies A3051028 and -36 were designed as 52-week, double-blind, placebo-controlled, randomised, multi-centre studies. Varenicline, bupropion or placebo was administered for 12 weeks, followed by a 40 week non-treatment phase. At screening, subjects were requested to select a Target Quit Day to coincide with the Week 1 visit, after the varenicline or bupropion dose had been up-titrated to 1 mg BID and 150 mg BID, respectively.

Clinical visits took place each week during the initial 12 weeks dosing period. At each visit, subjects were asked about cigarette and other nicotine use since the last study visit and in the past 7 days (using the Nicotine Use Inventory). End-expiratory exhaled carbon monoxide was measured at each clinic visit (nonsmoking status being confirmed with a measurement ≤ 10 ppm). During the non-treatment follow-up phase, clinical visits took place at weeks 13, 24, 36, 44, and 52. In addition, subjects received a telephone call at weeks 16, 20, 28, 32, 40, and 48. The Nicotine Use Inventory was administered at each visit and at each telephone call during the non-treatment phase.

Adjunctive Counselling: At baseline, candidates were asked to review an educational booklet on smoking cessation by the NCI. At each visit up to 10 minutes of counselling was provided. Counsellors acted according to guidance of the Agency for Healthcare Research and Quality. All subjects were contacted 3 days after the Target Quit Date, as a reminder and support. During the non-treatment phase, additional phone contacts were scheduled between clinic visits to encourage maintenance of abstinence.

Study Participants

Both adult men and women were included and the maximum age was 65 years in Phase II studies and 75 years in Phase III studies. The Phase III protocols were amended to include patients with mild or moderate COPD, hypertension, hyperlipidemia and subjects with a history of cardiovascular diseases (e.g. myocardial infarction, coronary bypass graft, PTCA, angina pectoris) other than in the past 6 months. Subjects treated for hypertension could be included in Phase III studies, provided that hypertension was adequately controlled.

Patients with conditions that are contraindicated for the comparator bupropion were excluded. These conditions were: seizures, diabetes mellitus, hepatic or renal impairment, bipolar disorder, alcoholism (current or in the recent past) and the use of MAO-inhibitors. In addition, chronic and episodic use of antidepressants and antipsychotics, benzodiazepines, naltrexone, systemic steroids (with exception of inhaled steroids), and theophylline was prohibited during the study.

Patients who had used bupropion in the past were not included into the Zyban-comparator studies. Participants who had used NRT, or other smoking cessation treatment like clonidine and nortryptiline other than the last month could be included.

Treatments

In these parallel placebo-controlled, double-blind, active-comparator studies, varenicline 1 mg BID, placebo or Zyban 150 mg BID was administered for 12 weeks. In week 1, varenicline and Zyban, or their placebo tablets, were titrated according to the following schedule:

varenicline	
Day 1-3	0.5 mg QD
Day 4-7	0.5 mg BID
Day 8-84 (week 12)	1 mg BID

Zyban (bupropion)	
Day 1-3	150 mg QD
Day 4-84 (week 12)	150 mg BID

Objectives

The primary objective of these studies was to compare the efficacy of varenicline to placebo and bupropion regarding smoking cessation at the end of treatment period of 12 weeks.

Secondary objectives were;
-Long term efficacy, till 40 weeks after end of treatment (Week 52)
-The effect on craving and withdrawal
-The effect on weight
-Safety data

Outcomes/endpoints

The primary efficacy outcome was the 4-weeks CQR (Continuous Quit Rate) at the end of treatment between week 9-12. Responders were subjects who remained totally abstinent from weeks 9-12 without a single puff, confirmed by CO-breath test. Key secondary variable was the long term efficacy, the Continuous Abstinence Rate (CAR) during weeks 9-52. Responders were subjects who remained totally abstinent from Weeks 9-52, without a single puff, confirmed by CO-breath test.

Craving, withdrawal and reinforcing effects of smoking were assessed by means of the MNWS (Minnesota Nicotine Withdrawal Scale), the QSU-Brief (Brief Questionnaire of Smoking Urges, measures craving), and SEI (Smoking Effects Inventory). The Urge to Smoke item, and the Negative Affect and Restlessness subscales of the MNWS were prespecified as subscales of primary interest. The Total Craving Score of the QSU-Brief was pre-specified as the endpoint of primary interest for that scale. The SEI included subscales that assessed smoking satisfaction and psychological reward in subjects who smoked since the last time the questionnaires were due.

The MNWS and QSU-Brief questionnaires were filled in by subjects at baseline, and at Week 1-7 and 12 during treatment. The MNWS was also scored at Week 13, one week after end of treatment. The SEI was assessed through Week 7.

Body weight was measured every clinical visit. For the assessment of total weight gain, body weight measured at Week 12 was compared to baseline value in Responders (i.e. Cessators) and the Total Population.

Sample size

Sample sizes were based on the comparison of varenicline 1 mg BID vs. bupropion 150 mg BID, using a continuity-corrected Chi-Squared test with a 0.05 two-sided significance level. The study was intended to be powered to detect differences for both the primary (4-week CQR) and the key secondary CAR endpoint. Sample size calculations were based on the bupropion response rate (varenicline OR of 1.721 over bupropion 4-week CQR of 28.6%). In each study, at least 335 subjects

per group would be needed to detect a difference between bupropion and varenicline, with 90% power.

Randomisation

Subjects were equally randomised over the 3 study arms (varenicline/bupropion/placebo arm).

Blinding (masking)

This was a double-dummy study, and there were both placebo tablets available for varenicline and Zyban. So patients received either varenicline + Zyban-placebo (varenicline-arm), varenicline - placebo + Zyban (bupropion-arm), or varenicline -placebo + Zyban-placebo (placebo-arm).

Statistical methods

For binary outcome (CQR week 9-12, CAR), logistic regression analysis, with study site and treatment included as fixed factor, was applied. A step-down procedure was employed for the analyses of primary and key secondary endpoints to preserve the family-wise error rate (alpha 0.05). The hierarchy of comparisons was as follows: 1. varenicline versus placebo and 2. varenicline versus Zyban. The withdrawal and craving subscales were analysed by repeated measures Mixed Effect Modelling.

RESULTS

Participant flow

	Study 1028	**1036**
Assessed for Eligibility (n)	1483	1413
Excluded (n)	458	386
Randomised (n)	1025	1027
Allocated to Varenicline (n)	**352 (Varenicline received 349)**	**344 (Varenicline received: 343)**
Allocated to Zyban (n)	**329 (Zyban received 329)**	**342 (Zyban received: 340)**
Allocated to Placebo (n)	**344 (Placebo received 344)**	**341(Placebo received: 340)**
Discontinued Varenicline (n)	**136 (39%)** *During Treatment Phase*: 90 (14 AE, 2 Lack of Efficacy, 4 Protocol Deviation, 23 Refusal, 43 Lost-to-follow-up, 4 Other) *During Follow-Up Phase*: 46 (11 Refusal, 34 Lost-to-follow-up, 1 Other)	**103 (30%)** *During Treatment Phase*: 83 (14 AE, 1 Lack of Efficacy, 2 Protocol Deviation, 28 Refusal, 33 Lost-to-follow-up, 5 Other) *During Follow-Up Phase*: 20 (3 Refusal, 14 Lost-to-follow-up, 3 Other)
Discontinued Zyban (n)	**145 (44%)** *During Treatment Phase*: 104 (34 AE, 1 Lack of Efficacy, 1 Protocol Deviation, 31 Refusal, 36 Lost-to-follow-up, 1 Other) *During Follow-Up Phase*: 41 (1 Protocol Deviation, 10 Refusal, 29 Lost-to-follow-up, 1 Other)	**119 (35%)** *During Treatment Phase*: 100 (16 AE, 0 Lack of Efficacy, 9 Protocol Deviation, 31 Refusal, 39 Lost-to-follow-up, 5 Other) *During Follow-Up Phase*: 19 (1 Death, 2 Protocol Deviation, 6 Refusal, 10 Lost-to-follow-up, 0 Other)
Discontinued Placebo (n)	**157 (46%)** *During Treatment Phase*: 129 (24 AE, 4 Lack of Efficacy, 6 Protocol Deviation, 42 Refusal, 49 Lost-to-follow-up, 4 Other) *During Follow-Up Phase*: 28 (1 Death, 5 Refusal, 22 Lost-to-follow-up)	**136 (40%)** *During Treatment Phase*: 118 (13 AE, 3 Lack of Efficacy, 4 Protocol Deviation, 51 Refusal, 43 Lost-to-follow-up, 4 Other) *During Follow-Up Phase*: 18 (1 Protocol Deviation, 4 Refusal, 12 Lost-to-follow-up, 1 Other)
Analysed: All subjects who received at least 1 dose of:	**Varenicline : 349** **Zyban: 329** **Placebo: 344**	**Varenicline: 343** **Zyban: 340** **Placebo: 340**

The most common reasons for study discontinuation in all three study arms were loss-to-follow-up, refusal to continue participation, and AEs. The discontinuation rate was higher in the placebo arm

compared to varenicline arm. Probably, this is due to the more severe withdrawal symptoms and because of the lack of efficacy in the placebo arm.
Discontinuation due to adverse events was more common in the Zyban arm (n = 50) and in the placebo-arm (n = 37) than in the varenicline-arm (n = 28).

Recruitment

Smokers were recruited from the general population, and were not referred by medical specialists.

Conduct of the study

Both phase 3 Protocols A3051028 and -36 were amended shortly after study start to allow enrolment of subjects with pre-existing medical conditions typical of the intended patient population.
Both 305A53010 Studies A3051028 and -36 took place in the US, in different study centres.

Baseline data

The demographics and smoking characteristics of subjects in the 2 identical Phase III studies were well balanced across treatment groups.

Demographics: Phase III trials A3051028 and -36 enrolled more men than women (56% versus 44%). The mean age was approximately 42 years (SD 11) in both studies. Approximately 80% of the participants were Caucasian, 10% were African and the remainder were from other ethnical origin. Sixty-two (27 + 35) subjects were older than 65 in study A30510-28 and -36, respectively. Only 17 varenicline treated subjects were 65 years of age or older.
The low number of elderly is a drawback in the assessment of safety. The plasma exposure may be similar in elderly compared to younger adults, but elderly may be more sensitive to side effect of varenicline, and the subgroup is considered too small to make a sound evaluation. This will be reflected in the SPC. Treatment in elderly should be monitored post-approval (see Risk Management Plan).

Concomitant diseases: in subjects who were included, the following present & past medical conditions were noted at screening (pooled data Study A30510-28 and -36):

Cardiac Disorders	2.4%
Dyspnea at exertion	<2%
COPD	<2%
Emphysema	<1%
History of depression	4.4%
History of alcoholism	4.6%

Smoker status: all participants were current smokers, who smoked at least 10 cigarettes a day. The baseline smoking behaviour features were similar in both studies, over all study arms. The mean Fagerström Total Score ranged between 5.16-5.40 (SD±2) across study arms, indicating that the average participant was a moderate smoker.
The mean age at which the subjects started smoking was approximately 17 years, and the average smoking years were approximately 24-25 years in all study arms (range 1-61). In the last month before entrance, the participants smoked on average 21 cigarettes (range 10-80) per day. The majority of participants, about 85%, had at least one serious quit attempt in lifetime.

Numbers analysed

Efficacy analyses occurred in the "All Subjects" group, i.e. all subjects who received at least 1 dose of the relevant study drug (further referred as ITT in this report). To test the robustness of the conclusions from ITT dataset, analyses took also place in "Evaluable Subjects" group, defined as subjects who took study medication at least for 14 days, and Completer Subjects group, i.e. subject who were for at

least 80% treatment compliant. In this report, efficacy parameters of the ITT population are presented, unless specified otherwise. For details see participant flow table above.
Subjects who withdrew from the study or who were lost to follow-up before the study was completed were considered as non-responders for subsequent smoking evaluations.

Outcomes and estimation

Main results of clinical efficacy

Varenicline at the recommended dosing regimen (1 mg BID for 12 weeks) is superior to placebo for smoking cessation at the end of treatment period and at one year from the start of treatment.

With regard to 4-Week CQR (Weeks 9-12) and Continuous abstinence Weeks 9-24 varenicline was significantly better than bupropion. At Continuous Abstinence Weeks 9-52 varenicline was statistically superior to bupropion in one of the two phase III studies.
The results of primary endpoints in the pivotal Phase III studies (A3051028 and -36) are summarised below in table III.3.2 below:

Table III.3.2 : Continuous Quit Rate (CQR) over Week 9-12 and Continuous Abstinence Rate (CAR) Week 9-52 in pivotal Phase III studies A3051028 and -36:

	Studies A3051028			**Studies A3051036**		
Study arm	**Varenicline 1 mg BID**	**Zyban 150 mg BID**	**Place-bo**	**Varenicline 1 mg BID**	**Zyban 150 mg BID**	**Place-bo**
N	349	329	344	343	340	340
Abstinent Week 9-12	**44.4%**	**29.5%**	**17.7%**	**44.0%**	**30.0%**	**17.6%**
OR ($CI_{95\%}$, p) *versus placebo*	3.91 (2.74-5.59) < 0.0001	2.00 (1.38- 2.89) 0.0002	-	3.85 (2.69- 5.50) <0.0001	2.03 (1.41- 2.94) 0.0001	
versus zyban	1.96 (1.42, 2.72) <0.0001		-	1.89 (1.37 -2.61) <0.0001		
RR ($CI_{95\%}$, p) *versus placebo*	2.50 (1.94- 3.24) < 0.0001	1.66 (1.25 - 2.21) 0.0003	-	2.49 (1.93- 3.23) < 0.0001	1.70 (1.28- 2.25) 0.0002	
versus Zyban	1.51 (1.23- 1.85) 0.0001		-	1.47 (1.20- 1.80) 0.0001		
AR ($CI_{95\%}$, p) *versus placebo*	26.7 (20.1- 33.3) < 0.0001	11.8 (5.4 -18.1) 0.0003	-	26.4 (19.7- 33.0) <0.0001	12.4 (6.01- 18.7) 0.0002	
versus Zyban	14.9 (7.8- 22.1) 0.0001		-	14.0 (6.86- 21.2) 0.0001		
Abstinent over 9-52 wks	**22.1%**	**16.4%**	**8.4%**	**23.0%**	**15.0%**	**10.3%**
OR ($CI_{95\%}$, p) *versus placebo*	3.13 (1.97- 4.97) <0.0001	2.16 (1.33- 3.51) 0.0014	-	2.66 (1.72- 4.11) <0.0001	1.54 (0.97-2.45) 0.0634	
versus Zyban	1.45 (0.98-2.14) 0.0640		-	1.72 (1.16- 2.55) 0.0062		
RR ($CI_{95\%}$, p) *versus placebo*	2.62 (1.75- 3.91) 0.0001	1.94 (1.27- 2.98) 0.0016	-	2.24 (1.55 - 3.23) <0.0001	1.46 (0.97- 2.18) 0.065	
versus Zyban	1.34 (0.98 -1.84) 0.063		-	1.54 (1.12 -2.11) 0.008		
AR ($CI_{95\%}$, p) *versus placebo*	13.6 (8.4 -18.9) 0.0001	8.0 (3.1-12.9) 0.0016	-	12.7 (7.2 - 18.2) < 0.0001	4.7 (-2.8 -9.7) 0.065	
versus Zyban	5.6 (-2.6 - 11.6) 0.063		-	8.0 (2.2 -13.9) 0.008		

AR=additive risk, OR=odds ratio, RR= relative risk

In the individual Phase III studies, varenicline significantly reduced craving, withdrawal characterised by symptoms of negative affect (depressed mood, irritability, frustration, or anger, anxiety, difficulty concentrating) and the reinforcing effects of smoking compared with placebo.

In the *All Subjects* population, mean weight gain was higher for varenicline than for placebo, while in the *Cessators* population, mean weight gain was lower for varenicline than for placebo.

Table: Change in Body Weight from Baseline (kg) to Week 12
[Mean Change (SE)]Study A3051028 and -36

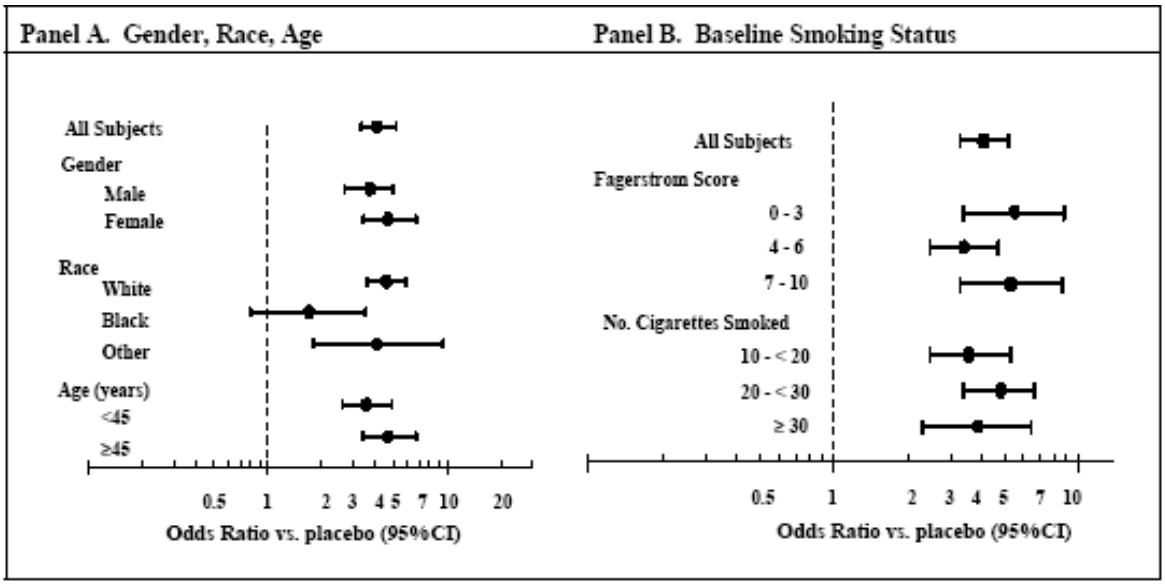
	All Subjects		Cessators[a]	
	N	Mean Change (SE)	N	Mean Change (SE)
		Study A3051028		
Varenicline	236	2.11 (0.18)	144	2.37 (0.23)
Placebo	198	1.40 (0.19)	56	2.92 (0.42)
Zyban	197	1.88 (0.17)	88	2.12 (0.24)
		Study A3051036		
Varenicline	230	2.29 (0.18)	136	2.89 (0.24)
Placebo	195	1.52 (0.21)	51	3.15 (0.53)
Zyban	213	1.32 (0.22)	94	1.88 (0.34)

SE = standard error [a] Cessators = subjects who were responders on the Week 9-12 CQR.

- Analysis performed across trials (pooled analyses and meta-analysis)

Overall, pooled data from studies A3051007/1018, A3051028 and A3051036 showed that varenicline is significantly better that placebo.
Subgroup analysis by age, gender, race, and baseline smoking characteristics.
Post hoc subgroup analyses based on gender, age, race, and baseline smoking characteristics (total Fagerström score and average number of cigarettes smoked during the month prior to study enrolment) were conducted using pooled data from Studies A3051028, -36 and the 1 mg BID arm of Study -07/18 (N = 1750).

Figure: Treatment Effect (as Odds Ratio) for 4-Week CQR (Weeks 9-12) by Gender, Race, Age and Baseline Smoking Status: Pooled Principal Smoking Cessation Studies



Source: Section 2.7.3 Tables A13.1, A13.2, A13.3, A13.4, A13.5
Pooled efficacy data: Studies A3051028, A3051036 and Study A3051007/1018 (1 mg BID varenicline + placebo)

The age analysis split subject ages <45 years and ≥45 years because the small number of subjects ≥65 years (39/1750, 2.2%) precluded a meaningful analysis based on the age groups designated in ICH-E7. No remarkable effects of gender or baseline Total Fagerström score/Average number of cigarettes smoked on either 4-week *CQR* (Weeks 9-12) or *Continuous Abstinence* (Weeks 9-52) were observed.

In the by-race analysis, the small number of non-White subjects limits the ability to estimate precisely the treatment effect in these subpopulations. The Weeks 9-12 *CQRs* and the *Continuous Abstinence* rates from Weeks 9-24 and Weeks 9-52 were similar in Whites and Other races. Similarly, the estimated treatment effects were strong and similar in these 2 subgroups. Varenicline also increased the rate of smoking cessation in Blacks compared with placebo, however, the Weeks 9-12 *CQR* (Table below) and *Continuous Abstinence* rates over both intervals were lower than those of Whites and Others and the treatment effect was smaller. The finding of a smaller treatment effect in Blacks is consistent with published survey data for the United States showing that fewer Blacks than Whites or Hispanics remained abstinent for at least one month.

Overall, pooled data from these three studies showed that the efficacy of varenicline in the above-mentioned subgroups was generally comparable to that observed in the total ITT population.

Pooled Analysis of Craving, Withdrawal, and the Reinforcing Effects of Smoking.

For pooled studies A3051028 and –36, varenicline significantly reduced craving compared with placebo, as measured by both MNWS Urge to Smoke and QSU-Brief Total Craving Score (see table below). Varenicline was superior to placebo in reducing withdrawal characterised by symptoms of negative affect (depressed mood, irritability, frustration, or anger, anxiety, difficulty concentrating) and the reinforcing effects of smoking in patients who smoked over treatment.

Table: Craving, Withdrawal, and Reinforcing Effects of Smoking in pooled analysis (Studies A3051028, -36)

	Average of Weeks 1-7		Comparison vs. Placebo			
	LS Mean (SE)	95% CI	Difference (SE)	95% CI	p-value	Effect Size
Craving						
MNWS Urge to Smoke (Item 1)						
Varenicline (N=672)	1.18 (0.03)	1.12, 1.24	-0.51 (0.04)	-0.59, -0.42	<0.0001	-0.65
Zyban (N=646)	1.38 (0.03)	1.32, 1.44	-0.31 (0.04)	-0.39, -0.23	<0.0001	-0.40
Placebo (N=669)	1.69 (0.03)	1.63, 1.74	--	--	--	--
QSU-Brief Total Craving Score						
Varenicline (N=671)	1.73 (0.03)	1.67, 1.80	-0.44 (0.05)	-0.53, -0.35	<0.0001	-0.33
Zyban (N=646)	1.90 (0.03)	1.83, 1.96	-0.28 (0.05)	-0.37, -0.19	<0.0001	-0.21
Placebo (N=670)	2.18 (0.03)	2.11, 2.24	--	--	--	--
Withdrawal						
MNWS Negative Affect (Items 2-5)[a]						
Varenicline (N=672)	0.60 (0.02)	0.56, 0.64	-0.16 (0.03)	-0.22, -0.11	<0.0001	-0.27
Zyban (N=646)	0.62 (0.02)	0.57, 0.66	-0.15 (0.03)	-0.21, -0.09	<0.0001	-0.24
Placebo (N=670)	0.76 (0.02)	0.72, 0.80	--	--	--	--
MNWS Restlessness (Item 6)[b]						
Varenicline (N=671)	0.75 (0.03)	0.70, 0.80	-0.12 (0.04)	-0.19, -0.05	0.0009	-0.14
Zyban (N=644)	0.79 (0.03)	0.74, 0.84	-0.08 (0.04)	-0.16, -0.01	0.0246	-0.10
Placebo (N=669)	0.87 (0.03)	0.82, 0.92	--	--	--	--
Reinforcing Effects of Smoking						
SEI/mCEQ Smoking Satisfaction (Questions 1, 2 &12)[c]						
Varenicline (N=598)	2.57 (0.05)	2.47, 2.67	-0.51 (0.07)	-0.64, -0.38	<0.0001	-0.41
Zyban (N=594)	2.85 (0.05)	2.75, 2.94	-0.24 (0.07)	-0.37, -0.11	0.0004	-0.19
Placebo (N=639)	3.08 (0.05)	3.00, 3.17	--	--	--	--
SEI/mCEQ Psychological Reward (Questions 4-8)[d]						
Varenicline (N=598)	2.14 (0.04)	2.06, 2.22	-0.40 (0.06)	-0.51, -0.29	<0.0001	-0.29
Zyban (N=594)	2.28 (0.04)	2.20, 2.36	-0.26 (0.06)	-0.37, -0.15	<0.0001	-0.19
Placebo (N=639)	2.54 (0.04)	2.47, 2.62	--	--	--	--

Note: Effect Size = LS mean treatment differences / pooled standard deviation at baseline (pooled by center and study)
Scoring: MNWS: Scores ranged from 0 (Not at all) to 4 (Extreme) with higher scores indicating greater intensity; QSU-Brief Scores range from 1 (strongly disagree) to 7 (strongly agree) with higher scores indicating greater craving; SEI/mCEQ: Scores ranged from 1 (not at all) to 7 (extremely) with higher scores indicating greater intensity
[a]Negative Affect scale =average of MNWS items # 2 (depressed mood);#3 (irritability, frustration, or anger); #4 (anxiety) and #5 (difficulty concentrating), [b]Restlessness scale= MNWS item # 6 (restlessness)
[c]Smoking Satisfaction scale =average of SEI/mCEQ questions #1 (Was smoking satisfying?), #2 (Did cigarettes taste good?), and # 12 (Did you enjoy smoking?); [d]Psychological Reward scale=average of SEI/mCEQ questions #4 (Does smoking calm you down?), #5 (Did smoking make you feel more awake?, # 6 (Did smoking make you fell less irritable?), #7 (Did smoking help you concentrate?) and #8 (Did smoking reduce your hunger for food?)

- Clinical studies in special populations

Not applicable.

- Supportive studies

Maintenance Study

Because published literature as well as observations from the varenicline clinical program indicate that most relapses to smoking occur in the first weeks following end of treatment. Study A3051035 examined whether an additional 12 weeks of varenicline treatment at 1 mg BID would increase long-term smoking abstinence rates in subjects who were abstinent for at least the last week of the initial treatment period.

The primary efficacy endpoint in this study was a comparison between varenicline and placebo in the rate of continuous abstinence for Weeks 13-24 in subjects responding to an initial 12-week course of smoking cessation therapy with varenicline. The rate of continuous abstinence form weeks 13-52 was a secondary endpoint.

Study design: This international multicentre study was conducted in 3 phases: a 12-week open-label phase in which all patients were treated with varenicline at 1 mg BID; a 12-week double-blind phase in which patients were randomised to either varenicline 1 mg BID or placebo (Weeks 13-24); and a non-treatment follow-up phase to Week 52. Patients who were abstinent during the last week of the open-label period were eligible to enter the double-blind treatment phase.

Results: Of the subjects who received open-label varenicline 1 mg BID, 1236 (64.1%) subjects were abstinent for the 7 days prior to and including the Week 12 visit. Of these, 1206 (602 varenicline, 604 placebo) took at least one dose of double-blind study medication and were included in efficacy evaluations.
For the *All Subjects* population, the *Continuous Abstinence* rate from Week 13 through Week 24 was statistically significantly higher for varenicline (425/602, 70.6%) than for placebo (301/604, 49.8%) ($p<0.0001$; odds ratio = 2.47). The Continuous Abstinence rate from Week 13 through Week 52 was significantly higher for subjects treated with double-blind varenicline (265/602, 44.0%) than for subjects treated with double-blind placebo (224/604; 37.1%) ($p = 0.0126$, odds ratio = 1.35).

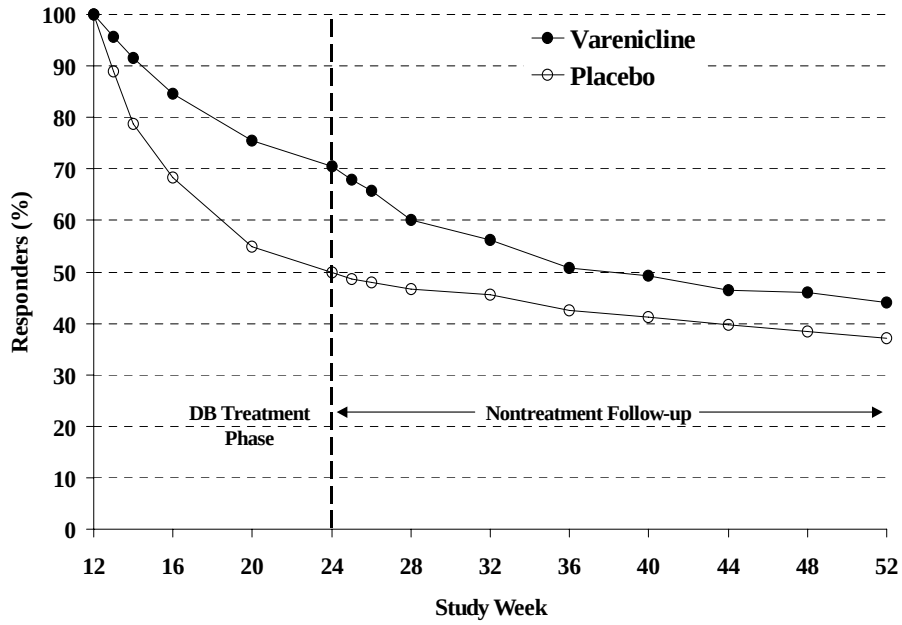
The Applicant concluded that subjects given an additional 12 weeks of varenicline treatment had significantly higher rates of complete smoking abstinence for Weeks 13 to 24 than subjects given placebo and the treatment effect of the additional 12 weeks of varenicline treatment remained statistically significant at the end of the non-treatment follow-up at Week 52. Based on these findings it was concluded that subjects who successfully quit smoking after 12 weeks treatment should take an additional 12 weeks of treatment in order to maintain abstinence.

- Discussion on clinical efficacy

The CHMP was concerned by the fact that comparing the response rates for the two groups at a time point where they have been without treatment for the same period of time, the response rates are equal.

Based on the observation of point Week 24 in the placebo group and point Week 36 in the varenicline group, both treatment groups share approximately 50 % response rate. Therefore it can not be ruled out that the two curves are approaching each other resulting in an insignificant difference after a drug free follow up period of 40 weeks.

The additional 12 weeks treatment with varenicline reduced the initial rate of relapse compared with the placebo as shown in the figure below. The abstinence rate in the varenicline group was 70.6% compared with 49.8% in the placebo group at Week 24, but the CHMP questioned whether this comparison was relevant.



The recommendation for treatment prolongation with another 12 weeks was therefore initially not supported and the Applicant was invited to further argue this issue or to amend the SPC accordingly.

The applicant contested the CHMP's interpretation of the A3051035 results on the following bases:

A: The comparison of the two treatment arms at equal time points after the end of varenicline treatment creates a staggered analysis that violates the principle of a randomized trial, in which study arms should differ solely in the quality of the intervention.

B: The protocol design and data analysis of Study A3051035 conform to the standard approach for smoking relapse prevention studies.

C: The statistically significant treatment effect of the 12 weeks varenicline maintenance treatment at final follow-up (40 weeks after randomization) represents a clinically meaningful impact on long-term health outcomes. Extrapolation of a model fitted to the observed relapse curves shows that a difference between varenicline and placebo lines is likely to persist beyond the observed period.

The CHMP, taking into account the arguments from the Applicant during the oral explanation and the following discussion within the CHMP meeting, agreed to the inclusion of maintenance data in the label to inform discussions of maintenance treatment between physicians and patients.

The CHMP was also concerned by abrupt withdrawal at the end of treatment and suggested that dose-tapering may be useful to prevent increased relapse the first week after stopping varenicline. Both after 12 and 24 week varenicline treatment, a sharp decline in treatment response (i.e. a sharp increase in relapse rate) was observed that is not fully understood. It may be related to withdrawal symptoms of weak AchR agonist activity of varenicline, or a rebound effect.

Although the elimination half-life of varenicline is indeed long, it may not be long enough for nAchRs to adapt to the absence of the partial agonist-antagonist varenicline. Though the exact mechanism underlying this phenomenon may not be fully understood, the initial sharper decline in success rate in varenicline arm is a fact, and it may be tempered by a more gradual decline of the dose.

Based on these observations, the Applicant was asked to discuss the feasibility of a clinical trial comparing the long term efficacy of abrupt discontinuation versus dose –tapering or whether dose – tapering should be proposed as an option for individual patient.

The applicant noted that there was a slightly higher relapse rate (3-6% compared with placebo or bupropion) in the varenicline group that was limited to the first week after stopping treatment. The Applicant agreed to amend the dosing recommendation in section 4.2 of the SPC to acknowledge that the risk for relapse to smoking is elevated in the period immediately following the end of treatment in smoking cessation therapy and that in patients with a high risk of relapse, dose tapering may be considered. In addition, the Applicant agreed to add a statement in section 4.4 outlining that there was an increase in irritability, urge to smoke, depression, and/or insomnia in up to 3% of patients on discontinuation of Champix and that the prescriber should inform the patient accordingly and discuss or consider the need for dose tapering.

Moreover, the Applicant committed to report back to the CHMP about the feasibility of a clinical trial evaluating dose tapering versus abrupt discontinuation in terms of long-term efficacy, as a post-authorisation follow-up measure.

Clinical safety

The safety profile of varenicline was investigated in a program of 32 studies. These studies included:

1) 8 completed Phase 2/3 studies, with a total of 5944 subjects in all treatment groups
2) 24 completed Phase 1 studies, with a total of 795 subjects in all treatment groups (include 2 studies with controlled release treatment arms)

Serious Adverse Events (SAEs) in subjects receiving the CR formulation are included in the listings of SAEs, but routine safety data from subjects who received only a CR formulation are not included.
A cut-off date of 15 July 2005 has been applied to data from 3 ongoing studies and to the Serious Adverse Event data.

- Patient exposure

As of 15 July 2005, the varenicline clinical development program safety database comprised of 6739 individuals who received at least one dose of study drug (5944 in Phase 2/3 studies; 795 subjects in Phase 1 studies). Of the 3298 subjects who received study drug in the Fixed-dose, Placebo-controlled Studies, 1575 received varenicline, 795 received bupropion (Zyban), and 928 received placebo. In all completed phase 2/3 trials, 3940 subjects received varenicline; 795 received bupropion, and 1209 received placebo.
More than 80% of the 3940 subjects who received varenicline in all completed phase 2/3 studies received the 1 mg BID dose. In the fixed-dose, placebo-controlled studies, 314 subjects received >12 weeks of varenicline at 1 mg BID. In addition, most subjects counted as receiving >11 weeks of the 1 mg BID dose actually completed the full 12 weeks of treatment (i.e. 84 days).

Table: Estimated subject-days exposure, by study and median duration of exposure by cohort

	Varenicline		Zyban	Placebo
	< 1 mg BID	1 mg BID		
All Completed Phase 2/3 Studies				
Fixed-dose, Placebo-controlled Studies				
Study A3051028	--	23679	20342	21090
Study A3051036	--	23060	22077	21633
Study A3051007	17098	16642	--	7030
Study A3051002	10186	5053	5053	4912
Subject-days[a]	27284	68434	47472	54665
Median Duration days (range)	49 (1-91)	83 (1-102)	83 (1-107)	80 (1-133)
Number of Subjects	505	1070	795	928
Study A3051037	--	60140	--	27967
Study A3051035				
Open-label		132339	--	--
Double-blind		46181	--	
Study A3051016	10980			10159
Study A3051043	1108			
Subject-days All Completed Phase 2/3 Studies[a]	346466		47472	92791
Median Duration days (range)	84 (1-413)		83 (1-107)	83 (1-379)
Number of Subjects	3940		795	1209

Source: Studies A3051002, A3051007, A3051016; A3051028, A3051036, A3051035, A3051037

[a] Subject-days of drug exposure is calculated from first day of dosing to (and including) last day of dosing.

In the All Completed Phase 2/3 Subjects cohort, 456 subjects had >24 weeks of treatment. In addition, many subjects counted as receiving >20 weeks of treatment completed the scheduled 24 weeks of dosing in Study A3051035 but had their final study day prior to Day 169. In Study A3051037, 95 subjects had >52 weeks of varenicline (1 mg BID) treatment, and 112 subjects received varenicline for ≥52 weeks (≥364 days), in compliance with ICH-E1A.

In All Completed Phase 2/3 Studies , approximately equal proportions of men and women received varenicline (49.7% versus 50.3%, respectively) (see table below). A greater proportion of men than women received bupropion (57.2% versus 42.8%) or placebo (54.3% versus 45.7%). The mean age across all groups was 43.4 years; a total of 165 (2.8%) subjects were 65 years of age or older. More than 87% of subjects were White, 7% were Black, and 6% belonged to other racial groups.

These data indicate that the number of subjects (White ≤ 65 years) exposed to varenicline at the dose and duration of exposure proposed in the label is adequate for the safety assessment of the product.

Table: Demographic Characteristics - All Completed Phase 2/3 Studies

Number (%)[a] of Treated Subjects	Varenicline N= 3940	Zyban N=795	Placebo N=1209
Gender			
Males	1959 (49.7%)	455 (57.2%)	656 (54.3%)
Females	1981 (50.3%)	340 (42.8%)	553 (45.7%)
Age (years):			
<18	0	0	0
18-44	2035 (51.6%)	462 (58.1%)	678 (56.1%)
45-64	1797 (45.6%)	308 (38.7%)	499 (41.3%)
≥65	108 (2.7%)	25 (3.1%)	32 (2.6%)
Mean	43.8±11.0	42.2±11.6	42.9±11.5
Range	18-75	18-75	18-75
Race[b]			
White	3538 (89.8%)	650 (81.8%)	998 (82.5%)
Black	211 (5.4%)	73 (9.2%)	129 (10.7%)
Other	191 (4.8%)	72 (9.1%)	82 (6.8%)
Weight (kg), Males			
N	1953	454	656
Mean±SD	85.4 ±14.7	85.5 ± 14.3	85.4±14.9
Weight (kg), Females			
N	1978	339	550
Mean±SD	69.4±13.3	70.9 ±14.2	70.8 ± 13.8

Protocols included: A3051002, A3051007, A3051016, A3051028, A3051035, A3051036 A3051037, A3051043

[a]: Percentages may not add to 100% due to rounding.

[b]: CRFs for some studies listed racial categories in addition to White, Black, and Other. Subjects in those additional racial categories are included in this summary as "Other".

- Adverse events

The ability to characterize the adverse event profile of varenicline is confounded by the fact that some subjects may continue to smoke while taking smoking cessation pharmacotherapy; and/or smoking cessation may be associated with symptoms of nicotine withdrawal (e.g. depressed mood, insomnia, irritability/frustration/anger, restlessness, difficulty concentrating). No attempt was made in the analysis of varenicline safety data to distinguish between adverse events associated with study drug treatment and those possibly associated with either of the two conditions mentioned above.

In the fixed-dose, placebo-controlled trials, varenicline-treated subjects most commonly reported treatment-emergent (and treatment-related) gastrointestinal, central nervous system and/or psychiatric system events. Nausea was the single most frequently reported adverse event among varenicline-treated subjects. In addition to nausea, the treatment-emergent adverse events most commonly reported (≥5% and ≥1.5 times placebo) by varenicline-treated subjects (1 mg BID) were gastrointestinal disorders (specifically, constipation, flatulence, dyspepsia, and vomiting). The treatment-emergent adverse events that increased in frequency with increasing varenicline dose were nausea, constipation, vomiting, abnormal dreams, and sleep disorder. These common treatment-emergent (and treatment-related) events were mild or moderate in severity in more than 98% of cases.

The percentage of varenicline-treated subjects (1 mg BID) reporting severe adverse events exceeded 1% only for nausea (1.3% vs. 0.4% for placebo) and headache (1.2% vs. 0.9% for placebo). Among the common treatment-emergent adverse events, the only two leading to discontinuation from 1 mg BID varenicline treatment at a rate ≥1% were nausea (3.1% vs. 0.5% placebo) and insomnia (1.2% vs. 1.1% placebo).

The adverse event profile in the all completed phase 2/3 Studies was similar to the Fixed-dose Placebo-controlled Studies, indicating that the safety and tolerability profile in subjects receiving 12 weeks treatment accurately reflected the overall varenicline safety experience (see table below).

The incidence of gastrointestinal disorders is high compared to the placebo group. However no weight loss was observed in the Cessator subjects who completed the studies.

Table: Most frequent all causality adverse events (≥5% in any treatment group) - All Completed Phase 2/3 Studies

MedDRA System Organ Class Preferred term[a] Subject-days of drug exposure[b]	Varenicline N= 3940 346466	Zyban N= 795 47472	Placebo N= 1209 92791
		n (%)	
Any adverse event	3274 (83.1)	633 (79.6)	925 (76.5)
Adverse event resulting in permanent discontinuation from treatment	510 (12.9)[c]	114 (14.3)[d]	109 (9.0)[e]
Gastrointestinal Disorders	**2081 (52.8)**	**270 (34.0)**	**363 (30.0)**
Constipation	325 (8.2)	62 (7.8)	38 (3.1)
Dry mouth	176 (4.5)	70 (8.8)	50 (4.1)
Dyspepsia	275 (7.0)	27 (3.4)	38 (3.1)
Flatulence	382 (9.7)	21 (2.6)	39 (3.2)
Nausea	1260 (32.0)	92 (11.6)	121 (10.0)
General Disorders and Administration Site Conditions	**582 (14.8)**	**82 (10.3)**	**143 (11.8)**
Fatigue	280 (7.1)	29 (3.6)	62 (5.1)
Infections & Infestations	**1155 (29.3)**	**201 (25.3)**	**367 (30.4)**
Nasopharyngitis	362 (9.2)	45 (5.7)	100 (8.3)
Upper respiratory tract infection	277 (7.0)	67 (8.4)	135 (11.2)
Metabolism & Nutrition Disorders	**318 (8.1)**	**56 (7.0)**	**53 (4.4)**
Increased appetite	220 (5.6)	27 (3.4)	27 (2.2)
Nervous System	**1325 (33.6)**	**244 (30.7)**	**359 (29.7)**
Dizziness	216 (5.5)	55 (6.9)	82 (6.8)
Dysgeusia	252 (6.4)	49 (6.2)	48 (4.0)
Headache	698 (17.7)	111 (14.0)	182 (15.1)
Psychiatric Disorders	**1632 (41.4)**	**335 (42.1)**	**340 (28.1)**
Abnormal dreams	545 (13.8)	53 (6.7)	61 (5.0)
Anxiety	120 (3.0)	44 (5.5)	54 (4.5)
Irritability	256 (6.7)	46 (5.8)	75 (6.2)
Insomnia	754 (19.1)	180 (22.6)	146 (12.1)
Sleep disorder	145 (3.7)	46 (5.8)	28 (2.3)

Protocols included: A3051028, A3051036, A3051037, A3051035, A3051002, A3051007, A3051016, A3051043

[a] Includes MedDRA Preferred Terms for adverse events present in ≥5% of any treatment group

[b] Subject-days of drug exposure is calculated from first day of dosing to (and including) last day of dosing.

[c] Total does not include one subject (Subject 103510321036) with an adverse event resulting in permanent discontinuation from treatment.

[d] Total includes one subject (Subject 102810181055) counted as permanently discontinued but was temporarily discontinued.

[e] Total includes one subject (Subject 102810131027) counted as permanently discontinued but was no action taken and one subject (Subject 103710061017) counted as no action taken but was permanently discontinued.

The treatment emergent adverse events observed in varenicline-treated subjects in the pooled Phase 1 studies were similar to those in Fixed-dose Placebo-controlled Studies with nausea, headache, and vomiting being the most commonly reported adverse events. The relatively high incidences of vomiting in the 2 mg and >2 mg daily dose groups (8.7% and 21.4%, respectively) may reflect the higher varenicline doses used in the Phase 1 studies (e.g. up to a 10 mg single dose in Study 305-001). The incidence of gastrointestinal disorders is high compared to the placebo group.

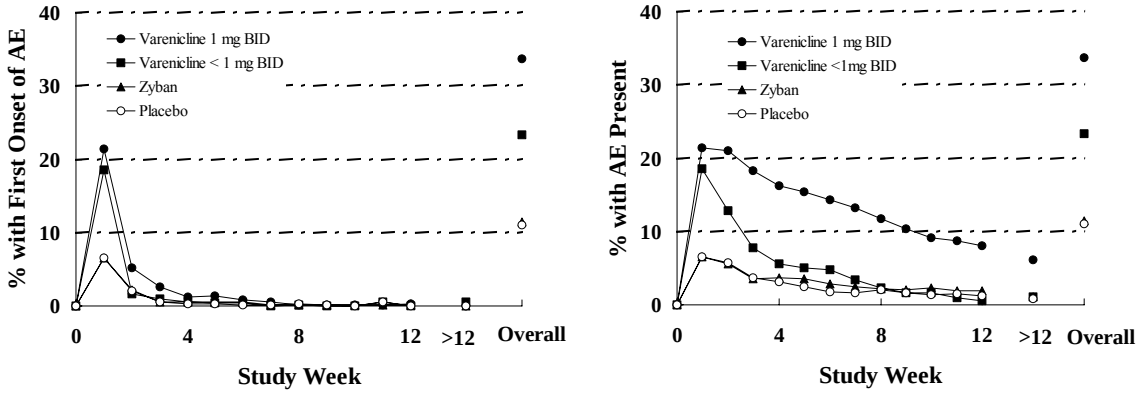
In Phase 2/3 studies, no weight loss was observed in the Cessator subjects who completed the studies.

Time to onset and persistence

The time to onset of first occurrence of an adverse event and the presence of that adverse event over time were assessed using the Fixed-dose, Placebo-controlled Studies dataset. The majority of subjects who experienced nausea reported the first occurrence during the first week of treatment. The proportion of subjects reporting nausea as "present" was greatest at Week 1 then decreased over time. Among subjects receiving varenicline at doses less than 1 mg BID, the percent reporting nausea approached placebo levels as early as Week 4. Among subjects receiving varenicline at 1 mg BID, the proportion with nausea decreased by about 50% over the 12 weeks of study treatment. The median duration of a nausea event for subjects receiving the 1 mg BID dose was 10 days.

This pattern of onset and presence is representative of that of other common AE.

Panel A. First Onset of Nausea, by Week **Panel B. Presence of Nausea, by Week**



Study A3051037 investigated the safety of 1 mg BID varenicline administered for 52 weeks. Adverse events that occurred in ≥5% of varenicline-treated subjects are summarized here:

Table:Long-Term Safety Study A3051037 : Most Frequent All Causality Adverse Events (≥ 5% in Any Treatment Group)

MedDRA System Organ Class Preferred term[a]	**Varenicline N=251**	**Placebo N=126**
	n (%)	
Any adverse event	242 (96.4)	104 (82.5)
Adverse event resulting in permanent discontinuation from treatment	71 (28.3)	12 (9.5) [b]
Gastrointestinal Disorders	**179 (71.3)**	**48 (38.1)**
Constipation	31 (12.4)	9 (7.1)
Diarrhea	20 (8.0)	12 (9.5)
Dry mouth	11 (4.4)	8 (6.3)
Dyspepsia	33 (13.1)	3 (2.4)
Flatulence	31 (12.4)	12 (9.5)
Nausea	101 (40.2)	10 (7.9)
Vomiting	17 (6.8)	2 (1.6)
General Disorders and Administration Site Conditions	**42 (16.7)**	**20 (15.9)**
Fatigue	6 (2.4)	8 (6.3)
Infections & Infestations	**123 (49.0)**	**58 (46.0)**
Bronchitis	3 (1.2)	7 (5.6)
Influenza	15 (6.0)	3 (2.4)
Nasopharyngitis	38 (15.1)	20 (15.9)
Sinusitis	17 (6.8)	8 (6.3)
Upper respiratory tract infection	34 (13.5)	12 (9.5)
Investigations	**50 (19.9)**	**12 (9.5)**
Weight increased	17 (6.8)	5 (4.0)
Metabolism & Nutrition Disorders	**28 (11.2)**	**8 (6.3)**
Increased appetite	13 (5.2)	4 (3.2)
Musculoskeletal & Connective Tissue Disorders	**65 (25.9)**	**25 (19.8)**
Arthralgia	18 (7.2)	7 (5.6)
Back Pain	16 (6.4)	6 (4.8)
Nervous System	**108 (43.0)**	**45 (35.7)**
Dizziness	19 (7.6)	6 (4.8)
Dysgeusia	27 (10.8)	3 (2.4)
Headache	43 (17.1)	26 (20.6)
Psychiatric Disorders	**109 (43.4)**	**39 (31.0)**
Abnormal dreams	57 (22.7)	9 (7.1)
Insomnia	48 (19.1)	12 (9.5)
Irritability	13 (5.2)	7 (5.6)
Vascular Disorders	**26 (10.4)**	**11 (8.7)**
Hypertension	15 (6.0)	5 (4.0)

[a] Includes MedDRA Preferred Terms for adverse events present in ≥5% of any treatment group
[b] Total includes one subject (Subject 103710061017) counted as no action taken but was permanently discontinued .

While the overall incidence of adverse events in subjects receiving varenicline for up to for 52 weeks (Study A3051037) was higher than in studies with 6- or 12-weeks varenicline treatment, no additional adverse events emerged that suggested an increase in risk with increased duration of exposure.

No clinically meaningful changes in laboratory test results were observed in the clinical trials nor were there any noteworthy changes in the QT/QTc interval or any other ECG parameter in either preclinical or clinical studies.

- Serious adverse event/deaths/other significant events

The SAE safety database included 134 cases (count includes deaths).

There were five deaths (3 varenicline, 1 bupropion, 1 placebo) reported in the safety database, no deaths were reported in ongoing studies. All deaths occurred post-treatment in Phase 3 studies. The bupropion and placebo deaths occurred outside the 30-day post-treatment reporting window. None of the deaths were considered treatment-related.

Table: Deaths in completed varenicline studies

Age/Race/ Gender[a]	Treatment/ Dose	Day of Death	Total exposure (days)	Cause[b]
Varenicline				
61/W/M	Varenicline 1 mg BID	Day 196 (post-therapy Day 27)	169 days	Suicide
71/W/M	Varenicline 1 mg BID	Day 188 (post-therapy Day 19)	169 days	Massive pericardial exudate Lung cancer Lymph node metastasis Right side pneumonia Cardiac arrest
29/W/M	Varenicline 1 mg BID	Day 218 [c] (post-therapy Day 197)	15 days	Rectal sarcoma
Zyban				
46/W/M	Bupropion 150 mg BID	Day 222[d] (post-therapy Day 137)	85 days	Accidental death (fatal motorcycle accident)
Placebo				
64/W/M	Placebo	Day 352[d] (post-therapy Day 239)	N/A	Death unexplained (fall, collapse of lung, elbow fracture)

N/A = not applicable.

[a] Race: W = White, Gender: M = male..

[b] Investigator's term(s).

[c] Although the death occurred on Day 218, the subject was diagnosed with rectal sarcoma <30 days after varenicline treatment.

[d] Event occurred beyond the required reporting period but is included for completeness.

A total of 134 SAE cases were reported in completed Phase 1, 2, and 3 varenicline studies. Of the 134 SAE cases, 120 (86 varenicline, 15 bupropion, 19 placebo) occurred while subjects were either on treatment or within 30 days of the last dose of study drug. The majority of SAE cases were single events. Among patients treated with varenicline, two SAE cases in Phase 1 and 7 cases in Phase 2/3 were considered treatment-related by the investigator. Among these 9 cases, no pattern was evident in either the event terms or the time to onset of event from the beginning of treatment. A summary of the serious adverse events by treatment group is provided below.

Table: Incidence of serious adverse events in completed varenicline studies by system organ class (All Causality and Treatment Related)

	Number of Events: All Causality (Treatment Related)			
	Varenicline	Varenicline/ Placebo[a]	Bupropion	Placebo
Cardiac Disorders	24 (2)	0	0	4
Neoplasms, benign, malignant and unspecified	12	0	1	2
Infections and infestations	11	1	3	4
Nervous system disorders	11 (2)	1	6 (5)	1
Gastrointestinal disorders	9 (2)	1	1 (1)	1
General disorders and administration site conditions	7 (3)	0	1	3
Psychiatric disorders	6 (1)	0	0	2
Vascular disorders	6	0	0	1
Eye disorders	5 (3)	0	0	0
Injury poisoning and procedural complications	6	0	3 (1)	5
Investigations	5 (1)	0	0	0
Musculoskeletal and connective tissue disorders	4	0	1	0
Metabolism and nutrition disorders	3	0	0	0
Renal and urinary disorders	3	0	0	0
Hepatobiliary disorders	2	1	1	0
Pregnancy, puerperium and perinatal conditions	2	0	2	0
Reproductive system and breast disorders	2	2	0	1
Respiratory, thoracic and mediastinal disorders	2 (1)	0	0	2
Ear and labyrinth disorders	1 (1)	0	0	0
Immune system disorder	0	0	0	1 (1)
Skin and subcutaneous tissue disorders	0	0	1 (1)	0

Note: Where present, numbers in parentheses are the number of treatment-related cases; if not present, no cases were treatment related.

[a] SAEs listed in this column occurred in those subjects who received placebo in the double-blind phase of Study A3051035.

Thirteen (8 varenicline, 4 bupropion, 1 placebo) of the 16 subjects with treatment-related SAEs discontinued treatment due to the SAE. In addition, 35 (23 varenicline, 4 Zyban, 8 placebo) subjects permanently discontinued treatment for SAEs not considered related to study drug. Of the 23 varenicline-treated subjects, 6 were discontinued for Cardiac Disorders (tachycardia; angina unstable; atrial fibrillation; acute coronary syndrome; myocardial infarction; coronary artery disease), 2 for Gastrointestinal Disorders (duodenal ulcer; abdominal pain), 6 for Nervous System Disorders (grand mal convulsion (2 cases); headache; cerebral infarct, cerebral thrombosis; loss of consciousness; multiple sclerosis); 3 for Neoplasms (cholesteatoma; adenocarcinoma; lung and brain neoplasm malignant); and 6 for SAEs affecting other body systems (chest pain; meningitis aseptic; back pain; calculus ureteric; epistaxis; acute psychosis, affect lability). No pattern was observed in either the event terms or the time to onset of event from the start of treatment.

Neither the number of deaths nor the number and severity of SAE are of concern from a safety perspective.

- Laboratory findings

Liver function

The clinical laboratory test database was reviewed for liver enzyme abnormalities based on non-clinical findings of hepatic changes and microscopic evidence of hepatocellular necrosis in rats given 100 mg/kg/day in a 10-day study. Few subjects (≤0.8% in any group) demonstrated clinically significant elevations in liver function tests (LFT) (AST and ALT (>3xULN), bilirubin (>1.5xULN). The proportion of varenicline-treated subjects with elevated LFTs was generally comparable to that in the placebo group. Additionally, there was no apparent relationship between dose and the incidence of elevated LFTs. Increasing the size of the safety database to All Completed Phase 2/3 Studies had no notable effect on the incidence of liver function test abnormalities in spite of including longer-term Studies A3051035 and A3051037.

Electrocardiogram
The effects of varenicline on the ECG and the QT/QTc interval were assessed in both non-clinical and clinical studies.

In the Phase 1 clinical program, on-treatment ECGs were collected in 19 of the 24 studies and manually read by a centralized ECG reader in 7 of those studies. Two of the 7 studies (A3051012 and A3051014) employed rigorous methods for assessing QT/QTc following single dose and multiple dose administration of varenicline, respectively. These two studies were among the 7 Phase 1 studies in which QT intervals from electronic ECG tracings were measured by a blinded centralized reader. Both performed baseline and post-baseline measurements in triplicate, measured QTc at the approximate Tmax, standardized the timing of ECGs with regard to meals, enrolled both males and females, included a within subject placebo control group and included pharmacokinetic sampling to provide for ECG/PK time matched pairs. Study A3051014 is particularly noteworthy for the number of subjects (n=120, 40 per treatment regimen) studied, and also for including a 1.5 mg BID dose, i.e., higher than the recommended dose of 1 mg BID. In these studies, the placebo-adjusted mean changes from baseline in QTcF were generally 0 msec or less, with isolated increases of <4 msec. For all measurements the nominal 90% confidence interval excluded 10 msec, the threshold of concern proposed in the ICH E14 guidance.

Additionally, because of the extensive collection of data in healthy male and female subjects, smokers and non-smokers, treated with both single- and multiple-doses of varenicline or placebo, a model-based analysis was performed to evaluate the exposure-response relationship between varenicline concentration and the heart rate corrected QT interval (QTc). The results of this analysis show that no concentration-related effect of varenicline on QT/QTc prolongation was detected in male and female subjects, as evidenced by a mean slope estimate near zero and an upper bound of the 95% confidence interval predicting a maximum mean effect on QTc of about 0.3 msec at the recommended 1 mg BID dose. Even with factors that can influence the pharmacokinetics of varenicline such as renal function, the upper extremes of predicted probability distributions for mean QTc prolongation do not exceed 2 msec.

Blood pressure and heart rate
Varenicline produced no clinically meaningful changes in standing/sitting diastolic or systolic blood pressure or pulse rate in Phase 1/2/3 studies. In Fixed-dose, Placebo-controlled Studies, median changes in blood pressure and pulse rate were comparable in the varenicline and placebo groups. The presence of an additional cardiovascular risk factor did not affect median change of either variable. The proportion of subjects with blood pressure or pulse rate measurements meeting categorical thresholds was small (≤1.5%) and showed no consistent pattern.

Lipids
Approximately 25 % of the subject had elevated non-fasting triglycerides without regard to baseline values. There were no differences between the varenicline, bupropion and placebo groups.

Renal function
Clinical laboratory assessments of renal function included BUN, creatinine, and qualitative urinalysis tests. No varenicline-treated subjects in the Phase 2/3 Fixed-Dose, Placebo-Controlled Studies had a clinically significant elevation of BUN or creatinine. Among the 3940 varenicline-treated subjects in the Phase 2/3 studies, 3 had clinically significant elevations of BUN, and none had clinically significant elevations of creatinine.

- Safety in special populations

Safety in subgroups
Analyses of the safety data revealed that the safety and tolerability profile of varenicline was independent of gender, age, race or presence of cardiovascular risk factors (additional to smoking) and within each of these subgroups there was a similar pattern of events in varenicline-treated subjects compared with placebo subjects. No children younger than 12 years have been treated with

varenicline. No systematic studies on the use of varenicline in pregnant or lactating women have been conducted.

It should be noticed that only a small percentage of the study population had any concurrent cardiovascular disease at study entrance (<3%), and most of them were mild of nature. The lack of experience in this special patient group is compensated for by the applicant´s commitment to perform further studies

Because of the use of bupropion as comparator, many specific populations could not be included in the clinical studies. Varenicline is not investigated in subjects with a history of seizures, diabetes mellitus, hepatic or renal impairment, bipolar disorder, alcoholism (current or in the recent past). Neither was varenicline investigated in combination with MAO-inhibitors, antidepressants, antipsychotics, benzodiazepines, naltrexon, systemic steroids (with exception of inhaled steroids), and theophylline. Cholinergic agents are known to induce psychoses. There were only two cases of acute psychosis (one possible drug-related) reported during varenicline use. In addition, there were 3 cases of seizures reported after varenicline use, but none of them was deemed to be drug-related. Despite the low incidence of psychoses and seizures, one should realise that patients at risk had not been included. Since there is no clinical experience in these special groups, no clear conclusion could be drawn concerning the risk of varenicline treatment in these patients.

- Safety related to drug-drug interactions and other interactions

In anticipation of probable co-administration in clinical practice, NRT was selected for drug interaction study. In Study A3051033 varenicline (1 mg BID) and NRT (patch, 21 mg/day) were co-administered to smokers for 12 days. A statistically significant decrease (mean = 2.6 mmHg) in systolic blood pressure was measured on the final day of the study. In this study, the incidences of nausea, headache, fatigue, vomiting, dizziness, and dyspepsia were greater for the combination than for NRT alone. Aside from this interaction, no evidence for clinically important pharmacokinetic interactions between varenicline and the other tested drugs were observed. Furthermore no other safety concerns were observed.

- Abuse potential

Examination of abuse-potential adverse event terms in all Phase 2/3 fixed-dose, placebo controlled studies showed that the only preferred term with an incidence in the varenicline groups higher than in the placebo group was somnolence (4.4% and 4.0% for varenicline <1 mg BID and 1 mg BID, respectively versus 2.6% for placebo). In study A3051002, where subjects were treated with varenicline for six weeks followed by one week placebo, subjects did not experience immediate relapse with the withdrawal of therapy nor was there any indication that subjects needed to smoke additional cigarettes to manage craving and withdrawal symptoms. This observation is consistent with the observations in rats and monkeys that varenicline does not produce physiological dependence. Study A3051016 demonstrated that when subjects were permitted to adjust their daily dose ad libitum between 0.5 mg and 2 mg, the mean modal dose for varenicline peaked at approximately 1.5 mg at Week 2 and declined to just above 1.0 mg at Week 12, supporting the claim that there is no pattern of abuse in subjects treated with varenicline and no psychic dependence liability.
The objective of the A3051039 study was to evaluate the abuse potential of varenicline relative to amphetamine in a population of recreational stimulant using subjects. The pattern of effects for both smokers and non-smokers is consistent with the profile of a drug that while having pharmacologic activity (i.e. some known action), has a dose-response profile unlike amphetamine and the general pattern for other drugs of abuse. This is based on the multivariate analysis of primary measures of abuse potential and further evaluation of secondary parameters, including physiological effects. For smokers, the data provide evidence that subjects are unmotivated to abuse varenicline. For non-smokers, 1 mg varenicline differentiated from placebo in the multivariate analysis, specifically with respect to the peak values for the VAS High and ARCI/Cole Abuse Potential scales. The VAS High measure, while capturing the sensation of receiving an active drug, was associated with a disliking of the sensation, especially compared with their liking of amphetamine. No reinforcing effects were

identified for varenicline as evidenced by the lack of significant difference from placebo on the multiple choice procedure.

The clinical and non-clinical data collected to date, taken together, indicate that varenicline is unlikely to be a substance of abuse.

- Discontinuation due to adverse events

In all completed phase 1 and 2/3 studies, 535 among 4748 varenicline treated subject discontinued due to AE. Most of the events resulting in discontinuation from treatment were gastrointestinal, nervous, and/or psychiatric system events. The median number of days to discontinuation was 28 days for the varenicline 1 mg BID in the fixed-dose, placebo-controlled trials. Few laboratory abnormalities resulted in treatment discontinuation for more than one subject in the Phase 2/3 Fixed-dose Studies. Most of the discontinuations resulted from abnormalities in liver function tests (LFTs). Fifteen varenicline-treated subjects in Phase 2/3 Fixed-dose, Placebo-controlled studies and 23 varenicline treated subjects in All Completed Phase 2/3 Studies were permanently discontinued due to clinically significant elevations in LFT values.
31 varenicline treated subjects discontinued treatment due to an SAE. Eight varenicline-treated subjects were discontinued due to SAEs that were considered treatment related: 3 subjects experienced altered visual acuity/transient loss of vision; 2 subjects were characterized by chest/abdominal pain; 2 subjects experienced multiple treatment-related SAEs affecting two or more organ systems; and 1 experienced acute psychosis. Additionally, one varenicline-treated subject had atrial fibrillation which was considered treatment related but was not noted until the Week 12 visit (end of treatment).

- Post marketing experience

NA

- Discussion on clinical safety

Overall, the analysis of routine adverse events identified no serious safety concerns in smokers receiving varenicline at doses up to 1 mg BID for up to 12 weeks.

The Applicant recommends 1 mg BID dose for all patients, except for patients with severe renal dysfunction. However, every patient that would stop varenicline use prematurely due to adverse events can be considered as a loss, as varenicline is an effective drug to promote smoking cessation. Therefore the CHMP considered that intolerant patients should be given the opportunity to change to a regimen of 0.5 mg BID. The Applicant was asked to introduce the 0.5 mg tablets as a separate pack size to accommodate the need for dosing of patients intolerant of 1.0 mg. The Applicant has implemented the requested measure.

Regarding carcinogenicity, the concern was raised by the fact that hibernomas were identified in rats. It is agreed that the risk for humans to develop hibernomas following treatment with varenicline is theoretical and most probably non-existent. Furthermore, it also agreed that the potential benefit of smoking cessation due to treatment with varenicline, which would prevent additional exposure to known carcinogens from smoking, would be expected to outweigh a hypothetical risk arising from the non clinical hibernoma finding. This is taken into account in the Section 5.3 of the SPC.

Concerning the cardiovascular effects, although there seems to be no suggestion for an increased risk for cardiovascular adverse reactions, the population of patients who stop smoking is a population at risk and therefore cardiovascular effects should be included in the safety specifications and be monitored. The applicant proposed that the specific Cardiovascular Study and monitoring for cardiovascular adverse events in the COPD and Psychosis Studies address the request for cardiovascular monitoring; the RMP will be updated as part of the follow-up measures.

Concerning the issue relating to rebound, withdrawal and dependence, this is a general issue for centrally acting products intended for smoking cessation, and therefore will be included in the safety specifications. A label change to address this issue can be found in Section 4.4 of the SPC where it

states: "At the end of treatment, discontinuation of CHAMPIX was associated with an increase in irritability, urge to smoke, depression, and insomnia in up to 3% of patients. The prescriber should inform the patient accordingly."

Concerning patients on antidepressants, antipsychotic agents, benzodiazepines, anticonvulsants, naltrexone, oral hypoglycaemic agents, insulin, steroids and theophylline, it is agreed that these drugs show low to very low affinity for the nicotinic α4β2 AchRs and that in turn, varenicline displays very low affinity for the target receptors of these classes of drugs. Pharmacodynamic interactions are therefore unlikely to occur. Nevertheless, the Applicant agreed to monitor for adverse events associated with drug-drug interactions in the Cardiovascular, COPD and Psychosis studies and modify the RMP accordingly.

As is the case with many medicinal products, there are very limited data from the clinical program on the use of varenicline in pregnant women. The Applicant recognized that some pregnant women may potentially be exposed to varenicline as they attempt to stop smoking. To assess the safety of varenicline exposure during pregnancy, the Applicant committed to conducting a prospective cohort study post-approval to compare women who use varenicline while pregnant to women who smoke while pregnant with respect to birth outcomes.

The Applicant will submit a study protocol to the EMEA within three months of the approval and a study report at the time of varenicline renewal.
The varenicline RMP has been updated to include the above proposed prospective cohort study in pregnant women.

5. Pharmacovigilance

Detailed description of the Pharmacovigilance system

In the data submitted the applicant has provided information which ensure that the necessary resources and systems are in place to support routine pharmacovigilance activities that meet the needs for this product.

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan, which included a risk minimisation plan.

Based on the results from the non-clinical and clinical development program, the Applicant identified areas of potential risk and areas with limited information, for continued pharmacovigilance.

Potential Risks: Effects of smoking cessation

Areas with Limited Information: Very elderly subjects (≥75 years old); cardiovascular Patients; COPD Patients; Psychosis Patients; Pregnancy; Adolescents and Overdose.

Post-launch safety monitoring activities will include routine periodic database searches for any varenicline report of a Designated Medical Event (DME, a predetermined list of medical events considered to be clinically important and frequently associated with drug use), adverse events reported in patients with severe renal impairment and/or aged 75 years or older. In addition, reviews of all events received post-launch will be conducted periodically and following the cut-off date of each Periodic safety Update Report (PSUR).

Routine pharmacovigilance will be employed. The Applicant will provide reviews of adverse events associated with the use of varenicline, and specific reviews of events reported in patients with severe renal impairment, in patients older than 74 years of age or younger than 18 years of age, overdose and

effects of use during pregnancy (mother and child) in PSURs. In addition, specific studies in cardiovascular, COPD, and psychosis subjects, adolescents and the prospective cohort study in pregnancy also will be conducted.

These activities are noted in Table RM-1 below:

Risks	**SPC**	**Patient Leaflet**	**Psychosis Clinical Trial**	**COPD Clinical Trial**	**Cardio-vascular Clinical Trial**	**Adolescent PK and Safety and Efficacy Trials**	**Pregnancy Prospective Cohort Study**	**PV**
Adverse Events associated Smoking Cessation	√	√						√
Limited Information								
Very Elderly	√	√						√
Cardiovascular Disease			√	√	√			√
COPD				√				√
Psychosis			√					√
Pregnancy - Lactation	√	√					√	√
Adolescents	√	√				√		√
Overdose	√	√						√

Studies proposed by the Applicant are summarized in the table below:

Study	**Ongoing**	**New**	**Estimated Start Date**	**Estimated End Date**
Cardiovascular Disease subjects	√			2008
COPD subjects	√			2008
Psychosis subjects		√	2007	2010
Pregnancy Prospective Cohort		√	2007	2011
Adolescent Multi-dose PK		√	2008	2010
Adolescent Efficacy and Safety		√	2010	2012

Table Summary of the risk management plan

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Adverse events associated with smoking cessation	Routine pharmacovigilance	Wording in Section 4.4 and 4.8 of the SPC and in the Package Leaflet in Section 2.
Limited Information		
Very Elderly	Routine pharmacovigilance	Noted in Section 5.2 of the SPC
Cardiovascular disease	Routine pharmacovigilance and an efficacy and safety study in subjects with cardiovascular disease ongoing	-
COPD	Routine pharmacovigilance and an efficacy and safety study in subjects with COPD ongoing	-
Psychosis	Routine pharmacovigilance and a study in subjects with psychosis planned	-
Pregnancy/Lactation	Routine pharmacovigilance and a prospective cohort study to compare women who use varenicline while pregnant to women who smoke while pregnant with respect to birth outcomes planned	Wording in Section 4.6 of the SPC and Section 2 of the Package Leaflet
Adolescents	Routine pharmacovigilance; a multi-dose pharmacokinetic study and an efficacy and safety study are planned	Wording in Sections 4.2 and 5.2 of the SPC
Overdose	Routine pharmacovigilance	Recommendation in Section 4.9 of the SPC and Section 3 of the Package Leaflet

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

2.1 Overall conclusions, risk/benefit assessment and recommendation

Quality

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

Non-clinical pharmacology and toxicology

Non-clinical pharmacology and toxicology were sufficiently documented in the non-clinal studies program, except for the functional immunological evaluation of varenicline in an animal model. Therefore, the Applicant will perform a functional immunotoxicity study as a post-approval commitment.

Efficacy

One thousand one hundred ninety-eight (1198) subjects were treated with varenicline and 805 were treated with placebo for up to 12 weeks in Studies A3051028, -36, -07/18. Six hundred ninety-two (692) and 669 subjects were treated with varenicline or bupropion, respectively, in Phase III trials

A3051028 and –36. In Study A3051035, 1927 subjects were treated with open-label varenicline for up to 12 weeks; of these 1236 (64.1%) had stopped smoking by Week 12. One thousand two hundred six (1206) subjects (602 varenicline, 604 placebo) were subsequently randomised and received up to 12 additional weeks of double-blind treatment.

Across the above-mentioned 12-week trials, varenicline was superior to placebo for smoking cessation at doses of 0.5 mg BID and 1 mg BID: Approximately 46% of the smokers in the 0.5 mg BID and 1 mg BID varenicline groups had stopped smoking over the last 4 weeks of treatment (Weeks 9-12), compared with 17% in the placebo arm.

Varenicline was also superior to bupropion at the end of the 12 weeks treatment. In pooled Studies A3051028, and -36, 44% of subjects treated with varenicline at 1 mg BID stopped smoking at Weeks 9-12 compared with 30% of bupropion-treated subjects.

In the pooled Studies A3051028, -36, and –07/18, 23% of subjects treated with varenicline at 1 mg BID were still abstinent at Week 52 compared with 9% in the placebo arm. In pooled Studies A3501028 and –36, 23% of varenicline treated subjects remained abstinent at Week 52 compared with 16% in the bupropion group.
In Study A3051035, subjects who received varenicline for an additional 12 weeks had higher abstinence rates at both Weeks 13-24 (71%) and Weeks 13-52 (44%) than the placebo group at the corresponding intervals (50% and 37%, respectively).

Safety

A total of 5944 subjects (3940 varenicline, 795 bupropion, 1209 placebo) comprised the varenicline Phase 2/3 safety database. In all completed Phase 2/3 studies, 1531 subjects have received varenicline 1 mg BID for >12 weeks, 456 subjects for >24 weeks and 112 subjects for ≥ 52 weeks.

The most commonly observed (≥10%) treatment-related adverse events (AEs) in varenicline-treated subjects in all completed Phase 2/3 studies were nausea, insomnia, abnormal dreams, and headache. Overall, 10.7% of varenicline-treated subjects discontinued treatment due to a treatment-related adverse event; 12.9% of varenicline-treated subjects discontinued treatment due to an all causality adverse event.

Some other special patients' groups were eligible for the varenicline trials, such as elderly and patients with cardiovascular diseases, but only low numbers were included. It is therefore difficult to draw conclusions concerning safety for these special patients' groups, and these patients should be monitored when varenicline is prescribed (see Risk Management Plan).

Overall, the well-established risks of smoking use outweigh the risks of varenicline, and this product is considered favourable from a safety point of view.

The safety profile of varenicline is considered acceptable, since the majority of AEs were reversible and not in need of acute medical attention. Most subjects became tolerant to nausea in due time.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

- User consultation

The applicant has provided detailed results of readability testing performed according to the European Commission Guideline on Packaging Information of Medicinal Products for Human Use Authorised by the Community and as per guidance provided by the EC "Guideline on the readability of the label and package leaflet (PL) of medicinal products for human use"

The Package Leaflet fully conforms to the standards set. The applicant has performed readability testing according to the "readability guideline" and has subsequently taken appropriate measures to improve the readability.

Risk-benefit assessment

Tobacco smoke is a major preventable factor in the development of a number of life-threatening diseases such as ischaemic heart disease, cancers and COPD. Nicotine is a strong addictive agent which is reflected in the low spontaneous quitting rate and rate of continuous abstinence among quitters not using any pharmacological aid. Nicotine replacement therapy and bupropion roughly doubles the chances for a successful attempt to quit as compared to no pharmacological aid, but there is still a need for therapies to aid smoking cessation in both healthy smokers and especially in patients with smoking-related diseases.

In three 12-week trials, varenicline at 1 mg BID was superior to placebo for stopping smoking at both the end of treatment and at one year from the start of the study. Forty-six percent (46%) of subjects treated with varenicline at 0.5 mg BID or 1 mg BID stopped smoking during the last 4 weeks of a 12-week treatment period (versus 17% in the placebo arm); the long-term abstinence rate (ie to 1 year from the start of the study) was 23% in subjects treated with varenicline compared with 9% in placebo-treated subjects.

The most common treatment-related adverse events were nausea (reported by approximately 30% of patients), insomnia, abnormal dreams, and headache. Most of these symptoms, including nausea, decreased over time. Overall, 10.7% of varenicline-treated subjects discontinued treatment due to a treatment-related adverse event; 12.9% discontinued treatment due to an all causality adverse event.

Some other special patients' groups were eligible for the varenicline trials, such as elderly and patients with cardiovascular diseases, but only low numbers were included. Therefore these patients will bemonitored post marketing (see Risk Management Plan).

Efficacy was demonstrated, and overall, the well-established risks of smoking outweigh the risks of varenicline.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns

and

- the following follow-up measures were needed:
  - an immunotoxicity study in an appropriate model, will be performed;
  - a prospective cohort study to compare women who use varenicline while pregnant to women who smoke while pregnant with respect to birth outcomes will be conducted;
  - a protocol for a study in patients with psychosis will be provided
  - information on the feasibility of performing a study for evaluating dose tapering versus abrupt discontinuation in terms of efficacy will be provided
  - final results of on-going clinical studies will be reported
  - the Risk management Plan will be updated, in line with the CHMP Guideline on Risk Management Systems for medicinal products for human use

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus decision that the risk-benefit balance of Champix in approved indication of smoking cessation was favourable and therefore recommended the granting of the marketing authorisation.