Comparative effectiveness of cytisinicline and varenicline for smoking cessation: A matching-adjusted indirect comparison (MAIC)

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Introduction

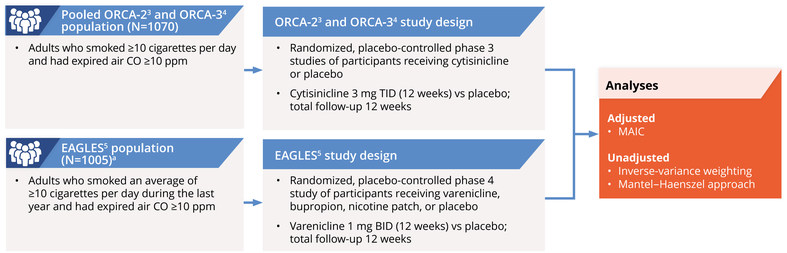
- No new smoking cessation medications have been approved by the US Food and Drug Administration in the last 20 years[1]
- Varenicline, the last approval in 2006, is limited by adverse events, particularly nausea, reported in up to 40.2% of patients[2]
- Cytisinicline is a plant-based alkaloid and partial agonist at α4β2 nicotinic acetylcholine receptors[3]
- A novel cytisinicline treatment regimen is currently under regulatory review for smoking cessation, consisting of a 3 mg tablet administered three times daily (TID) for 6 or 12 weeks
- In the phase 3 ORCA-2 and ORCA-3 trials, cytisinicline was more effective than placebo in achieving continuous smoking abstinence in adults, with a favorable safety profile[3,4]
- In the absence of direct head-to-head studies, this matching-adjusted indirect comparison (MAIC) evaluated the relative efficacy and safety of 12 weeks of cytisinicline vs varenicline, using pooled data from the phase 3 ORCA-2 and ORCA-3 trials for cytisinicline and the non-psychiatric cohort of the phase 4 EAGLES trial for varenicline[3–5]

Objective

To evaluate the relative safety and efficacy of 12 weeks of cytisinicline compared with 12 weeks of varenicline for smoking cessation

Materials and methods

Figure 1. Study design



[a]Randomized to varenicline treatment.
BID, twice daily; CO, carbon monoxide; MAIC, matching-adjusted indirect comparison; ppm, parts per million; TID, three times daily.

Assessments

- **Primary efficacy outcome**
  - Biochemically confirmed continuous smoking abstinence rate[a] from Weeks 9–12 and Weeks 9–24, reported as odds ratios (ORs)
- **Safety outcomes**
  - Treatment-emergent adverse events (TEAEs) and events leading to discontinuation

Statistical analyses

- **Matching–adjusted indirect comparison**
  - Propensity score weighting was used to adjust the de-identified pooled ORCA ORs based on prespecified treatment effect modifiers, including age, race, and Hospital Anxiety and Depression Scale score, to align with the summary statistics of the EAGLES non-psychiatric cohort and enable meaningful comparisons of the data
- **Inverse-variance weighting**
  - Unadjusted data were compared using log ORs of the pooled cytisinicline data vs the varenicline data to assess the impact of weighting on relative effect estimates and uncertainty
- **Mantel–Haenszel approach**
  - Unadjusted data were indirectly compared using the observed number of events in each study

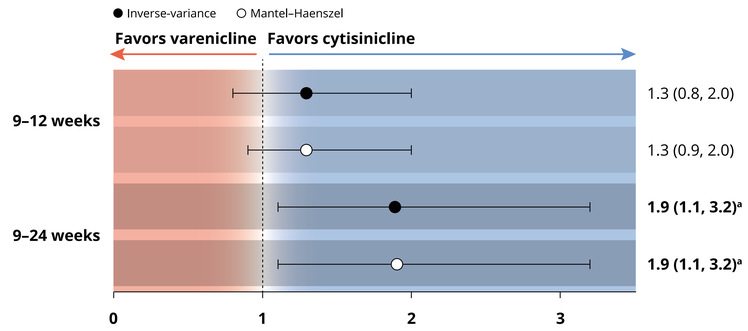
[a]Abstinence defined as self-reported smoking cessation confirmed by expired CO <10 ppm.[6]

Results

Continuous abstinence rates

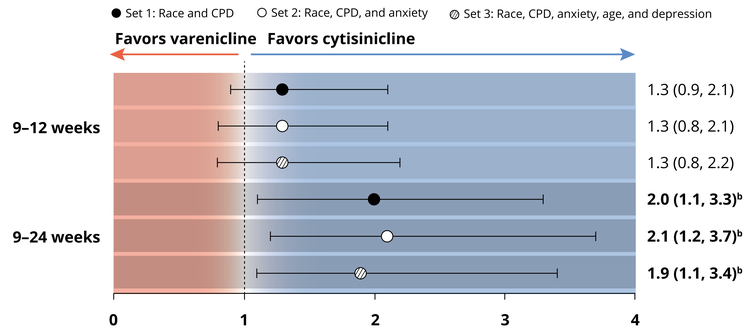
- There were no significant differences between adjusted or unadjusted 9–12-week abstinence for cytisinicline vs varenicline **(Figure 2, Figure 3)**
- Week 9–24 continuous abstinence was significantly higher for cytisinicline in both adjusted and unadjusted analyses vs varenicline **(Figure 2, Figure 3)**

Figure 2. Unadjusted ORs for continuous abstinence: Cytisinicline vs varenicline



Data presented as OR (95% CI).
[a]Bold for p<0.05. 95% CIs that do not contain the "null" value of 1.0 are significant.
CI, confidence interval; OR, odds ratio.

Figure 3. Adjusted ORs for continuous abstinence[a]: Cytisinicline vs varenicline



Data presented as OR (95% CI).
[a]Data adjusted based on prespecified potential treatment effect modifiers.
[b]Bold for p<0.05. 95% CIs that do not contain the "null" value of 1.0 are significant.
CI, confidence interval; CPD, average number of cigarettes per day in the last 30 days; OR, odds ratio.

Safety

- The odds of nausea were significantly lower for cytisinicline in both adjusted and unadjusted analyses vs varenicline **(Table 1, Table 2)**

Limitations

- As with all indirect comparisons, results may be influenced by residual confounding due to unmeasured differences between trials

Table 1. Unadjusted safety results: Cytisinicline vs varenicline

Outcome	Cytisinicline vs varenicline OR (95% CI)	
	Inverse-variance	**Mantel–Haenszel**
All-cause treatment discontinuations	0.8 (0.5, 1.2)	0.8 (0.5, 1.2)
Discontinuations due to TEAEs	1.0 (0.4, 2.4)	1.0 (0.4, 2.5)
Any TEAE	0.8 (0.6, 1.2)	0.8 (0.6, 1.2)
Insomnia	1.4 (0.8, 2.4)	1.4 (0.8, 2.4)
Abnormal dreams	0.8 (0.4, 1.6)	0.8 (0.4, 1.6)
Nausea	**0.2 (0.1, 0.3)[a]**	**0.2 (0.1, 0.3)[a]**

[a]Bold for p<0.05. 95% CIs that do not contain the "null" value of 1.0 are significant.
CI, confidence interval; TEAE, treatment-emergent adverse event.

Table 2. Adjusted safety results: Cytisinicline vs varenicline[a]

Outcome	Cytisinicline vs varenicline OR (95% CI)		
	Set 1 Race and CPD	**Set 2** Race, CPD, and anxiety	**Set 3** Race, CPD, anxiety, age, and depression
All-cause treatment discontinuations	0.8 (0.5, 1.2)	0.9 (0.6, 1.4)	0.8 (0.5, 1.4)
Discontinuations due to TEAEs	1.0 (0.4, 2.5)	1.2 (0.5, 3.0)	0.6 (0.2, 1.7)
Any TEAE	0.8 (0.6, 1.2)	0.9 (0.6, 1.2)	0.8 (0.5, 1.2)
Insomnia	1.3 (0.7, 2.3)	1.4 (0.8, 2.6)	1.2 (0.6, 2.3)
Abnormal dreams	0.9 (0.5, 1.7)	0.9 (0.5, 1.8)	0.8 (0.4, 1.8)
Nausea	**0.2 (0.1, 0.3)[b]**	**0.2 (0.1, 0.3)[b]**	**0.1 (0.1, 0.3)[b]**

[a]Data adjusted based on prespecified potential treatment effect modifiers; [b]Bold for p<0.05. 95% CIs that do not contain the "null" value of 1.0 are significant.
CI, confidence interval; CPD, average number of cigarettes per day in the last 30 days; TEAE, treatment-emergent adverse event.

Conclusions

- Cytisinicline demonstrated similar abstinence rates to varenicline at Weeks 9–12 and higher odds of maintaining continuous abstinence through Weeks 9–24 in both adjusted and unadjusted analyses
- Nausea was significantly less frequent with cytisinicline
- Results should be interpreted in the context of an indirect comparison
- These findings suggest that cytisinicline may offer comparable efficacy with improved tolerability and potential advantages in maintaining abstinence

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References: **1.** Foulds J et al. JAMA. 2023;330:129–30; **2.** Williams KE et al. Curr Med Res Opin. 2007;23:793–801; **3.** Rigotti NA et al. JAMA. 2023;330:152–60; **4.** Rigotti NA et al. JAMA Intern Med. 2025;185:648–55; **5.** Anthenelli RM et al. Lancet. 2016;387:2507–20; **6.** West R et al. Addiction. 2005;100:299–303.

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