Cytisinicline for cigarette smoking and e-cigarette vaping cessation: Long-term safety data from the ORCA-OL clinical trial

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Introduction

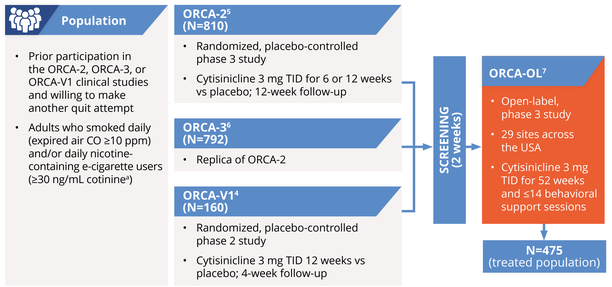
- Approximately 25 million adults in the USA smoke,[1] and no new FDA-approved smoking cessation therapies have been introduced since 2006[2]
- Approximately 18 million adults in the USA use electronic (e)-cigarettes,[3] with no FDA-approved treatments indicated specifically as an aid to nicotine e-cigarette cessation
- Cytisinicline is a plant-based alkaloid and partial agonist at α4β2 nicotinic acetylcholine receptors[4]
- A novel cytisinicline treatment regimen, consisting of a 3 mg tablet administered three times daily (TID) for 6 or 12 weeks, is currently under regulatory review
- In the phase 3 ORCA-2 and ORCA-3 trials, cytisinicline was more effective than placebo in achieving continuous smoking abstinence in adults, and in the phase 2 ORCA-V1 trial it was also more effective in achieving continuous abstinence from e-cigarettes, and was well tolerated across all studiess[4–6]
- Adult participants from the ORCA-2, ORCA-3, or ORCA-V1 trials who agreed to make another quit attempt were enrolled in a 52-week open-label (OL) safety trial: **ORCA-OL**[7]

Objective

To evaluate the long-term safety of cytisinicline in adults who smoke/vape who had previously participated in the ORCA-2, ORCA-3, or ORCA-V1 studies[4–6]

Materials and methods

Figure 1. Study design



[a]Using a point-of-care cotinine oral fluid screening device if self-reporting as users of nicotine-containing e-cigarettes. CO, carbon monoxide; e-cigarettes, electronic cigarettes; OL, open label; ppm, parts per million; TID, three times daily.

Assessments

- Treatment-emergent adverse event (TEAE) incidence was assessed, including serious adverse events (SAEs), severity (mild, moderate, severe), and events leading to dose reduction, interruption, or discontinuation

Results

Table 1. Baseline characteristics

Characteristic	Participants (N=475)
Female, n (%)	**275 (57.9)**
Age, median years (min, max)	**55 (22, 79)**
Race, n (%)[a]	
White	**386 (81.3)**
Black or African American	**79 (16.6)**
User type, n (%)	
Current smoker	**402 (84.6)**
Current e-cigarette user	**61 (12.8)**
Dual user	**12 (2.5)**
Cigarette intake per day in past 30 days, median	**20**
Vaping product intake days in past 30 days, median	**30**

[a]Other race categories (n [%]) were: American Indian or Alaska Native (3 [0.6%]), Asian (3 [0.6%]), and Other (4 [0.8%]). e-cigarette, electronic cigarette.

Table 2. Cytisinicline exposure

Exposure parameter	Participants (N=475)
Median cumulative duration of cytisinicline exposure,[a] days	**361**
Participants with cytisinicline exposure,[a] n (%)	
≥24 weeks duration	**392 (82.5)**
≥48 weeks duration	**319 (67.2)**
≥51 weeks duration	**281 (59.2)**

[a]Number of days where the participant received ≥1 dose of cytisinicline.

Long-term safety

No new safety signals were identified on independent Data Safety Monitoring Committee (DSMC) review

- Overall, 315 participants (66.3%) reported ≥1 TEAE over the 52-week treatment period; the majority were considered unlikely related or unrelated to cytisinicline
- Most TEAEs (94.8%) were mild or moderate in intensity
- Serious TEAEs occurred in 31 participants (6.5%)
- Two deaths (0.4%) occurred and were considered unrelated to treatment, in the context of underlying medical conditions
- TEAEs that occurred in ≥5.0% of participants included abnormal dreams (8.4%), insomnia (8.4%), and upper respiratory tract infection (6.7%) **(Table 3)**

Table 3. Summary of most commonly reported TEAEs

TEAEs reported in ≥5.0% of participants	Participants (N=475)
≥1 TEAE, n (%)	**315 (66.3)**
Abnormal dreams	**40 (8.4)**
Insomnia	**40 (8.4)**
Upper respiratory tract infection	**32 (6.7)**

TEAE, treatment-emergent adverse event.

Nausea, a common TEAE reported with other smoking cessation treatments, was reported in 12 participants (2.5%)

- 42 participants (8.8%) experienced ≥1 TEAE leading to dose reduction or interruption during the study **(Table 4)**
- TEAEs led to study discontinuation in 27 participants (5.7%); no individual TEAE leading to discontinuation occurred in ≥1% of participants

Table 4. Summary of TEAEs leading to dose reduction, interruption, or discontinuation

TEAEs reported in ≥1.0% of participants	Participants (N=475)
≥1 TEAE leading to dose reduction or interruption, n (%)	**42 (8.8)**
Abnormal dreams	**7 (1.5)**
Insomnia	**6 (1.3)**
≥1 TEAE leading to discontinuation, n (%)	**27 (5.7)**

TEAE, treatment-emergent adverse event.

Conclusions

- No new safety signals identified per independent DSMC review; cytisinicline 3 mg TID was generally well tolerated over 52 weeks in adults who smoke and/or use e-cigarettes who were attempting to quit
- Nausea was infrequently reported (2.5%) among participants receiving cytisinicline
- Overall, few participants (5.7%) discontinued due to TEAEs
- Taken together with previous studies, these findings further support cytisinicline as a well-tolerated treatment option for cigarette smoking and e-cigarette vaping cessation

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