Appendix 2. Actual use trial methodology

The OTC POP actual use trial was an interventional, Phase III, multi-center, 24-week, open label self-selection and actual use study designed to mimic an OTC-like environment, running from September 2019 to August 2021. Thirty-five physical research site locations participated, comprising retail pharmacy research sites (25) and women’s health clinics or adolescent clinics (10) distributed widely across the US. One decentralized site was used for remote follow-up data collection throughout the study and for remote enrollment after the onset of the SARS-CoV-2 pandemic. We recruited participants living within 35 or 100 miles of a site (for pharmacy sites) primarily via passive recruitment methods, such as in-store posters, newspaper advertisements, direct mail postcards, and digital space advertising, with ads inviting those interested in an over-the-counter oral contraceptive to participate.

We sent approximately 1.6 million print advertisement mailers to households and deployed digital ads which were collectively viewed over 98 million times. There were 48,410 respondents who began the pre-screening process over the course of the 18 months of enrollment. To facilitate recruitment of participants aged 11-17 years old, we supplemented the passive recruitment campaign with an active recruitment effort in the 10 clinic sites (3 clinical research facilities, 2 family medicine practices, 2 pediatric medicine practices, and 3 women’s health practices) wherein clinic staff offered adolescents who were seeking oral contraception the opportunity to participate in the study. We employed these active recruiting efforts for participants aged 11-17 years for the first 8 months of enrollment. With the onset of the SARS-CoV-2 pandemic, we shifted to a decentralized approach in which we recruited participants aged 11-17 across the entire US and remotely enrolled them without requiring a visit to a research site. Decentralized enrollment for this cohort lasted an additional 10 months.

Respondents to advertising either called a study number or visited a study website for initial screening (during which data regarding age, gender, and minimal study inclusion/exclusion criteria were collected) and scheduled an enrollment visit. Initial inclusion criteria included (1) able to read, speak and understand English; (2) 11 years of age or older; (3) can see well enough to read information on the label; (4) another member of the respondent’s household has not participated in this study; (5) consumer or someone else in the household does not work for a market research or advertising company, public relations firm, news organization, pharmacy or pharmaceutical company, medicine manufacturer, as a health care professional, or as part of a health care practice, managed care or health insurance company, and has not trained or worked as a health care professional or market research professional (eliminated for reasons of confidentiality and increased awareness of medicines and their labels); (6) has not participated in any research studies about health-related products in the past 12 months; (7) has not participated in a clinical trial in the past 12 months; (8) has never participated in a study about OTC birth control medicines.

During the enrollment visit, we asked potential participants who met the inclusion criteria for the study to review the OTC packaging and allowed them as much time as they needed to review the information on the outside of the entire package including the drug facts label. We then asked participants if the product was okay or not okay for them to use. We asked those who reported that it was okay for them to use if they would like to purchase it for their own use. Participants who enrolled at pharmacy sites obtained the product by purchase to mimic the OTC environment as closely as possible. They paid $10 per 1-month pack of product, or $20 for 3 packs. We reimbursed all participants for any purchase amount at the end of the study; however, we did not disclose to participants that they would be reimbursed. Participants who enrolled remotely and in healthcare clinics did not have to purchase the product since the purpose of these settings was to supplement the challenging recruitment of participants ages 11-17 and did not mimic the OTC environment as closely. We recorded the reasons for any non-purchase decision. Following the selection and purchase decisions, in response to a structured questionnaire, participants provided limited medical history, current medication use, current and historical contraception usage and demographic information.

We administered the Rapid Estimate of Adult Literacy in Medicine (REALM) or Rapid Estimate of Adolescent Literacy in Medicine (REALM-Teen) [20,21] and conducted the informed consent process. Participants that signed consent took a urine-based pregnancy test. Participants were excluded from the use phase of the study if they met any of the use phase exclusion criteria, including (1) unwilling to purchase study medication (pharmacy sites); (2) unwilling to be dispensed study product for use (clinical sites); (3) unwilling to provide informed consent; (4) unwilling or unable to provide contact information; (5) unwilling to state that the product is for their own use and no one else’s; (6) premenarchal; (7) pregnant (based on self-report or enrollment pregnancy test); (8) male; (9) known allergy to norgestrel or inactive ingredients; (10) history of any cancer.

Additional use phase inclusion criteria included (1) evidence of a personally signed and dated informed consent form indicating that the participant (or a legal guardian) has been informed of all pertinent aspects of the study, and (2) willing and able to comply with the initial enrollment visit, planned phone calls and other study procedures, and the end of study visit.

Qualified participants could then purchase (pharmacy sites) or be given (clinical sites/decentralized enrollment) the product to take home and use. Participants elected how much of the product to purchase/obtain initially. They could return to the site at any time for resupply. We allowed participants to purchase/obtain up to 8 28-count (4-week supply) packages during the study period, although we did not inform participants about that limit unless they attempted to purchase/obtain more than that. If a participant attempted to obtain more than 8 packages, we recorded that request.

There were 1,886 participants who began the enrollment interview, 1,772 of whom made an evaluable self-selection decision, 955 participants who purchased the product, and 883 of whom reported using the product. These 883 comprised the user population from whom data were abstracted for the modeling exercise.

During use, participants recorded use of the product using an online medication use diary. The electronic diary also captured self-reports of sexual activity for participants 18 years of age and older. We asked participants to record their use of the product daily, but we allowed for a look-back period of up to 10 days. All participants received reminders to complete the diary delivered by the e-diary application every 4 days.

Trained nurse interviewers working from a central research site conducted 7 scripted telephone interviews at weeks 2, 4, 8, 12, 16, 20, and 24, to gather information on if, how, and when the participant took the product, any adverse events, concomitant medications, and other actions the participant may have taken related to the use of the product. If a participant notified study staff of their intention to withdraw from the study early, or if a participant indicated that they stopped taking the study product entirely and had no intention to restart, the nurse interviewer documented the last day of use. They conducted the end of study interview at week 24, or at the time of discontinuation/withdrawal for those who did so prior to week 24.

After the end of study interview, we asked participants to take a self-administered urine-based home pregnancy test and record the results in their electronic diary. Prior to SARS-CoV-2, we asked participants to return to the study site for an additional pregnancy
test and to return any unused study medication and/or packaging. After the onset of the SARS-CoV-2 pandemic, we no longer asked participants to return to the site. Rather they completed an at-home home pregnancy test and returned study materials via mail. We compensated participants for their participation up to $483 according to the following schedule (all disclosed in the informed consent document):

- $75.00 for the enrollment visit
- $10.00 for the enrollment urine pregnancy test
- $25.00 each for each of the 7 follow-up phone interviews
- $0.50 for each day information was entered in the study diary (up to $14.00 for every 28 days)
  - If information was entered into the study diary for each day in the month (28 days, without missing any days), subject’s compensation was increased to $1.00 per day for that month ($28.00 for every 28-day period).
- $5.00 for taking the self-administered end of study urine-based pregnancy test at the end of the study and recording the results in the electronic diary
- $50.00 for returning to the site at the end of the study (or returning study materials via mail after the onset of the pandemic)

Additionally, we reimbursed participants at the end of the study for any purchase of investigational product, though participants were not aware until reimbursement was sent.