Clinical Evaluation of Avulux® Lenses as an Aid in Reducing the Impact of Migraine Headaches

Protocol # AVU-02 Version 1
February 21, 2020

Sponsor:
MATAP II LLC
#245 -2901 Clint Moore Road
Boca Raton, FL 33496

Statement of Compliance

The trial will be conducted in accordance with the Clinical Study Protocol, requirements of the IRB, the Investigator Agreement, and the following Code of Federal Regulations: 21 CFR 812, 21 CFR 50, 21 CFR 54, 21 CFR 56, and 21 CFR 11.

I hereby confirm that I approve of this Clinical Study Protocol and agree to comply with its terms as laid out in this document. I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Principal Investigator:

_____
(Print/Type Name)

Signed: _____

Date: _____

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1. Study Scope

This study is a prospective, multi-center, randomized, placebo-controlled study. A minimum of 68 subjects who suffer from acute migraine headaches and who provide written informed consent will be enrolled at a minimum of 3 clinical sites. Subjects will be randomized into one of two treatment groups (*i.e.* Avulux® device *vs*. control/sham device) in a one-to-one ratio. Subjects will participate in the study for a maximum of four (4) weeks after enrollment. Subjects will be directed to apply the study device specific to their study arm as soon as possible once they experience symptoms consistent with the onset of a migraine attack. Subjects will be asked to assess the severity of each headache using a pain score just prior to the application of the study device, and 2- and 4-hours following application of the device, for all severe or very severe migraine headaches that they experience while enrolled in the study.

This study will be conducted upon execution of a clinical study agreement and receipt of Institutional Review Board or Ethics Committee (IRB/EC) approval from each participating site.

2. Principle of the Device

Avulux® is intended to reduce the severity of headache pain in adult patients diagnosed with episodic migraine headache. In this study, the investigative Avulux® device shall consist of a pair of optical filters in the form of spectacle lenses, provided in a standard spectacle frame; the lenses contain a dye that effectively blocks light at specified wavelength ranges while minimizing distortion of the visible spectrum. The optical filters block a portion of the optical spectrum that is suspected to stimulate photophobic responses that trigger some, and exacerbate most, migraines.

The control/sham device for this study shall be a pair of plastic lenses provided in a standard spectacle frame, which will have negligible light-blocking properties at the optical wavelengths which are blocked by the Avulux® device.

3. Study Objectives

3.1 Primary Objective

The primary objective of this study is to evaluate the efficacy of the Avulux® device in reducing the impact of migraine headaches, as measured by improvement in an 11-point pain scale after 2 hours of device application, when compared to a control/sham device.

3.2 Secondary Objective

The secondary objective of this study is to evaluate the efficacy of the Avulux® device in reducing the impact of migraine headaches, as measured by improvement in an 11-point pain scale after 4 hours of device application, when compared to a control/sham device.

3.3 Exploratory Objectives

Exploratory objectives for this study are:

- To compare the proportion of subjects who show quantifiable improvement in overall migraine impact (as measured by a change in migraine pain from severe to mild/no pain) when using the Avulux® device *vs.* a control/sham device;
- To compare the proportion of subjects who require adjunctive medication to control their migraine headache when using the Avulux® device *vs.* a control/sham device; and
- To compare the proportion of subjects suffering from light sensitivity as a result of their migraine headache when using the Avulux® device *vs.* a control/sham device.

4. Study Endpoints

4.1 Primary Endpoint

The primary endpoint variable is the change in migraine pain as measured on an eleven-point pain scale, defined as the pain score after an elapsed time of 2 hours following application of the device minus the pain score at onset of migraine symptoms, with respect to the first severe or very severe migraine headache (defined as a pain score of 6 or greater at onset of migraine symptoms) experienced by an enrolled subject.

4.2 Secondary Endpoint

The secondary endpoint variable is the change in migraine pain as measured on an eleven-point pain scale, defined as the pain score after an elapsed time of 4 hours following application of the device minus the pain score at onset of migraine symptoms, with respect to the first severe or very severe migraine headache (defined as a pain score of 6 or greater at onset of migraine symptoms) experienced by an enrolled subject.

4.3 Exploratory Endpoints

Exploratory endpoint variables are:

- The proportion of subjects who report mild or no symptoms (defined as a pain score of 3 or less) after an elapsed time of 2 hours following application of the device, with respect to their first severe or very severe migraine headache;
- The proportion of subjects who require abortive medication to control their first severe or very severe migraine headache within 8 hours following application of the device; and
- The proportion of subjects who report sensitivity to light after elapsed times of 2 hours and 4 hours following application of the device, with respect to their first severe or very severe migraine headache.

5. Inclusion/Exclusion Criteria

5.1 Inclusion Criteria

All enrolled patients must meet all of the following inclusion criteria:

- Subject is 18 years or older;
- Subject is willing and able to provide written informed consent;
- Diagnosis of migraine, based on a history of at least 5 attacks per month with the following primary headache characteristics:
    - Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated);
    - Headache has at least two of the following characteristics:
        - unilateral location;
        - pulsating quality;
        - moderate or severe pain intensity;
        - aggravation by or causing avoidance of routine physical activity (*e.g*. walking or climbing stairs);
    - Headache occurs with at least one of the following symptoms:
        - nausea and/or vomiting;
        - photophobia and phonophobia;
- Subject has experienced at least 4 migraine attacks in the last month, with at least two migraine attacks resulting in severe pain prior to the use of any abortive medications;
- Migraines are not attributed to another disorder.

5.2 Exclusion Criteria

All enrolled patients must meet none of the following exclusion criteria:

- Subjects participating in another prospective, interventional clinical study;
- Subjects with other light sensitive conditions, such as iritis;
- Subjects who have less than 4 headache days per month with the above characteristics;
- Chronic migraine subjects (defined as subjects who experience a minimum of 15 headache days per month);
- Subjects with headaches due to medication overuse (defined as regular use of headache medication for a minimum of 10 days per month, for a minimum period of 3 months);
- Subjects who have had any change in their migraine treatment within 4 weeks prior to study enrollment.
- Subjects whose family members are currently participating in this study, or are employees of the study site, Avulux, or the coordinating CRO.

6. Study Procedures

6.1 Consent Procedures

After Institutional Review Board/Ethics Committee (IRB/EC) approval for the study is obtained at a given clinical site, the investigator (or appropriate designee) at the site will identify

potential subjects for the study, based on the inclusion/exclusion criteria outlined in Section 4. Eligible subjects will be asked to provide written informed consent. The informed consent process will be documented for each subject and will include a thorough discussion of study procedures involved. Each subject participating in the study shall sign and date the consent form prior to the initiation of any study procedures.

6.2 Enrollment and Randomization of Study Subjects

Subjects will be asked to provide demographic information (date of birth, gender, race/ethnicity) and relevant medical history related to migraine headaches. Subjects who meet all inclusion criteria and none of the exclusion criteria, and who provide written informed consent, will be enrolled in the study. Enrolled subjects will then be randomized to the Avulux® study glasses *vs*. control/sham study arm, with allocation on a 1:1 basis; subjects will be provided with the device specific to their assigned study arm. Subjects will be blinded to the type of device being assessed (both the blocking abilities when worn).

6.3 Pain Scale

Subjects will be asked to rate their headache pain using an 11-point scale, *i.e*. on an integer scale from 0 to 10 inclusive, with 0 indicating no pain and 10 indicating the worst pain imaginable. The scale can be interpreted clinically as follows:

- 10: worst pain imaginable;
- 8-9: very severe pain;
- 6-7: severe pain;
- 4-5: moderate pain;
- 1-3: mild pain;
- 0: no pain.

The 11-point pain scale has been validated for use in migraine headache evaluations.[1]

6.4 Procedures and Assessments

Subjects will be directed to:

- apply the study glasses at the first onset of aura, or as soon as possible once they experience symptoms consistent with the onset of a migraine attack.
- avoid taking abortive medication for the first four hours of a migraine attack. If abortive medications cannot be avoided, the subject should document use.
- record the following information for the first (and all subsequent) severe or very severe migraine headaches that they experience while enrolled in the study:
    - The date and time of symptom onset;

[1] Kwong WJ and Pathak DS. Validation of the eleven-point pain scale in the measurement of migraine headache pain. *Cephalgia* 2007; 27: 336-342.

- The pain score (as assessed on the 11-point pain scale) just prior to the application of the study glasses (score needs to be greater than or equal to 6 to qualify as a severe or very severe headache);
- The time at which the study glasses are applied;
- Whether the subject was wearing prescription eyewear in addition to the study glasses, or whether the study glasses alone were worn;
- The pain score (as assessed on the eleven-point pain scale) 2 hours after the study glasses are applied;
- The pain score (as assessed on the eleven-point pain scale) 4 hours after the study glasses are applied;
- The type of abortive medication taken (if any) to control headache symptoms, the dosage taken, and the time at which the medication is taken; and
- Any experience of light sensitivity within 4 hours after the study glasses are applied, and the time at which light sensitivity is first experienced.

Subjects will participate in the study for a maximum of four (4) weeks ± 3 days after enrollment; if a given subject does not experience a severe or very severe migraine headache within four (4) weeks, that subject will not be included in the evaluable study population.

Study coordinators will contact subjects once per week to ensure they are wearing the study device as instructed, and that they are recording the requested information related to their headaches. These weekly contacts will also enable coordinators to identify and address any barriers to adherence with the protocol.

After completion of study activities, subjects will return the glasses specific to their study arm, and be asked to complete a study questionnaire, to provide feedback regarding the wearability and ease of use of the glasses. Subjects will also be asked to provide an opinion as to which type of device they believe they were assigned to (Avulux® *vs.* control/sham *vs*. do not know).

7. Safety Reporting

7.1 Adverse Events

An adverse event (AE) is defined as an undesirable physical, psychological, or behavioral effect experienced by a subject related to headaches in conjunction with his/her participation in the clinical study, whether or not device related. Any subject may experience adverse events or complications while enrolled in the study. Should they occur, these events will be reported to the sponsor as detailed in section 7.3.1.

7.2 Serious Adverse Events

A *serious adverse event* (SAE), as defined by the International Conference on Harmonization (ICH) guidelines, is any adverse event that results in any of the following outcomes:

1. Death;

2. Life-threatening outcome (*i.e*. immediate risk of death from the reaction as it occurred);
3. Inpatient hospitalization or prolongation of existing hospitalization;
4. Persistent or significant disability or incapacity; or
5. Congenital anomaly.

7.3 Reporting of Events

7.3.1 Adverse Events

Adverse events will be reported to the sponsor in a timely manner. A case report form shall be completed for each event, with description of the event, onset date, end date, relation to study device, any treatment rendered and the outcome.

7.3.2 Serious Adverse Events

Serious adverse events should be reported to the sponsor within 24 hours of awareness of the event. The investigator or designee should report the event via telephone, email or fax with details describing the event, onset date, end date, severity of event, relation to study device treatment and outcome. If all details are not known at the time of reporting, an initial report is filed followed by a detailed report within 7 working days. It is the responsibility of the investigator to inform the IRB/EC as applicable according to their IRB/EC policies. It is the responsibility of the sponsor to inform the other sites of the event.

8. Risk/Benefit Analysis

8.1 Risks

There are no anticipated risks to study subjects as a result of application of the device. Any potential discomfort experienced from use of the device would be mitigated by removal of the device.

8.2 Benefits

The anticipated benefit of the device is the reduction in headache severity in patients with migraine headaches. Information gained from this study may aid in the future management of patients with episodic migraine headaches.

9. Subject Withdrawal

In accordance with Good Clinical Practice (GCP) guidelines, subjects who have consented to participate in the study are free to withdraw consent and discontinue participation in the study at any time, and without prejudice to further treatment as required for their condition.
If a subject decides to discontinue participation in the study, the investigator will note the reason for the discontinuation (and any potential AEs) on the applicable case report form.

10. Administrative Considerations

This protocol was designed and will be conducted, recorded, and reported in compliance with Good Clinical Practice (GCP) guidelines and with applicable U.S. Food and Drug Administration (FDA) Investigational Device Exemption (IDE) regulations.

10.1 Prior to Study Initiation

The following will be provided to the sponsor from the study site, prior to study initiation:

- Curriculum Vitae of the investigator;
- The "Statement of Compliance" page of the protocol, signed and dated by the investigator;
- An independent IRB/EC membership list current at the time of the review of this protocol;
- Financial Disclosure Form, signed and dated by the investigator;
- Written verification of IRB/EC approval for the study; and
- A duly executed clinical study agreement.

10.2 Amendments

Amendments to this study protocol must be agreed upon in writing between the investigator and the sponsor. Written verification of IRB/EC approval will be obtained before any amendment is implemented which affects subject safety or materially alters the study design. Modifications of the protocol which are administrative in nature do not require IRB/EC approval, but will be submitted to the IRB/EC for informational purposes.

If there are changes to the informed consent form utilized by a site, written verification of IRB/EC approval of the new form must be forwarded to the sponsor, along with a copy of the new form. If the changes in the content of the consent form are directly related to information that may influence the subject's decision to participate in the study, the subject may need to be reconsented.

10.3 Financial Disclosure of Clinical Investigators

The clinical investigator(s) participating in this study shall complete a financial disclosure form, so as to provide sufficient and accurate financial information to the sponsor pertaining to:

- Any arrangements between the sponsor and clinical investigator whereby the value of compensation to the investigator for conducting the study could be influenced by the outcome of the study;
- Any significant payments or other forms of compensation from the sponsor, such as grants to fund ongoing research, compensation in the form of equipment, retainers for ongoing consultation, or honoraria;

- Any proprietary interest in the product to be developed and held by the investigator involved in the study; and
- Any significant equity interest in the sponsor held by the investigator, his/her spouse or dependent children.

10.4 Subject Informed Consent

This study will be conducted in compliance with the principles of 'Informed Consent' described in the Declaration of Helsinki and FDA 21 CFR Part 50. It is the responsibility of the investigator, or designee, to obtain written informed consent from each subject prior to the subject's inclusion in the study.

The sponsor will provide each investigator with a sample informed consent document that the site may modify to meet individual IRB/EC requirements. The investigator should provide the sponsor with a copy of the proposed consent form, preferably prior to submitting it to the IRB/EC, so that the sponsor may ensure that all appropriate and required elements are incorporated into the document.

Prior to study initiation, the investigator must provide the sponsor with a copy of the informed consent form approved by the IRB/EC, and a copy of the IRB/EC letter stating that formal approval has been granted by the institution.

Study subjects must provide written consent using the IRB/EC-approved informed consent form in effect at the time of presentation of the subject to the study site. Participating subjects in the State of California will also be provided with the *Experimental Subject's Bill of Rights* as part of the informed consent form.

A copy of the IRB/EC-approved informed consent form and a copy of each subject's signed consent form will be maintained by each investigator in the site's study file. A copy of the signed and dated informed consent form must be given to each study subject. The original informed consent form for each subject must be kept on file at each of the participating study sites for a minimum retaining period, in accordance with applicable regulatory authority recommendations (refer to section 10.10).

10.5 Subject Confidentiality

The sponsor and the study investigators shall make every effort to protect the confidentiality of subjects participating in the study. All study information and data with respect to individual study subjects will be considered confidential. Only authorized personnel will have access to this confidential information.

Subject specimens will be identified using a unique identifier. All data used in the analysis and reporting of this evaluation will be without identifiable reference to the subjects.

10.6 Study Registration

Study information and final study results will be entered in the ClinicalTrials.gov registry database in compliance with the FDA Modernization Act of 1997 and the FDA Amendments Act of 2007.

10.7 Source Documents

The subject's site visit must be fully documented on source document worksheets or in the subject's medical records, or a combination of both.

During the monitoring process, information entered into the study case report forms will be verified against the source worksheets or subject medical records.

10.8 Device Accountability

Only the investigator and study staff identified in the clinical research agreement and/or study logs on file with the sponsor and at the study site may have access to the investigational device. The investigator must maintain a full accountability for any devices received. An accountability log will be provided to maintain current and accurate inventory records covering the receipt and return of the devices.

At the conclusion of the study, the site will return the devices to the sponsor. The site shall retain a copy of the accountability log for its study files.

10.9 Device Labeling

The study glasses and sham glasses will be labeled in accordance with U.S. federal regulations applicable to an investigational device. All device labeling, operating instructions, device warnings or precautions, and informational materials will include the following statement:

CAUTION - THIS IS AN INVESTIGATIONAL DEVICE. LIMITED BY FEDERAL (OR U.S.) LAW TO INVESTIGATIONAL USE.

10.10 Study Monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported study data are accurate, complete, and verifiable, and that the conduct of the trial is compliant with federal regulations, agreements with the sponsor, the currently approved protocol, and with any requirements imposed by the IRB/EC.

Site monitoring will be performed by a third-party contract research organization (CRO) working on behalf of the sponsor. A Clinical Monitoring Plan (CMP) will be developed to establish the plan for study oversight.

On-site monitoring is anticipated throughout the course of the study. The sponsor will be provided with written reports of these visits, and the sites will be provided with a follow-up letter describing the findings and defining any outstanding issues or action items required.

10.11 Retention of Study Records

The investigator will maintain adequate records for the study including informed consent forms, source documents (as applicable), medical records, safety reports (as applicable), and other pertinent study data.

For participating U.S. study sites, all records for this study must be retained by the Investigator for a minimum period of:

- two (2) years after the FDA approves the marketing notification for the product, **or**
- two (2) years following termination of the study if no marketing notification is ever sought or approved,

whichever is the longer elapsed time.

To avoid any possible misunderstandings, the investigator will contact the sponsor prior to the planned destruction of any study records, or if the investigator leaves the institution where the study was conducted. The investigator will notify the sponsor in the event of accidental loss or destruction of any study records.

10.12 Protocol Termination

Both the sponsor and the investigator have the right to terminate the study at their discretion, with written notice to the other party. This action should be taken only after appropriate consultation between the sponsor and investigator or institution. Termination of the study shall not affect the rights and obligations of either of the parties prior to the date of termination.

11. Data Analysis

11.1 Sample Size Justification

A pilot evaluation of the Avulux® and control/sham devices (n = 10 subjects using each type of device) demonstrated that users of the Avulux® device reported a mean decrease of 4.1 points in pain score (standard deviation = 1.9 points) after an elapsed time of 2 hours, and users of the placebo device reported a mean decrease of 1.9 points in pain score (standard deviation = 1.5 points) after an elapsed time of 2 hours. The difference between the performance of the two devices was statistically significant (p = 0.004).

Assuming that subjects with severe or very severe migraine headaches achieve a mean 4-point improvement in pain score when using the investigative device and at most a mean 2-point improvement when using the control/sham device, and assuming a standard deviation of at

most 2.0 points when estimating the mean difference in pain scores in individual study subjects after application of either device, a sample size of 27 subjects per study arm provides a minimum statistical power of 95% to detect a significant difference in mean results for the primary endpoint variable between the two (2) device types, at a significance level of $\alpha = 0.05$. Given an estimated dropout rate of up to 20% in each study arm, a minimum of 34 subjects per arm (or 68 total subjects) are required to be enrolled in this study.

The above assumptions imply that the mean improvement in pain score after 2 hours will be at least 2 points higher for the Avulux® device than for the control/sham device. Meta-analyses have shown that the minimal clinically important difference (MCID) to detect changes in acute pain as measured on the 11-point pain scale is 1.7 points;[2,3] therefore, a 2-point difference in mean improvement between study devices is considered to be clinically meaningful.

11.2 Proposed Analyses

A statistical analysis plan, containing detailed information regarding the proposed statistical analyses of study data, will be created and approved prior to database lock.

Unless otherwise stated, all statistical testing will be two-sided and will be performed using a significance level of $\alpha = 0.05$.

11.2.1 Analysis Populations

The *intention-to-treat* (ITT) population shall be defined as the population of all enrolled subjects who were assigned to a study group and who experienced a minimum of one severe or very severe headache within 4 weeks of enrollment. This population shall include subjects who were non-compliant with study procedures, and subjects who were assigned to the incorrect device specific to their study group.

The *per-protocol* population shall be defined as the population of all enrolled subjects who were assigned to the correct device specific to their study group, who experienced a minimum of one severe or very severe headache within 4 weeks of enrollment, and who were compliant with study procedures throughout the duration of their enrollment in the study.

Analyses of the primary and secondary endpoints shall be conducted using data from intention-to-treat population. Analyses of exploratory endpoints shall be conducted using data from the per-protocol population.

[2] Olsen MF, Bjerre E, Hansen MD *et al*. Pain relief that matters to patients: systematic review of empirical studies assessing the minimum clinically important difference in acute pain. *BMC Medicine* 2017, 15: 35.
[3] Farrar JT, Young JP Jr., LaMoreaux L *et al*. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain* 2001, 94: 149-158.

11.2.2 Subject Accountability

All subjects who provided informed consent (screened subjects) will be included in a summary of subject accountability. The number of subjects screened, the number and percentage of subjects who were screen failures, and the number and percentage of subjects who were enrolled in the study will be summarized by investigational site and overall. The reasons for screen failure will also be tabulated.

11.2.3 Handling of Missing Data

In the intention-to-treat population, any missing pain scores at time points of 2 and 4 hours after application of the device shall be imputed using a multiple imputation procedure, with study arm, age, sex, baseline pain score, number of severe or very severe headaches experienced while enrolled in the study, and pain scores at 2 and 4 hours after application of the device for subsequent severe or very severe headaches experienced while enrolled in the study as predictors. Imputation procedures shall utilize predictive mean matching.[4] A total of 50 sets of multiple imputations shall be generated; the analysis of the primary endpoint shall be conducted for each set, and a pooled estimate of the difference in mean improvement between the two devices will be computed, along with a 95% interval estimate and *p*-value associated with the null hypothesis.

In the per-protocol population, subjects with a missing value of an exploratory endpoint will not be included in the evaluable population for that endpoint.

11.2.4 Demographic and Baseline Characteristics

Descriptive statistics of demographic variables (sex, age, race/ethnicity) will be presented for all enrolled study subjects, and for subjects stratified by study site and by assigned study arm.

Continuous variables as a minimum will be described by number of non-missing observations (n), arithmetic mean, standard deviation (SD), minimum, median, and maximum. Categorical variables will be presented using the number of observations in each category, and corresponding proportions (expressed as percentages).

11.2.5 Analysis of Primary Endpoint

The null hypothesis to be tested is
H_o: $D_A - D_{C/S} = 0$,
where D_A is the change in pain score after an elapsed time of 2 hours using the active device, and $D_{C/S}$ is the change in pain score after an elapsed time of 2 hours using the control/sham device.

[4] Van Buuren S and Goothius-Oudshoorn K. *mice*: Multivariate imputation by chained equations. *Journal of Statistical Science* 2011, 45: 1-67.

In order to assess whether there is a possible baseline effect, the mean baseline pain score (*i.e*. mean pain score at symptom onset) using the active device shall be statistically compared to the mean baseline pain score using the active/sham device, using a two-sample *t*-test at a significance level of $\alpha = 0.05$.

In order to assess whether there is a possible effect of rescue medications on the primary endpoint, the proportion of subjects using rescue medications within 2 hours of symptom onset will be statistically compared between the two study arms, using Fisher's exact test at a significance level of $\alpha = 0.05$.

If there is no significant difference in baseline pain scores and no significant difference in early use of rescue medications between the two device types, the null hypothesis will be tested using the difference between the change in pain scores after 2 hours using the active device and the change in pain scores after 2 hours using the control/sham device.

The distributions of these differences will be tested for normality using the Shapiro-Wilk test at a significance level of $\alpha = 0.05$. If the distributions are consistent with a hypothesis of normality, the above null hypothesis will be tested using a two-sample *t*-test; otherwise, the null hypothesis will be tested using a non-parametric Mann-Whitney test. The mean and associated 95% confidence interval for the true difference between the two devices will be computed, along with the *p*-value associated with the null hypothesis.

If there is a significant difference in baseline pain scores and/or early use of rescue medications between the two study arms, an analysis of covariance (ANCOVA) model shall be fitted to the data, relating the difference in pain scores after 2 hours to the device type (active *vs*. control/sham), while controlling for any significant covariates. A *p*-value associated with the test of the hypothesis of no effect of the active device on change in pain score after 2 hours will be computed.

11.2.6 Analysis of Secondary Endpoint

In order to compare the mean change in pain score after an elapsed time of 4 hours using the active device to the mean change in pain score after an elapsed time of 4 hours using the control/sham device, the analyses as described in section 10.2.5 for the primary endpoint shall be followed.

11.2.7 Analysis of Exploratory Endpoints

In order to compare the proportion of subjects who report mild or no symptoms after an elapsed time of 2 hours using the active device to the corresponding proportion using the control/sham device, subjects will be stratified into two categories within each study arm, using the baseline pain score (6-7 *vs*. 8-10) as the basis for stratification. Within each of the two strata, the number of subjects with a pain score of ≤ 3 after 2 hours and the number of subjects with a pain score of > 3 after 2 hours shall be tabulated for both the active device and for the

control/sham device; results for each stratum shall be displayed in a 2 x 2 table. A Cochran-Mantel-Haenszel test shall be conducted to test the hypothesis of lack of association between the proportion of subjects reporting mild or no symptoms after 2 hours and the type of device, across all strata. An estimate of the pooled odds ratio and the associated exact 95% confidence interval will be computed, along with the *p*-value associated with the test of the null hypothesis.

The procedures described above shall also be conducted in order to compare the proportion of subjects who require abortive medication to control their migraine headache within 8 hours between the two device types, and to compare the proportion of subjects who report sensitivity to light after elapsed times of 2 hours and 4 hours between the two device types.

11.2.8 Blinding Assessment

As described in section 5.4, subjects who complete all study procedures will be asked at the final site visit to provide an opinion as to which type of device they believe they were assigned to (Avulux® *vs.* control/sham *vs*. do not know). Blinding assessments shall be performed on the resulting data, following procedures as described in James *et al*.[5] and in Bang *et al*.[6]

11.2.9 Adverse Event Data

Analyses of adverse event data shall be conducted with respect to all enrolled subjects who participated in the use of either the active device or the control/sham device during study procedures.

For each study device, the number of adverse events (AEs) shall be tabulated, and descriptive statistics shall be utilized to summarize the severity of AEs and their relationship to study procedures for each device.

All serious adverse events (SAEs) will be listed individually.

[5] James KE, Bloch DA, Lee KK *et al*. An index for assessing blindness in a multi-centre clinical trial: disulfiram for alcohol cessation – a VA cooperative study. *Stat Med* 1996, 15: 1421-1434.
[6] Bang H, Ni L and Davis CE. Assessment of blinding in clinical trials. *Control Clin Trials* 2004, 25: 143-156.