THE EFFICACY OF VARENICLINE COMPARED TO PLACEBO FOR SMOKING CESSATION USING A REDUCE-TO-QUIT STRATEGY: One Research Center's Results

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BACKGROUND

According to the World Health Organization [July 2013] Fact Sheet, 50% of all tobacco users die from a tobacco-related illness, this equates to approximately six million people each year. As members of the Society for Research on Nicotine and Tobacco **[SRNT]** and attendees at this conference, we understand that tobacco use is clearly the leading cause of preventable illness and premature death all across the world! A 2007 U.S.-based population survey indicated that 53% of smokers wanting and motivated to quit, preferred a **Reduce-to-Quit** strategy. Moreover, a 2009 U.K.-based study indicated that only 12% of smokers desiring to quit were willing to attempt doing so vis-à-vis a completely abrupt approach. The effectiveness of a Reduce-to-Quit methodology was never tested during the clinical trials prior to the FDA-approval of varenicline.

METHODS

This was a global Phase IV study, whereby 61 research centers from ten different countries collaborated in the randomization of 1,510 subjects. Here at the SRNT Annual Meeting, we are reporting (only) on data generated at our Southern California-based research site(s): Pharmacology Research Institute.

There was a 3-to-10 day ***Screening Phase***, into which 49 adult smokers were entered and five (5) failed to fulfill 100% of the Inclusionary Criteria. The 44 subjects meeting all of the entry criteria were randomly assigned, on a one-to-one ratio (i.e., n=22 per treatment group) to varenicline or placebo for a 24-week two-part treatment phase. In part one, the 12-Week ***Reduction Phase***, the smokers made incremental efforts to reduce their smoking. During the subsequent 12-Week ***Abstinence Phase***, the subjects were encouraged and counseled to be abstinent from smoking. Active (double-blind) treatment was concluded at Week-24. The subjects then entered into the 28-Week **Follow-Up (Post-Treatment) Phase**, eventually concluding their study participation at Week-52.

Brief, ten-minute, semi-standardized smoking cessation counseling sessions were integrated into each study visit, beginning at Baseline, Week-0. Successful cessation was pre-defined as an end-exhaled carbon monoxide (CO) measurement of < 10 ppm, as well as subject reports via the Nicotine Use Inventory (NUI).

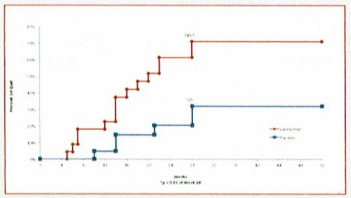
INCLUSION CRITERIA (PARTIAL)

- Female and male smokers age 18 and above
- Smoking at least 10 cigarettes per day during the past year
- No continuous abstinence for > 3 months within the past year
- Smokers who have an exhaled carbon monoxide (CO) > 10 ppm
- No clinically significant laboratory or electrocardiogram abnormalities

RESULTS

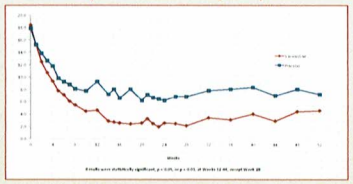
Notwithstanding the comparatively small sample size, both clinically and statistically significant efficacy-related results were demonstrated as early as Week-12 ($p<0.01$) [the beginning of the Abstinence Phase] and at numerous evaluative time points thereafter. By Week-28, the analysis of time to "First Quit" incidence demonstrated a 71% success rate for the varenicline group as compared with 32% for the placebo group. The time-to-quit or percent quit, a.k.a. "quitting incidence," was also estimated as a function of time using the non-parametric Kaplan-Meier method. Additionally, Kaplan-Meier incidence curves were compared between the two treatment groups using log rank test to compute the p values.

Weeks to 1st Quit - Quitting Incidence Curve

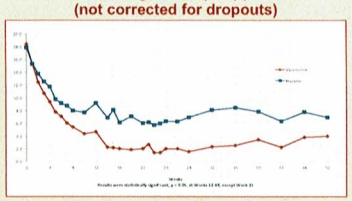


The mean number of cigarettes smoked, as captured by the Nicotine Use Inventory (NUI), was analyzed both with and without accounting for subjects who discontinued (i.e., dropped-out) from the study, under a repeated measure (mixed) analysis of variance model. So, the first of these two graphs shows less statistical bias. As can be seen, in both graphs, the mean differences are statistically significant at the vast majority of time points leading up to Weeks 44 and 48, respectively.

Mean Num Cigarettes (NUI) per Week (corrected for dropouts)

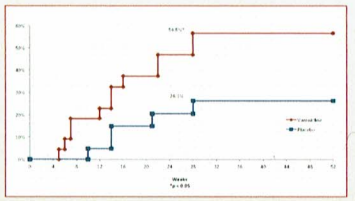


Mean Num Cigarettes (NUI) per Week (not corrected for dropouts)



In harmony with the overall tenacity of nicotine addiction, the sustained permanence of complete smoking cessation is often elusive at best. To that end, the overall comparative sustained cessation rates were of utmost interest. Illustrated below are the "Weeks to Permanent Quit" results, at Weeks 28 through 52, further demonstrating superior efficacy for varenicline versus placebo in terms of having a non-relapsing, sustained quit effort and outcome.

Weeks to Permanent Quit - Quitting Incidence Curve

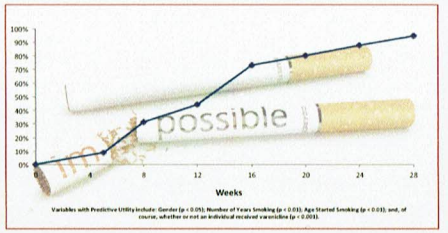


This sustained "permanent quit" analysis clearly demonstrated superior efficacy for varenicline (57%) versus placebo (26%), as defined and demonstrated by a non-relapsing, successfully sustained quit outcome ($p<.05$).

Additionally, recognizing that smoking cessation is a complex and multifactorial process, we statistically analyzed nine baseline variables to evaluate their potential impact on subjects' initial cessation efforts and their long-term results. The following variables did not demonstrate any statistically significant relationship or correlation with successful cessation: baseline body mass index (BMI), the average number of cigarettes smoked per day, the number of prior unsuccessful quit attempts, the longest period of prior abstinence and, quite atypically in our experience, the presence of another smoker in one's household… all did not significantly correlate with success or failure in quitting.

Admittedly, our comparatively small sample sizes substantially heightened the threshold for achieving statistical significance. The age of the individual at the time of study entry demonstrated a statistical trend ($p=0.08$) indicating that older study participants had a higher probability of successfully quitting and remaining smoke-free. One other very atypical finding was the fact that the subjects randomly assigned into the varenicline treatment group had a higher percentage of smokers living within their households (45.5% versus 18.2%) when compared to the placebo group and; yet, this (relatively small, n=22) treatment group reached and sustained statistically significant superiority.

Model Predicted Quit Incidence



DISCUSSION

We utilized the Cox proportional hazard model to analyze and calculate "Time to First Quit" results. As presented above, a female versus male smoker ($p<0.04$), who is over the age of 48.5 years at the time of randomization (i.e., initiating treatment) ($p=0.08$), who first began smoking at age 18, or older, $p<0.005$, who has smoked fewer years (i.e., <25.7 years of total smoking) $p<0.01$ had a 94.4% probability of successfully quitting and remaining as "quit" – at 52 weeks – in this study, at our site, *if* she had been randomly assigned into the varenicline treatment group.

While many of the aforementioned results are consistent with the literature pertaining to cessation, the level of statistical significance within this small sample was noteworthy. Also, while there was only a statistical trend (which did not reach the $p<0.05$ level of significance), the subjects assigned into the varenicline treatment group had a higher number of prior quit attempts and (surprisingly) a substantially higher percentage of current smokers living within their households when compared to the placebo group; and yet, this small (n=22) cohort reached and maintained statistically significant superiority.

CONCLUSIONS

- Our results provide additional strong clinical and statistical evidence of varenicline's superior efficacy when compared to placebo when utilizing a Reduce-to-Quit smoking cessation methodology.
- Our findings also demonstrate that a Reduce-to-Quit methodology may actually enhance the efficacy of varenicline in achieving and maintaining a "successfully quit" permanent outcome.

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