The Varenicline Adolescent Study and Lessons Learned

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1

Study Design Highlights

- Randomized, double-blind, placebo-controlled
- 2 doses of varenicline adjusted by weight
  - High dose: 1 mg twice a day (BID) for >55 kg, 0.5 mg BID for ≤55 kg
  - Low dose: 0.5 mg BID for >55 kg, 0.5 mg once a day (QD) for ≤55 kg
- 12 weeks of treatment with 40 weeks of follow-up
  - Dose titration for first 2 weeks of treatment (0.5 mg QD for all groups, except those taking 1 mg BID who take 0.5 mg QD for the first week and 0.5 mg BID for the second week)
  - Target quit date to coincide with the Week 1 visit
- Clinic visits were weekly for the first 16 weeks, then at Weeks 20, 28, 36, 44, and 52, with telephone visits at Weeks 24, 32, 40, and 48

2

Key Inclusion Criteria

- Healthy males and females aged 12–19 years
- Body weight ≥35 kg (77lbs), and body mass index (BMI) ≤35 kg/m^2
- Currently smoking at least an average of 5 cigarettes/day for past 30 days
- Score ≥4 on Fagerström test for nicotine dependence
- Motivated to stop smoking
- At least one prior quit attempt
- Assent and parental consent (ages 12–17 years) or subject consent (ages 18–19 years)

3

Key Exclusion Criteria

- Suicide attempt, hospitalization due to suicidal ideation or behavior, or having serious ideation or behavior within the past 12 months
- Clinically significant psychiatric disorder
- Evidence of alcohol or substance use disorder within 3 months of screening or a positive urine drug screen at screening and baseline
- Inability or unwillingness to refrain from use of other tobacco products, marijuana, or nicotine replacement therapy (NRT) during study participation

4

Efficacy Endpoints

- Primary Efficacy Endpoint:
  - 4 week Continuous Abstinence Rate (CAR, weeks 9–12)
  - The primary analysis for this endpoint was the overall study (ages 12–19 years)
- 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
  - CAR weeks 9–24
  - CAR weeks 9–52

5

Safety Endpoints

- Safety assessments
  - Adverse events (AEs) spontaneously volunteered or observed

    AND
  - Solicited AEs via the:
    - Neuropsychiatric Adverse Event Interview (NAEI)
    - Columbia Suicide Severity Rating Scale (C-SSRS)
    - Hospital Anxiety and Depression Scale (HADS)
    - Safety labs and vitals
- Pharmacokinetic and pharmacodynamic assessments
  - Varenicline plasma levels and exposure-response analyses for efficacy and nausea/vomiting

6

Smoking Cessation Counseling

- Every visit, starting at baseline included “up to 10 minutes” of smoking cessation counseling
- Counseling manual was created by Dr. Jaimee Heffner from University of Cincinnati
- Age appropriate adaptation of the Public Health Service guidelines
- All subjects were provided the “I Quit” booklet

7

STUDY RESULTS

8

Participant Characteristics (Safety Population)

Characteristic	Varenicline High Dose *N*=108	Varenicline Low Dose *N*=100	Placebo *N*=99
Age (years) Mean (SD)	16.0 (2.0)	16.0 (1.7)	15.8 (1.8)
Gender, *n* (%) Male Female	70 (64.8) 38 (35.2)	63 (63.0) 37 (37.0)	63 (63.6) 36 (36.4)
Race, n (%) White Black Asian	81 (75.0) 9 (8.3) 16 (14.8)	73 (73.0) 9 (9.0) 18 (18.0)	74 (74.7) 5 (5.1) 19 (19.2)
FTND Total Score Mean (SD) Range	5.4 (1.4) 1–9	5.5 (1.4) 3–9	5.3 (1.6) 0–9
Average cigs/day in last month Mean (SD) Range	12.8 (7.5) 5–40	12.3 (6.0) 5–30	12.0 (6.0) 5–30
Number of years smoked Mean (SD) Range	3.1 (1.7) 0–8	3.0 (2.3) 0–13	2.9 (1.7) 1–8

9

CAR 9–12, Urine Cotinine Confirmed: Full Analysis Set

CAR 9–12 (%)	**Overall n/N (%)**
Varenicline High Dose	22/109 (20.2)
Varenicline Low Dose	28/103 (27.2)
Placebo	18/100 (18.0)
Treatment Comparisons	**Estimated odds ratio in CAR 9–12 (95% CI) [p-value]***
Varenicline High Dose vs Placebo	1.18 (0.59, 2.37) [p=0.6354]
Varenicline Low Dose vs Placebo	1.73 (0.88, 3.38) [p=0.1119]

Full analysis set included all randomized subjects

* P-values and odds ratios based on a logistic regression model with terms treatment, age strata, and pooled center

CAR, continuous abstinence rate; N, number of subjects randomized; n, 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

10

Safety
Adverse Events (AEs) [participant *n* (%)]

	Varenicline High Dose *N*=108	Varenicline Low Dose *N*=100	Placebo *N*=99
Overall AEs	65 (60.2)	53 (53.0)	52 (52.5)
Neuropsychiatric AEs	18 (16.7)	11 (11.0)	12 (12.1)
Serious AEs	3 (2.8)	1 (1.0)	1 (1.0)
Severe AEs	3 (2.8)	3 (3.0)	1 (1.0)
Dose reduced or temporary discontinuation due to AEs	9 (8.3)	4 (4.0)	7 (7.1)
Discontinued drug due to AEs	6 (5.6)	1 (1.0)	4 (4.0)
Discontinued study due to AEs	1 (0.9)	0	3 (3.0)

11

Safety
AEs with ≥5% incidence in any treatment group [participant *n* (%)]

	Varenicline High Dose *N*=108	Varenicline Low Dose *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)

12

Additional Safety Data

- Overall, there were 5 subjects with treatment-emergent serious adverse events
  - 3 subjects on high dose varenicline
    - Situational exacerbation of adjustment disorder (16 year old)
    - Laryngitis (15 year old)
    - Campylobacter gastroenteritis (14 year old)
  - 1 subject on low dose varenicline
    - Acute cholecystitis and bile duct stone (18 year old)
  - 1 subject on placebo
    - Acute salpingitis (16 year old)
- 6 subjects had serious adverse events >30 days post-treatment

13

CONCLUSIONS AND LESSONS LEARNED

14

Efficacy and Safety

- Varenicline showed no significant benefit compared with placebo in achieving smoking cessation in nicotine-dependent adolescents who also received age appropriate counselling
- Both varenicline doses used in the A3051073 study were generally well tolerated 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
  - Regardless of treatment, most neuropsychiatric AEs were solicited by the NAEI and were mild. There were no notable differences between treatments and placebo.

15

Lessons Learned

- Study recruitment is very challenging
  - Recruiting 312 participants took almost 6 years and required adding ex-U.S. sites (about one-third of U.S. sites failed to randomize any subjects)
  - 151/463 (33%) of participants screened were screen failures
    - 106 did not meet I/E criteria (26 of these did not meet the smoking criteria); 8 were lost to follow-up, 22 were no longer willing to participate, and 15 were other reasons
  - The original plan to recruit participants through schools was not workable
  - Study participation was very demanding for participants and their parents – 1-year study, weekly clinic visits for the 1st 16 weeks, 4 blood draws from screening to week 12

16

Lessons Learned

- Study recruitment is very challenging
  - Study participation was very demanding for participants and their parents –
    - 1-year study
    - Weekly clinic visits for the 1st 16 weeks
    - 4 blood draws from screening to week 12
    - Participants ≤ 17 years old required parental consent, i.e. had to tell them that they were smokers

17

Lessons Learned

- Study retention is also challenging
  - 77/307 (25%) of those treated dropped out during treatment
  - The most common reasons were
    - 31 (10%) lost to follow-up
    - 22 (7%) no longer willing to participate
    - 16 (5%) other
  - 2 participants (1 varenicline high dose, 1 placebo) discontinued the study during treatment due to adverse events
  - 43/307 (14%) of those treated dropped out during the post-treatment follow-up period; the most common reasons were similar to those above

18

Lessons Learned

- Efficacy criteria may have been too strict
  - Admitting to smoking “even a puff” disqualified participants as responders
  - Adolescents may not see a reason to maintain strict abstinence
    - They likely do not have health concerns
    - They may not see small slip-ups as failing the study
    - They may succumb more readily to peer pressure

19