# Signatures for Multi-Disciplinary Review and Evaluation: NDA 021928/S-048

| Reviewer Discipline | Reviewer Name | Reviewer Signature (PDF with PIV card) |
|---|---|---|
| Nonclinical Reviewer | Kevin Snyder, PhD | Kevin P. Snyder -S<br>Digitally signed by Kevin P. Snyder -S<br>DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001528698, cn=Kevin P. Snyder -S<br>Date: 2019.02.19 13:58:00 -05'00' |
| Nonclinical Team Leader | Newton Woo, PhD | Newton Woo -S<br>Digitally signed by Newton Woo S<br>DN: c=US, o=U S Government, ou=HHS, ou=FDA, ou=People, cn=Newton Woo S, 0 9 2342 19200300 100 1 1=2000268920<br>Date: 2019 02 15 17:09:33 05'00' |
| Supervisory Pharmacologist | Daniel Mellon, PhD | Richard D. Mellon -S<br>Digitally signed by Richard D. Mellon -S<br>DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300169476, cn=Richard D. Mellon -S<br>Date: 2019.02.18 09:31:58 -05'00' |
| Office of Clinical Pharmacology Reviewer(s) | David Lee, PhD | David J. Lee -S<br>Digitally signed by David J Lee S<br>DN: c=US o=U S Government ou=HHS ou=FDA ou=People cn=David J Lee S<br>0 9 2342 19200300 100 1 1=1300083029<br>Date: 2019 02 19 10:21:27 05'00' |
| Office of Clinical Pharmacology Team Leader | Kevin Krudys, PhD | Kevin Krudys -S<br>Digitally signed by Kevin Krudys -S<br>DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Kevin Krudys -S,<br>0.9.2342.19200300.100.1.1=2000344822<br>Date: 2019.02.16 13 48:43 -05'00' |
| Office of Clinical Pharmacology Team Leader | Yun Xu, PhD | Yun Xu -S<br>Digitally signed by Yun Xu -S<br>DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Yun Xu -S,<br>0.9.2342.19200300.100.1.1=1300437807<br>Date: 2019.02.19 13:16:57 -05'00' |
| Clinical Reviewer | Maryam Afshar, MD | Maryam Afshar -S<br>Digitally signed by Maryam Afshar -S<br>DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Maryam Afshar -S,<br>0.9.2342.19200300.100.1.1=2002248031<br>Date: 2019.02.15 16:52:11 -05'00' |
| Clinical Team Leader and Cross-Disciplinary Team Leader | Celia Winchell, MD | Celia J. Winchell -S<br>Digitally signed by Celia J. Winchell -S<br>DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9 2342.19200300.100.1.1=1300101564, cn=Celia J. Winchell -S<br>Date: 2019.02.15 16:47:46 -05'00' |
| Statistical Reviewer | Kate Meaker, MS | Katherine B. Meaker -S<br>Digitally signed by Katherine B Meaker S<br>DN: c=US o=U S Government ou=HHS ou=FDA ou=People<br>0 9 2342 19200300 100 1 1=1300117588 cn=Katherine B Meaker S<br>Date: 2019 02 19 00:24:43 05'00' |
| Statistical Team Leader | David Petullo, MS | David M. Petullo -S<br>Digitally signed by David M. Petullo -S<br>DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300376368, cn=David M. Petullo -S<br>Date: 2019.02.19 08:09:38 -05'00' |
| Deputy Division Director/Signatory Authority | Rigoberto Roca, MD | Rigoberto A. Roca -S<br>Digitally signed by Rigoberto A. Roca -S<br>DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300096459, cn=Rigoberto A. Roca -S<br>Date: 2019.02.20 14:42:20 -05'00' |

# NDA/BLA Multi-Disciplinary Review and Evaluation

| | |
|---|---|
| **Application Type** | sNDA |
| **Application Number(s)** | 021928 |
| **Priority or Standard** | Priority |
| **Submit Date(s)** | 08/22/18 |
| **Received Date(s)** | 08/22/18 |
| **PDUFA Goal Date** | 02/22/19 |
| **Division/Office** | DAAAP/ODEII/OND |
| **Review Completion Date** | 02/15/2019 |
| **Established/Proper Name** | Varenicline tartrate |
| **(Proposed) Trade Name** | Chantix® |
| **Pharmacologic Class** | Selective α4β2 nicotinic acetylcholine partial agonist |
| **Applicant** | Pfizer, Inc. |
| **Doseage form** | Oral tablet 0.5 mg, 1 mg |
| **Applicant proposed Dosing Regimen** | N/A |
| **Applicant Proposed Indication(s)/Population(s)** | Aid to smoking cessation treatment in adults |
| **Recommendation on Regulatory Action** | Approve |
| **Recommended Indication(s)/Population(s)** (if applicable) | Aid to smoking cessation/ Adults |
| **Recommended Dosing Regimen** | 1 mg bid |

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## Reviewers of Multi-Disciplinary Review and Evaluation

| | |
|---|---|
| **Regulatory Project Manager** | Kimberly Compton,RPh |
| **Nonclinical Reviewer** | Kevin Snyder, Ph.D. |
| **Nonclinical Team Leader** | Newton Woo, Ph.D. |
| **Office of Clinical Pharmacology Reviewer(s)** | David Lee, Ph.D. |
| **Office of Clinical Pharmacology Team Leader(s)** | Kevin Krudys, Ph.D. Yun Xu, Ph.D. |
| **Clinical Reviewer** | Maryam Afshar, MD |
| **Clinical Team Leader** | Celia Winchell, MD |
| **Statistical Reviewer** | Kate Meaker, MS |
| **Statistical Team Leader** | David Petullo, MS |
| **Cross-Disciplinary Team Leader** | Celia Winchell, MD |
| **Deputy Division Director** | Rigoberto Roca, MD |

Glossary

| | |
|---|---|
| AC | advisory committee |
| ADME | absorption, distribution, metabolism, excretion |
| AE | adverse event |
| AR | adverse reaction |
| BLA | biologics license application |
| BPCA | Best Pharmaceuticals for Children Act |
| BRF | Benefit Risk Framework |
| CBER | Center for Biologics Evaluation and Research |
| CDER | Center for Drug Evaluation and Research |
| CDRH | Center for Devices and Radiological Health |
| CDTL | Cross-Discipline Team Leader |
| CFR | Code of Federal Regulations |
| CMC | chemistry, manufacturing, and controls |
| COSTART | Coding Symbols for Thesaurus of Adverse Reaction Terms |
| CRF | case report form |
| CRO | contract research organization |
| CRT | clinical review template |
| CSR | clinical study report |
| CSS | Controlled Substance Staff |
| DMC | data monitoring committee |
| ECG | electrocardiogram |
| eCTD | electronic common technical document |
| ETASU | elements to assure safe use |
| FDA | Food and Drug Administration |
| FDAAA | Food and Drug Administration Amendments Act of 2007 |
| FDASIA | Food and Drug Administration Safety and Innovation Act |
| GCP | good clinical practice |
| GRMP | good review management practice |
| ICH | International Conference on Harmonisation |
| IND | Investigational New Drug |
| ISE | integrated summary of effectiveness |
| ISS | integrated summary of safety |
| ITT | intent to treat |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mITT | modified intent to treat |
| NCI-CTCAE | National Cancer Institute-Common Terminology Criteria for Adverse Event |
| NDA | new drug application |
| NME | new molecular entity |
| OCS | Office of Computational Science |
| OPQ | Office of Pharmaceutical Quality |
| OSE | Office of Surveillance and Epidemiology |
| OSI | Office of Scientific Investigation |

| | |
|---|---|
| PBRER | Periodic Benefit-Risk Evaluation Report |
| PD | pharmacodynamics |
| PI | prescribing information |
| PK | pharmacokinetics |
| PMC | postmarketing commitment |
| PMR | postmarketing requirement |
| PP | per protocol |
| PPI | patient package insert (also known as Patient Information) |
| PREA | Pediatric Research Equity Act |
| PRO | patient reported outcome |
| PSUR | Periodic Safety Update report |
| REMS | risk evaluation and mitigation strategy |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SGE | special government employee |
| SOC | standard of care |
| TEAE | treatment emergent adverse event |

# 1 Executive Summary

## 1.1. Product Introduction

Chantix® (varenicline) is a partial α4β2 acetylcholine nicotinic receptor agonist approved on 5/10/06 as an aid to smoking cessation in adults. The recommended dose of Chantix is 1 mg orally twice daily following a 1- week titration as follow:

Days 1 – 3: 0.5 mg once daily
Days 4 – 7: 0.5 mg twice daily
Day 8 – end of treatment: 1 mg twice daily

## 1.2. Conclusions on the Substantial Evidence of Effectiveness

The effectiveness of Chantix® in adults has been established in several premarketing studies as well as multiple postmarket supplemental applications. However, the efficacy study in adolescents did not provide evidence of effectiveness.

## 1.3. Benefit-Risk Assessment

**Benefit-Risk Summary and Assessment**

It is well established that smoking can cause major health problems in all age groups, and remains one of the major preventable causes of morbidity and mortality. Most smokers have their first cigarette before age 18. Adolescent smokers are believed to smoke for reasons that are different from adults and their motivation to stop and response to treatment are affected by a variety of factors, including peer pressure.

Studies show that treatments that are effective in adults, including some behavioral approaches, are not effective in adolescents. Furthermore, nicotine replacement therapy studies and one bupropion study have not provided evidence for effectiveness in adolescents.

In 2006, Chantix was approved as smoking cessation aid for adults. Some of the established safety issues in adults are: Neuropsychiatric adverse events, seizures, cardiovascular events, somnambulism and nausea.

Efficacy and safety studies of Chantix in adolescents were required under the authorities of the Pediatric Research Equity Act (PREA). Although the safety data suggest a similar safety profile as what was seen in adults and no safety issues specific to youth were identified, the study in adolescents did not show evidence of effectiveness. Chantix is not recommended in adolescents for smoking cessation because its effectiveness is not demonstrated, and the benefits of treatment do not outweigh the risks.

| Dimension | Evidence and Uncertainties | Conclusions and Reasons |
|---|---|---|
| Analysis of Condition | Approximately 3.6 million middle and high school students were current tobacco users in 2017.[1] Adolescent smokers are believed to smoke for a variety of reasons such as peer pressure, impulsivity and risk-taking behavior. Bupropion and nicotine replacement therapies have not shown clear evidence for effectiveness. Furthermore, non- pharmacologic smoking cessation methods that are effective in adults are not effective in adolescents. | Smoking can cause major health problems in all age group. |
| Current Treatment Options | Treatment options in adults are:<br>• Nicotine replacement: (Nicorette gum and lozenge, nicotine patch, nicotine oral inhaler, nasal spray)<br>• Bupropion (Zyban)<br>• Varenicline tartrate (Chantix) | There are no approved pharmacotherapy agents for smoking cessation in adolescents. |
| Benefit | The study did not provide evidence that treatment with Chantix can provide benefit in smoking cessation in adolescents. | Chantix is not recommended for smoking cessation in adolescents. |
| Risk and Risk Management | Some of the established safety issues of Chantix in adults are: Neuropsychiatric adverse events, seizures, cardiovascular events, somnambulism and nausea. These are the same in adolescents. | Review of the safety data did not identify any safety issues specific to adolescents. Considering that effectiveness is not established, the benefits of treatment with Chantix in adolescents do not outweigh the risks. |

[1] Wang, T. W., Gentzke, A., Sharapova, S., Cullen, K. A., Ambrose, B. K., & Jamal, A. (2018, June 8). Tobacco product use among middle and high school students – United States, 2011-2017. *Morbidity and Mortality Weekly Report, 67*(22), 629-633. Retrieved from https://www.hhs.gov/ash/oah/adolescent-development/substance-use/drugs/tobacco/trends/index.html

### 1.4. Patient Experience Data

Patient experience data was not submitted as part of this application.

## 2 Therapeutic Context

### 2.1. Analysis of Condition

It is well-established that smoking has major health and economic consequences. According to National Youth Tobacco Survey, in 2018 the rate of cigarette smoking among youth was 8.1%. It is estimated that 1,180,000 high school students and 200,00 students in middle smoke cigarettes.[2] Smoking affects nearly every organ system and is a risk factor for cancer, cardiovascular disease and chronic obstructive pulmonary disease. Studies have shown link between smoking and some cancers such as lung and bladder cancer and association with other cancers including colorectal and liver.

Smoking causes major health problems in all age groups and remains one of the main preventable causes of morbidity and mortality.

### 2.2. Analysis of Current Treatment Options

Smoking cessation treatments include pharmacological and/or behavioral approaches. Nicotine replacement therapy (NRT), varenicline and bupropion, are FDA approved products for adults, however, there are no approved pharmacological products in children and adolescents.

[2] Gentzke AS, Creamer M, Cullen KA, et al. Vital Signs: Tobacco Product Use Among Middle and High School Students — United States, 2011–2018. MMWR Morb Mortal Wkly Rep. ePub: 11 February 2019. DOI

**Table 1 Drugs Used as Aids to Smoking Cessation**

| Generic Name | Trade Name | Application Holder(s) | Dosage Form(s) |
|---|---|---|---|
| Nicotine polacrilex | Nicorette gum, chewing (OTC, also generic) | GlaxoSmithKline Consumer Healthcare LP | Chewing pieces (transmucosal) |
| Nicotine polacrilex | Nicorette (F/K/A Commit) Lozenge (OTC; also generic) Nicorette Mini-Lozenge | GlaxoSmithKline Consumer Healthcare LP | Lozenges- buccal delivery system |
| Nicotine patch | Habitrol (also generic) | Dr. Reddy | Transdermal Film, extended release |
| Nicotine patch | Nicoderm CQ (also generic) | Sanofi Aventis/ GlaxoSmithKline Consumer Healthcare LP | Transdermal Film, extended release |
| Nicotine oral inhaler | Nicotrol | Pfizer/ Pharmacia and Upjohn | Cartridge with mouth pieces- buccal delivery system |
| Nicotine nasal spray | Nicotrol | Pfizer/ Pharmacia and Upjohn | Solution with metered spray pump |
| Bupropion | Zyban | GlaxoSmithKline | Oral tablets |
| Varenicline tartrate | Chantix® | Pfizer, Inc. | Oral tablets |

# 3 Regulatory Background

## 3.1. U.S. Regulatory Actions and Marketing History

Chantix® (varenicline) is a partial α4β2 acetylcholine nicotinic receptor agonist approved in May 2006 as an aid to smoking cessation in adults. The treatment regimen is 1 mg twice daily after an initial one-week titration, for 12 weeks. A second 12-week course may be taken to help with maintaining abstinence.

Since the initial approval, several efficacy supplements and modifications to the safety information in the labelling have been approved. One of the significant findings in postmarketing experience with Chantix has been neuropsychiatric symptoms including depression, suicidality, aggression and perceptual abnormalities included in the label under Warnings and Precautions.

## 3.2. Summary of Presubmission/Submission Regulatory Activity

This supplement is supported by an efficacy study (A3051073), to evaluate the safety and efficacy of varenicline for smoking cessation in adolescents, which was conducted to fulfill a post-marketing commitment made at the time of approval, as well as in response to a Pediatric Written Request (PWR).

The original approval letter contained the following text concerning pediatric studies:

Your deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) are considered required postmarketing study commitments. The status of these postmarketing studies shall be reported annually according to 21 CFR 314.81. These commitments are listed below.
1. To conduct a study to determine the multiple-dose pharmacokinetics of varenicline in pediatric patients in order to determine the appropriate doses for efficacy and safety evaluations in adolescent smokers, ages 12 through 16, inclusive, to determine the adverse event profile in adolescent patients, and to establish whether there is any age group (or weight group) for whom varenicline is so poorly tolerated that its utility as an aid to smoking cessation treatment should not be evaluated in that group.
Final Report Submission: by November 10, 2007

2. To conduct a study to determine whether varenicline, as part of an overall smoking cessation program, is effective in achieving and maintaining smoking cessation in tobacco-addicted adolescents, ages 12 through 16, inclusive, to determine a safe and effective dose, and to document the ability of treating physicians to select appropriate patients. You will need to develop a means for determining reliable criteria for appropriate patient selection of tobacco-addicted teens so that teenage smokers who are not addicted will not be recruited, and so that labeling can convey these criteria to physicians who may wish to use the drug in adolescents.

Final Report Submission: by May 10, 2011
In addition, under the Best Pharmaceuticals for Children Act (BPCA), a PWR was issued on June 12, 2007, requesting the studies also described in the approval letter. Satisfactory completion of these studies would qualify Pfizer for a 6-month period of Pediatric Exclusivity under BPCA. Due to difficulties with enrollment of the younger adolescent cohort, the WR was revised in 2010 to extend the timeframe of submitting the reports of the study until October 15, 2014. Subsequent revision # 2 extended the timeframe until April 15, 2016 and revision #3 until December 6, 2018. Revision 1 also included changes to the study design, eligibility criteria, and safety endpoints.

The sponsor randomized 312 subjects and the study report was submitted in August 2018.

# 4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

## 4.1. Office of Scientific Investigations (OSI)

Inspection was not requested because no efficacy claims were proposed by the Applicant based on the result of this study.

## 4.2. Product Quality

No new information.

## 4.3. Clinical Microbiology

Not applicable.

## 4.4. Devices and Companion Diagnostic Issues

Not applicable.

# 5 Nonclinical Pharmacology/Toxicology

## 5.1. Executive Summary

No new information.

## 5.2. Referenced NDAs, BLAs, DMFs

None.

## 5.3. Pharmacology

The text below, adapted from the approved labeling, summarizes the clinical pharmacology of Chantix:

Varenicline binds with high affinity and selectivity at α4β2 neuronal nicotinic acetylcholine receptors and stimulates receptor-mediated activity, but at a significantly lower level than nicotine. Varenicline blocks the ability of nicotine to activate α4β2 receptors and thus to stimulate the central nervous mesolimbic dopamine system, believed to be the neuronal mechanism underlying reinforcement and reward experienced upon smoking.

Absorption of varenicline is virtually complete after oral administration and systemic bioavailability is ~90%. Cmax occurs within 3-4 hours of administration, T1/2 is approximately 24 hours, and steady-state conditions are reached in 4 days. Bioavailability is unaffected by food or time of day. Plasma protein binding is low and independent of age and renal function. Varenicline undergoes minimal metabolism, with 92% excreted unchanged in the urine. There are no clinically meaningful differences in varenicline pharmacokinetics due to age, race, gender, smoking status, or use of concomitant medications, as demonstrated in specific pharmacokinetic studies and in population pharmacokinetic analyses.

In subjects with moderate renal impairment, varenicline exposure increased 1.5-fold compared with subjects with normal renal function. In subjects with severe renal impairment (estimated creatinine clearance <30 mL/min), varenicline exposure was increased 2.1-fold. Dose reduction is recommended for patients with renal impairment. Due to the absence of significant hepatic metabolism, varenicline pharmacokinetics should be unaffected in patients with hepatic impairment.

No clinically meaningful pharmacokinetic drug-drug interactions have been identified. In vitro studies demonstrated that varenicline does not inhibit renal transport systems or the following cytochrome P450 enzymes (IC50 >6400 ng/mL): 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and

3A4/5. Also, in human hepatocytes in vitro, varenicline does not induce the cytochrome P450 enzymes 1A2 and 3A4.

Although co-administration of varenicline (1 mg twice daily) and transdermal nicotine (21 mg/day) for up to 12 days did not affect nicotine pharmacokinetics, the incidence of adverse reactions was greater for the combination than for transdermal nicotine alone.

### 5.4. Toxicology

#### 5.4.1. General Toxicology

No new information.

# 6 Clinical Pharmacology

## 6.1. Executive Summary

The clinical pharmacology of varenicline in adolescent smokers was characterized in Studies A3051029, A3051070 and A3051073. Studies A3051029 and A3051070 are single- and multiple-dose PK studies, respectively, in adolescent smokers and were reviewed previously (Dr. Nallani, 10/05/2011). Conclusions from these two studies are included in the current label. The efficacy study, A3051073, included the collection of PK samples at random times at weeks 3, 6 and 12 or at an early termination visit. The Applicant performed a population PK analysis using pooled data from the three studies. Results were consistent with previous observations and demonstrated that varenicline clearance and volume of distribution increase with increasing body weight. No relationship between varenicline exposure ($AUC_{0\text{-}24h}$) and efficacy (Week 9-12 Continuous Abstinence Rate CAR) was observed, consistent with the negative findings for the primary endpoint in the study. The incidence of nausea/vomiting was found to increase with increasing varenicline exposure. Female adolescent smokers had a higher incidence of nausea relative to male adolescent smokers, regardless of treatment. This finding is consistent with observations in adult smokers.

# 7 Sources of Clinical Data and Review Strategy

## 7.1. Table of Clinical Studies

**Table 2 Listing of Clinical Trials Relevant to this NDA/BLA**

| Trial Identity | Trial Design | Regimen/ schedule/ route | Study Endpoints | Treatment Duration/ Follow Up | No. of patients enrolled | Study Population | No. of Centers and Countries |
|---|---|---|---|---|---|---|---|
| ***Controlled Studies to Support Efficacy and Safety*** | | | | | | | |
| A3051073 | 12 week, R, DB, PC, PG, dose-ranging with follow-up | 0.5 mg-1mg/ bid/po | 4-week continuous quit rate (CQR) from Week 9 to 12 | 12 wks/ 40 wks | 312 | Adolescent smokers (12-19 yo) | 74 sites/ 6 countries |
| Studies to Support Safety | | | | | | | |
| A3051070 | R, DB, PC, PG 14-day treatment period, 4-day follow-up period | 0.5-1 mg/ bid/ po | multiple-dose PK of varenicline in adolescent smokers | 14 days/ 4 days | 73 (72 dosed) | Adolescent smokers, 12 to 16 years of age | 16/2 |
| A3051029 | R, SO ISB, PC, PG, single dose | 0.5- 1 mg/ once/ po | single-dose pharmacokinetics of varenicline at 0.5 and 1 mg in adolescent smoking subjects | Single dose | 27 | Adolescent smokers (12-17 yo) | 1 |

### 7.2. Review Strategy

This review includes one efficacy study (A3051073) that the applicant considered negative. The study was further reviewed for any indication of a treatment response. In addition to the efficacy study, studies A3051070 (multi-dose PK study) and A3051029 (Single-dose PK study) were reviewed for safety.

# 8 Statistical and Clinical and Evaluation

## 8.1. Review of Relevant Individual Trials Used to Support Efficacy of Varenicline For Smoking Cessation in Healthy Adolescent Smokers

### 8.1.1. **Study A3051073** (Twelve-Week, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Dose-Ranging Study with Follow-Up Evaluating the Safety and Efficacy)

**Trial Design**

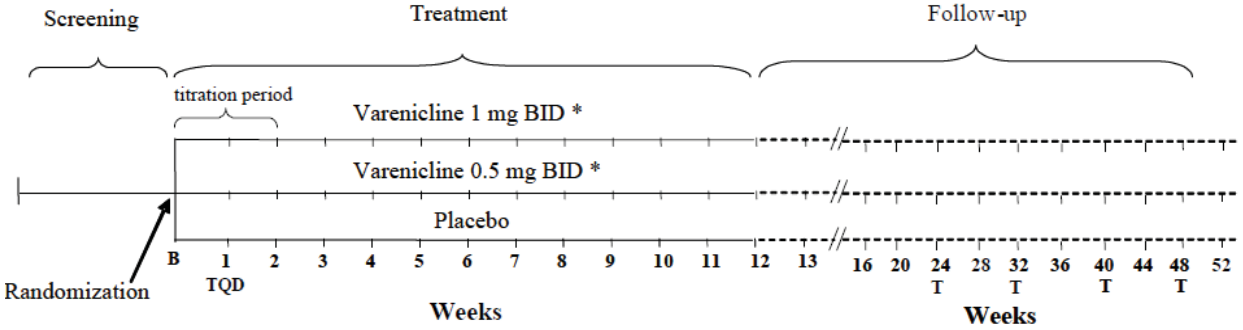
The efficacy trial (A3051073) was a randomized, double-blind, placebo-controlled, multicenter study that compared two doses of varenicline (1 mg BID and 0.5 mg BID) to placebo for smoking cessation in adolescent smokers aged 12-19 years who were motivated to quit. The varenicline dose was reduced by half in subjects with a body weight of ≤ 55 kg.

After signing the informed consent form (in subjects under 18, parental consent was required), eligible subjects were randomized to one of the 3 treatment arms. Randomization was stratified by age group (12-16 vs 17-19). In order to ensure a sufficient number of subjects in the 12-16 year old stratum, the 17-19 year old stratum was capped at a maximum of 90 subjects.

All subjects had a target quit date (TQD) to coincide with the Week 1 visit. Up to 10 minutes of age appropriate smoking cessation counselling was provided at each clinic or phone visit. Subjects had clinic visits weekly during treatment phase (baseline to W 12) and during follow-up period on Weeks 13, 16, 20, 28, 36, 44 and 52. Phone visits occurred on Weeks 24, 32, 40 and 48.

Subjects recorded daily cigarettes smoked and any other nicotine or tobacco use. This was reported on the Nicotine Use Inventory tool at each visit or phone contact. Starting at week 9, at each study visit, a urine cotinine test was done to confirm self-reported abstinence. The cut-off sensitivity for a positive cotinine test result was 200 ng/mL or greater. This cut-off is within range of published values for distinguishing smokers from nonsmokers.

**Figure 1 Study Schematic Efficacy Trial**




***Varenicline doses are titrated to target dose over the first weeks of treatment. Subjects whose body weight is ≤55 kg will have their randomized dose reduced by half.**

BL= Baseline
T = Telephone

Due to enrollment difficulties, this study was conducted at 74 sites in 6 countries. 312 subjects were randomized between Apr 2011 to Jan 2018.

*Key Inclusion Criteria include:*

1. Healthy male and female subjects between the ages of 12 and 19 years inclusive (at screening) and motivated to stop smoking.

2. Smoking at least an average of 5 cigarettes per day during 30 days prior to enrollment and a total score of 4 or higher on the Fagerström Test for Nicotine Dependence (FTND).

3. At least one prior failed attempt to quit smoking.

4. Total body weight at screening and randomization ≥35 kg (77 lbs.) and Body Mass Index (BMI) of ≤35 kg/m2 (and at the lower end, subject should be no more than 2 standard deviations or percentiles from normal BMI for age and stature).

5. Parental/ legal guardian consent for subjects under the age of 18.

6. Subjects of childbearing potential agree to use effective method of contraception (abstinence; any form of hormonal contraception such as Depo-Provera, daily oral contraceptive, transdermal patch, or Nuva-ring; intra-uterine device, sterilization; or double barrier contraception).

*Key Exclusion Criteria:*

1. Female subjects who were pregnant or nursing.

2. Prior suicide attempt, hospitalized due to suicide or serious suicidal ideation or suicidal behavior within twelve months of enrollment, active suicidal ideation or behavior identified at screening or baseline visits.

3. Score of >7 on the Suicide Behaviors Questionnaire-Revised (SBQ-R) at the Screening.

*4.* Current or history of clinically significant psychiatric disease (i.e. major depression disorder, anxiety disorders, panic disorder, hostility or aggression disorder, psychosis, bipolar disorder, personality disorder, severe emotional problems, or eating disorder), or use of medications for treatment of mania or psychosis.

5. Score ≥8 for either depression or anxiety on the Hospital Anxiety and Depression Rating Scale (HADS)

6. Subjects with evidence or history of clinically significant neurological, hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, or allergic disease (including serious drug allergies).

7. Evidence of alcohol and substance abuse/dependence (other than nicotine) within 3 months prior to screening deemed severe enough to interfere with study requirements.

8. History of prior use of or sensitivity to varenicline/Chantix®/Champix®

9. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality

10. Participation in other studies within 30 days of enrollment, or treatment with an investigational drug within 30 days or 5 half-lives (whichever is longer) preceding the first dose of study medication.

**Study Endpoints**

Primary efficacy endpoint: 4-week continuous quit rate (CQR) from Week 9 through Week 12 of treatment for varenicline compared with placebo.

Secondary efficacy endpoints:

- 7-day point-prevalence of smoking abstinence at Weeks 12, 24, and 52;

- Reduction in number of cigarettes smoked at Weeks 12, 24, and 52;

- Continuous abstinence rate (CAR) from Week 9 through Week 24;
- CAR from Week 9 through Week 52.

Safety Assessments: Adverse events volunteered or observed, adverse events elicited by the Neuropsychiatric Adverse Event Inventory (NAEI), Columbia Suicide Severity Rating Scale (CSSRS), Hospital Anxiety and Depression Scale (HADS) and adverse events associated with safety laboratory tests, or vital signs.

PK Assessments: Varenicline exposure at steady-state in adolescent smokers.

**Statistical Analysis Plan**

The primary efficacy variable was the Continuous Abstinence Rate (CAR) at Weeks 9-12. This was defined as a subject reporting no cigarette or other nicotine/tobacco use and confirmatory urine cotinine result, during the last four weeks on treatment (weeks 9-12 of study). Two secondary endpoints, CAR Weeks 9-24 and CAR Weeks 9-52, used the same definition with the indicated timeframes.

Logistic regression models, with terms for treatment, age strata, weight strata, and site, were used to test the primary efficacy variable using the odds ratio. The protocol specified a hierarchical order closed testing procedure for the CAR weeks 9-12 endpoint to control the overall Type I error rate for multiplicity. First the varenicline high dose group would be compared to placebo. If that comparison was successful (p-value < 0.05) then the varenicline low dose group would be compared to placebo.

The study was powered for comparisons on the overall group and for comparisons in the Age 12-16 year old group. The same ordered hierarchical testing was planned.

The sample size was planned for equal randomization to the three treatment arms, and assumed CAR responder rates of 24% for each varenicline arm and 9% for the placebo arm. The overall sample of 300 (100 per arm) would provide at least 80% power for the planned hypothesis tests. To ensure the 12-16 year old group had sufficient sample size to meet the PMR requirements, the sponsor planned to enroll at least 70 subjects in that age group per arm. The final sample size was 312 subjects enrolled, with 72 per arm in the 12-16 year strata.

**Protocol Amendments**

The protocol amendments were reviewed. There was a total of 5 protocol amendments. Some are reflected in the study description and some are minor editorial changes. The significant amendments are:

> In 2011, the exclusion criteria were modified so that use of psychoactive drugs in the 6 months prior to screening be discussed with the sponsor, rather than be prohibited (in

order to consider including ADHD subjects on stimulants).

In Amendment 4 (01/20/2012) an exploratory subgroup analysis for each dosing group by weight stratum for the primary efficacy endpoint was added.

In Amendment 5 (07/09/2012), drug dependency and drug abuse were added as examples of reportable AEs.

No other changes to study design, visit schedule, procedures, treatments and data collection were made.

### 8.1.2. Study Results

**Compliance with Good Clinical Practices**

The study was conducted according to ICH Good Clinical Practices.

**Financial Disclosure**

3 of the 341 clinical investigators in the study had financial information to disclose. The 3 investigators were at site 1078, 1017 and 1039. The number of subjects who were randomized, deemed screen failures, and who discontinued treatement at these clinical sites are summarized in the table below. These sites are unlikely to have influenced the overall conclusions of the study.

**Table 3: Recruitment at Sites with Financial Disclosure**

| Site | Subjects Randomized | Screen Failures | Treatment discontinuation |
|---|---|---|---|
| 1078 | 7 | 0 | 0 |
| 1017 | 8 | 2 | 4 |
| 1039 | 1 | 4 | 0 |

The Applicant has taken the following steps to minimize bias.

The study, was a multi-site, randomized, double-blind, placebo-controlled study with a double-dummy design (to accommodate the 2 different dose groups and the dose adjustment by

weight) that was conducted in 6 countries.

There was monitoring of investigator trial sites as defined in the Clinical Monitoring Plan.

The validity of the data was confirmed by the Applicant using their Data Management Plan. To resolve inconsistencies, queries were created. The study report was reviewed by members of the project team, by Quality Control and by Medical Quality Assurance.

Appropriate statistical methods were employed with an approved statistical analysis plan.

Pfizer's Medical Quality Assurance group conducted audits at 24 sites. In the case of 1 site, there was concern about GCP compliance. A pre-specified sensitivity analysis excluding this site's data was done that showed no impact on the study results.

**Patient Disposition**

463 volunteers were screened; of those 106 did not meet eligibility criteria. 45 were not screen failures but were not randomized (8 were lost to follow-up, 22 were no longer willing to participate and 15 for "Other" reasons). The most common reasons for failure to meet randomization criteria are summarized in the table below.

**Table 4: Screen Failures Based on Eligibility Criteria**

| Inclusion Criteria Not Met | n | Exclusion Criteria Met | n |
|---|---|---|---|
| Low FTDN/-cotinine | 28 | HADS score | 27 |
| Noncompliance with study | 8 | Substance Use Disorder/ + UDS | 19 |
| BMI | 7 | SBQ-R Score | 13 |
| | | Clinically Significant Psychiatric Dx | 12 |
| | | Previous Suicide Attempt | 9 |

Three hundred twelve were randomized and 307 received study drug/ placebo. 5 were randomized but did not receive treatment. 187 subjects completed the protocol.

In the 12 – 16 year-old-stratum, 216 subjects were randomized: 72 high-dose varenicline, 72 low-dose varenicline and 72 placebo. Of the 216 randomized subjects, 212 subjects 12-16 years old received study treatment and contributed to safety results: 71 high-dose varenicline, 70 low-dose varenicline and 71 placebo.

The subject disposition is summarized in the following table, reproduced from the Applicant's study report.

**Table 5: Subject Disposition**

| Subject Disposition | Varenicline High Dose N=109 | Varenicline Low Dose N=103 | Placebo N=100 |
|---|---|---|---|
| Randomized (FAS) | 109 (100%) | 103 (100%) | 100 (100%) |
| Received Study Treatment (Safety) | 108 (99%) | 100 (97%) | 99 (99%) |
| Discontinued Treatment (Wks 1-12) and Study | 29 (27%) | 23 (23%) | 36 (36%) |
| Adverse Event | 3 (3%) | 1 (1%) | 3 (3%) |
| Lack of Efficacy | 0 | 0 | 1 (1%) |
| Lost to Follow-up | 8 (7%) | 10 (10%) | 12 (12%) |
| Protocol Viol. /Non-compliance | 2 (2%) | 7 (7%) | 3 (3%) |
| Withdrew Consent | 7 (6%) | 0 | 9 (9%) |
| Other | 9 (8%) | 5 (5%) | 8 (8%) |
| Discontinued Treatment/ Completed Study | 4 (4%) | 3 (3%) | 1 (1%) |
| Adverse Event | 3 (3%) | 0 | 0 |
| Protocol Viol. /Non-compliance | 0 | 1 (1%) | 1 (1%) |
| Other | 1 (1%) | 2 (2%) | 0 |
| Discontinued Study after Trmt. (Wks 13-52) | 12 (11%) | 10 (10%) | 10 (9%) |
| Adverse Event | 0 | 0 | 1 (1%) |
| Lack of Efficacy | 0 | 0 | 0 |
| Lost to Follow-up | 8 (7%) | 6 (6%) | 7 (7%) |
| Protocol Viol. /Non-compliance | 0 | 0 | 0 |
| Withdrew Consent | 1 (1%) | 1 (1%) | 0 |
| Other | 3 (3%) | 3 (3%) | 2 (2%) |

Source: CSR Tables 6 and 7, and ADDS.xpt dataset
All percentages are calculated based on Randomized N per group as denominator.

## Protocol Violations/Deviations

Protocol deviations were classified by issue category.

For inclusion/exclusion criteria, a total of 25 (8.0%) subjects had 1 or more protocol deviations; 7.3% in the high-dose varenicline group, 4.9% in the low-dose varenicline group, and 12.0% in the placebo group. The most common of these deviations were a score of <4 on the FTND or not meeting smoking criteria. Of 11 subjects with low FTND, 3 were randomized to High-Dose, 1

to Low-Dose and 7 to Placebo. As discussed below, only one of these subjects, in the placebo group, was classified as a quitter, with no effect on the study results.

Other deviations included score of >8 on either the anxiety or the depression of Hospital Anxiety and Depression Scale (HADS) and positive urine drug screen at screening and baseline. Deviations occurring in single subjects were: age >19 years old, use of psychotropic medications within 6 months of screening, low BMI, The Suicide Behaviors Questionnaire-Revised (SBQ-R) >7 and no prior quit attempts.

**Table 6 Table of Demographic Characteristics**

| Demographic Parameters | **Treatment Group** | | **Control Group** (N= 99) n (%) |
|---|---|---|---|
| | High Dose Varenicline (N=108) n (%) | Low Dose Varenicline (N= 100) n (%) | |
| **Sex n (%)** | | | |
| Male | 70 (64.8) | 63 (63.6) | 63 (63.0) |
| Female | 38 (35.2) | 36 (36.4) | 37 (37.0) |
| **Age Group, n (%)** | | | |
| 12-16 | **71 (65.7)** | **71 (71.7)** | **70 (70.0)** |
| 17-19 | **37 (34.3)** | **28 (28.3)** | **30 (30.0)** |
| **Age (years)** | | | |
| Mean (SD) | **16.0 (2.0)** | **15.8 (1.8)** | **16.0 (1.7)** |
| Range | **12-20**[3] | **12-19** | **12-19** |
| **Race** | | | |
| White | **81 (75.0)** | **74 (74.7)** | **73 (73)** |
| Black or African American | **9 (8.3)** | **5 (5.1)** | **9 (9.0)** |
| Asian | **16 (14.8)** | **19 (19.2)** | **18 (18.0)** |
| American Indian or Alaska Native | | | |
| Native Hawaiian or Other Pacific Islander | | | |
| Other[1] | **2 (1.9)** | **1 (1.0)** | **0** |
| **Ethnicity** | | | |
| Hispanic or Latino | | | |
| Not Hispanic or Latino | | | |
| **Body Mass Index (kg/m2) n (%)** | | | |
| Mean (SD) | **23.1 (4.4)** | **23 (4.5)** | **22.5 (4.2)** |
| Range | **16.7-34.9** | **16.3-35.2** | **16.3-34.9** |
| **Years Smoked** | | | |
| Mean (SD) | **3.1 (1.74)** | **2.9 (1.70)** | **3.0 (2.26)** |
| Median | **3. 0** | **2.0** | **2.0** |
| Range | **0-8** | **1-8** | **0-13** |
| **Average number of cigarettes smoked per day (past month)** | | | |
| Mean (SD) | **12.8 (7.54)** | **12.0 (6.01)** | **12.3 (5.98)** |
| Median | **11.0** | **10.0** | **10.0** |
| Range | **5-40** | **5-30** | **5-30** |
| **FTND score** | | | |
| Mean (SD) | **5.36 (1.37)** | **5.30 (1.64)** | **5.47 (1.43)** |
| 0-3[4] | **3 (2.8)** | **7 (7.1)** | **1 (1.0)** |
| 4-6 | **86 (79.6)** | **71 (71.7)** | **75 (75)** |
| 7-10 | **19 (17.6)** | **21 (21.2)** | **24 (24.0)** |

**Treatment Compliance, Concomitant Medications, and Rescue Medication Use**

Pfizer reported the number and percent of subjects who took study medication for 80% of the planned number of days in the trial treatment period. Across treatment groups, the number/percent of subjects with 80% compliance was 76 (70.4%) in the high-dose varenicline group, 74 (74.0%) in the low-dose varenicline group, and 65 (65.7%) in the placebo group.

A total of 47 (15.1%) subjects took one or more prohibited concomitant medications; 12.8% in the high-dose varenicline group, 18.5% in the low-dose varenicline group, and 14.0% in the placebo group. The most common of these deviations was recreational marijuana use, followed by the use of other tobacco products including cigars, chewing tobacco, and e-cigarettes. One subject who reported using e-cigarettes (Day 35 to 49) was a responder. None of the subjects who reported using NRT were responders. It's not expected that the above deviations affected the study result. There were no deviations reported for prescription medications.

**Efficacy Results – Primary Endpoint**

The study did not demonstrate evidence of effectiveness.

**Efficacy Results – Primary Endpoint**

This study was powered to test for between group differences for all ages 12-19 and for the subgroups of smokers ages 12-16 years old. Randomization was stratified by age to ensure all treatment arms had enough subjects in the target age group. The protocol planned for at least 70 subjects in the 12-16-year age group per treatment arm.

Hypothesis tests were planned in a closed testing order, with the comparison of Varenicline High Dose to placebo first. If successful (p-value < 0.05) then the comparison of Varenicline Low Dose to placebo would be tested. There were no plans to control for multiplicity for testing of any secondary endpoints. The secondary endpoints presented here are of interest to the clinical review and for consistency with the results presented for previous studies of Varenicline in adults.

As shown in Table 7, the varenicline high dose arm was not statistically significantly different from placebo. In the planned closed testing procedure, no further hypothesis tests would be conducted for the overall patient population (ages 12-19).

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[3] 1 subject was enrolled 2 days after her 20th birthday; this was recorded as a protocol violation.
[4] FTND scores <4 were recorded as protocol deviation.

**Table 7 Efficacy Analysis Results (Study A3051073)**

| FAS Patient Population | | Varenicline High Dose N=109 | Varenicline Low Dose N=103 | Placebo N=100 |
|---|---|---|---|---|
| **Primary: Continuous Abstinence Weeks 9-12** | n/N | 22/109 | 28/103 | 18/100 |
| | % | 20% | 27% | 18% |
| | Odds Ratio [a] | 1.18 | 1.73 | |
| | 95% Conf. Interval | (0.59, 2.37) | (0.88, 3.39) | |
| | 2-sided p-value vs. placebo | 0.64 | 0.11 | |
| **Secondary: Continuous Abstinence Weeks 9-24** | n/N | 11/109 | 25/103 | 13/100 |
| | % | 10% | 24% | 13% |
| | Odds Ratio [b] | 0.80 | 2.26 | |
| | 95% Conf. Interval | (0.34, 1.90) | (1.07, 4.79) | |
| **Secondary: Continuous Abstinence Weeks 9-52** | n/N | 9/109 | 21/103 | 9/100 |
| | % | 8% | 20% | 9% |
| | Odds Ratio [b] | 0.99 | 2.79 | |
| | 95% Conf. Interval | (0.37, 2.65) | (1.19, 6.55) | |

Source: Clinical Study Report Tables 17 and 18
[a] The odds ratios, confidence intervals, and p-values were obtained from a logistic regression model including effects for treatment, age strata, weight strata, and site.
[b] The odds ratios and confidence intervals were obtained from a logistic regression model including effects for treatment, age strata, weight strata, and site. P-values are not appropriate for the secondary endpoints because there was no plan to control for multiplicity.

The applicant planned to repeat all analyses for the 12 – 16 year-old age strata. The randomization plan ensured sufficient subjects in this age group to meet the PMR specifications, but these subgroup analyses were not part of the prespecified hierarchical testing plan.

Based on the statistical analysis plan, no further testing was planned if the study did not meet the endpoint in the primary analysis. However, the clinical team was interested in exploring further whether the study results provided any support for further evaluation of varenicline in

adolescents. Noting that all studies of Chantix in adults have demonstrated superiority over placebo on the 9 – 12 week abstinence rate, the clinical review team sought to understand whether some subgroup might be identified that could benefit from Chantix in the pediatric population. Thus, additional exploratory analyses of subgroups and secondary endpoints were undertaken by the statistical reviewer.

As shown in Table 8, for the 12 – 16 year-old subjects, the varenicline high dose arm again was not statistically significantly different from placebo. While there was a significant difference noted for the varenicline low dose arm versus placebo for the primary and secondary endpoint, these results were considered exploratory. Additionally, further exploration of the data supports the conclusion that this apparent finding is spurious. See Section 8.3, Statistical Issues.

**Table 8 Efficacy Analysis Results Ages 12-16 Subgroup (Study A3051073)**

| Ages 12-16 Subgroup | | Varenicline High Dose N=72 | Varenicline Low Dose N=72 | Placebo N=72 |
|---|---|---|---|---|
| **Primary: Continuous Abstinence Weeks 9-12** | n/N | 14/72 | 25/72 | 13/72 |
| | % | 19% | 35% | 18% |
| | Odds Ratio [a] | 1.09 | 2.42 | |
| | 95% Conf. Interval | (0.47, 2.53) | (1.12, 5.26) | |
| | 2-sided p-value vs. placebo | 0.83 | 0.0250 | |
| **Secondary: Continuous Abstinence Weeks 9-24** | n/N | 10/72 | 23/72 | 10/72 |
| | % | 14% | 32% | 14% |
| | Odds Ratio [b] | 1.01 | 2.92 | |
| | 95% Conf. Interval | (0.39, 2.60) | (1.27, 6.72) | |
| **Secondary: Continuous Abstinence Weeks 9-52** | n/N | 8/72 | 20/72 | 8/72 |
| | % | 11% | 28% | 11% |
| | Odds Ratio [b] | 1.02 | 3.12 | |
| | 95% Conf. Interval | (0.36, 2.90) | (1.27, 7.69) | |

Source: Clinical Study Report Tables 17 and 18

[a] The odds ratios, confidence intervals, and p-values were obtained from a logistic regression model including effects for treatment, weight strata, and site.

[b] The odds ratios and confidence intervals were obtained from a logistic regression model including effects for treatment, weight strata, and site. P-values are not appropriate for the secondary endpoints because there was no plan to control for multiplicity.

**Data Quality and Integrity**

No potential issues concerning data integrity were identified.

All data was provided by the applicant to the CDER electronic data room (edr) in SAS transport format. The study reports, data, and documentation in the electronic submission are archived under the network path location: \\Cdsesub1\evsprod\NDA21928\0640.

**Efficacy Results – Secondary and other relevant endpoints**

The statistical reviewer produced exploratory analyses of the primary efficacy endpoint, continuous abstinence rate at weeks 9-12, for several subgroups, shown in Table #9. Randomization was stratified by age (12-16; 17-19) and weight (≤55 kg; >55kg). The statistical reviewer also presents the results for the four age-by- weight categories. Gender, race, and region (U.S.; Rest of World (ROW)) are standard subgroup analyses. Of the 312 subjects, 63% are male, 75% are Caucasian, and 60% were enrolled in the U.S.

The clinical team also requested that the statistical reviewer analyze efficacy by the categories of the Fagerström Test for Nicotine Dependence. This is of interest because the protocol specified a minimum screening score of 4 or higher (0-10 scale; 0 is lowest nicotine dependency, 10 is highest). A score of 4 is not considered a clear indicator of dependence in adult patients, but the cutoff was adjusted to acknowledge that adolescents may be constrained in the times they are able to smoke cigarettes. Many studies in adults classify a score of 7 or higher as an indicator of severe dependence. It is possible that only the more severely dependent patients might benefit from a pharmacologic treatment.

Over 75% of the enrolled subjects had Fagerstrom scores under 7. A total of 12 subjects were enrolled with scores of 0-3 and were classified as protocol deviations (3 in High Dose arm; 2 in Low Dose arm; 7 in Placebo). Of those, only one, in the placebo group, was a responder for Continuous Abstinence at Weeks 9-12.

The table below also illustrates that the subset of patients with Fagerstrom scores suggesting severe dependence did not have a different response to the behavioral intervention (placebo arm) from the less dependent subjects, and that the addition of varenicline did not result in a higher quit rate in these subjects.

**Table 9 Efficacy Subgroup Analyses (Study A3051073)**

| FAS Patient Population | | Varenicline High Dose N=109 | Varenicline Low Dose N=103 | Placebo N=100 |
|---|---|---|---|---|
| **Age:** | | | | |
| **12-16 years** | n/N | 14/72 | 25/72 | 13/72 |
| | % | 19% | 35% | 18% |
| **17-19 years** | n/N | 8/37 | 3/31 | 5/28 |
| | % | 22% | 10% | 18% |
| **Weight Strata:** | | | | |
| **≤55 kg** | n/N | 4/24 | 7/23 | 6/26 |
| | % | 16% | 30% | 23% |
| **>55 kg** | n/N | 18/85 | 21/80 | 12/74 |
| | % | 21% | 26% | 16% |
| **Age x Weight:** | | | | |
| **12-16 yrs and ≤55 kg** | n/N | 3/19 | 7/20 | 5/24 |
| | % | 16% | 35% | 21% |
| **12-16 yrs and >55 kg** | n/N | 11/53 | 18/52 | 8/48 |
| | % | 21% | 35% | 17% |
| **17-19 yrs and ≤55 kg** | n/N | 1/5 | 0/3 | 1/2 |
| | % | 20% | 0% | 50% |
| **17-19 yrs and >55 kg** | n/N | 7/32 | 3/28 | 4/26 |
| | % | 22% | 11% | 15% |
| **Gender:** | | | | |
| **Female** | n/N | 10/39 | 15/38 | 7/37 |
| | % | 26% | 39% | 19% |
| **Male** | n/N | 12/70 | 13/65 | 11/63 |
| | % | 17% | 20% | 17% |

| | | | | |
|---|---|---|---|---|
| **Race:** | | | | |
| **Caucasian** | n/N | 20/82 | 23/76 | 15/74 |
| | % | 24% | 30% | 20% |
| **Non-Caucasian** | n/N | 2/27 | 5/27 | 3/26 |
| | % | 7% | 19% | 12% |
| **Region:** | | | | |
| **United States** | n/N | 15/70 | 13/58 | 10/59 |
| | % | 21% | 22% | 17% |
| **Rest of World** [a] | n/N | 7/39 | 15/45 | 8/41 |
| | % | 18% | 33% | 20% |
| **Fagerström Nicotine Dependence Score:** [b] | | | | |
| **4-6** | n/N | 9/87 | 22/77 | 9/72 |
| | % | 10% | 29% | 13% |
| **7-10** | n/N | 2/19 | 3/24 | 3/21 |
| | % | 11% | 13% | 14% |

Source: adsl.xpt, adnu.xpt, and adftnd.xpt datasets
[a] Countries in Rest of World: Russia, Georgia, Korea, Taiwan, and Canada
[b] Subjects with Fagerström Nicotine Dependence Scores <4 were protocol violations

In almost all the subgroups, the responder rate (CAR) in the varenicline high dose group is similar to the responder rate in the placebo group. In most cases the responder rate for the varenicline low dose group is similar or somewhat higher than the other arms.

In the age-by-weight subgroups, there were very few subjects in the Age 17-19 and Weight ≤55 kg subset. Among the Age 17-19 and Weight >55 kg subset, the varenicline high dose group showed a better responder rate than the other two arms. That subgroup is most similar to the adult population, in which that dose of varenicline has shown consistent positive efficacy in prior studies.

These are descriptive analyses only and are not intended for inferential purposes. None of the results from the subgroup analyses give reason to question the overall efficacy conclusions.

The results of the statistical analyses of Study A3051073 do not show evidence of efficacy for varenicline compared to placebo in smokers ages 12-19. Neither the high nor low dose of

varenicline demonstrated a significant difference from placebo for the Continuous Abstinence Rate during Weeks 9-12 on treatment. The secondary endpoints, CAR at Weeks 9-24 and CAR at Weeks 9-52 were consistent with no notable differences between the treatment arms.

#### 8.1.3. Assessment of Efficacy Across Trials

There was only one efficacy study which did not meet the primary endpoint.

## 8.2. Review of Safety

### 8.2.1. Safety Review Approach

The safety review includes one efficacy study (A3051073) and 2 pharmacokinetic studies (A3051070 and A3051029). This safety review is based on Pfizer's presentation of the data in their clinical study report and an independent analysis was not performed because the efficacy finding does not support use in youth.

Review focused on death, SAE and dropouts were in all 3 studies and common adverse events in efficacy study.

### 8.2.2. Review of the Safety Database

**Overall Exposure**

In total, there have been 3 varenicline studies that enrolled adolescents including a single-dose PK and safety/tolerability study, a multiple-dose PK and safety/tolerability study and a safety and efficacy study. All subjects who took one dose of the study medication were included in the safety assessment. A total of 287 adolescent smokers were exposed to varenicline, and 119 exposed to placebo.

**Table 10: Safety Population, Size and Denominators**

| Clinical Trial Groups | New Drug (n=) | Placebo (n=) |
|---|---|---|
| A3051073 Adolescent safety and efficacy (12-19 years old) Total 307 | High does: 108<br>Low dose: 100 | 99 |
| A3051070 (Multiple dose PK in adolescent smokers (12-16 years old) Total 72 | HBW (High Body Weight)<br>High dose: 14<br>Low dose:14<br>LBW (Low Body Weight)<br>High dose:14<br>Low dose: 15 | HBW<br>7<br>LBW<br>8 |
| A3051029 Single dose PK in adolescent smokers (12-17 years old) Total:72 | 0.5 mg: 10<br>1 mg: 12 | 5 |

The efficacy study was a multisite trial with 74 centers in multiple countries. The study was started on April 26, 2011 and completed on Jan 18, 2018. The objective was to evaluate the efficacy, safety, and tolerability of varenicline compared with placebo in adolescent smokers 12-19 years of age.

Safety evaluations included reported or observed AEs, Neuropsychiatric Adverse Event Interview (NAEI), Columbia Suicide Severity Rating Scale (C-SSRS), and Hospital Anxiety and Depression Scale (HADS). Other safety assessments were: physical exam, vital signs (heart rate, blood pressure), weight and height, laboratory tests, urine pregnancy and urine drug screen.

Multi-dose PK study (A3051070) started on May 21, 2007 and was completed on Dec 1, 2007 with 16 sites in the US and UK. The objective of the study was to evaluate the multiple-dose pharmacokinetics (PK), safety and tolerability of varenicline in adolescent smokers. Safety evaluations included monitoring for AEs, vital signs, 12-lead electrocardiograms (ECGs), and safety laboratory tests. A total of 73 subjects were randomized, and 72 subjects were dosed with 70 subjects completing the study. 2 were withdrawn, one in LBW (Low Body Weight) due to lack of compliance and another due to withdrawing consent. Discontinued subjects were not replaced.

Study A3051029 was a single site study to evaluate single-dose pharmacokinetics, safety and tolerability of varenicline (0.5 and 1 mg) in adolescent smokers. Safety evaluations included

adverse events, vital signs, 12-lead electrocardiograms (ECGs), physical examinations, and safety laboratory tests.

**Adequacy of the safety database:**

The safety database is determined to be adequate.

### 8.2.3. Adequacy of Applicant's Clinical Safety Assessments

**Issues Regarding Data Integrity and Submission Quality**

This study was conducted in compliance with Good Clinical Practice (GCP) Guidelines.

**Categorization of Adverse Events**

The adverse events are categorized based on MedDRA (v 20.1) Preferred terms.

**Routine Clinical Tests**

Hematology: Hg, HCT, CBC with differential
Chemistry: BUN, Cr, glucose, Ca, Na, K, Cl, bicarbonate, AST, ALT, Total Bil., ALK phosphatase, Uric Acid, ALB, Total protein
Other: Urine pregnancy, cotinine and drug screen

### 8.2.4. Safety Results

**Deaths**

No deaths were reported in any of the 3 adolescent studies.

**Serious Adverse Events**

Efficacy study: During treatment phase, 5 subjects had at least 1 TEAE considered to be serious and 7 subjects had at least 1 post-treatment emergent SAE. None of the SAEs were considered to be related to study drug.

The following tables are submitted by the Applicant.

**Table 11 Treatment-Emergent Serious Adverse Events (All-Causality)**

| Subject ID | Sex/Age[a]/ Race | MedDRA Preferred Term | Study Start Day[b]/Study Stop Day[b] | Severity | Causality | Outcome |
|---|---|---|---|---|---|---|
| **High-Dose Varenicline** | | | | | | |
| (b) (6) | F/16/W | Adjustment disorder with mixed disturbance of emotion and conduct | 8/13 | Severe | Not Related | Resolved |
| | M/15/A | Laryngitis | 33/50 | Moderate | Not Related | Resolved |
| | M/14/W | Campylobacter gastroenteritis | 13/21 | Mild | Not Related | Resolved |
| **Low-Dose Varenicline** | | | | | | |
| (b) (6) | F/18/W | Bile duct stone | 19/24 | Severe | Not Related | Resolved |
| | | Cholecystitis acute | 19/24 | Severe | Not Related | Resolved |
| **Placebo** | | | | | | |
| (b) (6) | F/16/W | Salpingitis | 38/44 | Moderate | Not Related | Resolved |

Source: Table 16.2.7.
Medical Dictionary for Regulatory Activities (MedDRA) (v20.1) coding dictionary applied.
Abbreviations: A = Asian; F = female; M = male; W = white.
a. Age in years at screening.
b. Day relative to start of study treatment. First day of study treatment = Day 1.

**Table 12 Post-Treatment Emergent Serious Adverse Events (All-Causality)**

| Subject ID | Sex/Age[a]/ Race | MedDRA Preferred Term | Study Start Day[b]/Study Stop Day[b] | Severity | Causality | Outcome |
|---|---|---|---|---|---|---|
| **High-Dose Varenicline** | | | | | | |
| (b) (6) | F/16/W | Major depression | 187/187 | Severe | Not Related | Unknown |
| | | Suicidal ideation | 187/194 | Severe | Not Related | Resolved |
| | M/14/A | Radius fracture | 201/338 | Moderate | Not Related | Resolved |
| | M/14/A | Traumatic intracranial haemorrhage | 192/197 | Moderate | Not Related | Resolved |
| **Low-Dose Varenicline** | | | | | | |
| (b) (6) | F/16/A | Osteochondrosis | 239/280 | Severe | Not Related | Resolved |
| | | Synovitis | 239/280 | Severe | Not Related | Resolved |
| | F/15/W | Intentional self-injury | 260/261 | Severe | Not Related | Resolved |
| **Placebo** | | | | | | |
| (b) (6) | M/14/W | Homicidal ideation | 98/104 | Severe | Not Related | Resolved |
| | M/15/W | Intentional self-injury | 118/118 | Severe | Not Related | Resolved |
| | | Suicidal ideation | 118/118 | Severe | Not Related | Resolved |

Source: Table 16.2.7.
Medical Dictionary for Regulatory Activities (MedDRA) (v20.1) coding dictionary applied.
Abbreviations: A = Asian; F = female; M = male; W = white.
a. Age in years at screening.
b. Day relative to start of study treatment. First day of study treatment = Day 1.

Multi-dose PK Study: One SAE was reported before randomization. A 14 year old subject overdosed on 20 Tylenol in a suicide attempt before randomization but after signing the ICF. This subject's SAE was not included in the study safety database because it occurred before randomization.

Single-dose PK Study: No SAEs were reported.

**Dropouts and/or Discontinuations Due to Adverse Effects**

Efficacy study: During the treatment period, a total of 10 subjects were withdrawn from the study due to TEAEs and 2 subjects were withdrawn due to pregnancy.
Multi-dose PK study: There were no withdrawals due to AEs reported in this study.
Single-dose PK study: No withdrawals due to AEs reported for this study.

**Treatment Emergent Adverse Events and Adverse Reactions**

The following tables are submitted by the applicant.

**Efficacy Study**

The incidence of AEs were generally higher for the high-dose varenicline group than for the low-dose varenicline and placebo groups, which were similar. The AE profile was similar to adult studies with no new safety signals.

**Table 13 All Solicited and Volunteered Treatment-Emergent Adverse Events (All Causality) With 5% Incidence in Any Treatment Group by Preferred Term - Safety Analysis Set**

| MedDRA Preferred Term | High-Dose Varenicline (N=108) | Low-Dose Varenicline (N=100) | Placebo (N=99) |
|---|---|---|---|
| Nausea | 26 (24.1) | 19 (19.0) | 12 (12.1) |
| Headache | 14 (13.0) | 5 (5.0) | 8 (8.1) |
| Agitation | 9 (8.3) | 5 (5.0) | 5 (5.1) |
| Vomiting | 14 (13.0) | 2 (2.0) | 2 (2.0) |
| Abnormal dreams | 8 (7.4) | 5 (5.0) | 4 (4.0) |
| Anxiety | 6 (5.6) | 4 (4.0) | 7 (7.1) |
| Dizziness | 6 (5.6) | 7 (7.0) | 3 (3.0) |
| Hostility | 7 (6.5) | 3 (3.0) | 4 (4.0) |
| Upper respiratory tract infection | 6 (5.6) | 5 (5.0) | 2 (2.0) |
| Nasopharyngitis | 4 (3.7) | 3 (3.0) | 5 (5.1) |

Table includes data up to 30 days after last dose of study drug.
Abbreviation: MedDRA = Medical Dictionary for Regulatory Activities Version 20.1.

Source: CSR Table S8

**Table 14 Incidence of All Solicited and Volunteered Treatment-Emergent Neuropsychiatric Adverse Events by System Organ Class and Preferred Term**

| System Organ Class/ MedDRA (v20.1) Preferred Term | High-Dose Varenicline (N=108) | Low-Dose Varenicline (N=100) | Placebo (N=99) |
|---|---|---|---|
| Subjects with Neuropsychiatric Adverse Events | 18 (16.7) | 11 (11.0) | 12 (12.1) |
| 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) |

Table includes data up to 30 days after last dose of study drug.
Abbreviation: MedDRA = Medical Dictionary for Regulatory Activities.

Source: CSR Table S9

**Laboratory Findings**

Efficacy Study: Overall, most laboratory test values remained within normal reference ranges from screening to Week 12. There were no abnormal values in AST and/or ALT with elevation in total bilirubin that met the criteria for drug-induced liver injury (potential Hy's Law cases). The following table is submitted by the applicant.

Multi-dose PK Study: Two subjects experienced laboratory AEs (abnormal liver function tests and white blood cells in urine) judged by the investigator to be unrelated to the study medication. A 13 year old female subject in LBW group experienced elevated liver function test judged by the investigator to be related to 0.5 mg BID varenicline. The subject had elevated AST (5 times the ULN) and ALT (18 times ULN) levels on Day 14 and mild lymphadenopathy. The subject also experienced nausea and constipation prior to the onset of liver abnormalities. The values returned to normal range without concomitant treatment. There has not been an identified relationship between liver toxicity and varenicline, however this cannot be excluded.

A 16-year-old male subject had bilirubin level of 2.0 mg/dL on Day 8, with a baseline value of 2.3 mg/dL and a final value of 1.0 mg/dL on Day 15 (reference range 0.1 to 1.2 mg/dL).

Single-dose PK Study: There were no abnormal laboratory tests findings that were considered clinically significant by the investigator.

**Vital Signs**

Efficacy Study: Median changes from baseline to Week 12 in vital signs were not clinically significant.

Multi-dose PK Study: BP (systolic and diastolic) mean and median results were within normal limits, and changes from baseline were minor. No differences were observed between active and placebo treatments or between LBW and HBW groups.

Single-dose PK Study: There were no significant trends in mean change from baseline for HR or BP values.

**Electrocardiograms (ECGs)**

Efficacy Study: ECG was not evaluated.

Multi-dose PK Study: Mean and median ECG parameters (heart rate, PR, QRS, QT, and QTcF) were within normal limits at baseline. Mean and median changes from baseline were minor, with no differences between active and placebo treatments, or between BW groups.

Single-dose PK Study: There were no significant trends in the mean change from baseline for ECG values.

**QT**

Multi-dose PK Study: No subjects had ECG parameter (PR, QRS, QT, and QTcF) values that met criteria for clinical concern.

Single-dose PK Study: One asymptomatic subject ( (b) (6) ) had an isolated QT value of 504 msec and a heart rate of 43 bpm at 24 hours postdose, with QTcF and QTcB values of 451 msec and 427 msec, respectively. None of these values were considered clinically significant by the investigator.

### 8.2.5. Analysis of Submission-Specific Safety Issues

No submission specific safety issues were identified.

### 8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Not applicable.

### 8.2.7. Safety Analyses by Demographic Subgroups

The following tables are submitted by the Applicant.

**Age:**

**Table 15: Common All-Causality TEAE Reported by Higher Percentages of Varenicline than Placebo Subjects, Efficacy Study Safety Population Overall By Age Strata**

| | 12-16 year olds | | | 17-19 year olds | | |
|---|---|---|---|---|---|---|
| System Organ Class<br>High Level Group Term<br>Preferred Term | High-Dose Var N=71 | Low-Dose Var N=70 | Pbo N=71 | High-Dose Var N=37 | Low-Dose Var N=30 | Pbo N=28 |
| | number (%) of subjects | | | | | |
| **Gastrointestinal Disorders** | | | | | | |
| **Gastrointestinal signs and symptoms** | **21 (29.6)** | **16 (22.9)** | **7 (9.9)** | **13 (35.1)** | **7 (23.3)** | **8 (28.6)** |
| Abdominal discomfort | 3 (4.2) | 0 | 1 (1.4) | - | - | - |
| Abdominal pain | 1 (1.4) | 2 (2.9) | 0 | - | - | - |
| Nausea | 17 (23.9) | 14 (20.0) | 6 (8.5) | 9 (24.3) | 5 (16.7) | 6 (21.4) |
| Vomiting | 7 (9.9) | 1 (1.4) | 1 (1.4) | 7 (18.9) | 1 (3.3) | 1 (3.6) |
| **Musculoskeletal and Connective tissue disorders** | | | | | | |
| **Joint disorders** | - | - | - | **0** | **2 (6.7)** | **1 (3.6)** |
| Arthralgia | | - | - | 0 | 2 (6.7) | 1 (3.6) |
| **Musculoskeletal and connective tissue disorders NEC** | - | - | - | **2 (5.4)** | **0** | **1 (3.6)** |
| Musculoskeletal pain | - | - | - | 2 (5.4) | 0 | 0 |
| **Nervous System Disorders** | | | | | | |
| **Headaches** | **7 (9.9)** | **2 (2.9)** | **6 (8.5)** | **10 (27.0)** | **3 (10.0)** | **3 (10.7)** |
| Headache | - | - | - | 9 (24.3) | 3 (10.0) | 3 (10.7) |
| Migraine | 2 (2.8) | 0 | 0 | - | - | - |
| **Neurological disorders NEC** | **6 (8.5)** | **7 (10.0)** | **4 (5.6)** | - | - | - |
| Dizziness | 4 (5.6) | 6 (8.6) | 2 (2.8) | - | - | - |
| Somnolence | 2 (2.8) | 0 | 0 | - | - | - |
| **Psychiatric Disorders** | | | | | | |
| **Anxiety disorders and symptoms** | **5 (7.0)** | **1 (1.4)** | **3 (4.2)** | **7 (18.9)** | **7 (23.3)** | **6 (21.4)** |
| Agitation | 4 (5.6) | 1 (1.4) | 1 (1.4) | - | - | - |
| Anxiety | - | - | - | - | - | - |
| **Depressed mood disorders and disturbances** | - | - | - | **2 (5.4)** | **3 (10.0)** | **1 (3.6)** |
| Depressed mood | - | - | - | 0 | 2 (6.7) | 0 |
| Depression | - | - | - | 2 (5.4) | 1 (3.3) | 1 (3.6) |
| **Mood disorders and disturbances NEC** | | | | **1 (2.7)** | **2 (6.7)** | **1 (3.6)** |
| Irritability | - | - | - | 1 (2.7) | 2 (6.7) | 0 |
| **Personality disorders and disturbances in behaviour** | **5 (7.0)** | **3 (4.3)** | **0** | - | - | - |
| Hostility | 5 (7.0) | 2 (2.9) | 0 | - | - | - |
| **Sleep disorders and disturbances** | **4 (5.6)** | **1 (1.4)** | **2 (2.8)** | **7 (18.9)** | **4 (13.3)** | **2 (7.1)** |
| Abnormal dreams | - | - | - | 7 (18.9) | 4 (13.3) | 2 (7.1) |
| **Respiratory, Thoracic and Mediastinal Disorders** | | | | | | |
| **Respiratory disorders NEC** | **4 (5.6)** | **1 (1.4)** | **0** | **0** | **3 (10)** | **0** |
| Cough | 2 (2.8) | 1 (1.4) | 0 | - | - | - |

| System Organ Class<br>High Level Group Term<br>Preferred Term | 12-16 year olds<br>High-Dose Var<br>N=71 | <br>Low-Dose Var<br>N=70 | <br>Pbo<br>N=71 | 17-19 year olds<br>High-Dose Var<br>N=37 | <br>Low-Dose Var<br>N=30 | <br>Pbo<br>N=28 |
|---|---|---|---|---|---|---|
| | number (%) of subjects | | | | | |
| **Respiratory tract signs and symptoms** | - | - | - | 1 (2.7) | 2 (6.7) | 0 |
| Oropharyngeal pain | - | - | - | 1 (2.7) | 2 (6.7) | 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; BID=twice daily; Var=varenicline; Pbo=placebo; NEC=Not elsewhere classified.
- =no PTs met table criteria in this age stratum.
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: SCS Supplemental Table F14.3.1.2.6.3.3.

Overall AEs were similar to adults. The 12-16 year old group did not experience more AEs than the older group.

The following TEAE table from the label shows the rates in adults.

**Table 16: Common TEAE in Placebo-Controlled Studies in Adults**

| SYSTEM ORGAN CLASS<br>High Level Group Term<br>Preferred Term | CHANTIX<br>0.5 mg BID<br>N=129 | CHANTIX<br>1 mg BID<br>N=821 | Placebo<br><br>N=805 |
|---|---|---|---|
| GASTROINTESTINAL (GI) | | | |
| GI Signs and Symptoms | | | |
| Nausea | 16 | 30 | 10 |
| Abdominal Pain * | 5 | 7 | 5 |
| Flatulence | 9 | 6 | 3 |
| Dyspepsia | 5 | 5 | 3 |
| Vomiting | 1 | 5 | 2 |
| GI Motility/Defecation Conditions | | | |
| Constipation | 5 | 8 | 3 |
| Gastroesophageal reflux disease | 1 | 1 | 0 |
| Salivary Gland Conditions | | | |
| Dry mouth | 4 | 6 | 4 |
| PSYCHIATRIC DISORDERS | | | |
| Sleep Disorder/Disturbances | | | |
| Insomnia ** | 19 | 18 | 13 |
| Abnormal dreams | 9 | 13 | 5 |
| Sleep disorder | 2 | 5 | 3 |
| Nightmare | 2 | 1 | 0 |
| NERVOUS SYSTEM | | | |
| Headaches | | | |
| Headache | 19 | 15 | 13 |
| Neurological Disorders | | | |

| | | | |
|---|---|---|---|
| NEC | | | |
| Dysgeusia | 8 | 5 | 4 |
| Somnolence | 3 | 3 | 2 |
| Lethargy | 2 | 1 | 0 |
| GENERAL DISORDERS | | | |
| General Disorders NEC | | | |
| Fatigue/Malaise/Asthenia | 4 | 7 | 6 |
| RESPIR/THORACIC/MEDIAST | | | |
| Respiratory Disorders NEC | | | |
| Rhinorrhea | 0 | 1 | 0 |
| Dyspnea | 2 | 1 | 1 |
| Upper Respiratory Tract Disorder | 7 | 5 | 4 |
| SKIN/SUBCUTANEOUS TISSUE | | | |
| Epidermal and Dermal Conditions | | | |
| Rash | 1 | 3 | 2 |
| Pruritis | 0 | 1 | 1 |
| METABOLISM and NUTRITION | | | |
| Appetite/General Nutrition Disorders | | | |
| Increased appetite | 4 | 3 | 2 |
| Decreased appetite/ Anorexia | 1 | 2 | 1 |

* Includes PTs Abdominal (pain, pain upper, pain lower, discomfort, tenderness, distension) and Stomach discomfort
** Includes PTs Insomnia/Initial insomnia/Middle insomnia/Early morning awakening

**Gender:**

Overall, females experienced higher rate of AEs including SAEs, severe AEs and AEs that resulted in treatment discontinuation.

**Table 17: All Causality TEAE, Efficacy Study Safety Population Overall by Gender**

| System Organ Class<br>Preferred Term | Male | | | Female | | |
|---|---|---|---|---|---|---|
| | High-Dose Var N=70 | Low-Dose Var N=63 | Pbo N=63 | High-Dose Var N=38 | Low-Dose Var N=37 | Pbo N=36 |
| | number of subjects (%) | | | | | |
| Subjects with AEs | 40 (57.1) | 30 (47.6) | 30 (47.6) | 25 (65.8) | 23 (62.2) | 22 (61.1) |
| Subjects with SAEs | 2 (2.9) | 0 | 0 | 1 (2.6) | 1 (2.7) | 1 (2.8) |
| Subjects with Severe AEs | 0 | 1 (1.6) | 0 | 3 (7.9) | 2 (5.4) | 1 (2.8) |
| Subjects Discontinued Treatment Due to AEs | 2 (2.9) | 1 (1.6) | 3 (4.8) | 4 (10.5) | 1 (2.7) | 1 (2.8) |
| Subjects Discontinued Study Due to AEs | 0 | 0 | 1 (1.6) | 1 (2.6) | 0 | 0 |
| Subjects with Dose Reduced or Temporary Discontinuation Due to AEs | 5 (7.1) | 2 (3.2) | 4 (6.3) | 4 (10.5) | 2 (5.4) | 3 (8.3) |

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: SCS Supplemental Table F14.3.1.2.1.1.3.

**Race:**

**Table 18: All-Causality TEAE, Efficacy Study Safety Population Overall by Race**

| | High-Dose Varenicline | Low-Dose Varenicline | Placebo |
|---|---|---|---|
| | number (%) of subjects | | |
| **White** | **N=81** | **N=73** | **N=74** |
| Subjects with AEs | 47 (58.0) | 39 (53.4) | 41 (55.4) |
| Subjects with SAEs | 2 (2.5) | 1 (1.4) | 1 (1.4) |
| Subjects with Severe AEs | 3 (3.7) | 3 (4.1) | 1 (1.4) |
| Subjects Discontinued Treatment Due to AEs | 5 (6.2) | 2 (2.7) | 3 (4.1) |
| Subjects Discontinued Study Due to AEs | 1 (1.2) | 0 | 0 |
| Subjects with Dose Reduced or Temporary Discontinuation Due to AEs | 6 (7.4) | 2 (2.70) | 4 (5.4) |
| **Black or African American** | **N=9** | **N=9** | **N=5** |
| Subjects with AEs | 6 (66.7) | 3 (33.3) | 3 (60.0) |
| Subjects with SAEs | 0 | 0 | 0 |
| Subjects with Severe AEs | 0 | 0 | 0 |
| Subjects Discontinued Treatment Due to AEs | 1 (11.1) | 0 | 0 |
| Subjects Discontinued Study Due to AEs | 0 | 0 | 0 |
| Subjects with Dose Reduced or Temporary Discontinuation Due to AEs | 1 (11.1) | 1 (11.1) | 0 |
| **Asian** | **N=16** | **N=18** | **N=19** |
| Subjects with AEs | 11 (68.8) | 11 (61.1) | 7 (36.8) |
| Subjects with SAEs | 1 (6.3) | 0 | 0 |
| Subjects with Severe AEs | 0 | 0 | 0 |
| Subjects Discontinued Treatment Due to AEs | 0 | 0 | 1 (5.3) |
| Subjects Discontinued Study Due to AEs | 0 | 0 | 1 (5.3) |
| Subjects with Dose Reduced or Temporary Discontinuation Due to AEs | 2 (12.5) | 1 (5.6) | 3 (15.8) |
| **Other** | **N=2** | **N=0** | **N=1** |
| Subjects with AEs | 1 (50.0) | 0 | 1 (100.0) |
| Subjects with SAEs | 0 | 0 | 0 |
| Subjects with Severe AEs | 0 | 0 | 0 |
| Subjects Discontinued Treatment Due to AEs | 0 | 0 | 0 |
| Subjects Discontinued Study Due to AEs | 0 | 0 | 0 |
| Subjects with Dose Reduced or Temporary Discontinuation Due to AEs | 0 | 0 | 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.
AE=adverse event; SAE=serious adverse event; N=number of subjects; n=number of subjects in subset; 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.
MedDRA v20.1.
Source: SCS Supplemental Table F14.3.1.2.1.1.4.

**Weight:**

In this study there was no clear correlation between weight and AEs.

**Table 19: All-Causality TEAE, Efficacy Study Safety Population by Weight Strata in 12-16 yo**

| System Organ Class<br>Preferred Term | ≤55 kg<br>High-Dose Var<br>N=19 | ≤55 kg<br>Low-Dose Var<br>N=19 | ≤55 kg<br>Pbo<br>N=24 | >55 kg<br>High-Dose Var<br>N=52 | >55 kg<br>Low-Dose Var<br>N=51 | >55 kg<br>Pbo<br>N=47 |
|---|---|---|---|---|---|---|
| | number of subjects (%) | | | | | |
| Subjects with AEs | 8 (42.1) | 9 (47.4) | 13 (54.2) | 31 (59.6) | 25 (49.0) | 20 (42.6) |
| Subjects with SAEs | 1 (5.3) | 0 | 1 (4.2) | 2 (3.8) | 0 | 0 |
| Subjects with Severe AEs | 0 | 0 | 0 | 2 (3.8) | 0 | 0 |
| Subjects Discontinued Treatment Due to AEs | 1 (5.3) | 0 | 1 (4.2) | 2 (3.8) | 0 | 2 (4.3) |
| Subjects Discontinued Study Due to AEs | 0 | 0 | 0 | 1 (1.9) | 0 | 1 (2.1) |
| Subjects with Dose Reduced or Temporary Discontinuation Due to AEs | 2 (10.5) | 0 | 2 (8.3) | 2 (3.8) | 1 (2.0) | 2 (4.3) |

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 CSR Table 14.3.1.2.1.1.4.

As illustrated in the tables above, in 17-19 years old group, higher percentages of subjects in each treatment group experienced AEs than in the 12-16 year olds. A higher percentage of females in all treatment groups reported AEs compared to males. Females also had more SAEs, severe AEs, and AEs that resulted in treatment discontinuation. Higher percentages of high-dose varenicline Black or African American and Asian subjects reported AEs compared to high-dose varenicline White subjects. SAEs and severe AEs were reported more by White subjects in all treatment groups compared to non-White subjects, except for SAEs which were reported in a higher percentage of high-dose varenicline Asian subjects (although the percentage in Asians represented a single subject). Certain AEs, including vomiting and the psychiatric AEs were reported primarily by White subjects. In this study the data did not show a clear correlation between weight and AEs.

### 8.2.8. Specific Safety Studies/Clinical Trials

Not applicable.

### 8.2.9. Additional Safety Explorations

**Human Carcinogenicity or Tumor Development**

No new information.

**Human Reproduction and Pregnancy**

No new information.

**Pediatrics and Assessment of Effects on Growth**

Effects on growth were not evaluated. Studies were a maximum of 12 weeks in treatment duration.

**Overdose, Drug Abuse Potential, Withdrawal, and Rebound**

No new information.

### 8.2.10. Safety in the Postmarket Setting

**Safety Concerns Identified Through Postmarket Experience**

In adults, number of postmarket safety concerns have been identified and added to the label including neuropsychiatric adverse events, cardiovascular events, somnambulism, seizures and potential interaction with alcohol.

**Expectations on Safety in the Postmarket Setting**

If used in adolescents, it is expected that varenicline will have similar safety profile as in adults.

### 8.2.11. Integrated Assessment of Safety

Overall, the safety profile in adolescents is similar to adults. In placebo-controlled studies in adults, 12% of subjects on Chantix discontinued treatment due to adverse events compared to 10% in placebo group. In the adolescent efficacy study; discontinuation of treatment/study due to adverse event was 3% in high dose varenicline group compared to 1% in low dose varenicline and 3% in placebo group. Additionally, 3% in high dose varenicline group stopped the study medication and completed the study. The types and frequencies of common adverse events were also similar to those reported in adult studies. Overall, the safety profile in adolescents is similar to adults.

## 8.3. Statistical Issues

The only statistical concern was that the first of the hierarchical planned efficacy comparisons did not show statistical significance for the varenicline high dose group vs. placebo. The

hypothesis testing appropriately stopped at that point to protect the overall Type I level of significance.

The secondary comparison for the CAR Week 9-12 responder rate in the 12-16 year old age group of varenicline low dose to placebo had a p-value of 0.025. The clinical team requested that the statistical reviewer confirm that this was not valid indication of efficacy for this dose in that age group. Ms. Meaker considered the discontinuations and subgroup analyses but did not find further evidence to suggest that result was more than spurious. The applicant presented three sensitivity analyses (CSR Section 11.4.1.2) in which the imputation was determined by discontinuation status, and all the results were similar to the overall results, not suggesting efficacy in this age group.

## 8.4. Conclusions and Recommendations

The effectiveness of Chantix is well established in adult smokers (18 years of age and older). The efficacy trial in this supplement did not demonstrate that varenicline is effective in adolescent smokers 12 to 16 years old. The study was not powered to assess the efficacy in 17 to 19 year old group. Considering that the side effect profile of varenicline including neuropsychiatric side effects is similar to adult population and the effectiveness is not demonstrated in smokers 12 to 16 years of age, the risks outweigh the benefits. As such, varenicline is not recommended in pediatric population 16 years of age and younger.

# 9 Advisory Committee Meeting and Other External Consultations

Not applicable.

# 10 Pediatrics

Pediatric Exclusivity was granted effective November 15, 2018, under section 505A of the Federal Food, Drug and Cosmetic Act.

# 11 Labeling Recommendations

## 11.1. Prescription Drug Labeling

The Applicant's proposed labeling under 8.4 Pediatric Use:

(b) (4)

Based on the recommendations of the Pediatric Review Committee (PeRC), the specifics about the dosing should not be included in labeling. The following text is proposed:

CHANTIX is not recommended for use in pediatric patients 16 years of age and under because its efficacy in this population was not demonstrated.

Single and multiple-dose pharmacokinetics of varenicline have been investigated in pediatric patients aged 12 to 17 years old (inclusive) and were approximately dose-proportional over the 0.5 mg to 2 mg daily dose range studied. Steady-state systemic exposure in adolescent patients of bodyweight >55 kg, as assessed by AUC (0-24), was comparable to that noted for the same doses in the adult population. When 0.5 mg BID was given, steady-state daily exposure of varenicline was, on average, higher (by approximately 40%) in adolescent patients with bodyweight ≤ 55 kg compared to that noted in the adult population.

The efficacy and safety of varenicline was evaluated in a randomized, 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, and at least one previous failed quit attempt. Patients were stratified by age (12 to 16 years of age and 17 to 19 years of age) and by body weight (≤55 kg and >55 kg). Following two-week titration, patients randomized to two weight-adjusted doses of varenicline intended to provide plasma levels in efficacious range) and placebo. *[see Clinical Pharmacology (12.3)]*. 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 varenicline, at either dose studied, did not significantly increase continuous abstinence rates at weeks 9 through 12 of treatment compared with placebo in subjects 12 to 19 years of age. The varenicline safety profile in this study was consistent with that shown in adult studies.

## 12 Risk Evaluation and Mitigation Strategies (REMS)

Not applicable.

## 13 Postmarketing Requirements and Commitment

Not applicable.

# 14 Appendices

## 14.1. Financial Disclosure

**Covered Clinical Study (Name and/or Number):** A3051073

| | | |
|---|---|---|
| Was a list of clinical investigators provided: | Yes ☒ | No ☐ (Request list from Applicant) |
| Total number of investigators identified: 341 | | |
| Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0 | | |
| Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 3 | | |
| If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):<br>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____<br>Significant payments of other sorts: 3<br>Proprietary interest in the product tested held by investigator: _____<br>Significant equity interest held by investigator in S<br>Sponsor of covered study: _____ | | |
| Is an attachment provided with details of the disclosable financial interests/arrangements: | Yes ☒ | No ☐ (Request details from Applicant) |
| Is a description of the steps taken to minimize potential bias provided: | Yes ☒ | No ☐ (Request information from Applicant) |
| Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0 | | |
| Is an attachment provided with the reason: | Yes ☒ | No ☐ (Request explanation from Applicant) |

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02/20/2019 04:43:59 PM

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