EMA/CHMP/327148/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Champix

International non-proprietary name: varenicline

Procedure No. EMEA/H/C/000699/II/0074

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Pfizer Europe MA EEIG submitted to the European Medicines Agency on 19 December 2018 an application for a variation.

The following changes were proposed:

Variation requested		Type	Annexes affected
C.I.3.b	C.I.3.b - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Change(s) with new additional data submitted by the MAH	Type II	I and IIIB

Update of sections 4.2, 5.1 and 5.2 of the SmPC to reflect results of the paediatric study A3051073 (MEA 047) " A Phase 4, Twelve-Week, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Dose-Ranging Study With Follow-Up, Evaluating The Safety And Efficacy Of Varenicline For Smoking Cessation In Healthy Adolescent Smokers." The PL is updated accordingly. RMP version 11.0 was submitted.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

2. Overall conclusion and impact on the benefit/risk balance

The MAH presents data from Study A3051073 a study of varenicline in adolescents age 12-19, designed and conducted to satisfy the post-marketing requirement for CHAMPIX under PAM (MEA 047), as well as data from two phase 1 studies of varenicline in this age group. Proposed CHAMPIX labelling revisions based on Study A3051073 updating relevant sections of the SmPC (Sections 4.2, 5.1 and 5.2) and Package Leaflet, as recommended in the Article 46 Assessment Report, are being provided as part of this Type II variation.

A3051073 was designed with 3 study groups (2 active-treatment arms and one placebo arm) of a 100 study subjects per group, from postulated CAR rates week 9-12 (primary endpoint) of 24% for varenicline and of 9% for placebo. This turned out to be an unrealistically low expected placebo response rate, as the study resulted in a placebo response rate that is twice as high as was projected with in the study power calculation. The analysis of efficacy results showed no significant treatment effect of varenicline, but the efficacy results for varenicline to adolescent smokers are difficult to interpret with certainty, as it must be suspected that the MAH's rejection of vareniclines efficacy in adolescent smokers could be due to a Type II error.

The safety results showed that varenicline is generally well tolerated in adolescents. The pattern of adverse events in A3051073 was similar to the adverse events profile of varenicline in adults.
There are no signals indicating new safety concerns arising from study A3051073, or from the two Phase 1 adolescent studies. This includes neuropsychiatric adverse events, which could conceivably be of special concern in an immature study population.

Based on A3051073's efficacy outcomes, the benefits of varenicline treatment in adolescents of 12-17 years of age has not been demonstrated to outweigh the risks.

The proposed labelling changes, including the changes in the wording of the update of 5.1 in the SmPC, are approvable.

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation accepted		Type	Annexes affected
C.I.3.b	C.I.3.b - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Change(s) with new additional data submitted by the MAH	Type II	I and IIIB

Update of sections 4.2, 5.1 and 5.2 of the SmPC to reflect results of the paediatric study A3051073 (MEA 047) " A Phase 4, Twelve-Week, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Dose-Ranging Study With Follow-Up, Evaluating The Safety And Efficacy Of Varenicline For Smoking Cessation In Healthy Adolescent Smokers". The PL is updated accordingly. RMP version 11.1 was submitted.

☒ is recommended for approval.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

4. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above

Summary

Please refer to Scientific Discussion Champix/H/C/000699/II/0074

Annex: Rapporteur's assessment comments on the type II variation

5. Introduction

This Type II Variation being submitted to update the CHAMPIX Product Information (Summary of Product Characteristics [SmPC] Sections 4.2, 5.1, and 5.2 and the Package Leaflet) with the results from Study A3051073, *A Phase 4 Twelve-Week, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Dose-Ranging Study With Follow-Up, Evaluating The Safety And Efficacy Of Varenicline For Smoking Cessation In Healthy Adolescent Smokers*.

Study A3051073 was a Post-Authorisation Safety Study (PASS) and a regulatory Post-Authorisation Measure (MEA 047) in the European Union (EU). The A3051073 Clinical Study Report (CSR) was initially submitted to the European Medicines Agency (EMA) on 9 July 2018 in accordance with Article 46 of the Paediatric Regulation (European Commission) No. 1901/2006). The study was part of a Written Request for paediatric studies for CHANTIX issued by the United States (US) Food and Drug Administration (FDA), and a post-marketing study requirement for CHANTIX under the US Pediatric Research Equity Act.

Product Development Rationale

Smoking Cessation in Adolescents

Adolescent smoking continues to be a public health concern despite the decline in smoking rates over the past decade. In the US, data from the Centres for Disease Control's (CDC)2017 National Youth Risk Behavior Survey showed that 8.8% of students were current cigarette users (i.e., had smoked cigarettes on at least one of the 30 days preceding the survey), 2.6% were current frequent cigarette users (ie, had smoked ≥cigarettes on 20 of the 30 days preceding the survey) and 2.0% were current daily cigarette users (i.e., had smoked every day during the 30 days preceding the survey). According to the 2013 National Survey on Drug Use and Health, five adolescents (12–17 years) accounted for half of the approximately 5,700 people per day who started smoking cigarettes.

From a global perspective, a recent CDC assessment of data from the Global Youth Tobacco Survey (GYTS) (school-based survey among students 13 to 15 years old) for 2012-2015 showed that across 61 countries, the median current tobacco smoking prevalence was 10.7% with 14.6% among males and 7.5% among females.6 Another recent analysis of data from the GYTS including a broader time frame (2000-2015) and more countries (154) showed current any tobacco use was 15.7% overall with higher rates in males than females (20.2% versus [vs] 10.4%, respectively).

Studies have shown that many adolescent smokers want to quit. In a 2015 CDC survey, among students who reported current cigarette use, 45.4% had tried to quit smoking during the 12 months preceding the survey. Other studies have reported over 50% of current adolescent smokers had intentions to quit and over 50% made quit attempts.6,7,9 Many, if not most, of these quit attempts are not successful.10,11 It is now accepted that addiction to smoking routine, making unassisted quitting difficult even among those without a long smoking history.

As noted in two recent reviews on smoking cessation treatments in adolescents, there is a paucity of quality studies on the effectiveness of smoking cessation treatments in adolescent smokers, particularly regarding the use of pharmacotherapies. The limited data that are available suggest that treatments proven efficacious in adult smokers are not necessarily efficacious in adolescents. The Cochrane review3 analysed four controlled pharmacotherapy studies that evaluated nicotine replacement therapies (NRTs) and/or bupropion and met their quality criteria. These studies evaluated the use of nicotine patch, nicotine patch vs nicotine gum, bupropion, and nicotine patch plus bupropion vs nicotine patch alone. All four studies also included some form of patient counselling. The outcome measure was cessation rates at the 6-month or later follow-up point and none of the pharmacotherapies showed statistically significant treatment effects. Of note, in the bupropion versus placebo study a significant treatment effect for

bupropion 300 mg was reported at 6 weeks (end of treatment) but it was not maintained at 26 weeks. In addition, new evaluation of the study data showed that adherence to treatment strongly predicted successful cessation. The Towns review included 10 studies that evaluated the use of NRT or bupropion in adolescent smokers (some overlapping with those reported in the Cochrane review), 7 of which included a comparator and 3 of which were single arm studies. It was noted that no additional benefit of active treatment was found in 5 out of 7 comparison group studies. Two of the 3 single arm studies reported a 5% quit rate with nicotine patches, and the third, a small study (n=16) in adolescent smokers with Attention Deficit Hyperactivity Disorder, reported a 31% quit rate after 4 weeks of bupropion.

Adolescents face added difficulties in achieving successful cessation compared to adults even when they are motivated to quit, and these difficulties could help explain the lack of treatment effect in adolescents of smoking treatments with proven efficacy in adults.

Adolescence is a developmental stage characterized by rapid neurocognitive and hormonal change. Differences in smoking patterns, lifestyle and attitudes towards seeking help in adolescents compared to adults may influence treatment effectiveness. Additionally, factors such as peer pressure, impulsivity and willingness to engage in risky behaviours, which are characteristic of that developmental stage, play a role in the initiation of smoking and are likely to have a negative impact on cessation attempts.

Varenicline Background

Varenicline was approved, as an aid to smoking cessation treatment for adults by the US FDA in May 2006 under the trade name of CHANTIX and by the EMA in September 2006, under the trade name CHAMPIX. As of 07 February 2018, the data cut-off date for this submission, varenicline had received marketing authorization in 116 countries and was marketed in 94 countries.

Varenicline, a highly selective partial agonist at the $\alpha_4\beta_2$-subtype neuronal nicotinic acetylcholine receptor (nAChR), was specifically developed as an aid to smoking cessation.

Data suggest that it is the α4β2 nAChR that mediates the dependence-producing effects of nicotine. The hypothesis underlying the efficacy of varenicline is that, as a partial agonist, varenicline blocks the behaviourally reinforcing effects of exogenous nicotine while also reducing the craving (or the urge to smoke) and withdrawal associated with smoking cessation.

Results of the varenicline Phase 2-3 clinical trial program, which supported the initial approval, showed that varenicline is highly efficacious for smoking cessation compared with placebo and is well tolerated. Two identical double blind, placebo-controlled, Phase 3 pivotal studies additionally demonstrated that varenicline is more effective than bupropion (Zyban) for smoking cessation. In these two studies combined, the continuous abstinence rate (CAR) for Weeks 9-12 was 44.2% for varenicline, 29.7% for Zyban and 17.7% for placebo.

The odds ratio (OR) for varenicline vs placebo was 3.69 (95% confidence interval [CI]: 2.88, 4.72) with a p-value of <0.0001 and the OR for varenicline vs bupropion was 1.87 (95% CI: 1.50, 2.34) with a p-value of <0.0001 (original SCE, Section 2.7.3.3.2.1.1).

The pre-approval studies were conducted in adult smokers (18 years and older) who were otherwise generally healthy. Subsequent randomized, placebo-controlled smoking cessation studies in adult subjects with co-morbidities including stable cardiovascular disease, mild to moderate chronic obstructive pulmonary disease, major depressive disorder under stable treatment or successfully treated within the previous 2 years, a small study in subjects with schizophrenia or schizoaffective disorder, and a large study in subjects without and with a history of psychiatric disorders, have demonstrated that varenicline is efficacious and generally well-tolerated in these targeted populations as well. Other post-approval studies in adult smokers have demonstrated the safety and efficacy of varenicline in subjects previously

treated with varenicline who failed to quit smoking or quit but relapsed, subjects who were given an option to choose a target-quit-date (TQD) between days 8 and 35 of treatment, and subjects who were not able or willing to quit within a month but were willing to reduce their smoking with the goal of reaching complete abstinence by week 12 and then continue treatment for an additional 12 weeks for a total of 24 weeks of treatment.

The approved dosing regimen for adults (≥18 years old) is 1 mg twice daily (BID) for 12 weeks starting with a 1-week up-titration at the beginning of treatment. In patients who have stopped smoking, an additional 12 weeks of treatment is recommended to further increase the likelihood of maintaining long-term abstinence. Prescribing instructions recommend that the patient should determine a date to stop smoking, and varenicline dosing should begin 1 week before that date. Alternatively, patients can start treatment and then choose a quit date between days 8 and 35 of treatment. Patients who are not able or willing to quit abruptly can start treatment with varenicline and reduce their smoking with the goal of reaching complete abstinence by 12 weeks and then continue treatment for an additional 12 weeks for a total of 24 weeks of treatment.

Varenicline Adolescent Program

The varenicline adolescent program consists of three studies, a Phase 1 single-dose pharmacokinetic (PK) and safety/tolerability study, A3051029, a Phase 1 multiple-dose PK and safety/tolerability study, A3051070, and a Phase 4 efficacy/safety study, A3051073. The studies are summarised in **Table 1**. All three studies contributed PK and safety data; Study A3051073 was the only study that evaluated efficacy.

Table 1 Description of Varenicline Adolescent Studies Completed as of 7 February 2018

Study	Design	Duration	Treatment Groups	Number of Subjects[a]
PHASE 4 STUDY				
A3051073 Adolescent safety and efficacy (12-19 years old)	R, DB, PC, PG	12 weeks of treatment, plus nontreatment follow-up thru Week 52	High-dose varenicline (1 mg BID >55 kg; 0.5 mg BID ≤55 kg) Low-dose varenicline (0.5 mg BID >55 kg; 0.5 mg QD ≤55 kg) Placebo	108 100 99 Total: 307
PHASE 1 STUDIES				
A3051070 Multiple dose PK in adolescent smokers (12-16 years old)	R, DB, PC, PG	14 days of treatment plus follow-up thru Day 18	**HBW** (>55 kg): High-dose varenicline (1 mg BID); Low-dose varenicline (0.5 mg BID) Placebo **LBW** (≤55 kg): High-dose varenicline (0.5 mg BID); Low-dose varenicline (0.5 mg QD Placebo	 14 14 7 14 15 8 Total: 72
A3051029 Single dose PK in adolescents smokers (12-17 years old)	R, ISBSO, PC, PG	Single-dose treatment, follow-up thru 48 hours postdose	0.5 mg varenicline (single dose) 1 mg varenicline (single dose) Placebo	10 12 5 Total: 27

a. number of treated subjects (took at least 1 dose of study medication) by treatment group and in total.
Note: All studies enrolled smokers.
DB=Double-blind; PC=placebo-controlled; PG=parallel-group; R=randomized; ISBSO=investigator- and subject-blind, sponsor-open; QD=once daily; BID=twice daily; PK=pharmacokinetic; HBW=high body weight; LBW=low body weight; CSR=Clinical Study Report.
b. number of treated subjects (took at least 1 dose of study medication) by treatment group and in total.
Source: A3051073 CSR, Section 9.1 and Section 10.1, A3051070 CSR, Section 5.1 and Section 6.1, A3051029 CSR, Section 5.1 and Section 6.1.

Study A3051029 was conducted early in the varenicline clinical development program and the results were submitted with the original Marketing Authorisation Application.

Study A3051070 was completed after the initial application and a Type II Variation, EMEA/H/C/000699/II-039, was submitted on 15 December 2011 (eCTD 0115) to update the product information with the results from the study. Additionally, the SCP that was included in the CHAMPIX Marketing Authorisation Renewal submitted on 18 December 2015 (eCTD 0180), also included a summary of the data from Study A3051070.

Study A3051073 is a Post-Authorisation Safety Study (PASS) and a regulatory commitment in the European Union for varenicline (CHAMPIX). As noted above, the A3051073 CSR was initially submitted to the European Medicines Agency (EMA) on 9 July 2018 in accordance with Article 46 of the Paediatric Regulation (European Commission [EC]) No. 1901/2006).

The formulation of varenicline used in Studies A3051073 and A3051070 was the clinical image of the immediate release commercial formulation and the formulation used in Study A3051029 was the Phase 3 tartrate tablet formulation. These formulations are bioequivalent.

Studies A3051073 and A3051029 used 0.5 mg varenicline tablets and Study A3051070 used 0.5 mg and 1 mg varenicline tablets (SCP Appendix 1).

The varenicline doses evaluated in Study A3051029 were selected based on safety and tolerability in Phase 1 adult studies and the observed trend for higher systemic exposure to varenicline in female adult smokers, who tended to have lower bodyweights relative to males. Because smaller individuals were expected in the adolescent population and lower body weight was associated with decreased tolerability, the study evaluated 0.5 mg and 1 mg as single oral doses.

Varenicline doses evaluated in Study A3051070, in accordance with the WR, did not exceed 1 mg BID and included the recommended adult dose of 1 mg BID and a lower dose of 0.5 mg BID. Based on PK data from study A3051029 and adult population PK analyses, low body weight subjects (≤55 kg) received half the dose of high body weight subjects (>55 kg).

The doses evaluated in Study A3051073 were based on the results of Study A3051070, as well as A3051029 and adult data. Because Study A3051070 demonstrated that varenicline exposure was adequately adjusted by halving the total daily dose of varenicline in subjects weighing ≤55 kg, subjects in A3051073 weighing ≤55 kg also had their randomised dose reduced by half; those randomised to 1 mg BID received 0.5 mg BID and those randomized to 0.5 mg BID received 0.5 mg once daily (QD). This dosing regimen was expected to provide exposure levels of varenicline in adolescent smokers that would be efficacious and tolerable, based on available adult data.

All studies were conducted as per International Conference on Harmonization guidelines and Good Clinical Practice (GCP) standards.

6. Clinical Pharmacology

The varenicline paediatric program included the following three clinical varenicline studies in adolescent subjects:

- A3051029, *Phase 1, Randomized, Sponsor-Open, Investigator and Subject-Blind, Parallel-Group, Placebo-Controlled Study to Evaluate the Single-Dose Pharmacokinetics, Safety, and Tolerability of Varenicline in Healthy Adolescent Smokers;*
- A3051070, *Phase 1, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Multiple-Dose Pharmacokinetics, Safety and Tolerability of Varenicline in Healthy Adolescent Smokers; and*
- A3051073, *A Twelve-Week, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Dose-Ranging Study with Follow-Up Evaluating the Safety and Efficacy of Varenicline for Smoking Cessation in Healthy Adolescent Smokers.*

The Summary of Clinical Pharmacology Studies (SCP) for varenicline (CP 526,555) submitted with the initial Marketing Authorisation Application (MAA) in adults included a comprehensive evaluation of pharmacokinetics (PK) and pharmacodynamics (PD) of varenicline in healthy adult subjects who were smokers and non-smokers and also included Study A3051029 in adolescent subjects [original SCP].

Since the initial submission, a Type II Variation EMEA/H/C/000699/II-039 to update the product information with the results from clinical study A3051070 was submitted on 15Dec2011 (eCTD 0115). In

addition, the renewal SCP that was included in the MA Renewal, submitted on 18Dec2015 (eCTD 0180) also included a summary of the data from submitted seven additional studies, including Study A3051070 in adolescent subjects [renewal SCP].

For the convenience of reviewers, this SCP provides PK and PD information from all three varenicline studies in adolescent subjects, including Study A3051029, and Study A3051070 and A3051073. The new information in this Type II Variation submission is the population PK and exposure response (ER) analyses of varenicline in adolescent smokers including data from Study A3051073. The results of the three paediatric studies are generally consistent with those of previous studies in adults, and support the following conclusions:

- Varenicline in adolescent subjects exhibits linear PK following single or multiple dosing in adolescent smokers. In adolescent smokers, systemic exposure and renal clearance were comparable with those of an adult population. The median time to reach maximum concentrations (T_{max}) following a single dose is approximately 3-4 hours, the elimination half-life is 10.9 hours, and steady state is reached within ~4 days of repeat dosing.
- A population PK analysis in adolescent smokers showed that varenicline PK was adequately characterised by a 1-compartment model with first-order absorption and first-order elimination. Apparent clearance (CL/F) and volume of distribution (V/F) were estimated to be 12.5 L/hr and 231 L, respectively for the reference adolescent subject: a 70 kg, white male. CL/F and V/F increased with increasing body weight, consistent with the known allometric scaling in pediatrics. Varenicline PK in adolescent smokers, systemic exposure and oral clearance were generally comparable with those of an adult population.
- In Study A3051073, the observed range of varenicline exposure was consistent with that expected for each dose and body weight group from the results obtained in the single and multiple dose adolescent PK studies, supporting that varenicline dose and administration were appropriate.
- In Study A3051073, the Week 9-12 continuous abstinence rate (CAR) did not increase with increasing varenicline systemic exposure [ie, Area Under the Concentration-time Curve from 0-24 hours at Steady-State (AUC24)], supporting the negative findings for the primary endpoint from the overall study.
- In Study A3051073, nausea/vomiting incidence increased with increasing varenicline exposure; there was a statistically significant trend as a linear function of increasing AUC24 (p-value <0.001). In addition, the probability of nausea/vomiting incidence increased in females relative to males. The results were consistent with that observed in adult smokers.

Background and Overview

Varenicline is a selective nicotinic acetylcholine receptor (nAChR) partial agonist designed to have specific and potent binding at the $\alpha_4\beta_2$ receptor subtype, which mediates the behaviour reinforcing effects of nicotine while simultaneously preventing nicotine binding to these receptors. Because of its mixed agonist-antagonist properties, varenicline offers the therapeutic benefit of relieving symptoms of nicotine withdrawal and cigarette craving during abstinence while blocking the reinforcing effects of chronic nicotine. The approved varenicline dosing regimen for adults is 1 mg twice a day (BID) for 12 Weeks starting with a 1-week titration at the beginning of treatment.

These PK and PD of varenicline in adults, submitted with the initial MAA, are briefly summarised below for the convenience of the reviewer:

- Orally administered varenicline is virtually completely absorbed and is highly available systemically. Oral bioavailability is unaffected by food or time-of-day dosing.
- Varenicline exhibits linear PK following single or multiple dosing. The median Tmax following a single dose is ~3 hr, the elimination half-life is ~24 hr, and steady state is reached within ~4 days of repeat dosing.
- Protein binding of varenicline is low (≤20%) and independent of age and renal function.
- Varenicline is almost exclusively excreted unchanged in the urine (92%), primarily via glomerular filtration, with an additional component of active secretion via the human organic cation transport system. Varenicline does not undergo significant hepatic metabolism.
- Varenicline PK is unaffected by mild renal impairment. Systemic exposure (AUC) of varenicline increased 1.5-fold in subjects with moderate renal impairment and 2.1-fold in subjects with severe renal impairment.
- Varenicline PK is independent of race and sex, and is not changed in the elderly.
- No clinically relevant drug-drug interactions were observed when varenicline was co-administered with the narrow therapeutic index drugs digoxin or warfarin, the smoking cessation therapies bupropion (Zyban®), nicotine replacement therapy, or the renally secreted drugs cimetidine or metformin.
- In a population PK analysis conducted on pooled data from 1878 adult smokers, renal function (on systemic clearance) and body weight (on volume of distribution) were important factors contributing to inter individual variability in the PK of varenicline.
- In ER analyses involving ~2,000 adult smokers from 5 Phase 2/3 Studies, logistic regression results showed that the end-of-treatment abstinence rate increased as a linear function of increasing varenicline exposure at steady-state (AUC24), from 38% at 0.5 mg BID to 56% at 1 mg BID (vs. 22% for placebo). Baseline smoking status and age were predictive of smoking cessation, whereas race and sex showed little or no influence. Nausea/ vomiting incidence was sex-related (approximately 2-fold higher in females than males) and increased with varenicline exposure; at a dosage of 1 mg BID vs placebo, the predicted probability of nausea was 24 % vs. 7 % in male subjects and 40 % vs. 14 % in female subjects.

For varenicline Phase 1 studies in adolescent subjects, varenicline plasma concentration-time data were analysed by standard non-compartmental analysis (NCA) for A3051029 CSR and by a population PK analysis approach using nonlinear mixed effects modelling methodology for A3051070 CSR.

In this SCP, the population PK analysis was conducted using nonlinear mixed effects modelling methodology for combined varenicline concentration-time data from all three clinical studies in adolescent subjects (A3051029, A3051070, and A3051073). The ER analyses were conducted using a logistic regression model for data from Study A3051073.

Further details of population PK and ER analyses are provided in a separate report in Module 5 (PMAR-EQDD-A305-Other-502).

All plasma and urine samples in adolescent subjects were assayed for varenicline concentrations at Intertek (formerly Alta Analytical Laboratory, San Diego, CA, United States [US]) using validated analytical assays in compliance with Pfizer standard operating procedures. Bioanalytical reports for each of the studies can be found in the individual CSRs (A3051029 CSR, A3051070 CSR, and A3051073 CSR).

Summary of Results of Individual Studies in Healthy Adolescent Subjects

The information in this section was previously submitted: Study A3051029 was included in SCP with the initial MAA and Study A3051070 was included in Type II Variation EMEA/H/C/000699/II-039 (eCTD 0115) and the SCP with the renewal in 2015 (eCTD 0180). This information is included in this submission for the convenience of reviewers.

Pharmacokinetic Assessments in Single- and Multiple-Dose Studies in Healthy Adolescent Subjects

Two Phase 1 studies evaluated the PK of varenicline following administration of the oral immediate release formulation (**Table 2**). All subjects were healthy adolescent volunteers who were smokers. Brief summaries of the results in each study are provided below.

Table 2 Phase 1 Pharmacokinetic Studies of Varenicline in Healthy Adolescent Subjects

Study No. Objectives	Population (Age)	No. of Subjects[a]	Design	Dosage/Regimen/Comparator/ Duration
A3051029 SD PK in adolescents	HV smokers (12-17 years)	27 (22 varenicline, 5 placebo)	R, ISBSO, PC, PG	0.5 mg SD 1 mg SD Placebo SD
A3051070 MD PK in adolescents	HV Smokers (12-16 years)	72 (57 varenicline, 15 placebo)	R, DB, PC, PG, MD	BWT 30-55 kg: 0.5 mg QD, 0.5 mg BID[b] BWT >55 kg: 0.5 mg BID, 1 mg BID Placebo 14 days

BID=twice a day; BWT=body weight; DB=double blind; HV=healthy volunteer; ISBSO=investigator and subject blind, sponsor open; MD=multiple dose; No.=number; PC=placebo controlled; PG=parallel group; PK=pharmacokinetics; QD=once daily; R=randomized; SD=single dose.
a. Subjects randomised and received at least 1 dose of study drug.
b. The evening dose was to be administered approximately 10 hours after the morning dose.
Source: A3051029 CSR; A3051070 CSR

Pharmacokinetic Assessments in Single-Dose Study (A3051029)

Study A3051029. Phase 1, Randomized, Sponsor-Open, Investigator- and Subject-Blind, Parallel-Group, Placebo-Controlled Study to Evaluate the Single-Dose Pharmacokinetics, Safety, and Tolerability of Varenicline in Healthy Adolescent Smokers.

Dates of Conduct: 16 September 2004 to 05 December 2004

This study evaluated the PK, safety, and tolerability of single doses of 0.5 mg and 1 mg varenicline in 27 adolescent smokers (12-17 years of age, 14 male and 13 female). Exposure, as assessed by area under the concentration-time curve from time zero to infinity (AUC_{inf}) and maximum concentration (C_{max}), was approximately dose proportional between the 0.5 mg and 1 mg doses in adolescents. Mean plasma peak concentrations occurred within 3-4 hours after single-dose oral administration. Renal clearance of varenicline in the adolescent population using 48-hour urinary excretion data were 116 mL/min and 103 mL/min following administration of single oral dose of 0.5 mg and 1 mg, respectively. The mean elimination half-life was 10.9 hours for both doses of varenicline.

Pharmacokinetic Assessments in Multiple-Dose Study (A3051070)

Study A3051070. Phase 1, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Multiple-Dose Pharmacokinetics, Safety and Tolerability of Varenicline in Healthy Adolescent Smokers

Dates of Conduct: 23 May 2007 to 01 December 2007.

This study evaluated the multiple-dose PK, safety, and tolerability of varenicline in 72 healthy adolescent smokers aged 12 to 16 years, in which 57 subjects received varenicline. Subjects were enrolled into a low body weight (LBW) group (N = 29; 10 males and 19 females) and a high body weight (HBW) group (N = 28; 19 males and 9 females), defined as body weight (BWT) 30 to 55 kg and >55 kg, respectively. Subjects in each BWT group were randomised in a 2:2:1 ratio to one of two dosing regimens of varenicline or placebo for a treatment duration of 14 days. The varenicline doses were 0.5 mg QD or 0.5 mg BID in the LBW group and 0.5 mg BID or 1 mg BID in the HBW group. Dosing was titrated over 7 days for the 0.5 mg BID and 1 mg BID treatment groups (0.5 mg QD for 7 days for the former and 0.5 mg QD for 3 days, followed by 0.5 mg BID for 4 days for the latter). All doses were administered with food.

Sparse blood sampling for measurement of varenicline concentrations was included on Days 1, 8 and 14, as well as a single sample within 48 to 84 hours after the last dose of study drug, and a population PK approach was used to characterise the multiple-dose PK of varenicline in this adolescent population (A3051070 CSR Appendix 14). A 1-compartment model defined in terms of CL/F and V/F and a first-order absorption rate constant (k_a) was used to fit the data; CL/F and V/F estimates (95% CIs) for a typical 70-kg subject were 10.4 L/hr (9.2-11.5) and 215 L (204-238), respectively. Body weight described a large fraction of the total observed inter individual variability in V/F (64.3%), but had less influence on inter individual variability of CL/F (18.9%). The estimated covariate effects of BWT on CL/F and V/F were in good agreement with allometric scaling laws of biology. Varenicline exposure increased in a dose-proportional manner after multiple doses of varenicline. Predicted steady-state median (range) exposures (AUC24) in adolescents weighing >55 kg (HBW) were 95.7 (49.0 - 189) ng·hr/mL and 197 (123 - 367) ng·hr/mL for 0.5 mg BID and 1 mg BID, respectively. In adolescents of LBW, median exposures were 60.1 (44.4 - 102) ng·hr/mL and 126 (80.7 - 179) ng·hr/mL after administration of 0.5 mg QD and 0.5 mg BID, respectively.

Pharmacokinetic Characteristics

In adolescent subjects, as in adults, C_{max} and AUC_{inf} increased in a dose-proportional manner after a single dose of varenicline. Doubling the dose from 0.5 to 1.0 mg increased mean C_{max} and AUC_{inf} by 2.12- and 2.09-fold, respectively. PK parameters and associated summary statistics for 0.5 mg and 1 mg single oral doses of varenicline in adolescents are compared with those obtained in adult subjects in **Table 3**.

Table 3 Comparison of Mean (SD) PK Parameters after Single Doses of Varenicline in Adolescent (A3051029) and Adult Smokers (A3051026)

	N	T_{max}[a] (h)	C_{max} (ng/mL)	AUC_{inf} (ng·h/mL)	t1/2 (h)	CLr (mL/min)
0.5 mg						
12-17 years old	10	3.00 [2.00-4.00]	3.01 (0.46)	50.6 (13.3)	10.9 (3.1)	116 (42.8)
18-55 years old	12	3.00 [1.00-4.00]	2.37 (0.459)	57.9 (10.0)[b]	20.1 (3.1)[b]	NA
1 mg						
12-17 years old	12	4.00 [2.00-4.00]	6.38 (1.50)	106 (24.3)	10.9 (1.93)	103 (39.8)
18-55 years old	12	2.50 [1.00-4.00]	4.82 (0.976)	104 (29.0)[c]	18.4 (3.65)[c]	NA

CLr=Renal clearance; C_{max}= Maximum plasma concentration; NA=not available; SD=Standard deviation; T_{max}= Time to C_{max}; t1/2 =Elimination half-life

[a] T_{max} values presented as median [range] [b] N=5 [c] N=9

Source: A3051029 CSR Tables 13.5.2.1-6; A3051026 CSR Table 5.2.1.

Varenicline systemic exposure in adolescents, as assessed by AUC_{inf}, was comparable to that in adults. Higher plasma varenicline concentrations during the first 24 hours and a shorter elimination half-life were observed in adolescents compared with adults. Since renal clearance was comparable between the 2 doses, and consistent with that seen in an adult population (117.3 mL/min in Initial MAA, SCP Section 2.7.2.3.1), the observed shorter half-life in adolescent subjects was likely due to decreased volume of distribution of varenicline in adolescents.

Population Pharmacokinetic and Exposure-Response Analyses

This section describes the pharmacometric analyses conducted to characterize the population pharmacokinetics of varenicline and to explore the relationships between varenicline systemic exposure and measures of efficacy and tolerability in adolescent smokers. Detailed methods and results of these analyses are provided in a separate report in Module 5 (PMAR-EQDD-A305-Other-502).

The population PK analysis included combined varenicline concentration-time data in adolescent smokers from a total of 3 clinical studies (two Phase 1 studies [A3051029 and A3051070] and one Phase 4 study [A3051073]). The ER analyses used data from Study A3051073.

Key findings of these analyses include:

- Varenicline PK in adolescent subjects was adequately characterised by a 1-compartment model with first-order absorption and first-order elimination.
- Apparent clearance and volume of distribution were estimated to be 12.5 L/hr and 231 L, respectively for the reference adolescent subject: a 70 kg, white male.
- Covariates that were included on varenicline CL/F were baseline body weight, sex, and race. Apparent clearance increased with increasing body weight. In addition, CL/F decreased in females and the effects of race on CL/F were not significant.
- Covariates that were included on varenicline V/F were baseline body weight, sex, and race. Apparent volume of distribution increased with increasing body weight. In addition, V/F decreased in females, subjects with black race, and subjects with other race.
- No varenicline ER relationship was demonstrated for the probability of Continuous Abstinence Rate (CAR) and Point Prevalence of Smoking Abstinence (PP) across the AUC24 range from study A3051073.
- A significant varenicline ER relationship was demonstrated for the probability of nausea/vomiting incidence across the AUC24 range from Study A3051073. In addition, the probability of nausea/vomiting incidence increased by 86% in females relative to males.

Rationale for Dose Selection in Study A3051073

Varenicline doses in Study A3051073 were selected based on the safety, tolerability, PK, and efficacy data from the clinical trials in adult smokers and the safety, tolerability, and PK data from Studies A3051029 and A3051070 in adolescent smokers.

Study A3051073 was a Phase 4, randomized, double-blind, placebo-controlled, multicentre study to evaluate the efficacy, safety, tolerability, and pharmacokinetics of two doses of varenicline (1 mg BID and 0.5 mg BID) in nicotine-dependent adolescent smokers (12-19 years) in conjunction with age appropriate cessation counselling. Since varenicline exposure was related to body weight in Phase 1 studies, subjects with a body weight ≤55 kg had their varenicline dose reduced by half (those randomized to 1 mg BID received 0.5 mg BID and those randomized to 0.5 mg BID received 0.5 mg QD). The treatment period was 12 weeks, initiated with dose titration over the first two weeks, and subjects' smoking status was followed for additional 40 weeks.

Results of the varenicline Phase 2-3 clinical trial program, which supported the initial approval in adults, showed that varenicline is highly efficacious for smoking cessation compared with placebo and is well tolerated in smokers 18 years of age and older. Exposure-response information from 5 Phase 2/3 Studies further indicated that higher systemic exposure to varenicline was associated with greater probability of 4-week smoking cessation. Since adolescents may have a different risk/benefit profile from adults, Study A3051073 investigated both 1 mg BID recommended in adults and a lower dose of varenicline (0.5 mg BID) compared with placebo in the adolescent smokers (Paediatric Written Request by the US Food and Drug Administration).

In Study A3051029, varenicline exposure (AUC_{inf}) was similar to that in adult smokers, and there was a trend for higher C_{max} values and a shorter half-life, suggestive of a smaller volume of distribution (A3051029 CSR). Characterisation of the multiple-dose PK in adolescent smokers 12 to 16 years old in Study A3051070 confirmed these results; CL/F estimate in a typical subject weighing 70 kg was 10.4 L/hr, similar to that in adults (10.4 L/hr), whereas the estimate of V/F (215 L) was lower than the estimate (337 L) in adults. Body weight was estimated to be an important predictor of the inter-individual variability in V/F, with less impact on CL/F. Predicted median steady-state AUC_{24} in adolescents weighing > 55 kg was consistent with that previously reported for adult smokers at an equivalent daily dose, and exposure was higher in adolescents of smaller body size. Adjusting the dose to half in adolescents weighing ≤ 55 kg in Study A3051070 resulted in predicted exposures at the lower end of the range expected in adults.

Since Study A3051070 demonstrated that varenicline exposure was adequately adjusted by halving the total daily dose of varenicline in subjects weighing ≤55 kg, adolescent subjects weighing ≤55 kg in Study A3051073 also had their randomized dose reduced by half. Those randomized to 1 mg BID received 0.5 mg BID and those randomized to 0.5 mg BID received 0.5 mg QD in Study A3051073. This dosing regimen was expected to provide efficacious and tolerable exposures of varenicline in adolescent smokers based on adult data.

Completion of Study A3051073 provided no new information relevant to dosing recommendations in adolescent smokers given the negative efficacy results.

Population Pharmacokinetic Analyses

Subject Characteristics and Disposition: The studies and samples included in the population PK analysis are summarized in **Table 4**. A total of 1097 plasma varenicline concentrations from 218 subjects were used in the population PK analysis, including 284 concentrations from 139 subjects in Study A3051073.

Table 4 Studies and Samples Included in the Population Pharmacokinetic Analysis

Study No.	Population	PK Sampling	Dosage / Regimen	No. of PK Samples (No. of subjects)
A3051029	HV smokers (12-17 years)	0 hour (predose), and 1, 2, 3, 4, 8, 12, 24, and 48 hours after morning dosing on Day 1	0.5 mg SD 1 mg SD	171 (22)
A3051070	HV Smokers (12-16 years)	0 hour (predose) and at the following times: Day 1 at 1.5, 3, 6, and 10 hours post morning dose; Day 8 at 0 hour and 3 hours post morning dose; Day 14 at 0 hour and 1.5, 3, 6, and 10 hours post morning dose, and within 48 to 84 hours after the last dose of study medication	0.5 mg QD LBW 0.5 mg BID LBW 0.5 mg BID HBW 1 mg BID HBW for 14 days	642 (57)
A3051073	Nicotine-dependent adolescent smokers (12-19 years)	One random time at Weeks 3, 6, and 12 or at an early termination visit	0.5 mg QD LBW 0.5 mg BID LBW 0.5 mg BID HBW 1 mg BID HBW for 12 weeks	284 (139)

BID=Twice a day; HBW=High body weight (>55 kg); HV=Healthy volunteer; LBW=Low body weight (≤55 kg); No.=number; PK=Pharmacokinetics ; QD=Once daily; SD=Single dose
Source: A3051029 CSR; A3051070 CSR; PMAR-EQDD-A305-Other-502 Table 3

Table 5 provides summary statistics of the baseline demographic covariates in the population PK analysis dataset. Approximately 99% of adolescent subjects had normal renal function (CRCL >80 mL/min). For the analysis, subjects who reported as Asian and other race were grouped together (defined as “other” for the analysis) since the densely sampled Phase 1 studies (i.e., A3051029 and A3051070) consisted of only 1 subject with Asian race vs 18 subjects with other race.

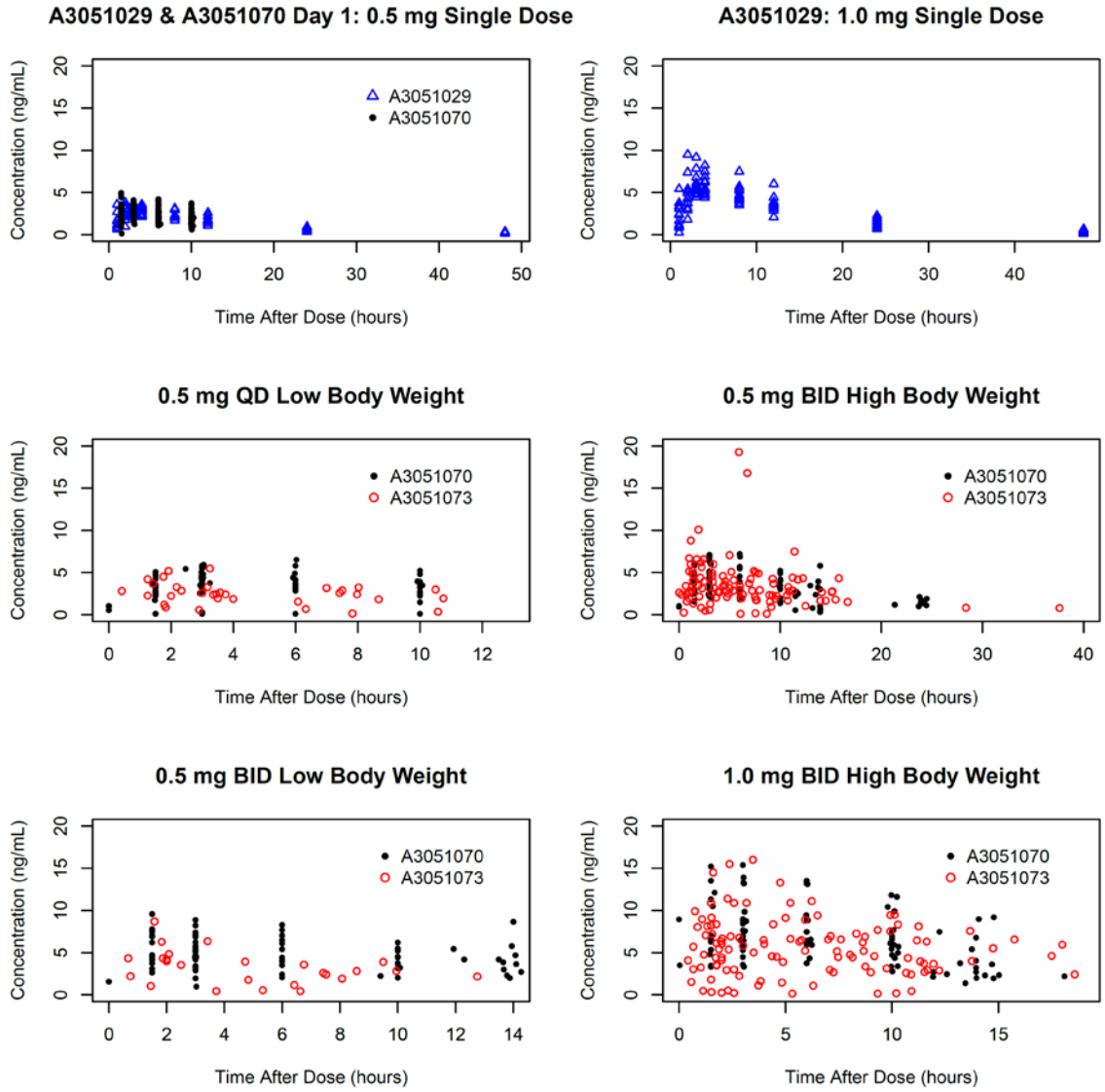
Table 5 Summary of Baseline Demographic Covariates for Population PK Analysis

Covariate	Statistic	A3051029	A3051070	A3051073	Total
BWT (kg)	N	22	57	139	218
	Mean (SD)	65.5 (12.9)	59.9 (14.2)	65.3 (13.1)	63.9 (13.5)
	Median	66.5	55.0	62.7	62.1
	(Min,Max)	(35.0,121)	(35.0,121)	(35.2,110)	(35.0,121)
Age (year)	N	22	57	139	218
	Mean (SD)	14.7 (1.70)	14.8 (1.15)	15.8 (1.81)	15.4 (1.71)
	Median	15.0	15.0	16.0	16.0
	(Min,Max)	(12.0,17.0)	(12.0,16.0)	(12.0,20.0*)	(12.0,20.0)
CRCL (mL/min)	N	22	57	139	218
	Mean (SD)	115 (20.7)	132 (29.6)	129 (32.7)	128 (31.1)
	Median	112	129	123	124
	(Min,Max)	(85.3,163)	(51.7,222)	(53.2,257)	(51.7,257)
Sex					
Male	N (%)	13 (59.1)	29 (50.9)	94 (67.6)	136 (62.4)
Female	N (%)	9 (40.9)	28 (49.1)	45 (32.4)	82 (37.6)
Race					
White	N (%)	3 (13.6)	37 (64.9)	102 (73.4)	142 (65.1)
Black	N (%)	19 (86.4)	1 (1.75)	11 (7.91)	31 (14.2)
Asian	N (%)	0 (0)	1 (1.75)	25 (18.0)	26 (11.9)
Other	N (%)	0 (0)	18 (31.6)	1 (0.719)	19 (8.72)

*1 subject was screened 2 days after the 20th birthday in violation of the protocol. Abbreviations: BWT=Baseline body weight, CRCL=Baseline creatinine clearance, Max=Maximum, Min=Minimum, N=Number of subjects, SD=Standard deviation, Source: PMAR-EQDD-A305-Other-502 Table 4.

The observed varenicline concentration-time profiles are shown in **Figure 1**. In Study A3051073, the observed range of varenicline exposure was consistent with that expected for each dose and body weight group from the results obtained in Study A3051070.

Figure 1 Concentration-Time Profiles for Studies A3051029, A3051070, and A3051073



Source: PMAR-EQDD-A305-Other-502 Figure 2
Abbreviations: BID=Twice a day; QD=Once-daily.

Final Pharmacokinetic Model: An one-compartment model with first-order absorption and elimination adequately described the plasma concentration-time profile of varenicline in adolescent smokers. This model was parameterized in terms of CL/F, V/F and k_a.

For covariate testing, BWT, race, and sex were added on CL/F and V/F using the FME procedure. Since BWT and CRCL were correlated and most adolescents were expected to have normal renal function, CRCL was not included as a covariate on CL/F. Additionally, since BWT and age were correlated; age was not included as a covariate on CL/F and V/F. Equations below describe the incorporation of covariate effects into the final model:

$$CL/F = \left[\theta_1 \cdot \left(\frac{BWT}{70}\right)^{\theta_4} \cdot \theta_6^{RACE2} \cdot \theta_7^{RACE3} \cdot \theta_8^{NSEX}\right] \cdot e^{\eta_{1,i}}$$

$$V/F = \left[\theta_2 \cdot \left(\frac{BWT}{70}\right)^{\theta_5} \cdot \theta_9^{RACE2} \cdot \theta_{10}^{RACE3} \cdot \theta_{11}^{NSEX}\right] \cdot e^{\eta_{2,i}}$$

Where θ represents fixed effect parameters, and Empirical Bayes prediction of the inter individual random effect (η) represents a subject-specific random effect. The continuous covariate of baseline body weight was represented by BWT. Categorical covariates were categorised in order to create indicator variables that equal one if the relevant condition is true and zero otherwise. These indicator variables included female sex (where NSEX describes male=0 and female=1), black (RACE2), and other (RACE3).

The parameter estimates for the final model are listed in **Table 6**.

Table 6 Parameter Estimates (RSE) and Bootstrap Medians (95% CI) for the Final Model

Parameter (unit)	Estimate	RSE(%)	Median (95% CI)
CL/F (L/hr) (θ1)	12.5	5.06	12.4 (11.3, 13.9)
Effect of body weight (θ4)	0.567	23.3	0.583 (0.317, 0.904)
Effect of $race_{black}$ (θ6)	1.01	8.59	1.01 (0.840, 1.22)
Effect of $race_{other}$ (θ7)	1.12	6.57	1.12 (0.982, 1.31)
Effect of sex_{female} (θ8)	0.850	5.87	0.849 (0.756, 0.953)
V/F (L) (θ2)	231	5.02	230 (199, 256)
Effect of body weight (θ5)	0.872	10.3	0.864 (0.638, 1.05)
Effect of $race_{black}$ (θ9)	0.757	5.46	0.754 (0.677, 0.844)
Effect of $race_{other}$ (θ10)	0.854	4.78	0.858 (0.775, 0.946)
Effect of sex_{female} (θ11)	0.861	4.02	0.858 (0.793, 0.934)
ka (θ3) (hr−1)	0.860	12.3	0.844 (0.668, 1.12)
ω2-CL/F	0.102	26.3	0.0988 (0.0553, 0.170)
ω2-V/F	0.0182	42.6	0.0169 (0.00370, 0.0375)
ω2-k_a	0.174	48.5	0.182 (0.0483, 0.389)
cov*CL/F·V/F*	-0.00162	895	-0.000885 (-0.0369, 0.0317)
cov*CL/F·*k_a	-0.0582	71.0	-0.0541 (-0.151, 0.0306)
cov*V/F·*k_a	0.0307	73.3	0.0319 (-0.00836, 0.0802)
σ^2_{add} Phase 1	0.0577 (0.240)*a*	51.3	0.0579 (0.00245, 0.205)
σ^2_{prop} Phase 1	0.0847	17.2	0.0810 (0.0455, 0.114)
σ^2_{add} Phase 4	0.336 (0.580)*a*	71.4	0.338 (0.0912, 0.857)
σ^2_{prop} Phase 4	0.187	14.5	0.183 (0.126, 0.230)

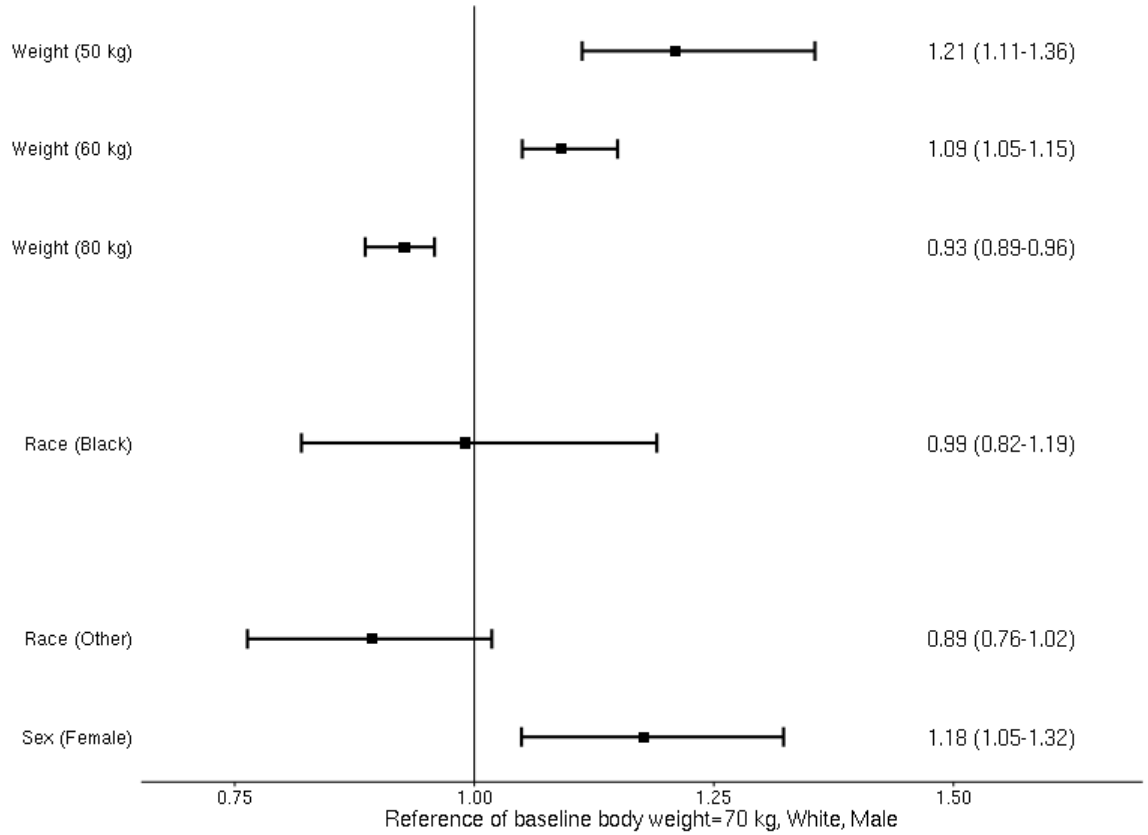
*a*Standard deviations are shown in parentheses; Point estimates and relative standard errors (RSE) of the estimates were estimated using NONMEM; Median and 95% confidence intervals of the estimates were obtained from nonparametric bootstrap estimates (N=1400, 53 runs with minimization terminated and 284 runs with estimates near a boundary were skipped when calculating the bootstrap results)
Abbreviations: add=Additive; CL/F= Apparent clearance; CI=Confidence interval; cov=Covariance; ka= First-order aabsorption rate constant; prop=Proportional; RSE= Relative standard error; V/F= Apparent volume of distribution;
Source: PMAR-EQDD-A305-Other-502 Table 8.

For a reference adolescent smoker (a white male, 16 years-old, weighing 70 kg), CL/F and V/F of varenicline were estimated to be 12.5 L/hr and 231 L, respectively. All fixed effect parameters were estimated with reasonable precision (relative standard error [RSE] was <25%). Inter-individual variance for CL/F, V/F, and k_a (expressed as percent CV) was reduced from the base model (35%, 29%, and 47%, respectively) to the final model (32%, 13%, and 44%, respectively) with the inclusion of the covariate effects (i.e., BWT, race, and sex on both CL/F and V/F). Residual variability was lower in the Phase 1 studies than the Phase 4 study. This was expected, as measurement error of dosing information can often be larger in sparsely sampled out-patient studies with non-witnessed dosing relative to in-patient Phase 1 studies.

Covariate effects on AUC_{24} relative to the reference adolescent subject are illustrated in **Figure 2**. AUC_{24} increased with decreasing BWT. For example, subjects with a BWT of 60 kg and 50 kg would have 9% and 21% greater exposure, respectively, relative to a reference adolescent subject with a BWT of 70 kg. Additionally, the effect of female sex on AUC_{24} was significant (based upon the confidence intervals [CIs] from the bootstrap), but the magnitude of the effect was relatively small (i.e., 18%). The effects of black race and other race on AUC_{24} were not significant (based upon the CIs from the bootstrap).

In addition, the effects of BWT, black race, other race, and female sex were significant on V/F. Over the range of 46.6 to 89.8 kg (corresponding to the 5th and 95th percentiles of the observed weights), V/F increased from 162 to 287 L representing a <30% change relative to the reference subject weighing 70 kg. Black race, other race, and female sex were found to decrease V/F by approximately 24%, 15%, and 14% relative to a white male, respectively.

Figure 2 Covariate Effects on Area Under the Concentration-Time Curve from Zero to 24 Hours (95% CI)



Source PMAR-EQDD-A305-Other-502 Figure 7
Abbreviation: CI=Confidence Interval; The 95% CI of the ratio was generated from 1400 non-parametric bootstrapped sets of population parameter values using the final population PK model (where 50 runs with minimization terminated and 241 runs with estimates near a boundary were skipped when calculating the bootstrap results). Solid squares represent the ratio of the typical predicted AUC24 relative to the reference adolescent subject of a white male weighing 70 kg. Thus, a value of one (1.0) represents unity or a null covariate effect. The error bars represent the 95% CI of the ratio.

One site in Study A3051073 was terminated due to concerns regarding International Conference on Harmonization Good Clinical Practice non-compliance. The impact of including the data of seven subjects from site 1097 was explored as a sensitivity analysis by re-estimating the final model that excluded the data from the subjects at site 1097. This was consistent with the A3051073 study statistical analysis plan, which provided for a sensitivity analysis related to the site 1097 data (A3051073 CSR). When these subjects were excluded, the changes in the key fixed parameters (i.e., CL/F or V/F) were less than 3% compared to the parameter estimates from the final model including these subjects. Therefore, the subjects from site 1097 were not determined to be influential and were retained in the analysis.

Table 7 provides a summary of predicted AUC24 of varenicline in adolescent smokers from Study A3051073 using the final population PK analysis model and estimates.

Table 7 Predicted Varenicline Steady State Exposure (AUC24) for Adolescent Smokers in A3051073

Treatment regimen	Number of Subjects Contributing to Steady State AUC24	AUC24 (ng*hr/mL) Median (5th, 95th percentiles)
0.5 mg QD LBW	14	50.2 (34.0,57.9)
0.5 mg BID HBW	50	79.5 (58.3,117)
0.5 mg BID LBW	14	84.0 (71.2,110)
1 mg BID HBW	61	153 (113,233)

Abbreviations: AUC24=Area under the concentration-time curve from zero to 24 hours, BID=Twice a day, HBW=High body weight (>55 kg), LBW=Low body weight (≤55 kg), QD=Once-daily
Source: PMAR-EQDD-A305-Other-502 Table 9.

Exposure-Response Analyses

Efficacy and tolerability data along with the covariate information were pooled together and merged with the individual varenicline AUC_{24} values predicted from the final population PK model and parameter estimates for Study A3051073. The daily AUC_{24} was obtained from the empirical Bayes' predictions of each subject's CL/F value and total daily dose. For subjects in the placebo group, AUC24 values were set to zero.

The following endpoints were included for ER analyses:

- The CAR from Week 9 through Week 12 was defined as the proportion of subjects who remained abstinent from Week 9 to Week 12 (confirmed by urine cotinine testing);
- The CAR from Week 9 through Week 52 was defined as the proportion of subjects who remained abstinent from Week 9 to Week 52 (confirmed by urine cotinine testing);
- The Weekly PP at Weeks 12 and 52 was defined as the proportion of subjects abstaining from smoking during the preceding 7 days;
- The reduction in number of cigarettes smoked at Weeks 12 and 52 was calculated at each visit by subtracting the reported average number of cigarettes smoked per day in the past 7 days at each visit from the average number of cigarettes smoked per day in the past 7 days reported at the baseline visit;
- The incidence of nausea/vomiting was defined as treatment-emergent adverse events (AEs) that began on or after the first day of study medication and until the last dose of study medication.

Each endpoint was a dichotomous categorical variable representing a successful quit (1 = yes, 0 = no) or the occurrence of an AE (nausea/vomiting). The ER data were viewed as a probabilistic outcome and analysed using a logistic regression model.

The Weeks 9-12 CAR, Weeks 9-52 CAR, and nausea/vomiting incidence ER analysis data files consisted of 238 observations from 238 subjects. The Week 12 7-day PP and Week 52 7-day PP ER analysis data files consisted of 185 and 158 observations from 185 and 158 subjects, respectively. **Table 8** provides summary statistics of the baseline demographic covariates from the final ER analysis data file for Weeks 9-12 CAR, Weeks 9-52 CAR, and nausea/vomiting incidence endpoints. For consistency with the population PK analysis, subjects with Asian and other race were grouped together for the ER analyses.

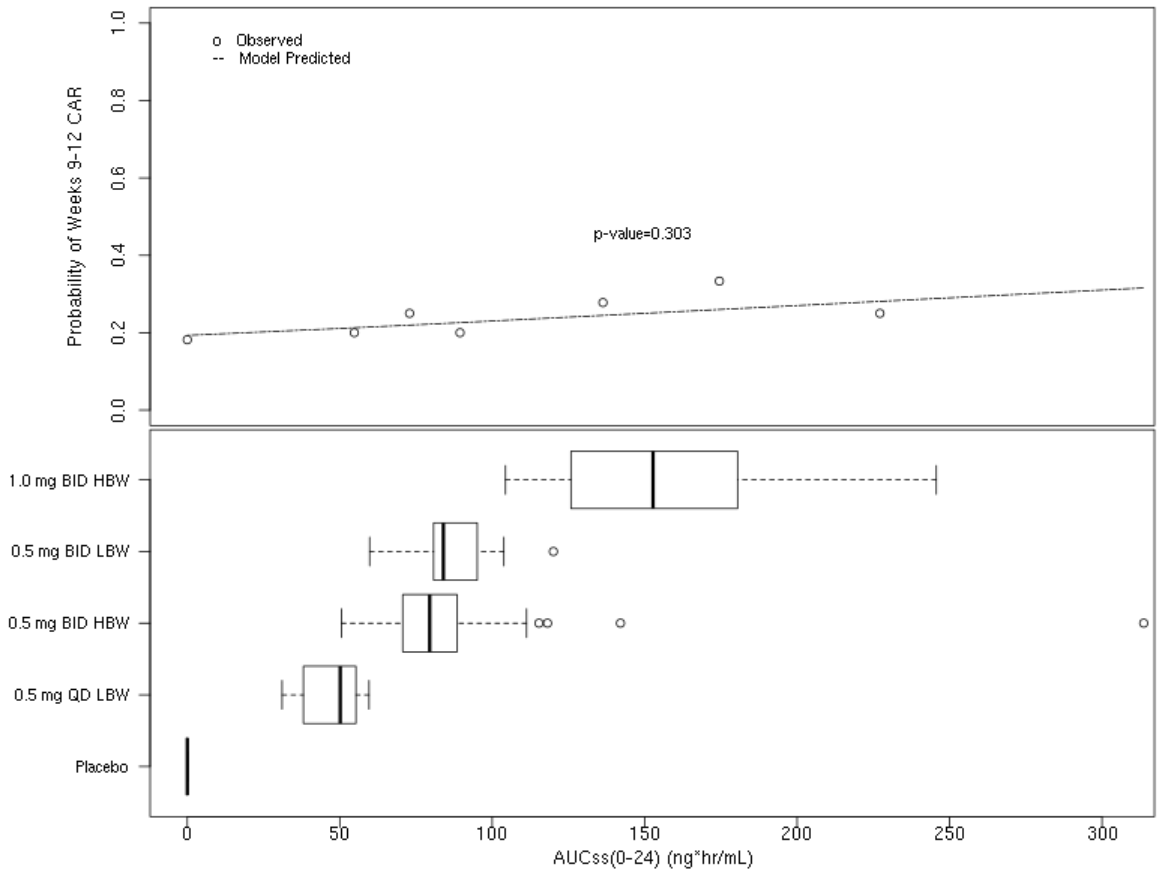
Table 8 Summary of Baseline Demographic Covariates in A3051073 for ER Analyses for Efficacy and Tolerability

Covariates	Statistic	Total
Age (years)	N	238
	Mean (SD)	15.8 (1.81)
	Median	16.0
	(Min, Max)	(12.0, 20.0)
Sex		
Male	N (%)	157 (66.0)
Female	N (%)	81 (34.0)
Race		
White	N (%)	176 (73.9)
Black	N (%)	16 (6.72)
Asian	N (%)	44 (18.5)
Other	N (%)	2 (0.840)
FSQ1 (time to the first cigarette)		
3 (<5 minutes)	N (%)	98 (41.2)
2 (6-30 minutes)	N (%)	96 (40.3)
1 (31-60 minutes)	N (%)	39 (16.4)
0 (>60 minutes)	N (%)	5 (2.10)

Abbreviations: FSQ1=Fagerström score question 1; Max=Maximum; Min=Minimum; N=Number of subjects; SD=Standard deviation
Source: PMAR-EQDD-A305-Other-502 Table 5.

The result of the logistic regression analysis for Weeks 9-12 CAR is shown in **Figure 3**. There was no statistically significant trend (p-value for slope estimate was 0.303) and no further model development was performed for Weeks 9-12 CAR ER analysis.

Figure 3 Varenicline ER Relationship for Continuous Abstinence Rate (CAR) Weeks 9-12 in Adolescent Smokers in A3051073

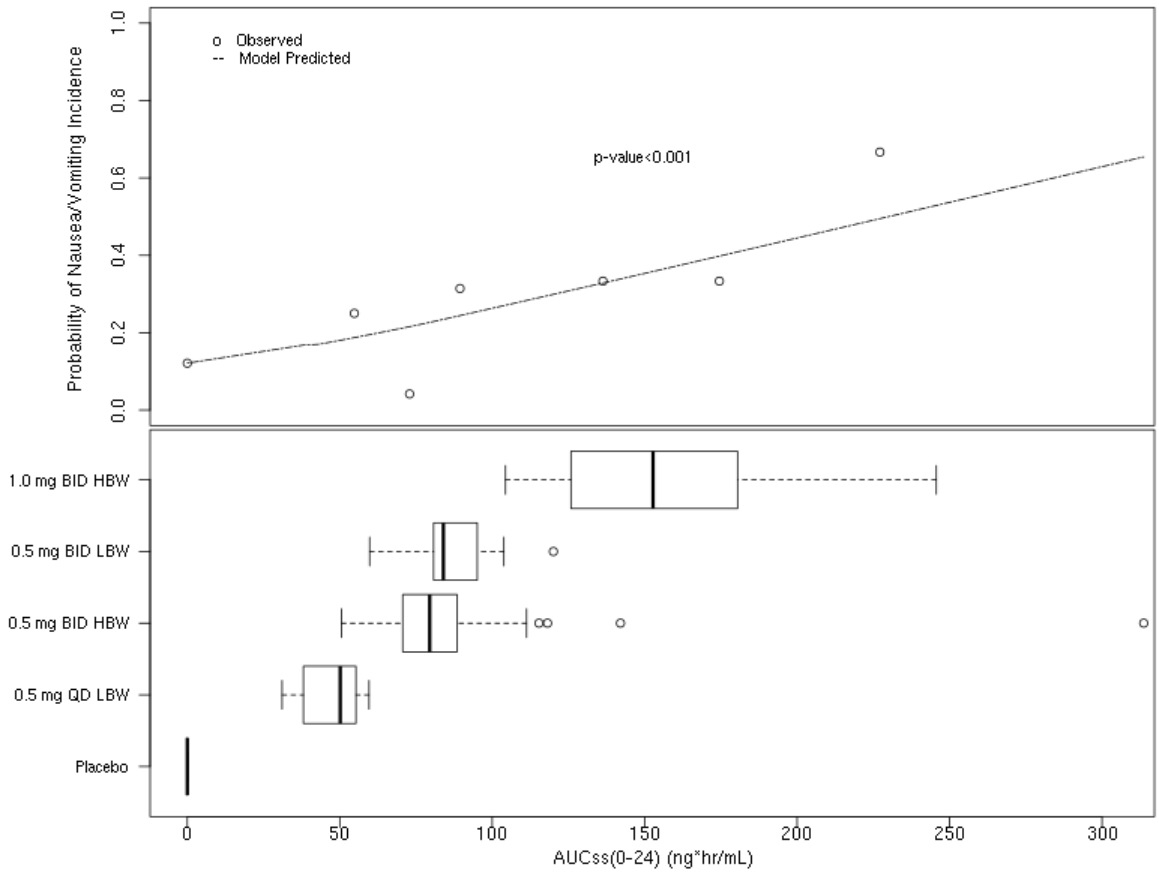


Source: PMAR-EQDD-A305-Other-502 Figure 9
Top: Open circles indicate the observed probability in each of the six AUC bins. The dotted line represents the predicted probability of quit using the base intercept model with linear AUC. Bottom: The medians are the black lines in the box while the box edges on the left and the right are the 25th and 75th percentiles, respectively. The whiskers extend up to 1.5 times the interquartile range.
Abbreviations: BID=Twice a day, CAR=Continuous abstinence rate, ER=Exposure-Response; HBW=High Body Weight (>55 kg), LBW=Low Body Weight (≤55 kg), QD=Once-daily.

Similarly, there was no relationship between the other efficacy endpoints (Weeks 9-52 CAR, PP at Weeks 12 and 52, and the reduction in number of cigarettes smoked at Weeks 12 and 52) and varenicline exposure, and thus no further model development was performed for these endpoints. In addition, a dose-response analysis was also explored for the Weeks 9-12 CAR endpoint. This allowed for an investigation of a potential trend when subjects without a reported AUC_{24} from the population PK analysis were included in the data file. This dose-response analysis showed no statistically significant trend (p-value for slope estimate was 0.494), consistent with the ER analysis using AUC_{24}.

The results of the logistic regression analysis for nausea incidence are shown in **Figure 4**. The addition of varenicline steady-state exposure (AUC24) as a linear function resulted in an improved goodness of fit based on the objective function value and demonstrated a statistically significant trend (p-value for slope estimate was <0.001).

Figure 4 Varenicline ER Relationship for Nausea/Vomiting Incidence in Adolescent Smokers in A3051073



Source: PMAR-EQDD-A305-Other-502 Figure 14
Top: Open circles indicate the observed probability in each of the six AUC bins. The dotted line represents the predicted probability of nausea/vomiting using the base intercept model with linear AUC. Bottom: The medians are the black lines in the box while the box edges on the left and the right are the 25th and 75th percentiles, respectively. The whiskers extend up to 1.5 times the interquartile range.
Abbreviations: BID=Twice a day, ER=Exposure-Response, HBW=High Body Weight (>55 kg), LBW=Low Body Weight (≤55 kg), QD=Once-daily.

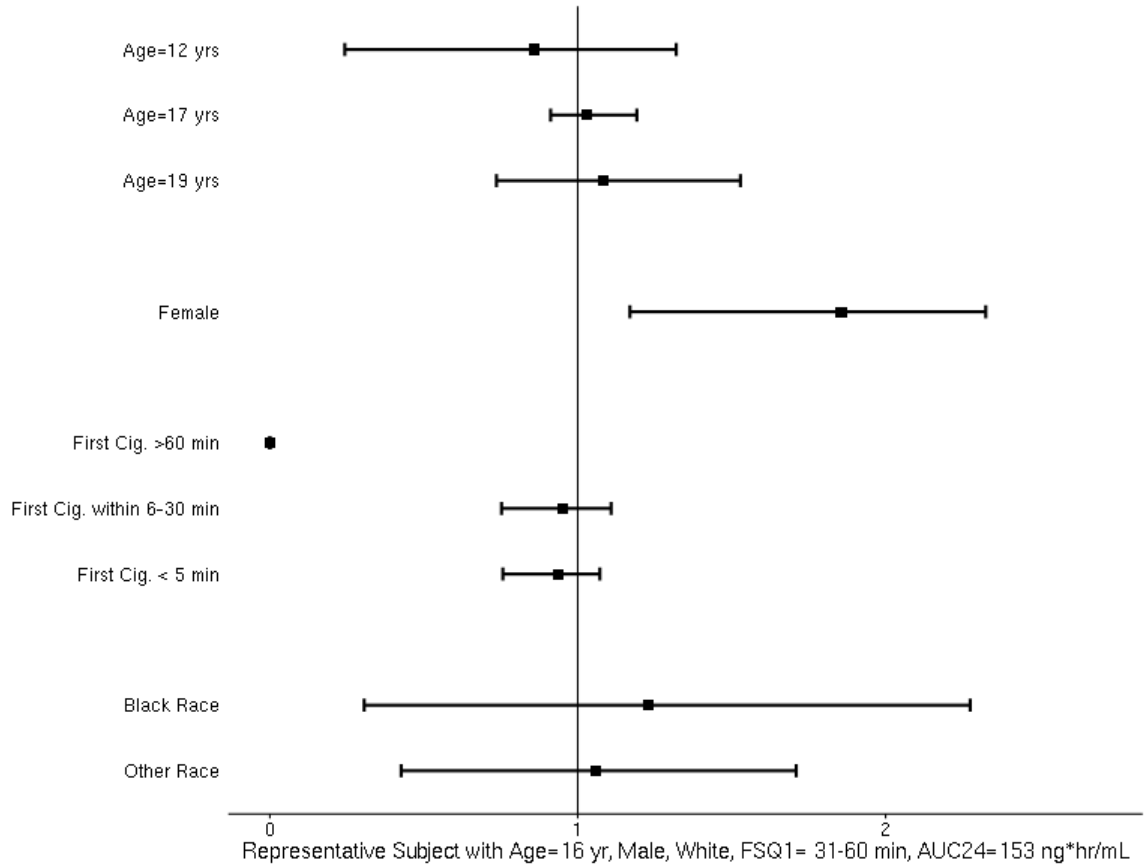
Further model development was performed including covariate testing. Covariate parameters including Fagerström score question 1 (FSQ1) ("How soon after you wake up do you smoke your first cigarette?"), age, sex, and race were added to the base intercept model with AUC24 as a linear function using the FME procedure and was considered a final model. The equation below describes the incorporation of covariate effects in the final model:

$$\lambda_i = \theta_1 \cdot \theta_3^{FSQ1(1)} \cdot \theta_4^{FSQ1(2)} \cdot \theta_5^{FSQ1(3)} \cdot (AGE/16)^{\theta_6} \cdot \theta_7^{NSEX} \cdot \theta_8^{RACE2} \cdot \theta_9^{RACE3} + \theta_2 \cdot AUC_{24}$$

Where θ represents fixed effect parameters and AGE is a continuous covariate. Categorical covariates were categorised in order to create indicator variables that equal one if the relevant condition is true and zero otherwise. These indicator variables included time to first cigarette between 31-60 min [FSQ1(1)], time to first cigarette between 6-30 min [FSQ1(2)], time to first cigarette less than 5 min [FSQ1(3)], female sex (where NSEX describes male=0 and female=1), black (RACE2), and other (RACE3). The reference adolescent subject was defined as a 16-year-old white male that smokes their first cigarette greater than 60 minutes after waking up in the morning.

The final model showed that the nausea/vomiting incidence increased with increasing AUC_{24}. For a 16 year-old white male who smokes the first cigarette between 31-60 minutes after waking up in the morning, the probability of nausea/vomiting incidence increased to 13%, 17%, 28%, and 43% at a varenicline AUC_{24} of 50, 80, 150, and 225 ng*hr/mL, compared to 9% with placebo, respectively.

Figure 5 Covariate Effects on Nausea/Vomiting Incidence (95% CI)



Source PMAR-EQDD-A305-Other-502 Figure 15
The 95% CI of the ratio was generated from 2800 non-parametric bootstrapped sets of population parameter values using the final nausea/vomiting incidence model (where 754 runs with minimization terminated were skipped when calculating the bootstrap results). Solid squares represent the point estimate for the covariate effect relative to the representative subject. The error bars represent the 95% CI of the ratio. Abbreviations: AUC24=Area under the concentration-time curve from zero to 24 hours; cig= cigarette; FSQ1=Fagerström score question 1; yr=years.

As shown in **Figure 5**, the covariate effects of age, FSQ1: first cigarette within 6-30 min, FSQ1: first cigarette<5 min, and race were not significant (based upon the CIs from the bootstrap and relative to the reference adolescent subject of a 16 year-old white male that smokes their first cigarette between 31-60 minutes after waking up in the morning and has a varenicline steady state exposure of 153 ng*hr/mL). The probability of nausea/vomiting incidence was approximately zero for FSQ1: first cigarette >60 min (relative to the reference subject) as the number of subjects in this category was very small (five subjects as shown in **Table 8**). The point estimate and the bootstrapped 95% CIs for the sex effect on the probability relative to the reference subject demonstrated a significant increase of approximately 86% in nausea/vomiting incidence for female smokers. This was consistent with that observed in adult smokers as nausea/vomiting incidence was approximately 2-fold higher in adult females than adult males.

MAH's overall Summary and Conclusions on the Clinical Pharmacology

The PK data of varenicline in adolescent smokers from Studies A3051029, A3051070, and A3051073 showed generally consistent results with those of previous studies in adults. Varenicline exhibits linear PK, and systemic exposure and renal clearance were generally comparable with those of an adult population. The population PK analysis showed that CL/F and V/F estimates of varenicline were 12.5 L/hr and 231 L, respectively for a reference 70-kg male adolescent smoker. The CL/F and V/F estimates in adolescent smokers were approximately 20% higher and 31% lower than the estimates in adults. Considering that 20% higher CL/F translates into ~17% lower AUC24, this difference is not considered clinically meaningful. Decreases in V/F would result in an increase in C_{max}, but would not impact AUC_{24}. As efficacy and safety of varenicline was driven by AUC in adult smokers, the changes in V/F are not considered clinically relevant. The half-life in adolescent smokers was shorter than ~24 hours in adults. Since the renal clearance was comparable between both 0.5 mg and 1 mg single doses in Study A3051029 and was consistent with that seen in an adult population, the more rapid decline in the plasma varenicline concentrations was a result of reduced V/F after oral administration of varenicline in adolescents. The reason for the observed difference in distribution properties between adolescents and adults is unclear, although it may be related to a different distribution pattern of lean tissue and fat mass. This difference is not considered significant, as the overall exposure was comparable to that in adults when dosed twice daily.

Study A3051073 randomized adolescent smokers to the recommended adult dose of 1 mg BID and a lower dose of 0.5 mg BID, with each of these doses adjusted to half in subjects ≤55 kg. The observed range of exposure in Study A3051073 was consistent with that expected for each dose and body weight group from the results obtained in adolescent PK studies, supporting that varenicline dose and administration were appropriate in the study. In Study A3051073, the Week 9-12 CAR did not increase with increasing varenicline exposure as the logistic regression analyses for efficacy showed no significant relationship with AUC_{24}, supporting the negative findings for the primary endpoint from the overall study. Nausea/vomiting incidence, however, increased linearly with increasing varenicline exposure; there was a statistically significant trend with the addition of AUC24 as a linear function (p-value <0.001). The nausea/vomiting might be attributed to its pharmacological activity on nAChRs at the central and peripheral levels. The result was consistent with that observed for nausea/vomiting in adult smokers.

In summary, the results from Studies A3051029, A3051070, and A3051073 support the following conclusions:

- Varenicline in adolescent subjects exhibits linear PK following single or multiple dosing in adolescent smokers. In adolescent smokers, systemic exposure and renal clearance were comparable with those of an adult population. The median time to reach maximum concentrations following a single dose is approximately 3-4 hours, the elimination half-life is 10.9 hours, and steady state is reached within ~4 days of repeat dosing.
- A population PK analysis in adolescent smokers showed that varenicline PK was adequately characterised by a 1-compartment model with first-order absorption and first-order elimination. Apparent clearance and volume of distribution were estimated to be 12.5 L/hr and 231 L, respectively for the reference adolescent subject: a 70 kg, white male. CL/F and V/F increased with increasing body weight, consistent with the known allometric scaling in paediatrics. Varenicline PK in adolescent smokers, systemic exposure and oral clearance were generally comparable with those of an adult population.
- In Study A3051073, the observed range of varenicline exposure was consistent with that expected for each dose and body weight group from the results obtained in the single and

multiple dose adolescent PK studies, supporting that varenicline dose and administration were appropriate.

- In Study A3051073, the Week 9-12 CAR did not increase with increasing varenicline systemic exposure [ie, AUC_{24}], supporting the negative findings for the primary endpoint from the overall study.
- In Study A3051073, nausea/vomiting incidence increased with increasing varenicline exposure; there was a statistically significant trend as a linear function of increasing AUC_{24} (p-value <0.001). In addition, the probability of nausea/vomiting incidence increased in females relative to males. The results were consistent with that observed in adult smokers.

CHMP comments on the Clinical Pharmacology

The MAH's analysis of the pharmacokinetic data from the three presented studies support that varenicline dose and administration were appropriate in study A3051073.

Varenicline in adolescent subjects exhibits linear PK following single or multiple dosing in adolescent smokers. Systemic exposure and renal clearance were comparable with those of an adult population.

In adolescent smokers showed that varenicline PK was adequately characterized by a 1-compartment model with first-order absorption and first-order elimination. Systemic exposure and oral clearance were generally comparable with those of an adult population.

In Study A3051073, the Week 9-12 CAR did not increase with increasing varenicline systemic exposure. This suggests that adolescent smokers may respond differently to varenicline systemic exposure than adult smokers do, and the finding does to some extent lend support for the validity of the negative efficacy findings of the study.

The AE's nausea/vomiting incidence increased with increasing varenicline exposure, at a pattern that was consistent with what is observed in adults

7. Clinical Efficacy aspects

The efficacy of varenicline in adolescent smokers 12-19 years old was evaluated in Study A3051073. The information summarized in this section and in the accompanying SCE is focused on the study population overall and the subgroup of subjects 12-17 years old. Full information on these groups of subjects, as well as the 12-16 year old and 17-19 year old age strata, is provided in the A3051073 CSR.

7.1. Methods – analysis of data submitted

Objective(s)

The primary objective of Study A3051073 was to evaluate the efficacy, safety, and tolerability of varenicline compared with placebo in adolescent smokers 12 19 years old.

Study design

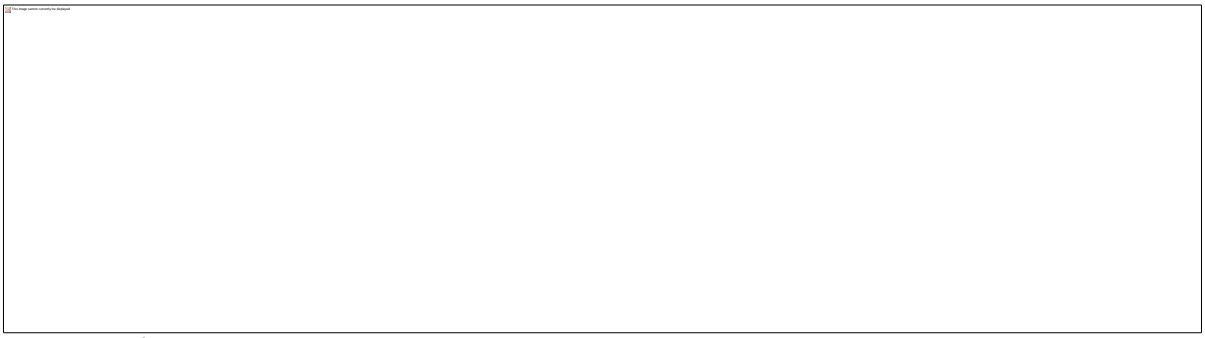
Study A3051073 was a randomised, double-blind, placebo-controlled, parallel-group, multicentre study, designed to compare 2 doses of varenicline with placebo for smoking cessation in nicotine-dependent adolescent smokers 12-19 years old who were motivated to quit. As noted above (Section 2.5.1.3), the two doses evaluated were 1.0 mg BID (high-dose) and 0.5 mg BID (low-dose). Doses were reduced by half for subjects who weighed ≤55 kg.

Randomisation was stratified by age (12-16 years old and 17-19 years old) and body weight (≤55 kg and >55 kg). Enrolment of 17-19 year olds was capped to ensure an adequate number of 12-16 year olds, the age group of primary interest in the US. The inclusion of 12-19 year olds allowed for the evaluation of a 12-17 year old subgroup, the age group of primary interest in the EU.

The treatment period was 12 weeks. Dosing began with a 2-week titration period with respective adjustments for the low-body weight subjects as described in the A3051073 Protocol Section 5.6. This longer titration (relative to the 1 week recommended in adults) was chosen to potentially minimise treatment-related side effects. All subjects were to set their TQD to coincide with the Week 1 visit. After the treatment period, there was a 40-week non-treatment follow-up period.

An overview of the study design is shown in (**Figure 6**). Additional details are provided in the A3051073 CSR Section 9.1.

Figure 6 Clinical Trial Design



Source: Section 16.1.1
* Varenicline doses were titrated to target dose over the first 2 weeks of treatment. Subjects whose body weight was ≤55 kg had their randomized dose reduced by half.
Abbreviations: BID = twice daily; BL = baseline; kg = kilogram; TC = telephone contact.

Study population

As noted above, the study enrolled 12-19 year-old smokers (overall study population); the subset of subjects 12-17 years old was the population of interest to the EU. To participate in the study subjects were required to have been smoking an average of at least 5 cigarettes per day during the past 30 days, have a total score of 4 or higher on the Fagerström Test for Nicotine Dependence (adolescent version, FTND32), which is consistent with at least moderate dependence, be motivated to stop smoking and have made at least 1 prior serious quit attempt. Complete lists of inclusion and exclusion criteria are provided in A3051073 CSR Sections 9.3.1 and 9.3.2, respectively.

Initially, Study A3051073 was conducted at sites in the US only; however, due to enrolment difficulties, study sites were also opened outside of the US. In total, subjects were randomized at 57 sites in six countries: 34 in the US, 2 in Canada, 1 in the Republic of Georgia, 4 in the Republic of Korea, 10 in the Russian Federation, and 6 in Taiwan. While smoking prevalence rates differ by country, there is no reason to believe that ex-US adolescent subjects would have a different response to treatment than US adolescent subjects.

In previous studies, varenicline has been shown to be efficacious in adults in these regions. Subject disposition for the overall study population and the 12-17 year olds is shown in **Table 9**.

Table 9 Subject Disposition – Study A3051073, Study Population Overall and 12-17 Year Olds

In the overall study population, a total of 463 subjects were screened, of which 312 subjects were randomised to treatment. Among the 151 screen failures, 26 failed because they did not meet the inclusion criterion of a FTND score ≥4 and/or smoking five or more cigarettes per day and/or were motivated to stop smoking (CSR A3051073, Table 16.2.1.1.1). In total, 307 of the 312 randomized subjects received study drug. Completion of treatment (69.4% high-dose varenicline, 74.0% low-dose varenicline, 62.6% placebo) and completion of study rates (62.0%, 67.0%, 53.5%, respectively) were higher in the varenicline groups than placebo and were highest in the low-dose varenicline group.

Among 12-17 year olds, 315 subjects were screened, of which 234 were randomised and 230 received study drug. Completion of treatment (75.9% high-dose varenicline, 82.9% lowdose varenicline, 62.7% placebo) and completion of study rates (74.7%, 76.3%, 54.7%, respectively) were higher in the varenicline groups than placebo and were highest in the low-dose varenicline group.

Table 10

Table 3. Summary of Baseline Characteristics Including Smoking History, A3051073, Safety Population Overall and 12-17 Year Olds

	Overall			12-17 year olds		
Baseline Characteristics	**High-Dose Var N=108**	**Low-Dose Var N=100**	**Pbo N=99**	**High-Dose Var N=79**	**Low-Dose Var N=76**	**Pbo N=75**
Age (years)						
Mean (SD)	16.0 (2.0)	16.0 (1.7)	15.8 (1.8)	15.1 (1.4)	15.3 (1.1)	14.9 (1.2)
Range	12-20[a]	12-19	12-19	12-17	12-17	12-17
Gender, n (%)						
Male	70 (64.8)	63 (63.0)	63 (63.6)	55 (69.6)	47 (61.8)	51 (68.0)
Female	38 (35.2)	37 (37.0)	36 (36.4)	24 (30.4)	29 (38.2)	24 (32.0)
Race, n (%)						
White	81 (75.0)	73 (73.0)	74 (74.7)	58 (73.4)	52 (68.4)	53 (70.7)
Black or African American	9 (8.3)	9 (9.0)	5 (5.1)	4 (5.1)	6 (7.9)	2 (2.7)
Asian	16 (14.8)	18 (18.0)	19 (19.2)	16 (20.3)	18 (23.7)	19 (25.3)
Other[b]	2 (1.9)	0	1 (1.0)	1 (1.3)	0	1 (1.3)
Body Mass Index (kg/m^2) n (%)						
Mean (SD)	23.1 (4.4)	22.5 (4.2)	23.0 (4.5)	22.5 (4.2)	22.3 (4.2)	22.4 (4.5)
Range	16.7-34.9	16.3-34.9	16.3-35.2	16.7-34.8	16.3-34.9	16.3-35.2
Years smoked						
Mean (SD)	3.1 (1.74)	3.0 (2.26)	2.9 (1.70)	2.7 (1.58)	2.4 (1.50)	2.6 (1.50)
Median	3.0	2.0	2.0	3.0	2.0	2.0
Range	0-8	0-13	1-8	0-7	0-6	1-7
Average number of cigarettes smoked per day (past month)						
Mean (SD)	12.8 (7.54)	12.3 (5.98)	12.0 (6.01)	11.6 (6.62)	11.5 (5.81)	10.9 (5.13)
Median	11.0	10.0	10.0	10.0	10.0	10.0
Range	5-40	5-30	5-30	5-40	5-30	5-30
FTND score						
Mean (SD)	5.36 (1.37)	5.47 (1.43)	5.30 (1.64)	5.22 (1.25)	5.26 (1.44)	5.12 (1.61)
0-3[c]	3 (2.8)	1 (1.0)	7 (7.1)	2 (2.5)	1 (1.3)	6 (8.0)
4-6	86 (79.6)	75 (75.0)	71 (71.7)	65 (82.3)	60 (78.9)	56 (74.7)
7-10	19 (17.6)	24 (24.0)	21 (21.2)	12 (15.2)	15 (19.7)	13 (17.3)
Frequent contact with someone who smokes						
Yes	105 (97.2)	94 (94.0)	91 (91.9)	77 (97.5)	71 (93.4)	71 (94.7)
No	3 (2.8)	6 (6.0)	8 (8.1)	2 (2.5)	5 (6.6)	4 (5.3)
Live with someone who smokes						
Yes	83 (76.9)	73 (73.0)	70 (70.7)	64 (81.0)	55 (72.4)	56 (74.7)
No	25 (23.1)	27 (27.0)	29 (29.3)	15 (19.0)	21 (27.6)	19 (25.3)

a. 1 subject was enrolled 2 days after her 20th birthday; this was recorded as a protocol deviation.
b. In the overall population 2 subjects were 'Hispanic' and 1 identified as 'Black and White'. One Hispanic subject and the mixed race subject were in the 12-17 year-old age group.
c. FTND scores <4 were recorded as protocol deviations.
Safety Population: All subjects who received at least 1 partial dose of study drug.
High Dose=1.0 mg BID or low body weight equivalent; Low Dose=0.5 mg BID or low body weight equivalent.
N=total number of subjects; n=number of subjects of interest; SD=standard deviation; FTND= Fagerström Test for Nicotine Dependence; Var=varenicline; Pbo=placebo.
Source: A3051073 Clinical Study Report Table 14.1.2.1, Table 14.1.2.3.1, Table 14.1.2.4.1, Table 14.1.2.1.1.a, Table 14.1.2.3.1.a, Table 14.1.2.4.1.a, Table 16.2.2, and Table 16.2.4.1.

In the overall study population (Safety Population), baseline characteristics were balanced across treatment groups. The mean age was 15.9 years old, there were approximately twice as many males as females, and approximately 75% of the subjects were White. Subjects had been smoking for a mean of approximately 3 years and were smoking an average of approximately 12 cigarettes per day at screening. Approximately 75% of subjects had a FTND score of 4-6, which can be categorised as moderate dependence on the scale of 0-10.

It is noteworthy that across all treatment groups over 90% of subjects reported having frequent contact with someone who smokes and approximately 75% reported living with someone who smokes, as these factors contribute to difficulty in achieving abstinence.

Among 12-17 year olds, baseline characteristics were balanced across treatment groups. In this age group, the mean age was 15.1 years old, approximately twice as many subjects were male as female, and approximately 70% of subjects were White. Subjects had been smoking for a mean of approximately 2.5 years and were smoking an average of approximately 11 cigarettes per day. Approximately 80% of subjects had FTND scores of 4-6. Across all treatment groups, over 90% of subjects reported having frequent contact with someone who smokes and approximately 75% reported living with someone who smokes.

7-Day Point Prevalence of Abstinence

The 7-day point prevalence of smoking abstinence was assessed by the subject's report of cigarette or other nicotine/tobacco use in the previous 7 days, using the NUI and confirmed by urine cotinine at clinic visits (note: urine cotinine was not tested at clinic visits from Week 3 through Week 8 or at any telephone visits [Weeks 24, 32, 40, and 48]). The 7-day point prevalence of abstinence was assessed weekly from Week 3 through Week 52. Subjects who did not smoke for the 7-day period being analyaed were considered responders.

The 7-day point prevalence of abstinence at Weeks 12, 24 and 52 were secondary efficacy endpoints.

Reduction in Number of Cigarettes Smoked

The reduction in the number of the cigarettes smoked was calculated at each visit by subtracting the reported average number of cigarettes smoked per day in the past 7 days at each visit from the average number of cigarettes smoked per day in the past 7 days reported at the Baseline visit, as reported on the NUI. Weekly reduction in the number of cigarettes smoked was calculated from Week 1 through Week 52.

Reduction in cigarettes smoked at Weeks 12, 24 and 52 were secondary efficacy endpoints.

Efficacy Analyses

The primary efficacy analysis for the Study A3051073 was the comparison of varenicline to placebo for the CAR for Week 9 through Week 12 for the overall study population using the Full Analysis Set (FAS). All other analyses were considered secondary. An overview of the efficacy analyses is provided below, further details are provided in the A3051073 CSR, Section 9.7 and in the A3051073 Statistical Analysis Plan (SAP).

Analysis Methods

Efficacy analyses included descriptive statistics and model-based analyses.

Analysis of smoking cessation endpoints, CAR and 7-day point prevalence, used a logistic regression model. The model included strata and pooled centre as independent variables.

Treatment by centre, treatment by age stratum (as appropriate), and treatment by body weight stratum (as appropriate) were investigated. If interactions were significant in the model, then exploratory analyses were undertaken to explain the nature and source of the interaction.

However, the reported p-values were based on the main effects model (CSR A3051073, Section 9.7.3.1).

Statistical hypotheses for the primary endpoint were tested in an ordered fashion to preserve overall Type I Error. The high-dose varenicline group was tested against placebo, and if a statistically significant difference was observed, the low-dose varenicline group was tested against placebo. A p-value of ≤0.05 was considered statistically significant in both tests.

Both tests were presented regardless of the p-value obtained.

Subjects who discontinued the study were assumed to be smokers from the time point of discontinuation through the end of the study. In computing responder rates, subjects who discontinued the study were included in the denominator but not in the numerator, regardless of their last smoking status evaluation.

Reduction in the mean number of cigarettes smoked per day was analysed using longitudinal repeated measures models with terms as described above for CAR and 7-day point prevalence. In addition to treatment and visit, baseline number of cigarettes smoked, pooled study centre, age stratum, and body weight stratum were included as covariates. A treatment by visit interaction was included for estimation purposes.

Analysis Populations

Statistical analyses were performed on the following groups of subjects:

- Overall study (12-19 year olds);
- 12-16 year old age stratum;
- 12-16 year old age stratum, ≤55 kg weight stratum;
- 12-16 year old age stratum, >55 kg weight stratum;
- 17-19 year old age stratum (descriptive statistics only; enrolment for this stratum was capped and it was not powered to detect treatment differences);
- 12-17 year old age group (post hoc analyses).

The primary efficacy analysis population was the FAS, defined as all subjects who were randomised whether or not they received treatment.

All efficacy analyses were also performed on the Completer Subjects population, which was defined as the subset of the FAS who had at least 80% treatment compliance, as measured by having any dose of study medication for 80% of the planned number of days in the trial treatment period.

Several sensitivity analyses were performed on the primary endpoint including one to exclude data from site 1097, which was terminated based on concerns regarding GCP non-compliance; another to evaluate, using multiple imputation methods, the impact of missing data due to study discontinuation, and a third based on discontinuation from treatment, regardless of study completion status, also used multiple imputation methods to evaluate the impact of missing data.

CHMP comments

Study A3051073 was designed in agreement with, and with input from, the US FDA, and secondarily complies with EMA's article 46 requirement of an assessment of the use of varenicline in 12-17-years old adolescents by added post hoc analyses.

The clinical trial was designed with similar methodology as previously conducted varenicline trials in adult smokers. The choice of primary and secondary endpoints, and the trial design with 12-week treatment duration and a 40-week follow-up period, trial visits and telephone contacts can be endorsed. Some changes have been made from previous trial designs, to adjust to the different conditions in treating adolescent study subjects. The trial used a longer titration period to reduce potential side effects and thus ensure compliance; this approach can be endorsed. In order to correct varenicline exposure for differences in body weight among study subjects who were still undergoing growth, the subjects were stratified in a lighter than 55 kg group and a heavier than 55 kg group, where the heavier adolescents received adult dosing (both high and low dose group) and the lighter adolescents received half of an adult dose. This approach is justified.

The statistical methods are not described above, but it should be repeated from previous assessments that A3051073 was designed with 3 study groups (2 active-treatment arms and one placebo arm) of a 100 study subjects per group, from postulated CAR rates week 9-12 (primary endpoint) of 24% for varenicline and of 9% for placebo.

7.2. Results

Results of efficacy analyses are presented below for the FAS population overall and for the FAS 12-17 year-old subgroup. Efficacy analyses for the 12-16 year-old age stratum are provided in the A3051073 CSR, Section 11.4. Descriptive statistics for the 17-19 year old age stratum are also provided in the A3051073 CSR (see specifically A3051073 CSR Table 14.2.2.1.3, Table 14.2.2.2.3, Table 14.2.2.4.3, and Table 14.2.2.3.3.1). The study was not powered to detect treatment differences in the 17-19 year old stratum and therefore, no model-based analyses were performed and no efficacy conclusions can be made in this age group. Additionally, results for the Completer Subjects population and by weight strata in 12-16 year olds are provided in the A3051073 CSR, Section 11.4.

Primary Endpoint

The analysis of CAR Week 9 through Week 12 for the FAS population overall and FAS 12-17 year olds is shown in **Table 11**.

Table 11 Treatment Comparison of Continuous Abstinence, Weeks 9-12, Confirmed by Urine Cotinine, Study A3051073, FAS Population Overall and 12-17 Year Olds

CAR 9-12 (%)	Overall n/N (%)	12-to-17-Year Olds n/N (%)
High-Dose Varenicline	22/109 (20.2%)	15/80 (18.8%)
Low-Dose Varenicline	28/103 (27.2%)	25/78 (32.1%)
Placebo	18/100 (18.0%)	13/76 (17.1%)
Treatment Comparisons	**Odds ratio in CAR 9-12 (95% CI) [p-value][a]**	
High-Dose Varenicline vs Placebo	1.18 (0.59, 2.37) [0.6337]	1.13 (0.50, 2.56) [0.7753]
Low-Dose Varenicline vs Placebo	1.73 (0.88, 3.39) [0.1114]	2.28 (1.06, 4.89) [0.0347]

a. P-values and odds ratios based on a logistic regression model with terms treatment, age stratum (not included in the 12-17-year-old model), weight stratum, and pooled center.
CAR=continuous abstinence rate; CI=confidence interval; FAS=full analysis set; N=number of subjects randomized; n=the number of subjects who, at each visit from Weeks 9 to 12 (inclusive), reported no smoking and no use of other nicotine-containing products since the last study visit/last contact (on the Nicotine Use Inventory) and at any of these visits were confirmed to have quit based on urine cotinine.
Source: A3051073 Clinical Study Report Table 14.2.2.1.1.a, Table 14.2.2.1.3.a.

In the FAS population overall, the observed CARs were 20.2% for high-dose varenicline subjects, 27.2% for low-dose varenicline subjects, and 18.0% for placebo subjects. Neither high-dose varenicline (OR 1.18 [95% CI: 0.59 to 2.37], p=0.6337) nor low-dose varenicline (OR 1.73 [95% CI: 0.88 to 3.39], p=0.1114) were shown to be statistically significantly different from placebo.

Among 12-17 year olds, the observed CARs were 18.8% for high-dose varenicline subjects, 32.1% for low-dose varenicline subjects, and 17.1% for placebo subjects. High-dose varenicline was shown not to be statistically significantly different compared with placebo (OR 1.13 [95% CI: 0.50, 2.56], p=0.7753). For low-dose varenicline compared with placebo, the OR was 2.28 (95% CI: 1.06 to 4.89), p=0.0347. Given the pre-specified statistical decision rules and the lack of statistical significance for the high-dose varenicline group, this result was considered nominal and not statistically significant.

None of the Completer Subjects analyses and none of the sensitivity analyses of the primary endpoint demonstrated statistically significant differences between either dose of varenicline and placebo either in the overall study population or in the 12-17 year-old subgroup, supporting the negative findings of the primary analysis.

Secondary Endpoints

7-Day Point Prevalence of Abstinence

In the FAS population overall, at each weekly assessment, a greater percentage of subjects treated with high- or low-dose varenicline reported being abstinent for 7-days than subjects treated with placebo. Over the 12-week treatment period, the 7-day-point prevalence of abstinence rates generally increased, although the highest percentage of high-dose varenicline subjects was at Week 8. After the 12-week treatment phase, 7-day-point prevalence of abstinence rates generally declined over the post-treatment period, to a lesser extent for both varenicline groups than for placebo.

Among 12-17 year olds, at each weekly assessment a greater percentage of subjects treated with high- or low-dose varenicline reported being abstinent for 7-days than subjects treated with placebo. Over the 12-week treatment period, the 7-day-point prevalence of abstinence rates generally increased, although the highest percentage of high-dose varenicline subjects was at Week 8. After the 12-week treatment phase, 7-day-point prevalence of abstinence rates generally declined over the follow-up period for the placebo group but not for either varenicline group.

Table 12 summarises the analysis of 7-day point prevalence at Weeks 12, 24 and 52.

Table 12 Summary of 7-Day Point Prevalence of Abstinence for Weeks 12. 24 and 52, Study A3051073, FAS Population Overall and 12-17 Year Olds

	Full Analysis Set	
	Overall	**12-to-17-Year Olds**
Week 12	Estimated 7-Day Point Prevalence at Week 12, n/N (%)	
High-dose Varenicline	34/109 (31.2)	26/80 (32.5)
Low-dose Varenicline	39/103 (37.9)	33/78 (42.3)
Placebo	23/100 (23.0)	18/76 (23.7)
Treatment Comparison[a]	Estimated Odds Ratio at Week 12 (95% CI) [p-value]	
High-dose Varenicline vs Placebo	1.21 (0.62, 2.38) [0.5793]	1.13 (0.52, 2.44) [0.7588]
Low-dose Varenicline vs Placebo	1.79 (0.91, 3.51) [0.0932]	1.84 (0.86, 3.94) [0.1141]
Week 24[b]	Estimated 7-Day Point Prevalence at Week 24, n/N (%)	
High-dose Varenicline	34/109 (31.2)	30/80 (37.5)
Low-dose Varenicline	37/103 (35.9)	33/78 (42.3)
Placebo	23/100 (23.0)	17/76 (22.4)
Treatment Comparison[a]	Estimated Odds Ratio at Week 24 (95% CI) [p-value]	
High-dose Varenicline vs Placebo	1.23 (0.61, 2.5) [0.5647]	1.60 (0.72, 3.57) [0.2495]
Low-dose Varenicline vs Placebo	1.46 (0.72, 2.96) [0.2917]	1.78 (0.81, 3.91) [0.1521]

	Full Analysis Set	
	Overall	**12-to-17-Year Olds**
Week 52	Estimated 7-Day Point Prevalence at Week 52, n/N (%)	
High-dose Varenicline	31/109 (28.4)	30/80 (37.5)
Low-dose Varenicline	36/103 (35.0)	34/78 (43.6)
Placebo	20/100 (20.0)	15/76 (19.7)
Treatment Comparison[a]	Estimated Odds Ratio at Week 52 (95% CI) [p-value]	
High-dose Varenicline vs Placebo	1.25 (0.58, 2.69) [0.5616]	1.77 (0.77, 4.07) [0.1804]
Low-dose Varenicline vs Placebo	1.79 (0.84, 3.78) [0.1300]	2.47 (1.08, 5.65) [0.0323]

n=the number of subjects who reported no smoking and no use of other nicotine-containing products (Weeks 3-12) or tobacco products (Weeks 13-52) on the Nicotine Use Inventory in the 7 days prior to the study visits or telephone contacts; N= number of randomized subjects in group; FAS=Full Analysis Set; CI=confidence interval.

a. Odds ratios and p-values were obtained from separate logistic regression models including the main effects of treatment, pooled center, age stratum (not included in the 12-16-year-old model), and body weight stratum.

b. Week 24 was a telephone contact, urine cotinine data not collected.

Source: A3051073 Clinical Study Report Table 14.2.2.2.1 and Table 14.2.2.2.3.a.

In the FAS population overall, none of the ORs were statistically significant at Weeks 12, 24 and 52 for the comparisons between high-dose varenicline and placebo or between low-dose varenicline and placebo.

Among 12-17 year olds, none of the OR's were statistically significant at Weeks 12, 24 and 52, for the comparisons between high-dose varenicline and placebo or between low-dose varenicline and placebo; although for Week 52 there was a nominal p-value of 0.0323 for the comparison of low-dose varenicline and placebo.

Reduction from Baseline in Daily Number of Cigarettes Smoked

The weekly reduction in number of cigarettes smoked relative to Baseline in the FAS population overall and in 12-17 year olds is provided in A3051073 CSR Table 14.2.2.3.1.1 and Table 14.2.2.3.3.1.a, respectively.

In the FAS population overall, subjects in all treatment groups showed a downward trend in the number of cigarettes smoked through Week 12. This trend reversed slightly from Week 12 to Week 24 and then appears to plateau through the end of study.

Among 12-17 year olds, subjects in all treatment groups showed a downward trend in the number of cigarettes smoked through around Week 12. This trend reversed slightly from Week 12 to Week 24 and then appears to plateau through the end of study.

Results of the statistical analysis of reduction in number of cigarettes smoked for Weeks 12, 24, and 52 for the FAS population overall and 12-17 year olds are shown in **Table 13**.

Table 13 Reduction in Number of Cigarettes Smoked at Weeks 12, 24, and 52, Study A3051073, FAS Population Overall and 12-17 Year Olds

	Week 12	Week 24	Week 52
FAS Population Overall			
	Least squares mean (SE) [95%CI]		
High-Dose Varenicline (N=109)	-8.56 (0.43) [-9.40, -7.71]	-6.93 (0.44) [-7.80, -6.06]	-6.80 (0.45) [-7.68, -5.91]
Low-Dose Varenicline (N=103)	-8.20 (0.44) [-9.07, -7.33]	-7.31 (0.45) [-8.20, -6.42]	-7.74 (0.46) [-8.64, -6.85]
Placebo (N=100)	-8.01 (0.46) [-8.92, -7.11]	-6.59 (0.48) [-7.52, -5.65]	-6.98 (0.48) [-7.93, -6.03]
Treatment Comparisons	**Mean (SE) Difference from Placebo [95% CI] {p-value}[a]**		
High-Dose Varenicline vs Placebo	-0.54 (0.58) [-1.69, 0.60] {0.3540}	-0.34 (0.60) [-1.53, 0.84] {0.5676}	0.18 (0.62) [-1.03, 1.38] {0.7730}
Low-Dose Varenicline vs Placebo	-0.18 (0.59) [-1.35, 0.98] {0.7574}	-0.72 (0.61) [-1.92, 0.47] {0.2356}	-0.77 (0.62) [-1.99, 0.45] {0.2166}
FAS 12-17 Year Olds			
	Least squares mean (SE) [95%CI]		
High-Dose Varenicline (N=80)	-7.35 (0.44) [-8.20, -6.49]	-6.20 (0.45) [-7.08, -5.33]	-5.89 (0.45) [-6.76, -5.01]
Low-Dose Varenicline (N=78)	-7.41 (0.45) [-8.29, -6.53]	-6.61 (0.45) [-7.50, -5.72]	-7.00 (0.46) [-7.89, -6.10]
Placebo (N=76)	-6.69 (0.47) [-7.61, -5.77]	-5.73 (0.49) [-6.68, -4.77]	-5.88 (0.49) [-6.85, -4.92]
Treatment Comparisons	**Mean (SE) Difference from Placebo [95% CI] {p-value}[a]**		
High-Dose Varenicline vs Placebo	-0.66 (0.63) [-1.89, 0.58] {0.2980}	-0.47 (0.65) [-1.75, 0.80] {0.4669}	-0.00 (0.65) [-1.29, 1.28] {0.9939}
Low-Dose Varenicline vs Placebo	-0.72 (0.64) [-1.97, 0.52] {0.2541}	-0.88 (0.65) [-2.16, 0.40] {0.1766}	-1.12 (0.66) [-2.41, 0.18] {0.0902}

CI=confidence interval; FAS=full analysis set; N=number of subjects randomized; SE=standard error.

a. Inferential statistics are obtained from a longitudinal repeated measures model with the change from baseline average number of Cigarettes Smoked as the dependent variable, including terms treatment, visit, age strata (not included in the 12-17-year-old model), body weight strata, pooled center, baseline measure and treatment by visit interaction.

Source: A3051073 Clinical Study Report Table 14.2.2.3.1.2 and Table 14.2.2.3.3.2.a.

In the FAS population overall, there were no statistically significant differences in the reduction in number of cigarettes smoked for the comparison of high-dose varenicline and placebo or low-dose varenicline and placebo at Weeks 12, 24, or 52.

Among 12-17 year olds, there were no statistically significant differences in the reduction in number of cigarettes smoked for the comparison of high-dose varenicline and placebo or low-dose varenicline and placebo at Weeks 12, 24, or 52.

Continuous Abstinence Rates from Week 9 through Week 24 and Week 9 through Week 52

Table 14 shows the analysis of CAR Week 9 through Week 24 and CAR Week 9 through Week 52 for the FAS population overall and for 12-17 year olds.

Table 14 Summary of Continuous Abstinence Rate from Week 9 through Week 24 and Week 52, Study A3051073, FAS Population Overall and 12-17 Year Olds

Population	High-Dose Varenicline	Low-Dose Varenicline	Placebo
FAS Overall	**(N=109)**	**(N=103)**	**(N=100)**
Week 9 through Week 24			
Responders, n (%)	11 (10.1)	25 (24.3)	13 (13.0)
Odds Ratio (95% CI) [p-value][a]	0.80 (0.34, 1.90) [0.6133]	2.26 (1.07, 4.79) [0.0335]	
Week 9 through Week 52			
Responders, n (%)	9 (8.3)	21 (20.4)	9 (9.0)
Odds Ratio (95% CI) [p-value][a]	0.99 (0.37, 2.65) [0.9874]	2.79 (1.19, 6.55) [0.0188]	
FAS – 12-to-17 Year Olds	**(N=80)**	**(N=78)**	**(N=76)**
Week 9 through Week 24			
Responders, n (%)	11 (13.8)	23 (29.5)	10 (13.2)
Odds Ratio (95% CI) [p-value][a]	1.07 (0.43, 2.69) [0.8850]	2.76 (1.21, 6.30) [0.0162]	
Week 9 through Week 52			
Responders, n (%)	9 (11.3)	20 (25.6)	8 (10.5)
Odds Ratio (95% CI) [p-value][a]	1.11 (0.40, 3.04) [0.8442]	2.96 (1.21, 7.24) [0.0176]	

Week 24 was a telephone contact.
n=The number of subjects who, at each visit from Weeks 9 to 52 (inclusive), reported no smoking and no use of other nicotine-containing products (Weeks 9-12) or tobacco products (Weeks 13-52) since the last study visit/last contact (on the Nicotine Use Inventory) and at any of the study clinic visits were confirmed to have quit based on urine cotinine (responders); N=total number of subjects in group.
CI = confidence interval; FAS = Full Analysis Set (includes all randomized subjects).
a. P-values and odds ratios are based on logistic regression models with terms treatment, age stratum (not included in the 12-16-year-old model), weight stratum, and pooled center.
Source: A3051073 Clinical Study Report Table 14.2.2.4.1 and Table 14.2.2.4.3.a.

In the FAS population overall, CAR Week 9 through Week 24 and CAR Week 9 through Week 52 were 10.1% and 8.3% for high-dose varenicline subjects, 24.3% and 20.4% for low-dose varenicline subjects, and 13.0% and 9.0% for placebo subjects, respectively. For the high-dose varenicline comparison to placebo, none of the OR's were statistically significant. For the low-dose varenicline comparison to placebo, nominal p-values were obtained for both CAR Week 9 through Week 24 (p=0.0335) and for CAR Week 9 through Week 52 (p =0.0188).

Among 12-17 year olds, CARs for the Week 9 through Week 24 and Week 9 through Week 52 were 13.8% and 11.3% for high-dose varenicline subjects, 29.5% and 25.6% low-dose varenicline subjects, and 13.2% and 10.5% for placebo subjects, respectively. For the high-dose varenicline comparison to placebo, none of the OR's were statistically significant. For the low-dose varenicline comparison to placebo, nominal p-values were obtained for both CAR Week 9 through Week 24 (p=0.0162) and for CAR Week 9 through Week 52 (p=0.0176).

CHMP comments

For the FAS overall study population, no significant difference between groups was found for the primary efficacy endpoint, CAR week 9-12. Related to the prior expectations of a 24 % abstinence rate in treatment groups that the study design was based on, the CAR 9-12 for high-dose varenicline and low-dose varenicline was -3.8 % and + 3.2 %, respectively. However, the CAR 9-12 for placebo treated subjects was 18% that is twice as high as projected.

For the post-hoc analysis of the subset of 12-17 years-olds that is of special interest to EMA, the corresponding percentages were -5.2, +8.1, and +8.1, respectively. In this subset, a significant treatment effect of low-dose varenicline was found, but as this result arises from a post-hoc analysis (although a similar result was found in the pre-specified analysis of the 12-16 year old subset) and from a violation of the pre-specified statistical analysis plan, it cannot be used as a scientific proof of clinical efficacy; it is a nominal finding.

Regarding the secondary efficacy endpoints, most did not show significant differences between treatment groups. However, it seems to be a general trend that low-dose varenicline-treated subjects fared somewhat better than high-dose- or placebo-treated subjects are. This impression seems to be reflected in the CAR 9-24 and CAR 9-52; these are significantly higher than placebo, but must be viewed as nominal findings according to the pre-specified statistical analysis plan.

Efficacy Conclusions

The efficacy results from Study A3051073 support the following conclusions:

- The primary efficacy endpoint of the A3051073 study was not met. In the overall study population of nicotine-dependent adolescent smokers 12-19 years old, treatment with varenicline (1.0 BID and 0.5 mg BID, both doses weight adjusted) along with age appropriate counselling did not result in statistically significant improvement in smoking abstinence rates relative to placebo at Weeks 9-12.
- Varenicline was not shown to be efficacious in the subgroup of nicotine-dependent adolescents 12-16 years old.
- Varenicline was not shown to be efficacious in the subgroup of nicotine-dependent adolescents 12-17 years old, the population of adolescents of interest in the EU, in post hoc analyses.
- Secondary efficacy endpoint analyses, including CAR Weeks 9-24 and Weeks 9-52, 7-day point prevalence, and reduction in the number of cigarettes smoked, support the negative findings for the primary endpoint, as do analyses based on the Completer Subjects population and all sensitivity analyses.
- The study was not powered in the 17- 19-year-old stratum and therefore, no model-based analyses were performed and no efficacy conclusions can be made in this age group.

7.3. Discussion

These conclusions from the presented data are formally correct. However, as has been pointed out in previous assessments, study A3051073 must be suspected to be underpowered to demonstrate treatment efficacy from the statistical planning phase, with realistic expectations for the treatment effect of varenicline, but with an unrealistically low expected placebo response rate. The end-result has been a placebo response rate that is twice as high as has been projected in the study power calculation. Notably, the low-dose varenicline-treated adolescents seemed to have similar efficacy-results as varenicline-treated adult study subjects in previous studies, both with regard to the primary endpoint and with regard to several secondary endpoints. The high-dose varenicline-treated adolescents had less favourable efficacy results, resulting in statistically insignificant efficacy results compared to placebo. In all, it must be suspected, that the MAH's rejection of vareniclines efficacy in adolescent smokers could be due to a Type II error, and the interpretation of the efficacy results for varenicline to adolescent smokers remain difficult to interpret with certainty.

8. Clinical Safety aspects

All three adolescent studies, A3051073, A3051070, and A3051029, contributed safety data on the use of varenicline in adolescent smokers. The information summarised in this section and in the accompanying SCS regarding A3051073 is focused on the safety results in the study population overall and the subgroup of subjects 12-17 years old. Full information on the safety results in these groups of subjects, as well as in the 12-16 year old and 17-19 year old age strata is provided in the A3051073 CSR.

Due to the differences in study design apparent in **Table 1**, notably treatment and follow-up durations, data from the three studies are presented individually. For each study, the data presented represent all subjects who took at least one dose of study medication, including partial doses. All adverse events (AEs) were coded using Medical Dictionary for Regulatory Activities (MedDRA) version (v) 20.1 and the treatment-emergent period was standardized to include the day of first dose of study medication through 30 days after the last dose.

8.1. Methods – analysis of data submitted

Study Design

Study A3051073

The design of Study A3051073 is described above in Section 2.5.4.1 and in greater detail in the A3051073 CSR.

Phase 1 Studies

Study A3051070 was a Phase 1, randomised, double blind, placebo-controlled study designed to evaluate the multiple-dose PK, safety, and tolerability of varenicline in healthy adolescent smokers 12 to 16 years old. Subjects were enrolled into a low-body weight (LBW) group (≤55 kg [minimum weight 30 kg]) and a high-body weight (HBW) group (>55 kg). Subjects in each body weight group were randomized in a 2:2:1 ratio to 1 of 2 varenicline doses or placebo. The varenicline doses were 0.5 mg QD or 0.5 mg BID in the LBW group and 0.5 mg BID or 1 mg BID in the HBW group. Dosing was titrated over 7 days for the 0.5 mg BID and 1 mg BID treatment groups (0.5 mg QD for 7 days for the former and 0.5 mg QD for 3 days, followed by 0.5 mg BID for 4 days for the latter). The treatment period was 14 days and subjects were followed through Day 18. Subjects were admitted to the Clinical Research Unit (CRU) on Days 1, 8 and 14 during treatment and Day 16 or 17 during follow-up for PK blood sampling. Subjects were allowed to continue smoking at will during the course of the study, although they were offered smoking cessation

counselling at the end of the study. Additional details regarding the study design are provided in A3051070 CSR Section 5.1.

Study A3051029 was a Phase 1, randomized, sponsor-open, investigator- and subject-blind, parallel-group, placebo-controlled study designed to evaluate the single-dose PK, safety, and tolerability of varenicline in healthy adolescent smokers 12-17 years old. This study evaluated single doses of 0.5 mg and 1 mg varenicline compared to placebo. Subjects were admitted to the CRU the day before dosing (Day 0) and remained in the CRU for 48 hours postdose. Additional details regarding the study design are provided in the A3051029 CSR Section 5.1.

Study Population

All three adolescent studies, A3051073, A3051070, and A3051029, enrolled adolescent smokers who were otherwise generally healthy. Inclusion/exclusion study criteria are provided in the individual study reports.

In these three studies, a combined total of 287 adolescent smokers were exposed to varenicline, along with 119 adolescent smokers exposed to placebo (**Table 1**). All subjects who took at least one dose of study drug were evaluated for safety.

Study A3051073

In Study A3051073, the Safety Population (all subjects who took at least 1 dose of study medication) overall included a total of 307 subjects; 108 in the varenicline high-dose group, 100 in the varenicline low-dose group and 99 in the placebo group (A3051073 CSR Table 14.1.1.1). The 12-17 year old subgroup included a total of 230 subjects; 79 in the varenicline high-dose group, 76 the varenicline low-dose group and 75 in the placebo group (A3051073 CSR Table 14.1.1.1.1.a).

In the Safety Population overall, the majority of subjects in all treatment groups completed treatment; the percentages were higher for varenicline than placebo: 69.4% high-dose varenicline subjects, 74.0% low-dose varenicline subjects, and 62.6% placebo subjects (A3051073 CSR Table 14.1.1.4).

Among 12-17 year-olds, the majority of subjects in all treatment groups completed treatment; the percentages were higher for varenicline than placebo: 75.9% high-dose varenicline subjects, 82.9% low-dose varenicline subjects, and 62.7% placebo subjects (A3051073 CSR Table 14.1.1.4.1.a).

Demographic and other baseline characteristics for the Safety Population overall and the 12-17 year olds are presented above in Section 2.5.4.2.

Phase 1 Studies

In Study A3051070, all 72 randomized subjects took study medication; 37 in the LBW group and 35 in the HBW group. In the LBW group, this included 14 high dose varenicline subjects, 15 low-dose varenicline subjects and 8 placebo subjects and in the HBW group, 14 high-dose varenicline subjects, 14 low-dose varenicline subjects, and 7 placebo subjects.

Two LBW subjects discontinued early, 1 low dose varenicline subject and 1 placebo subject. All HBW subjects completed treatment (A3051070 CSR Table 13.1.1).

Demographic and other baseline characteristics of the subjects in Study A3051070 are provided in A3051070 CSR Table 13.2, 13.11 and Appendix B and summarized in SCS **Table 15**.

In Study A3051029, all 27 randomized subjects took study medication; 10 varenicline 0.5 mg, 12 varenicline 1.0 mg and five placebo subjects. All subjects completed the study. (A3051029 CSR Table 13.1.1).

Demographic and other baseline characteristics of the subjects in Study A3051029 are summarised in A3051029 CSR Table 13.2.1 and summarized in SCS **Table 16**.

CHMP comments

The adolescent combined safety population comprises 287 adolescent smokers who were exposed to varenicline. It is interesting to note, that in A3051073, the percentages who completed treatment were higher for varenicline than placebo, with the highest completer-rate in the low-dose group: 75.9% high-dose varenicline subjects, 82.9% low-dose varenicline subjects, and 62.7% placebo subjects. This might suggest that subjects in especially the low-dose varenicline group found treatment more worthwhile to comply with than the placebo-treated subjects did, which further might suggest that they may have been more motivated to complete treatment because they experienced greater efficacy of the treatment towards their objective of quitting smoking.

8.2. Results

AE data for all three studies are summarised in the sections below. Data from clinical laboratory testing, vital signs, and physical examinations (primarily height and weight) are provided in the individual study reports.

For Study A3051073, data are presented below for the Safety Population overall and for the 12-17 year old subgroup. AE data by race, gender and body weight (in 12-16 year olds) are provided in the SCS Section 2.7.4.5.2. The analyses of these subpopulations did not identify any group at greater risk for safety concerns.

Common Adverse Events

A3051073

An overview of AEs is presented in **Table 15** for the Safety Population overall and in **Table 16** for 12-17 year olds.

Table 15 All-Causality Treatment-Emergent Adverse Events, Study A3051073, Safety Population Overall

	High-Dose Varenicline N=108	Low-Dose Varenicline N=100	Placebo N=99
	number (%) of subjects		
Subjects with AEs	65 (60.2)	53 (53.0)	52 (52.5)
Subjects with SAEs	3 (2.8)	1 (1.0)	1 (1.0)
Subjects with Severe AEs	3 (2.8)	3 (3.0)	1 (1.0)
Subjects Discontinued Treatment Due to AEs[a]	6 (5.6)	2 (2.0)	4 (4.0)
Subjects Discontinued Study Due to AEs	1 (0.9)	0	1 (1.0)
Subjects with Dose Reduced or Temporary Discontinuation Due to AEs	9 (8.3)	4 (4.0)	7 (7.1)

Safety Population: All subjects who received at least 1 partial dose of study drug.
High Dose=1.0 mg BID or low body weight equivalent; Low Dose=0.5 mg BID or low body weight equivalent.
AE=adverse event; SAE=serious adverse event; N=number of treated subjects; BID=twice daily.
Treatment-emergent adverse events included the interval from first date of study drug to last date of study drug plus 30 days.
Subjects were counted only once per treatment in each row.
Serious adverse events - according to the Investigator's assessment.
a. Includes 2 subjects, 1 low-dose varenicline and 1 placebo, whose final treatment status was withdrawn due to pregnancy.
MedDRA v20.1.
Source: A3051073 Clinical Study Report Table 14.3.1.2.1.1.1 and Table 14.1.1.4.

The percentage of subjects experiencing AEs was higher in the high-dose varenicline group (60.2%) than in the low-dose varenicline group (53.0%), which was similar to placebo (52.5%). There were few subjects with serious adverse events (SAEs) (5 total) or severe AEs (7 total) overall, and these occurred in higher percentages of varenicline subjects than placebo subjects. A higher percentage of high-dose varenicline subjects (5.6%) discontinued treatment due to an AE than either low-dose varenicline (2.0%) or placebo subjects (4.0%) while the percentage of placebo subjects was higher than low-dose varenicline subjects.

Table 16 All-Causality Treatment-Emergent Adverse Events, Study A3051073, Safety Population 12-17 Year Olds

System Organ Class Preferred Term	High-Dose Var N=79	Low-Dose Var N=76	Pbo N=75
	number (%) of subjects		
Subjects with AEs	43 (54.4)	38 (50.0)	35 (46.7)
Subjects with SAEs	3 (3.8)	0	1 (1.3)
Subjects with Severe AEs	2 (2.5)	0	0
Subjects Discontinued Treatment Due to AEs	3 (3.8)	0	3 (4.0)
Subjects Discontinued Study Due to AEs	1 (1.3)	0	1 (1.3)
Subjects with Dose Reduced or Temporary Discontinuation Due to AEs	5 (6.3)	1 (1.3)	4 (5.3)

Safety Population: All subjects who received at least 1 partial dose of study drug.
High Dose=1.0 mg BID or low body weight equivalent; Low Dose=0.5 mg BID or low body weight equivalent.
AE=adverse event; SAE=serious adverse event; N=number of subjects; BID=twice daily; Var=varenicline; Pbo=placebo.
Treatment-emergent adverse events included the interval from first date of study drug to last date of study drug plus 30 days.
Subjects were counted only once per treatment in each row.
Serious adverse events - according to the Investigator's assessment.
MedDRA v20.1.
Source: A3051073 Clinical Study Report Table 14.3.1.2.1.1.3.a.

Among 12-17 year olds, the percentage of subjects experiencing AEs was higher in the high-dose varenicline group (54.4%) than in the low-dose varenicline group (50.0%), which was higher than placebo (46.7%). The percentage of subjects who experienced SAEs or severe AEs was higher in the high-dose varenicline group than in the placebo group; no low-dose varenicline subjects experienced these types of AEs.

The most frequent treatment-emergent AEs (reported in ≥5% of subjects in any treatment group) are listed in **Table 17** for the Safety Population overall and in **Table 18** for 12-17 year olds.

Table 17 Most Frequently Reported All-Causality Treatment-Emergent Adverse Events (Preferred Terms ≥5% of Subjects in any Treatment Group), Study A3051073, Safety Population Overall

System Organ Class Preferred Term	High-Dose Varenicline N=108	Low-Dose Varenicline N=100	Placebo N=99
	number (%) of subjects		
Subjects with Adverse Events	**65 (60.2)**	**53 (53.0)**	**52 (52.5)**
Gastrointestinal Disorders			
Nausea	**26 (24.1)**	**19 (19.0)**	**12 (12.1)**
Vomiting	**14 (13.0)**	2 (2.0)	2 (2.0)
Infections and Infestations			
Nasopharyngitis	4 (3.7)	3 (3.0)	**5 (5.1)**
Upper respiratory tract infection	**6 (5.6)**	**5 (5.0)**	2 (2.0)
Nervous system disorders			
Headache	**14 (13.0)**	**5 (5.0)**	**8 (8.1)**
Dizziness	**6 (5.6)**	**7 (7.0)**	3 (3.0)
Psychiatric disorders			
Agitation	**9 (8.3)**	**5 (5.0)**	**5 (5.1)**
Anxiety	**6 (5.6)**	4 (4.0)	**7 (7.1)**
Hostility	**7 (6.5)**	3 (3.0)	4 (4.0)
Abnormal dreams	**8 (7.4)**	**5 (5.0)**	4 (4.0)

Safety Population: All subjects who received at least 1 partial dose of study drug.
High Dose=1.0 mg BID or low body weight equivalent; Low Dose=0.5 mg BID or low body weight equivalent.
N=number of treated subjects.
Treatment-emergent adverse events included the interval from first date of study drug to last date of study drug plus 30 days.
Subjects were counted only once per treatment in each row.
Bolded values met frequency criteria.
MedDRA v20.1.
Source: SCS Supplemental Table F14.3.1.2.6.4.1.

Most of the frequently reported AEs were reported in a higher percentage of high-dose varenicline subjects than low-dose varenicline subjects or placebo subjects. Two AEs, Nasopharyngitis and Anxiety, were reported in a higher percentage of placebo subjects than varenicline subjects.

Table 18 Most Frequently Reported All-Causality Treatment-Emergent Adverse Events (Preferred Terms ≥5% of Subjects in any Treatment Group), Study A3051073, Safety Population 12-17 Year Olds

System Organ Class Preferred Term	High-Dose Var N=79	Low-Dose Var N=76	Pbo N=75
	number (%) of subjects		
Subjects with Adverse Events	**43 (54.4)**	**38 (50.0)**	**35 (46.7)**
Gastrointestinal Disorders			
Nausea	**18 (22.8)**	**15 (19.7)**	**6 (8.0)**
Vomiting	**8 (10.1)**	1 (1.3)	1 (1.3)
Infections and Infestations			
Nasopharyngitis	3 (3.8)	2 (2.6)	**4 (5.3)**
Upper respiratory tract infection	**5 (6.3)**	**4 (5.3)**	0
Nervous system disorders			
Headache	**7 (8.9)**	2 (2.6)	**5 (6.7)**
Dizziness	**4 (5.1)**	**7 (9.2)**	2 (2.7)
Psychiatric disorders			
Agitation	**4 (5.1)**	1 (1.3)	1 (1.3)
Hostility	**6 (7.6)**	2 (2.6)	0

Safety Population: All subjects who received at least 1 partial dose of study drug.
High Dose=1.0 mg BID or low body weight equivalent; Low Dose=0.5 mg BID or low body weight equivalent.
N=number of subjects; n=number of subjects in subset; BID=twice daily; Var=varenicline; Pbo=placebo.
Treatment-emergent adverse events included the interval from first date of study drug to last date of study drug plus 30 days.
Bolded values met frequency criteria.
Subjects were counted only once per treatment in each row.
MedDRA v20.1.
Source: A3051073 Clinical Study Report Table 14.3.1.2.6.1.3.a.

Among 12-17 year olds most of the frequent AEs were reported in a higher percentage of high-dose varenicline subjects than low-dose varenicline subjects or placebo subject; the two exceptions were Nasopharyngitis and Dizziness. Nasopharyngitis was reported in a higher percentage of placebo subjects than varenicline subjects were.

Phase 1 Studies

In Study A3051070, AEs were reported in low body weight (LBW) subjects by 9/14 high-dose varenicline subjects, 11/15 low-dose varenicline subjects and 1/8 placebo subjects. In the high body weight (HBW) group AEs were reported by 8/14 high-dose varenicline subjects, 8/14 low-dose varenicline subjects and 1/7 placebo subjects. No subjects reported SAEs or discontinued due to an AE. One low-dose varenicline LBW subject had a severe AE of nausea (SCS Supplemental Table bF14.3.1.2.1 and Table bF14.3.1.2.6).

AEs reported by 2 or more subjects in any treatment group in Study A3051070 included: Nausea, Vomiting, Decreased appetite, Fatigue, Dizziness, Oropharyngeal pain, and Headache in the LBW group and Flatulence, Nausea, Vomiting, Abdominal pain upper, and Headache in the HBW group. All these events were reported by a greater number of subjects in at least 1 varenicline group than placebo (SCS Supplemental Table bF14.3.1.2.6).

In Study A3051029, AEs were reported in 1/10 0.5 mg varenicline subjects, 2/12 1.0 mg varenicline subjects and 1/5 placebo subjects. No subjects reported severe AEs, SAEs or discontinued due to an AE (SCS Supplemental Table aF14.3.1.2.1).

The 4 subjects in Study A3051029 who experienced AEs reported Dizziness (1 varenicline 0.5 mg, 2 varenicline 1.0 mg) and Abdominal pain (1 placebo) (SCS Supplemental Table aF14.3.1.2.6).

Serious Adverse Events

Study A3051073

A total of 5 subjects had at least 1 treatment-emergent SAE; 3 (2.8%) high-dose varenicline, 1 (1.0%) low-dose varenicline, and 1 (1.0%) placebo subject (A3051073 CSR Table 14.3.1.2.1.1.1). None of the treatment-emergent SAE's were considered to be related to study drug as judged by the Investigator. Four of the 5 SAEs occurred in 12-17 year olds (A3051073 CSR Table 14.3.1.2.1.1.3.a).

A total of 7 subjects had at least 1 post-treatment-emergent SAE; 3 (2.8%) high-dose varenicline, 2 (2.0%) low-dose varenicline, and 2 (2.0%) placebo subjects (A3051073 CSR Table 14.3.1.2.1.1.2). None of the post-treatment-emergent SAE's were considered to be related to study drug as judged by the Investigator. All of the post-treatment-emergent SAEs occurred in 12-17 year olds (A3051073 CSR Table 14.3.1.2.1.1.3.1.a).

Phase 1 Studies

No subjects in Study A3051070 had treatment-emergent SAE's (SCS Supplemental Table bF14.3.1.2.1).

No subjects in Study A3051029 had treatment-emergent SAE's (SCS Supplemental Table aF14.3.1.2.1).

Discontinuations Due to Adverse Events

Study A3051073

In the Safety Population overall, a total of 12 subjects discontinued study treatment due to an AE: 6 (5.6%) varenicline high-dose, 2 (2.0%) low-dose varenicline, and 4 (4.0%) placebo subjects. Two of these subjects discontinued study treatment due to pregnancy (1 low-dose varenicline and 1 placebo; both remained in the study). Two of the subjects who discontinued treatment also discontinued the study; 1 (0.9%) high-dose varenicline and 1 (1.0%) placebo subject. Two additional subjects, both placebo, discontinued the study in the post-treatment phase due to post-treatment emergent AEs, 1 of which had discontinued study treatment due to previous AEs (A3051073 CSR Table 14.3.1.1.4, Table 14.3.1.1.1).

Among 12-17 year olds, 3 (3.8%) high-dose varenicline and 3 (4.0%) placebo subjects discontinued study treatment due to AEs, 1 subject in each of these treatment groups also discontinued the study due to the AEs. In addition, the 2 placebo subjects who discontinued the study in the post-treatment phase were 12-17 year olds (A3051073 CSR Table 14.3.1.1.4.1.a, Table 14.3.1.1.1.1.a)

Phase 1 Studies

No subjects discontinued due to an AE in Study A3051070 (SCS Supplemental Table bF14.3.1.2.1).

No subjects discontinued due to an AE in Study A3051029 (SCS Supplemental Table aF14.3.1.2.1).

Neuropsychiatric Adverse Events

Study A3051073

At the time of protocol development for Study A3051073, neuropsychiatric (NPS) events were emerging as a potential safety concern with the use of varenicline in adult smokers.

Therefore, an analysis of NPS events was included in Study A3051073.

A pre-specified list of NPS events of interest was used in the analysis (Study A3051073 SAP Appendix 1). In addition to volunteered NPS AEs, the study utilized the Neuropsychiatric Adverse Event Interview

(NAEI) to solicit NPS events (see Study A3051073 Protocol, Appendix 4). Treatment-emergent NPS AEs are summarized for the Safety Population overall in **Table 19** and for 12-17 year olds in **Table 20**.

Table 19 All-Causality Treatment-Emergent Neuropsychiatric Adverse Events, Study A3051073, Safety Population Overall

System Organ Class/ MedDRA Preferred Term	High-Dose Varenicline (N=108)	Low-Dose Varenicline (N=100)	Placebo (N=99)
	number of subjects (%)		
Number of subjects with NPS AEs	**18 (16.7)**	**11 (11.0)**	**12 (12.1)**
Number of NPS AEs	**30**	**18**	**23**
Number of volunteered NPS AEs	7	3	3
Number of solicited NPS AEs[a]	23	15	20
Nervous System Disorders	**1 (0.9)**	**0**	**0**
Disturbance in attention	1 (0.9)	0	0
Psychiatric Disorders	**17 (15.7)**	**11 (11.0)**	**12 (12.1)**
Agitation	9 (8.3)	5 (5.0)	5 (5.1)
Anxiety	6 (5.6)	4 (4.0)	7 (7.1)
Restlessness	1 (0.9)	0	1 (1.0)
Depressed mood	0	2 (2.0)	0
Depression	3 (2.8)	2 (2.0)	3 (3.0)
Dissociation	0	1 (1.0)	0
Hallucination	1 (0.9)	0	2 (2.0)
Mania	1 (0.9)	1 (1.0)	0
Flat affect	1 (0.9)	0	1 (1.0)
Hostility	7 (6.5)	3 (3.0)	4 (4.0)

a. Solicited through use of the Neuropsychiatric Adverse Event Interview.
Safety Population: All subjects who received at least 1 partial dose of study drug.
High Dose=1.0 mg BID or low body weight equivalent; Low Dose=0.5 mg BID or low body weight equivalent.
N=number of treated subjects; NPS=neuropsychiatric; AE=adverse event.
Treatment-emergent adverse events included the interval from first date of study drug to last date of study drug plus 30 days.
Subjects were counted only once per treatment in each row.
MedDRA v20.1.
Source: A3051073 Clinical Study Report Table 14.3.1.5.1.1, Table 14.3.1.5.6.1.1, Table 14.3.1.5.6.1.2.

NPS AEs were reported by 16.7%, 11.0% and 12.1% of high-dose varenicline subjects, low dose varenicline subjects, and placebo subjects, respectively. The majority of NPS events were solicited. The most frequent NPS AEs were Agitation (8.3%, 5.0%, 5.1%; high-dose varenicline, low-dose varenicline and placebo, respectively), Anxiety (5.6%, 4.0%, 7.1%), and Hostility (6.5%, 3.0%, and 4.0%). The majority of events were mild (27/30, 13/18, and 16/23) and none were severe (A3051073 CSR Table 14.3.1.5.6.1.1). None of the NPS AE's were SAEs and 1 low-dose varenicline subject and 3 placebo subjects discontinued treatment due to an NPS AE (A3051073 CSR Table 14.3.1.5.1.1).

Table 20 All-Causality Treatment-Emergent Neuropsychiatric Adverse Events, Study A3051073, Safety Population 12-17 Year Olds

System Organ Class/ MedDRA Preferred Term	High-Dose Var N=79	Low-Dose Var N=76	Pbo N=75
	Number of subjects (%)		
Number of subjects with NPS AEs	**11 (13.9)**	**4 (5.3)**	**4 (5.3)**
Number of NPS AEs	**18**	**5**	**8**
Number of volunteered NPS AEs	4	2	1
Number of solicited NPS AEs[a]	14	3	7
Nervous System Disorders	**1 (1.3)**	**0**	**0**
Disturbance in attention	1 (1.3)	0	0
Psychiatric Disorders	**10 (12.7)**	**4 (5.3)**	**4 (5.3)**
Agitation	4 (5.1)	1 (1.3)	1 (1.3)
Anxiety	3 (3.8)	1 (1.3)	3 (4.0)
Depression	1 (1.3)	1 (1.3)	2 (2.7)
Hallucination	1 (1.3)	0	2 (2.7)
Mania	1 (1.3)	0	0
Flat affect	1 (1.3)	0	0
Hostility	6 (7.6)	2 (2.6)	0

a. Solicited through use of the Neuropsychiatric Adverse Event Interview.
Safety Population: All subjects who received at least 1 partial dose of study drug.
High Dose=1.0 mg BID or low body weight equivalent; Low Dose=0.5 mg BID or low body weight equivalent.
N=number of subjects; BID=twice daily; NPS=neuropsychiatric; AEs=adverse events.
Treatment-emergent adverse events included the interval from first date of study drug to last date of study drug plus 30 days.
MedDRA v20.1.
Source: A3051073 Clinical Study Report Table 14.3.1.5.1.1.1.a; Table 14.3.1.5.6.1.1.1.a, Table 14.3.1.5.6.1.2.1.a.

Among 12-17 year olds, NPS AE's were reported by a higher percentage of high-dose varenicline subjects (13.9%) than low-dose varenicline (5.3%) and placebo subjects (5.3%).

The majority of NPS events were solicited. The most frequent NPS AEs were Agitation (5.1%, 1.3%, 1.3%; high-dose varenicline, low-dose varenicline and placebo, respectively), Anxiety (3.8%, 1.3%, 4.0%), and Hostility (7.6%, 2.6%, 0%). All NPS events were mild except for 1 report of Hallucination in a high-dose varenicline subject and 1 report of Anxiety in a low-dose varenicline subject which were moderate (A3051073 CSR Table 14.3.1.5.6.1.1.1.a), none were SAEs and none in varenicline subjects led to treatment discontinuation, although 3 placebo subjects discontinued treatment due to NPS AEs (A3051073 CSR Table 14.3.1.5.1.1.1.a).

Phase 1 Studies

In Study A3051070, two subjects reported NPS AEs of interest: 1 HBW high-dose varenicline subject reported mild Anger and 1 LBW low-dose varenicline subject reported moderate Mood swings. (SCS Supplemental Table bF14.3.1.2.6)

No subjects in Study A3051029 reported NPS AEs of interest. (SCS Supplemental Table aF14.3.1.2.6)

Other Psychiatric Assessments

In Study A3051073, the C-SSRS was administered at each clinic visit along with the Hospital Anxiety and Depression Scale (HADS). These scales were not administered in Studies A3051070 and A3051029.

In Study A3051073, psychiatric assessments were performed and reviewed by a qualified mental health professional who was a paediatric/adolescent psychiatrist or PhD paediatric/adolescent psychologist.

Columbia-Suicide Severity Rating Scale

In Study A3051073, there were few positive responses on the C-SSRS. During treatment (and up through 30 days after last study dose), 2 subjects had positive responses: 1 high-dose varenicline subject reported suicidal ideation and 1 placebo subject reported both suicidal ideation and self-injurious behaviour with no suicidal intent. During follow-up (31 days post-treatment to end of study), there were no positive C-SSRS responses. Additional information regarding C-SSRS responses is provided in the A3051073 CSR, Section 12.3.5.

There were two other subjects who had suicide-related post-treatment emergent AEs that were not reported on the C-SSRS. One high-dose varenicline subject was hospitalized for severe suicidal ideation 152 days after the last dose of study medication, and 1 low-dose varenicline subject was hospitalized for severe, non-suicidal self-injurious behaviour 178 days after the last dose of study medication. Details regarding these two subjects are provided in A3051073 CSR Section 14.3.3.

Hospital Anxiety and Depression Scale

Over the 12-week treatment period, there was a decline in mean HADS sub-scores for both anxiety and depression in all treatment groups, indicating slight improvement. Over the 40-week non-treatment follow-up period, sub-scores for anxiety and depression remained at or slightly below end-of-treatment levels in all treatment groups (A3051073 CSR Table 14.5.4.1.1).

Few subjects in any treatment group ([redacted] scores for [redacted] subjects) showed a ca either anxiety or depression. In most cases, this shift represented a worsening of scores, e.g., normal (0-7) to suggestive (8-10) or suggestive to probable (11+) (A3051073 CSR Table 14.5.4.2.1 and Table 14.5.4.3.1). One high-dose varenicline subject and 1 placebo subject improved at least 1 category in anxiety sub-score and 2 subjects in the high dose varenicline group improved at least 1 category in depression sub-score.

Postmarketing Data

A search of the Sponsor's safety database identified a total of 113 cases, out of the total of 134,996 varenicline cases as of 07 February 2018, which involved adolescent patients 12-17 years old. Among the 113 cases were 10 cases in which an overdose of varenicline was taken, 5 of the cases specified the overdose was a suicide attempt and four cases specified that the varenicline belonged to the patient's mother/grandmother. There were three cases of accidental ingestion of varenicline. In addition, there were eight cases in which it was stated the patient did not take varenicline/fill the prescription or it was unclear whether they had. These 21 cases were not considered in further case analysis.

Review of the remaining 92 cases identified 27 that included no AEs other than those that coded to a Preferred Term (PT) associated with the use of the drug in an adolescent. The 27 cases reported the following PTs: Product use issue (22), Drug administered to patient of inappropriate age (2), Drug prescribing error (1), Drug administration error (1), and off label use (1). One other case reported only the event of Tobacco user and one additional case reported only Blood carbon monoxide increased, which was related to the patient smoking and was not considered an adverse event by the reporter.

Among the remaining 63 cases, 27 had insufficient information to properly assess the case (including the Victim of homicide case). Another 10 cases included factors that could have contributed to the event(s), primarily medical history conditions (including the Completed suicide case). In the remaining 26 cases, a role for varenicline could not be ruled out. The PTs reported in these 26 cases do not suggest any new safety concerns in adolescents treated with varenicline relative to the known safety profile of varenicline in adults.

Additional details about the post marketing cases, which involved adolescent patients 12-17 years old, are provided in SCS Section 2.7.4.6.

CHMP comments

The pattern of adverse events in A3051073 was similar to the known adverse events profile of varenicline in adults. There are no signals indicating new safety concerns arising from study A3051073, or signals indicating that special concern for specific adverse events among adolescent varenicline-treated patients is warranted. Notably, this includes neuropsychiatric adverse events. The adverse event profile seems to be dose-related, with the low-dose varenicline group experiencing fewer adverse events than the high dose group, with an adverse events profile that is very similar to placebo, with the exception of higher percentages of nausea. The safety data from the two additional studies did not raise new concerns, and the post marketing data do not present any clear signals of concern.

MAH's Safety Conclusions

The safety results from Studies A3051073, A3051070 and A3051029 support the following conclusions:

- The most commonly reported AEs for all varenicline doses used in these studies were consistent with the known safety profile of varenicline in adults.
- In Study A3051073, in general, common AEs (reported in ≥5% of subjects) were reported in a higher percentage of high-dose varenicline subjects than low-dose varenicline subjects, overall (12-19 year olds) and in subgroups including 12-17 year olds and 12-16 year olds and 17-19 year olds.
- Based on categories pre-specified in Study A3051073 SAP, neuropsychiatric (NPS) AEs were analysed in this study. In general, the types of events, as well as their frequency and severity, raised no new safety concerns relative to the known safety profile of varenicline use in adults. Overall, the majority of NPS AEs (70%-90%) were mild, and none was severe.
- In Study A3051073, no differences in positive Columbia Suicide Severity Rating Scale (C-SSRS) responses or suicide-related AE's were seen among treatment groups.
- Based on analyses of safety data in subpopulations of subjects in A3051073 based on age, race, gender, and weight, no subpopulation of adolescents was identified to be at greater risk for safety concerns.
- Review of adolescent post marketing cases in the Sponsor's safety database did not identify any safety concerns specific to the adolescent population.

8.3. Discussion

Study A3051073 provided safety results suggesting that the adverse event profile of varenicline is similar among adolescents to the adverse event profile among adult smokers. This seems to be the case regardless of sex, weight, maturity or race. The incidence of adverse events increases with increased varenicline dose, probably resulting in lower compliance and treatment adherence, which the results of Study A3051073 may seem to suggest. Notably, there does not seem to be increased risk of neuropsychiatric adverse events, including suicide-related AE's, associated with varenicline treatment among adolescents. In all, the safety results in the studies of varenicline in adolescents do not give rise to new concerns about the drug's safety.

9. The MAH's Benefits and Risks Conclusions

Adolescents both in the US and globally continue to initiate cigarette smoking and research has shown that they can quickly become dependent on nicotine. Survey data show that many of these adolescent smokers want to quit but most are not successful.

Considering that in the US, 88% of adult daily smokers reported their first use of cigarettes occurred by 18 years of age and in the United Kingdom, 40% of regular smokers began smoking before the age of 16 years, and that the benefits of stopping smoking are greater for smokers who quit at a younger age, effective smoking cessation treatments for nicotine dependent adolescents represents an important and unmet medical need. To date, there has been only limited research to address this need and the results of the few studies that have been conducted have, for the most part, not been positive. Previous studies with smoking cessation methods, both pharmacological (bupropion and NRT) and non-pharmacological, that have shown efficacy in adults have failed to show consistent positive effects in adolescents.

Varenicline Study A3051073, the design of which was agreed with FDA and secondarily complied with EMA's Article 46 requirement of an assessment of the use of varenicline in 12-17-years old adolescents, addressed several elements of specific concern when treating adolescent smokers including: a longer titration period (2 weeks compared to the recommended 1 week in adults) to potentially improve tolerability, weight adjusted dosing to account for the smaller body size of adolescents compared to adults, evaluation of both the recommended adult dose (1 mg BID) and a lower dose (0.5 mg BID) and age-appropriate counselling that allowed flexibility to tailor to an individual subject's needs. The study inclusion criteria ensured the requirement for a nicotine-dependent adolescent population was met. Study inclusion criteria required subjects to have been smoking an average of at least 5 cigarettes per day during the 30 days prior to screening, to have a total score of 4 or higher on the FTND (adolescent version), which is consistent with at least moderate dependence, to be motivated to stop smoking and to have made at least 1 prior serious quit attempt.

Efficacy results from Study A3051073 showed that neither high-dose varenicline nor low dose varenicline had a statistically significant benefit compared to placebo in achieving smoking cessation in the study population overall (12-19 year olds) or in the subset of adolescents 12-17 years old. Regarding the primary endpoint of CAR for Week 9 through Week 12, among the 12-17 year olds in the FAS population, rates were 18.8% for high-dose varenicline subjects, 32.1% for low-dose varenicline subjects, and 17.1% for placebo subjects, with an OR for the high-dose vs placebo comparison of 1.13 (95% CI: 0.50 to 2.56) and a p-value of 0.7753 and an OR for low-dose varenicline vs placebo of 2.28 (95% CI: 1.06 to 4.89) and a p-value of 0.0347 (considered nominal and not statistically significant based on pre-specified statistical decision rules). Analyses of secondary cessation endpoints including CARs for Week 9 through Week 24 and Week 9 through Week 52, and 7-day point prevalence of abstinence at Weeks 12, 24 and 52, all supported the negative findings for the primary endpoint; no statistically significant differences

were noted for the high-dose varenicline vs placebo comparisons or the low-dose vs placebo comparisons. Likewise, reduction in number of cigarettes smoked at Weeks 12, 24 and 52 showed no statistically significant differences between varenicline and placebo. In addition, analyses of the primary and secondary endpoints in the Completer Subjects population and various sensitivity analyses did not demonstrate statistically significant efficacy results for either varenicline treatment group compared to placebo.

Safety results showed that both high-dose varenicline and low-dose varenicline were generally well tolerated in the overall study population and in 12-17 year olds and no new safety concerns were identified. The type and relative frequencies of common AEs were similar to those seen in adults treated with varenicline. The most common AEs in varenicline subjects 12-17 years old (5% of subjects either varenicline group) were: Nausea (22.8% high-dose varenicline, 19.7% low-dose varenicline, 8.0% placebo), Vomiting (10.1%, 1.3%, 1.3%), Upper respiratory tract infection (6.3%, 5.3%, 0%), Dizziness (5.1%, 9.2%, 2.7%), Agitation (5.1%, 1.3%, 1.3%), Headache (8.9%, 2.6%, 6.7%), and Hostility (7.6%, 2.6%, 0%). A total of 5 subjects had treatment-emergent SAEs, 4 of whom were 12-17 years old (3 high–dose varenicline, 1 placebo); none of the SAEs were considered related to study drug as judged by the Investigator. There were no deaths in the study. The safety profile in the two Phase 1 adolescent studies likewise raised no safety concerns.

PK analyses for Study A3051073 showed that the observed range of varenicline exposure was consistent with that expected for each dose and body weight group from the results obtained in the Phase 1 adolescent PK studies, supporting that varenicline dose and administration were appropriate.

The exposure-response analyses in Study A3051073 showed that the CAR Week 9 through Week 12 did not increase with increasing varenicline systemic exposure [i.e., AUC_{24}], as the logistic regression analyses for efficacy showed no significant relationship with AUC_{24}.

This finding, which is not consistent with what was seen in adults, supports the negative findings for the primary endpoint from the study. The nausea/vomiting incidence did increase linearly with increasing varenicline exposure; there was a statistically significant trend with the addition of AUC24 as a linear function (p-value <0.001). This finding, which is consistent with what was seen in adults, shows that varenicline was pharmacologically active in the adolescent subjects.

The relatively high rate of smoking abstinence in placebo-treated subjects (e.g., 17.1% in 12-17 year olds for CAR Week 9 through Week 12), which was similar to that seen in placebo groups in adult varenicline studies, suggests that the counselling provided to the adolescent subjects as part of the study conduct was appropriate and effective.

There was no evidence found of randomization failure, systematic study drug dispensing errors, or systematic errors in study conduct that would have impacted study outcomes.

Sensitivity analyses excluding data from a site that had GCP concerns, showed that those data had no impact on study outcomes.

In spite of the negative efficacy findings from Study A3051073, this study makes an important contribution to the limited body of research on pharmacotherapy smoking cessation treatments for adolescent smokers. The results are consistent with those of previous studies that have found that therapies that are efficacious in adults are not necessarily efficacious in adolescents.

Based on the A3051073 efficacy outcomes, the benefits of varenicline treatment in adolescents 12-19 years old or 12-17 years old have not been shown to outweigh the risks.

The MAH believes that Study A3051073 as designed and conducted satisfies the postmarketing requirement for CHAMPIX under PAM (MEA 047). Proposed CHAMPIX labeling revisions based on Study

A3051073 updating relevant sections of the SmPC (Sections 4.2, 5.1 and 5.2) and Package Leaflet, as recommended in the Article 46 Assessment Report, are being provided as part of this Type II variation.

CHMP comments

Adolescent smoking is a public health problem. There is limited research of pharmacological therapy for smokers in this age group, prior studies of bupropion and NRT have not shown efficacy, and A3051073 is the only clinical study of efficacy and safety of varenicline for young smokers, age 12-19.

The study design was agreed with the FDA and secondarily complied with EMA's Article 46 requirement of an assessment of the use of varenicline in 12-17-years old adolescents. The fundamental study design is deemed appropriate for demonstrating efficacy and safety in this population of smokers.

A3051073 was designed with 3 study groups (2 active-treatment arms and one placebo arm) and projected with a 100 study subjects per group, from postulated CAR rates week 9-12 (primary endpoint) of 24% for varenicline and of 9% for placebo. This turned out to be an unrealistically low expected placebo response rate, as the study resulted in a placebo response rate that is twice as high as was projected with in the study power calculation. Thus, the study may not be sufficiently powered to detect statistically significant differences between the active treatment groups and the placebo group. The analysis of efficacy results showed no significant treatment effect of varenicline at a high dose, while low-dose varenicline did result in reduced smoking as measured by the primary endpoint. The secondary endpoint of CAR response 9 to 52 weeks was also significantly better in the low-dose varenicline group. However, as the pre-specified analysis plan requires significant efficacy of high-dose treatment before a secondary analysis of low-dose treatment is made, these findings cannot serve as scientifically valid proof of efficacy of low-dose varenicline treatment. However, the results of A3051073 suggests that a clinically meaningful effect of low-dose varenicline treatment in adolescents may exist.

In conclusion, the efficacy results for varenicline in adolescent smokers are difficult to interpret with certainty, as it must be suspected that the MAH's rejection of vareniclines efficacy in adolescent smokers could be due to a Type II error.

However, the observation that the CAR Week 9 -12 did not increase with increasing varenicline systemic exposure in the pattern that has been observed in adults is interesting, and to some extent supports the efficacy results in A3051073.

The safety results showed that both high-dose varenicline and low-dose varenicline were generally well tolerated. The pattern of adverse events in A3051073 was similar to the adverse events profile of varenicline in adults. The adverse event profile seems dose-related, with the low-dose varenicline group experiencing fewer adverse events than the high-dose group, with an adverse events profile that is very similar to placebo, with the exception of higher percentages of nausea. There are no signals indicating new safety concerns arising from study A3051073, or from the two Phase 1 adolescent studies. This includes neuropsychiatric adverse events, which could conceivably be of concern in an immature target population. The MAH's post marketing database does not suggest new safety concerns in adolescents relative to the known safety profile of varenicline in adult smokers. In all, the safety results of the adolescent studies are reassuring, with the caveat that the overall Safety Population is of limited size.

Based on A3051073's efficacy outcomes, the benefits of varenicline treatment in adolescents of 12-17 years of age has not been demonstrated to outweigh the risks. However, it is debatable whether the Study A3051073 as designed and conducted satisfies the post marketing requirement for CHAMPIX under PAM (MEA 047).

The proposed labelling changes could be approvable, pending changes in the wording of the update of 5.1 in the SmPC.

10. PRAC advice

N/A

11. Risk management plan

The MAH submitted an updated RMP version 11.0 with data lock point of 31-05-2018 and final sign off date of 11-09-2018 with this application. The main proposed RMP changes were the following:

- The RMP has been updated to include information from the study A3051073 – "A twelve week randomised, double-blind, placebo controlled, parallel group, dose ranging study with follow-up evaluating the safety and efficacy of varanicline for smoking cessation in healthy adolescent smokers"
- The RMP has been rewritten to comply with the GVP module V (revision 2) format

In addition to the above, the following changes have been implemented to the safety concerns in the RMP (version 11.0) as a consequence of procedure EMEA/H/C/PSUSA/00003099/201705 (PSUR assessment for the reporting period 10-05-2014 to 09-05-2017) and endorsed by PRAC.

- The important potential risk "neuropsychiatric symptoms" has been removed from the RMP
- The missing information regarding "use in adolescents" has been removed from the RMP

Part II – SI Epidemiology of the indications and target population

Target Population and Indication
The target population for varenicline is adult smokers and the indication for which varenicline treatment is intended is smoking cessation. It was approved in the USA as Chantix in May 2006 and in Europe as Champix in September 2006 as an aid to smoking cessation treatment in adults, and smoking cessation in adults, respectively.

Incidence
Every year the Office of Applied Studies at the Substance Abuse and Mental Health Services Administration uses data from their annual National Survey of Drug Use and Health to retrospectively estimate the incidence of daily smoking in the USA. This incidence is expressed as number of persons initiating daily smoking for the first time per 1000 person-years. Since smoking typically begins during adolescence or early adulthood, incidence rates are estimated for these age groups only.

The incidence of daily smoking during 2003 was 29.5 among 12-17 years old subjects and 26.3 among 18-25 year-olds. Incidence rates for Europe were not found.

Prevalence
According to the WHO's "European Health for All" database, 28.8% of the adult population of the European Union (EU) smoked on a daily basis in 2002. In Europe, 29.4% smoked on a daily basis in 2002. The available data for individual countries in the EU indicate the highest smoking prevalence rates in Greece (37.6%), Germany (33.9%), and Hungary (33.8%). The lowest rates are in Sweden (16.2%), Belgium (20%), and Portugal (20.5%). The prevalence of daily smoking in the three most populous EU member states is 33.9% in Germany, 30% in France, and 26% in the United Kingdom.

CHMP comments

The module needs further updating as the requirements for the content have changed as outlined in the GVP module V guideline revision 2. Therefore, the module should give an overview of the epidemiology, avoid detailed discussions on specific epidemiology studies or published articles and should only present information that is relevant for the identification of the safety concerns. Furthermore, the module still refers to data e.g. for incidence and prevalence as they were in 2003. This should be updated with more recent data to give a more accurate overview of the epidemiology.

Part II – SII Non-clinical part of the safety specification

This module has been updated to comply with the GVP module V (rev 2) guideline. The module is acceptable as is.

Part II – SIII Clinical trial exposure

This module has been updated with data from the recently finalised study A3051073. The module is acceptable as is.

Part II – SIV Populations not studied in clinical trials

The following exclusion criteria were used in the pivotal studies within the development programme:

- Paediatric patients
  No longer considered missing information due to the study A3051073
- Use in pregnancy
  Still considered missing information
- Patients with chronic obstructive pulmonary disease
  No longer considered missing information due to the study A3051054
- Patients with cardiovascular disease
  Still considered missing information
- Patients with mental disorders
  No longer considered missing information due to the studies A3051072, A3051122 and A3051123

CHMP comments

As endorsed by PRAC, use in adolescents should no longer be considered missing information. The module is acceptable and in accordance with the GVP module V (rev 2) guideline.

Part II – SV Post authorisation experience

Method used to calculate exposure

Estimated patient exposure is based on an extrapolation of worldwide unit sales of varenicline, as reported by IQVIA (formerly IMS Health Prescribing Insights Medical) during the third quarter of 2006 through the first quarter of 2018. Dividing the total Standard Units by an estimated daily regimen of 2 units daily and by 365.25 days per year yields an estimate of total patient-years of exposure to varenicline. This estimate provides only an approximation of patient exposure. Many factors such as varying dosing levels and frequency, compliance issues and relationship between sales data and actual prescriptions confound a precise calculation of exposure.

Please note that these estimations of patient-years provide only a gross approximation of patient exposure, and should not be used to determine Adverse Event (AE) incidence or rates. The following factors hamper an accurate calculation of the total number of patients exposed to varenicline:

- Dosing and frequency vary for this product, particularly during the titration phase. The patient exposure estimate has been calculated using the typical dosing frequency, 2 times daily.
- Lack of adherence, as not all patients comply with their prescribed dosage regimen.

- As the patient exposure calculation is based on sales data, it does not necessarily correlate with the amount of varenicline administered.

Exposure
The cumulative worldwide marketing exposure to varenicline from 31-07-2006 (date of first marketing) through 31-05-2018 is estimated to be 5,789,363 patient-years. This estimated patient exposure is based on an extrapolation of worldwide sales of 4,229,129,793 units as reported by IQVIA during the third quarter of 2006 through the first quarter of 2018 and an estimated regimen of two units of varenicline daily. The sales from 01-04-2018 to 31-05-2018 have been extrapolated by taking the average of sales of previous 4 quarters.

Cumulative estimated exposure by indication, gender, age group, dose, formulation, and region extrapolated from data are tabulated in the RMP.

CHMP comments
The module has been updated to comply with the GVP module V (rev 2) guideline. The exposure data for varenicline has been updated to data lock point (31-05-2018) and tabulated by indication, age, gender, dose, formulation and region. The module is acceptable as is.

Part II – SVI Additional EU requirements for the safety specification
The chemical properties of varenicline make it an unlikely candidate for illegal, illicit, or surreptitious use. It can be synthesised only in an industrial setting. Its bitter taste would be difficult to mask. Varenicline is not a precursor for any currently controlled substance. Because of dose-limiting nausea and vomiting, it is unlikely that individuals would be able to increase the dose of varenicline in order to obtain increased pharmacologic effect.

CHMP comments
It is agreed that the potential for varenicline abuse or misuse is very limited. The module is acceptable as is.

Part II – SVII Identified and potential risks

SVII.1 - Identification of safety concerns in the initial RMP submission
No important identified risks were included in the initial EU-Risk Management Plan (RMP) submission, dated January 2006. The single important potential risk of effects of smoking cessation was included in the initial RMP submission.

Summary of safety concerns in the initial RMP	
Important identified risks	None
Important potential risks	Effects of smoking

SVII.2 - New safety concerns and reclassification with a submission of an updated RMP

There have been no newly identified safety concerns since submission of the previous EU- RMP that are considered to warrant inclusion in this update. From the previous RMP, there were no important identified risks, and the following important potential risks identified in the previous RMP remain in the current version.

Important Potential Risk 1: Myocardial Infarction
Following Post-Marketing (PM) reports of myocardial infarction (MI) in patients taking varenicline, the CHMP requested the varenicline SmPC to be updated with this information. The MAH reviewed the PM database and analysed all cases reporting MI-related events. From the analysis of the reported cases, it was concluded that the case frequency does not exceed the rate that could be expected based on current epidemiological knowledge, with most cases reporting coexisting cardiovascular risk factors. However, in

the opinion of the CHMP, the presence of cardiovascular risk factors does not exclude an additional contributory risk from the use of varenicline. Therefore, upon request by the CHMP, the following information was added to Section 4.8 of the SmPC: “PM cases of MI have been reported in patients taking varenicline.”

Based on the outcomes of the FDA review of Study A3051049 in smokers with stable CVD, it was noted that certain events, including heart attack, were reported more frequently in patients treated with varenicline than in patients treated with placebo. In addition, on 06-07-2011, following publication of a cardiovascular meta-analysis by Singh et al. in the Canadian Medical Association Journal (CMAJ), EMA requested the MAH to submit a variation to include more information on cardiovascular events in the Champix product information. On 22-07-2011, FDA requested conduct of a meta-analysis evaluating the incidence of cardiovascular AEs in varenicline-treated patients compared to control patients in MAH sponsored randomised CTs. The final study report for this analysis was submitted to EMA on 13-02-2012. On 22-09-2011, FDA issued a request for an amendment to Study A3051123 to include additional cardiovascular safety data collection and independent adjudication of cardiovascular events, including hospitalisation for cardiovascular and certain pulmonary diagnoses, including a non-treatment, 28-week extension (A3051148). Study A3051148 completed LSLV on 10-07-2015; the final clinical study report submission is due by March 2017. On 18-10-2012, the varenicline SmPC was updated following review of the meta-analysis of cardiovascular AEs in controlled varenicline clinical studies.

Important Potential Risk 2: Suicide/suicidal ideation

Since the submission of the January 2007 varenicline RMP, the Rapporteur communicated a request to assess suicidal ideation/suicide in relation to varenicline. Subsequently, a cumulative review of PM experience has been provided in each submitted PSUR. PhV and risk management activities relating to suicidal ideation/suicide are further discussed in III.1 and V.1, respectively. An analysis of varenicline benefit risk, with focus on suicide-related events was submitted to CHMP on 28-11-2008. The analysis outlined the phenomenon of stimulated PM reporting of suicide-related events that appeared to occur subsequent to initial media activity around a well-publicised case, followed by regulatory actions and MAH communications. Given the absence of a control group to inform the understanding of spontaneous reported events, their interpretation requires consideration of the population in which those events are occurring. When compared with the general population, the prevalence of depression and other psychiatric illnesses is significantly increased in smokers, who are at increased risk of suicide (in the absence of treatment with varenicline), thus complicating the understanding of the potential role of varenicline in the suicides reported in PM data. The analysis also contained a systematic review of what is known of the properties of varenicline relative to depression and suicide-related events, as demonstrated in the CT database and as described in the CT literature, which indicate that varenicline does not have a profile that would suggest a causal relationship to suicide-related events. Specifically, in controlled CTs, there was no evidence for an increased risk of depression or suicide-related events in smokers treated with varenicline compared to smokers receiving control treatments-in fact, the available evidence suggests that symptoms of depressed mood show some improvement in varenicline-treated patients compared to those treated with placebo. The MAH concluded that with appropriate continuing efforts to mitigate and to quantify risk, varenicline provides the best treatment option to aid patients seeking to escape the health consequences of smoking, and that the benefit/risk profile of varenicline remains very favourable. The Scientific Advisory Group (SAG) for Clinical Neuroscience (CNS) concluded that there is (at present) no suggestive evidence that depressed smokers on varenicline are at increased risk with regards to suicide-related events, over and above the increased risk they carry as a result of their previous history of depression, in line with the information currently reported in the SmPC. The view of the SAG was endorsed by CHMP.

The SAG also recommended that the MAH perform a CT in a population of smokers with previous and/concomitant depression, and missing information in patients with depression was added to the RMP

at that time. This double-blind, placebo controlled study in patients with a clinical diagnosis of major depressive disorder has been completed, and results are provided in the SmPC. No new safety concerns were identified in this study and the category of missing information in patients with depression has been removed at the time of update of the RMP.

A non-interventional study has also completed (A3051143; formerly NRA3050022), for which the primary objective was to assess whether current clinical practices among the Health Improvement Network GPs in the UK in managing individuals attempting to quit smoking with varenicline are consistent with the updated SmPC.

An overall evaluation of psychiatric events from pooled data (PAM 038) from clinical studies A3051072, A3051115, A3051095, A3051122 and A3051139 has also been conducted. A meta-analysis of these 5 randomised, double-blind, placebo-controlled trials, including a total of 1,907 subjects (1,130 varenicline, 777 placebo), was conducted to assess suicidal ideation and behaviour as reported on the Columbia Suicide Severity Rating Scale (C-SSRS). This meta-analysis included one trial (N = 127) in subjects with a history of schizophrenia or schizoaffective disorder and another trial (N = 525) in subjects with a history of depression. The results showed no increase in the incidence of suicidal ideation and/or behaviour in subjects treated with varenicline compared to subjects treated with placebo, with a Risk Ratio (RR) of 0.79 (95% CI: 0.46, 1.36). Forty-eight (48) of the 55 subjects who reported suicidal ideation or behaviour (24 varenicline, 24 placebo) were from the two trials that enrolled patients with a history of schizophrenia, schizoaffective disorder, or depression. Few patients reported these events in the other three trials (4 varenicline, 3 placebo). A second meta-analysis assessed a broad range of NPS AEs, including all High Level Group Terms (HLGTs) in the Psychiatric disorders SOC and was based on data from 18 completed randomised, double-blind, placebo-controlled trials (including the 5 trials in the C-SSRS meta-analysis). These 18 trials included a total of 8,521 subjects (5,072 varenicline and 3,449 placebo). The results of the analysis showed an increase in the HLGT Sleep disorders and disturbance for varenicline versus placebo; however, sleep-related AEs are known to be associated with varenicline treatment. Excluding events in the Sleep disorders and disturbances HLGT, the RR for varenicline versus placebo, per 100 subject years of exposure, for the Psychiatric disorders SOC overall was 1.01 (95% CI: 0.89, 1.15). When only moderate and severe AEs were considered, the RR was 0.90 (95% CI: 0.74, 1.09), showing no evidence of a statistically significant difference in risk between varenicline and placebo. The most frequent AEs in both treatment groups coded to the HLGTs Anxiety disorders and symptoms, depressed mood disorders and disturbances, and mood disorders and disturbances NEC, all of which encompass common nicotine withdrawal symptoms. Information regarding these analyses, as well as newly available observational study data, has been included in the varenicline SmPC.

On 29-10-2015, the A3051123 NPS safety study was completed, providing high-level evidence that the use of varenicline, bupropion, and NRT are not associated with an increased risk of NPS AEs, based on a composite primary endpoint of AE terms for which concern had been raised by PM reports for varenicline and bupropion. These study results add and confirm above data from meta-analyses of CT data and recently published large observational studies, outlined below.

Data from four large, independent population-based observational studies, which found no increased risk of serious NPS events, were previously added to the SmPC. These studies included patients with and without a history of psychiatric disorders and evaluated NPS hospitalisations, diagnoses of NPS events during emergency department visits and in-patient admissions, and fatal and non-fatal self-harm. Since these studies were included in the SmPC, the MAH has become aware of three additional independent population-based observational studies that have been published.

One of the studies was a national cohort study, which identified all Swedish residents aged 15 and older treated with varenicline between November 2006 and December 2009 using the Swedish national registers. The primary analyses evaluated the association of use of varenicline with three psychiatric

conditions (psychoses, mood conditions, and anxiety conditions), suicidal behaviour, criminal behaviour and traffic accidents and traffic offences. The study used a within person analyses to control for confounding by indication, such that each study subject served as his/her own control and time during varenicline treatment (12 weeks from the date of the first collected prescription) was compared to time while not treated with varenicline. The analyses also considered people with pre-existing psychiatric conditions and those without such conditions. A total of 69,757 individuals treated with varenicline were identified. There was no evidence that varenicline treatment was associated with an increased risk of suicidal behaviour, conviction for or suspicion of criminal offences, transport accidents, or conviction for or suspicion of traffic offences. Among those with pre-existing psychiatric conditions, varenicline treatment was associated with a small increased risk of incident anxiety conditions (Hazard Ratio [HR] =1.23; 95% CI: 1.01-1.51) and incident mood conditions (HR=1.31; 95% CI: 1.06-1.63) but not incident psychoses. Among those with no pre-existing psychiatric conditions, varenicline treatment was not associated with an increased risk of any of the three incident psychiatric conditions studied.

The second study compared the mental health status of adult smokers using varenicline or bupropion to smokers quitting without medication, current smokers and non-smokers using data from the 2006-2011 US Medical Expenditure Panel Survey. Mental health status was assessed using the mental component summary from the 12-item Short Form survey, 2-item Patient Health Questionnaire, and Kessler 6 Scale. A cross-sectional analysis of 125 new episodes of varenicline use, 453 new episodes of bupropion use, 1550 subjects who quit smoking without using drug, 7117 current smokers and 39,347 non-smokers was conducted. The results showed that after adjusting for potential confounders, the mental health status of varenicline users was not different from current smokers or former smokers who quit without medication, but was worse than non-smokers. Use of bupropion was strongly associated with lower mental health status compared to smokers, former smokers who quit without medication, and non-smokers, even after adjusting for pre-existing psychiatric disorders.

The third was a cohort study of National Health Service patients from England, which were identified from the validated QResearch database. Patients aged 18–100 years who received a prescription of NRT, bupropion, or varenicline were followed up for 6 months to compare NPS and cardiovascular events. In total, 164,766 patients who received a prescription (106,759 for nicotine replacement treatment; 6557 for bupropion; 51,450 for varenicline) between 01-01-2007 and 30-06-2012 were included in the analysis. Treatment with varenicline or bupropion resulted in no increased risk of any NPS or cardiovascular events compared with NRT. Varenicline was associated with a significantly reduced risk compared to NRT of depression (HR 0.66 [95% CI: 0.63, 0.69]) and self-harm (HR 0.56 [95% CI: 0.46, 0.68]), as well as cardiovascular events including the following:

- Ischaemic heart disease (HR 0.80 [95% CI: 0.72, 0.87),
- Cerebral infarction (HR 0.62 [95% CI: 0.52, 0.73]),
- Heart failure (HR 0.61 [95% CI: 0.45, 0.83]),
- Arrhythmia (HR 0.73 [95% CI: 0.60, 0.88]).

Important Potential Risk 3: Seizure events

Upon review of reported seizure cases presented in PSUR 3, the CHMP requested an update to the varenicline SmPC. It was noted by the Rapporteur that where varenicline was discontinued, the reported seizures resolved with no recurrences, and that the cases reported on seizure-related events gave rise to suspicion that varenicline further lowers the threshold for seizures in persons with predisposing risk factors, which lower the seizure threshold. Seizure-related events were first reviewed by the MAH in PSUR 2, and cumulative analyses were presented in PSUR 3, 4, 5 and 6. The cumulative review of seizure-related events for PSUR 6 compared seizure-related events in patients with a medical history of seizures with those in patients without a medical history of seizure. In addition, seizure-related events were previously discussed in the MAH's review submitted to the EMEA entitled “Champix (varenicline

tartrate)-PSUR 3 review: Response to the Rapporteur's Preliminary Assessment Report" (16-05-2008) and in the MAH's response "Overdose and seizure" (FUM 0030). A Retrospective Claims Database Analysis of New Onset Seizure Diagnosis in Varenicline Patients was also included and discussed in PSUR 5 (Section 9.2.1.4 and Appendix 12). PSUR 7 included a cumulative perspective and an analysis of current reporting period cases reporting seizure-related events. In addition, the results of a pre-clinical study examining the effect of varenicline on seizure threshold in rats and the occurrence of seizure-related events in varenicline CTs and in a prescription event monitoring study were discussed in PSUR 7. The MAH continues to monitor reported seizure cases, and a review of reported cases for the period is presented in PSURs. All reviews to date have concluded that an update to the varenicline labelling information is not warranted. However, based on the seriousness of the event, the potential risk of seizures was previously added to the RMP (Varenicline RMP version 8.0, Section 2.3.3). With the submission of PSUR 9 (DLP 10-05-2011- 09-05-2012), the Pharmacovigilance Risk Assessment Committee (PRAC) requested a cumulative report on seizure-like events and a revision of SmPC Sections 4.4, 4.8 and the Package Leaflet (PL), Sections 2 and 4. The CHMP adopted the PRAC recommendation on 13-12-2012, followed by the Commission Decision on 11-03-2013.

Important Risks Removed from the List of Safety Concerns
In accordance with the final PSUR assessment report (dated 11-01-2018) of the varenicline PSUR covering the reporting period of 10-05-2014 through 09-05-2017, the MAH in agreement with the PRAC recommendation has removed the important potential risk of neuropsychiatric symptoms since there is no evidence to support an increased risk of NPS with the use of varenicline.

SVII.3 – Details of important identified, important potential and missing information
The MAH has provided sufficient details for each of the safety concerns for varenicline.

CHMP comments
The information in sections SVII.1 and SVII.3 is sufficient and the sections are acceptable as is. Section SVII.2 however, needs revision, as only the recent changes to the safety concerns should be included and described in this section. Therefore, the text regarding myocardial infarction, suicide / suicidal ideation and seizure events should be deleted. Consequently, the focus should be on the removal of the safety concerns "neuropsychiatric symptoms" and "use in adolescents" and the reasoning behind this should be further elaborated.

Part II – SVIII Summary of the safety concerns
The MAH has provided the following summary table of the safety concerns.

Summary of safety concerns	
Important identified risks	• None
Important potential risks	• Myocardial infarction • Suicide / suicidal ideation • Seizure events
Missing information	• Use in patients with cardiovascular disease • Use in pregnancy

CHMP comments

The removal of the important potential risk "neuropsychiatric symptoms" is acceptable and in accordance with the conclusions of PSUSA procedure EMEA/H/C/00003099/201705.

As study A3051073 "a double-blind, placebo-controlled smoking cessation study in healthy adolescent smokers" has been finalised, it is agreed that the missing information "use in adolescents" can be deleted. This is also in line with PRAC endorsement following the above PSUSA procedure.

The module is acceptable as is. However, the MAH should reassess the safety concerns in light of the updated GVP module V (rev 2) as there are no additional risk minimisation measures or additional pharmacovigilance activities attached. Any changes to the safety concerns should be presented in module SVII.2 and properly justified. The entire RMP should be updated with any changes to the safety concerns.

Part III – Pharmacovigilance plan

Routine pharmacovigilance activities

There are no routine pharmacovigilance activities beyond adverse event reporting and signal detection.

Additional pharmacovigilance activities

There are no ongoing or planned additional pharmacovigilance activities to assess effectiveness of risk minimisation measures.

Summary table of additional pharmacovigilance activities

Not applicable.

CHMP comments

The specific adverse drug reaction follow-up questionnaires for "homicide" and for the safety concerns "suicide / suicidal ideation" and "seizure events" should be included and described in section III.1 – Routine pharmacovigilance activities. The format of Part III is otherwise in accordance with the GVP module V (rev 2) guideline.

Part IV – Plans for post authorisation efficacy studies

There are no planned post-authorisation efficacy studies that are conditions of the marketing authorisation or that are a specific obligation at this time.

Part V – Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

The MAH has provided the following summary table of pharmacovigilance activities and risk minimisation measures.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Myocardial infarction	Routine risk minimisation measures: SmPC sections 4.4, 4.8 & 5.1 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Suicide / suicidal ideation	Routine risk minimisation measures: SmPC sections 4.4, 4.8 & 5.1 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Seizure events	Routine risk minimisation measures: SmPC sections 4.4 & 4.8 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Use in patients with cardiovascular disease	Routine risk minimisation measures: SmPC sections 4.4 & 5.1 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None
Use in pregnancy	Routine risk minimisation measures: SmPC sections 4.6 & 5.1 Additional risk minimisation measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None

CHMP comments

The tables in modules V.1 and V.3 should be updated with references to the PIL, as the patient information leaflet is part of both routine risk minimisation measures and routine pharmacovigilance activities. The format of Part V is otherwise in accordance with the GVP module V (rev 2) guideline.

Part VI – Summary of the risk management plan

The modules I – II.C are acceptable and in accordance with the format outlined in the GVP module V (rev 2) guideline.

Annexes

In Annex 2 (tabulated summary of planned, ongoing and completed pharmacovigilance study programme), only three completed PASS studies are listed. However, according to GVP module V (rev 2) guideline, this annex should list all completed studies from previous RMP versions. The annexes are otherwise appropriate.

11.1. Overall conclusion on the RMP

☒ The changes to the RMP could be acceptable provided an updated RMP and satisfactory responses to the request for supplementary information are submitted.

On 08 May 2019 the MAH submitted RMP version 11.1, together with satisfactory responses to the request for supplementary information above outlined.

RMP version 11.1 is considered acceptable.

12. Changes to the Product Information

As a result of this variation, section(s) 4.2, 5.1 and 5.2 of the SmPC are being updated to

reflect that CHAMPIX is not recommended for use in paediatric patients because its efficacy in this population was not demonstrated . The Package Leaflet (PL) is updated accordingly.

Please refer to attachment 1 which includes all agreed changes to the Product Information.

13. Request for supplementary information

13.1. Major objections

Clinical aspects

None

RMP aspects

None

13.2. Other concerns

Clinical aspects

1. Instead of the proposed wording of the update of SmPC point 5.1:

   “Results from this study showed that neither varenicline dose significantly increased continuous abstinence rates at weeks 9 through 12 of treatment compared with placebo in subjects 12-19 years of age or in subjects 12-16 years of age. The study was not powered to assess efficacy in adolescent smokers 17-19 years of age, and in this group conclusions cannot be drawn.”

The MAH should present the actual results from **Table 5**, for the overall population and the 12-17 year-olds, with Confidence Intervals for the treatment comparisons. This should be done in order for the SmPC reader to get an overview of the study data.

RMP aspects

2. In Part II, module SI needs further updating as the requirements for the content have changed as outlined in the GVP module V guideline revision 2. Therefore, the module should give an overview of the epidemiology, avoid detailed discussions on specific epidemiology studies or published articles and should only present information that is relevant for the identification of the safety concerns. Furthermore, the module refers to data e.g. for incidence and prevalence as they were in 2003. This should be updated with more recent data to give a more accurate overview of the epidemiology.
3. In Part II, section SVII.2 requires revision, as only the recent changes to the safety concerns should be included and described in this section. Therefore, the text regarding myocardial infarction, suicide / suicidal ideation and seizure events should be deleted. Consequently, the focus should be on the removal of the safety concerns “neuropsychiatric symptoms” and “use in adolescents” and the reasoning behind this should be further elaborated.
4. In Part II module SVIII, the MAH should reassess the safety concerns in light of the updated GVP module V (rev 2) as there are no additional risk minimisation measures or additional pharmacovigilance activities attached to any of the safety concerns for Champix. Any changes to the safety concerns should be presented in module SVII.2 and properly justified. The entire RMP should be updated with any changes made to the safety concerns.
5. The pharmacovigilance plan (Part III.1 of the RMP) should be updated with information regarding the specific adverse drug reaction follow-up questionnaires for “homicide” and for the safety concerns “suicide / suicidal ideation” and “seizure events”.
6. In Part V, the tables in modules V.1 and V.3 should be updated with references to the PIL, as the patient information leaflet is part of both routine risk minimisation measures and routine pharmacovigilance activities.
7. In Annex 2 (tabulated summary of planned, ongoing and completed pharmacovigilance study programme), only three completed PASS studies are listed. However, according to GVP module V (rev 2) guideline, this annex should list all completed studies from previous RMP versions.

14. Assessment of the responses to the request for supplementary information

14.1. Major objections

Clinical aspects

None

RMP aspects

None

14.2. Other concerns

Clinical aspects

Question 1

Instead of the proposed wording of the update of SmPC point 5.1:

"Results from this study showed that neither varenicline dose significantly increased continuous abstinence rates at weeks 9 through 12 of treatment compared with placebo in subjects 12-19 years of age or in subjects 12-16 years of age. The study was not powered to assess efficacy in adolescent smokers 17-19 years of age, and in this group conclusions cannot be drawn."

The MAH should present the actual results from Table 11, for the overall population and the 12-17 year-olds, with Confidence Intervals for the treatment comparisons. This should be done in order for the SmPC reader to get an overview of the study data.

MAH's response

The MAH proposes to update Section 5.1 of the Summary of Product Characteristics with the results from Table 11 of the clinical overview as follows [deletions are shown in strike-through and additions in underlined red text].

As acknowledged in the Assessment report (Section 7.2 Results), the MAH has added a footnote to the table in the SmPC, to clarify the results for the prescriber that given the pre-specified statistical decision rules and the lack of statistical significance for the high-dose varenicline group, the p-value for the low dose varenicline vs. placebo result was also considered nominal and is therefore not statistically significant.

Paediatric Population

The efficacy and safety of varenicline was evaluated in a randomised, double-blind, placebo controlled study of 312 patients aged 12 to 19 years, who smoked an average of at least 5 cigarettes per day during the 30 days prior to recruitment, and had a score of at least 4 on the Fagerstrom Test for Nicotine Dependence scale. Patients were stratified by age (12-16 years of age and 17-19 years of age) and by body weight (≤55 kg and >55 kg). Following two-week titration, patients randomised to varenicline with a body weight >55 kg received 1 mg twice daily (high dose group) or 0.5 mg twice daily (low dose group), while patients with a body weight ≤55 kg received 0.5 mg twice daily (high dose group) or 0.5 mg once daily (low dose group). Patients received treatment for 12 weeks, followed by a non-treatment period of 40 weeks, along with age-appropriate counseling throughout the study.

~~Results from this study showed that neither varenicline dose significantly increased continuous abstinence rates at weeks 9 through 12 of treatment compared with placebo in subjects 12-19 years of age or in subjects 12-16 years of age. The study was not powered to assess efficacy in adolescent smokers 17-19 years of age, and in this group conclusions cannot be drawn. The varenicline safety profile in this study was consistent with that shown in adult studies (see sections 4.2 and 5.2).~~

The following table from the above paediatric study shows a comparison of continuous abstinence rates (CAR) from weeks 9-12, confirmed by urine cotinine test, for the full analysis set overall study population and the 12-17 year old population.

CAR 9-12 (%)	**Overall n/N (%)**	**12-to-17-Year Olds n/N (%)**
High-Dose Varenicline	22/109 (20.2%)	15/80 (18.8%)
Low-Dose Varenicline	28/103 (27.2%)	25/78 (32.1%)
Placebo	18/100 (18.0%)	13/76 (17.1%)
Treatment Comparisons	**Odds ratio in CAR 9-12 (95% CI) [p-value]**	
High-Dose Varenicline vs Placebo	1.18 (0.59, 2.37) [0.6337]	1.13 (0.50, 2.56) [0.7753]
Low-Dose Varenicline vs Placebo	1.73 (0.88, 3.39) [0.1114]	2.28 (1.06, 4.89) [0.0347]*

** This p value is not considered statistically significant. The prespecified statistical testing procedures stopped testing after the high dose varenicline vs Placebo treatment comparison in the overall study did not achieve statistical significance.*

CI=confidence interval; N=number of subjects randomized; n=the number of subjects who, at each visit from Weeks 9 to 12 (inclusive), reported no smoking and no use of other nicotine-containing products since the last study visit/last contact (on the Nicotine Use Inventory) and at any of these visits were confirmed to have quit based on urine cotinine test.

Assessment of the MAH's response

The proposed update of 5.1 presents the data from study A3051073, as requested. The inserted footnote is deemed necessary in order to avoid misunderstandings arising from the presented low p-value for Low-Dose Varenicline vs Placebo. In all, the update succinctly summarizes the study and its results.

Issue solved.

Conclusion

☒ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☐ No need to update overall conclusion and impact on benefit-risk balance

RMP aspects

Question 2

In Part II, module SI needs further updating as the requirements for the content have changed as outlined in the GVP module V guideline revision 2. Therefore, the module should give an overview of the epidemiology, avoid detailed discussions on specific epidemiology studies or published articles and should only present information that is relevant for the identification of the safety concerns. Furthermore, the module refers to data e.g. for incidence and prevalence as they were in 2003. This should be updated with more recent data to give a more accurate overview of the epidemiology.

Summary of MAH's response

The United States (US) National Library of Medicine PubMed and Embase databases were searched for primary research and literature reviews in the English language in humans published between 01-01-2000 and 28.02-2019. Particular focus was placed on identifying studies of European populations. The following search terms were used: "smoking" OR "cigarettes" OR "lung cancer" OR "other cancers" OR "coronary heart disease" OR "stroke/cerebrovascular disease" OR "respiratory disease" OR "suicide" OR "suicidal ideation" AND "incidence" OR "initiation" OR "prevalence" OR "risk factors" OR "comorbidities" OR "morbidity" OR "mortality".

Incidence and Prevalence

Every year the Substance Abuse and Mental Health Services Administration (SAMHSA) uses data from their annual National Survey of Drug Use and Health (NSDUH) to retrospectively estimate the incidence of daily smoking in the USA. This incidence is expressed as the number of persons who smoked part or all of a cigarette for the first time in the past 12 months. Since smoking typically begins during adolescence or early adulthood, incidence information is estimated for these age groups only. In 2017, an estimated 604,000 adolescents aged 12 to 17 years (i.e., 2.4% of adolescents) smoked part or all of a cigarette for the first time in the past year; this number averages to approximately 1,700 adolescents each day who initiated cigarette smoking. In 2017, 1.2 million young adults aged 18 to 25 years (i.e., 3.4% of young adults) initiated cigarette use in the past year, which translates to about 3,200 young adults who initiated cigarette use each day.

Similar information on cigarette initiation in Europe was not found. However, a 2018 pooled data analysis of six multicentre studies involved in the Ageing Lungs in European Cohorts consortium, which included 119,104 subjects from 17 countries, provided crude rates of smoking initiation per 1,000/year. In the male population, the crude incidence ranged from 15.2 to 66.4 among 11- to 15-year-olds, 18.1 to 67.1 among 16- to 20-year-olds, and 3.2 to 8.9 among 21- to 25-year-olds; in the female population, the crude incidene ranged from 22.3 to 80.2 among 11- to 15-year-olds, 20.1 to 67.3 among 16- to 20-year-olds, and 2.8 to 10.7 among 21- to 25-yeard-olds.

Demographics of the target population

Among EU member states, more men smoke as compared with women. The sole exception is Denmark, where 15% of male subjects and 17% of female subjects smoke.3 At the EU level, 2014 Eurostat data illustrate that the proportion of daily smokers of cigarettes was 17.5% among men aged 15 to 24 years vs. 13.5% among women aged 15 to 24 years, 29.7% among men aged 25 to 34 years vs. 19.2% among women aged 25 to 34 years, 28.0% among men aged 35 to 44 years vs. 19.0% among women aged 35 to 44 years, 25.9% among men aged 45 to 54 years vs. 20.6% among women aged 45 to 54 years, 22.3% among men aged 55 to 64 years vs. 16.8% among women aged 55 to 64 years, 12.2% among men aged 65 to 74 years vs. 8.4% among women aged 65 to 74 years, and 5.5% among men aged 75 years or older vs. 3.2% among women aged 75 years or older. The age profile of daily smokers was similar for men and women: the proportion increased between the age groups 15–24 years and 25–34 years; for the age groups from 25–34 years to 45–54 years, the proportion of daily smokers remained

generally high; thereafter the proportions fell, with by far the lowest proportion of daily smokers among the older age groups. Most EU member states follow this broad pattern, with the highest proportions reported between the ages of 25 and 54 and the lowest in the age groups over 65.6

No studies that evaluated smoking by race/ethnic origin at the EU level were found. However, studies in the UK revealed mixed results. A 2017 cross-sectional study that included routinely collected primary care data from four multi-ethnic London boroughs found that over half of white British and white Irish respondents had ever smoked while only a fifth of black African and Indian respondents had ever smoked. The researchers also discovered that respondents in all ethnic groups other than white Irish were significantly less likely to have ever smoked than white British, with odds ratios ranging from 0.21 (95% CI 0.21 to 0.22) for the Indian group to 0.90 (95% CI 0.89 to 0.91) for the other white group. However, a 2011 crude analysis of data from the Health Surveys for England indicated that Bangladeshi and Black Caribbean men report higher current smoking rates than other men, while white and Black Caribbean women smoke more frequently than other women do. Nonetheless, the smoking rates of Pakistani men and Black Caribbean women were significantly lower than white English people after adjusting for socio-economic status.

Assessment of the MAH's response

The module has been updated with recent data and the long descriptive paragraphs have been removed. The module is acceptable.

Issue resolved

Conclusion

☐ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒ No need to update overall conclusion and impact on benefit-risk balance

Question 3

In Part II, section SVII.2 requires revision, as only the recent changes to the safety concerns should be included and described in this section. Therefore, the text regarding myocardial infarction, suicide / suicidal ideation and seizure events should be shorten. Consequently, the focus should be on the removal of the safety concerns "neuropsychiatric symptoms" and "use in adolescents" and the reasoning behind this should be further elaborated.

MAH's response

All background information regarding myocardial infarction, suicide / suicidal ideation, and seizure events has been deleted from Section SVII.2.

Based on further evaluation regarding Question 4, the text in Section SVII.2 has been revised to include a rationale for removal of the important potential risk of neuropsychiatric symptoms, and the proposed removal of important potential risks of myocardial infarction, suicide / suicidal ideation, and seizure events that is consistent with criteria provided in GVP Module 5 (rev 2). The entire RMP has accordingly been updated to remove these safety concerns throughout. The rationale for removal of "use in adolescents" is also provided in Section SVII.2, as requested.

The following text is provided in module SVII.2.

There have been no newly identified safety concerns since submission of the previous EU- RMP that are considered to warrant inclusion in this update.

Regarding neuropsychiatric symptoms, Study A3051123 ('EAGLES' NPS Study) showed that the use of varenicline for smoking cessation in patients with or without history of psychiatric disorder was not associated with an increased risk of serious NPS AEs compared with placebo. In the final PSUR assessment report (dated 11-01-2018) of the varenicline PSUR covering reporting period of 10-05-2014 through 09-05-2017, PRAC concluded that there is no evidence to support an increased risk of neuropsychiatric symptoms with the use of varenicline. The MAH is in agreement with the PRAC's conclusion and has removed the important potential risk of NPS as a safety concern for varenicline.

The important potential risks of myocardial Infarction, suicide / suicidal ideation, and seizure events included in the prior version of this RMP were reassessed in light of the updated GVP module V (Rev 2) in order to determine the appropriateness of their continued inclusion at the time of the current update. For each of these risks, additional pharmacovigilance activities have been concluded and none of the safety concerns has been confirmed as important identified risks. No further additional pharmacovigilance activities are planned and there is no reasonable expectation that any pharmacovigilance activity could further characterise the risk. In addition, there are no additional risk minimisation measures attached to any of the safety concerns, beyond communication to healthcare professionals and patients via the SmPC and Patient Information Leaflet, respectively.

As there are no additional risk minimisation measures or additional pharmacovigilance activities attached to any of the safety concerns, including myocardial infarction, suicide / suicidal ideation, and seizure events, the MAH proposes to remove these safety concerns as important potential risks.

Missing information for use in adolescents is being removed at the time of this update, following completion of Study A3051073, A Twelve Week, Randomized, Double Blind, Placebo Controlled, Parallel Group, Dose Ranging Study with Follow up Evaluating the Safety and Efficacy of Varenicline for Smoking Cessation in Healthy Adolescent Smokers.

Although safety results of study A3051073 showed that varenicline was generally well tolerated and no new safety concerns were identified in the overall safety population at both high- and low-doses, the primary endpoint of continuous abstinence rate Week 9 through Week 12 was not met. Based on the A3051073 efficacy outcomes, the benefits of varenicline treatment in nicotine dependent adolescent smokers have not been shown to outweigh the risks. The SmPC will reflect this information to state that varenicline is not recommended in paediatric patients due to a lack of efficacy. Use in adolescents is no longer considered an area of missing information.

Assessment of the MAH's response

The module has been updated and the text regarding the safety concerns myocardial infarction, suicide / suicidal ideation, and seizure events has been updated as requested. Furthermore, the MAH's proposal to remove these risks from the RMP is agreed. The risks are well-known and fully characterised and furthermore, there are no additional pharmacovigilance or additional risk minimisation measures associated with these risks under use of varencline.

Issue resolved

Conclusion

☐ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒ No need to update overall conclusion and impact on benefit-risk balance

Question 4

In Part II module SVIII, the MAH should reassess the safety concerns in light of the updated GVP module V (rev 2) as there are no additional risk minimisation measures or additional pharmacovigilance activities attached to any of the safety concerns for Champix. Any changes to the safety concerns should be presented in module SVII.2 and properly justified. The entire RMP should be updated with any changes made to the safety concerns.

Summary of the MAH's response

Please see the response to Question 3. As per the updated GVP module V (rev 2), all important potential risks have been proposed to be removed from the varenicline RMP, since there are no additional risk minimisation measures or additional pharmacovigilance activities attached to any of the important potential risks.

Assessment of the MAH's response

The proposal to remove the important identified risks of myocardial infarction, suicide / suicidal ideation, and seizure events can be agreed as the risks are fully characterised and sufficiently managed in clinical settings. The missing information regarding use in patients with cardiovascular disease and use in pregnancy remain as safety concerns in the RMP.

Issue resolved

Conclusion

☐ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒ No need to update overall conclusion and impact on benefit-risk balance

Question 5

The pharmacovigilance plan (Part III.1 of the RMP) should be updated with information regarding the specific adverse drug reaction follow-up questionnaires for "homicide" and for the safety concerns "suicide / suicidal ideation" and "seizure events".

MAH's response

Since the MAH is proposing to remove all important potential risks from the varenicline RMP, the follow-up questionnaires have been removed from Annex 4.

Assessment of the MAH's response

The removal of the follow-up questionnaires is agreed.

Issue resolved

Conclusion

☐ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒ No need to update overall conclusion and impact on benefit-risk balance

Question 6

In Part V, the tables in modules V.1 and V.3 should be updated with references to the PIL, as the patient information leaflet is part of both routine risk minimisation measures and routine pharmacovigilance activities.

Summary of the MAH's response

Since the MAH is proposing to remove all important potential risks from the varenicline RMP, there are no routine risk minimization measures described in the RMP that require reference to the PIL. The PIL has now been referenced in the tables regarding areas of missing information.

Assessment of the MAH's response

The references made to the PIL are appropriate.

Issue resolved

Conclusion

☐ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒ No need to update overall conclusion and impact on benefit-risk balance

Question 7

In Annex 2 (tabulated summary of planned, ongoing and completed pharmacovigilance study programme), only three completed PASS studies are listed. However, according to GVP module V (rev 2) guideline, this annex should list all completed studies from previous RMP versions.

MAH's response

The MAH has updated RMP Annex 2 as requested.

Assessment of the MAH's response

The MAH has provided a tabulated summary of all planned ongoing and completed pharmacovigilance studies for Champix as requested.

Conclusion

☐ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒ No need to update overall conclusion and impact on benefit-risk balance

15. Attachments

1. Product Information (changes highlighted) as adopted by the CHMP on 16 May 2019.