

## 1. TITLE PAGE

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**Study Title:** A Multi-Center, Randomized, Double Masked, Placebo Controlled Clinical Study to Assess the Safety and Efficacy of BRM421 Ophthalmic Solution in Subjects With Dry Eye Using a Controlled Adverse Environment (CAE®) Model

**Investigational Product:** BRM421 Ophthalmic Solution

**Indication Studied:** Dry Eye Syndrome (DES)

**Brief Description:** This is a multi-center, double-masked, randomized, vehicle-controlled, phase 2/3 CAE study in approximately 200 subjects. (100 per treatment arm).

**Name of the Sponsor:** BRIM Biotechnology, Inc.  
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Taiwan, Republic of China

**Protocol Identification:** BRM421-18-C001-PR

**Development Phase:** 2/3

**Study Initiated:** January 15, 2020

**Study Completed:** June 23, 2020

**NCT number:** NCT04343287

**Document Date** IRB approval on December 10 2019

**Date of Report:** December 30 2020

Statement of Compliance with  
Good Clinical Practice

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**This study was performed in compliance with the ethical principles of the Declaration of Helsinki and the International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline for Good Clinical Practice (GCP).  
Confidentiality Statement**

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## **2. TABLE OF CONTENTS**

<b>1. TITLE PAGE.....</b>	<b>1</b>
<b>2. TABLE OF CONTENTS.....</b>	<b>2</b>
<b>3. STUDY PROTOCOL.....</b>	<b>3</b>
<b>4. STATISTICAL ANALYSIS PLAN.....</b>	<b>3</b>

### **3. STUDY PROTOCOL**

This was a multi-center, double-masked (participants and research team), randomized, placebo-controlled, phase 2/3 study conducted between January 2020 and June 2020 at 4 sites in the United States (Total Eye Care, Andover Eye Associates, Eye Research Foundation and Midwest Cornea Associates, LLC). This study (ClinicalTrials.gov identifier: NCT04343287) was performed in compliance with the ethical principles of the Declaration of Helsinki and the International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline for good clinical practice (GCP). Institutional Review Board (IRB)/Ethics Committee approval was obtained. All potential subjects provided written informed consent before screening.

After the screening visit, eligible subjects entered a one-week run-in period to receive preservative-free placebo solution bilaterally three times daily (TID) to minimize the placebo effect. Subjects that exhibited improvements in symptoms of dry eye syndrome (DES) at the end of the run-in period, relative to screening values, were disqualified. Eligible subjects were subsequently randomized in a 1:1 ratio to receive placebo or BRM421 Ophthalmic Solution three times daily (TID) in each eye for total 2 weeks, and the efficacy and safety assessments were performed at 1 and 2 weeks after treatment.

### **4. STATISTICAL ANALYSIS PLAN**

The primary efficacy analyses, including FCS and ODS dryness, were performed using the last observation carried forward (LOCF) imputation method of the intent-to-treat (ITT) population at week 2 for missing values. The treatment effect in each group was calculated by change from baseline in pre-controlled adverse environment (CAE) mode.

The difference from baseline in pre-CAE values for active treatment was tested versus placebo using a two-way ANCOVA model adjusting for baseline at  $\alpha = 0.05$ . A Wilcoxon rank sum test and a two-sample *t*-test were also assessed where appropriate.

The continuous and ordinal secondary efficacy variables were analyzed with an ANCOVA model adjusting for baseline and also evaluated with a two-sample *t*-test comparing active treatment to placebo. No imputation was performed for secondary efficacy variables.