LIFITEGRAST 5% FOR THE TREATMENT OF DRY EYE IN HABITUAL SOFT CONTACT LENS WEARERS

Principal Investigator: Danielle Iacono, OD, FAAO
Version Number: v.5.0
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V5.0 PROTOCOL CHANGE SUMMARY	
Control Treatment	Changed from single use vials of Systane Original Preservative Free artificial tears to lifitegrast vehicle.
Randomization and Masking	Changed to explain labeling on lifitegrast vs vehicle.
Minor Formatting Changes	Minor changes for clarification.
V4.0 PROTOCOL CHANGE SUMMARY	
Adverse Events	Edited to add detail to adverse events section.
V3.0 PROTOCOL CHANGE SUMMARY	
Sponsor	Clarified that Novartis is not the sponsor of the study, but rather providing drug and budget.
Study Duration	Clarified Study Timeline
Control Treatment	Changed from lifitegrast vehicle to single use vials of Systane Original Preservative Free artificial tears.
Overall Design	Added language to require subjects who are currently using reusable contact lenses to use Clear Care solution to clean and disinfect the lenses.
Eligibility Criteria	Added Inclusion 10: Subjects currently wearing reusable contact lenses must be willing to use Clear Care solution for cleaning and disinfecting throughout the study.
	Added Exclusion 11: Punctal plug insertion in the last 3 months, or presence of punctal plugs at the time of the exam.
Randomization	Edited to include information regarding updated randomization method.
Sample Size Justification	Updated sample size justification
Statistics	Updated statistical methods.
Grammatical /Formatting Edits	Minor grammatical/ formatting changes to clarify content.
V2.0 PROTOCOL CHANGE SUMMARY	
Sponsor	Changed from Shire Human Genetic Therapies, Inc. to Novartis Pharmaceuticals Corporation.
Control Treatment	Changed from single use vials of preservative free artificial tears to lifitegrast vehicle.
Masking	Changed wording from “branding” to “any labeling” in relation to how masking will be maintained.
Study Procedures	Added Monocular High Contrast, High Luminance Visual Acuity to each visit.
Inclusion Criteria	Clarified Inclusion 9 to specify that entrance Snellen visual acuity will be utilized to determine subject eligibility.

STATEMENT OF COMPLIANCE

This clinical trial will be conducted in accordance with the principles of The Declaration of Helsinki, and will follow GCP guidelines. The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. The study will be registered on clinicaltrials.gov.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	**Lifitegrast 5% for the Treatment of Dry Eye in Habitual Soft Contact Lens Wearers**
Principal Investigator:	**Danielle Iacono, OD**
Study Drug/ Budget Provided by:	**Novartis Pharmaceuticals Corporation**
Description of Study Intervention:	**This is a prospective, single site, randomized, double masked, comparator-controlled study designed to evaluate the efficacy of lifitegrast ophthalmic solution 5% in treating the symptoms of dry eye in soft contact lens (CL) wearers as compared to control. We hypothesize that there will be a significant improvement in dry eye symptoms in contact lens wearers using lifitegrast as compared to those being treated with control (lifitegrast vehicle).**
Objectives:	**Primary Outcome: To determine the efficacy of lifitegrast ophthalmic solution 5% in treating the symptoms of dry eye in contact lens wearers as measured by change in total score on the Contact Lens Dry Eye Questionnaire-8 (CLDEQ-8) after 8 weeks of treatment.** **Secondary and Exploratory Outcomes:** **a. Change in tear osmolarity at 8 weeks in the lifitegrast 5% group compared to the control** **b. Forced choice questionnaire at week 8 asking if the participant felt that their symptoms improved to the point that they would continue treatment outside of the study** **c. Change in total score on the CLDEQ- 8 at 2 weeks and 4 weeks** **d. Trends in responses to individual questions**
Estimated duration from FPFV to Study Report:	**14 months**
Participant Duration:	**Visit 1: Day 0 (Baseline Visit)** **Visit 2: Week 2** **Visit 3: Week 4** **Visit 4: Week 8**

2 STUDY DESIGN

2.1 STUDY RATIONALE

Dry eye disease (DED) is commonly encountered as part of clinical practice. It has been estimated that more than 16 million adults in the United States have diagnosed DED.[1] DED is defined as "a multifactorial disease of the ocular surface characterized by loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles."[2] DED can be associated with or induced by the use of contact lenses.[2] Changes to the tear film in contact lens (CL) wearers with dry eye include a thinner lipid layer, tear film instability, lower basal tear turnover rate and decreased tear meniscus volume.[2]

Lifitegrast ophthalmic solution 5% is an anti-inflammatory drug approved to treat both the signs and symptoms of DED. It acts as a lymphocyte function associated antigen-1 antagonist (LFA-1). This allows for inhibition of T-cell adhesion, migration and proliferation.[3] This study will seek to determine if using lifitegrast ophthalmic solution 5% will help improve dry eye symptoms in subjects who are existing habitual soft CL wearers as compared to control (lifitegrast vehicle).

The Contact Lens Dry Eye Questionnaire-8 (CLDEQ-8) will be utilized to establish baseline symptoms and to monitor for changes with treatment. This questionnaire has been validated to reflect subject opinion of soft CLs in clinical trials.[4] A score of greater than or equal to 12 has be shown to identify soft CL wearers who would benefit from management of their CL related symptoms, with a change of 3 identifying a clinically important difference on the CLDEQ-8 total score.[5] For this study, subjects must have a score of 12 or greater on at baseline in order to be eligible for participation.

2.2 OVERALL DESIGN

This is a prospective, single site, randomized, double masked, comparator-controlled study designed to evaluate the efficacy of lifitegrast ophthalmic solution 5% in treating the symptoms of dry eye in soft contact lens wearers as compared to control. We hypothesize that there will be a significant improvement in dry eye symptoms in contact lens wearers using lifitegrast 5% as compared to those being treated with control (lifitegrast vehicle).

Potential study candidates will sign an informed consent form prior to any clinical procedures or tests specific to the protocol are performed. All screening examination procedures will be performed by the investigator or trained personnel working under the investigator's supervision. Subjects will undergo examination to determine eligibility at the Baseline visit. A complete medical, ocular and medication history will be obtained. Subjects who elect to participate will complete the study as outlined in Section 2.4. Signs and symptoms will be evaluated at baseline, 2 weeks, 4 weeks and 8 weeks. All tests and measurements will be obtained in accordance with the procedures specified in this protocol.

If found to be eligible, subjects will be randomized in a 1:1 ratio to either the test product (lifitegrast 5%) or control (lifitegrast vehicle) arm. Subjects will be instructed to use the drops twice a day in each eye. Drops are to be instilled in the morning at least 15 minutes before CL insertion, and after CL removal in the evening.

Subjects who are currently using reusable contact lenses will be required to use Clear Care solution to clean and disinfect their lenses.

Subjects will be asked to return to each visit with all of the used and unused vials dispensed at the prior visit. Subject accountability will be assessed at each follow up visit by comparing the amount of used vials to the amount of expected days of use. Trends in compliance will be considered during analysis of study data.

2.2.1 OUTCOME MEASURES

The primary outcome measure is the efficacy of lifitegrast ophthalmic solution 5% in treating the symptoms of dry eye in contact lens wearers as measured by change in total score on the CLDEQ-8 after 8 weeks of treatment.

Secondary and exploratory outcomes include:

a. Change in tear osmolarity (measured via Tear Lab) at 8 weeks in the lifitegrast 5% group compared to the control
b. Forced choice questionnaire at week 8 asking if the participant felt that their symptoms improved to the point that they would continue treatment outside of the study
c. Change in total score on the CLDEQ-8 at 2 weeks and 4 weeks
d. Trends in responses to individual questions

2.3 RANDOMIZATION AND MASKING

The randomization schedule will be generated by a biostatistician using simple random sampling. Participants will be randomized within center at the first visit. After all baseline assessments are completed, the delegated unmasked study coordinator will refer to the randomization scheme to assign each subject to one of the two study arms. All study participants who are randomized into the study will comprise the intent-to-treat population. Participants will be randomized into 1 of 2 different treatment arms.

The labeling differences between the lifitegrast and the vehicle will be known to only the unmasked coordinator. The unmasked coordinator will dispense the appropriate treatment to the subject. All drug dispensing and accountability will be done by an unmasked study coordinator so the investigator can remain masked.

2.4 STUDY PROCEDURES

Procedures	Visit 1 (Baseline)	Visit 2 (2 weeks ±3 days)	Visit 3 (4 weeks±5 days)	Visit 4 (8 weeks ±5days)
Informed consent	X			
Medical/ Ocular History (including artificial tear/ rewetting drop use, habitual contact lens information and typical wearing time, concomitant medications and allergies)[a]	X	X	X	X
Drug Accountability[b]		X	X	X
Entering Acuity (Snellen)[c]	X	X	X	X
LogMAR Visual Acuity, High Contrast, High Luminance, OD and OS	X	X	X	X
CLDEQ-8 Administration	X	X	X	X
Tear Osmolarity[d]	X			X
Habitual Contact Lens Fit Assessment[e]	X	X	X	X
Removal of Contact Lenses	X	X	X	X
Slit lamp Biomicroscopy[f]	X	X	X	X
Corneal Staining Assessment (NaFl)[g]	X	X	X	X
Tear Break Up Time (TBUT) in seconds[h]	X	X	X	X
Lissamine Green Staining[i]	X	X	X	X
Schirmer Testing[j]	X	X	X	X
Randomization	X			
Drug Dispensing	X	X	X	
Forced Choice Questionnaire[k]				X
Contact Lens Re-Insertion (with irrigation if necessary)	X	X	X	X
Exit Acuity (Snellen)	X	X	X	X
Adverse Events	X	X	X	X

a. Artificial Tear (AT)/ Rewetting drop use will include date of last use and average use per week.
b. Amount of vials used will be compared to amount of expected vials used based on number of days since the subject's last visit.
c. Subjects are to report to each visit wearing their habitual lenses. Acuity will be recorded as the last line in which the subject was able to read at least half of the letters. Plus and minus notation will be used to indicate additional letters read beyond the recorded acuity line or missed on the recorded acuity line.
d. TearLab will be used per manufacturer's guidelines to measure tear osmolarity. This procedure must be performed prior to any drops being instilled in the eye for at least 2 hours prior.
e. Lenses must have an adequate fit (centration, limbal/corneal exposure and movement) as determined by the investigator. Lens wettability and deposits will also be assessed.
f. Slit lamp grading scale will be based on: Efron Grading Scale[6]
g. Grading scale: NEI/Industry Grading System[7]
h. TBUT will be recorded in number of seconds 0-15 or greater than 15 seconds
i. Grading scale: NEI/ Industry Grading System[7]
j. Schirmer testing will be performed without anesthesia for 5 minutes in each eye.
k. The questionnaire will ask the subject if he/she felt their symptoms improved to the point that he/she would continue outside the study.

2.5 RISK/BENEFIT ASSESSMENT

2.5.1 KNOWN POTENTIAL RISKS

Lifitegrast ophthalmic solution 5% will be dispensed to subjects in the test arm and will be used for 8 weeks.

The common (5-25%) risks associated with lifitegrast 5% are[8]:

- Instillation site irritation
- Dysguesia
- Reduced Visual Acuity

Less common (1-5%) side effects include[8]:

- Blurred vision
- Conjunctival hyperemia
- Eye irritation
- Headache
- Increased lacrimation
- Eye discharge
- Eye discomfort
- Eye pruritis
- Sinusitis

As with any medication, allergic reactions are possible. A serious, potentially life-threatening allergic reaction known as anaphylaxis is possible.

Subjects will be required to wear their habitual contact lenses throughout the study. The most common risks associated with CL wear include:

- Burning, stinging, tearing, redness and/or itching of the eyes
- Contact lens related ocular discomfort
- Foreign body sensation
- Dryness

More serious side effects of CL wear are less common, and include:

- Corneal infiltrates, ulcers or erosions
- Corneal edema
- Corneal neovascularization
- Iritis

2.5.2 KNOWN POTENTIAL BENEFITS

Subjects may experience an improvement in signs and symptoms of dry eye if they are in the treatment arm. They might not experience any benefits if they are in the control arm. The efficacy of lifitegrast in contact lens wearers is not known.

2.5.3 ADVERSE EVENTS

An adverse event (AE) is “any untoward occurrence (physical, psychological, social, or economic) in a human subject participating in research”. The event is not necessarily unexpected. The event may have

been described in the informed consent as a risk of the study. Adverse events include abnormal laboratory findings, a symptom, or disease temporally associated with the use of an investigational agent, or the progression of disease, whether or not related to the investigational product.

Anticipated Adverse Events: Anticipated adverse events include those listed in the Known Potential Risks section, informed consent documents, the lifitegrast package insert and/or those known to be associated with contact lens wear or dry eye.

Anticipated adverse events will be recorded in the appropriate source documents and case report forms. At a minimum, the following data will be collected:

- Description of the event
- Onset
- Location
- Seriousness
- Relation to study drug
- Expectedness
- Actions taken
- Follow up
- Resolution date and outcome

Serious Adverse Event (SAE): Serious adverse events are any untoward medical occurrences such as death, significant disability/incapacity, In-patient hospitalization or prolongation of existing hospitalization or congenital anomaly/birth defect.

Unexpected Adverse Effect (UAE): An unanticipated problem involving risk to human participants or others is one that was unforeseen at the time of its occurrence and indicates that participants or others are at an increased risk of harm. Unexpected adverse events are those that are not already described as potential risks in in the Known Potential Risks section, informed consent documents, the lifitegrast package insert and/or those known to be associated with contact lens wear or dry eye or not part of an underlying disease.

SAE/UAE Reporting

An event is considered reportable if it is unexpected or serious. Once an event is **s**uspected by the investigator as reportable, the PI shall be consulted to determine how the event should be reported. When the event is determined to be reportable by the PI, the Novartis shall be contacted immediately (within 24 hours) by e-mail or phone. A written report will then be submitted to the sponsor and the IRB as soon as possible, but no later than 5 working days after discovery of the event (or sooner, as specified by the sponsor or IRB).

- The PI will report (within 24 hours) the SAE/UAE to the IRB and Novartis as per the "Safety Data Collection and Reporting Responsibilities" agreement with Novartis. This information will be reported as soon as it becomes available.
- The PI will also report any drug exposure during pregnancy and any instances of drug misuse or abuse to Novartis.
- At a minimum, the following will be reported: the person who reported the event, information about the patient, details of the study drug, and details on the safety events experienced by the patient.
- The PI or designee shall submit a SAE/UAE Initial Report to the IRB.
- For suspected unexpected SAEs (SUSARs), safety reports such as Investigator Notifications or SUSAR listings will be prepared as per the "Safety Data Collection and Reporting Responsibilities" agreement with Novartis.

SAE/UAE Follow-up

Follow up reports shall be made to Novartis and the IRB until resolution of the event.

- The SAE (or AE) follow-up information shall be submitted following the "Safety Data Collection and Reporting Responsibilities" agreement with Novartis.
- A Follow-up Report shall be submitted to the IRB as required.

The source documents must indicate:

- The event being followed
- The current status of the event
- What treatment was provided
- Any follow-up action taken/recommended
- The outcome of the event

Unmasking of Investigators and Subjects

Unmasking will be performed on an as needing basis, such as in the following scenarios:

- Serious adverse event, where unmasking is relevant to either subject care or reporting
- Drug/device recall
- Potential safety or risk management concern
- The Investigator deems knowledge of the treatment group to be essential to subject care or safety

3 STUDY POPULATION

3.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Subjects must read, understand and sign the Statement of Informed Consent
2. Subjects must be at least 18 years of age
3. Subjects must be habitual soft contact lens (CL) wearers, with a daily, weekly, bi- weekly or

monthly replacement schedule
4. Habitual contact lenses must have a suitable fit as determined by the investigator
5. Subjects must report a history of dry eye symptoms, for which they have used rewetting drops or Artificial Tears (ATs) in the past 30 days
6. Subjects must be willing to discontinue the use of Artificial Tears (ATs) and rewetting drops for the duration of the study
7. Subjects must have a score of 12 or higher on the CLDEQ at baseline
8. Subjects must have at least 2 of the following signs of dry eye disease:
    a. High tear osmolarity > 308mOsm/L, or a difference greater than 8 mOsm/L between eyes
    b. Any corneal staining
    c. Any bulbar conjunctival staining
    d. Low TBUT (<10s)
    e. Schirmer <10mm in either eye
9. Subjects must be able to read at least half of the 20/25 (via entrance Snellen visual acuity) or better in each eye in their current contact lens prescription.
10. Subjects currently wearing reusable contact lenses must be willing to use Clear Care solution for cleaning and disinfecting throughout the study.

3.2 EXCLUSION CRITERIA

An individual will be ineligible to participate or continue in this study if:
1. Currently pregnant or breastfeeding by self-report
2. Allergy to lifitegrast ophthalmic solution 5% (Xiidra)
3. Habitual extended wear contact lens schedule
4. Any active ocular disease that may affect the ocular surface other than dry eye (significant blepharitis, allergic conjunctivitis, lagophthalmos, chalazia, hordeolum etc.)
5. Any meibomian gland dysfunction, blepharitis, corneal neovascularization or papillary conjunctivitis that is grade 3 or higher using the Efron Grading Scale.
6. Excessive corneal staining, that in the opinion of the investigator, is a contraindication to contact lens use.
7. History of ocular surgery
8. Any active ocular infection
9. Use of any topical ophthalmic medications other than artificial tears or rewetting drops
10. Inability to perform necessary visual function assessments
11. Punctal plug insertion in the last 3 months, or presence of punctal plugs at the time of the exam.

3.3 SAMPLE SIZE JUSTIFICATION

Assuming normality, we calculated the statistical power for various detectable effect sizes using unpaired t-test in a two-sided hypothesis test with a significance level, 0.05, where the ratio of sample size of 1:1 is assumed between study arms. **Table 1** shows that our sample size will have adequate power to detect listed effect size. For example, we will achieve 84% power to detect a standardized mean difference of 1.12 between two groups of a size of 15 for each, which corresponds to a difference of score change by 3 with standard deviations 3.2 and 2.0 for each group[5]. Up to 40 subjects will be enrolled with the goal of randomizing 30 subjects (15 per arm). This will allow for a 25% screen-failure rate. Note that for each

domain score and the overall score, the power is the same for each effect size since they are standardized, but the mean change corresponding to a given effect size differs.

Table 1

Sample size (N) N1 vs. n2	Unpaired t-test	
	Effect size [1]	Power (%)
15 vs. 15	1	75.3
	1.12	84.4
	1.2	87.5

[1] standardized mean difference of 2 groups

3.4 STRATEGIES FOR RECRUITMENT AND RETENTION

Participants will be recruited from the patients, students, and faculty of the SUNY State College of Optometry without regard to gender, economic status, sexuality, or race. Subjects will also be recruited from outside sources via online recruitment efforts. It will be made clear to those recruited that their participation is completely voluntary, and that failure to participate will have no consequences with respect to their standing within the SUNY community. Participants may withdraw from the study at any time and need not give a reason for doing so.

3.5 ENROLLMENT OF VULNERABLE SUBJECTS

Vulnerable subjects with the exception of employees of the site, and students of the respective university will not be recruited. Staff that is listed on the delegation form are excluded from participation.

3.6 SCREEN FAILURES

Individuals who do not meet the criteria for participation in this trial (screen failure) will not be randomized. There will be no opportunity for rescreening.

4 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/ WITHDRAWAL

Participants are free to withdraw from participation in the study at any time upon request. An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Cannot comply with instructions in the protocol
- Lost to follow up
- Subject no longer meets eligibility criteria
- Sustain a clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every possible effort to contact the subject.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

DATA SAFETY AND MONITORING

4.1 CONFIDENTIALITY

All information obtained during the course of the study will be regarded as confidential. The Institutional Review Board (IRB), and/or the sponsor may inspect the investigator's records pertaining to the subject as a participant in the clinical study. The results of this study may also be used for medical and/or scientific publications but the subject's identity will not be disclosed. All data to be collected in accordance with HIPAA. All data to be kept as a de-identified data set for subsequent analysis by the investigator.

4.2 HOW WILL CONFIDENTIALITY BE MAINTAINED?

The Principal Investigator and research team will maintain research subject's confidentiality by using coded identifiers on protocol-required information that is reported to the sponsor or leaves the designated research team in any form unless otherwise allowed by the subject through written consent. In order to maintain confidentiality and safety of the human subject, the Principal Investigator and research team will assure that a documented verifiable link exists to identify study subjects throughout the course of the research, including, maintaining the study- specific subject log in a secure location with other regulatory documents at the end of the research study.
To protect the privacy interests of participants, the Clinical Vision Research Center (CVRC) adheres to the following guidelines:

- All study personnel are required to maintain research ethics certification.
- Paper study documents are kept in locked storage in the CVRC and are accessible only by study personnel.
- Electronic study documents are kept in password-protected computer files that are accessible only by study personnel.
- Discussions by study personnel and participants should occur only in the CVRC or in areas where non-study staff or other participants cannot overhear discussions.
- When communicating verbally, by email or by telephone with participants, study staff must ensure they are safeguarding subject confidentiality.
- Only information necessary for the research study is collected from study subjects.

MONITORING

Study initiation, routine and close-out visits are planned and conducted over the lifespan of a study. Study monitoring will be carried out by monitors of the CVRC.

A Site Initiation Visit (SIV) will be conducted prior to site activation to confirm preparedness for protocol execution, satisfactory site facilities, clarify the applicable regulations and requirements of the protocol, carefully review the process of implementing the protocol at the site and conduct any necessary training

prior to the assigned Program Official activating the site for enrollment. The site initiation visit will be conducted as soon as all the necessary approvals have been obtained.

Interim Monitoring Visits (IMVs) will be conducted to confirm subjects' rights are being protected; the study is being conducted according to the protocol and applicable regulations, including GCP; confirm accurate reporting of subject safety data and study endpoints. The first routine monitoring visit will occur as soon as the first subject is recruited or within 2 weeks of the first subject being recruited. The frequency of monitoring will be established at the start of the study.

A Close-Out Visit (COV) will be conducted to ensure that all study data and other study documentation is complete and accurate and that all study records have been reconciled. The COV is completed after data cleansing and data lock.

4.3 RECORD RETENTION

At the end of the study, all study materials (i.e., source, regulatory documents) will be kept on site in a secure area at SUNY College of Optometry. Study materials will only be accessible by research personnel and will be kept for a minimum duration of seven (7) years or longer, if specified in the study contract. Any change to storage location off site will be communicated with the sponsor in advance. Sponsors will be contacted regarding destruction of study material at the end of the prescribed time.

4.4 ANALYSIS

All source data will be collected on paper source documents. Data will be entered into an Excel spreadsheet with double data entry to check for error before locking the data set.

5 STATISTICS

The clinical characteristics of subjects including demographics and lens modality will be first summarized using descriptive statistics in mean $\pm$ SD for continuous variables or % (counts) for categorical variables, with attention to assessing balance in these characteristics by study arms, and with assessment of the distribution of variables, relevant to the choice of statistical tests. For the continuous outcomes, we will conduct the Kolmogorov-Smirnov or the Shapiro-Wilk test to confirm normality of measurements prior to performing statistical analyses. Detection of outliers will be done using histograms, box-plots, normal plots and summary statistics. Where appropriate, logarithmic transformation will be further done.

All analyses will be conducted using the principle of "intent-to-treat" in which every participant is assumed to have received his/her assigned intervention, regardless of adherence. In order to assess for the significant difference between study arms for the primary outcomes of change in total score on the CLDEQ-8 after 8 weeks of treatment or continuous secondary outcomes (change in tear osmolarity), bivariate comparisons will be first conducted using t-tests. Alternatively Wilcoxon nonparametric counterpart will be used for continuous variables that deviate from normality. The forced choice questionnaire will be compared as a percentage of "yes" responses between the two groups by a two-sample test of proportion. These univariate analyses will be followed by multivariable regression methods for an adjustment of all other potential confounding variables such as baseline clinical and demographic characteristics that differ by study arms.

Alternatively, we will use longitudinal linear models to analyze the difference of changes in total score between study arms from the baseline to the follow-up times across baseline, 2nd, 4th and 8th weeks (i.e., mixed-effects regression models with a random subject effect and GEE with exchangeable and independent correlations). The models will be specified with random intercepts and slopes such that a linear trajectory representing outcome will be compared between groups. Group (arm)-specific (as well as individual-level) intercepts and slopes over the period of follow-up will be included as random effects, while other covariates will be modeled as fixed effects. All models will be adjusted for other clinical or demographic confounders. Residual-based diagnostics will be used to evaluate validity of model assumptions. Two sided p-values <0.05 will be considered to be statistically significant. All statistical procedures were performed using R statistical package (www.R-project.org).

6 REFERENCES

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