A Multi-Center, Randomized, Double-Masked, Active Controlled, Parallel Group Bioequivalence Study with Clinical Endpoint Comparing Brinzolamide Ophthalmic Suspension 1% of Perrigo Pharma International DAC to Azopt® (brinzolamide ophthalmic suspension) 1% of Novartis Pharmaceuticals Corporation in the Treatment of Primary Open Angle Glaucoma or Ocular Hypertension in Both Eyes

Protocol No: PRG-NY-19-001

NCT04024072

07-01-2019

STATISTICAL ANALYSIS PLAN

PRG-NY-19-001: Brinzolamide Ophthalmic Suspension 1%

[redacted]

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Table of Contents

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List of Abbreviations

AE	Adverse Event
ANOVA	Analysis of Variance
[redacted]	[redacted]
BE	Bioequivalence
CI	Confidence Interval
CMH	Cochran–Mantel–Haenszel Test
IOP	Intraocular Pressure
MedDRA	Medical Dictionary for Regulatory Activities
OH	Ocular Hypertension
PD	Protocol Deviation
POAG	Primary Open Angle Glaucoma
PP	Per-Protocol (Population)
PV	Protocol Violation
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
TEAE	Treatment-Emergent Adverse Event
TESAE	Treatment-Emergent Serious Adverse Event
WHO Drug	World Health Organization Drug Dictionary

Statistical Analysis Plan

1 Purpose of Statistical Analysis Plan

The purpose of the statistical analysis plan is to describe in detail all the data, statistical methods, and summary tables required to implement the statistical analysis of Clinical Study Protocol PRG-NY-19-001 [redacted]

In the event that the protocol has amendment(s) that do not have an impact on the statistical analysis methodology, this SAP will not require an amendment. This SAP has been developed and finalized prior to database lock of the clinical database for Protocol PRG-NY-19-001.

[redacted]

2 Study Objectives

To demonstrate bioequivalence of brinzolamide ophthalmic suspension 1% (Perrigo Pharma International DAC) to Azopt® (brinzolamide ophthalmic suspension) 1% (Novartis Pharmaceutical Corporation) by comparing their efficacy and safety in the treatment of subjects with Primary Open Angle Glaucoma (POAG) or Ocular Hypertension (OH) in both eyes.

3 Study Design and Sample Size

3.1 Study Design

For the purpose of exploring the above objectives, the study will be conducted as a double-masked, randomized, multi-center, active-controlled, parallel-group study.

Each subject will be randomly assigned to one of the following treatment groups [redacted]:

(1) Test: Brinzolamide Ophthalmic Suspension, 1%, Perrigo Pharma International DAC, Ireland, [redacted]

(2) Reference: Azopt® (brinzolamide ophthalmic suspension), 1%, manufactured by Novartis Pharmaceuticals Corporation.

The study consists of a run-in phase and a six-week treatment (42 ± 4 days) period.

[redacted]

[redacted]

At Baseline/Visit 2, eligible subjects who meet all inclusion criteria and do not meet any exclusion criteria will be randomized [redacted] to either the test or reference product for the 6-week treatment period. Subjects will apply one drop of either test product or reference product in both eyes three times daily at approximately 08:00 am, 04:00 pm and 10:00 pm for six weeks (42 ± 4 days)

Subjects will come to the study site for clinical evaluations Visit 1/Screening, Visit 2/Day 0 (Baseline), Visit 3/Week 2/Day 14 (±4 days), and Visit 4/Week 6/Day 42 (±4 days) (End of Study) or at early discontinuation. Safety will be assessed by monitoring adverse events at each visit.

3.2 Sample Size

[redacted]

4 Analysis Populations

The analysis populations are defined as follows:

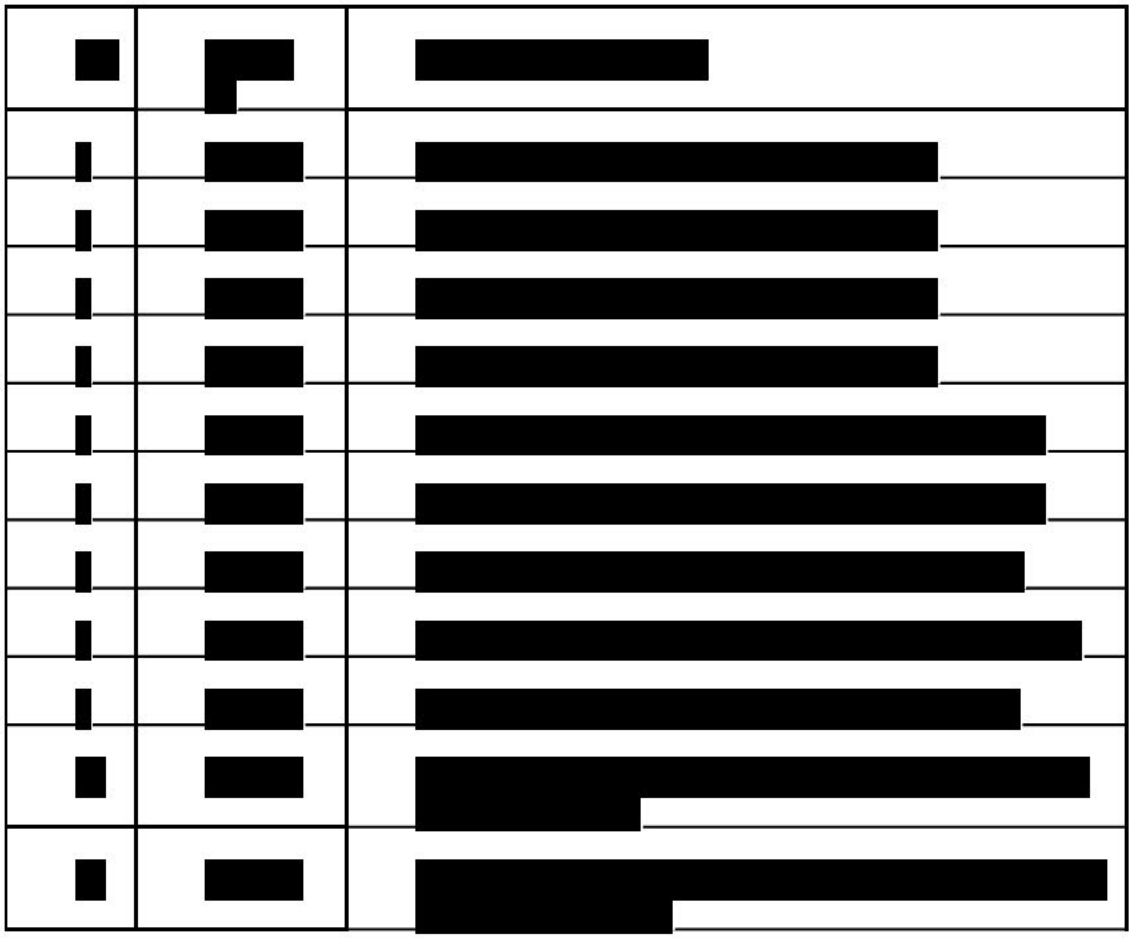
(1) Safety population: all randomized subject who received study product;

(2) Per Protocol (PP) population; any randomized subject who (a) met all inclusion/exclusion criteria; (b) received and used study medication; (c) met compliance [redacted] (e) complete IOP evaluations for both eyes at Visit 3/Day 14 (week 2) and Visit 4/Day 42 (week 6) within the designated visit window (i.e. +/- 4 days for each visit); (f) have no significant protocol violations that could have interfered with the administration of the treatment or the precise evaluation of treatment efficacy.

[redacted]

[redacted]

[redacted]



Subjects whose condition worsens (e.g., IOP $\geq$ 36 mm Hg in either eye) to a degree that they require alternative or supplemental therapy for the treatment of their primary open angle glaucoma or ocular hypertension during the study, should be discontinued and excluded from the PP population analysis.

5 Planned Analyses

5.1 Methodological Considerations

Tables will have columns corresponding to or be stratified by the treatment groups.

[redacted]

All data will be listed by treatment group, subject and visit/time point where appropriate. The total number of subjects under the stated population (N) will be displayed in the header of summary tables. Efficacy data will be tabulated by site and if obviously inconsistent discrepancies will be observed with the results across all sites, then these differences will be explored and addressed in the final study report.

Data will be summarized using descriptive statistics for continuous variables. Unless otherwise specified, descriptive statistics will include number of subjects, mean, standard deviation, minimum, median and maximum. The statistic "Missing" will also be presented as the number of missing entries/subjects, if any at that visit/timepoint, and presented as a summary statistic only when non-zero. The minimum and maximum statistics will be presented to the same number of decimal places as the original data. The mean and median will be presented to one more decimal place than the original data, whereas the standard deviation will be presented to two more decimal places than the original data.

Categorical variables will be summarized by frequency (n) and percentage (%). Percentage will be obtained as (n/N)*100. Unless otherwise stated, all percentages will be expressed to one decimal place.

Study days will be calculated as follows:

- For events or findings on or after the date of the first study treatment:
    - Study Day = Date of the event or finding – Date of the first treatment + 1
- For events or findings prior to the date of the first study treatment:
    - Study Day = Date of the event or finding – Date of the first treatment

All dates will be displayed in DDMMMYYYY format.

Two-sided hypothesis testing will be conducted for all the tests. The p-values less than 0.05 will be considered statistically significant. No adjustments of p-values for multiple comparisons will be made. No interim analyses are planned.

All statistical analysis will be conducted using SAS® version 9.4 or higher (SAS® Institute, Cary, North Carolina).

[redacted]

[redacted]

5.3 Demographics and Baseline Characteristics

Baseline variables (e.g., sex, age, ethnic origin) will be summarized descriptively by treatment group. Any significant baseline differences will be reviewed for their potential impact on the efficacy findings.

Continuous variable at baseline will be summarized by descriptive statistics. The summary tables will include the mean, standard deviation, minimum and maximum. For each categorical variable, the summary will include frequencies and percentages.

[redacted]

5.4 Subject Disposition

The numbers of subjects enrolled, treated, discontinued from treatment (by reason) will be presented by treatment group.

A summary of subject disposition will be provided for all subjects. Descriptive summaries of subject disposition, reason for discontinuation, and analyses populations will be provided by treatment group. The data will also be presented in subject data listings.

[redacted]

5.6 Study Drug Exposure and Compliance

Number of applications, days of exposure (i.e. duration of treatment), and compliance rate will be summarized by treatment group using descriptive statistics. For each subject, the duration of treatment (days) will be calculated using the following formula:

(Date of last application of study medication) - (Date of first application of study medication) + 1.

Medication compliance rate (%) will be calculated for each subject as follows:

(Total number of applications used) / (Expected number of applications) *100%.

[redacted]

[redacted]

5.7 Efficacy Analyses

5.7.1 Primary Endpoint

The primary efficacy endpoint is mean change from baseline in IOP of both eyes at four time points, i.e., at approximately 8:00 a.m. (hour 0; before the morning drop) and approximately 10:00 a.m. (hour 2) at Day 14 (Week 2) and Day 42 (Week 6) visits. The IOP at hour 8:00 a.m. (hour 0) on day 0 will serve as baseline for IOP at hour 8:00 a.m. for Day 14 and Day 42, while IOP at hour 10:00 a.m. (hour 2) on day 0 will serve as baseline for IOP at hour 10:00 a.m. for Day 14 and Day 42. Mean change from baseline to Day X Hour Y in IOP for each subject will be derived as the average difference IOP of (Day X Hour Y – Day 0 Hour Y) from the left and right eyes, where X = 14, 42 and Y = 0, 2.

[redacted]

For test formulation to be considered bioequivalent to the reference formulation, the limits of each two-sided 95% confidence interval of the treatment difference (test – reference) for mean change from baseline IOP of both eyes at all four follow-up points (i.e., at approximately 8:00 a.m. (hour 0; before the morning drop) and 10:00 a.m. (hour 2) at the Day 14 (week 2) and Day 42 (week 6) visits must be within ± 1.5 mm Hg using the PP population and within ± 1.0 mm Hg using the PP population for the majority of time points measured.

[redacted]

[redacted]

[redacted]

[redacted]

5.8 Safety Variables and Analyses

All safety data will be listed and tabulated. The analysis will be performed on the safety population. Safety parameters include adverse events, vital signs, physical examination findings.

Adverse Events

Adverse events (AEs) will be coded in MedDRA, version 22.0. Treatment-Emergent Adverse Event (TEAE) is defined as any AE occurs on or after application of the first dose of study drug. Number and percent of subjects reporting TEAEs will be tabulated by treatment group. Summaries of TEAEs will be presented by body system and preferred term, and further by severity and relationship to study medication. Most common TEAEs will include those reported by 5% or more subjects for any treatment group will be summarized by preferred term. In the summaries of incidence rates (frequencies and percentages), severity and relationship to study drug, subjects who report more than one event that are mapped to the same preferred term will be counted only once under the strongest severity and relationship, accordingly. The difference between Test and Reference treatments with regard to severity and frequency of their adverse events will be statistically evaluated using Chi-Square or Fisher's exact test to compare the proportions of subjects of the two treatment groups who report any TEAE.

Treatment-Emergent Serious Adverse Events (TESAEs) will be discussed within the clinical study report. TEAEs, TESAEs and TEAEs that led to study treatment interrupted temporarily or study treatment discontinued permanently will be presented in data listings.

All information pertaining to adverse events will be listed by subject, detailing verbatim term given by the investigator, preferred term, system organ class, start date, stop date, severity, outcome, action taken and formula relatedness. Separate listings will be created for Serious TEAEs and TEAEs leading to study formula discontinuation.

Concomitant Medications and Vital Signs

Concomitant medications will be coded using the WHO Drug Dictionary, version March 2019, and will be presented in data listings. All vital signs data will be displayed in listings.

6 Appendices

6.1 Handling of Missing or Incomplete Dates for Adverse Events and Concomitant Medications

Adverse Events

Handling of partial dates is only considered for the start date. An adverse event with a partial start date is considered treatment emergent if:

- only the day is missing and the start month/year is the same or after the month/year of the first dose
- the day and month are missing and the start year is the same or greater than the year of

[redacted]

the first dose date

- the start date is completely missing

Concomitant Medications

Handling of partial dates is only considered for the stop date. A medication with a partial stop date is considered concomitant if:

- only the day is missing and the stop month/year is the same or after the month/year of the first dose

- the day and month are missing and the stop year is the same or greater than the year of the first dose date

- the stop date is completely missing or the medication is ongoing

[redacted]

[redacted]