CLINICAL STATISTICAL ANALYSIS PLAN

A Multi-Center Oral Contraceptive Pill Use Trial Conducted In an OTC Naturalistic Environment (OPTION)
151042-001

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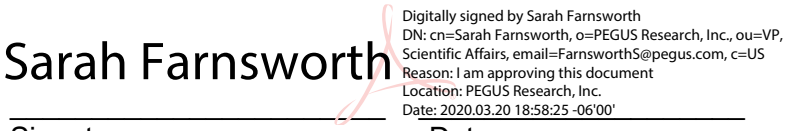

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1. Introduction

Opill® (norgestrel 0.075 mg) is proposed for an Rx-to-OTC (over-the-counter) switch. This combined Self-Selection (SS) / Actual Use Trial (AUT) was intended to be conducted to demonstrate appropriate consumer selection and use behavior as guided by OTC labeling when using the product in the absence of a physician or other learned intermediary.

Due to technical issues with the e-diary application, the study was terminated shortly after the study was initiated, resulting in a sample size that is statistically insufficient to analyze the Primary and Secondary Endpoints as well as the Other Analyses described in Section 9.3 of the protocol. As such, only analyses relating to subject safety, including the number of pregnancies observed over the course of the study, will be completed for this study.

2. Trial Objectives

The objective of this study was to evaluate the adequacy of the proposed OTC labeling to guide the behavior of subjects in an OTC-like setting when selecting and using Opill®; however, only the safety outcomes will be reported on for this study due to the early termination of the study.

3. Trial Design

This was an observational, open-label, multi-center, 16-week study designed to create as much as possible an OTC-like environment in which participants made an initial self-selection and purchase decision about Opill® based only on their reading of the outside of the package including the DFL. Qualified participants who chose to do so purchased the study medication, left the study site and used the product on their own, guided by the OTC labeling. The study was designed to assess if, when and how subjects use the medication in an OTC-like environment.

It is important to note that none of the information gathered at screening, enrollment, or during the 16-week study period was only discussed with subjects at the End-of-Study interview.

3.1 Naturalistic Design

This was a multi-center trial conducted in a simulated OTC environment. Study characteristics and procedures were designed to make it as naturalistic as possible. Some of the key naturalistic elements included the following:

- There were minimal exclusionary criteria imposed on participants, making this trial nearly an all-comers study to mimic the likely OTC population.
- The study was conducted in retail pharmacies, representing typical locations where consumers now commonly purchase OTC medicines (adult and adolescent subjects) and women's health clinics (adolescent subjects).
- The proposed OTC packaging and labeling was the only product information provided to participants during the study. Participants only reviewed the outer packaging including DFL at the initial visit. Study staff did not provide any

additional information or encouragement regarding product selection at that visit. Staff did not answer participant questions about the study medication and instead referred subjects to the labeling. However, any questions related to the "Ask a doctor or pharmacist before use" section of the DFL that were asked of study staff in their capacity as healthcare provider or pharmacist were recorded.

After purchasing the study product, participants took the package with them when they left the site. The package included the outer packaging, and, inside the package, the consumer information leaflet (CIL), a reminder card (which highlights the key messages about directions for use from the DFL) and study medication.

3.2 Eligibility Criteria

3.2.1 Self-Selection Phase / Initial Enrollment Visit

In order to enroll a sample as representative as possible of the likely OTC consumer population, the study inclusion criteria were defined as broadly as it is feasible. Subjects were required to meet the following initial screening study inclusion criteria:

1. Able to read, speak and understand English
2. 12 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 healthcare professional, or as part of a healthcare practice, managed care or health insurance company, trained or worked as a healthcare 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 over-the-counter birth control medicines

3.2.2 Use Phase Exclusion Criteria

All subjects who agreed to participate in the study and attended the initial enrollment visit at the site were asked to make a self-selection and purchase (or use) decision. Subjects presenting with any of the following were not included in the use phase of the study (i.e., were not allowed to purchase and use study medication though their self-selection decision and desire to purchase was recorded):

1. Unwilling to purchase study medication (pharmacy sites)
2. Unwilling to be dispensed study product for use (clinic 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 females
7. Pregnant
8. Male
9. Known allergy to norgestrel or inactive ingredients.
10. History of any cancer

Additionally, subjects must have met all of the following study inclusion criteria to be eligible for enrollment into the use phase of the study:

- Evidence of a personally signed and dated informed consent form indicating that the subject (or a legal guardian) has been informed of all pertinent aspects of the study.
- Willing and able to comply with the initial enrollment visit, planned phone calls and other study procedures, and the end of study visit.

Subject eligibility was reviewed and documented by the Investigator or his/her designee before subjects were allowed to be dispensed the study medication and begin the use phase of the study.

3.3 Sample Size Determination

For the purposes of this AUT, sample size was set at approximately 900 purchasers (use phase participants). Given that subjects were responding to recruitment aimed at those interested in an OTC birth control medicine, most subjects who chose to purchase the study product were expected to actually use the product during the study.

Assuming approximately 900 purchasers, if 80% of those purchasers used the product within the study period, that would yield an actual user population of approximately 720. Allowing for a further 20% loss to follow-up would yield a measurable user population of approximately 576.

Because AUTs are not hypothesis-testing comparative trials, study sample size was designed to allow for adequate evaluation of key endpoints across all participants and among several subgroups. As the analysis of AUTs typically focuses on estimating the proportion (and associated 95% confidence intervals) of correct behavior for individual endpoints, sample size is most often based on the number of participants needed to constrain the confidence interval (CI) to a limited range. As an illustration, for this study, assuming an 85% correct behavior to any single endpoint (of course, the CI depends on the actual point estimate and is calculated based on the data), a sample of 720 participants would constrain the CI to ±2.8%. Table 1 provides the 2-sided 95% CI for various sample sizes around a point estimate of 85%.

Table 1 Two-sided 95% CIs for Various Sample Sizes Around 85% Point Estimate

	N=900[a]	N=720[b]	N=576[c]	N=135[d]
95% CI around a point estimate of 85%	+/-2.5%	+/-2.8%	+/-3.2%	+/-7.2%

[a] Purchasers
[b] User population (allowing for 20% non-users)
[c] User population (allowing for 20% loss-to-follow up)
[d] Low literacy subjects

3.4 Randomization

There was no randomization in this study.

4. General Statistical Considerations

4.1 General Principles

Statistical analyses of the data will be performed by PEGUS Research using the SAS System for Windows v 9.4 (SAS Institute, Cary, NC). All analyses performed in this study will be descriptive.

Frequencies and percentages will be presented for categorical data, mean, standard deviation (SD); median, and range will be presented for numerical data. Percentages will be rounded to one decimal place. The category of missing data will be displayed only if there are actually missing values. Frequencies, percentages and 2-sided 95% CIs will be calculated using the exact method.

4.2 Handling of Withdrawn Subjects

For subjects that chose to withdraw at any point during the study, an attempt was made to collect End-of-Study (EOS) information and the reasons for the subject's early termination. Data gathered prior to subject withdrawal and any ongoing data collection will be included in the analysis for completed questions, unless the subject withdrew consent or requested otherwise. Subjects who did not complete the study will be described in a disposition table. Any subjects who withdrew their consent or were determined to be lost to follow-up will be described in the disposition table as well. Withdrawn subjects were not replaced.

4.3 Handling of Missing Data

Missing data will not be imputed; the statistical analyses will be based on cases with relevant data available. For endpoint calculations, if missing data makes it so a case (subject or a dosing instance) cannot be classified as to whether or not it belongs in the numerator, that case will also be excluded from the denominator. All missing data will be flagged, and a reason for why the data are missing will be described in a footnote in each applicable statistical table.

4.4 Handling Protocol Violations

All deviations from the protocol will be reviewed and any decision regarding inclusion or exclusion of subjects in study analyses due to the presence of a deviation will be made and documented before database lock.

Events that qualify as protocol deviations will be identified in a separate document. All protocol deviations will be categorized and assessed to determine the severity of the deviation and reviewed before database lock.

A full list of protocol deviations will be included in the final Clinical Study Report (CSR).

4.5 Interim Analyses and Data Monitoring

No interim analyses are planned for this study. Final data analyses will be performed upon database lock. Data were monitored by site monitors and PEGUS data management staff on an ongoing basis to ensure protocol procedures were being followed. While a formal Independent Data Monitoring Committee was not established for this study, the sponsor was informed of study progress, amount and nature of data queries, and protocol violations.

4.6 Data Capture and Processing

Data were collected in structured one-on-one interviews using a standardized questionnaire either in person (at the initial enrollment visit), by telephone (in four follow-up interviews), and in an electronic diary. The interviews were administered by a trained interviewer using an internet-based EDC application in which the interviewer read the introductory scripts and the questions from the screen and entered the responses directly into the study database. The questionnaires included primarily open-ended questions. Question types included direct questions and follow-up questions for clarification. To facilitate the accurate capture of responses, open-ended questions had pre-coded answer alternatives. It is important to note that these response alternatives were not read to the participants, nor were participants able to see them on the screen. Where close-ended questions were used (e.g., yes/no, or ok/not ok), participants were asked to explain their answers so behavior could be adequately assessed. When interviewers recorded open-ended responses, they captured short responses verbatim, and accurately summarized longer responses.

During the self-selection interview at the initial visit, the Opill® outer package including DFL remained in front of the participant and the participant was informed that they could refer to the outer package at any time. However, the participant was neither encouraged nor discouraged from referring to the package in response to any specific question.

Subjects who entered the use phase of the study were asked to use an online diary to record their use of the study product daily. Of note, a device was provided for subjects who did not have easy access to a device with internet access.

Information collected during the participant interviews was entered directly into an EDC application (DATATRAK ONE, DATATRAK International, Inc.). Automatic data checks alerted users of discrepancies and inconsistencies, where applicable. In the event of a data entry error, users had the ability to correct information previously entered. Data Management staff reviewed the information entered as defined in this protocol.

All users had a unique login user name and password, and system access privileges were strictly controlled and documented. Whenever data was modified after the initial data entry process, a computer-generated audit trail entry was created. The audit trail, user access privilege processes, and electronic signatures collected by the system were compliant with 21 CFR Part 11 requirements.

A web-based electronic diary was provided to all subjects with a reliable internet connection. The e-diary was programmed and hosted by a qualified vendor

(eClinicalHealth Ltd, Stirling, United Kingdom). Subjects were instructed to record information regarding their use of the study product every day. Subjects were also asked to enter additional data regarding sexual behaviors (heterosexual vaginal intercourse) and additional contraception methods to fully evaluate adherence to label directions. The electronic diary was intended to serve as the primary means of reporting the results of the EOS at-home self-administered pregnancy test. Diary data were imported into the EDC system to be included in the study database.

However, as noted previously, problems with the usability and reliability of the e-diary system led to the premature termination of this study.

4.7 Data Review

Data review were ongoing during the course of this study. Data were reviewed by PEGUS Research for accuracy, and all validation and documentation will be completed before database lock.

5. Analysis Sets

The populations of interest are defined as follows:

- Screening Population: All those who respond to study advertisements and begin initial screening questions.
- Self-Selection Population: Participants who accept the invitation to participate and meet study inclusion criteria, participate in a face-to-face interview at the study site, make a self-selection decision, and provide responses to all relevant medical history questions.
- Safety Population: Subjects who signed the informed consent document.
- Purchasers: Responders who meet study enrollment criteria and purchase/obtain the study medication.
- User Population: Subjects who take at least one dose of study medication during the study.

6. Statistical Methodology

This is a naturalistic, observational trial to assess selection and use patterns from the prospective OTC population in a simulated OTC setting. The analyses will largely employ descriptive statistics including frequencies, percentages and appropriate summary statistics.

Tabulations of frequencies for categorical data will include all possible categories and will display the number of observations in a category as well as the percentage (%) relative to the respective subject set. Percentages will be rounded to one decimal place. The category of missing data will be displayed only if there are actually missing values.

Each of the categorical endpoints will be evaluated by computing point estimates and their binomial two-sided 95% confidence intervals (CIs) (calculated using the exact Clopper-Pearson method).

6.1 Efficacy

Not applicable for this study.

6.2 Pharmacokinetics / Pharmacodynamics

Not applicable for this study.

6.2.1 Primary Endpoint Analysis

As discussed in Section 2, only endpoints related to safety outcomes will be analyzed and reported on for this study.

6.2.2 Secondary Endpoint Analysis

Only Secondary Endpoint F will be analyzed and reported on for this study:
Actual Use: Number of pregnancies reported during the course of the study

6.2.3 Other Analyses

Only Other Measure A will be analyzed and reported on for this study:
Actual Use: Character and frequency of adverse events as reported by the user population

6.2.4 Safety and Compliance

6.2.4.1 Adverse Events and Serious Adverse Events

Adverse event (AE) and Serious Adverse Event (SAE) analyses will include all events which initially occurred or worsened following treatment. Adverse events will be summarized by the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and Preferred Term (PT) and classified according to their severity (mild, moderate, or severe) and relationship (related or not related) to study product. For the summary by severity, subjects who have multiple occurrences of the same AE/SAE will be classified according to the worst reported severity of the AE/SAE. Similarly, for the summary by relationship to the study product, the AE/SAE will be classified according to the worst relationship.

6.2.4.2 Pregnancies

All pregnancies that were reported during the study will be described including an assessment of whether they occurred on or off the study drug.

6.2.4.3 Protocol Deviations

A listing of all protocol deviations reported during the study will be created and included in the final clinical study report.

7. Datasets and Supporting Documentation

7.1 Datasets

All table analyses data points will come from the locked study datasets.

7.2 Supporting Documentation

PEGUS Research will maintain accurate and complete records of the study. Study files and critical documents were maintained at PEGUS Research throughout the study period, and

will be retained or transferred to the Sponsor at its direction. PEGUS Research holds all study-related documents and communications in the strictest confidence. PEGUS Research will ensure that the participant's anonymity is maintained. On documents submitted to the Sponsor, participants will not be identified by name or other personally identifiable information, but by numerical identification code generated by the EDC system.

8. Document History and Changes in the Planned Statistical Analysis

Document	Version / Date	Summary of Changes
Final SAP	Final v1.0_20MAR2020	N/A

9. References

Not applicable for this study.