November 17, 2025

Sarah K. Emond, MPP
President and Chief Executive Officer
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14 Beacon Street, Suite 800
Boston, MA 02108

Subject: Achieve Comments to ICER Draft Evidence Report

Dear Ms. Emond:

Achieve Life Sciences appreciates the opportunity to comment on ICER's Draft Evidence Report on cytisinicline for smoking cessation.

ICER appropriately recognizes cytisinicline's improved efficacy over behavioral support alone. And we agree with ICER that safety and tolerability with cytisinicline, particularly the lower rate of gastrointestinal side effects such as nausea, is differentiating over varenicline. We commend ICER on its patient-centric positioning that many more smokers who are motivated to quit can be helped with cytisinicline. Further, as you are aware, QALY or evLY measurements have many detractors, including payers, because those measures are long-term vs. short-term value indicators. However, the payer community recognizes – as does the public health community – the value of prevention and the robust existing evidence that links smoking to diseases such as CVD, COPD, and lung cancer.

We have several specific concerns with the Draft Evidence Report:

Cytisinicline is a new chemical entity – Throughout the Draft Evidence Report, reference is made to comparators using studies that reviewed the efficacy of cytisine for smoking cessation. As we pointed out when submitting our comments to ICER's Draft Scoping Document in June, cytisinicline and the older ex-U.S. cytisine products are different and distinct treatments. The FDA considers cytisinicline as a "new chemical entity" (NCE). An NCE is "a drug that contains no active moiety that has been approved by FDA in any other application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, or has been previously marketed as a drug in the U.S. Achieve Life Sciences (Achieve) filed an Investigational New Drug (IND) application in 2017 for developing cytisinicline as a new treatment for nicotine dependence and recently filed a New Drug Application (NDA) with the FDA. Ex-U.S., cytisine is given in a

complex 25-day treatment regimen with the dosage starting at six 1.5 mg tablets daily for the first three days, then with a specific reduction schedule over three weeks ending with one 1.5mg dosage on the last day. In trials, Achieve has optimized cytisinicline treatment using a novel tablet dosing, revised schedule, and longer treatment durations: a 3 mg tablet formulation given orally three times per day (TID) for 6 or 12 weeks. The formulation, dosage and duration of treatment are unique to cytisinicline. Cytisinicline used in the Achieve Life Sciences product is being manufactured under strict GMP standards required for distribution and use in the U.S. with additional purification not present in the manufacture of cytisine. In short, the Achieve-developed cytisinicline product is distinct from the older ex-U.S. cytisine product, and the Draft Evidence Report should treat it accordingly.

Reliance on 2023 Cochrane Review – Throughout the Draft Evidence Report, ICER reviewers rely on the 2023 Cochrane review, *Pharmacological and electronic cigarette interventions for smoking cessation in adults: component network meta-analyses*. The Cochrane meta-analysis compares cytisine with varenicline and other interventions. As noted above, cytisine and cytisinicline are different chemical entities, with novel formulation, dosing, schedules, and treatment durations. It is inappropriate, therefore, to base any conclusions regarding the efficacy of cytisinicline versus varenicline or other therapies on this Cochrane review. We suggest relying instead on the Phase 3 cytisinicline data from ORCA-2 and ORCA-3 and odds ratios referenced below.

Odds Ratios

As the Draft Evidence Report notes, in two large Phase 3 trials (ORCA-2 and ORCA-3), cytisinicline treatment regimens for 6 or 12 weeks were significantly more effective than placebo treatment with standard behavioral support in achieving long-term (through Week 24) smoking cessation success as demonstrated by odds ratios (ORs) below.

- ORCA-2: At Week 24, continuous abstinence rates remained significantly higher than placebo plus behavioral support for:
    - 6-weeks: abstinence from Week 3 to 24: OR 3.7 (95%CI, 1.5–10.2; P = .002);
    - 12-weeks: abstinence from Week 9 to 24: OR 5.3 (95%CI, 2.8–11.1; P < .001)
- ORCA-3: Replicated these findings with:
    - 6-weeks: abstinence from Week 3 to 24: OR 6.3 (95%CI, 1.9–34.6; P < .001);
    - 12-weeks: abstinence from Week 9 to 24: OR 5.8 (95%CI, 2.9–12.4; P < .001)

While no direct head-to-head trial comparisons have been conducted, the efficacy for cytisinicline in ORCA-2 and ORCA-3 (as demonstrated by ORs) was higher than what has been

reported for other prescription therapies (Anthenelli, 2016) including varenicline (OR of 2.7 for Week 9 to 24 continuous abstinence) and bupropion (OR of 1.8 for Week 9 to 24 continuous abstinence). In addition, smokers who had previously unsuccessfully used both varenicline and bupropion to quit smoking achieved long-term smoking cessation through Week 24 when treated with cytisinicline for 6 or 12 weeks, compared to placebo with standard behavioral support.

Thank you for the opportunity to comment on the Draft Evidence Report. If you have any questions or require further information, please do not hesitate to contact Dr. Mark Rubinstein, Interim Chief Medical Officer at mrubinstein@achievelifesciences.com.

Sincerely,

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