

**A Multi-Center, Double-Masked, Randomized, Two-Arm, Parallel-Group, Safety and Efficacy
Study to Compare Perrigo Pharmaceuticals International DAC Brinzolamide and Brimonidine
Tartrate Ophthalmic Suspension 1%/0.2% to Novartis Pharmaceuticals Simbrinza®
(brinzolamide/brimonidine tartrate 1%/0.2% ophthalmic suspension) in the Treatment of
Chronic Open Angle Glaucoma or Ocular Hypertension in both Eyes**

Protocol No.: PRG-NY-20-002

NCT04944290

Protocol Date: May 27, 2021

STATISTICAL ANALYSIS PLAN

PRG-NY-20-002: Brinzolamide and Brimonidine Tartrate Ophthalmic Suspension 1%/0.2%

A Multi-Center, Double-Masked, Randomized, Two-Arm, Parallel-Group, Safety and Efficacy Study to Compare Perrigo Pharmaceuticals International DAC Brinzolamide and Brimonidine Tartrate Ophthalmic Suspension 1%/0.2% to Novartis Pharmaceuticals Simbrinza® (brinzolamide/brimonidine tartrate 1%/0.2% ophthalmic suspension) in the Treatment of Chronic Open Angle Glaucoma or Ocular Hypertension in both Eyes

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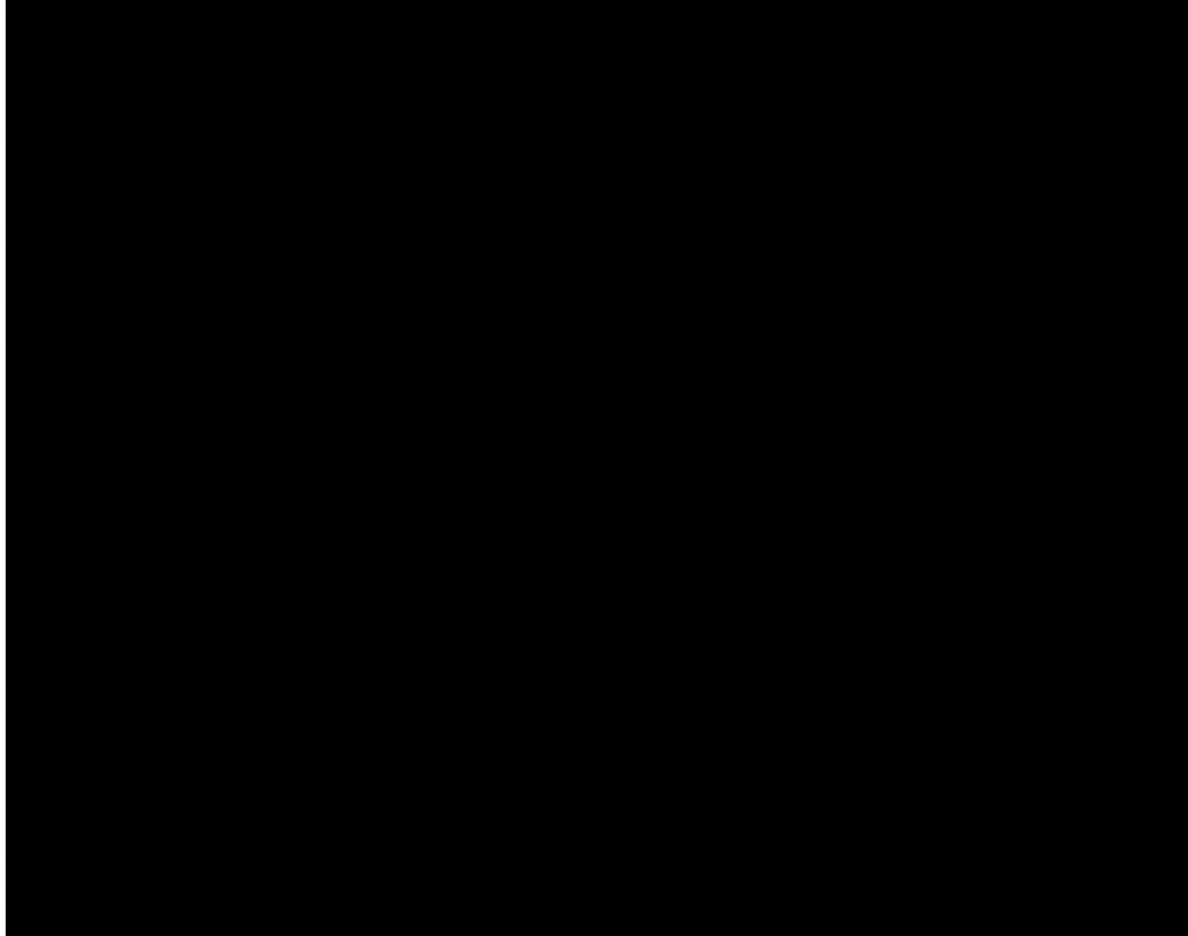


Table of Contents

1	Purpose of Statistical Analysis Plan.....	4
2	Study Objectives.....	4
3	Study Design and Sample Size	4
3.1	Study Design.....	4
3.2	Sample Size.....	5
4	Analysis Populations	5
5	Planned Analyses.....	6
5.1	Methodological Considerations	6
5.2	Handling of Dropouts or Missing Data.....	7
5.3	Demographics and Baseline Characteristics	7
5.4	Subject Disposition	7
5.5	Protocol Deviations/Violations	7
5.6	Study Drug Exposure and Compliance	8
5.7	Efficacy Analyses	8
5.7.1	Primary Endpoint.....	8
5.7.2	Comparison to Historic Data.....	10
5.8	Safety Variables and Analyses.....	10
6	Appendices	11
6.1	Handling of Missing or Incomplete Dates for Adverse Events and Concomitant Medications.....	11
6.2	Summary of Assessments	12
7	Tables and Listings.....	15
	Table 14.1.1 - Subject Disposition	17
	Table 14.1.2 - Subject Population (General).....	18
	Table 14.1.3 - Subject Enrollment by Study Site	19
	Table 14.1.4.1 - Demographic Characteristics Intent-to-Treat Population.....	20
	Table 14.1.4.2 - Demographic Characteristics Per-Protocol Population.....	21
	Table 14.1.5.1- Baseline Vital Signs Intent-to-Treat Population	22
	Table 14.1.5.2- Baseline Vital Signs Per-Protocol Population.....	23
	Table 14.1.6.1- Intraocular Pressure (IOP) Measurement at Baseline Intent-to-Treat Population.....	24
	Table 14.1.6.2- Intraocular Pressure (IOP) Measurement at Baseline Per-Protocol Population	25
	Table 14.1.6.3- Study Eye Baseline Mean IOP: Comparison with Historical Data* Intent-to-Treat Population....	26
	Table 14.1.7 – Days of Exposure and Medication Compliance Rate Intent-to-Treat Population	27
	Table 14.2.1.1- Primary Efficacy Analysis: Mean Change from Baseline in IOP of Both Eyes Per-Protocol Population.....	29
	Table 14.2.1.2- Study Eye Mean IOP and Mean Change from Baseline IOP at /Week 2 and Week 6: A Comparison with Historical Data* Intent-to-Treat Population.....	30
	Table 14.3.2.1 - Overall Summary of Treatment Emergent Adverse Events (TEAEs) Intent-to-Treat Population	31
	Table 14.3.2.2- Summary of Treatment-Emergent Adverse Events (TEAEs) by MedDRA System Organ Class and Preferred Term Intent-to-Treat Population	32

Table 14.3.2.3 – Summary of Treatment-Emergent Adverse Events (TEAEs) by MedDRA System Organ Class, Preferred Term, and Severity Intent-to-Treat Population.....	33
Table 14.3.2.4- Summary of Treatment-Emergent Adverse Events (TEAEs) by MedDRA System Organ Class, Preferred Term, and Relationship to Study Medication Intent-to-Treat Population.....	34
Table 14.3.2.5 – Common Treatment-Emergent Adverse Events (TEAEs) by MedDRA Preferred Term Intent-to-Treat Population	35
Subject Listings	36
Listing 16.2.1.1 – Subject Analysis Status	37
Listing 16.2.1.2 – Subject End-of-Study Status	38
Listing 16.2.1.3 – Dates of Visits	39
Listing 16.2.2.1 – Protocol Violations and Protocol Deviations	40
Listing 16.2.2.2 – Comments	41
Listing 16.2.2.3 - Inclusion/Exclusion Criteria	42
Listing 16.2.3 – Subjects Excluded from Efficacy Analyses	43
Listing 16.2.4.1 – Demographics and Informed Consent.....	44
Listing 16.2.4.2 – Ocular and Surgical History.....	45
Listing 16.2.4.3 – Medical and Surgical History (with Past and Current Findings).....	46
Listing 16.2.4.4 – Previous or Concomitant Medications	47
Listing 16.2.4.5 – Vital Signs.....	48
Listing 16.2.4.6 – Iris Color, [REDACTED]	49
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Listing 16.2.5.1 – Study Medication and Diary Card Dispensing at Visit 1 and Visit 2	55
Listing 16.2.5.2 – Study Medication Dispensing and Diary Card Review at Visit 3 and 4	56
Listing 16.2.5.3 – Treatment Record at End of Study	57
Listing 16.2.5.4 – COVID-19 Summary and Subject Compliance for End of Study.....	58
Listing 16.2.5.5 – Study Medication Reconciliation.....	59
Listing 16.2.6.1 – Intraocular Pressure (IOP) Measurement.....	60
Listing 16.2.6.2 – Derived Primary Efficacy Data on Intraocular Pressure (IOP) for Per-Protocol Population	61
Listing 16.2.6.3 – Study Eye: Derived Data on Intraocular Pressure (IOP) for Intent-to-Treat Subjects	62
Listing 16.2.7.1 – Adverse Events	63
Listing 16.2.7.2 – Adverse Events Leading to Study Treatment Interruption Temporarily/ Study Treatment Discontinued Permanently.....	63
Listing 16.2.7.3 – Serious Adverse Events.....	63
Listing 16.2.8 – Urine Pregnancy Tests (Female Subjects Only).....	64
Listing 16.2.9.1 – COVID-19 Impact by Visit.....	65
Listing 16.2.9.2 – COVID-19 Impact by Assessment.....	66

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
ITT	Intent- to-treat (population)
LS	Least squares
MedDRA	Medical Dictionary for Regulatory Activities
OH	Ocular Hypertension
PD	Protocol Deviation
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-20-002 [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-20-002.

[REDACTED]

2 Study Objectives

To compare the safety and efficacy profiles of Perrigo Pharmaceuticals International DAC Brinzolamide and Brimonidine Tartrate Ophthalmic Suspension 1%/0.2% to Novartis Pharmaceuticals Simbrinza® (brinzolamide/brimonidine tartrate 1%/0.2% ophthalmic suspension), in order to prove bioequivalence between them in the treatment of chronic open angle glaucoma or ocular hypertension 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 multi-center, double-masked, randomized, two-arm, parallel-group study.

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

- (1) Test: Brinzolamide and Brimonidine Tartrate Ophthalmic Suspension 1%/0.2% Perrigo Pharmaceuticals International DAC, [REDACTED]
- (2) Reference: Simbrinza® (brinzolamide/brimonidine tartrate 1%/0.2% ophthalmic suspension), manufactured by Novartis Pharmaceuticals.

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

[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 with all doses having \pm 1-hour window for six weeks (42 \pm 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 (\pm 4 days), and Visit 4/Week 6/Day 42 (\pm 4 days) (End of Study or Early Termination). Safety will be assessed by monitoring adverse events at each visit.

3.2 Sample Size

[REDACTED]

[REDACTED]

4 Analysis Populations

The analysis populations are defined as follows:

- (1) Intent-to-Treat (ITT) (safety population): Any subject that was enrolled, randomized, received, and used study medication.
- (2) Per Protocol (PP) population; any subject who (a) met all inclusion/exclusion criteria; (b) was randomized, received and used study medication; (c) met the protocol criteria for compliance [REDACTED]

[REDACTED] e)
complete IOP evaluations for both eyes at Visit 3/Week 2/Day 14 and Visit 4/Week 6/Day 42 within the designated visit window (\pm 4 days) for each visit; (f) had no significant protocol violations that could have interfered with the administration of the treatment or the precise evaluation of treatment efficacy.

5 Planned Analyses

5.1 Methodological Considerations

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

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:
 - o 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:
 - o Study Day = Date of the event or finding – Date of the first treatment

All dates will be displayed in DDMMYY 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).

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.

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]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[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%.



5.7 Efficacy Analyses

5.7.1 Primary Endpoint

The primary efficacy endpoint is mean change from baseline in intraocular pressure (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 Visit 3/ Week 2/Day 14 and Visit 4/Week 6/Day 42. 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.



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 (three of four follow-up points).

the first time in the history of the world, the people of the United States have been called upon to determine whether they will submit to the law of force, or the law of the Constitution. We have said to the world, we will not submit.

[REDACTED]

[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 24.0. 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 2021, 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 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]

A 16x16 grid of black and white blocks, likely a Minesweeper board. The grid contains various black shapes: a 2x2 square in the top-left, a 3x3 square in the top-right, a 4x4 square in the middle-right, a 5x2 rectangle in the middle-left, and several smaller black rectangles and squares scattered throughout. The background is white, and the blocks are black.

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