This report may include approved and non-approved uses, formulations, or treatment regimens. The results reported may not reflect the overall profile of a product. Before prescribing any product mentioned in this report, healthcare professionals should consult local prescribing information for the product approved in their country.

SPONSOR is committed to publicly disclosing all medical research results that are significant to patients, health care providers or payers—whether favorable or unfavorable to the SPONSOR product—in an accurate, objective and balanced manner in order for our customers to make more informed decisions about our products.

Personally identifiable information (PII) within this document is either removed or redacted (i.e., specific content is masked irreversibly from view with a black bar) to protect personal privacy. Personally identifiable information includes:

- All named persons associated with the study
- Patient identifiers within text, tables, or figures
- By-patient data listings

Anonymized patient data may be made available subject to an approved research proposal submitted. Information which is considered intellectual property or company confidential was also redacted.
# STUDY SYNOPSIS

<table>
<thead>
<tr>
<th><strong>Name of sponsor/company:</strong></th>
<th>SARcode Bioscience, Inc.</th>
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<tr>
<td><strong>Name of finished product:</strong></td>
<td>Lifitegrast 5.0% ophthalmic solution</td>
</tr>
<tr>
<td><strong>Name of active ingredient:</strong></td>
<td>(S)—2—(2—benzofuran—6—carbonyl)—5,7—dichloro—1,2,3,4—tetrahydroisoquinoline—6—carboxamido)—3—(3—(methylsulfonyl)phenyl) propanoic acid</td>
</tr>
<tr>
<td><strong>Title of the study:</strong></td>
<td>A Phase 3, Multicenter, Randomized, Double–Masked and Placebo–Controlled Study Evaluating the Safety of a 5.0% Concentration of Lifitegrast Ophthalmic Solution Compared to Placebo in Subjects with Dry Eye (SONATA)</td>
</tr>
<tr>
<td><strong>Investigator(s):</strong></td>
<td>This was a multicenter study; no coordinating principal investigator was appointed.</td>
</tr>
<tr>
<td><strong>Study center(s):</strong></td>
<td>There were a total of 22 sites in the United States.</td>
</tr>
<tr>
<td><strong>Publications (references):</strong></td>
<td>None.</td>
</tr>
<tr>
<td><strong>Study period:</strong></td>
<td>16 Oct 2012 to 03 Mar 2014 (First subject’s consent to last subject’s last protocol-defined assessment)</td>
</tr>
<tr>
<td><strong>Phase of development:</strong></td>
<td>Phase 3</td>
</tr>
<tr>
<td><strong>Objectives:</strong></td>
<td>The primary objective of the study was:</td>
</tr>
<tr>
<td></td>
<td>• To evaluate the safety of lifitegrast ophthalmic solution (5.0%) compared to placebo in the treatment of dry eye as assessed by ocular and non-ocular adverse events (AEs) when administered twice daily for 360 days (approximately 1 year).</td>
</tr>
<tr>
<td></td>
<td>The secondary objective of the study was:</td>
</tr>
<tr>
<td></td>
<td>• To evaluate the ocular safety measures of lifitegrast ophthalmic solution (5.0%) compared to placebo in subjects with dry eye when administered twice daily for 360 days (approximately 1 year).</td>
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Name of active ingredient: (S)–2–(2–benzofuran–6–carbonyl)–5,7–dichloro–1,2,3,4–tetrahydroisoquinoline–6–carboxamido)–3–(3–(methylsulfonyl)phenyl) propanoic acid

Objectives (continued):
The exploratory objectives of the study were:

- To assess clinical laboratory values (hematologic, renal, and liver panels) at Visit 1 (Day -7, Week -1) (baseline for safety clinical laboratory tests on all subjects who met entrance criteria), Visit 5 (Day 180, Month 6), and Visit 7 (Day 360, Month 12) comparing subjects assigned to lifitegrast (5.0%) to placebo in approximately 25% (N=75) of study subjects

- To assess the concentration of lifitegrast in plasma at Visit 2 (Day 0, Month 0) (baseline for lifitegrast levels), Visit 5 (Day 180, Month 6), and Visit 7 (Day 360, Month 12) in subjects assigned to lifitegrast (5.0%) in approximately 25% (N=75) of study subjects

- To assess CD3, CD4, and CD8 lymphocyte counts in whole blood at Visit 2 (Day 0, Month 0) (baseline for lymphocyte counts), Visit 5 (Day 180, Month 6), and Visit 7 (Day 360, Month 12) comparing subjects assigned to lifitegrast (5.0%) to placebo in approximately 25% (N=75) of study subjects

- To assess corneal endothelial cell counts (specular microscopy) at Visit 2 (Day 0, Month 0) (baseline for corneal endothelial cell counts), Visit 5 (Day 180, Month 6), and Visit 7 (Day 360, Month 12) comparing subjects assigned to lifitegrast (5.0%) to placebo in approximately 60% (N=180) of study subjects

- To evaluate AEs in subjects using lifitegrast in conjunction with other topical eye drops including artificial tears, steroids, mast cell stabilizers, and/or antihistamines

- To evaluate AEs in subjects using lifitegrast in conjunction with contact lenses.

Methodology:
This was a Phase 3, multicenter, randomized, prospective, double-masked, placebo-controlled, parallel-arm study conducted in the United States. Approximately 300 subjects with dry eye were planned to be randomized (2:1; lifitegrast:placebo) to receive either lifitegrast ophthalmic solution (5.0%) or placebo solution as topical ophthalmic drops administered bilaterally twice daily for 360 days (approximately 1 year).
**Name of sponsor/company:** SARcode Bioscience, Inc.

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**Number of subjects (planned and analyzed):**

Approximately 300 subjects were planned to be randomized in a 2:1 ratio (lifitegrast:placebo). The number of subjects in each analysis population was as follows:

<table>
<thead>
<tr>
<th></th>
<th>Placebo n (%)</th>
<th>Lifitegrast n (%)</th>
<th>Total n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screened subjects a</td>
<td></td>
<td></td>
<td>504</td>
</tr>
<tr>
<td>Randomized Population</td>
<td>111</td>
<td>221</td>
<td>332</td>
</tr>
<tr>
<td>Safety Population b</td>
<td>111 (100.0)</td>
<td>220 (99.5) c</td>
<td>331 (99.7)</td>
</tr>
<tr>
<td>Completed study b</td>
<td>92 (82.9)</td>
<td>170 (76.9)</td>
<td>262 (78.9)</td>
</tr>
<tr>
<td>Withdrew from study b</td>
<td>19 (17.1)</td>
<td>51 (23.1)</td>
<td>70 (21.1)</td>
</tr>
</tbody>
</table>

a Number may reflect multiple screenings for the same subject.

b Percentages based on Randomized Population.

d

**Diagnosis and main criteria for inclusion:**

- Male or female, at least 18 years of age at the time of enrollment, with a subject-reported history of dry eye in both eyes
- Use and/or desire to use artificial tear substitute for symptoms of dry eye within past 6 months
- Best corrected visual acuity of 0.7 minimum angle of resolution or better (Snellen equivalent score of 20/100 or better) in each eye using a refraction within 6 months prior to Visit 1 (Day -7, Week -1)
- Corneal fluorescein staining score \(\geq 2.0\) (0-4 point scale) in at least 1 region in either eye at both Visits 1 and 2 (Days -7 and 0, Weeks -1 and 0)
- Visual analogue scale score \(\geq 40\) in either symptom of eye dryness or discomfort at Visit 1 (Day -7, Week -1)
- Schirmer Tear Test (without anesthesia) \(\geq 1\) and \(\leq 10\)mm in either eye at Visit 1 (Day -7, Week -1)
- Subjects with secondary Sjögren’s syndrome or other autoimmune diseases were eligible for enrollment consideration provided the subject met all other inclusion and exclusion criteria, AND, were not in a medical state – in the opinion of the principal investigator – that could have interfered with study parameters, were not taking systemic steroids, and were not immunodeficient/immunosuppressed
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**Diagnosis and main criteria for inclusion (continued):**

- Subjects who electively used contact lenses may have participated in the study provided they:
  - Had corrective eyeglasses (required for ALL visits including Visit 1 [Day -7, Week -1]); refraction should have been no older than 6 months prior to Visit 1 (Day -7, Week -1)
  - Were not required to use contact lenses for medical reasons
  - Could refrain from contact lens use from Visit 1 (Day -7, Week -1) until after Visit 3 (Day 14, Week 2) assessments were complete, and not within 15 minutes after investigational product administration throughout the remainder of the study
  - Had the contact lenses fitted >90 days prior to enrollment
  - Had no ongoing medical problems with the comfort or fit of the contact lenses
  - Did not anticipate any change in contact lenses or corrective eyeglasses in the next 12 months
  - Used only daily disposable lenses for this study.
- No ocular condition that, in the opinion of the investigator, could have affected study parameters
- No use of any topical medication and/or antibiotics for the treatment of blepharitis or meibomian gland disease
- No active or history of ocular herpes; any other ocular infection within the last 30 days
- No history of laser-assisted in situ keratomileusis or similar type of corneal refractive surgery within 12 months prior to Visit 1 (Day -7, Week -1), and/or any other ocular surgical procedure within 12 months prior to Visit 1 (Day -7, Week -1); or any scheduled ocular surgical procedure to be conducted during the study period
- No history of yttrium aluminum garnet laser capsulotomy within 6 months prior to Visit 1 (Day -7, Week -1)
- Subjects with dry eye secondary to scarring or destruction of conjunctival goblet cells were not eligible for the study. Subjects with incidental scars secondary to refractory surgery that in the opinion of the principal investigator would not interfere with study compliance and/or outcome measures were not excluded from the study.

**Investigational product, dose, mode of administration, and batch number(s):**

Lifitegrast 5.0% ophthalmic solution was administered twice daily to the ocular surface as a single eye drop in both eyes. The batch number for lifitegrast was [redacted].
**Name of sponsor/company:**
SARcode Bioscience, Inc.

**Name of finished product:**
Lifitegrast 5.0% ophthalmic solution

**Name of active ingredient:**
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**Reference product(s), dose, mode of administration, and batch number(s):**
Placebo ophthalmic solution was administered twice daily to the ocular surface as a single eye drop in both eyes. The batch numbers for placebo were [redacted] and [redacted]

**Duration of treatment:**
The Screening Period was approximately 7 days and the Treatment Period was 360 days.

**Criteria for evaluation:**
The trough concentration of lifitegrast in plasma was assessed at Visits 2, 5, and 7 (Days 0, 180, and 360; Months 0, 6, and 12) in approximately 25% of subjects (N=75).

No efficacy assessments were performed.

The following safety measurements were collected:
- Adverse events (ocular and non-ocular) (all visits)
- Clinical laboratory measurements (all subjects at Visit 1 [Day -7, Week -1]; approximately 25% of subjects at Visits 5 and 7 [Days 180 and 360, Months 6 and 12])
- Corneal fluorescein staining (all visits)
- Drop comfort (Visits 2-7 [Days 0-360, Months 0-12])
- Best corrected visual acuity (all visits)
- Slit lamp biomicroscopy (all visits)
- Dilated fundoscopy (Visits 1, 5, and 7 [Days -7, 180, and 360; Week -1, Months 6 and 12])
- Intraocular pressure (Visits 1, 5, and 7 [Days -7, 180, and 360; Week -1, Months 6 and 12])
- Lymphocyte counts (25% of subjects at Visits 2, 5, and 7 [Days 0, 180, and 360; Months 0, 6, and 12])
- Corneal endothelial cell counts (approximately 60% of subjects at Visits 2, 5, and 7 [Days 0, 180, and 360; Months 0, 6, and 12]).
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**Individual Study Table Referring to Part of the Dossier**

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**Volume:**

**Page:**

**Statistical methods:**

The Randomized Population included all randomized subjects. The Safety Population included all randomized subjects who received at least 1 dose of investigational product.

The study sample size was based on guidance provided by the United States Food and Drug Administration and is consistent with the International Conference on Harmonisation Guidance E1A on exposure for drugs intended for long-term treatment of non-life-threatening conditions. The sample size was not based on statistical calculations or statistical assumptions.

The primary safety assessment was based upon the percentage and severity of ocular and non-ocular treatment-emergent AEs (TEAEs). Adverse events were classified by the investigator as ocular (right eye, left eye, both) or non-ocular. Statistical analyses were descriptive in nature.

The secondary analyses consisted of a descriptive summary of safety measures (corneal fluorescein staining, best corrected visual acuity, slit lamp biomicroscopy, drop comfort, intraocular pressure, and dilated fundoscopy) by treatment at all measured time points.

The exploratory analyses consisted of descriptive statistics by treatment group produced for each of the following exploratory endpoints:

- Clinical laboratory values (all subjects at Visit 1 [Day -7, Week -1]; approximately 25% of subjects at Visits 5 and 7 [Days 180 and 360, Months 6 and 12])
- Concentration of lifitegrast in plasma (approximately 25% of subjects)
- Lymphocyte counts (CD3, CD4, and CD8) (approximately 25% of subjects)
- Corneal endothelial cell counts (approximately 60% of subjects)
- Use of artificial tears, topical ophthalmic steroids, topical antiallergy agents (mast cell stabilizers/antihistamines), and contact lenses for the purpose of evaluating AEs for subjects using these products.

**Results:**

**Pharmacokinetic results:**

There was no evidence of accumulation of lifitegrast in plasma over time; the mean trough concentration of lifitegrast in plasma was below the lower limit of quantification (0.500ng/mL) at Days 0, 180, and 360 (Months 0, 6, and 12; Visits 2, 5, and 7).
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**Safety results:**

Lifitegrast was generally well tolerated. The observed safety profile demonstrated no pattern of AEs suggesting systemic toxicities or localized infectious complications due to chronic immunosuppression.

The lifitegrast group had a higher percentage of subjects with ocular TEAEs (53.6%) than the placebo group (34.2%), the majority of which were administration site TEAEs. The most common (>5%) TEAEs occurring in either treatment group were:

**Ocular:**
- Instillation site irritation (lifitegrast: 15.0%; placebo: 4.5%)
- Instillation site reaction (lifitegrast: 13.2%; placebo: 1.8%)
- Visual acuity reduced (lifitegrast: 11.4%; placebo: 6.3%)
- Dry eye (lifitegrast: 1.8%; placebo: 5.4%)

**Non-ocular:**
- Dysgeusia (lifitegrast: 16.4%; placebo: 1.8%)

The lifitegrast group had a higher frequency of subjects with ocular and non-ocular TEAEs considered probably related to the investigational product (26.4% and 15.9%, respectively) than the placebo group (6.3% and 2.7%, respectively). The frequency of subjects with ocular and non-ocular TEAEs considered not related or possibly related to the investigational product was similar between treatment groups. Most of the ocular and non-ocular TEAEs in both treatment groups were mild to moderate in severity.

One subject had a serious, non-ocular TEAE (arrhythmia) that resulted in death. There were no serious ocular TEAEs. Discontinuations due to TEAEs were infrequent (lifitegrast: 12.3%; placebo: 9.0%). The most common TEAEs that led to discontinuation were increased lacrimation, instillation site irritation, instillation site reaction, and dysgeusia.
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Safety results (continued):

After Visit 3 (Day 14, Week 2), subjects could have used artificial tears, topical ophthalmic or nasal steroids, antihistamines, mast cell stabilizers, and contact lenses as needed. Subjects in both treatment groups who used artificial tears had a higher frequency of TEAEs (placebo: 65.1%; lifitegrast: 85.9%) than subjects who did not use artificial tears (placebo: 41.8%; lifitegrast: 64.9%). Subjects who used artificial tears had a low rate of discontinuation due to TEAEs (placebo: 0%; lifitegrast: 3.1%). Few subjects used topical ophthalmic or nasal steroids, antihistamines, or mast cell stabilizers. Due to the small number of subjects who used topical ophthalmic or nasal steroids (placebo: 5 subjects; lifitegrast: 13 subjects), antihistamines or mast cell stabilizers (placebo: 5 subjects; lifitegrast: 10 subjects), and contact lenses (placebo: 4 subjects; lifitegrast: 5 subjects), no TEAE trends can be established. Within the subgroups of subjects who used artificial tears, topical ophthalmic or nasal steroids, antihistamines, mast cell stabilizers, and contact lenses, there were no trends signaling unique safety concerns between the 2 subgroups; the AE profile is consistent with that of the overall study population.

The other ocular safety parameters (corneal fluorescein staining, best corrected visual acuity, slit lamp biomicroscopy, dilated fundoscopy, intraocular pressure, and drop comfort) were comparable between the lifitegrast and placebo groups. Numerical improvements in drop comfort were observed over time in both treatment groups, but the lifitegrast group had consistently higher drop comfort scores (indicating a higher level of discomfort) than the placebo group.

In the hematologic, renal, and liver panels, the changes from baseline (Day -7, Week -1, Visit 1) to Days 180 and 360 (Months 6 and 12, Visits 5 and 7) were minimal and similar between treatment groups for all parameters.

The mean changes from baseline (Day 0, Month 0, Visit 2) to Days 180 and 360 (Months 6 and 12, Visits 5 and 7) in CD3, CD4, and CD8 counts were minimal and similar between treatment groups. The placebo group had slight numerical mean decreases and the lifitegrast group had slight numerical mean increases from Day 0 (Month 0, Visit 2) to Days 180 and 360 (Months 6 and 12, Visits 5 and 7) in corneal endothelial cell counts.

Revised 18 Mar 2015
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**Conclusions:**

This section contained Summary and Conclusion information which could be considered promotional in nature. This section has been removed to allow the reader to draw their own conclusions.

**Date of report:** 15 Jul 2014, Version 1.0