Successful Smoking Abstinence with Cytisinicline in the ORCA-1 Trial: What Happens Next?

AUTHORS

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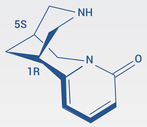
BACKGROUND



(-)-Cytisinicline

(-)-Cytisine or cytisinicline is a naturally occurring plant-based alkaloid isolated from seeds of *Cytisus laburnum* (Golden chain).

Studies have shown that cytisinicline 1.5 mg is effective in helping smokers to quit using a titration schedule comprising a gradual reduction from 6 to 1 tablets per day over a 25 day period.

The **O**ngoing **R**esearch of **C**ytisinicline for **A**ddiction ORCA-1 study aimed to explore a more simplified dosing schedule (3 times daily, TID) and an increased unit dose (3.0 mg).

OBJECTIVES

Efficacy Objectives

Comparison of 1.5 mg or 3.0 mg doses of cytisinicline using a downward titration or simplified TID dosing schedule versus placebo:

- Overall reduction in cigarette smoking during the study treatment period (Day 1-25)
- Week 4 quit rate at the end of 25 days of treatment
- Continuous abstinence rate from Week 5 to week 8 (subjects off treatment).

Safety Objectives

- To evaluate overall safety profile of cytisinicline compared with placebo

STUDY DESIGN

Six-arm, double-blind, randomized, placebo-controlled, Phase 2b study conducted in 8 centers in the United States. The study was blinded to dose but not to the administration schedule. Subjects agreed to a quit date 5 to 7 days randomization and initiation of study treatment. Subjects meeting the eligibility criteria (Table 1) were randomized. A total of 50 subjects per group (cytisinicline) or 25 per group (placebo) was planned. The study dosing schedules are shown in Figure 1 and the study visits in Figure 2.

Table 1: Eligibility Criteria

Main Inclusion Criteria	Main Exclusion Criteria
▪ Male or female subjects, age ≥18 years	▪ Positive urinary drugs of abuse screen
▪ Current daily cigarette smokers (≥10 cigarettes per day) who intend to quit	▪ Clinically significant abnormal serum chemistry or hematology values
▪ Expired air carbon monoxide (CO) >10 ppm	▪ BMI classification of underweight (<18.5 kg/m2) or ≥Class 2 obesity (≥35 kg/m2).
▪ Failed at least one previous attempt to quit with/without therapeutic support	▪ Recent history of acute myocardial infarction, unstable angina, stroke, cerebrovascular incident or hospitalization for congestive heart failure.
▪ Willing to initiate study treatment on the day after randomization and set a quit date within 5-7 days of starting treatment.	▪ Current uncontrolled hypertension (BP ≥160/100 mmHg).
▪ Willing to actively participate in the study's smoking cessation behavioral support provided throughout the study	▪ Documented diagnosis of schizophrenia or bipolar psychiatric illness; currently psychotic; having suicidal ideation (SBQ-R score ≥7); or current symptoms of moderate to severe depression (HAD score ≥11).
	▪ Treatment with other smoking cessation medications (bupropion, varenicline, nortriptyline, or any nicotine replacement therapy [NRT]) within 4 weeks of randomization or planned use of these other smoking cessation medications during the study.
	▪ Use within 2 weeks of randomization or planned use during the study of non-cigarette nicotine products (e-cigarettes, pipe tobacco, cigars, snuff, chewing tobacco, hookah) or marijuana vaping or smoking.

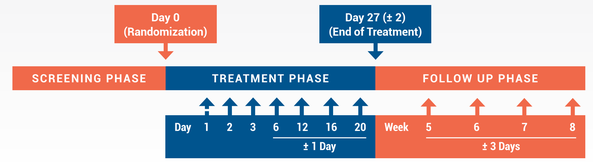
Figure 1: Study Dosing Schedules

Traditional Downward Titration					
Day	Number of Days	Daily Frequency	Total Dose (mg)		
			1.5 mg (n = 50)	3.0 mg (n = 50)	Placebo (n = 25)
1-3	3	6 times	9	18	-
4-12	9	5 times	7.5	15	-
13-16	4	4 times	6	12	-
17-20	4	3 times	4.5	9	-
21-24	4	2 times	3	6	-
25	1	1 time only	1.5	3	-
		TOTAL	150 mg	300 mg	-

Simplified 3-Times Daily (TID)					
Day	Number of Days	Daily Frequency	Total Dose (mg)		
			1.5 mg (n = 50)	3.0 mg (n = 50)	Placebo (n = 25)
1-20	3	3 times	4.5	9	-
					-
					-
					-
21-24	4	2 times	3	6	-
25	1	1 time only	1.5	3	-
		TOTAL	103.5 mg	207 mg	-

Figure 2: Study Visits

Subjects completed a daily diary of the number of cigarettes smoked. Self-reported abstinence was confirmed by expired CO at the end of treatment and weeks 5, 6, 7 & 8.



RESULTS

The demographics and smoking history of subjects in each treatment arm were broadly similar – see Tables 2 & 3.

Efficacy results for the two placebo arms were comparable and the data pooled.

All cytisinicline-treated arms showed a greater reduction in cigarettes smoked than pooled placebo (Figure 3) although the self-reported reductions were not matched by a corresponding decrease in expired CO in the placebo arms (Figure 4).

Overall, cytisinicline was well tolerated. There were no clinically significant effects on vital signs or ECG. The Treatment-Emergent Adverse Events are shown in Table 4.

Table 2: Demographics

	TID		Downward Titration		
	1.5 mg (n=52)	3.0 mg (n=50)	1.5 mg (n=51)	3.0 mg (n=50)	Pooled Placebo (n=51)
Sex					
Female	29 (56%)	25 (50%)	28 (55%)	20 (40%)	31 (61%)
Race					
White	37 (71%)	41 (82%)	43 (84%)	40 (80%)	39 (76%)
Black	13 (25%)	7 (14%)	7 (14%)	9 (18%)	10 (20%)
Other	2 (4%)	2 (4%)	1 (2%)	1 (2%)	2 (4%)
Mean Age (years)	47.0	46.3	49.8	50.0	49.0
Mean Weight (kg)	80.7	79.5	82.1	83.0	80.2

Table 3: Smoking History

	TID		Downward Titration		
	1.5 mg (n=52)	3.0 mg (n=50)	1.5 mg (n=51)	3.0 mg (n=50)	Pooled Placebo (n=51)
Smoking duration (mean years)	30.9	30.0	33.3	33.2	33.0
Daily smoking (median cigarettes)	20	18	20	20	20
Prev. quit attempts (mean)	4.7	3.8	5.4	3.8	4.9
Previous treatments					
Varenicline	21 (40%)	18 (36%)	21 (41%)	13 (26%)	19 (37%)
Bupropion	9 (17%)	7 (14%)	9 (18%)	3 (6%)	12 (24%)
NRT					
Patch	27 (52%)	25 (50%)	23 (45%)	19 (38%)	28 (55%)
All other NRT	22 (42%)	16 (32%)	21 (41%)	12 (24%)	26 (51%)
e-cigarettes	19 (37%)	13 (26%)	15 (29%)	11 (22%)	18 (35%)

Figure 3: Self-Reported Daily Cigarettes Smoked

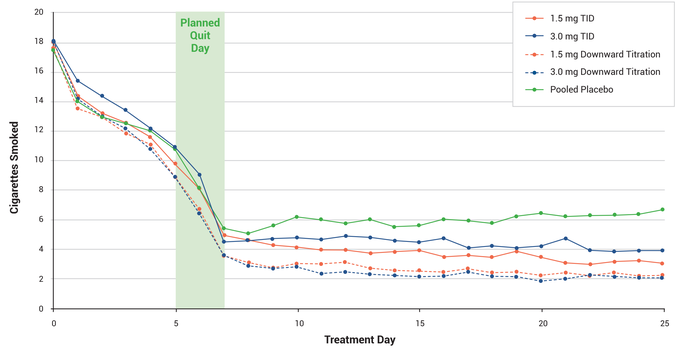


Figure 4: Reduction in Cigarettes Smoked and Expired CO

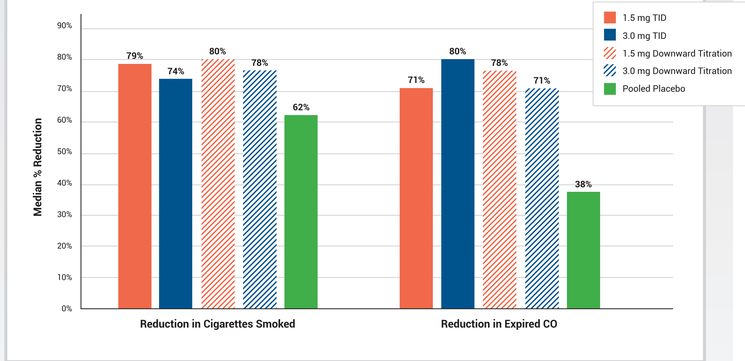
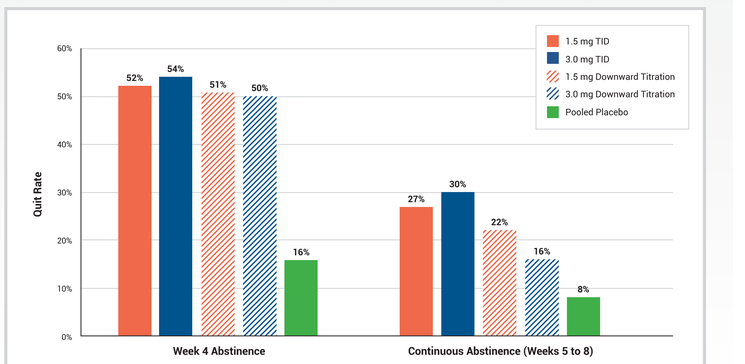


Table 4 Treatment-Emergent Adverse Events

	TID		Downward Titration		
	1.5 mg (n=52)	3.0 mg (n=50)	1.5 mg (n=51)	3.0 mg (n=50)	Pooled Placebo (n=51)
At least 1 AE	20 (39%)	21 (42%)	29 (57%)	23 (46%)	24 (47%)
URTI	5 (10%)	3 (6%)	3 (6%)	2 (4%)	7 (14%)
Abnormal dreams	4 (8%)	3 (6%)	4 (8%)	7 (14%)	1 (2%)
Nausea	1 (2%)	3 (6%)	5 (10%)	3 (6%)	5 (10%)
Insomnia	4 (8%)	3 (6%)	3 (6%)	4 (8%)	1 (2%)
Headache	6 (12%)	2 (4%)	1 (2%)	1 (2%)	2 (4%)
Fatigue	3 (6%)	1 (2%)	1 (2%)	2 (4%)	2 (4%)

Figure 5: Quit Rates and the End of Treatment (Week 4) & Continuous Abstinence (Off Treatment) at Weeks 5 to 8



CONCLUSIONS

- Overall reduction in cigarette smoking was greater in cytisinicline-treated subjects, but self-reported reductions in cigarettes smoked was not paralleled by a reduction in expired CO in placebo-treated subjects.
- All cytsinicline schedules resulted better quit rates than placebo (OR > 5) at the end of treatment. Both TID schedules resulted better quit rates than placebo (OR > 4) at week 5 to week 8 (off treatment).
- Cytisinicline was well tolerated.
- Continuous abstinence rates were low with behavioral support alone.

What happens next?

- A slightly longer treatment period might enhance treatment benefit and reduce relapses in recent, vulnerable non-smokers.
- Planned Phase 3 studies will use 3 mg TID for 6 weeks

SPONSOR INFORMATION

This research is supported by **Achieve Life Sciences, Inc.** (-)-Cytisine, was developed by Sopharma and first marketed in 1980 in Bulgaria as a smoking cessation aid (Tabex®). Tabex is currently marketed by Sopharma in 20 countries within Central and Eastern Europe using a 1.5 mg dose over a 25 day titration schedule (total of 100 tablets over 25 days). Achieve Life Sciences Inc. has acquired the license for cytisine as a smoking cessation treatment for development in the United States (US), Western Europe, Japan and other countries outside of Sopharma's marketed territories. Achieve is initially focusing efforts in the US and submitted IND 112969 in June, 2017. Achieve is conducting new clinical studies to current Good Clinical Practice (GCP) standards under IND 112969 in order to address requests made by FDA, confirming and expanding previous efficacy and safety findings for cytisine as a smoking cessation agent.

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