

**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**

**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**

[REDACTED]  
[REDACTED]

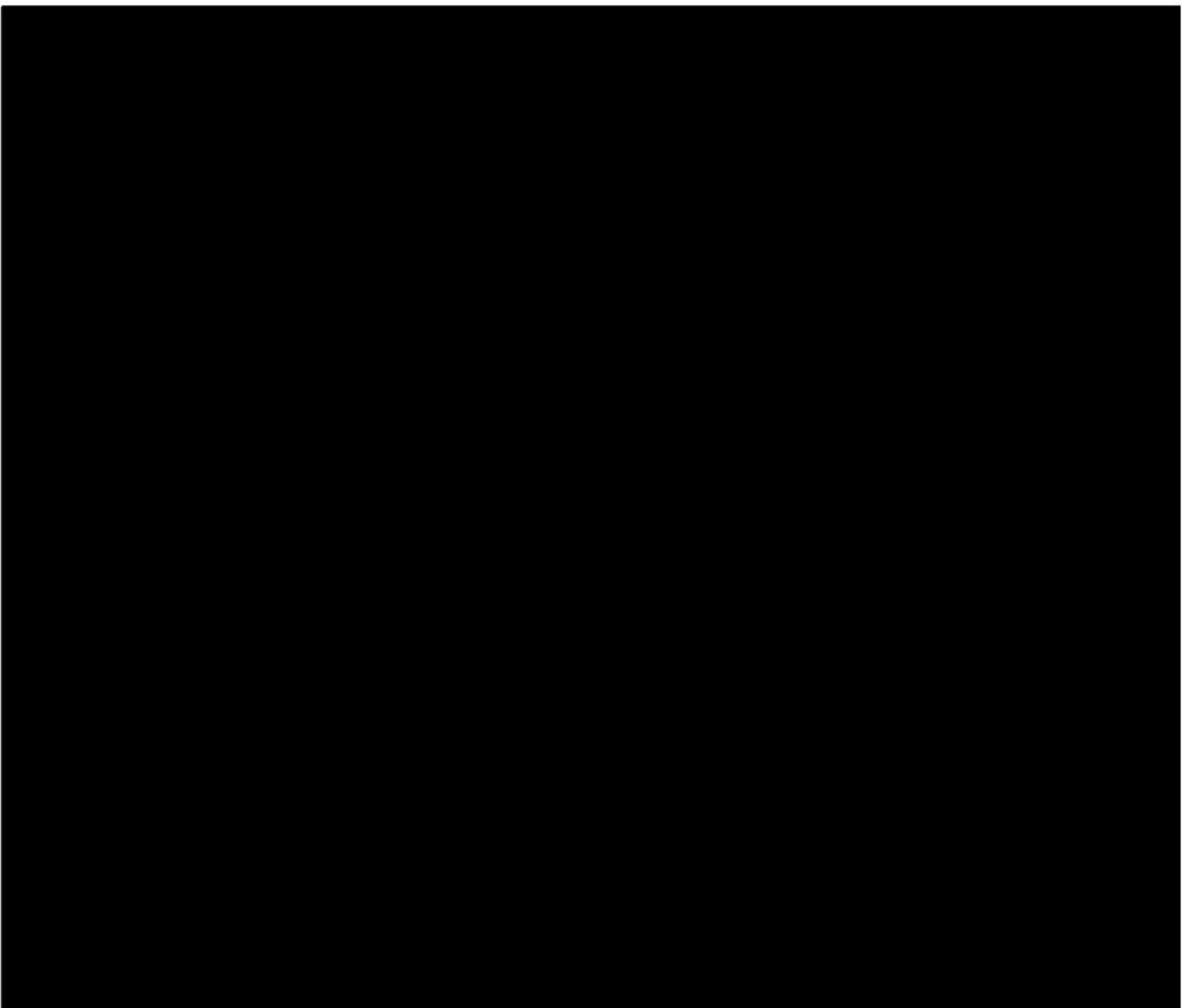
**Confidential**

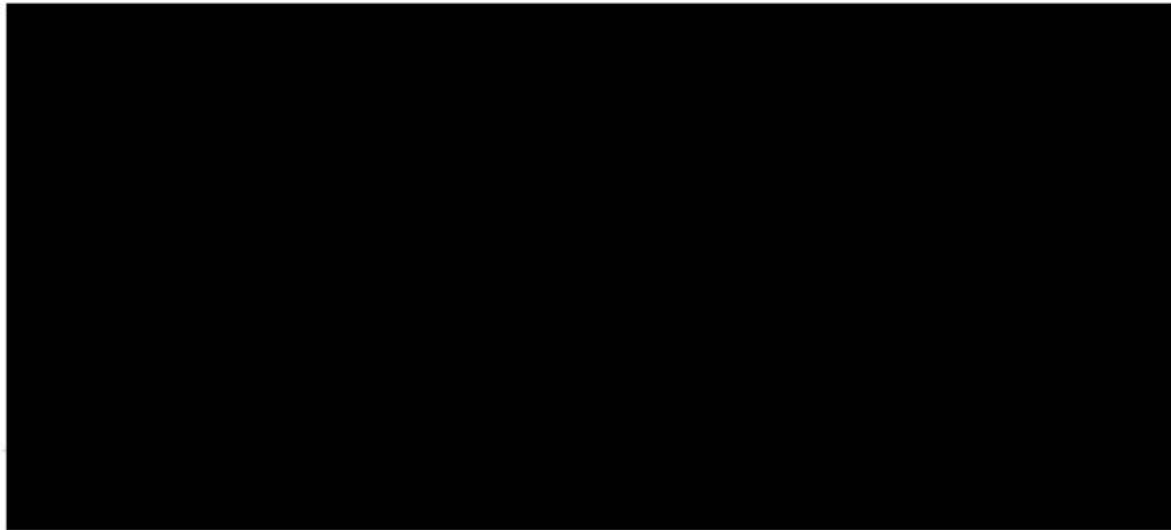
**The confidential information provided in this document is for use by parties directly involved  
in this investigation. By accepting this document, you agree that the information contained  
herein will not be disclosed to any person not directly involved in this investigation without  
written authorization from Perrigo Pharmaceuticals International DAC**

**PROTOCOL SIGNATURE PAGE**

PROTOCOL NUMBER: PRG-NY-20-002

PROTOCOL TITLE: 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



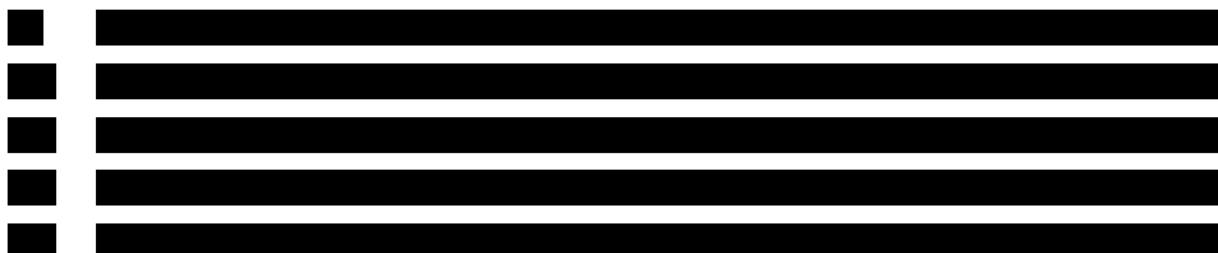


PRG-NY-20-002 Brinzolamide and Brimonidine Tartrate 1%/0.2% Ophthalmic Suspension

Page 3 of 66

## Contents

<b>1</b>	<b>BACKGROUND .....</b>	<b>10</b>
<b>2</b>	<b>STUDY OBJECTIVES .....</b>	<b>11</b>
2.1	<i>Endpoint .....</i>	11
2.2	<i>Safety .....</i>	11
<b>3</b>	<b>STUDY DESIGN.....</b>	<b>11</b>
3.1	<i>Type/Design of Study .....</i>	11
3.1.1	<i>Screening and Run-In Phase .....</i>	12
3.1.2	<i>Randomization and Double-Masked Treatment Phase.....</i>	12
3.2	<i>Study Population .....</i>	12
<b>4</b>	<b>SELECTION AND WITHDRAWAL OF STUDY SUBJECTS.....</b>	<b>12</b>
4.1	<i>Inclusion Criteria.....</i>	12
4.2	<i>Exclusion Criteria.....</i>	14
4.3	<i>Prohibited Medications .....</i>	17
4.4	<i>Precautions.....</i>	19
<b>5</b>	<b>PROCEDURES.....</b>	<b>21</b>
5.1	<i>Subject Screening, Informed Consent and Enrollment .....</i>	21
5.1.1	<i>Assignment of Subject Number .....</i>	21
5.2	<i>Demographics/Medical History.....</i>	21
5.3	<i>Ocular History.....</i>	21
5.4	<i>Concomitant Medications .....</i>	22
5.5	<i>Vital Signs.....</i>	22
5.6	<i>Urine Pregnancy Test .....</i>	22
5.7	<i>External Eye Exam.....</i>	22
5.7.1	<i>Iris Color .....</i>	23
5.8	<i>Intraocular Pressure (IOP) Measurement.....</i>	23
5.8.1	<i>Visit 1/Screening IOP Measurements .....</i>	24
5.8.2	<i>Visit 2/Baseline/Day 0.....</i>	24
5.8.3	<i>Visit 3/Week 2/Day 14 (<math>\pm</math> 4 days) and Visit 4/Week 6/Day 42 (<math>\pm</math> 4 days) IOP Measurements .....</i>	24



5.15	<i>Study Medication Masking</i> .....	27
5.15.1	Third-Party Dispenser .....	27
5.15.2	Study Medication Use, Subject Instructions and Diary .....	29
5.15.3	Visit 2/Baseline/Day 0 Study Medication & Diary Dispensing.....	30
5.15.4	Visit 3/Week 2 /Day 14 ( $\pm$ 4 days) and Visit 4/Week 6/Day 42 Study Medication and Diary Dispensing & Accountability .....	31
5.15.5	Unscheduled Visit.....	32
5.16	<i>Visit Specific Procedures</i> .....	32
5.16.1	Visit 1/Screening.....	32
5.16.2	Visit 2/Baseline/Day 0 .....	33
5.16.3	Visit 3/Week 2/Day 14 ( $\pm$ 4 days) .....	34
5.16.4	Visit 4/Week 6/Day 42 ( $\pm$ 4 days) End of Study or Early Termination Visit .....	35
5.16.5	Unscheduled Visit.....	35
5.17	<i>Summary of Assessments</i> .....	36
5.18	<i>Screen Failures</i> .....	39
5.19	<i>Protocol Deviations/Violations</i> .....	39
5.20	<i>Subject/Treatment Compliance</i> .....	39
5.21	<i>Discontinuation/Withdrawal of Study Subjects</i> .....	40
<b>6</b>	<b>MATERIALS AND SUPPLIES</b> .....	<b>41</b>
6.1	<i>Study Medication</i> .....	41
6.2	<i>Medication Management</i> .....	41
6.2.1	Labeling, Packaging and Distribution.....	41
6.2.2	Retention Samples.....	42
6.2.3	Storage and Test Article Accountability.....	43
6.2.4	Randomization.....	43
6.2.5	Procedure for Breaking the Blind.....	43
<b>7</b>	<b>ADVERSE REACTIONS</b> .....	<b>44</b>
7.1	<i>Departure from the Protocol for Individual Subjects</i> .....	44
7.2	<i>Definitions</i> .....	45
7.3	<i>Eliciting and Reporting of Adverse Events</i> .....	46
7.3.1	Expedited Reporting Responsibilities of the Study Center .....	47
7.3.2	Submitting an Expedited Safety Report to the IRB .....	47
7.4	<i>SAE &amp; AEs Requiring Discontinuation of Study Drug, including Pregnancies</i> .....	48
7.4.1	Pregnancy .....	49
7.5	<i>Post Study Adverse Events</i> .....	50
7.5.1	Non-serious Adverse Events .....	50
7.5.2	Serious Adverse Events.....	50
<b>8</b>	<b>Statistical Analysis</b> .....	<b>50</b>

8.1	<i>Statistical Analysis Plan</i> .....	50
8.1.1	Analysis Populations.....	51
8.1.2	Planned Analysis .....	51
8.1.3	Sample Size Considerations .....	51
8.1.4	Efficacy Measures and Analysis .....	52
8.1.5	Safety and Adverse Events Analysis.....	53
8.2	<i>Comparability of Subjects at Baseline</i> .....	53
<b>9</b>	<b>CONSENT/ASSENT CONSIDERATIONS AND PROCEDURES</b> .....	<b>53</b>
9.1	<i>Subject Confidentiality</i> .....	54
<b>10</b>	<b>CONDUCT OF STUDY</b> .....	<b>55</b>
10.1	<i>Completion of Study</i> .....	55
10.2	<i>Protocol Amendments</i> .....	55
10.3	<i>COVID-19 Risk Mitigation</i> .....	55
10.4	<i>Alternative protocol assessments during the COVID-19 Pandemic only</i> .....	56
10.4.1	Subject Disposition due to COVID-19 Infection.....	56
10.4.2	Regulatory and Study Oversight Considerations.....	56
10.4.3	Documentation of Protocol Deviations related to COVID-19.....	56
<b>11</b>	<b>RECORDS MANAGEMENT</b> .....	<b>56</b>
11.1	<i>Data Collection</i> .....	56
11.2	<i>Source Documents</i> .....	58
11.3	<i>File Management at the Study Site</i> .....	58
11.4	<i>Records Retention at the Study Site</i> .....	58
<b>12</b>	<b>QUALITY CONTROL AND QUALITY ASSURANCE</b> .....	<b>58</b>
12.1	<i>Monitoring</i> .....	58
12.2	<i>Auditing</i> .....	58
<b>13</b>	<b>ETHICS AND RESPONSIBILITY</b> .....	<b>59</b>
<b>14</b>	<b>USE OF INFORMATION AND PUBLICATION</b> .....	<b>59</b>
<b>15</b>	<b>INVESTIGATOR AGREEMENT</b> .....	<b>60</b>
<b>16</b>	<b>APPENDICES</b> .....	<b>61</b>
16.1	<i>Appendix A: Study Personnel Contacts</i> .....	61
16.2	<i>Appendix B: Instructions for the Subject</i> .....	62
<b>17</b>	<b>References</b> .....	<b>66</b>

STUDY SYNOPSIS

Title:	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
Study Period:	6 weeks (42 Days)
Study Medication:	<ol style="list-style-type: none"> <li>1. Brinzolamide and Brimonidine Tartrate Ophthalmic Suspension 1%/0.2% Perrigo Pharmaceuticals International DAC [REDACTED] [REDACTED]</li> <li>2. Simbrinza® (brinzolamide/brimonidine tartrate 1%/0.2% ophthalmic suspension), manufactured by Novartis Pharmaceuticals.</li> </ol>
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.
Study Design:	Subjects in this multi-center, double-masked, randomized, Two Arm, parallel-group study will be admitted into the study only after written informed consent/assent (as applicable) has been obtained and after all inclusion/exclusion criteria have been met. Male and female subjects at least 18 years with chronic open angle glaucoma or ocular hypertension in both eyes will be eligible for enrollment.
Study Population:	Approximately [REDACTED] healthy males and females, at least 18 years of age, inclusive, who meet the inclusion/exclusion criteria, will be enrolled to obtain approximately [REDACTED] per-protocol (PP) subjects.
Dosing:	Subjects will be randomized [REDACTED] to either the test product or reference product treatment group, respectively, and will apply one drop in both eyes three (3) times daily at approximately 8:00 am, 4:00 pm, and 10:00 pm with all doses having a $\pm$ 1 hour window for 6 weeks (42 days).
Study Visits:	Clinical Evaluations will be performed at: Visit 1/Screening Visit 2/Week 1/ Day 0 (Baseline) Visit 3/Week 2/Day 14 ( $\pm$ 4 days)(Interim) 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.
Evaluations:	At Visit 1/Screening the following evaluations: [REDACTED] [REDACTED].

	The intraocular pressure (IOP)/ Goldmann Applanation Tonometry (GAT) [REDACTED] will be performed and recorded at Visit 2/Baseline and all subsequent visits.
Endpoints:	The primary efficacy endpoint will be the mean change from Baseline in intraocular pressure (IOP) of both eyes at all four time points (e.g., at approximately 8:00 am (hour 0, before the morning drop) and 10:00 am (hour 2) at Visit 3/Week 2/Day 14 ( $\pm 4$ days) and Visit 4/Week 6/Day 42 ( $\pm 4$ days)
Safety:	The incidence of all adverse events reported during the study will be summarized by treatment group. Equivalence of the test and reference with regard to safety will be evaluated by comparing the nature, severity and frequency of their adverse event profiles.

## ABBREVIATIONS

AE	Adverse Event
CAI	Carbonic Anhydrous Inhibitor
CI	Confidence Interval
CRA	Clinical Research Associate
COAG	Chronic Open Angle Glaucoma
CRO	Contract Research Organization
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FDA	US Food and Drug Administration
GCP	Good Clinical Practices
hr	Hour
ICH	International Conference on Harmonization
IOP	Intraocular Pressure
IRB	Institutional Review Board
ITT	Intent- to-treat (population)
IU	International Unit
IUD	Intra-Uterine Device
LogMar	Logarithm of the Minimum Angle of Resolution
LS	Least squares
MR	Manifest refraction
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minutes
NSAID	Non-Steroidal Anti-Inflammatory Drug
OH	Ocular Hypertension
OTC	Over the counter
PI	Principal Investigator
PP	Per-protocol (population)
RLD	Reference Listed Drug
Rx	Prescription
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SITA	Swedish Interactive Testing Algorithm
Sub-I	Sub-Investigator
UPT	Urine Pregnancy Test

## 1 BACKGROUND

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

## **2 STUDY OBJECTIVES**

The objectives of this study are to compare the efficacy and safety 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.

### **2.1 Endpoint**

The primary efficacy endpoint will be the mean change from Baseline in intraocular pressure (IOP) of both eyes at all four time points (e.g., at approximately 8:00 am (hour 0, before the morning drop) and 10:00 am (hour 2) at Visit 3/Week 2/Day 14 ( $\pm 4$  days) and Visit 4/Week 6/Day 42 ( $\pm 4$  days)).

### **2.2 Safety**

Safety of the test and reference products will be compared by evaluating the nature, severity and frequency of their adverse event profiles. All adverse events that occur during the study will be recorded whether or not they are considered to be related to the study medication. Descriptions of reactions or complaints will include the approximate date of onset, the date the adverse event ended, the severity of the adverse event, and the outcome. Comparisons between the treatment groups will be made by tabulating the frequency of subjects with one or more adverse events (classified into MedDRA terms) during the study. Pearson's Chi-Square test or Fisher's Exact test, whichever is most appropriate, will be used to compare the proportion of subjects in each treatment group with any adverse event. The adverse events reported by at least five percent of the subjects in any treatment group will be summarized descriptively.

## **3 STUDY DESIGN**

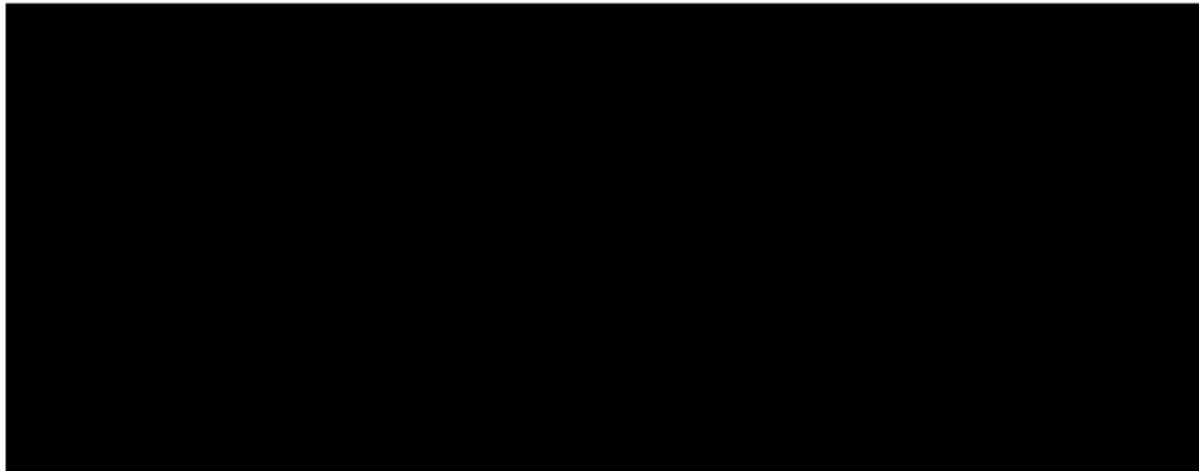
### **3.1 Type/Design of Study**

Subjects in this multi-center, double-masked, randomized, parallel-group study who meet eligibility criteria at Visit 2 /Baseline (Day 0), will be assigned [REDACTED] to test product or reference product, respectively. One drop of the assigned study medication will be applied in both eyes three (3) times daily at approximately 8:00 am, 4:00 pm, and 10:00 pm for 6 weeks (42 days).

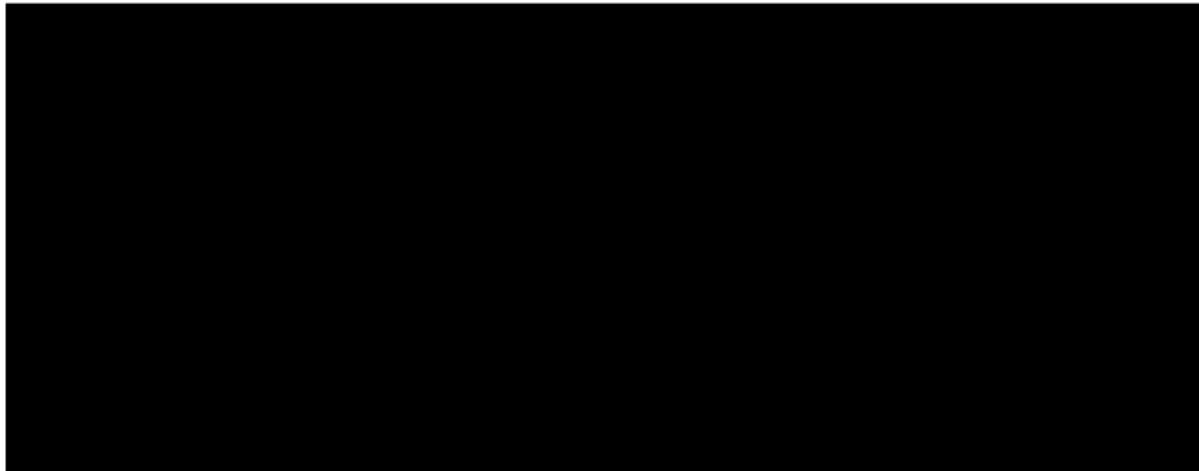
Males and females, at least 18 years of age with chronic open angle glaucoma or ocular hypertension in both eyes will be eligible for enrollment. Visits to the study site are scheduled at Visit 1 /Screening, Visit 2/Baseline (Day 0), Visit 3/Week 2/Day 14 ( $\pm 4$  days) and Visit 4/ Week 6/Day 42 ( $\pm 4$  days).

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

### **3.1.1 Screening and Run-In Phase**



### **3.1.2 Randomization and Double-Masked Treatment Phase**



## **3.2 Study Population**

Male and female subjects, at least 18 years of age, with chronic open angle glaucoma or ocular hypertension in both eyes.

██████████ healthy male and female subjects will be enrolled at approximately ██████████ per-protocol (PP) subjects.

As much as possible, the study population should consist of subjects with light colored irises and subjects with dark colored irises in similar proportion to the US population.

## **4 SELECTION AND WITHDRAWAL OF STUDY SUBJECTS**

### **4.1 Inclusion Criteria**

Subjects must meet all of the following criteria:

1. Subjects must sign an Institutional Review Board (IRB) approved written informed consent for this study before enrolling into the study. [REDACTED]
2. Subjects must be male or female, at least 18 years of age with chronic open angle glaucoma or ocular hypertension in both eyes.
3. [REDACTED]

A long, solid black horizontal bar with a small white rectangular cutout on the right side.

0	1	0	0	1
1	0	1	0	1
0	1	0	1	0
1	0	1	0	1
0	1	0	1	0



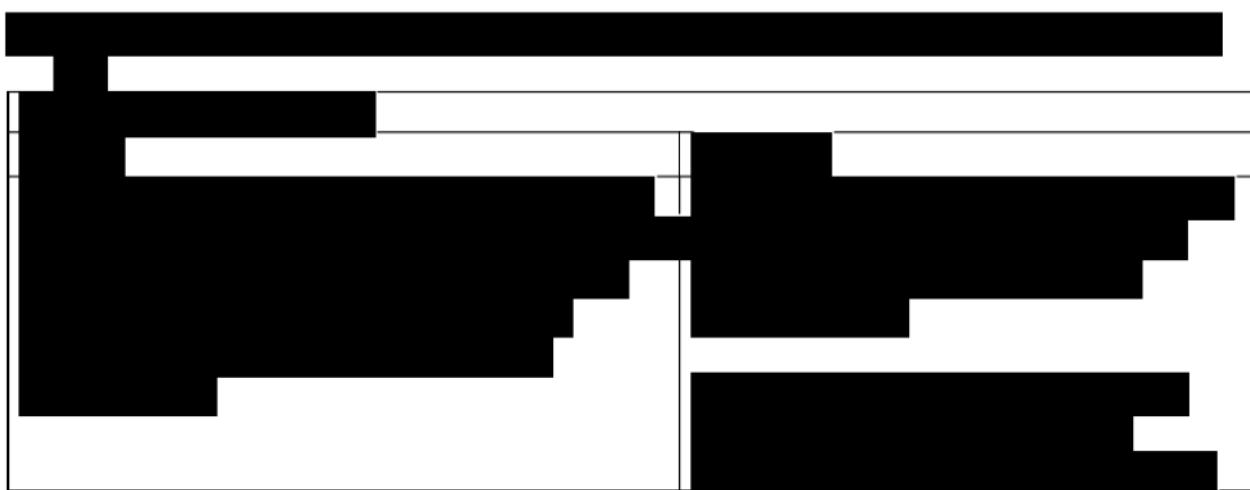
#### 4.2 Exclusion Criteria

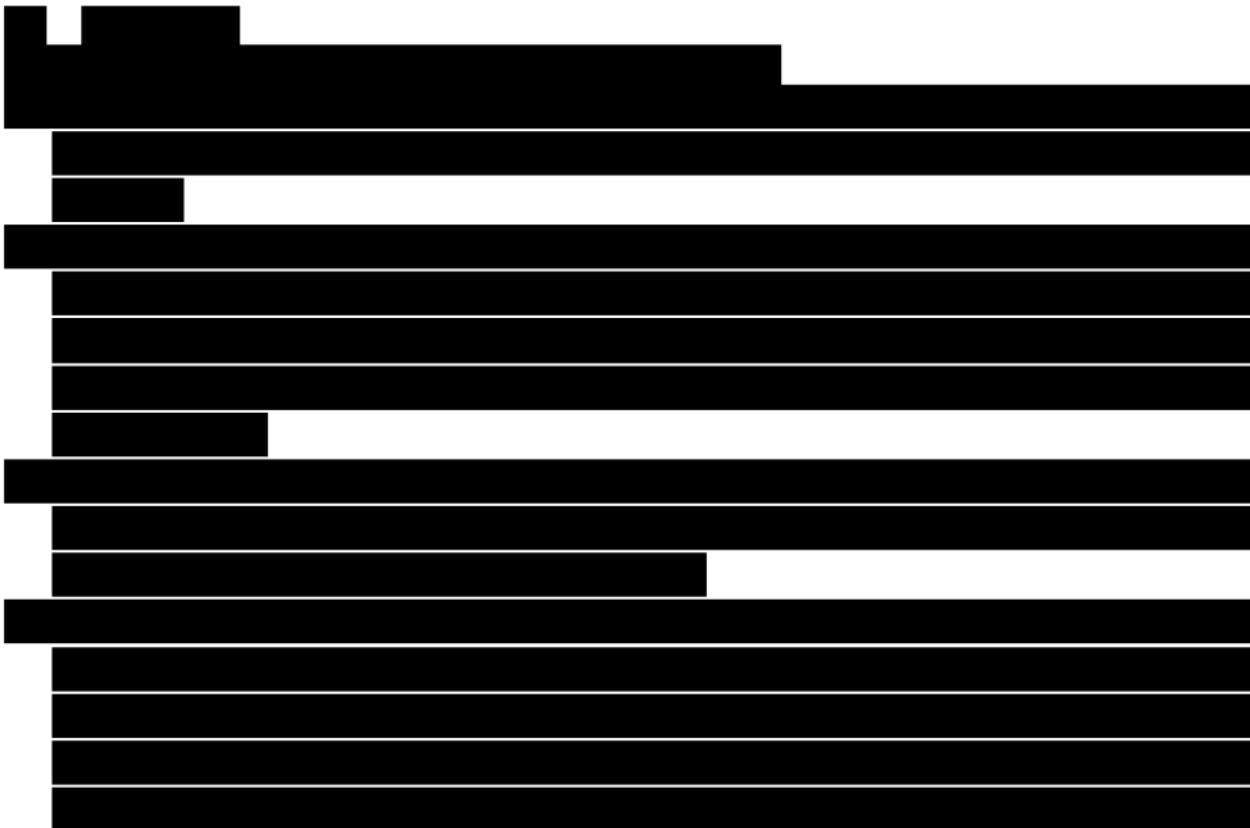
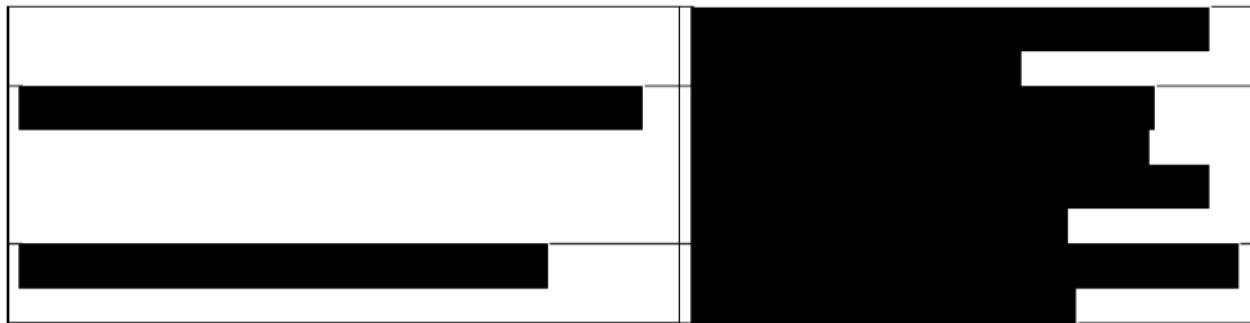
Subjects may **not** be selected if any of the following criteria exist:

1. Subjects who are pregnant, breastfeeding or planning a pregnancy within the study participation period.
2. Subjects who are females, of childbearing potential who do not agree to utilize an adequate form of contraception.
3. [REDACTED]



The image is a high-contrast, black-and-white graphic. It features a complex arrangement of thick, solid black horizontal and vertical lines, creating a sense of a grid or a technical drawing. Interspersed among these black lines are numerous thin, white horizontal and vertical lines, which act as separators or highlights. The pattern is dense and layered, with some sections appearing more open than others. The overall aesthetic is minimalist and graphic, resembling a stylized document or a technical diagram.





A bar chart consisting of 20 horizontal bars. All bars are black and of varying lengths, decreasing from top to bottom. The bars are arranged in a single column from top to bottom.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED].

## 5 PROCEDURES

### 5.1 Subject Screening, Informed Consent and Enrollment

The study personnel will review the IRB approved informed consent form and assent form (if applicable), with each subject and give the subject an opportunity to have all questions answered before proceeding. The IRB approved informed consent/assent form must be signed by each subject before the subject is enrolled into the study. A copy of the signed consent/assent will be given to every participant (or legally authorized representative) and the original will be maintained with the participant's records.

[REDACTED]

[REDACTED].

Subjects that require a wash-out of more than 30 days from their initial informed consent/assent signing must be re-consented before any further study procedures can begin.

#### 5.1.1 Assignment of Subject Number

[REDACTED]

[REDACTED]

[REDACTED]

### 5.2 Demographics/Medical History

A demographic profile and complete medical history will be recorded prior to starting study medication. The medical history will include a complete review of all current diseases and their respective treatments.

### 5.3 Ocular History

A complete ocular and surgical history will be recorded prior to starting study medication. The ocular history will include a complete review of all prior and current ocular diseases and their respective treatments.

[REDACTED]

[REDACTED]

## **5.6 Urine Pregnancy Test**

A urine pregnancy test will be conducted at Visit 1/Screening, Visit 2/Baseline /Day 0 (before the subjects applies the first dose of the study medication at the site) and Visit 4/ Week 6/Day 42(+/- 4 days). An investigator may repeat the pregnancy test anytime during the study visit if there is any suspicion or possibility that the subject may be pregnant. Females of childbearing potential (excluding women who are surgically sterilized or post- menopausal for at least 2 years), must have a negative urine pregnancy test at baseline, and must be willing to use an acceptable form of birth control during the study.

[REDACTED]

[REDACTED]

### 5.7.1 Iris Color

At Visit 1/Screening, the investigator or designee will classify the color of the iris of each eye to one of the following categories: Blue, Gray, Green, Hazel, Brown. In the electronic case report forms (eCRFs), [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

A series of 12 horizontal black bars of varying lengths, decreasing in length from left to right. The bars are positioned at different vertical intervals, creating a stepped effect. The first bar is the longest and is located at the top. The last bar is the shortest and is located at the bottom. The bars are set against a white background.

A high-contrast, black and white image showing a series of horizontal bands. The top section features several thick, dark horizontal bars of varying lengths, some with white gaps. Below this is a thin dark band. The middle section contains a long, thin dark bar. The bottom section is dominated by a very thick, dark horizontal bar, with a thin dark band above it and a small white area at the very bottom edge.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

PRG-NY-20-002 Brinzolamide and Brimonidine Tartrate 1%/0.2% Ophthalmic Suspension  
[REDACTED]  
Page 26 of 66

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

Page 27 of 66



[REDACTED]

For more information, contact the Office of the Vice President for Research and Economic Development at 319-273-2500 or [research@uiowa.edu](mailto:research@uiowa.edu).

For more information, contact the Office of the Vice President for Research and Economic Development at 505-272-2311 or [research@unm.edu](mailto:research@unm.edu).

100%     

© 2013 Pearson Education, Inc.

[REDACTED]

This figure is a 2D histogram representing the distribution of two variables. The horizontal axis (x-axis) and vertical axis (y-axis) both range from 0 to 100, with major tick marks every 20 units. The distribution is heavily skewed towards the bottom-left of the plot. A prominent, very high peak is located at approximately (20, 20). Below this, there is a smaller peak at (40, 40). Further down the y-axis, there are two more peaks: one at (60, 60) and another at (80, 80). The distribution then tapers off, with a few isolated points scattered at higher values. For example, there are points at (10, 90), (30, 90), (50, 90), (70, 90), (90, 90), and (90, 80). The overall shape is roughly triangular, with the highest density in the lower-left corner.

Category	Group 1 (Black)	Group 2 (White)
A	85	15
B	75	25
C	65	35
D	55	45

A black and white image showing a large, dark, irregular shape with a white rectangular cutout in the center. The shape is positioned above a white horizontal line. Below the line, there is a dark rectangular shape on the left and a dark, stepped rectangular shape on the right.



A black and white film strip graphic, consisting of a series of vertical black bars on the left and several white rectangular frames of varying sizes on the right, suggesting a film reel or a sequence of frames.

[REDACTED]



This figure consists of a 20x20 grid of black and white pixels. The grid is mostly white. Black blocks of various sizes and shapes are scattered across the grid. Some blocks are solid black, while others are partially filled. The pattern is non-repeating and appears to be a random or pseudorandom arrangement.

A 10x10 grid of black and white blocks. The grid is mostly white with black blocks in the top-left, top-right, and bottom-right corners. The bottom-right corner contains a large black cross-shaped block. The top-left corner has a smaller black cross-shaped block. The top-right corner has a black L-shaped block. The bottom edge of the grid is mostly black with white gaps. The right edge of the grid is mostly black with white gaps. The left edge of the grid is mostly white with black gaps. The top edge of the grid is mostly white with black gaps.

11. **What is the primary purpose of the following statement?**

For more information, visit [www.ams.org](http://www.ams.org).

113  
114  
115  
116  
117  
118  
119  
120  
121  
122  
123  
124  
125  
126  
127  
128  
129  
130  
131  
132  
133  
134  
135  
136  
137  
138  
139  
140  
141  
142  
143  
144  
145  
146  
147  
148  
149  
150  
151  
152  
153  
154  
155  
156  
157  
158  
159  
160  
161  
162  
163  
164  
165  
166  
167  
168  
169  
170  
171  
172  
173  
174  
175  
176  
177  
178  
179  
180  
181  
182  
183  
184  
185  
186  
187  
188  
189  
190  
191  
192  
193  
194  
195  
196  
197  
198  
199  
200  
201  
202  
203  
204  
205  
206  
207  
208  
209  
210  
211  
212  
213  
214  
215  
216  
217  
218  
219  
220  
221  
222  
223  
224  
225  
226  
227  
228  
229  
230  
231  
232  
233  
234  
235  
236  
237  
238  
239  
240  
241  
242  
243  
244  
245  
246  
247  
248  
249  
250  
251  
252  
253  
254  
255  
256  
257  
258  
259  
260  
261  
262  
263  
264  
265  
266  
267  
268  
269  
270  
271  
272  
273  
274  
275  
276  
277  
278  
279  
280  
281  
282  
283  
284  
285  
286  
287  
288  
289  
290  
291  
292  
293  
294  
295  
296  
297  
298  
299  
300  
301  
302  
303  
304  
305  
306  
307  
308  
309  
310  
311  
312  
313  
314  
315  
316  
317  
318  
319  
320  
321  
322  
323  
324  
325  
326  
327  
328  
329  
330  
331  
332  
333  
334  
335  
336  
337  
338  
339  
340  
341  
342  
343  
344  
345  
346  
347  
348  
349  
350  
351  
352  
353  
354  
355  
356  
357  
358  
359  
360  
361  
362  
363  
364  
365  
366  
367  
368  
369  
370  
371  
372  
373  
374  
375  
376  
377  
378  
379  
380  
381  
382  
383  
384  
385  
386  
387  
388  
389  
390  
391  
392  
393  
394  
395  
396  
397  
398  
399  
400  
401  
402  
403  
404  
405  
406  
407  
408  
409  
410  
411  
412  
413  
414  
415  
416  
417  
418  
419  
420  
421  
422  
423  
424  
425  
426  
427  
428  
429  
430  
431  
432  
433  
434  
435  
436  
437  
438  
439  
440  
441  
442  
443  
444  
445  
446  
447  
448  
449  
450  
451  
452  
453  
454  
455  
456  
457  
458  
459  
460  
461  
462  
463  
464  
465  
466  
467  
468  
469  
470  
471  
472  
473  
474  
475  
476  
477  
478  
479  
480  
481  
482  
483  
484  
485  
486  
487  
488  
489  
490  
491  
492  
493  
494  
495  
496  
497  
498  
499  
500  
501  
502  
503  
504  
505  
506  
507  
508  
509  
510  
511  
512  
513  
514  
515  
516  
517  
518  
519  
520  
521  
522  
523  
524  
525  
526  
527  
528  
529  
530  
531  
532  
533  
534  
535  
536  
537  
538  
539  
540  
541  
542  
543  
544  
545  
546  
547  
548  
549  
550  
551  
552  
553  
554  
555  
556  
557  
558  
559  
559  
560  
561  
562  
563  
564  
565  
566  
567  
568  
569  
569  
570  
571  
572  
573  
574  
575  
576  
577  
578  
579  
579  
580  
581  
582  
583  
584  
585  
586  
587  
588  
589  
589  
590  
591  
592  
593  
594  
595  
596  
597  
598  
599  
599  
600  
601  
602  
603  
604  
605  
606  
607  
608  
609  
609  
610  
611  
612  
613  
614  
615  
616  
617  
618  
619  
619  
620  
621  
622  
623  
624  
625  
626  
627  
628  
629  
629  
630  
631  
632  
633  
634  
635  
636  
637  
638  
639  
639  
640  
641  
642  
643  
644  
645  
646  
647  
648  
649  
649  
650  
651  
652  
653  
654  
655  
656  
657  
658  
659  
659  
660  
661  
662  
663  
664  
665  
666  
667  
668  
669  
669  
670  
671  
672  
673  
674  
675  
676  
677  
678  
679  
679  
680  
681  
682  
683  
684  
685  
686  
687  
688  
689  
689  
690  
691  
692  
693  
694  
695  
696  
697  
698  
699  
699  
700  
701  
702  
703  
704  
705  
706  
707  
708  
709  
709  
710  
711  
712  
713  
714  
715  
716  
717  
718  
719  
719  
720  
721  
722  
723  
724  
725  
726  
727  
728  
729  
729  
730  
731  
732  
733  
734  
735  
736  
737  
738  
739  
739  
740  
741  
742  
743  
744  
745  
746  
747  
748  
749  
749  
750  
751  
752  
753  
754  
755  
756  
757  
758  
759  
759  
760  
761  
762  
763  
764  
765  
766  
767  
768  
769  
769  
770  
771  
772  
773  
774  
775  
776  
777  
778  
779  
779  
780  
781  
782  
783  
784  
785  
786  
787  
788  
789  
789  
790  
791  
792  
793  
794  
795  
796  
797  
798  
799  
799  
800  
801  
802  
803  
804  
805  
806  
807  
808  
809  
809  
810  
811  
812  
813  
814  
815  
816  
817  
818  
819  
819  
820  
821  
822  
823  
824  
825  
826  
827  
828  
829  
829  
830  
831  
832  
833  
834  
835  
836  
837  
838  
839  
839  
840  
841  
842  
843  
844  
845  
846  
847  
848  
849  
849  
850  
851  
852  
853  
854  
855  
856  
857  
858  
859  
859  
860  
861  
862  
863  
864  
865  
866  
867  
868  
869  
869  
870  
871  
872  
873  
874  
875  
876  
877  
878  
879  
879  
880  
881  
882  
883  
884  
885  
886  
887  
888  
889  
889  
890  
891  
892  
893  
894  
895  
896  
897  
898  
899  
899  
900  
901  
902  
903  
904  
905  
906  
907  
908  
909  
909  
910  
911  
912  
913  
914  
915  
916  
917  
918  
919  
919  
920  
921  
922  
923  
924  
925  
926  
927  
928  
929  
929  
930  
931  
932  
933  
934  
935  
936  
937  
938  
939  
939  
940  
941  
942  
943  
944  
945  
946  
947  
948  
949  
949  
950  
951  
952  
953  
954  
955  
956  
957  
958  
959  
959  
960  
961  
962  
963  
964  
965  
966  
967  
968  
969  
969  
970  
971  
972  
973  
974  
975  
976  
977  
978  
979  
979  
980  
981  
982  
983  
984  
985  
986  
987  
988  
989  
989  
990  
991  
992  
993  
994  
995  
996  
997  
998  
999  
999  
1000  
1001  
1002  
1003  
1004  
1005  
1006  
1007  
1008  
1009  
1009  
1010  
1011  
1012  
1013  
1014  
1015  
1016  
1017  
1018  
1019  
1019  
1020  
1021  
1022  
1023  
1024  
1025  
1026  
1027  
1028  
1029  
1029  
1030  
1031  
1032  
1033  
1034  
1035  
1036  
1037  
1038  
1039  
1039  
1040  
1041  
1042  
1043  
1044  
1045  
1046  
1047  
1048  
1049  
1049  
1050  
1051  
1052  
1053  
1054  
1055  
1056  
1057  
1058  
1059  
1059  
1060  
1061  
1062  
1063  
1064  
1065  
1066  
1067  
1068  
1069  
1069  
1070  
1071  
1072  
1073  
1074  
1075  
1076  
1077  
1078  
1079  
1079  
1080  
1081  
1082  
1083  
1084  
1085  
1086  
1087  
1088  
1089  
1089  
1090  
1091  
1092  
1093  
1094  
1095  
1096  
1097  
1098  
1099  
1099  
1100  
1101  
1102  
1103  
1104  
1105  
1106  
1107  
1108  
1109  
1109  
1110  
1111  
1112  
1113  
1114  
1115  
1116  
1117  
1118  
1119  
1119  
1120  
1121  
1122  
1123  
1124  
1125  
1126  
1127  
1128  
1129  
1129  
1130  
1131  
1132  
1133  
1134  
1135  
1136  
1137  
1138  
1139  
1139  
1140  
1141  
1142  
1143  
1144  
1145  
1146  
1147  
1148  
1149  
1149  
1150  
1151  
1152  
1153  
1154  
1155  
1156  
1157  
1158  
1159  
1159  
1160  
1161  
1162  
1163  
1164  
1165  
1166  
1167  
1168  
1169  
1169  
1170  
1171  
1172  
1173  
1174  
1175  
1176  
1177  
1178  
1179  
1179  
1180  
1181  
1182  
1183  
1184  
1185  
1186  
1187  
1188  
1189  
1189  
1190  
1191  
1192  
1193  
1194  
1195  
1196  
1197  
1198  
1199  
1199  
1200  
1201  
1202  
1203  
1204  
1205  
1206  
1207  
1208  
1209  
1209  
1210  
1211  
1212  
1213  
1214  
1215  
1216  
1217  
1218  
1219  
1219  
1220  
1221  
1222  
1223  
1224  
1225  
1226  
1227  
1228  
1229  
1229  
1230  
1231  
1232  
1233  
1234  
1235  
1236  
1237  
1238  
1239  
1239  
1240  
1241  
1242  
1243  
1244  
1245  
1246  
1247  
1248  
1249  
1249  
1250  
1251  
1252  
1253  
1254  
1255  
1256  
1257  
1258  
1259  
1259  
1260  
1261  
1262  
1263  
1264  
1265  
1266  
1267  
1268  
1269  
1269  
1270  
1271  
1272  
1273  
1274  
1275  
1276  
1277  
1278  
1279  
1279  
1280  
1281  
1282  
1283  
1284  
1285  
1286  
1287  
1288  
1289  
1289  
1290  
1291  
1292  
1293  
1294  
1295  
1296  
1297  
1298  
1299  
1299  
1300  
1301  
1302  
1303  
1304  
1305  
1306  
1307  
1308  
1309  
1309  
1310  
1311  
1312  
1313  
1314  
1315  
1316  
1317  
1318  
1319  
1319  
1320  
1321  
1322  
1323  
1324  
1325  
1326  
1327  
1328  
1329  
1329  
1330  
1331  
1332  
1333  
1334  
1335  
1336  
1337  
1338  
1339  
1339  
1340  
1341  
1342  
1343  
1344  
1345  
1346  
1347  
1348  
1349  
1349  
1350  
1351  
1352  
1353  
1354  
1355  
1356  
1357  
1358  
1359  
1359  
1360  
1361  
1362  
1363  
1364  
1365  
1366  
1367  
1368  
1369  
1369  
1370  
1371  
1372  
1373  
1374  
1375  
1376  
1377  
1378  
1379  
1379  
1380  
1381  
1382  
1383  
1384  
1385  
1386  
1387  
1388  
1389  
1389  
1390  
1391  
1392  
1393  
1394  
1395  
1396  
1397  
1398  
1399  
1399  
1400  
1401  
1402  
1403  
1404  
1405  
1406  
1407  
1408  
1409  
1409  
1410  
1411  
1412  
1413  
1414  
1415  
1416  
1417  
1418  
1419  
1419  
1420  
1421  
1422  
1423  
1424  
1425  
1426  
1427  
1428  
1429  
1429  
1430  
1431  
1432  
1433  
1434  
1435  
1436  
1437  
1438  
1439  
1439  
1440  
1441  
1442  
1443  
1444  
1445  
1446  
1447  
1448  
1449  
1449  
1450  
1451  
1452  
1453  
1454  
1455  
1456  
1457  
1458  
1459  
1459  
1460  
1461  
1462  
1463  
1464  
1465  
1466  
1467  
1468  
1469  
1469  
1470  
1471  
1472  
1473  
1474  
1475  
1476  
1477  
1478  
1479  
1479  
1480  
1481  
1482  
1483  
1484  
1485  
1486  
1487  
1488  
1489  
1489  
1490  
1491  
1492  
1493  
1494  
1495  
1496  
1497  
1498  
1499  
1499  
1500  
1501  
1502  
1503  
1504  
1505  
1506  
1507  
1508  
1509  
1509  
1510  
1511  
1512  
1513  
1514  
1515  
1516  
1517  
1518  
1519  
1519  
1520  
1521  
1522  
1523  
1524  
1525  
1526  
1527  
1528  
1529  
1529  
1530  
1531  
1532  
1533  
1534  
1535  
1536  
1537  
1538  
1539  
1539  
1540  
1541  
1542  
1543  
1544  
1545  
1546  
1547  
1548  
1549  
1549  
1550  
1551  
1552  
1553  
1554  
1555  
1556  
1557  
1558  
1559  
1559  
1560  
1561  
1562  
1563  
1564  
1565  
1566  
1567  
1568  
1569  
1569  
1570  
1571  
1572  
1573  
1574  
1575  
1576  
1577  
1578  
1579  
1579  
1580  
1581  
1582  
1583  
1584  
1585  
1586  
1587  
1588  
1589  
1589  
1590  
1591  
1592  
1593  
1594  
1595  
1596  
1597  
1598  
1599  
1599  
1600  
1601  
1602  
1603  
1604  
1605  
1606  
1607  
1608  
1609  
1609  
1610  
1611  
1612  
1613  
1614  
1615  
1616  
1617  
1618  
1619  
1619  
1620  
1621  
1622  
1623  
1624  
1625  
1626  
1627  
1628  
1629  
1629  
1630  
1631  
1632  
1633  
1634  
1635  
1636  
1637  
1638  
1639  
1639  
1640  
1641  
1642  
1643  
1644  
1645  
1646  
1647  
1648  
1649  
1649  
1650  
1651  
1652  
1653  
1654  
1655  
1656  
1657  
1658  
1659  
1659  
1660  
1661  
1662  
1663  
1664  
1665  
1666  
1667  
1668  
1669  
1669  
1670  
1671  
1672  
1673  
1674  
1675  
1676  
1677  
1678  
1679  
1679  
1680  
1681  
1682  
1683  
1684  
1685  
1686  
1687  
1688  
1689  
1689  
1690  
1691  
1692  
1693  
1694  
1695  
1696  
1697  
1698  
1699  
1699  
1700  
1701  
1702  
1703  
1704  
1705  
1706  
1707  
1708  
1709  
1709  
1710  
1711  
1712  
1713  
1714  
1715  
1716  
1717  
1718  
1719  
1719  
1720  
1721  
1722  
1723  
1724  
1725  
1726  
1727  
1728  
1729  
1729  
1730  
1731  
1732  
1733  
1734  
1735  
1736  
1737  
1738  
1739  
1739  
1740  
1741  
1742  
1743  
1744  
1745  
1746  
1747  
1748  
1749  
1749  
1750  
1751  
1752  
1753  
1754  
1755  
1756  
1757  
1758  
1759  
1759  
1760  
1761  
1762  
1763  
1764  
1765  
1766  
1767  
1768  
1769  
1769  
1770  
1771  
1772  
1773  
1774  
1775  
1776  
1777  
1778  
1779  
1779  
1780  
1781  
1782  
1783  
1784  
1785  
1786  
1787  
1788  
1789  
1789  
1790  
1791  
1792  
1793  
1794  
1795  
1796  
1797  
1798  
1799  
1799  
1800  
1801  
1802  
1803  
1804  
1805  
1806  
1807  
1808  
1809  
1809  
1810  
1811  
1812  
1813  
1814  
1815  
1816  
1817  
1818  
1819  
1819  
1820  
1821  
1822  
1823  
1824  
1825  
1826  
1827  
1828  
1829  
1829  
1830  
1831  
1832  
1833  
1834  
1835  
1836  
1837  
1838  
1839  
1839  
1840  
1841  
1842  
1843  
1844  
1845  
1846  
1847  
1848  
1849  
1849  
1850  
1851  
1852  
1853  
1854  
1855  
1856  
1857  
1858  
1859  
1859  
1860  
1861  
1862  
1863  
1864  
1865  
1866  
1867  
1868  
1869  
1869  
1870  
1871  
1872  
1873  
1874  
1875  
1876  
1877  
1878  
1879  
1879  
1880  
1881  
1882  
1883  
1884  
1885  
1886  
1887  
1888  
1889  
1889  
1890  
1891  
1892  
1893  
1894  
1895  
1896  
1897  
1898  
1899  
1899  
1900  
1901  
1902  
1903  
1904  
1905  
1906  
1907  
1908  
1909  
1909  
1910  
1911  
1912  
1913  
1914  
1915  
1916  
1917  
1918  
1919  
1919  
1920  
1921  
1922  
1923  
1924  
1925  
1926  
1927  
1928  
1929  
1929  
1930  
1931  
1932  
1933  
1934  
1935  
1936  
1937  
1938  
1939  
1939  
1940  
1941  
1942  
1943  
1944  
1945  
1946  
1947  
1948  
1949  
1949  
1950  
1951  
1952  
1953  
1954  
1955  
1956  
1957  
1958  
1959  
1959  
1960  
1961  
1962  
1963  
1964  
1965  
1966  
1967  
1968  
1969  
1969  
1970  
1971  
1972  
1973  
1974  
1975  
1976  
1977  
1978  
1979  
1979  
1980  
1981  
1982  
1983  
1984  
1985  
1986  
1987  
1988  
1989  
1989  
1990  
1991  
1992  
1993  
1994  
1995  
1996  
1997  
1998  
1999  
1999  
2000  
2001  
2002  
2003  
2004  
2005  
2006  
2007  
2008  
2009  
2009  
2010  
2011  
2012  
2013  
2014  
2015  
2016  
2017  
2018  
2019  
2019  
2020  
2021  
2022  
2023  
2024  
2025  
2026  
2027  
2028  
2029  
2029  
2030  
2031  
2032  
2033  
2034  
2035  
2036  
2037  
2038  
2039  
2039  
2040  
2041  
2042  
2043  
2044  
2045  
2046  
2047  
2048  
2049  
2049  
2050  
2051  
2052  
2053  
2054  
2055  
2056  
2057  
2058  
2059  
2059  
2060  
2061  
2062  
2063  
2064  
2065  
2066  
2067  
2068  
2069  
2069  
2070  
2071  
2072  
2073  
2074  
2075  
2076  
2077  
2078  
2079  
2079  
2080  
2081  
2082  
2083  
2084  
2085  
2086  
2087  
2088  
2089  
2089  
2090  
2091  
2092  
2093  
2094  
2095  
2096  
2097  
2098  
2099  
2099  
2100  
2101  
2102  
2103  
2104  
2105  
2106  
2107  
2108  
2109  
2109  
2110  
2111  
2112  
2113  
2114  
2115  
2116  
2117  
2118  
2119  
2119  
2120  
2121  
2122  
2123  
2124  
2125  
2126  
2127  
2128  
2129  
2129  
2130  
2131  
2132  
2133  
2134  
2135  
2136  
2137  
2138  
2139  
2139  
2140  
2141  
2142  
2143  
2144  
2145  
2146  
2147  
2148  
2149  
2149  
2150  
2151  
2152  
2153  
2154  
2155  
2156  
2157  
2158  
2159  
2159  
2160  
2161  
2162  
2163  
2164  
2165  
2166

11. **What is the primary purpose of the *Journal of Clinical Endocrinology and Metabolism*?**

1. **What is the primary purpose of the study?** The study aims to evaluate the effectiveness of a new treatment for hypertension in a diverse population.

## 5.20 Subject/Treatment Compliance

Subjects will instill one drop of the study medication in each eye three (3) times daily at approximately 8:00 am, 4:00 pm and 10:00 pm [REDACTED] for 6 weeks (42 days). Subjects should avoid allowing the tip of the dispensing container to come into contact with their eye or the area surrounding the eyes, or other surfaces.

On Day 0, subjects/caregiver will apply their initial dose of study medication at the study site under the supervision of the third-party dispenser staff. Compliance will be determined from the diary card, in which the subject will be instructed to record all applications made or missed. █

A large black rectangular redaction box covers the bottom portion of the page content, starting below the table and ending at the bottom of the page. It is positioned to the left of a white vertical margin line.

A high-contrast, black and white abstract image. On the far left, there is a vertical column of black bars of varying heights, resembling a film strip. To the right of this column, a series of horizontal white bars of varying lengths extend across the frame. These white bars are positioned at different heights, creating a sense of depth or a stepped pattern. The background is solid black, making the white bars stand out sharply.

For more information, contact the Office of the Vice President for Research and Economic Development at 515-294-6450 or [research@iastate.edu](mailto:research@iastate.edu).

10. **What is the primary purpose of the *Journal of Clinical Endocrinology and Metabolism*?**

11. **What is the primary purpose of the *Journal of Clinical Endocrinology and Metabolism*?**

follow-up.

## 6 MATERIALS AND SUPPLIES

### 6.1 Study Medication

The study medication supplied by Perrigo will consist of:

Test Product: Brinzolamide and Brimonidine Tartrate Ophthalmic Suspension 1%/0.2%,  
Perrigo Pharmaceuticals International DAC, [REDACTED]

Reference Product: Simbrinza® (brinzolamide/brimonidine tartrate 1%/0.2% ophthalmic suspension), manufactured by Novartis Pharmaceuticals.

### 6.2 Medication Management

#### 6.2.1 Labeling, Packaging and Distribution

All study medications will be supplied to the subjects in 10ml plastic bottles. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]



### 6.2.2 Retention Samples

Each investigational site where study medication is dispensed to at least one subject will be required to randomly select [REDACTED] study medication to be maintained as retain samples. The investigator will maintain [REDACTED] study medication from each shipment of study medication received. As per the Code of Federal Regulations Part 21, Section 320.38(e), Each reserve sample shall be stored under conditions consistent with product labeling and in an area segregated from the area where testing is conducted and with access limited to authorized personnel (in an upright position away from heat and protected from light at temperature, 2°C-25°C (36°F-77°F) even after the study has concluded. At the conclusion of the study, each investigational site should continue to track and record daily the temperature of the storage room where the retention samples are stored and report any temperature excursion to Perrigo and Symbio for the duration of the retention period. Each retention sample shall be retained for a period of at least 5 years following the date on which the application or supplemental application is approved, or, if such application or supplemental application is not approved, at least 5 years following the date of completion of the bioavailability study in which the sample from which the reserve sample was obtained or was used." The investigator will store

the retain sample study medication until such time as notification is received from Perrigo that the samples are no longer required.

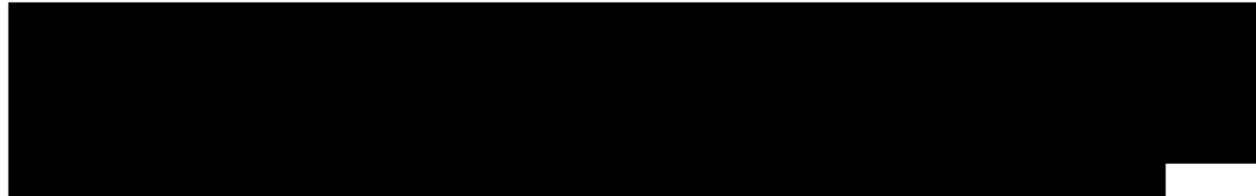
#### **6.2.3 Storage and Test Article Accountability**

Study articles used to conduct this study will be maintained under adequate security by the investigator or designee. Each investigator site will ensure that the temperature of study medication is monitored and recorded throughout the study. The study medication should be stored at temperature in a secured area with limited access, 2°C-25°C (36°F-77°F), and bottles must be kept in an upright position and tightly closed. The medication should not be frozen, should be protected from light, kept away from children, heat and kept tightly closed. The investigator will not supply study medication to any person not enrolled in this study, or to any physician or scientist except those named as sub-investigators.

The third-party dispenser at each investigator site will keep a running inventory of study medication dispensed that will include subject numbers assigned and the date each bottle of study medication is dispensed and returned. A study medication accountability form will be provided to the investigator to document all medications received, dispensed by and used by each subject. The third-party dispenser and monitor will perform drug accountability and reconciliation tasks of the study medication throughout the study.

At the conclusion of the study all unused, partially used, and empty bottles must be inventoried by the third-party dispenser and /or the monitor and returned to Perrigo, or designee, for destruction, with the exception of retention samples which shall remain at the investigator site.

#### **6.2.4 Randomization**



#### **6.2.5 Procedure for Breaking the Blind**



## 7 ADVERSE REACTIONS

The potential adverse reactions of generic Brinzolamide and Brimonidine Tartrate Ophthalmic Suspension 1%/0.2%, are anticipated to be similar to those observed in Simbrinza® (brinzolamide/brimonidine tartrate 1%/0.2%) ophthalmic suspension),

The following adverse reactions occurred in 3% to 5% of patients treated with Simbrinza® include blurred vision, eye irritation, dysgeusia (bad taste), dry mouth, and eye allergy may occur.

### Other adverse reactions reported with individual active ingredients of Simbrinza® Ophthalmic Suspension

The most frequently reported adverse reactions occurring in 1% to 5% of patients treated with Brinzolamide ophthalmic suspension 1% in clinical studies were blepharitis, dermatitis, dry, eye, foreign body sensation, headache, hyperemia, ocular discharge, ocular discomfort, ocular keratitis, ocular pain, ocular pruritus and rhinitis. The following adverse reactions were reported in 1% of patients treated with Brinzolamide ophthalmic suspension 1%: allergic reactions, chest pain, conjunctivitis, diarrhea, diplopia, dizziness, dry mouth, dyspnea, dyspepsia, eye fatigue, hypertonia, keratoconjunctivitis, keratopathy, kidney pain, lid margin crusting or sticky sensation, nausea, pharyngitis, tearing and urticaria.

The most frequently reported adverse reactions occurring in 10% to 30% of patients treated with Brimonidine Tartrate 0.2% ophthalmic suspension in clinical studies were oral dryness, ocular hyperemia, burning and stinging, headache, blurring, foreign body sensation, fatigue/drowsiness, conjunctival follicles, ocular allergic reactions and ocular pruritus. The following adverse reactions were reported in 3% to 9% of patients treated with Brimonidine Tartrate 0.2% ophthalmic suspension: corneal staining/erosion, photophobia, eyelid erythema, ocular ache/pain, ocular dryness, tearing, upper respiratory symptoms, eyelid edema, conjunctival edema, dizziness, blepharitis, ocular irritation, gastrointestinal symptoms, asthenia, conjunctival blanching, abnormal vision and muscular pain. The following adverse reactions were reported in ≤ 3% of patients treated with Brimonidine Tartrate 0.2% ophthalmic suspension: lid crusting, conjunctival hemorrhage abnormal taste, insomnia, conjunctival discharge, depression, hypertension, anxiety, palpitations/arrhythmias, nasal dryness and syncope.

There is no post marketing experience with Simbrinza® ophthalmic suspension. The following adverse reactions have been identified during post-approval use of brimonidine tartrate ophthalmic solutions in clinical practice, a similar drug containing brimonidine tartrate as an active ingredient are bradycardia, hypersensitivity, iritis, keratoconjunctivitis sicca, miosis, nausea, skin reactions (including erythema, eyelid pruritus, rash, and vasodilation) and tachycardia. pain of skin, pruritus, swelling face, conjunctivitis, skin discoloration, rash, eczema, throat tightness and allergic contact dermatitis.

### 7.1 Departure from the Protocol for Individual Subjects

When an emergency occurs requiring a departure from the protocol for a subject, departure will be only for that subject. In such circumstances, the investigator or other physician in attendance will contact the Medical Monitor or Perrigo by telephone and follow up with a written description

as soon as possible. The overseeing IRB should also be notified in accordance with the IRB's guidelines.

## 7.2 Definitions

An adverse event (AE) is defined as any untoward medical occurrence in a subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product.

A serious adverse event (SAE) is an adverse event that results in any of the following outcomes:

- Death
- Life-threatening event (e.g., the subject was, in the opinion of the investigator, at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more severe form, might have caused death)
- Requires in-subject hospitalization or prolongs hospitalization
- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital anomaly/birth defect
- Other adverse events that may be considered serious based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Immediately Reportable Adverse Events (IRAE): Any serious AE or any AE that necessitates discontinuation of study medication, including pregnancy.

Unexpected Adverse Event: An unexpected event is any adverse drug experience, the specificity or severity of which is not consistent with the current approved product labeling (package insert) for the study medication, the Investigator's Brochure, or as described in the clinical protocol and consent materials.

Intensity of Adverse Events: The maximum intensity of an AE during a day should be recorded on the CRF. If the intensity of an AE changes over a number of days, then separate entries should be made having distinct onset dates for the changes in severity.

Mild - AEs are usually transient, requiring no special treatment, and do not interfere with subject's daily activities.

Moderate - AEs typically introduce a low level of inconvenience or concern to the subject and may interfere with daily activities, but are usually ameliorated by simple therapeutic measures.

Severe - AEs interrupt a subject's usual daily activity and traditionally require systemic drug therapy or other treatment.

Causal Relationship to Study Medication: The following criteria should be used in assessing the apparent causal relationship of an AE to study medication.

Definitely - The AE:

- follows a reasonable temporal sequence from study medication administration
- abates upon discontinuation of the study medication (dechallenge)
- is confirmed by reappearance of the reaction on repeat exposure

Probably - The AE:

- follows a reasonable temporal sequence from study medication administration
- abates upon discontinuation of the study medication (dechallenge)
- cannot be reasonably explained by the known characteristics of the subject's state.

Possible - The AE:

- follows a reasonable temporal sequence from study medication administration
- but that could readily be produced by a number of other factors.

Unlikely - The AE:

- follows a reasonable temporal sequence from study medication administration.
- could have been produced by either the subject's clinical state or by study medication administration.

Not related - The AE:

- does not have a reasonable temporal association with the administration of study medication
- has some other obvious explanation for the event.

### 7.3 Eliciting and Reporting of Adverse Events

The investigator will periodically assess subjects for the occurrence of adverse events. [REDACTED]

[REDACTED] II adverse events (as defined in Section 7.2), either observed by the Investigator or one of his/her medical collaborators, or reported by the participant spontaneously, or in response to direct questioning, will be reported and documented in the source document and the study reporting forms. When reporting an adverse event, the Investigator must assign a severity grade to each event and declare an opinion on the relatedness of the event to the study medication or procedure. Serious or unexpected adverse events must be reported to [REDACTED] **within 24 hours** of when the Investigator first learns of the occurrence of the event.

Adverse events will be documented in the source document and recorded in a timely manner on the eCRFs. Adverse events (e.g., worsening of chronic open angle glaucoma or ocular hypertension define as IOP  $\geq$  36 mm Hg in either eye) that are identified at the last assessment visit (or the early termination visit) must be recorded on the AE eCRF with the status of the AE noted.

Adverse event reporting begins from the signing of informed consent/assent. Adverse events should be followed until resolved or 30 days after the final study treatment. In any case, serious adverse events that are not resolved or considered to be chronic within 30 days of the final study treatment must be followed by the investigator until they become resolved or are considered to be chronic (stabilized for at least 30 days). All events that are ongoing at this time will be recorded as ongoing on the eCRF.

### **7.3.1 Expedited Reporting Responsibilities of the Study Center**

For any serious or unexpected adverse event, [REDACTED] must be notified ***within 24 hours*** of when the Investigator first learns of the occurrence of the event. Expedited reporting requirements for serious adverse events are described below. Adequate information must be collected with supporting documentation to complete a standard report for submission to Perrigo. The adverse event term on the AE eCRF and the SAE report should agree exactly. Special attention should be given to recording hospitalizations and concomitant medications.

Subjects with unresolved adverse event(s) or serious adverse event(s) should be followed by the investigator until the events are resolved, events determined to be chronic or the subject is lost to follow-up. Resolution means the subject has returned to the baseline state of health, or the investigator does not expect any further improvement or worsening of the adverse event. The investigator should continue to report any significant follow-up information to the sponsor up to the point that the event has resolved. Any serious adverse event reported by the subject to the investigator that occurs within 30 days after the last assessment and are determined by the investigator to be reasonably associated with the use of the study medication, should be reported to the sponsor within 24 hours of when the Investigator first learns of the occurrence of the event.

When reporting a serious adverse event (SAE) the Investigator (or the Study Coordinator) will promptly report any serious adverse event or pregnancy by telephone [REDACTED] [REDACTED] immediately after the investigator becomes aware of the event. An SAE form should be completed and sent by fax, email, or overnight courier to Symbio within 24 hours of knowledge of the event by the site. In many cases, only preliminary information will be available. Appropriate follow up information should be sought (hospital discharge summaries, operative reports etc.) and a follow up SAE report form submitted. A designation of causality from the study medication should always be included with a follow up report. Assess and report the causality of the event.

### **7.3.2 Submitting an Expedited Safety Report to the IRB**

Once [REDACTED] receives all supporting documentation for the reported event, the Medical Monitor, in conjunction with [REDACTED], will determine if the safety report is eligible for expedited review. [REDACTED] will log the initial event and will notify the sponsor that an event has been reported within 1 business day after initial receipt. [REDACTED] will complete the review of the event, enter information into their safety database and generate the report. This form, as well as other supporting documentation, will be forwarded to [REDACTED] Medical Monitor for review. [REDACTED]

will finalize the report and distribute it to the sponsor within 1 day (one) after initial receipt. When expedited safety reporting to regulatory authorities is indeed required, the Investigator should review and update any newly available materials at once. Follow-up queries may be sent to the study center to further clarify the event.

Each expedited safety report will routinely include a brief cover memorandum, the completed report, and any additional pertinent information recommended by [REDACTED] Perrigo, or study Medical Monitor. Once the report is assembled, the Principal Investigator must submit the expedited safety report to the IRB within the required reporting timeframe. Follow-up reports should be submitted when requested or when pertinent information becomes available.

When a Principal Investigator receives an expedited safety report from [REDACTED] or the sponsor detailing adverse events occurring at other study centers under this protocol, it must be promptly submitted to the study center's IRB. The Principal Investigator must retain a copy of such reports as submitted to their IRB in the site's study Regulatory Binder.

#### **7.4 SAE & AEs Requiring Discontinuation of Study Drug, including Pregnancies**

ANY SAE, WHICH OCCURS AFTER A SUBJECT HAS ENTERED THE STUDY, WHETHER OR NOT RELATED TO STUDY MEDICATION, MUST BE REPORTED TO [REDACTED] AND PERRIGO IMMEDIATELY (WITHIN 24 HOURS, OF WHEN THE INVESTIGATOR FIRST LEARNS OF THE OCCURENCE) VIA TELEPHONE OR FACSIMILE. IF INITIALLY REPORTED VIA TELEPHONE, THIS MUST BE FOLLOWED-UP BY A FACSIMILE OF THE WRITTEN SAE REPORT WITHIN 24 HOURS OF THE CALL TO [REDACTED].

Non-serious events that require discontinuation of study medication (including laboratory abnormalities) should be reported [REDACTED] immediately and within 1 working day.

Subjects who discontinue due to experiencing adverse events should be followed clinically until their health has returned to baseline status, or until all parameters have returned to normal. It is expected that the investigator will provide or arrange appropriate supportive care for the subject.

A subject who experiences a severe adverse event related to study drug will be discontinued from the study.

The notification about any serious adverse event should be directed to:

[REDACTED]  
[REDACTED]  
[REDACTED]

[REDACTED]

#### 7.4.1 Pregnancy

At the time a Principal Investigator or site personnel becomes aware that a study participant became pregnant following study participation, the Principal Investigator or designee will report the pregnancy immediately by phone and/or by faxing a completed Pregnancy Report to Symbio within one working day of being notified of the pregnancy report.

The report will include the following elements:

- Participant (mother's) coded study identifier;
- Date of participant's last menstrual period;
- Total accumulated dose of study treatment administered to date;
- Date of study medication administration.

The investigator will follow the subject until completion of the pregnancy and must assess the outcome in the shortest possible time but not more than 30 days within completion of the pregnancy.

Upon delivery, miscarriage or abortion, the Principal Investigator or designee must forward a follow-up Pregnancy Report with any relevant information on the present condition of the fetus [REDACTED], including:

- Mother's coded study identifier(s);
- Gestational age at delivery, miscarriage or abortion;
- Birth weight, gender, length and head circumference, if available;
- Apgar scores recorded after birth, if available;
- Any abnormalities.

If the outcome of the pregnancy **meets the criteria for immediate classification of an SAE** (e.g., spontaneous or therapeutic abortion [any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or congenital anomaly), the investigator will report the event by phone and by faxing a completed SAE report form to Symbio within one working day of being notified of the pregnancy report.

If the trial is completed before the outcome of the pregnancy is known, Symbio will assume the responsibility for following up on the pregnancy. Symbio will contact the Investigator or Study coordinator on or around the potential expected date of delivery to follow-up on the outcome of pregnancy and will also check on the status of the infant 8 weeks post-delivery. Upon awareness of the pregnancy outcome and known status of the infant following 8 weeks of delivery, the investigator will complete the applicable pregnancy report forms [REDACTED] within 1 day of being notified.

## **7.5 Post Study Adverse Events**

### **7.5.1 Non-serious Adverse Events**

Adverse events that are identified at the last assessment visit (or the early termination visit) must be recorded on the AE eCRF with the status of the AE noted. These adverse events must be followed by the investigator until the events are resolved, events determined to be chronic or the subject is lost to follow-up. Resolution means the subject has returned to the baseline state of health, or the investigator does not expect any further improvement or worsening of the adverse event.

### **7.5.2 Serious Adverse Events**

Serious adverse events that are identified on the last assessment visit (or the early termination visit) must be recorded on the AE eCRF page and reported to Perrigo according to the procedures outlined above. Subjects with unresolved previously reported serious adverse events, or any new serious adverse events identified on the last assessment visit, should be followed by the investigator until the events are resolved, or the subject is lost to follow-up. Resolution means the subject has returned to the baseline state of health, or the investigator does not expect any further improvement or worsening of the adverse event. The investigator should continue to report any significant follow-up information to Perrigo up to the point that the event has resolved. Any serious adverse event reported by the subject to the investigator that occurs after the last assessment and are determined by the investigator to be reasonably associated with the use of the study drug, should be reported to Perrigo.

## **8 Statistical Analysis**

The sections that follow highlight sample size determination and the planned analyses for this study. A statistical analysis plan (SAP) will be prepared separately from this protocol which gives descriptions of the statistical methods, models, hypotheses and subject populations to be analyzed. The SAP will be completed and approved before locking the database and unblinding the study and will serve as a companion to the protocol and the *de facto* documentation of the proposed statistical evaluation. The SAP will be completed and finalized prior to breaking the blind.

### **8.1 Statistical Analysis Plan**

### 8.1.1 Analysis Populations

The following populations are defined for the purpose of analyses:

- Intent-to-Treat (ITT) (safety population): Any subject that was enrolled, randomized, received and used study medication.
- Per Protocol (PP): Any subject who:
  - met inclusion/exclusion criteria,
  - was randomized, received and used study medication,
  - [REDACTED]
  - completed 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
  - had no significant protocol violations that could have interfered with the administration of the treatment or the precise evaluation of treatment efficacy.

### 8.1.2 Planned Analysis

The safety analysis will be performed for the ITT subjects. The efficacy analysis will be conducted on the PP subjects. Two-sided hypothesis testing will be conducted. Resulting 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. SAS software will be used for all data analyses and tabulations.

The treatment response will be summarized by treatment group.

The primary efficacy endpoint will be the mean change from Baseline in intraocular pressure (IOP) of both eyes at four time points (e.g., at approximately 8:00 am (hour 0, before the morning drop) and 10:00 am (hour 2) at Visit 3/week 2/Day 14 ( $\pm 4$  days) and Visit 4/week 6/Day 42 ( $\pm 4$  days)

#### **8.1.4 Efficacy Measures and Analysis**

##### **Clinical endpoints**

The primary efficacy measure is the mean change from baseline in IOP of both eyes at four (4) time points (e.g., at approximately 8:00 am (hour 0, before the morning drop) and approximately at 10:00 am (hour 2) at Visit 3/week 2/Day 14 and Visit 4/Week 6/Day 42. The IOP at hour 0 (8:00 am) on Day 0 will serve as baseline for the IOP at hour 8:00am for Day 14 and Day 42, while the IOP at hour 2 (10:00am) on Day 0 will serve as baseline for the IOP at hour 10:00am for Days 14 and Day 42. The hypothesis testing for statistical bioequivalence at each of the four time points will be

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

### **8.1.5 Safety and Adverse Events Analysis**

The frequency and percent of subjects with adverse events will be summarized by MedDRA system organ class and preferred term and by severity and relationship to study drug for all treatment groups.

[REDACTED] comparable safety of the Test and Reference treatments will be evaluated by statistical comparison of the proportion of subjects who reported any adverse events. Safety comparisons will be performed only for the safety intent-to-treat population.

### **8.2 Comparability of Subjects at Baseline**

Descriptive statistics will be presented, by treatment group, for subject baseline characteristics. The significance of any obvious treatment group differences will be discussed in the CSR.

## **9 CONSENT/ASSENT CONSIDERATIONS AND PROCEDURES**

It will be made clear to the subject that, for the purposes of the study, they are consenting only for ophthalmic application of test or reference product. Investigators may discuss the availability of the study and the possibility for entry with a potential subject without first obtaining consent/assent. However, informed consent/assent must be obtained and documented prior to initiation of any procedures that are performed solely for the purpose of determining eligibility for research, including withdrawal from current medication(s). When this is done in anticipation of, or in preparation for, the research, it is considered to be part of the research.

The study must be approved in writing by an appropriate IRB as defined by FDA regulations. A copy of the Letter of Approval from the IRB, which also contains specific identification of the documents approved, must be received by Perrigo, prior to study commencement.

Periodic status reports must be submitted to the IRB at least annually as required by the site's IRB, as well as notification of completion of the study and a final report within three months of study completion or termination. A copy of all reports submitted to the IRB must be sent to Perrigo.

The investigator(s) has both ethical and legal responsibility to ensure that each subject being considered for inclusion in this study is given a full explanation of the protocol. This shall be

documented on a written informed consent/assent form, which shall be approved by the same Institutional Review Board (IRB) responsible for approval of this protocol. Each informed consent/assent form shall include the elements required by FDA regulations in 21 CFR Part 50. The investigator agrees to obtain approval from Perrigo of any written informed consent/assent form used in the study, preferably prior to submission to the IRB.

Once the appropriate essential information has been provided to the subject and fully explained by the investigators (or a qualified designee) and it is felt that the subject understands the implications of participating and had the opportunity to have all questions answered, the IRB-approved written informed consent/assent form shall be signed by the subject (or their parent/legally authorized representative) and the person obtaining consent/assent (investigator or designee). The subject shall be given a copy of the signed informed consent/assent form and the investigator shall keep the original on file.

If the subject fails to meet the inclusion/exclusion criteria at the conclusion of the screening phase, the subject will be withdrawn from study participation. In the event, that the subject is re-screened for study participation, thirty days (30) or more beyond the initial screening, a new informed consent/assent form must be signed.

### **9.1 Subject Confidentiality**

All participants are concerned for the individual subject's privacy and, therefore, all subject data will be identified only by a subject identification number and subject initials. However, in compliance with federal guidelines regarding the monitoring of clinical studies and in fulfillment of his/her obligations to Perrigo, it is required that the investigator permit the study monitor, any Perrigo authorized representative, and/or FDA representative to review that portion of the subject's medical record that is directly related to the study. This shall include all study relevant documentation including subject medical histories to verify eligibility, laboratory test result reports to verify transcription accuracy, admission/discharge summaries for hospital stays occurring while the subject is enrolled in the study and autopsy reports for deaths occurring during the study.

As part of the required content of informed consent, the subject must be informed that his/her medical chart may be reviewed by Perrigo or their authorized representative, or a representative of the FDA. Should access to the medical record require a separate waiver or authorization, it is the investigator's responsibility to obtain such permission from the subject in writing before the subject is entered into the study.

To preserve the subject's confidentiality, the data collected will be available only to the investigators of the study, their support staff, Perrigo or their authorized representative and possibly the FDA.

All reports and communications relating to the subject in the study will identify each subject only by the subject's initials and by the subject number. The investigator agrees to furnish Perrigo with complete subject identification, if necessary on a confidential follow-up form, which will be used for the purpose of a long-term follow-up, if needed. This will be treated with strict adherence to

professional standards of confidentiality and will be filed at Perrigo under adequate security and restricted accessibility.

## **10 CONDUCT OF STUDY**

The investigational site is to maintain complete documentation of all events and the times at which they occur.

### **10.1 Completion of Study**

The investigational site will complete the study and complete all documentation required, in satisfactory compliance with the protocol, within 3.5 months of enrollment of the last subject and extending beyond as needed to complete necessary data queries.

It is agreed that, for reasonable cause, either the investigator or Perrigo may terminate this study before completion provided written notice is submitted at a reasonable time in advance of intended termination. Any extension of this study must be mutually agreed upon in writing by both the investigator and Perrigo.

### **10.2 Protocol Amendments**

The Investigator will not make any changes to this protocol without prior written consent from Perrigo and subsequent approval by the IRB. Any permanent change to the protocol, whether it is an overall change or a change for specific study center(s), must be handled as a protocol amendment. Any amendment to the protocol that appears indicated as the study progresses will be fully discussed between Symbio LLC and Perrigo. If agreement is reached regarding the need for an amendment, the amendment will be written by Perrigo. The written amendment must be submitted to the chairman of the IRB identified with this responsibility. Except for 'administrative amendments', investigators must await IRB approval of protocol amendments before implementing the change(s). Administrative amendments are defined to have no effect on the safety of the research subjects, scope of the investigation, or quality of the trial. However, a protocol change intended to eliminate an apparent immediate hazard to subjects should be implemented immediately, and the IRB notified within five days. Perrigo will submit protocol amendments to the FDA or other regulatory agencies.

When, in the judgment of the reviewing IRB, the investigators and/or Perrigo, the amendment to the protocol substantially alters the study design and/or increases the potential risk to the subject, the currently approved written informed consent form will require similar modification. In such cases, repeat informed consent will be obtained from subjects enrolled in the study before expecting continued participation.

### **10.3 COVID-19 Risk Mitigation**

The study center will use risk mitigation to prevent COVID-19 spread. Processes and procedures implemented will be in accordance with guidelines and recommendations issued by World Health Organization (WHO), Centers for Disease Control (CDC), local, federal and Investigator guidelines. Such guidelines shall include pre-screening procedures including questionnaires pertaining to

symptoms of and exposure to COVID-19, encouragement of hand washing and sanitizing, staff use of personal protective equipment (PPE), subjects' and staff use of masks, cleaning and disinfecting procedures of equipment and furniture, and social distancing in the study unit.

#### **10.4 Alternative protocol assessments during the COVID-19 Pandemic only**

To mitigate any risks that may occur due to the COVID-19 pandemic that might impact the conduct of the trial, the following may be considered if a site is not able to participate at full capacity or on-site subject participation is compromised due to local regulations caused by COVID-19 restrictions (e.g., temporary site closures, subjects unable to complete on-site visit):

- Sites may be placed on a temporary enrollment hold.
- Remote monitoring visits may be conducted.

##### **10.4.1 Subject Disposition due to COVID-19 Infection**

If a subject is confirmed to have tested positive for COVID-19, the investigator will be instructed to record the event as an AE or SAE. The subjects should further be immediately discontinued from study medication and study participation and instructed to quarantine.

##### **10.4.2 Regulatory and Study Oversight Considerations**

Remote monitoring may be substituted for physical visits to the site(s) in the event that the CRA or Sites are not able to conduct an on-site visit due to site closure, local or federal guidelines, or safety guidelines in relation to COVID-19.

##### **10.4.3 Documentation of Protocol Deviations related to COVID-19**

All protocol violations and protocol deviations (PV/PD) that occur as a result of the COVID-19 pandemic should be documented in the source documents as PV/PDs specifically occurring due to the COVID-19 pandemic. As much as possible, detailed reasons for the PV/PD (e.g., subject is ill, site closed, subject unable to travel to site) should be included in the source documents, including any procedures/activities not undertaken or visits missed as a result of COVID-19. All protocol deviations and AEs impacted by COVID-19 will be documented in the COVID-19 eCRF form.

## **11 RECORDS MANAGEMENT**

### **11.1 Data Collection**

Database set-up will be performed [REDACTED] in collaboration with the Electronic Data Capture (EDC) vendor, using an appropriate fully validated, 21 CFR Part 11 compliant EDC system. eCRFs will be provided to each site via a secured web link. All applicable study data collected on each subject will be recorded by approved site personnel into the eCRF. Only authorized site personnel will be able to enter/modify/correct data to the eCRF.

Approved staff at Symbio will verify all data entered into eCRFs for completeness and accuracy with reference to the source documents and records and will issue manual data queries to correct missing data or discrepancies found against the source within the EDC system.

Data validation will consist of automated and manual edit checks that are created directly into EDC. Automated edit checks will be executed on all data points defined and documented by the study team and data management. Study metrics will be reported from the EDC system.

After all data have been verified by approved staff at Symbio, an Investigator or Sub-Investigator (listed on Form FDA 1572) is required to review and approve all eCRFs prior to database lock and breaking of the blind.

After database lock, each site will be provided with a password protected USB that will include the eCRF data from their site for local archival purposes.

Quality assurance verification via a 10% database audit of eCRF data will be conducted before the treatment assignment code is broken.

During each subject's visit to the clinic, a designee participating in the study will record progress notes to document all significant observations. At a minimum, these notes will contain:

- a) Documentation of the informed consent process;
- b) The date of the visit and the corresponding Visit or Week in the study schedule;
- c) General subject status remarks, including any significant medical findings. The severity, frequency, and duration of any adverse events and the investigator's assessment of relationship to study medication must also be recorded.
- d) Any changes in concomitant medications or dosages;
- e) A general reference to the procedures completed; and
- f) The signature (or initials) and date of all clinicians who made an entry in the progress notes.

In addition, any contact with the subject via telephone or other means that provides significant clinical information will also be documented in the progress notes as described above.

Any changes to information in the study progress notes and other source documents, will be entered in **black or blue ink, initialed and dated** by the authorized person making the correction/addition. Changes will be made by striking a single line through erroneous data, and clearly entering the correct data. (e.g., ~~wrong data~~ right data). Entries may not be erased or masked with white-out fluid. If the reason for the change is not apparent, a brief explanation for the change will be written adjacent to the change by the clinician.

For transmission to Perrigo, information from the study progress notes and other source documents will be promptly entered into the database. The database also contains a complete audit trail to capture all regulatory components of data corrections (e.g. initial entry, new value, initials and date of the change).

## **11.2 Source Documents**

Source documents are defined as the results of original observations and activities of a clinical investigation. Source documents will include, but are not limited to, progress notes and screening logs. All source documents pertaining to this study will be maintained by the investigators and made available for inspection by authorized persons. The original signed informed consent/assent form for each participating subject shall be filed with records kept by the investigators and a copy given to the subject.

## **11.3 File Management at the Study Site**

It is the responsibility of the investigator to ensure that the study center file is maintained in accordance with Section 8 of the International Conference on Harmonization (ICH) Guideline for Good Clinical Practices (GCP).

## **11.4 Records Retention at the Study Site**

FDA regulations 21 CFR§312.57 require all investigators participating in clinical drug studies to maintain detailed clinical data for one of the following periods:

- a) A period of at least two years following the date on which a New Drug Application is approved by the FDA;
- b) A period of two years after Perrigo notifies the investigator that no further application is to be filed with the FDA.

The investigator must not dispose of any records relevant to this study without either (1) written permission from Perrigo or (2) providing an opportunity for Perrigo to collect such records. The investigator shall take responsibility for maintaining adequate and accurate electronic or hard copy source documents of all observations and data generated during this study. Such documentation is subject to inspection by Perrigo and Regulatory authorities such as the Food & Drug Administration.

# **12 QUALITY CONTROL AND QUALITY ASSURANCE**

## **12.1 Monitoring**

Perrigo has ethical, legal and scientific obligations to carefully follow this study in a detailed and orderly manner in accordance with established research principles and FDA regulations. All medical records (source documents) of the subjects participating in this study must be presented for review and verification of eCRFs.

## **12.2 Auditing**

Perrigo (or representative) may conduct audits at the study center(s). Audits will include, but are not be limited to, drug supply, presence of required documents, the informed consent process, and comparison of electronic case report forms with source documents. The investigator agrees to participate with audits conducted at a reasonable time in a reasonable manner.

Regulatory authorities worldwide may also audit the investigator during or after the study. The investigator should contact Perrigo immediately if notified of such an audit and must fully cooperate with the audits conducted at a reasonable time in a reasonable manner.

### **13 ETHICS AND RESPONSIBILITY**

This study must be conducted in compliance with the protocol, the United States Food and Drug Administration (FDA) regulations, any other countries regulations, and ICH GCP Guidelines.

### **14 USE OF INFORMATION AND PUBLICATION**

All information supplied by Perrigo in connection with this study and not previously published, is considered confidential information. This information includes, but is not limited to, data, materials (e.g., the clinical protocol, eCRFs), equipment, experience (whether of a scientific, technical, engineering, operational, or commercial nature), designs, specifications, know-how, product uses, processes, formulae, costs, financial data, marketing plans and direct selling systems, customer lists and technical and commercial information relating to customers or business projections used by Perrigo in its business. Any data, inventions, or discoveries collected or developed, as a result of this study is considered confidential. This confidential information shall remain the sole property of Perrigo, shall not be disclosed to any unauthorized person or used in any unauthorized manner without written consent of Perrigo, and shall not be used except in the performance of the study. As such, confidential study-related information should not be included on the curriculum vitae of any participating investigator or study staff.

The information developed during the course of this clinical study is also considered confidential and will be used by Perrigo in connection with the development of the drug. The information may be disclosed as deemed necessary by Perrigo to allow the use of the information derived from this clinical study, the investigator is obliged to provide Perrigo with complete test results and all data developed in the study. The information obtained during this study may be made available to other investigators who are conducting similar studies.

The investigator shall not make any publication related to this study without the express written permission of Perrigo.



## 15 INVESTIGATOR AGREEMENT

PROTOCOL NUMBER: PRG-NY-20-002

PROTOCOL TITLE:

A Multi-Center, Double-Masked, Randomized, Active-Controlled, 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

I have carefully read the foregoing protocol and agree that it contains all the necessary information for conducting this study safely. I will conduct this study in strict accordance with this protocol, ICH Guidelines for Good Clinical Practices, the Code of Federal Regulations, the Health Insurance Portability and Accountability Act (HIPAA) and any local regulatory requirements and will attempt to complete the study within the time designated. I will provide access to copies of the protocol and all other information relating to pre-clinical and prior clinical experience submitted by Perrigo to all personnel responsible to me who participate in the study. I will discuss this information with them to assure that they are adequately informed regarding the drug and conduct of the study. I agree to keep records on all subject information in accordance with FDA regulations.

---

Principal Investigator's Printed Name

---

Principal Investigator's Signature

---

Date

## 16 APPENDICES

## 16.1 Appendix A: Study Personnel Contacts

A large black rectangular redaction box covers the majority of the page content, from approximately [113, 111] to [886, 300].

1

A small black square icon, likely a placeholder or a logo.

10

## 16.2 Appendix B: Instructions for the Subject

### Check Visit Dispensed:

Visit 2:  Visit 3:  Unscheduled visit:  Date: \_\_\_\_\_

SUBJECT INITIALS: \_\_\_\_\_ SUBJECT NUMBER: \_\_\_\_\_

SITE NUMBER: \_\_\_\_\_

1. Your doctor has given you the study medication, for your use in the study. Store the study medication at temperature 2°C-25°C (36°F-77°F) in a secured area and bottles must be kept in an upright position and tightly closed. Keep this and all medications out of the reach of children. Keep the study medication bottle tightly closed, protect it from light and heat. For ophthalmic use only. Not for oral, topical, or intranasal use.

A 2D grayscale heatmap showing a complex, multi-layered structure. The image is mostly black, with several horizontal white bands of varying widths and positions. There are also vertical white lines and small white spots scattered across the dark background.

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

Page 63 of 66





You are scheduled to return at:

\_\_\_\_\_ on \_\_\_\_\_ (Visit 3, Study Week 2)  
(Time) (Date)

\_\_\_\_\_ on \_\_\_\_\_ (Visit 4, Study Week 6)  
(Time) (Date)

**ALL APPOINTMENTS ARE IMPORTANT! IF YOU NEED TO RE-SCHEDULE YOUR APPOINTMENT,  
PLEASE CALL YOUR STUDY DOCTOR'S OFFICE IMMEDIATELY.**

---

Name and Telephone Number of Study Coordinator/Study Site

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

PRG-NY-20-002 Brinzolamide and Brimonidine Tartrate 1%/0.2% Ophthalmic Suspension  
[REDACTED] Page 66 of 66