1. TITLE PAGE

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 CAE study in approximately 150 subjects. (75 per treatment arm).
Name of the Sponsor:	BRIM Biotechnology, Inc. 8F, No. 1, Alley 30, Lane 358, Ruiguang Rd. Neihu District, Taipei 11492 Taiwan, Republic of China
Protocol Identification:	BRM421-16-C001-PR amendment 1,03 February 2017
Development Phase:	2
Study Initiated:	07 February 2017 (first subject first visit)
Study Completed:	20 May 2017 (last subject last visit)
NCT number:	NCT03066219
Document Date	IRB approval on 06 February 2017
Date of Report:	11 September 2019

Statement of Compliance with Good Clinical Practice

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

2. TABLE OF CONTENTS

3. STUDY PROTOCOL

This was a multi-center, double-masked (participants and research team), randomized, placebo-controlled, phase 2 study conducted between February 2017 and May 2017 at 2 sites in the United States (Andover Eye Associates and Central Maine Eye Care). This study (ClinicalTrials.gov identifier: NCT03066219) 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 4 weeks, and the efficacy and safety assessments were performed at 1, 2 and 4 weeks after treatment.

4. STATISTICAL ANALYSIS PLAN

The primary efficacy analyses, including FCS and ocular discomfort score, were performed using the last observation carried forward (LOCF) imputation method of the intent-to-treat (ITT) population at week 4 for missing values. The treatment effect in each group was calculated by change from baseline in pre- to post-controlled adverse environment (CAE) mode.

The difference from baseline in pre- to post-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.

All analyses were performed using SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA).